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The Anatomical Substrate for Telencephalic Function



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The relation between structure and function shows some degree of freedom.
At the moment
it is not clear
whether
this is due to lack of information
or
a fundamental aspect.

(P. Dullemeijer, 1974)

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List of Abbreviations

acv	ventral part of amygdaloid complex
acd	dorsal part of amygdaloid complex
apr	rostral pallial area
bo	olfactory bulb
boa	accessory olfactory bulb
ca	anterior commissure
cdr	rostral dorsal commissure
cer	cerebellum
ch	habenular commissure
cp	pallial commissure
cpo	posterior commissure
dien	diencephalon
ea	anterior entopeduncular nucleus
ep	posterior entopeduncular nucleus
fpl	lateral forebrain bundle
gpo	preoptic gray
hd	dorsal habenular nucleus
hpd	dorsal part of hypothalamus
hvp	ventral part of hypothalamus
hv	ventral habenular nucleus
hyp	hypothalamus
ip	nucleus interpeduncularis
mes	mesencephalon
met	metencephalon
myel	myelencephalon
noa	accessory olfactory nerve
pal	pallium
pia	pia mater
pd	dorsal pallium
pl	lateral pallium
pm	medial pallium
ptd	dorsal pretectal nucleus
ri	infundibular recess
rpo	preoptic recess
s	striatum
sa	peripheral layer of white matter
sgp	first neuronal layer
sgs	second neuronal layer
sl	lateral septum
sls	striated part of lateral septum
sm	medial septum
tdc	caudal dorsal thalamus
tdr	rostral dorsal thalamus
tel	telencephalon
teo	optic tectum

tla	anterior lateral thalamic nucleus
tlc	central lateral thalamic nucleus
tlp	posterior lateral thalamic nucleus
tol	lateral olfactory tract
tos	torus semicircularis
tv	ventral thalamus
v	ventricle
vI/II	lateral telencephalic ventricles
vIII	diencephalic ventricle
I	olfactory nerve or bulb
II	optic nerve
III	oculomotor nerve
IV	trochlear nerve
V	trigeminal nerve

1 Introduction: Theoretical Basis for Telencephalic Function

C.L. Veenman

1.1 Telencephalic Function

What differentiates the telencephalon from the rest of the central nervous system is the following function: The telencephalon allows an animal (human) to make decisions in new situations. All other telencephalon related behaviors like arousal, responsiveness, exploration, discrimination, inhibition, disinhibition, reversal learning, escape, avoidance, caution, aggression, etc. can be judged to be needed for this function, but are subordinate (for a review see Ebbesson, 1980). The latter processes lead to and result from decision making and can also be performed by non-telencephalic brainparts. Especially in lower vertebrates motor templates for simple to complex behavior are ready in the medulla (Hutchison and Poynton 1963/1964; Schmidt 1976; van Mier 1986, 1988), the cerebellum is involved in learning, memory, and motivation (Thompson 1983; Supple et al. 1987), and the reticular formation and raphe nuclei are involved in arousal (Hobson and Brazier 1980; Cordona and Rudomin 1983; Heimer 1983).

For the above mentioned specific telencephalic function it is necessary that information from one situation can be transferred to another, and fit into the new context. After finishing this process behavior must be determined. That such processes indeed take place in the telencephalon becomes clear from an experiment carried out by Farr and Savage (1978). Normal animals change their preference when in a certain familiar situation (choosing a leg in a t-maze) a conditioned stimulus from another situation is given. This is in contrast with telencephalon-ablated animals, which do not change their preference under these circumstances. The necessary controls to exclude other explanations for this phenomenon were carried out. The theoretical basis for this experiment was constructed by Overmier (Flood et al. 1976; Savage 1980).

The conclusion can be drawn that animals with an intact telencephalon can make predictions from new combinations of known stimuli, whereas animals with a damaged telencephalon are less able to do so. Other workers using other experimental designs have also concluded that animals with an intact telencephalon anticipate events whereas animals with a damaged telencephalon do not (Hollis and Overmier 1982; Rosenkilde 1983; Overmier and Papini 1986). In humans elementary processes of the overall telencephalic function are impaired after specific telencephalic lesions (Poeck 1982; Creutzfeldt 1983; Heimer 1983; Esslinger and Damasio 1985; Ivnik et al. 1987).

A question is how the telencephalon can perform this specific function of decision making in new situations, and whether for this function a general principle of organization for vertebrates can be found.

1.2 Dual Sensorimotor and Selection System

It has been proposed (Veenman and Gottschaldt 1986) that for complex behavior at least two systems are necessary: one in which different behavioral patterns can be generated from a certain stimulus situation (a sensorimotor system) and another one that allows for selection from these optional behavioral patterns (a selection system) (see also Fig. 1A). That such systems do exist is concluded from several studies, including work on bird telencephalon (Veenman and Gottschaldt 1986). It was noticed that in birds the nucleus basalis–neostriatum complex (probably a pallial derivative) receives a straightforward sensory input (Gottschaldt et al. 1980). The organization of the nucleus basalis–neostriatum complex in Anseriformes shows a high degree of internal order, and there are two output pathways: one over the paleostriatum complex (basal ganglia) and one over the archistriatum (amygdala) (Veenman and Gottschaldt 1986; Dubbeldam and Visser 1987). This circuitry can be compared with the thalamocortical system, sensorimotor cortex, and dual output pathway of the extrapyramidal and pyramidal systems in mammals.

1.3 Position of the Pallium

One hypothesis is that the pallium forms the sensory leg of the sensorimotor system, the basal ganglia the motor leg, and the amygdala the selection system (Veenman and Gottschaldt 1986). A subsidiary hypothesis following from this is that the development of the telencephalon is related to a refined dexterity of limbs, which also have good sensory capacities, in such a way that the pallium becomes more directly involved in motor functions (Gerritsen 1983; Veenman 1984). Work on fishes with limbs having refined sensory and motor capacities clarified that between the development of the telencephalon and such limbs no clear, direct correlation is necessary (Veenman and van Nierop 1986). Here, these capacities seem to be more related to enlargements (bulbs) on the brain stem and spinal cord at the segments innervating these limbs, whereas the telencephalon is not relatively enlarged (*Mulloidichthys martinicus*) or is even relatively small (*Trigla lucerna*).

Research on the pyramidal system (fibers reaching from the pallium to at least the mesencephalon, medulla oblongata, and medulla spinalis) indicates that this system is not directly necessary for the design of motor patterns but is rather necessary for the rapidity of reactions, which includes reflex facilitation and inhibition (Wiesendanger 1969). Another interesting fact is that children who at a young age have their cortex removed unilaterally still develop a surprising dexterity on the contralateral side (Poeck 1982). Possibly here the basal ganglia suffice to control motor performance, although in animals it is seen that in young stages unilateral ablation of the cortex allows the contralateral cortex to project bilaterally into the nucleus ruber and the thalamus (Leonard and Goldberger 1987). Not in all birds does the frontal neostriatum project directly into the paleostriatum (Wild et al. 1985). Thus, when the pallium does not unequivocally play a role in the sensorimotor system, it probably somehow participates in the selection system. When this is a general feature, it must be possible to show this for any vertebrate.

1.4 Working Hypotheses

In the present study, the postulated combination of a selection system with a sensorimotor system (Fig. 1A) is tested on the organization of the CNS in a single species, the clawed toad (*Xenopus laevis*), an amphibian. In amphibians the connections between the pallium and the striatum are scarce (Wilczynski and Northcutt 1983a, b; Veenman and Crzan 1986). The pallium and the striatum each have their thalamic and olfactory input (Wilczynski and Northcutt 1983a; Neary 1984; Wicht and Himstedt 1986; Veenman and Crzan 1986). In amphibians an output system from the pallium reaching the medulla is not obvious, whereas the striatum clearly contributes to the fiber systems reaching the brain stem and the spinal cord (Kokoros and Northcutt 1977; Kicliter 1979; ten Donkelaar et al. 1981; Wilczynski and Northcutt 1983b; Veenman and Crzan 1986). Thus, since the amphibian striatum has its own input-output system, it can probably perform the functions of the sensorimotor system. Thus, the pallium can possibly be included in the selection system.

The selection system should fulfil the following requirements: accessibility for present and past events, capacity to process this information, access to motor-affecting systems (the sensorimotor system) and, most importantly, the ability to

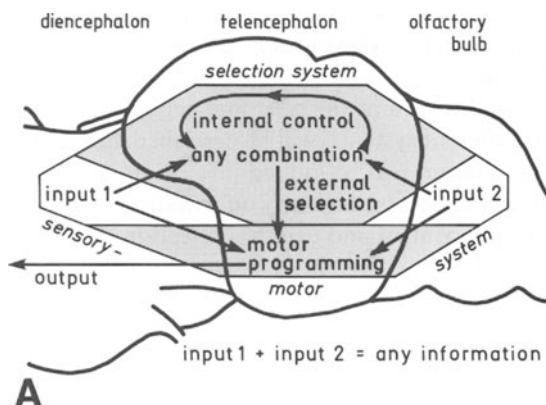


Fig. 1. A Structural concept of telencephalic function namely, a selection system determining the output of a sensorimotor system. **B** Our research object *Xenopus laevis*

correlate any information in any combination in a nonpredetermined way. When the correlations are predetermined then the behavior is also determined; this is a sensorimotor system. The capability to change responses or to make decisions in new situations, which is essentially the same, is then excluded. The ability to change responses or adaptation, however, is one of the aspects of telencephalic-controlled behavior (Pearson and Pearson 1976; Savage 1980; Overmier and Papini 1986). "Free" associations can be performed in an open system, which consists of a large number of nonlinear relationships.

The theoretical background for the idea of how the pallial network should be organized stems from Johannesma et al. (1986). They state that the outcome of information processing in a network consisting of reciprocal connections is unpredictable. Creutzfeldt (1983) also mentioned that functions describing events in reciprocal relationships are nonlinear. The idea itself stemmed from the realization that an adaptive system should be able to follow and predict events in its environment. Since an ecological system consists for a large part of nonlinear relationships, one can expect from an adaptive system that it is able to replicate these relationships, in order to be a match for its environment. But, for a behaving animal the outcome of the information processing of the CNS should not just be nonpredetermined (show a high degree of freedom) but should also be adequate and well balanced; this requires the capability for internal control and poses the question of how this can be done. For the sensorimotor system it is sufficient to have afferents relaying sensory information and efferents which reach the motor systems.

In this volume the neuronal network of *Xenopus laevis* pallium, plus its afferent and efferent systems, will be described, and also the afferent and efferent systems of the striatum will be looked into, in order to see whether the anatomical basis for the ability to associate any information in any combination plus the capabilities for internal control and external selection of motor programs can be recognized (see Fig. 1A).

1.5 Choice of Animal

1.5.1 Scientific Grounds

Since the aim of this study was to understand the telencephalon as a complete system in relation to the rest of the CNS, *Xenopus laevis* (Fig. 1B), a "lower" vertebrate with a relatively small and simple brain, was chosen as a subject. "If the amphibian brain is not the simplest of all vertebrate brains it nevertheless displays an organization which is readily interpretable as the common denominator of many others" (Pearson and Pearson 1976). Others also consider the amphibian brain as the simplest vertebrate brain (Herrick 1948; Northcutt and Kicliter 1980). Central nervous systems of amphibians generally have a balanced appearance, no brain parts being extensively enlarged in relation to the others. The cell masses remain grouped around the ventricle system, leaving the fiber systems peripherally. The telencephalon of amphibians shows a relatively simple evagination into dorsal, lateral, rostral, and caudal directions. There is no extensive nucleization or lamination (Ariens-Kappers et al. 1936; Herrick 1927, 1948; Kuhlenbeck

1967–1978; Northcutt and Kicliter 1980), although some workers differentiate more than seems appropriate.

The CNS of *Xenopus laevis* does not differ essentially from those of other amphibians (Northcutt and Kicliter 1980). The telencephalon of mature *Xenopus laevis* (Figs. 3, 5, 6, 8, 9, 10) like that of other amphibians, consists of a number of longitudinal zones, generally called: medial pallium, dorsal pallium, lateral pallium, striatum, nucleus accumbens, and septum (Herrick 1927, 1948; Kuhlenbeck 1967–1978; Kicliter and Ebbesson 1976; Northcutt and Kicliter 1980). Traditionally, an exception to this rule of longitudinal zones is made for the amygdala, which is generally thought to be restricted to the ventral caudal part of the telencephalon (Herrick 1948; Kuhlenbeck 1967–1978). Our histological data obtained from *Xenopus laevis* show that there is a prominent cell region stretching along the lateral wall of the telencephalon, in between the pallium and striatum, which extends from the olfactory bulb to the diencephalon. On the basis of position, connectivity, and neurotransmitter content it was concluded that this region is an equivalent for the amygdala (Veenman et al. 1987). This region combines the traditional lateral amygdala with the so-called dorsal striatum (Kicliter and Ebbesson 1976) and the nucleus of the dorsal lateral olfactory tract (Herrick 1927; Kuhlenbeck 1967–1978). The amygdala pars medialis (Herrick 1948) is excluded from this concept. Acceptance of this allows the statement that the telencephalon of amphibians is differentiated consequently into subunits which all form longitudinal zones throughout the length of the telencephalon.

This relatively simple organization contrasts with those of mammals, birds, and most fishes, in which especially the telencephalon is a highly differentiated structure with strong lamination, nucleization, and a complex arrangement of fiber systems (Ariens-Kappers et al. 1936; Hassler and Stephan 1966; Pearson and Pearson 1976; Ebbesson 1980; Kuhlenbeck 1967–1978). The organization of the CNS of reptiles can be considered to have a level of organization intermediate between that of amphibians and of birds and mammals (Northcutt 1981) and knowledge of the telencephalon of the various reptilian radiations is accumulating rapidly (Brauth and Kitt 1980; Pritz 1980; Pritz and Northcutt 1980; Reiner et al. 1980, 1984a; Ulinsky 1981, 1986; Brauth et al. 1983; Reiner and Schade Powers 1983; Bruce and Butler 1984a,b; Belekova et al. 1985; Ouimet et al. 1985; Kriegstein et al. 1986; Smeets et al. 1986; Russchen et al. 1987b).

There are other vertebrates which have brains of which the complexity does not exceed that of amphibians, namely, Cyclostomata, Holocephali, Dipnoi, and Polypteriformes (Hassler and Stephan 1966; Pearson and Pearson 1976; Ebbesson 1980). Amphibians, together with the Cyclostomata, Holocephali, and Dipnoi, have an evaginated telencephalon, whereas Polypteriformes have an everted telencephalon. All these groups have in common that they lack an extensive proliferation of cell masses in the telencephalon. This means that they all have a relatively simple telencephalon. Since this is a shared characteristic it can be concluded that this type of organization stems from a common ancestor and therefore is primitive (Northcutt 1981). Stated more carefully, the simple evaginated telencephalon of amphibians probably resembles the ancestral form and as such can be the link by which the telencephala of the other, more evolved groups can be interrelated. Only for practical reasons was *Xenopus laevis* chosen from these different groups.

The determination of an anatomical substrate for telencephalon controlled behavior with this animal, however, is subject to a dilemma: (1) the effects of telencephalic lesions or other manipulations are best researched in the groups of mammals, birds, and fishes, but there it is hard to grasp the system as a whole, (2) the brain of *Xenopus laevis* is relatively simple, but there has been very little research on behavior after manipulations, or on other amphibians for that matter (Hutchison and Poynton 1963/64; Laming et al. 1984; Stehouwer 1987; K.E. Zittlau, personal communication). However, an additional problem that occurs when considering work on “higher” vertebrates tilts the balance in favor of doing research on the telencephalon of amphibians, namely, that the arrangements within the telencephala of the groups of fishes, birds, and mammals are essentially different from one another. The telencephalon of bony fishes is generally everted, with possibly a rearrangement of regions (Nieuwenhuys 1966). The telencephalon of the other groups is evaginated with probably a conservative topology (Northcutt 1981). The telencephalon of mammals is characterized by a highly organized cortex which as such is lacking in the other groups (Creutzfeldt 1983). These differences make it difficult directly to transfer conclusions derived from results in one group to the other groups. It was expected that the telencephala of all the “higher evolved” groups could be compared directly with those of amphibians.

We decided to determine the anatomical substrate of telencephalic controlled behavior in *Xenopus laevis* because our aim is to see the system as a whole and not as a patchwork of results from innumerable vertebrate species. In any case, to be able to derive general conclusions from research on a single species one needs a tool like comparative neuroanatomy. The determination of homologies is interesting and important. It can be done on phylogenetic grounds, but this is extremely difficult because of the scarcity of fossils. The concepts and problems behind the determination of homologies in comparative neuroanatomy are often discussed (Bock 1969; Campbell and Hodos 1970; Northcutt 1981; Rehkämper 1984). The determination of homologies through the determination of ontogenetic development, alas, is too rarely undertaken (Källen 1951, 1953; Haefelfinger 1958; Senn 1970; Reiner et al. 1984b). A way of avoiding the problems inherent in the determination of homologies is to determine analogies. In fact, most so-called determinations of homologies based on connectivity, morphology of elements, and neurotransmitter content are rather determinations of analogies since these parameters are closely related to the functions of the structures in question. This, however, is what interests us most: “What is the morphological basis for telencephalic function? Is this specific for the subject in question or can it be generalized?” To study forms and relations between forms can teach much about how functions are executed (Dullemeijer 1974).

In conclusion, on scientific grounds *Xenopus laevis* is an adequate animal for the conceived project.

1.5.2 Practical Grounds

On pragmatic grounds *Xenopus laevis* (Fig. 1B) was chosen as a subject for this study: it is sturdy as a laboratory animal (Hutchison and Poynton 1963/64; Deuchar 1975); it is not a species threatened with extinction (Nilsson 1986); it can

be obtained easily and bred in captivity (Nieuwkoop and Faber 1975); information on the ascending visual, auditory, and lateral line systems is available (Levine 1980; Fritsch et al. 1984; Will et al. 1985a, b; Lowe 1986, 1987; Zittlau et al. 1986, 1987; Elepfandt 1987) as well as on the output systems of the telencephalon (ten Donkelaar et al. 1981); behavioral experiments are being carried out (Elepfandt 1987; Traub and Elepfandt 1987; Zittlau et al. 1987); and also more and more information about the development of the CNS of this animal is becoming available (Nordlander 1984, 1986; Boymel Udin and Fisher 1985; Nordlander et al. 1985; Sperry and Grobstein 1985; Gallagher and Moody 1987; van Mier 1988).

1.6 Methods Employed

The main method used in our study was the determination of connections in the brain of *Xenopus laevis* with the help of the tracer horseradish peroxidase (HRP). A series of small injections was distributed over the pallium to determine its intrinsic and extrinsic connections. Several, mostly larger injections were placed in the mesencephalon, diencephalon, ventral telencephalon, and olfactory bulb to obtain an insight into the input and output systems related to the telencephalon, and as a control to the pallial injections. Histological methods (Nissl stains and silver impregnations) were used to obtain an overview of the general anatomy of *Xenopus laevis* brain. Immunohistochemistry was used to test hypotheses on homologies (Veenman et al. 1987) and to deepen our insight into the differentiation of *Xenopus laevis* telencephalon.

2 Methods and Results: Study of Prosencephalic Connectivity and Structural Organization

C.L. Veenman and D. Crzan

2.1 Extra-experimental Procedures

The subjects used for this study were from one of the subspecies of *Xenopus laevis*. Animals were either bred and reared in captivity according to Nieuwkoop and Faber (1975) (30 individuals) or obtained from the Herpetological Institute in Den Dolder, the Netherlands (80 individuals), from where animals were sent to us in batches of 10–20 by fast train, in cushioned crates (15 × 30 × 50 cm) filled with moistened foam plastic. Until they were used the animals were kept in our laboratory in a white plastic opaque tank (40 × 40 × 60 cm) half filled with tap water at room temperature. The water was aerated, filtered continuously, and refreshed regularly. The animals were fed with beef or pork heart and occasionally vitamins were added to the water. Excrement was removed daily. Basalt plates obtained from a nearby extinct volcano (Barterode) provided shelter on the bottom and a brown plastic lid (15 × 30 cm) floating on the surface provided cover at the higher level. Without these hiding places the animals swim wildly around the tank when approached, bumping into the sides and into each other.

During the periods in between the manipulations the tank was covered with a white opaque plastic lid. In this environment the animals spend most of the time motionless under or on top of the rocks, or on the free parts of the bottom. When an observer is noticeably present, the animals only occasionally swim up to the surface in fast reflex-like movements to breathe. When the observer is quiet and distant, the animals spend long times at the surface. When food is placed in the water the animals start moving around, and wave their forelimbs to and fro in sideward movements. In this way they cause vibrations which are reflected from objects and can subsequently be detected via the lateral line system. Without the surface cover they often do not move from under the stones until nothing is visibly hovering over the tank. When the forepaws touch a food particle or the foot of another frog the object is quickly snapped up with the jaws. Detachments from a foot occurs quickly, and food is kept in the mouth for some time before ingestion. Sometimes some animals can be hand fed; after repetition they even come to the surface and snatch offered food particles. After some other animals are removed for experiments (with or without return for a survival period) this behavior no longer occurs. During summer evenings the males come to the surface and make their mating calls.

Judging from the behavior of the animals, the subjects were kept under satisfactory conditions. It also appears that they can learn, unlearn, and change their behavior according to circumstances. This implies that they have a functioning telencephalon and an overall activity of the CNS which stimulates its metabolism and possibly axonal transport which is required for the anterograde and retrograde HRP labeling of neuronal elements.

2.2 Experimental Procedures

2.2.1 Preparation

For experiments the animals were caught by hand. One hand was positioned behind the animal to keep it from turning around, the other hand shielded the eyes and was cupped around the head and body to lift it out of the water. Animals held in this way are immobilized, and it is not necessary to exert any pressure. Prior to surgery the animals were anesthetized by placing them for $\frac{1}{2}$ h in 500 ml tap water containing 1 g tricaine methanesulfonate (MS222) (Sigma). MS222 penetrates the skin, causing local

anesthesia in humans. Anesthesia was considered completed when the animals no longer showed movements after being turned on their backs. Awake animals show a strong righting reflex and cannot be kept upside down.

For the HRP experiments 74 animals were used. The animals were placed in a head-body holder designed for *Xenopus*. The animal lay on a sponge damp with tap water and was covered with a tissue moistened with the MS222 solution. The head was held with a clamp fitting into the vomeronasal organ and into the eye sockets right next to the skull. With the skull held in this way the eyes sink freely from the bottomless eye socket into the mouth cavity. The body was held with a thread stretching over the shoulder girdle. In this way, although not rigidly held, the head was stable, the animal being motionless through anesthesia. The skin was incised along the midline from close to the nostrils until close to the thread over the shoulder girdle, and retracted sideways with sutures. The periosteum over the skull was pushed sideways with a dull instrument. When necessary, muscles were detached from the skull in a similar fashion and retracted with sutures running through the epimysium. The skull was perforated with a dental drill. The site for drilling was determined by localizing the black dotted meningeal over the tectum and telencephalon, which are visible through the skull. The dura was opened and retracted with fine forceps. The pia was mostly perforated with the fine tip of a micropipette or an insect needle to allow smooth penetration for injections.

For injections micropipettes (tip diameter 20–50 μm) were filled with 20% HRP (Boehringer grade II or III) dissolved in Tris buffer (pH 7.6, 0.5 M), saline 0.7%, or distilled water using a 10- μl syringe (Hamilton). The injections were performed iontophoretically (1 μA , constant current, 30 min) or by pressure with the help of an attached Hamilton 1- μl syringe (0.05–0.2 μl). In five animals wheatgerm agglutinin conjugated HRP (Sigma) (2% in 0.01 M Tris buffer, pH 8.0) was injected iontophoretically. Prior to pressure injections both the pipette and the 1- μl Hamilton syringe were filled with the HRP solution, glued together with dental cement or histoacryl (Braun, Melsungen), and checked to see whether HRP solution could be driven from the tip of the pipette. The pipettes with or without the attached Hamilton syringe were clamped in a microdrive. The pipette could be moved, as well as tilted, in any direction.

After surgery, injections in the pallium or tectum only required short penetration tracts, leaving the HRP dumps restricted to the intended sites. Injections in the more ventral regions usually required long tracts reaching from the more dorsal surfaces; in these cases leakage along the penetration tract could not be prevented. Another technique employed to reach ventral regions was an in vitro method (see below). During iontophoresis the pipette was vibrated by attaching the running dental drill to the holder. After pressure injections the pipette was left in place for 30 min. The wound was kept moist with saline. The hole in the skull was filled with paraffin oil. After retraction of the pipette, the skull was sealed with bone wax and covered with histoacryl (Braun Melsungen) or dental cement. The skin incision was sutured or glued. The animals were returned to the tank and kept apart from the other animals with a perforated Perspex plate. Survival time could be 2–4 days but was usually 72 h.

Prior to perfusion the animals were deeply anesthetized with MS222. The animal was placed on its back, and the limbs spread and fastened by driving pins through the skin into a Styropore plate. The thorax and abdomen were opened with scissors and the breast case remained spread from the pull of the stretched out forelimbs. To produce anesthesia during perfusion the body cavity was filled with the MS222 solution; on some occasions MS222 was added to the saline used for rinsing out the blood. Perfusion was performed transcardially. Pressure was 100–150 cm H_2O . The ventricle was opened at the tip with fine scissors. The perfusion canula was led through the ventricle until up into the bulbus arteriosus. Infusion of saline was started, and the right atrium was perforated with fine scissors upon the swelling which occurred. The swelling was an indication of the circulation system being under pressure, with the blood vessels widened as a consequence. Overpressure causes vessels in the lungs to rupture. Saline was run through until clear fluid came from the atrium. Fixation was usually established by perfusion with 2% paraformaldehyde solution in phosphate buffer, or with 1% glutaraldehyde–1% paraformaldehyde in the same phosphate buffer (pH 7.4, 0.1 M). Subsequently the fixative was rinsed out with saline.

The complete CNS was dissected. The pia was stripped away with fine forceps. This was necessary to allow penetration of diaminobenzidine (DAB) in the subsequent incubations. The spinal cord was used as a handle to hold the brain during transfer from one solution to the other.

The in vitro method (Ekström 1985) was used to reach the ventral diencephalon. An anesthetized animal was perfused with the cold incubation solution to rinse out the blood. Either Ekström's (1985) or a slice medium for electrophysiological recordings (U. Kuhnt, personal communication) were used.

With such solutions a frog's CNS remains biologically active for at least 6 h (Schmidt 1976). The CNS was dissected, placed in a drop of the incubation solution on a Styropore plate, and with the help of the pipette holder pressure injections were made (0.1 μ l, excess HRP was rinsed from the brain). The brain was kept overnight at 4°C in the incubation solution. After this "survival" time the brain was fixated in 2% paraformaldehyde in phosphate buffer (pH 7.4, 0.1 M) containing 2% DMSO for 2 h at room temperature. These brains were incubated for HRP determination according to the whole mount method.

2.2.2 Horseradish Peroxidase Determination

From 11 brains sections were alternately prepared according to an on-the-slide benzidine dihydrochloride (BDHC) incubation (Ebbesson et al. 1981) and a DAB-CoCl₂ method for HRP determination (Adams 1977). The rest was processed as "whole mounts" (Fritsch and Nikundiwe 1984; van Mier 1986, 1988) with a modified DAB-CoCl₂ method. For whole mount incubation the brains were preincubated in 1% CoCl₂ and 2% dimethyl sulfoxide (DMSO) in a 1:1 mixture of Tris buffer (pH 7.4, 0.1 M) and methanol for 3h, followed by a preincubation in 0.2% DAB, 2% DMSO dissolved in 1:1 phosphate buffer (pH 5.1, 0.1 M) and methanol for 45 min. Then in three, 10 min steps with increasing H₂O₂ concentrations the brains were brought to the final incubation solution: 0.02% H₂O₂ in a DAB solution as described. Here they stayed until the surface blackened (ca. 45 min). The reaction was terminated by rinsing three times in the 1:1 phosphate buffer-methanol mixture. Two attempts were also made to incubate by perfusion with a DAB-CoCl₂ solution; no staining of neuronal elements occurred.

After incubation the brain was dehydrated through an alcohol series (several days). Then it was soaked in cedar wood oil and xylene, or run through a series of propanol, methylbenzoate (several days), benzene, and benzene/Paraplast. After this, it was impregnated (several days) and embedded in Paraplast. Sagittal, transversal, or horizontal 10- μ m sections were taken using a Leitz slide microtome. The sections were mounted, and all sections or every second one was counterstained with neutral red, and coverslipped with Eukit.

Horseradish peroxidase labeling was determined with a light microscope and from good series every fourth section was photographed with a Wild photomicroscope to produce forebrain overviews either including or not including the brain stem. Prints (18 \times 24 cm) were made with a developing machine (Metoform 5040, Meteor Siegen). In such documented series HRP reaction product was determined systematically with the help of a light microscope and indicated on the photos with ballpoint or felt-tip pens. Photos from representative sections were used to make black and white drawings describing the HRP transport. The side ventricles of the mesencephalon were used to align the drawings of the sagittal sections. Summarizing reconstructions of the patterns of connections appearing after single experiments were made by drawing them into a graph of a representative cross section through the telencephalon and into a schematic top view onto the brain.

In Sect. 5 the combined results are summarized in outlines and reconstructions of the brain. The reconstructions were made after serial cross sections. Photographs of high magnifications using a Leitz photomicroscope were made to show HRP-labeled neuronal elements and histological details. The results of the injections in the diencephalon and in the optic tectum are documented with photos.

2.2.3 General Histological Techniques

Thirty-seven animals were used to produce histological overviews: including Nissl (Romeis 1968), Rager (Rager et al. 1979), Gallyas (Gallyas 1979), and Golgi stains (Valverde 1970; Peters and Fairén 1978). The material from the first three stainings was embedded in Paraplast and cut into 10- μ m sections. The Golgi material was embedded in soft Epon and cut into 100- μ m sections on an Autocut microtome (Reichert and Jung). The brains were cut in horizontal, sagittal, and transverse planes. The Nissl material formed the basis for the reconstructions and an atlas of *Xenopus laevis* forebrain used in our work.

2.3 Horseradish Peroxidase Labeling

Horseradish peroxidase labeling determined with BDHC is characterized by reaction product overgrown with crystals. Details of neuronal elements are thereby obscured and it is also difficult to distinguish between reaction product resulting from HRP transport and from endogeneous reactions in non-neuronal structures. The on-the-slide DAB-CoCl₂ method employed frequently caused sections to float from object carriers. A pure DAB method is not sensitive enough (Veenman and Gottschaldt 1986). The whole-mount DAB-CoCl₂ method gave satisfying results: neuronal elements from the surface to deep in the CNS, up to the ventricle, showed HRP reaction product. This method shows ample details, making it easy to tell labeled neuronal elements apart from other stained structures like: macrophages, erythrocytes, and the walls of blood vessels. It was important to remove the pia prior to incubation since it blocks the penetration of DAB, resulting in an intense black staining of the surface but leaving the interior of the CNS blank. After incubation, care had to be taken not to use too high temperatures during the procedures for Paraplast embedding, since that causes blurring of labeled structures. Therefore, temperatures were maintained around 60°C.

The injections in the pallium were always kept as small as possible (Fig. 2). Whether the amount indicated on the scale of the Hamilton syringe was always ejected completely is unclear. In any case, the injections in the pallium were often so small that no substantial HRP transport could be determined. This problem did not occur with tectal injections where the same method was used. Injections in the diencephalon in vivo sometimes had as an unwanted result that the brain broke apart in that region during the procedures of Paraplast embedding, possibly because of the deterioration of tissue. Because of this, the exact injection site could not be determined. This problem did not occur with in vitro injections in the diencephalon. However, we could not determine HRP transport after injections in the striatum with the in vitro method. Injections in the dorsal superficial areas were well restricted to the intended sites. Injections in more ventral regions (mesencephalic brain stem, amygdaloid complex, striatum complex) with dorsal approaches were accompanied by HRP leakage in the penetration tract. Injections with ventral approaches in the in vitro method resulted in well-restricted dumps. The Boehringer HRP gave the best results. Wheatgerm agglutinin conjugated HRP is not suitable for use in the determination of connectivity in amphibian telencephalon – it is not easily visible.

In many cases anterograde transport was clearer than retrograde transport. Anterograde transport was easiest to follow since it is mostly continuous with the injection site, or the fragments show at least a certain direction. The retrogradely labeled cells had to be located by systematic searching through all of the sections, also because frequently they are not accompanied by labeled fibers. The labeled cells are mostly evenly stained without showing grains; the labeling could be very vague, very intense, or anything in between. Since the staining of cells is often not intense, especially of those farther away from the injection site, it was better first to search for them in noncounterstained sections. When the location of labeled cells was determined, they could also be found in counterstained sections. Neutral red was preferred to cresyl violet since it stains less darkly and thereby allows weak labeling to be seen better.

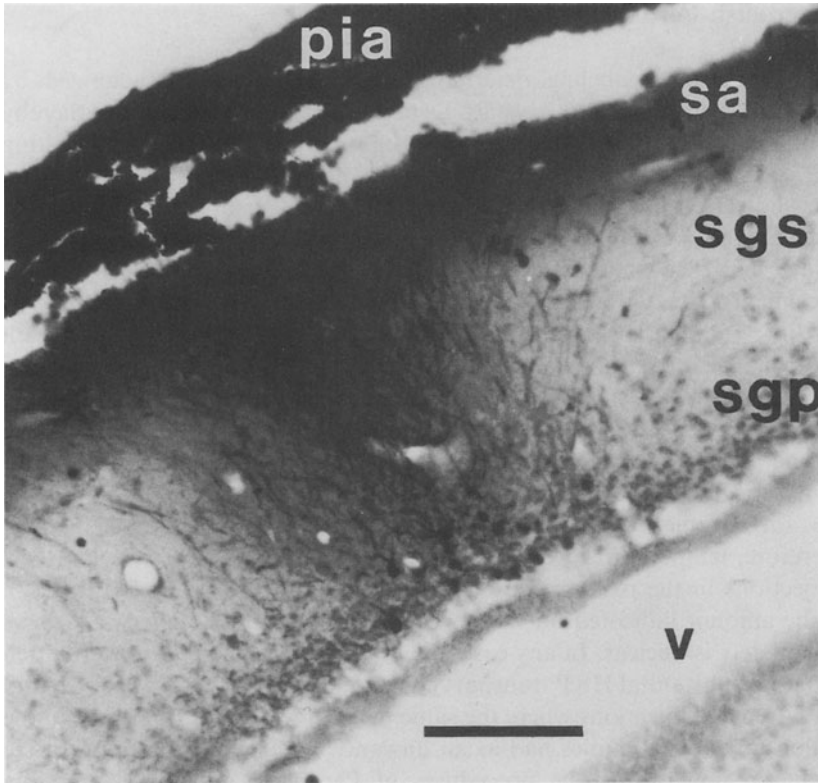


Fig. 2. An HRP iontophoretic *injection site* in the dorsal pallium. On the slide incubation with DAB- CoCl_2 . The pipette was only pressed against the surface and vibrated. The *pia* is black from reaction product. A haze fills out *sa*. Neurons close to *v* are completely filled. Filled processes stretch from *sgp*, through *sgs* into *sa*. For abbreviations see list. Bar, 100 μm

It cannot be excluded that neurons do send axons into the injected sites, but do not take up enough HRP to show labeling after incubation. Something else that can happen is that macrophages eat labeled cells. In some experiments numerous macrophages appear in sometimes restricted areas. Occasionally a macrophage filled with HRP can be seen sitting on the ghost of a labeled cell. So, it was also hoped that the *in vitro* method would improve the labeling, since here most macrophages are rinsed out with the blood and removed with the body, and by using low temperatures the metabolic rate in the neurons would slow down allowing an accumulation of HRP in the cell bodies. In one case after *in vitro* injection no long-distance retrograde labeling was seen; in another case several populations of labeled neurons were detected.

Anterograde HRP labeling in the telencephalon occurred as thin fibers mostly accompanied by an even brown haze (Fig. 2). This brown haze also appears with injections in the diencephalon and in the roof of the mesencephalon. This haze can occur independently of labeled fibers. With light microscopy no neuronal elements causing this even brown haze could be distinguished. The question was whether this haze was caused by labeled neuronal elements having dimensions less than

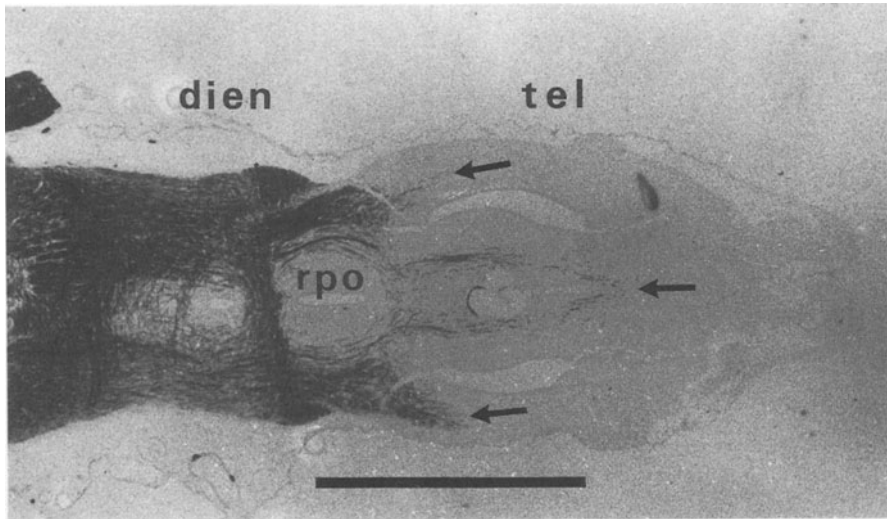


Fig. 3. Gallyas stain. Caudal from *tel*, the brain stem, including *dien*, is filled out with *myelinated* fibers. *Tel* and the region around *rpo* are relatively free from *myelinated* fibers. Arrows point at *myelinated* fibers in *tel*. For abbreviations see list, Bar, 2 mm

1 μ m or artifact, for example diffusion from the injection site or diffusion from labeled fibers. The small injections in the diencephalon and the mesencephalon often caused heavy labeling of many thick fibers together with the brown haze. Thus, small injections were good enough to cause neuronal transport. As long as recognizable fibers occurred among the haze there was no problem. However, the appearance of this haze without a simultaneous occurrence of distinguishable fibers, especially after the injection in the amygdaloid complex, made it important to determine whether this haze stemmed from narrow neuronal elements.

Gallyas stains show that myelinated fibers are rare in the telencephalon and can be attributed to extrinsic input and output fibers (Fig. 3). Rager stains (Fig. 4) show that caudal to the telencephalon masses of thick fibers occur whereas within the telencephalon singular thin fibers appear within an evenly stained background. This, however, does not mean that the even brown haze occurring after HRP injections is not artifact. Finally, electron microscopy showed that in the areas with the haze labeled neuronal elements smaller than 1 μ l occur (Sect. 3).

2.4 Display of the Forebrain and Injection Sites

2.4.1 Nissl Stain

In the pallium a dense cell layer borders the ventricle (Figs. 4A, 5, 6). More peripherally there is a less dense cell layer (Fig. 4A). In the lateral and dorsal pallium this second layer is narrow, whereas in the medial pallium it forms the bulk of the cellular mass (Figs. 5, 6). The striatum consists of a dense cell layer which is detached from the ventricle; more peripherally it has a characteristic neuropil which stains dark relative to the surrounding white matter (Fig. 5). Caudally, at the

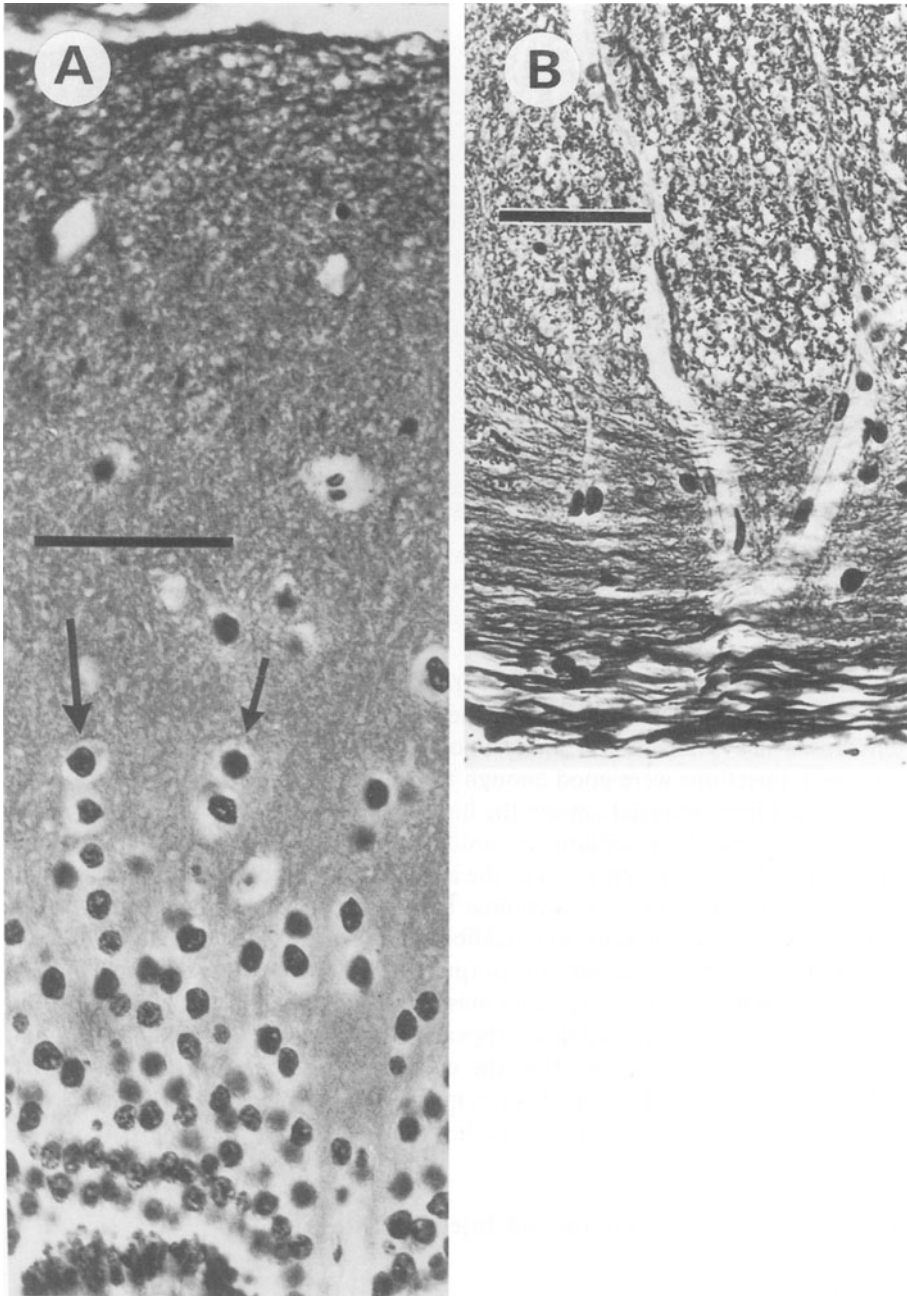


Fig. 4A, B. Rager stain. **A** In the pallium in sa (*top*) axons become barely visible. Neurons are tightly packed close to the ventricle in sgp (*bottom*), and are arranged in columns (*arrows*) in sgs. **B** In the myelencephalon thick (peripherally, *bottom*) and thin (centrally, *top*) fibers can be seen. For abbreviations see list. Bars, 100 μ m

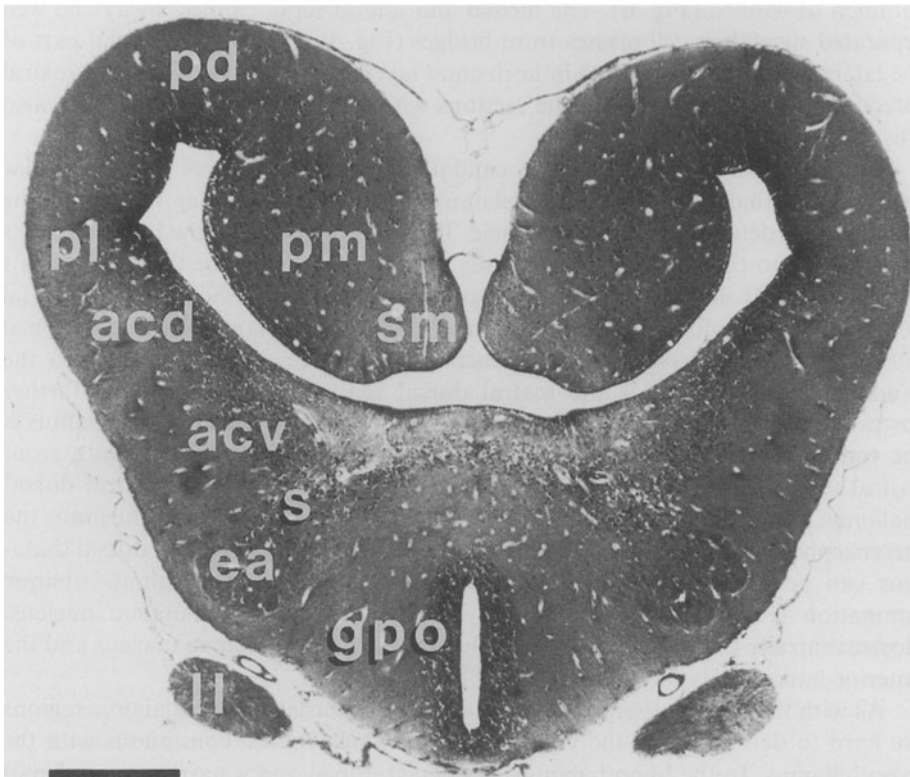
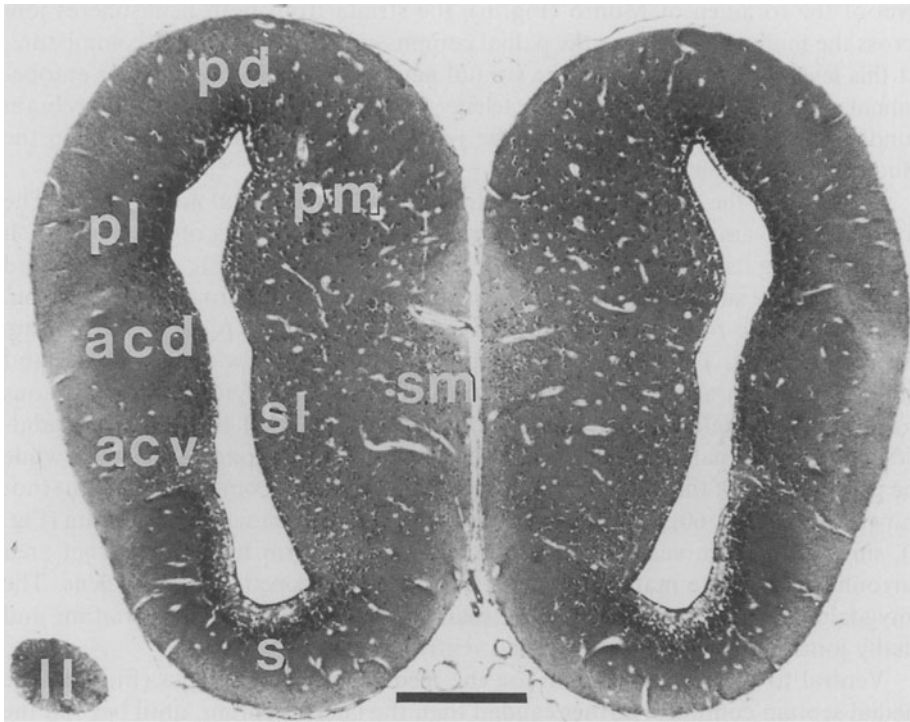
level of the foramen of Monro (Fig. 6), the striata from both hemispheres join across the midline in between the pallial commissure and the anterior commissure. At this level, at the position of the striatal neuropil, appears the anterior entopeduncular nucleus (Fig. 6), the main telencephalic source for the lateral forebrain bundle which can be followed into the posterior entopeduncular nucleus in the caudal diencephalon (Fig. 7).

In between the pallium and the striatum is the amygdaloid complex. The position of the amygdaloid complex is marked by a round area of neuropil which stretches along its entire length (Figs. 5, 6). Over its entire length, the amygdaloid complex can be subdivided into a narrow dorsal band and a broad ventral region. Especially in the rostral part of the amygdaloid complex a prominence appears ventrally (Fig. 5). The borders of the amygdaloid complex with the pallium and with the striatum are hard to define, since their cellular regions are continuous (Figs. 5, 6). Especially in the central part of the hemisphere, the striatum, amygdaloid complex, and pallium form a continuous band of cells along the ventricle while the prominences of the lateral pallium and the amygdaloid complex are absent (not shown, but see Fig. 60). More caudally the amygdaloid complex widens again (Fig. 6), shifts to a more ventral and medial position to form finally a distinct area surrounded by white matter dorsal to the anterior entopeduncular nucleus. The amygdaloid complex reaches farther than the caudal pole of the striatum and finally joins the preoptic gray and the ventral thalamus.

Ventral to the medial pallium are the medial and lateral septa (Fig. 5). The medial septum continues farther caudad than the lateral septum, until beyond the foramen of Monro (Fig. 6). The medial and lateral septa cannot always be well separated since their cell masses form bridges (Fig. 5). The ventral caudal part of the lateral septum is laminated in horizontal layers which curve upward in rostral directions (not shown, but see the sections with the HRP experiments). See also Fig. 8C.

The cross section through the caudal diencephalon shows the habenular commissure, thalamus, and hypothalamus (Fig. 7). The cellular masses of the thalamus are detached from the ventricle. The cellular masses of the hypothalamus are adjacent to the ventricle. Peripherally is white matter. In the thalamus at this level the caudal dorsal thalamus appears most dorsally. In between the caudal dorsal thalamus and the habenular commissure are remnant cells of the dorsal habenular nucleus, which stretches rostrally from here. Directly ventral to the caudal dorsal thalamus is the rostral dorsal thalamus, which reaches farther rostrally than the caudal dorsal thalamus. The most ventral area of the thalamus is the ventral thalamus, which has the longest rostrocaudal extension. Thus, from rostral to caudal appears: first, the ventral thalamus, second, the rostral dorsal thalamus, third, the caudal dorsal thalamus (Fig. 8C), which all continue into the mesencephalon, where their distinction becomes unclear. The rostral dorsal thalamus can be distinguished from the other thalamic areas through its oblique lamination (Fig. 7). Dorsolaterally is the posterior lateral thalamic nucleus. Rostroventrally to this nucleus appear the central lateral thalamic nucleus and the anterior lateral thalamic nucleus (Fig. 8B).

As with the other prosencephalic structures the borders of the thalamic regions are hard to define. Along the ventricle the thalamus is even continuous with the hypothalamus. In the hypothalamus a widened dorsal and a narrow ventral part



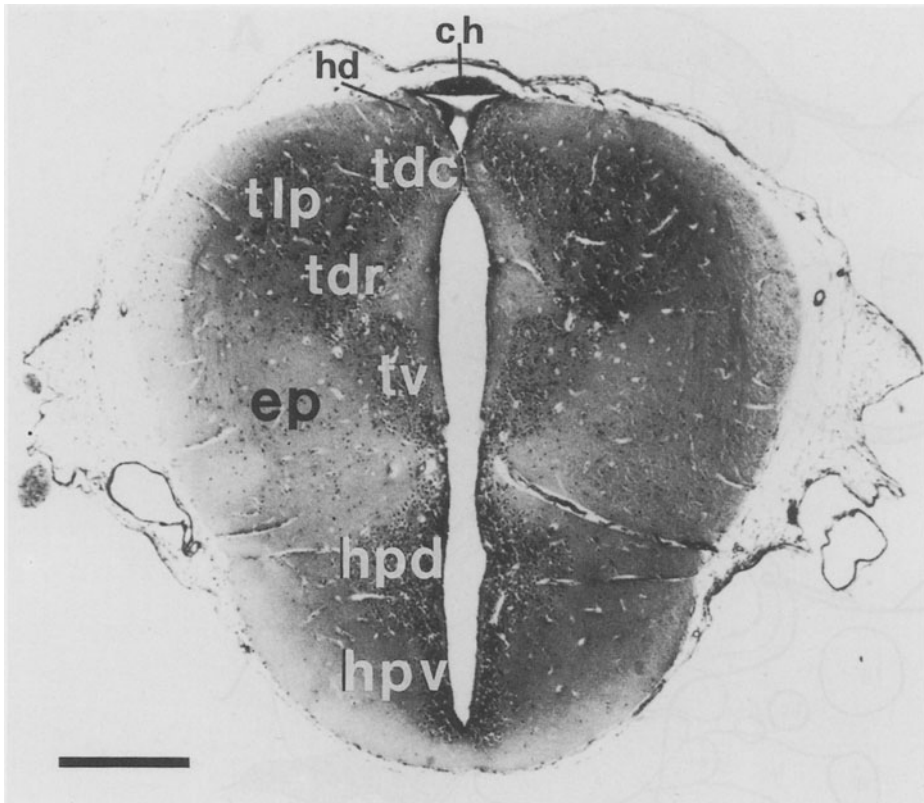


Fig. 7. Nissl stain. *Cross section through the caudal third of the diencephalon.* For *abbreviations* see list. *Bar*, 0.5 mm

can be distinguished. Laterally, the white matter in between the thalamus and hypothalamus contains scattered cells of the posterior entopeduncular nucleus in the lateral forebrain bundle (Fig. 7).

These three cross sections are part of a series which formed the basis for the reconstructions shown (Fig. 8A–C).

2.4.2 Reconstructions

For orientation three reconstructions of the forebrain are given: The first reconstruction (Fig. 8A) shows the ventricle system. The second reconstruction (Fig. 8B) shows lateral structures: dorsal pallium, lateral pallium, dorsal and ventral parts of the amygdaloid complex, olfactory and accessory olfactory bulb

◁ **Fig. 5.** (top) Nissl stain. *Cross section through the rostral third of the telencephalic hemispheres.* For *abbreviations* see list. *Bar*, 0.5 mm

Fig. 6. (bottom) Nissl stain. *Cross section through the caudal third of the telencephalic hemisphere at the level of the foramen of Monro.* For *Abbreviations* see list. *Bar*, 0.5 mm

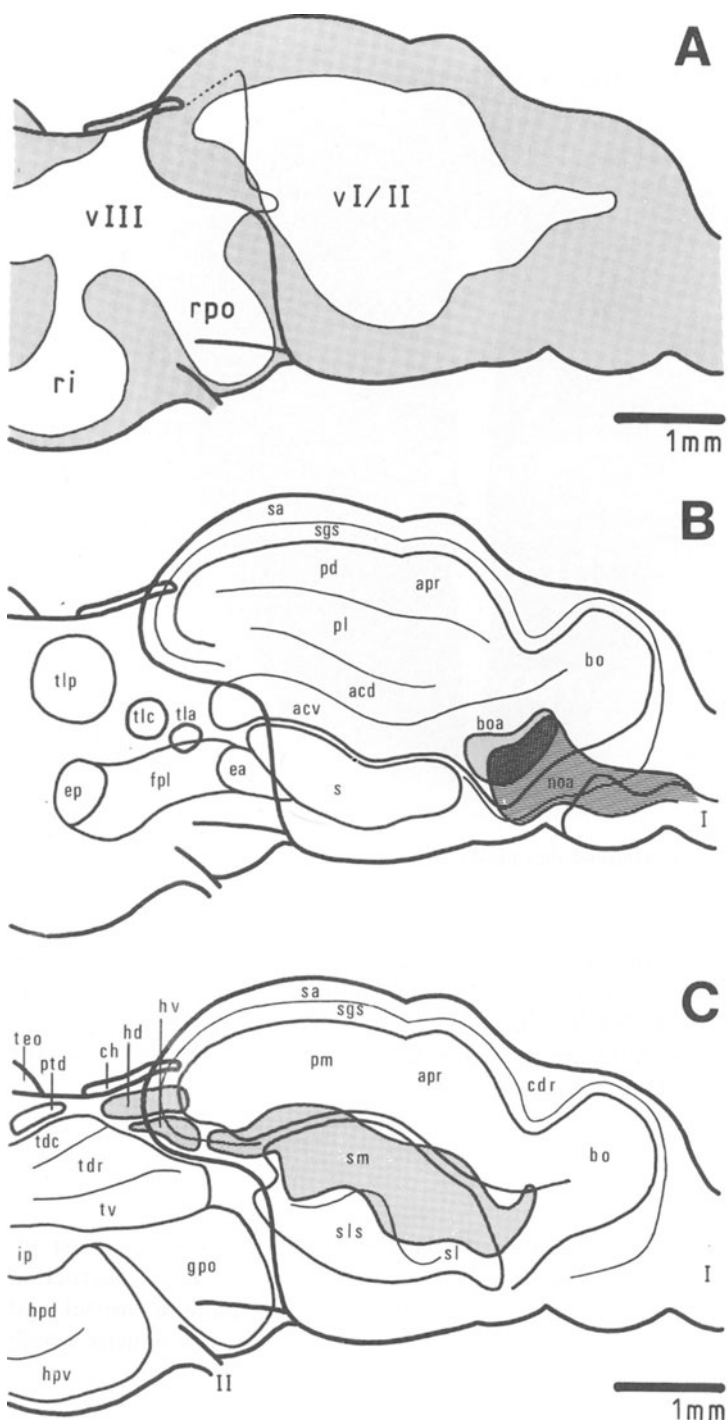


Fig. 8A–C. Parasagittal reconstructions of the forebrain. **A** Ventricle system; **B** lateral structures; **C** medial structures. For abbreviations see list

with their nerves, striatum, anterior entopeduncular nucleus, lateral forebrain bundle, posterior entopeduncular nucleus, and anterior, central, and posterior lateral thalamic nuclei. The pallium and olfactory bulb have an intermediate layer consisting of a loose arrangement of cells and fibers (sgs) in between the dense cell masses adjacent to the ventricle (sgp) and the fiber layer adjacent to the peripheral surface (sa). The third reconstruction (Fig. 8C) shows structures close to, or crossing the midline: olfactory bulb, rostral dorsal commissure, medial pallium, medial septum, lateral septum with its laminated caudal ventral part, habenular commissure, dorsal and ventral habenular nuclei, ventral thalamus, rostral dorsal thalamus, caudal dorsal thalamus, dorsal pretectal nucleus, preoptic gray, interpeduncular nucleus, and dorsal and ventral hypothalamus.

2.4.3 Cross Sections

Two telencephalic cross sections (Fig. 9), at a point one-third of the way along the pallium rostrocaudally (Fig. 9A) and at the level of the foramen of Monro (Fig. 9B), are used to indicate the patterns of connectivity in the telencephalon. All the structures of the telencephalic hemispheres appear within these sections: medial and lateral septum, medial, dorsal, and lateral pallium, dorsal and ventral parts of the amygdaloid complex, striatum, a nondefined region between the striatum and septum, anterior entopeduncular nucleus, preoptic gray, anterior commissure, and pallial commissure.

2.4.4 Locations of the Injection Sites

The top view and the bottom view (Fig. 10), which indicate the locations of the injection sites, involve the olfactory bulb, telencephalic hemispheres, diencephalon, mesencephalon, and rostral myelencephalon. Top views are also used to indicate patterns of connections after HRP injections.

The injections demonstrated are numbered: in the pallium 1–12, in other telencephalic regions 13–16, in the diencephalon 17–19, and in the mesencephalon 20–22. The injections located dorsally are drawn inside the top view (Fig. 10, left), and here the other injections are marked at the side. The injections involving ventral regions are indicated in the bottom view (Fig. 10, right). The injection in the amygdaloid complex (14) remains marked on the side. The numbers are also used when the single experiments are described.

2.5 Horseradish Peroxidase Injections in the Pallium (1–12)

2.5.1 Description of the Format

The HRP transport is followed through series of sagittal sections. The longitudinal reconstructions (Fig. 8) can be used for orientation. The numbers adjacent to the drawings of the sections indicate the distance from the midline in millimeters. A dash (—) in front of a number indicates that the section is contralateral to the injection site. The outline of the brain and of the ventricle are drawn with bold lines.

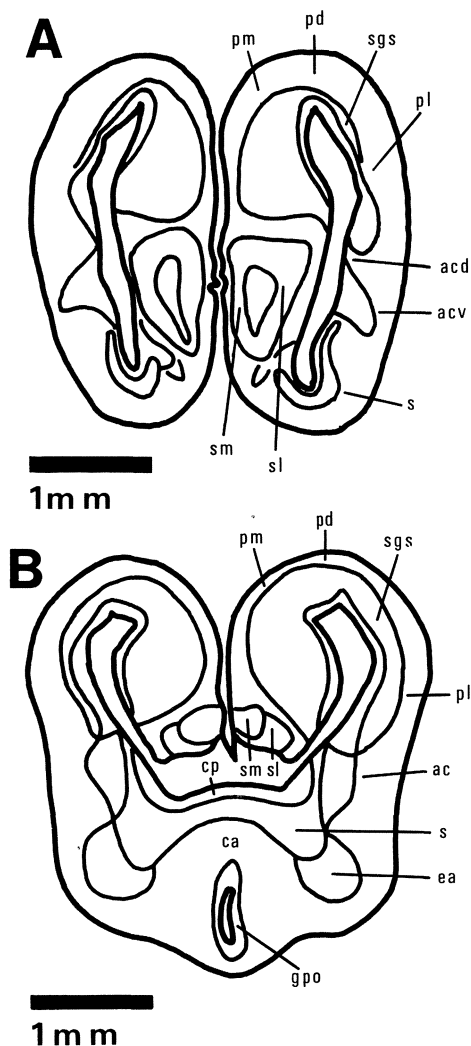


Fig. 9A, B. Diagrammatic cross sections of the telencephalon used for the reconstructions of the connectivity determined with the *HRP* experiments. **A** At the level of Fig. 5. **B** At the level of Fig. 6. For abbreviations see list

Aggregations of cells and related neuropil are circumscribed with thinner lines. Laminations as they occur in the septum, thalamic nuclei, and forebrain bundles are drawn as arrangements of parallel lines or elongated ovals.

The criteria for choosing the sections were the appearance of labeled cells, fibers, and terminals. When a structure held labeled cells the section with the most labeled cells was chosen. When neighboring sections held comparable numbers of cells in a particular structure, the section with the most additional information (labeled cells, fibers, and terminals in other structures) was chosen. Sections with clear fields of labeled fibers and terminals and sections with the farthest reach of labeled fibers from the injection site were also chosen. Anterograde labeling is indicated by: shading, fine lines, and crosses, and black when very intense. The shading indicates the brown haze with or without the simultaneous occurrence of distinguishable fibers. The fine lines indicate distinguishable fibers, whether or not accompanied by the brown haze, without explicitly giving the eventual appearance of en passant

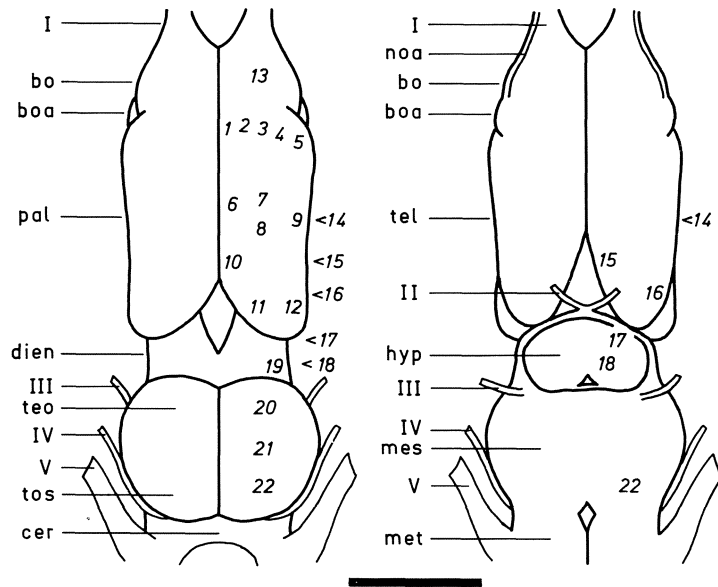


Fig. 10. Top view (*left*) and bottom view (*right*) with the *locations* of the HRP injections: 1–12 in the pallium, 13 in the olfactory bulb, 14 in the amygdaloid complex, 15 at the position of 10 but in the septum and the preoptic region, 16 at the position of 12 but in the anterior entopeduncular nucleus, 17 in the rostral ventral hypothalamus, 18 in the caudal hypothalamus, 19 in the caudal lateral thalamus, 20 in the rostral tectum, 21 in the central tectum, and 22 in the torus semicircularis and underlying brain stem. *Top views* are also used for reconstructions of the *connectivity* determined with HRP experiments. For *abbreviations* see list. *Bar*, 2 mm

boutons or terminals. The little crosses mark regions with labeled fibers and terminals. Labeled cells are marked with dots.

The findings of the single experiments are summarized in diagrammatic cross sections and in top views onto the brain as given in Figs. 9 and 10. Retrograde labeling is marked by arrows pointing to the injected site and having a dot at their base. Anterograde labeling is marked by arrows pointing away from the injected site. When the transport is not continuous within the given diagrams it is indicated with oblique hatches.

2.5.2 Descriptions of the HRP Transport (Injections 1–12)

1. Horseradish Peroxidase Injection in the Rostral Medial Pallium (Fig. 11)

Whole mount incubation was performed. The injection site centers at 0.10. Anterograde labeling can be followed throughout the rostral two-thirds of the medial pallium (0.10–0.20), the rostral two-thirds of the dorsal pallium (0.50–0.60), and the rostral half of the lateral pallium (1.00). A field of anterograde labeling can be detected in the rostral lateral septum (0.50–0.60). On the contralateral side anterograde labeling can be seen in the rostral third of the medial pallium (–0.10); this transport crosses via the rostral dorsal commissure at the level of the border between the pallium and the olfactory bulb.

The cross section (Fig. 12A) indicates the ipsilateral projections to the septum and pallial regions, and to the contralateral medial pallium. The top view

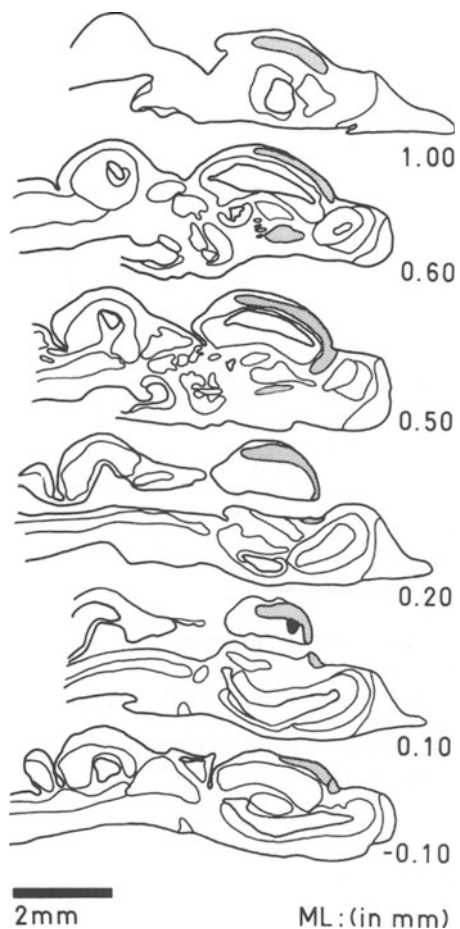


Fig. 11. Horseradish peroxidase injection 1. Sagittal sections showing *HRP* transport. See text and description of format

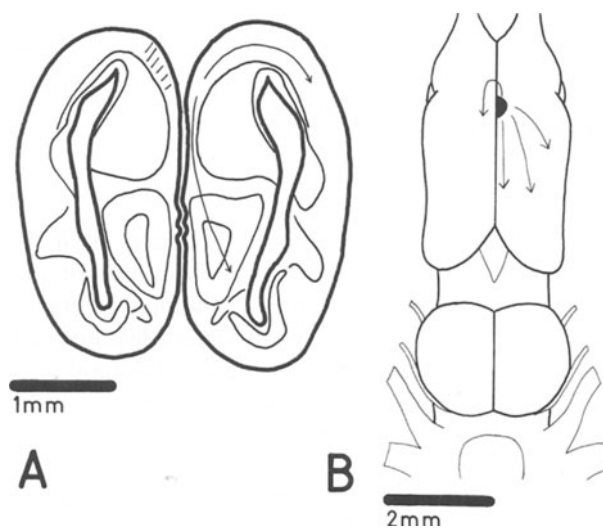


Fig. 12A,B. Horseradish peroxidase injection 1. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

(Fig. 12B) shows the extension of the projections: ipsilaterally, into the medial, dorsal, and lateral pallium, and deeper into the medial septum; contralaterally, via the rostral dorsal commissure into the medial pallium. (see also "Note" in experiment 10).

2. *Horseradish Peroxidase Injection in the Rostral Dorsal Pallium (Medially)*
(Fig. 13)

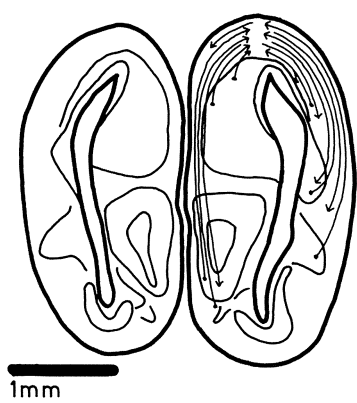
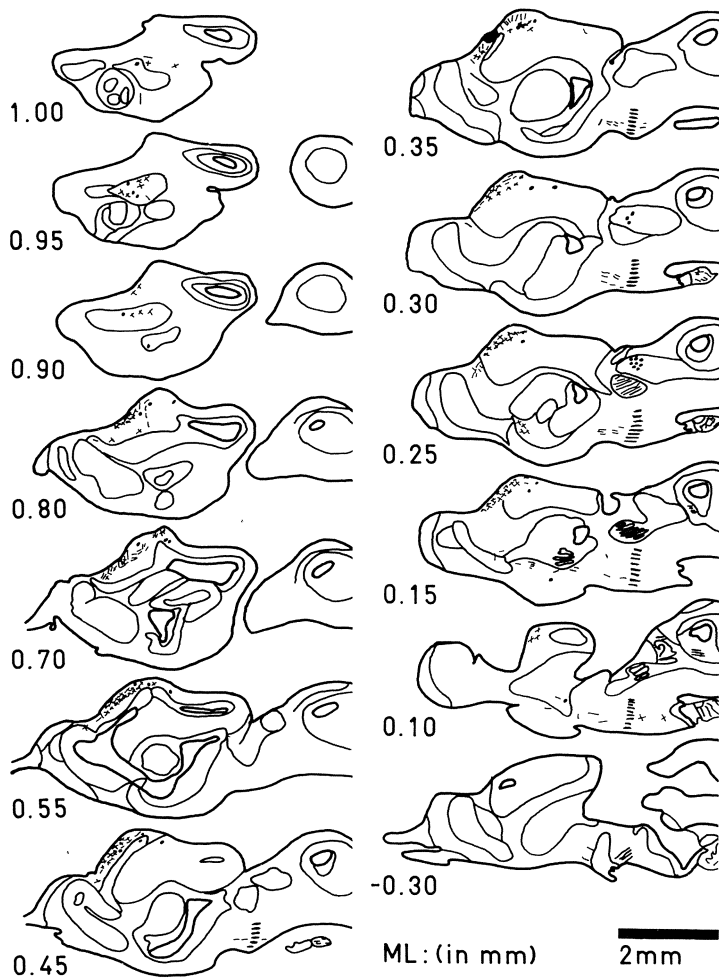
Whole mount incubation was performed. The injection site centers at 0.35. Labeled cells, fibers, and terminals can be found throughout the entire width of the rostral pallial regions (0.10–0.95). Labeled cells can be seen in the rostral amygdaloid complex (0.90), and labeled fibers reach the neuropil of the amygdaloid complex (0.95–1.00). A single fiber reaches the caudal medial pallium (0.35), and labeled cells appear as far as the caudal third of the medial pallium (0.30). A population of labeled cells appears in the rostral medial dorsal thalamus (0.30–0.25). There are also labeled cells around the ventral border of the septum (0.15–0.10). Labeled fibers reach into the septum (0.25–0.10), into the ipsilateral (0.45–0.10) and contralateral (–0.30) preoptic region, and as far down as the ipsilateral ventral hypothalamus (0.10).

In the cross section (Fig. 14A) the telencephalic connections of the medial rostral dorsal pallium with the septum, medial, dorsal and lateral pallium, and amygdaloid complex are indicated. These connections are all more or less reciprocal. No transport to the contralateral hemisphere could be discerned. The top view (Fig. 14B) shows the following: the connections within the rostral third of the pallium; the projection from the more caudal medial pallium; the afferents from the rostral medial dorsal thalamus; and the efferents to the ipsilateral preoptic region and ventral hypothalamus, and to the contralateral preoptic region.

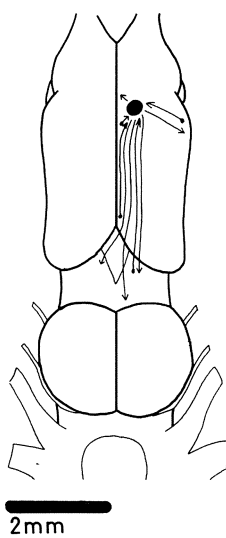
3. *Horseradish Peroxidase Injection in the Rostral Dorsal Pallium (Centrally)*
(Fig. 15)

On the slide incubation was performed. The injection site centers at 0.60. This injection resulted in the most extensive intrahemispheric transport. Labeled fibers can be followed throughout the lengths of the dorsal pallium, lateral pallium, and amygdaloid complex (0.90–1.35), and can be seen to reach large parts of the striatum (0.90–1.15), septum (0.60–0.45), and medial pallium (0.45–0.20). Single fibers reach the caudal part of the olfactory bulb (0.20–1.00), ipsilateral rostral ventral thalamus (0.60–0.90), and cross via the habenular commissure (0.90–0.20) to the contralateral area around the caudal striatum where a few singular fibers also reach the amygdaloid complex. Also via the rostral dorsal commissure fibers cross over. (The contralateral sections are not shown.) Within the hemisphere, labeled cells can be seen in the caudal medial pallium (0.60), rostral medial pallium (0.20), medial septum (0.45), striatum (0.90), and amygdaloid complex and rostral lateral pallium (1.00). Afferents come from the olfactory bulb (0.20–1.00) and from the rostral dorsal thalamus (0.60).

The cross section (Fig. 16A) shows the intrahemispheric connections with the septum, medial pallium, lateral pallium, amygdaloid complex, and striatum. These connections are all more or less reciprocal. Projections to the contralateral caudal striatal regions and to the amygdaloid complex are indicated. The top view (Fig. 16B) shows the extension of the connections over the ipsilateral hemisphere.



A



B

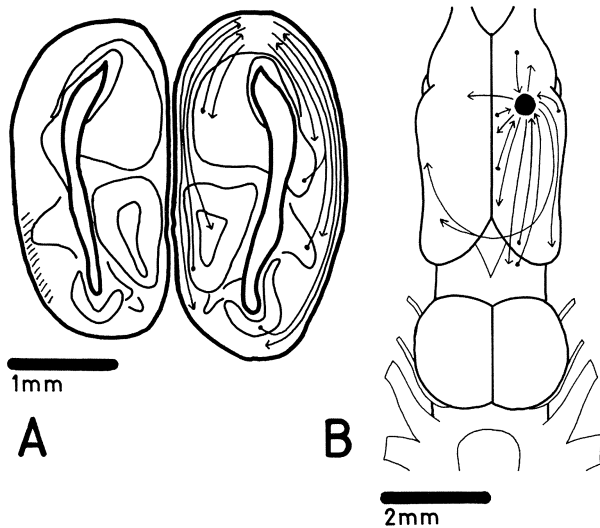
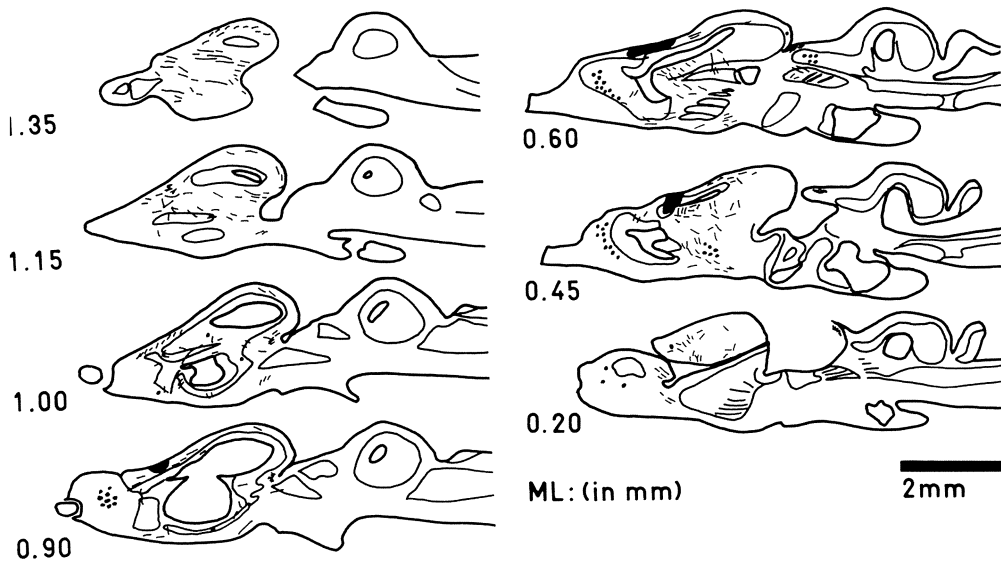


Fig. 15. (top) Horseradish peroxidase injection 3. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 16A, B. (bottom) Horseradish peroxidase injection 3. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

◁ **Fig. 13.** (top) Horseradish peroxidase injection 2. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 14A, B. (bottom) Horseradish peroxidase injection 2. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

Connectivity is most abundant within the rostral third of the pallium. Efferents can be seen to pass along the lateral wall to the rest of the telencephalon. Reciprocal connections exist with more medial regions. Apart from the ipsilateral hemisphere, afferents come from the olfactory bulb and from the rostral dorsal thalamus. Efferents reach the caudal part of the olfactory bulb, into the rostral dorsal commissure, rostral ventral thalamus, and over the habenular commissure to the contralateral caudal striatal areas and contralateral amygdaloid complex.

4. *Horseradish Peroxidase Injection in the Rostral Dorsal Pallium (Laterally)* (Fig. 17)

Whole mount incubation was performed. The injection site centers at 0.85. The amygdaloid complex is completely covered with labeled fibers and terminals (1.00–1.10). The lateral pallium is largely covered with labeled fibers and terminals and its rostral half also contains labeled cells (0.85–1.10). The rostral three-fourths of the dorsal pallium (0.60–0.35) and medial pallium (0.35–0.00) have labeled fibers, terminals, and cells. Labeled fibers and terminals reach as far down as the rostral septum (0.35–0.20), can be seen around the caudal aspect of the striatum (1.10–0.85), and a few fibers enter the diencephalon (0.85). Anterograde labeling covers the dorsal lateral half of the olfactory bulb (1.00–0.45) and most laterally in the olfactory bulb retrogradely labeled cells can also be seen (1.00). A few labeled cells (0.60) occur in the posterior lateral nucleus of the thalamus.

The cross section (Fig. 18A) shows the reciprocal connections with the pallial regions; and the projections to the amygdaloid complex, striatum, and region ventral to the rostral septum. The top view (Fig. 18B) shows the reciprocal connections covering most of the pallial regions and with the lateral part of the olfactory bulb; and the projections around the rostral septum (nicked arrow), along the lateral wall of the telencephalon, and from the central lateral thalamic nucleus.

5. *Horseradish Peroxidase Injection in the Rostral Lateral Pallium (Fig. 19)*

Whole mount incubation was performed. The injection site centers at 1.00. Labeled fibers reach all of the lateral pallium (0.90–1.25) and the rostral two-thirds of the dorsal (0.65–0.50) and medial pallium (0.25–0.15). There are reciprocal connections with the amygdaloid complex (1.00), and with the olfactory bulb (0.90–0.00). There is also a reciprocal connectivity with the rostral dorsal pallium (0.65). Bilaterally, fibers reach regions ventral to the medial septum (0.25–0.00). Fibers cross over via the rostral dorsal commissure to reach the contralateral rostral pallium (–0.50) and the dorsal olfactory bulb (0.00– –0.85). Via the habenular commissure (0.90– –0.50) fibers reach the contralateral amygdaloid complex (–0.85– –1.05) and the caudal aspect of the contralateral striatum (–0.90). The ipsilateral striatum remains free of labeling.

The cross section (Fig. 20A) shows the connections with the ipsilateral pallial regions, amygdaloid complex, and with the region ventral to the medial septum. Contralaterally, labeled fibers and terminals are found in the rostral pallium, caudal part of the striatum, amygdaloid complex, and region ventral to the medial septum. The top view (Fig. 20B) shows the following: the reciprocal connections with the ipsilateral olfactory bulb and with the other rostral pallial regions; and the

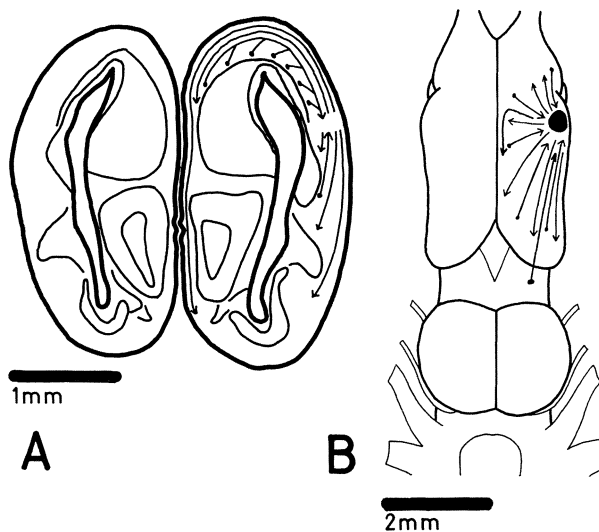
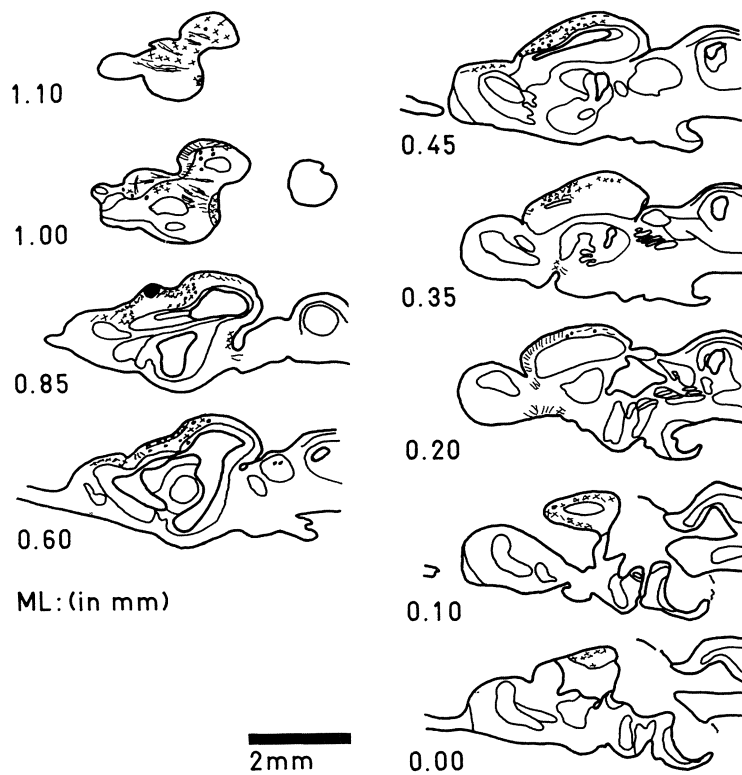
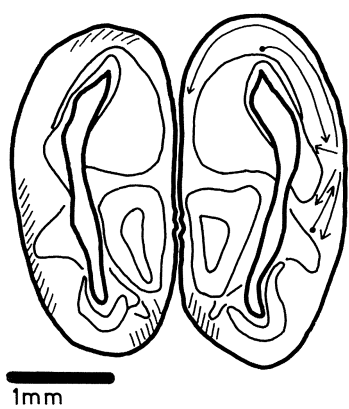
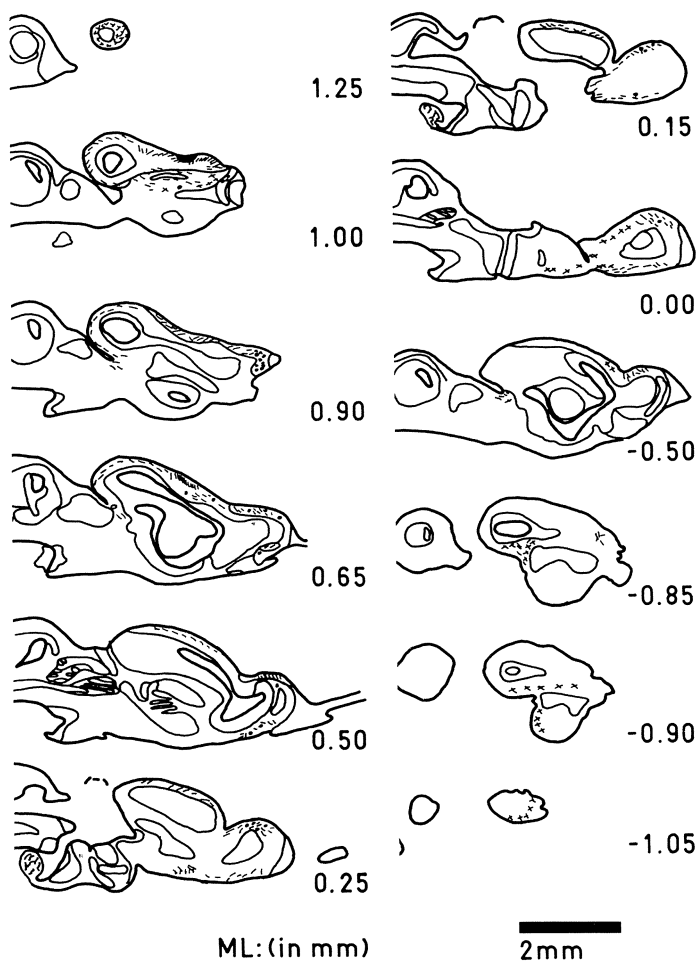
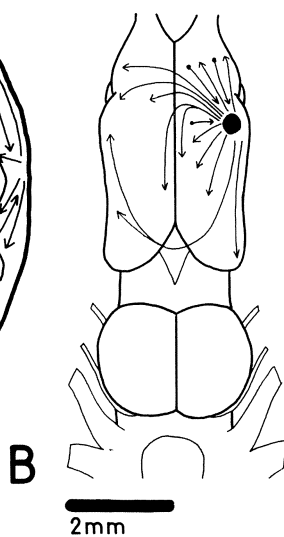


Fig. 17.(*top*) Horseradish peroxidase injection 4. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 18A, B.(*bottom*) Horseradish peroxidase injection 4. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format



A



B

following projections: ipsilaterally, to the pallial regions; bilaterally, to the regions ventral to the medial septum (rostral forked arrow); contralaterally, to the olfactory bulb and the rostral pallium via the rostral dorsal commissure, and via the habenular commissure to the caudal striatum and the amygdaloid complex (caudal split arrow) (see also “Note” in experiment 9).

6. *Horseradish Peroxidase Injection in the Central Medial Pallium (Fig. 21)*

Whole mount incubation was performed. The injection site centers at 0.10. Anterogradely labeled fibers spread over most of the pallial regions (0.10–0.90). Labeled fibers can also be followed coursing along the medial septum (0.10) and reaching the ventral hypothalamus (0.10–0.25). Labeled cells are found in the rostral dorsal pallium (0.35–0.70), in the caudal medial pallium (0.25), and in the caudal lateral pallium (0.80). The striatum, amygdaloid complex, olfactory bulbs, and contralateral hemisphere remain free from labeling.

The cross section (Fig. 22A) shows the reciprocal connectivity with the dorsal and lateral pallium. The top view (Fig. 22B) shows the reciprocal connectivity with the rostral pallial areas and with the caudal medial and lateral pallium; and the projections to the lateral pallium, dorsal pallium, and ventral hypothalamus (see also “Note” in experiment 10).

7. *Horseradish Peroxidase Injection in the Central Dorsal Pallium (Rostrally) (Fig. 23)*

On the slide incubation was performed. The injection centers at 0.70. Anterogradely labeled fibers and terminals cover most of the pallial regions (1.25–0.35); however, the rostral half of the medial pallium remains free of labeling (0.70–0.35). Fibers can be seen to reach the level of the amygdaloid complex (0.85), the border region between the striatum and the rostral septum (0.70), the septal regions themselves (0.70–0.35), and as far down as the preoptic region (0.70). Labeled cells can be seen in the medial pallium (0.45) and septum (0.45–0.35).

The cross section (Fig. 24A) shows the projections to the lateral pallium, amygdaloid complex, and the region between the septum and striatum; the reciprocal connections with the medial and lateral septum, and with the medial pallium. The top view (Fig. 24B) shows the projections to the rostral dorsal pallium, and to the regions in the lateral wall of the telencephalon, namely, the lateral pallium and amygdaloid complex; and the reciprocal connections with the regions in the medial wall of the telencephalon, namely, the medial pallium, and medial and lateral septum; and finally the projection to the preoptic region in the diencephalon.

8. *Horseradish Peroxidase Injection in the Central Dorsal Pallium (Caudally) (Fig. 39)*

On the slide incubation was performed. The injection site centers at 0.85. Anterograde labeling is found in the pallium in rostral directions (0.85), lateral directions

◁ **Fig. 19.** (top) Horseradish peroxidase injection 5. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 20A, B. (bottom) Horseradish peroxidase injection 5. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

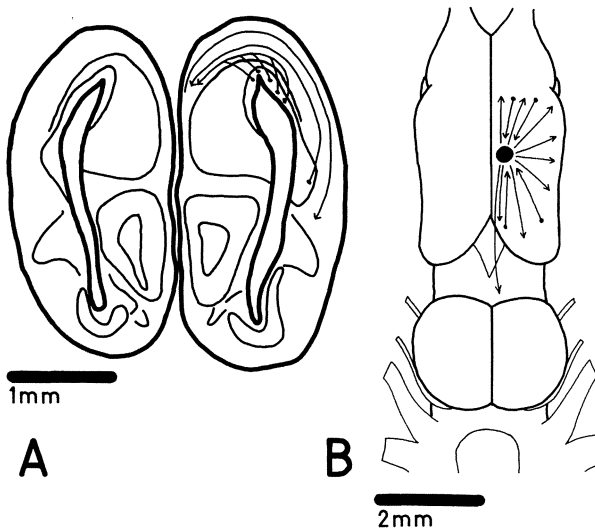
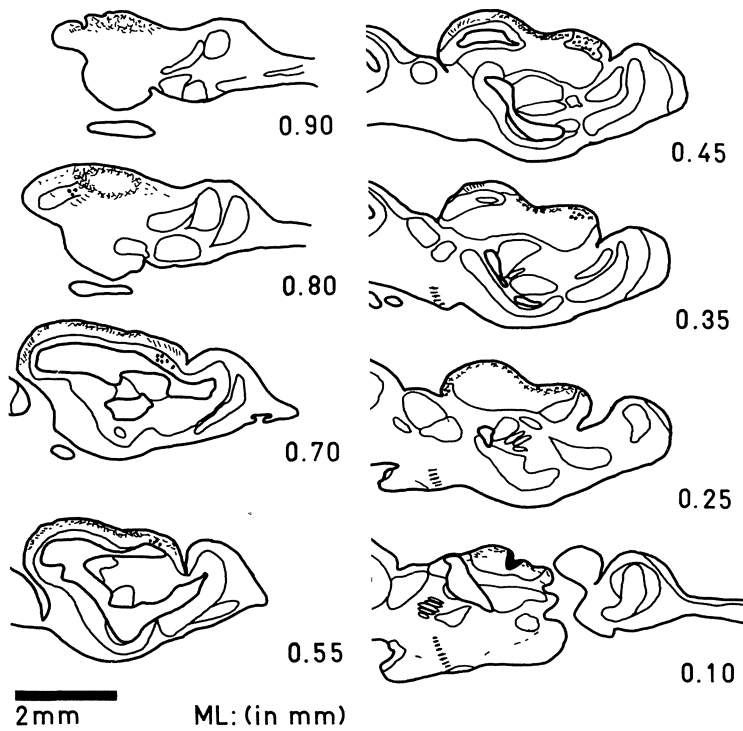


Fig. 21. (top) Horseradish peroxidase injection 6. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 22A, B. (bottom) Horseradish peroxidase injection 6. Diagrammatic cross section A and top view B with reconstructions of *connectivity*. See text and description of format

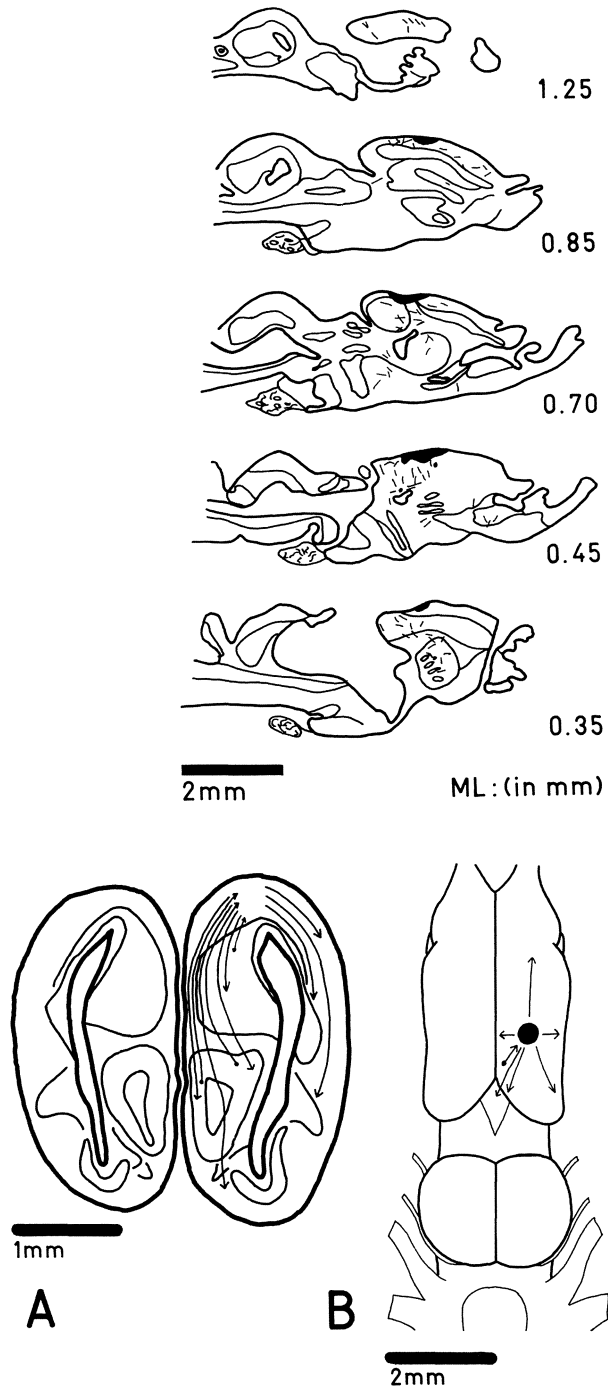


Fig. 23. (top) Horseradish peroxidase injection 7: Sagittal sections showing *HRP* transport. See text and description of format

Fig. 24A,B. (bottom) Horseradish peroxidase injection 7. Diagrammatic cross section A and top view B with reconstructions of *connectivity*. See text and description of format

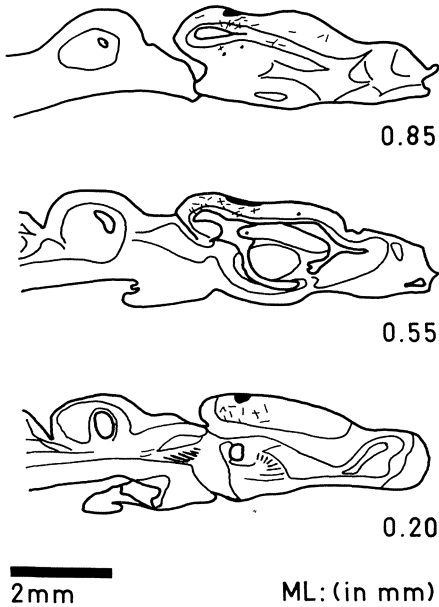


Fig. 25. Horseradish peroxidase injection 8. Sagittal sections showing *HRP* transport. See text and description of format

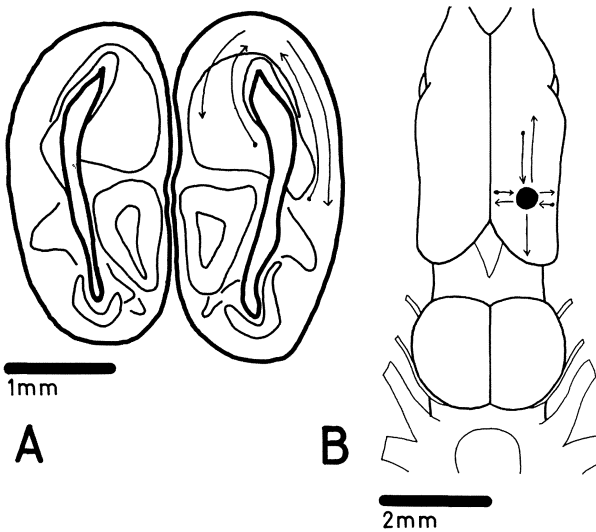


Fig. 26A, B. Horseradish peroxidase injection 8. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

(0.85), caudal directions (0.55), and medial directions (0.20). Labeled cells are found ventrally in the lateral pallium (0.85), in the rostral dorsal pallium (0.55), and in the medial pallium (0.20).

The cross section (Fig. 26A) shows that in this case the connections of the central dorsal pallium are restricted to pallial regions and reciprocal with both the medial and lateral pallium. The top view (Fig. 26B) shows that the connections to the rostral dorsal pallium, medial pallium, and lateral pallium are reciprocal, and unidirectional to the caudal pallium.

Note: Several more injections were made in the central regions of the dorsal pallium; these showed similar results to this one.

9. *Horseradish Peroxidase Injection in the Central Lateral Pallium (Fig. 27)*

Whole mount incubation was performed. The injection site centers at 1.20 (vertical streak). This injection resulted in relatively little transport in the ipsilateral hemisphere. Retrogradely filled cells are visible in the olfactory bulb (1.05–0.85) and the habenula (0.60). Anterograde transport courses along the lateral wall of the telencephalon, ventral to the lateral pallium. This transport reaches the dorsal (1.05–0.15) and ventral (1.05–0.85) surface of the ipsilateral olfactory bulb. Anterograde labeling can be followed over the rostral dorsal commissure to the contralateral hemisphere (–0.25– –1.10). Most laterally (–1.20) this labeling fuses with transport coming via the habenular commissure (1.05– –0.80). This transport reaches the contralateral amygdaloid complex where the labeling intensifies (black).

The cross section (Fig. 28A) shows the location of ipsilateral and contralateral projections coursing past the amygdaloid complexes. The top view (Fig. 28B) shows the projections via the rostral dorsal and the habenular commissures. The location of labeled cells in the olfactory bulb and the habenula is indicated.

Note: Injections in the more ventral regions of the lateral wall of the hemisphere (lateral pallium, amygdaloid complex, and striatum) are relatively difficult to perform *in vivo*. These regions have to be approached obliquely from the dorsal direction, since the side of the skull is covered with jaw muscles which can only be retracted partly, and also since a big blood vessel runs along the border region of the lateral pallium and the amygdaloid complex. The sharp angle the pipette makes with the surface of the brain, especially in caudal regions of the hemisphere where the ventral lateral wall tilts inward, causes the tract to run past several regions before the target is reached. Thus, in contrast with all the dorsal and most of the rostral regions of the pallium, few injections in the lateral wall of the hemisphere gave usable results.

10. *Horseradish Peroxidase Injection in the Caudal Medial Pallium (Fig. 29)*

Whole mount incubation was performed. The injection site centers at 0.15–0.20. The sections are not exactly parallel to the midline but run straight through the ventral three-fourths of the lateral ventricle. In the pallium transport is mainly restricted to the caudal parts. Labeled fibers and boutons cover the caudal three-fourths of the dorsal medial pallium (0.15–0.30) and the caudal half of the ventral medial pallium (0.45–0.65). More anterograde labeling stretches in a narrowing band mediolaterally over the dorsal pallium (0.45–0.90), widening again in the lateral pallium (0.80–0.90). In the dorsal and medial pallium labeled cells are found in a fairly straight band running laterad from the injection site (0.30–0.80). Labeled cells, fibers, and terminals appear in the medial septum (0.15–0.20), whereas in the lateral septum only labeled fibers and terminals (0.30–0.60) appear. Labeled cells, fibers, and terminals also occur in the border region of the septum and striatum (0.30). Labeled fibers are seen to course through the preoptic region (0.20). In the ventral hypothalamus labeled fibers and terminals (0.00) appear.

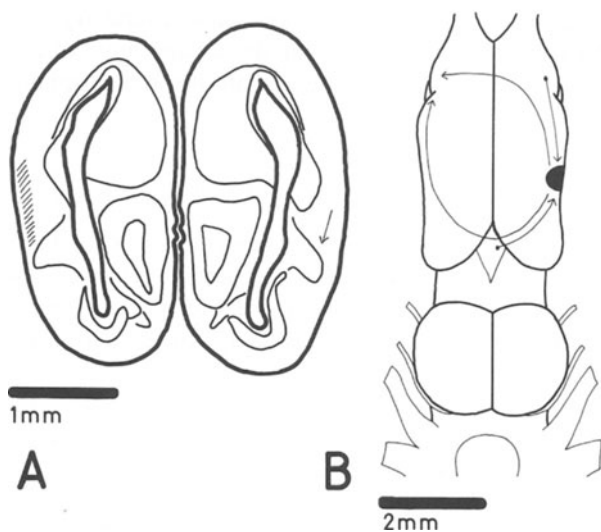
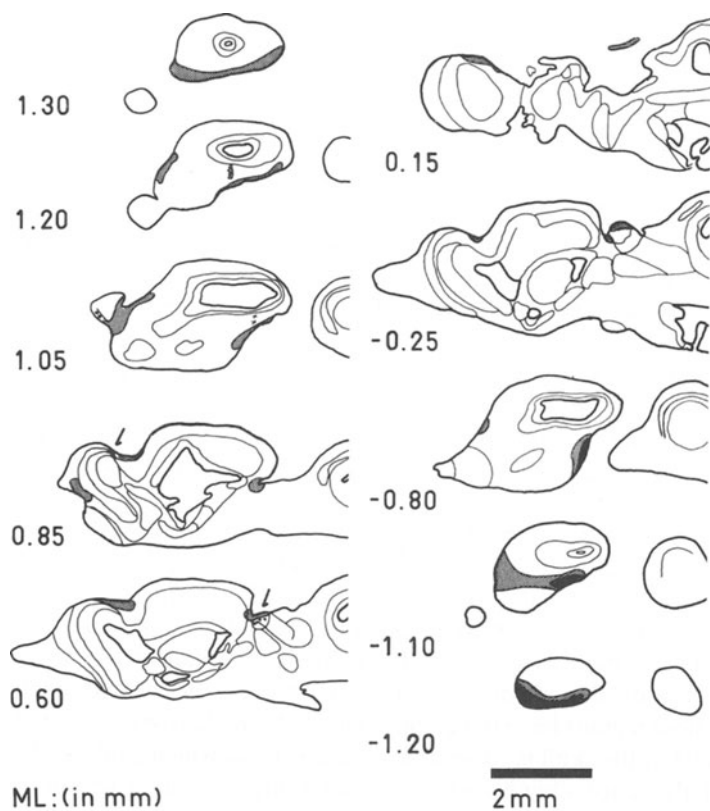


Fig. 27. (top) Horseradish peroxidase injection 9. Sagittal sections showing *HRP* transport. See text and description of format

Fig. 28A, B. (bottom) Horseradish peroxidase injection 9. Diagrammatic cross section A and top view B with reconstructions of *connectivity*. See text and description of format

The cross section (Fig. 30A) shows the reciprocal connections with the medial and dorsal pallial regions; and the projection reaching the lateral pallium. Other reciprocal connections are those with the medial septum and the border region of the striatum and septum; and the projection to the lateral septum is shown. The top view (Fig. 30B) shows the projections to the surrounding pallial regions, the connections with the septum (medial arrows), the reciprocity of the pallial connectivity in the lateral orientation, and the projection to the hypothalamus.

Note: The injections in the medial pallium were restricted to surface regions. The hemispheres were pushed apart to allow injections as distant as possible from the dorsal pallium. This was performed best in the rostral regions, since the caudal part of the midline is covered by the plexus choroideus and a large blood vessel.

11. Horseradish Peroxidase Injection in the Caudal Dorsal Pallium (Fig. 31)

Whole mount incubation was performed. Only a cross section is shown (Fig. 31). Labeled cells remained restricted to the area immediately below the injection site and labeled fibers and terminals only reached as far as the lateral pallium. Injections in the caudal tip of the hemisphere were made repeatedly and always this type of transport was seen.

12. Horseradish Peroxidase Injection in the Caudal Lateral Pallium (Fig. 32)

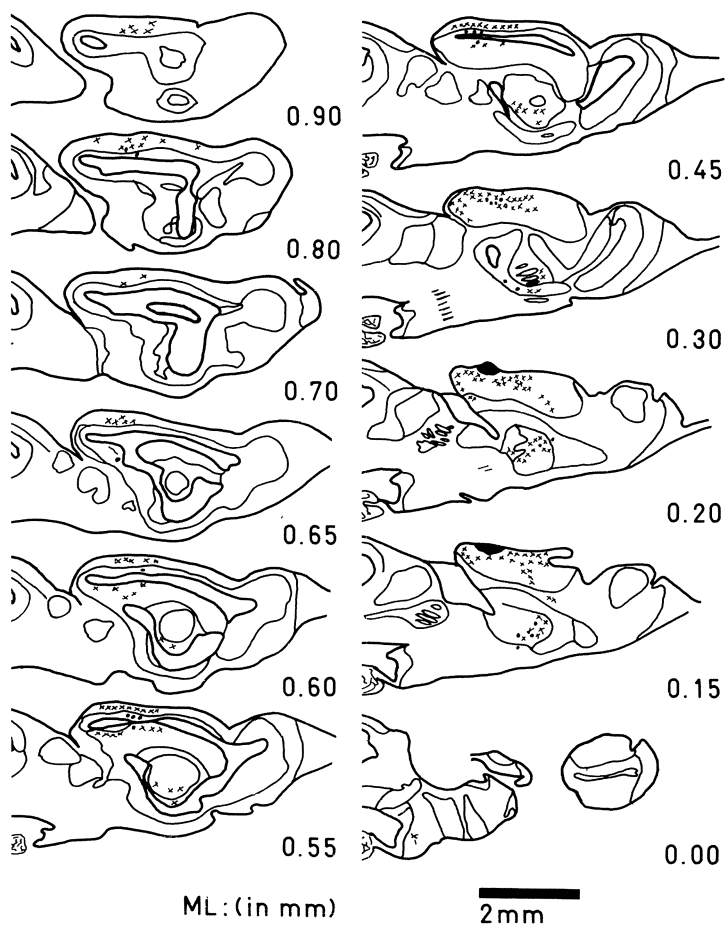
Whole mount incubation was performed. The injection site(s) center at 1.10. Two dumps resulted from the penetration; however, both are restricted to the caudal lateral pallium. One projection of anterograde labeling reaches rostrad along the lateral pallium (1.10); another projection stretches past the caudal tip of the hemisphere (0.90–0.70) to reach deep into the medial pallium (0.45–0.35). Labeled cells are found medially and ventrally to the injection sites (1.10–0.90). Anterograde labeling can be seen at the caudal aspect of the amygdaloid complex (0.90–0.70), in the rostral dorsal thalamus (0.70, 0.35), and in the habenula (0.35).

The cross section (Fig. 33A) shows the projection to the medial pallium; the reciprocal connections with the dorsal pallium and the more ventral lateral pallium; and the projection to the amygdaloid complex. The top view (Fig. 33B) shows the rostral projections along the lateral pallium and over the caudal tip of the hemisphere into the medial pallium; the reciprocity of the connectivity with the dorsal pallium; and the projections to the habenula, rostral dorsal thalamic, and central lateral thalamic nucleus (see also “Note” in experiment 9).

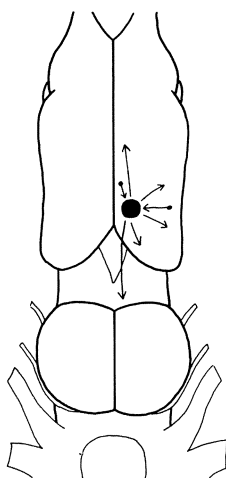
2.6 Horseradish Peroxidase Injections in Extrapallial Telencephalic Areas (13–16)

2.6.1 Description of the Format

The format is similar to that used for the pallial injections 1–12 described in Sect. 2.5.1 except when indicated otherwise.



A



B

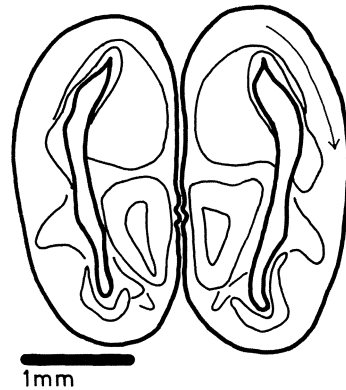


Fig. 31. Horseradish peroxidase injection 11. Diagrammatic cross section with reconstruction of connectivity. See text and description of format

2.6.2 Descriptions of the HRP Transport (Injections 13–16)

13. *Horseradish Peroxidase Injection in the Olfactory Bulb (Fig. 34)*

On the slide incubation was performed. The dump covers most of the olfactory bulb (0.10–0.20). Labeled cells are found in the rostral lateral septum (0.25) and ventrally in the contralateral olfactory bulb (–0.20). A most pronounced broad band of labeled fibers and terminals covers the amygdaloid complex and the ventral lateral pallium (hatched area in 1.30–1.10, Fig. 35); ventrally and dorsally this labeling rapidly thins out (1.10). From this broad band a group of fibers enters the habenular commissure (0.65–0.75) and reaches the contralateral amygdaloid complex (–1.30), another group of fibers reaches the caudal tip of the hemisphere (1.10), labeled fibers also reach past the striatum, and a single one enters the ventral thalamus (0.65). In the medial wall of the hemisphere labeled fibers pass through and along the septum to the preoptic region (0.20–0.65). Fibers course in between the septum and the medial pallium to reach the caudal tip of the hemisphere (0.20–0.65). Labeled fibers reach the dorsal surface of the contralateral olfactory bulb (–0.20–0.75) and some course through the rostral dorsal commissure to mingle with the labeling along the contralateral amygdaloid complex (–0.30). Some fibers enter the contralateral ventral rostral medial septum (–0.20).

The cross section (Fig. 36A) shows the ipsilateral projections coursing past the amygdaloid complex, lateral pallium, and striatum in the lateral wall of the hemisphere; in the medial wall through the medial septum, and in between the medial pallium and the septum. Contralaterally, the projection to the medial septum and the amygdaloid complex is indicated. The top view (Fig. 36B) shows the projections over the rostral dorsal commissure to the contralateral olfactory

◁ **Fig. 29.** (top) Horseradish peroxidase injection 10. Sagittal sections showing *HRP* transport. See text and description of format

Fig. 30A, B. (bottom) Horseradish peroxidase injection 10. Diagrammatic cross section A and top view B with reconstructions of connectivity. See text and description of format

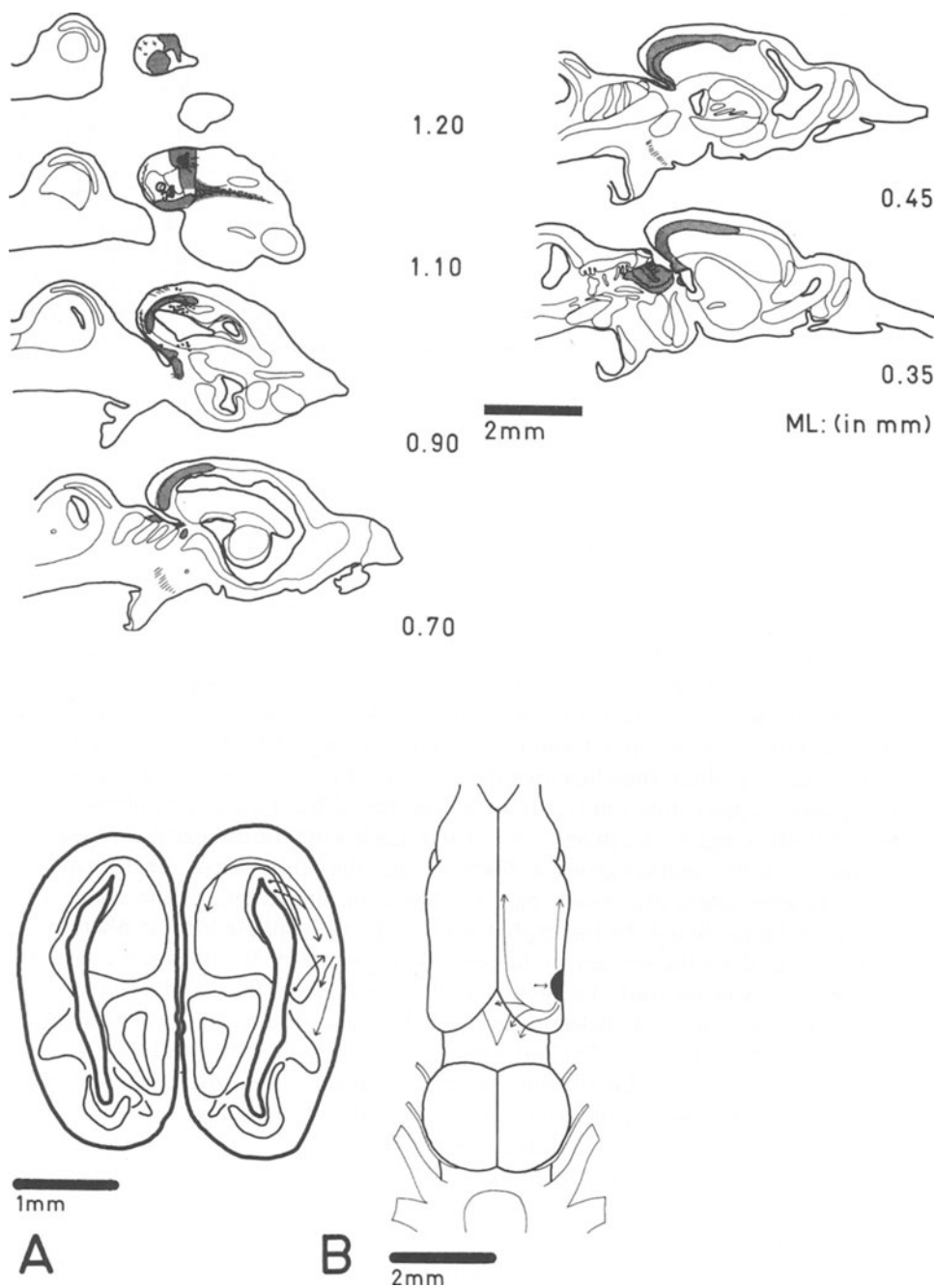


Fig. 32. (top) Horseradish peroxidase injection 12. Sagittal sections showing *HRP* transport. See text and description of format

Fig. 33A, B. (bottom) Horseradish peroxidase injection 12. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

bulb, and over the habenular commissure to the contralateral amygdaloid complex. Ipsilaterally, the projections along the lateral wall of the hemisphere (amygdaloid complex, lateral pallium, striatum) and to the caudal tip of the hemisphere are shown; and along the medial wall to the septum, caudal pallium, and preoptic region.

14. *Horseradish Peroxidase Injection in the Amygdaloid Complex (Fig. 37)*

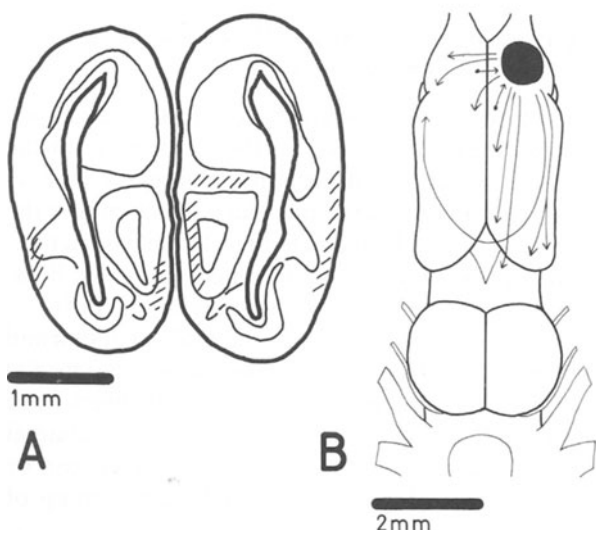
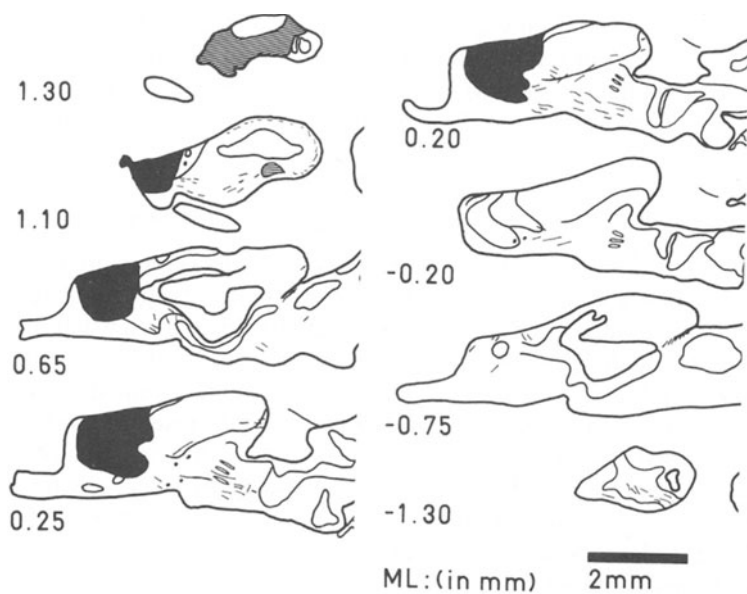
Whole mount incubation was performed. The injection site centers in 0.70. Virtually all of the labeling appears as a diffuse brown haze, except for a few labeled cells in the lateral pallium (1.10) and the striatum (0.70), and a few labeled fibers and terminals in the diencephalon and mesencephalon (0.70, 0.35, -0.70). This result led to two HRP injections for electron microscopy in two animals at the same site, to control whether this type of reaction product was the result of labeling neuronal elements with diameters less than 1 μm . As shown in Sect. 3, such a brown haze indeed contains labeled fibers and terminals with diameters less than 1 μm . The brown haze covers large parts of the ipsilateral pallium (1.10-0.25), stretches around the ipsilateral and contralateral olfactory bulbs (0.35-1.20), and reaches all of the ipsilateral striatum (0.70-0.25) and most of the contralateral striatum (-0.25- -0.70). It is found bilaterally in the habenulas (0.35, -0.25), rostral dorsal thalamic regions (0.70- -0.70), and preoptic region and ventral hypothalamus (0.35-0.70). Contralaterally, the brown haze reaches the caudal aspect of the amygdaloid complex (-0.70- -1.20).

The cross section (Fig. 38A) shows the ipsilateral reciprocal connections with the striatum and the lateral pallium; and the projection over the dorsal and medial pallium. Contralaterally, the projections to the striatum and the amygdaloid complex are marked. The top view (Fig. 38B) shows the following projections: ipsilaterally over the pallial regions; bilaterally to olfactory bulbs; via the habenular commissure contralaterally to the amygdaloid complex and bilaterally to the habenulas and the rostral thalamic areas; further to the preoptic region and ventral hypothalamus (combined), and finally to the ventral mesencephalic regions.

15. *Horseradish Peroxidase Injection in the Septum and Hitting the Border Region of the Telencephalon and Diencephalon (Fig. 39)*

On the slide incubation was performed. A series of cross sections (a-i) is shown (Fig. 39). The position of the cross sections is shown in the top view onto the rostral CNS (Fig. 40B). The injection site centers in section c. (Note: the parallel lines in the dorsal pallium indicate its columnar structure; the parallel lines in the amygdaloid complex and the diencephalic nuclei indicate their laminar structure. Labeled cells are indicated with dots, labeled fibers are indicated with short lines, and terminal fields are surrounded by broken lines or marked with fine dots.)

From the dump in the septum fibers can be seen to cross the medial pallium and to course over the dorsal pallium (b). Other fibers run rostrad through the medial and lateral septum and past the medial pallium (b-a). Ventrocaudally, fibers leave this dump for the pallial commissure (b) and cross over to the contralateral striatum, septum, and medial pallium (c-a, d-e). Another group of fibers can be followed into the rostral dorsal thalamus (d), where they end with a group of labeled cells (e).



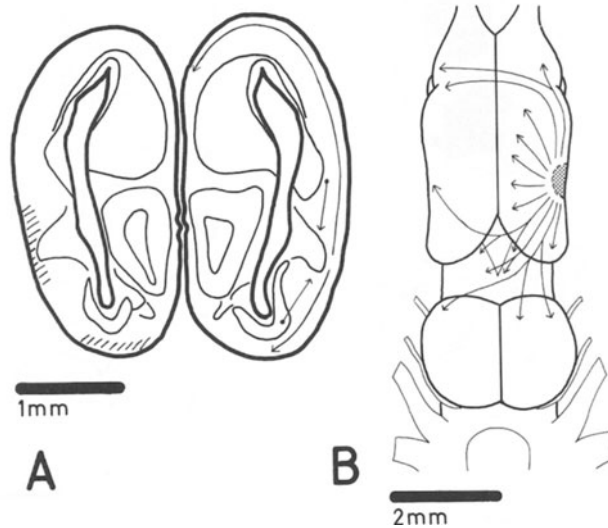
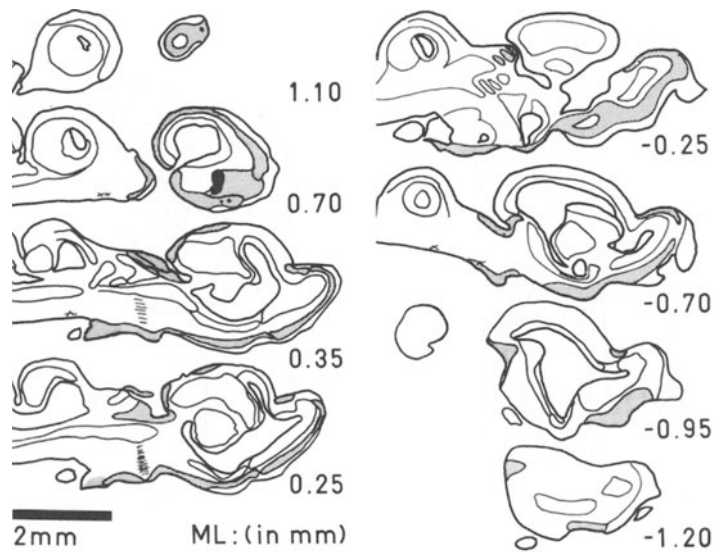


Fig. 37. (top) Horseradish peroxidase injection 14. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 38A, B. (bottom) Horseradish peroxidase injection 14. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

◁ **Fig. 34.** (top) Horseradish peroxidase injection 13. Sagittal sections showing *HRP transport*. See text and description of format

Fig. 35. (middle) Horseradish peroxidase injection 13. Photo showing *HRP transport* along the amygdaloid complex at the level of 1.30 in Fig. 34. See text. For *abbreviations* see list. Bar, 2 mm

Fig. 36A, B. (bottom) Horseradish peroxidase injection 13. Diagrammatic cross section **A** and top view **B** with reconstructions of *connectivity*. See text and description of format

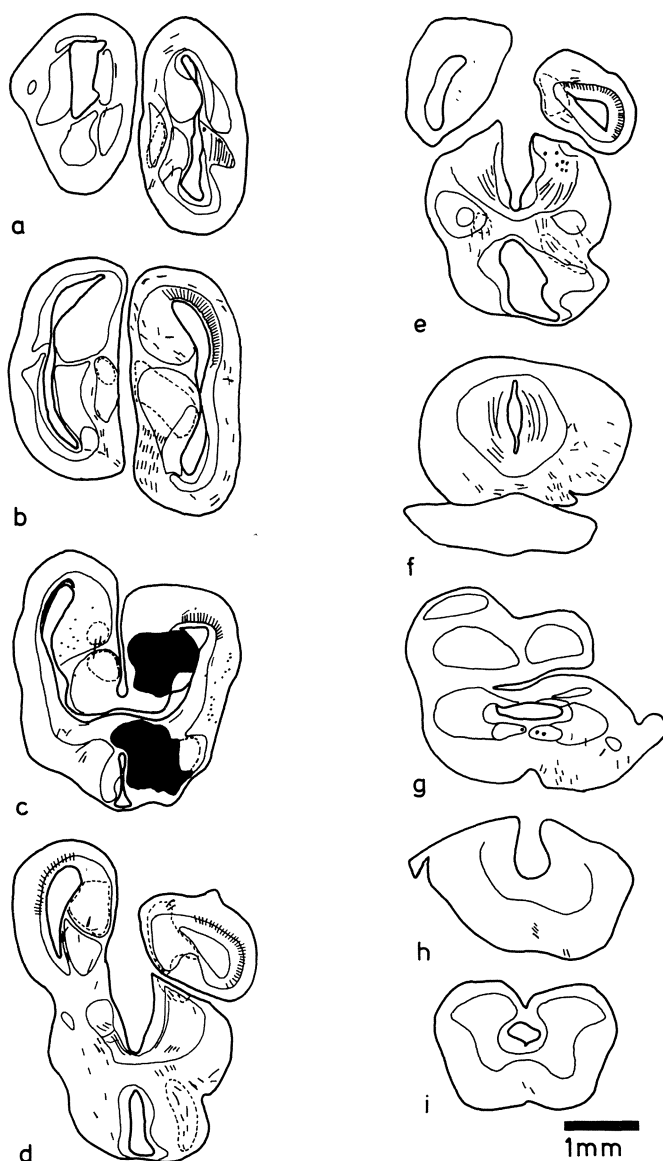


Fig. 39. Horseradish peroxidase injection 15. Cross sections showing *HRP* transport. *a-i* indicate the positions of the sections in the top view given in Fig. 40B. See text and description of format

From the dump at the border of the tel- and diencephalon, which involves parts of the anterior entopeduncular nucleus, the striatum, and the preoptic region, fibers can be followed into several directions. Bilaterally fibers reach up into the medial septum (b), and fibers cross over to the neuropil of the contralateral preoptic region (c). The fibers and terminals in the ipsilateral striatum (c-b) probably also result from this dump. Masses of fibers project caudad: A fairly large group crosses over at the ventral level of the caudal diencephalon (f) to turn

rostrad through the contralateral diencephalon (e–d). Descending fibers spread over the ventral half of the brain stem (f–i). A group remains medioventral (g) and partly crosses below the fourth ventricle (h) to reach bilaterally just beyond the obex (i). The labeled cells in the amygdaloid complex (a) probably result from this last dump. The labeled cells in the raphe nuclei (g) can result from both dumps.

The diagrammatic cross section (Fig. 40A) taken at the level of the foramen of Monro shows the projection from the medial wall of one hemisphere to the other, and the projection from the preoptic region to its contralateral equivalent and bilaterally to the medial septum. The top view (Fig. 40B) shows the projections through the medial walls of the hemisphere, over the ipsilateral dorsal pallium, the returning projection through the contralateral ventral diencephalon, and the projection down the brain stem, which finally reaches bilaterally into the cervical cord.

16. *Horseradish Peroxidase Injection in the Anterior Entopeduncular Nucleus*
(Figs. 41, 42)

Whole mount incubation was performed. The injection site centers at 0.80 and is characterized by numerous labeled cells. The tract is marked at 1.10 and 1.25. (Note: The brain is not cut straight in respect of the medial plane, at the level of the olfactory bulb medial is at 0.25, and at the level of the cerebellum medial is at –0.35). Ipsilaterally, labeled cells occur in the following regions: the striatum and amygdaloid complex (1.25), accessory olfactory bulb (1.10), caudal lateral pallium (0.80), rostral dorsal pallium (0.50), posterior lateral thalamic nucleus (0.50), posterior entopeduncular nucleus and caudal ventral thalamus (0.40), caudal dorsal thalamus (0.25), ventral caudal mesencephalon (0.10), torus semicircularis

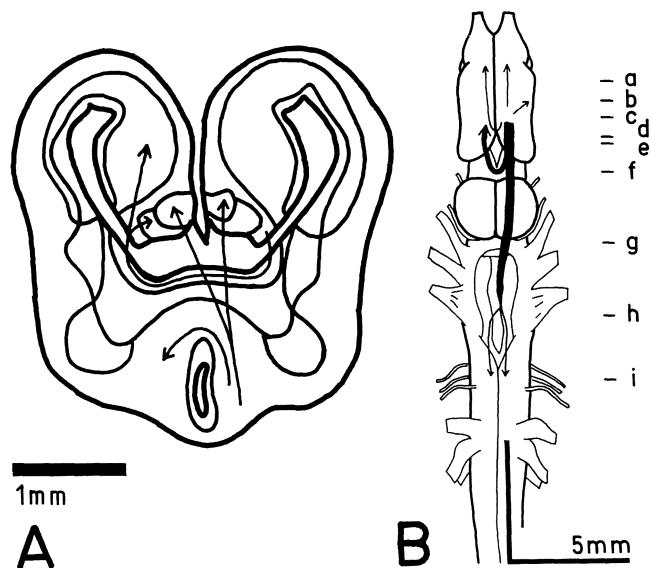


Fig. 40A, B. Horseradish peroxidase injection 15. Diagrammatic cross section A and top view B with reconstructions of *connectivity*. See text and description of format

(0.00– –0.10), and ventral to the cerebellum (–0.10). Contralaterally, labeled cells occur where the anterior commissure widens (–0.45) and in the amygdaloid complex (–1.00). Anterograde labeling (brown haze) can be followed over the lateral pallium (1.10–1.25), over the dorsal pallium (0.80–0.50), into the medial pallium (0.40–0.25), into the olfactory bulb (0.80–0.15), and over the thalamus to the optic tectum (0.50–0.00). Contralaterally, this type of labeling mingled with distinguishable fibers can be traced over the rostral dorsal commissure and the anterior commissure to reach the opposite amygdaloid complex (–0.45– –1.00), where different fields of anterograde labeling can be discerned. The hazy labeling can also be seen to reach caudally, ventral through the brain stem, until into the mesencephalon (0.50–0.00). Distinguishable labeled fibers and terminals are ob-

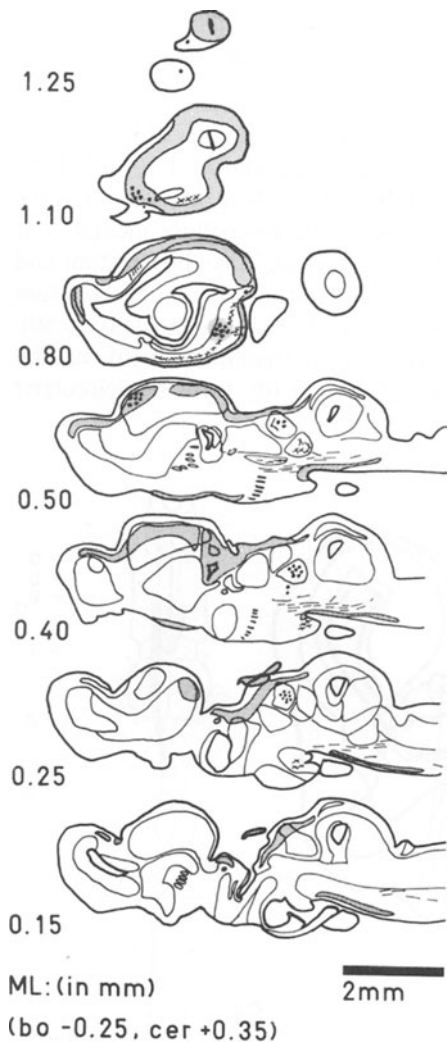


Fig. 41. Horseradish peroxidase injection 16. Sagittal sections showing *HRP transport*. See text and description of format

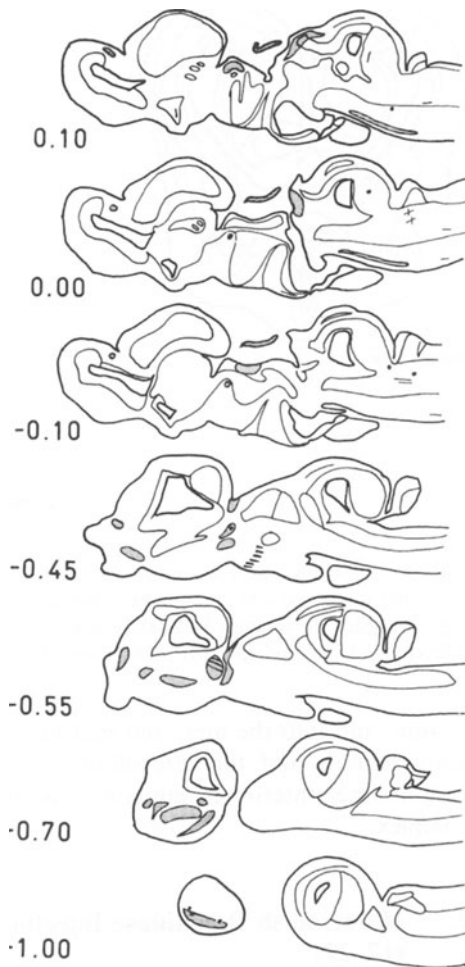


Fig. 42. Continuation of Fig. 41

served in the striatum (0.80–1.10) and the rostral dorsal pallium (0.80); and to course via the ventral thalamus (0.80–0.40) to reach ventral thalamic regions (0.50), ventral hypothalamus (0.40–0.25), torus semicircularis (a single fiber, 0.10), cerebellum (a few terminals, 0.00), and into the myelencephalon (0.00– –0.10).

The cross section (Fig. 43) taken at the level of the foramen of Monro shows the following projections: from the ipsilateral striatum, amygdaloid complex, and lateral pallium; to the ipsilateral pallial regions and down into the brain stem; and reciprocally with the contralateral amygdaloid complex. The left top view (Fig. 44) shows the projections to the anterior entopeduncular nucleus: ipsilaterally from the striatum, amygdaloid complex, rostral dorsal pallium, accessory olfactory bulb caudal lateral pallium, posterior lateral thalamic nucleus, posterior entopeduncular nucleus, and caudal dorsal thalamus, and mes- and metencephalon; and contralaterally from the amygdaloid complex. The right top view (Fig. 44) shows the projections from the anterior entopeduncular nucleus: ipsilaterally, over the pallium, to the lateral caudal thalamic nuclei, to the hypothalamus, to the optic

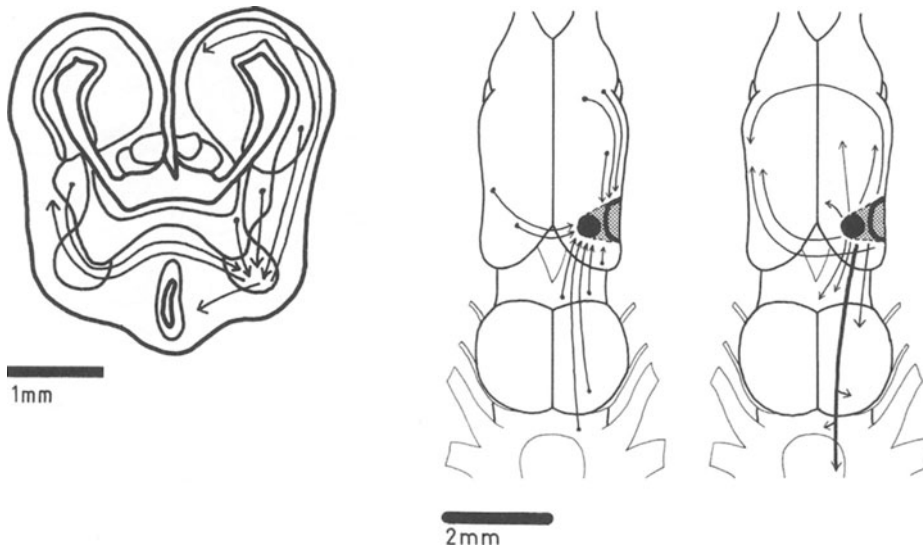


Fig. 43. (left) Horseradish peroxidase injection 16. Diagrammatic cross section with reconstruction of *connectivity*. See text and description of format

Fig. 44. (right) Horseradish peroxidase injection 16. Top views with reconstruction of *connectivity*. Afferents (left) to, and efferents (right) from, the injection site. See text and description of format

tectum, and into the mes- and metencephalon with subprojections into the torus semicircularis and the cerebellum; and, contralaterally, via the rostral dorsal commissure, anterior commissure, and habenular commissure to the amygdaloid complex.

2.7 Horseradish Peroxidase Injections in Extratelencephalic Regions (17–22)

2.7.1 Description of the Format

The results are documented with photos (17–21) or with drawings (22) to show the essential features arising from the experiments. See also related text and Sect. 2.5.1.

2.7.2 Descriptions of the HRP Transport (Injections 17–22)

17. Horseradish Peroxidase Injection in the Rostral Ventral Hypothalamus

This was an in vitro experiment with a whole mount incubation. The injection site is in the white matter of the ventral hypothalamus (Fig. 45B). No labeled cells were seen except directly at the injection site. Peripherally, a brown haze rises ipsilaterally past the caudal thalamus to reach the optic tectum (Fig. 45B). Contralaterally, a brown haze spreads through the white matter of the ventral hypothalamus (Fig. 45B). Ipsilaterally, the peripheral brown haze also reaches the lateral rostral thalamic nuclei (not shown). Labeled fibers appear bilaterally in the optic nerves

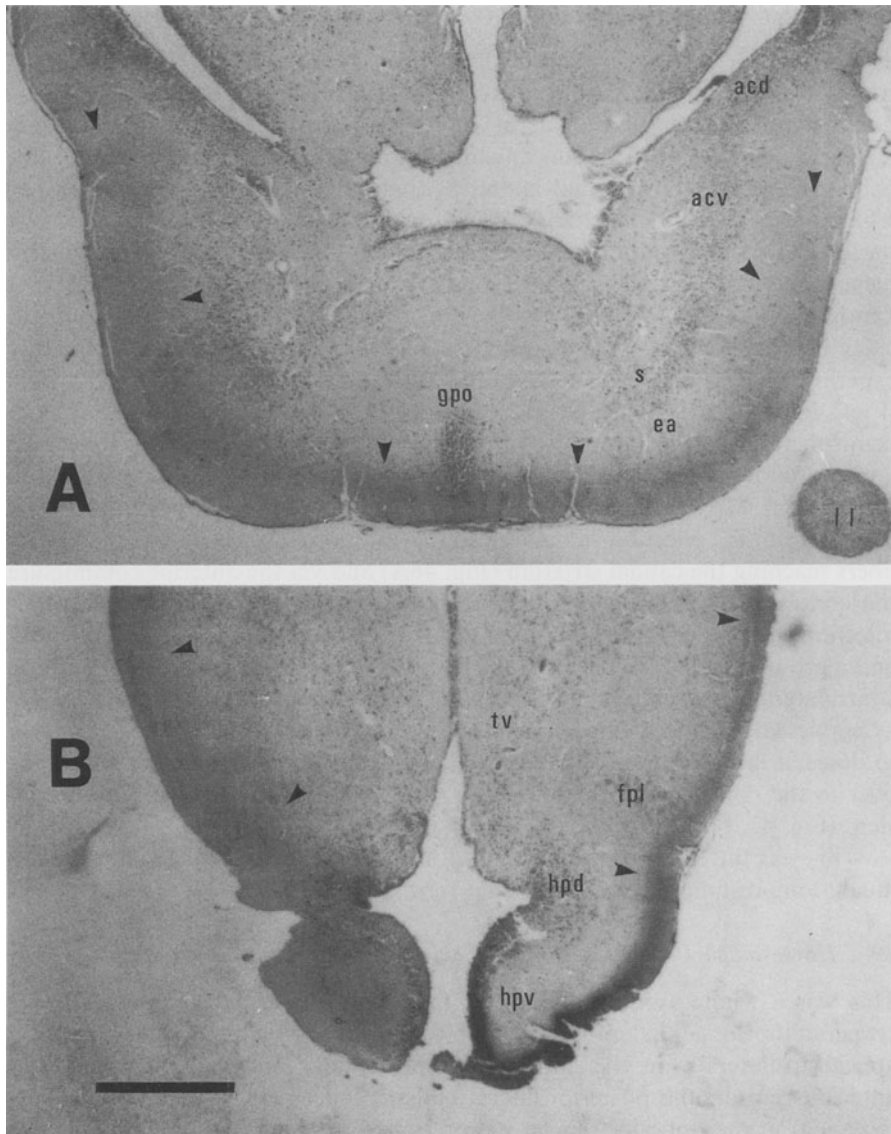


Fig. 45A,B. Cross sections. *HRP* injection 17 (see Fig.10) in the rostral *hpv*. **A** Rostrally, the haze (arrowheads) reaches *gpo*, *ea*, *s*, *acv*, and *acd*. **B** Ipsilaterally (right) *HRP* transport (Arrowheads) restricted to the diencephalic surface and contralaterally (left) diffuse and spreading deeper. Bar, 0.5 mm. For abbreviations see list

(not shown). Ventrally, the brown haze reaches both sides of the preoptic region, and more rostrally the brown haze rises into the striatal neuropil, reaching as far as the amygdaloid complex (Fig. 45A).

18. *Horseradish Peroxidase Injection in the Caudal Hypothalamus*

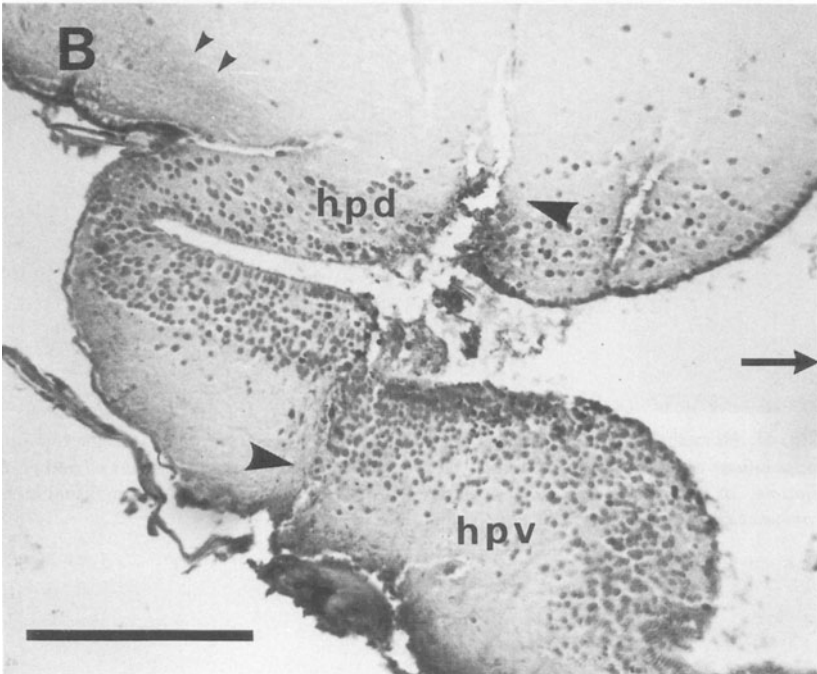
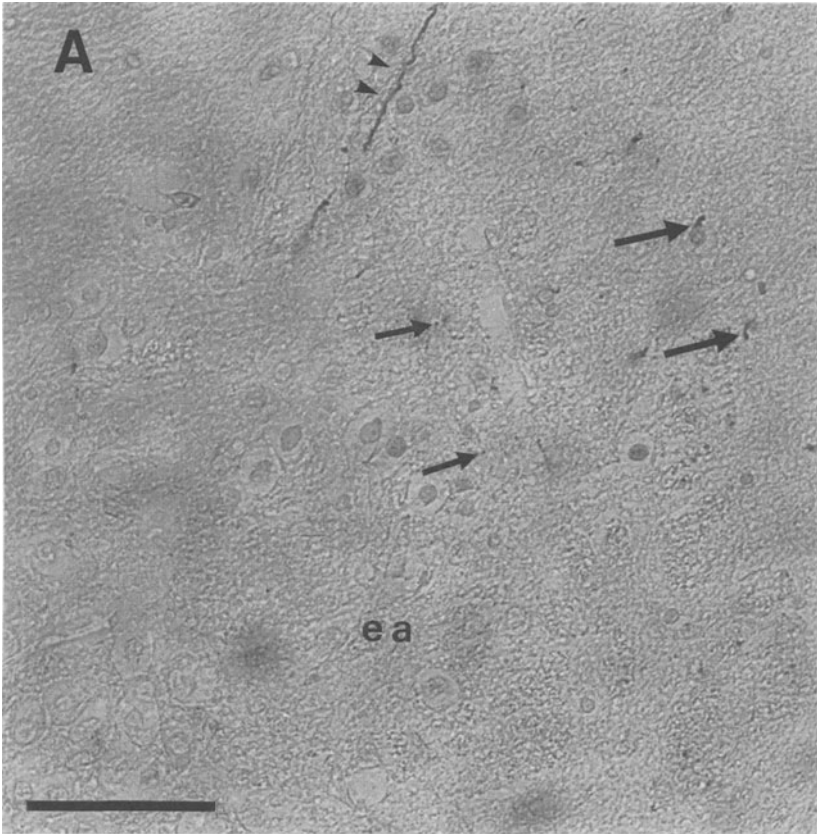
This was an *in vitro* experiment with a whole mount incubation. The penetration tract runs through the caudal ventral hypothalamus and penetrates the caudal dorsal hypothalamus via the lateral wing of the ventricle (Fig. 46B). Labeled cells appear in various caudal telencephalic regions: bilaterally, in the caudal dorsal pallium (Fig. 47, top), caudal lateral pallium (Fig. 47, top), and caudal medial pallium (large, 20–30 μm , triangular cells with long dendrites); and ipsilaterally in the caudal medial septum (a group caudal to the foramen of Monro). In the diencephalon labeled cells appear bilaterally in the preoptic gray and ventral hypothalamus; and ipsilaterally in the dorsal hypothalamus, posterior entopeduncular nucleus, ventral thalamus, and central lateral thalamic nucleus. With this experiment both the brown haze and distinguishable labeled fibers appeared (Figs. 46–48). The brown haze surrounds the olfactory bulbs and the telencephalic hemispheres, is vague at the level of the preoptic region, again becomes clear at the lateral and dorsomedial walls of the diencephalon, and rises into the optic tectum (not shown). Most distinguishable labeled fibers and terminals appear ipsilaterally; rostrad from the injection site until into the anterior entopeduncular nucleus, with fibers reaching the caudal striatum (Fig. 46A) and via the anterior commissure to the contralateral anterior entopeduncular nucleus (Fig. 48A). Dorsal from the injection site fibers course past the caudal thalamic nuclei to reach the optic tectum and a group crosses over through the posterior commissure (Fig. 48C) to descend contralaterally through the caudal thalamic nuclei. Another group of fibers assembles laterally to the injection site at the ventrolateral wall of the diencephalon to descend into the brain stem (Fig. 47, bottom). A much smaller group crosses over to the opposite ventrolateral wall (Fig. 48B) also to descend into the brain stem (Fig. 47, bottom).

This was the *in vitro* injection which fulfilled all expectations: no artifact and much, long-distance, anterograde and retrograde transport.

19. *Horseradish Peroxidase Injection in the Lateral Caudal Thalamic Nucleus*

This was a whole mount incubation. The injection is in the most caudolateral corner of the dorsal thalamus, very close to the posterior commissure. Labeled cells appear ipsilaterally in the anterior entopeduncular nucleus (Fig. 49B), in the anterior, central, and posterior lateral thalamic nuclei (Fig. 49A, C), from rostral to caudal in the optic tectum, in the preoptic gray, and bilaterally in the dorsal hypothalamus (not shown). The brown haze is found ipsilaterally and covers the roof of the thalamus (Fig. 49C), optic tectum, and torus semicircularis (not shown). As with experiment 20, distinguishable labeled fibers appear bilaterally, running in dorsoventral tracts at the lateral wall of the diencephalon. In the optic tectum and in the dorsal hypothalamus these fibers are accompanied by terminals. In addition, labeled fibers can be followed into the contralateral optic nerve. No labeled fibers are seen to enter the telencephalon.

Fig. 46A, B. Cross sections. *HRP* injection 18 (see Fig. 10) in the caudal hypothalamus. **A** Ipsilaterally \triangleright fibers (large arrows) and terminals (small arrows) in *ea*, and reaching *s* (double arrowheads). Bar, 50 μm . **B** Injection tract (large arrowheads) penetrates *hvp* and *hpd*. Laterally a haze appears (small arrowheads). Arrow in the ventricle points at the midline. Bar, 20 μm . For abbreviations see list



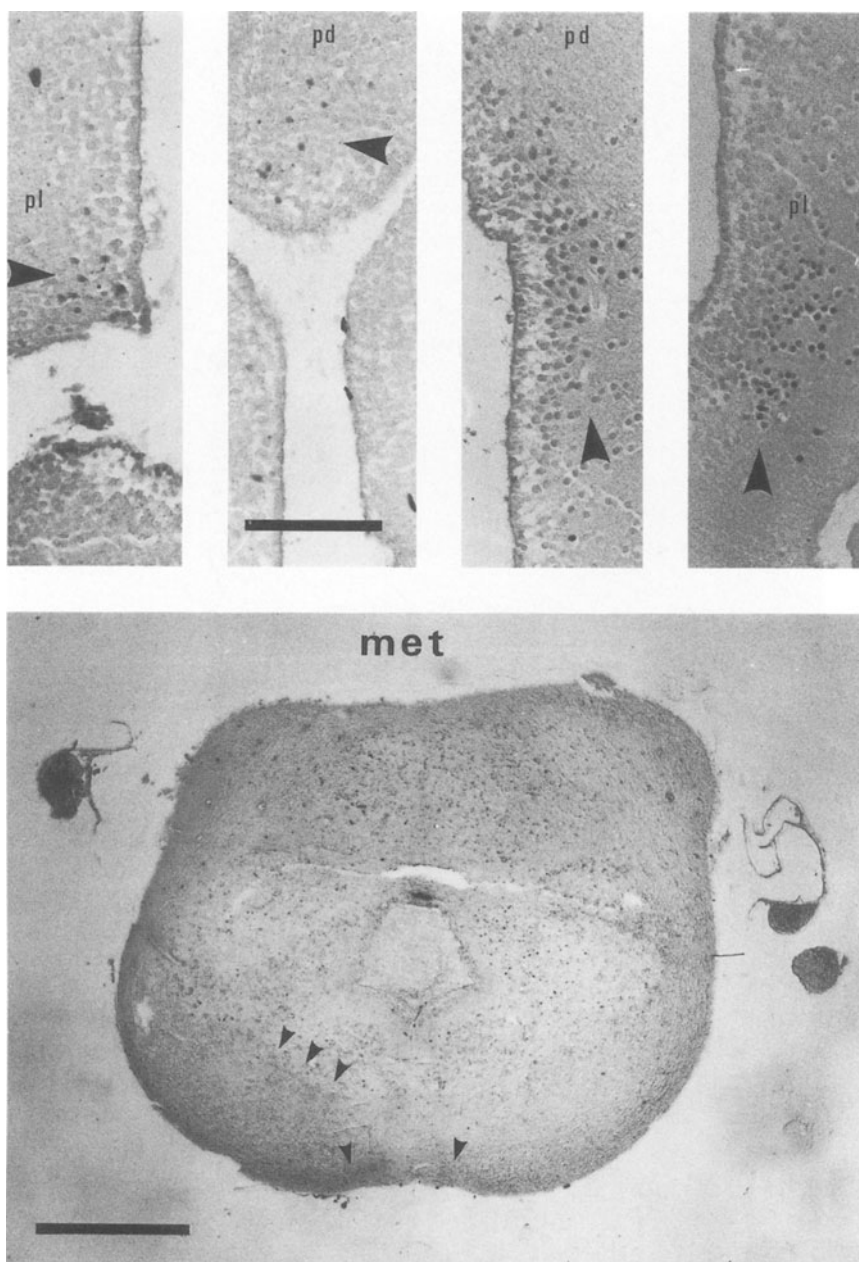


Fig. 47. Horseradish peroxidase injection 18 (see Fig. 46). *Top.* Arrowheads in the top figures point at populations of labeled neurons in the ipsilateral (*left*) and contralateral (*right*) *pd* and *pl*. *Bar*, 100 μ m. *Bottom.* In *met* ipsilateral a haze (*triple arrowheads*) and bilateral distinguishable fibers (*single arrowheads*). *Bar*, 0.50 mm. For abbreviations see list

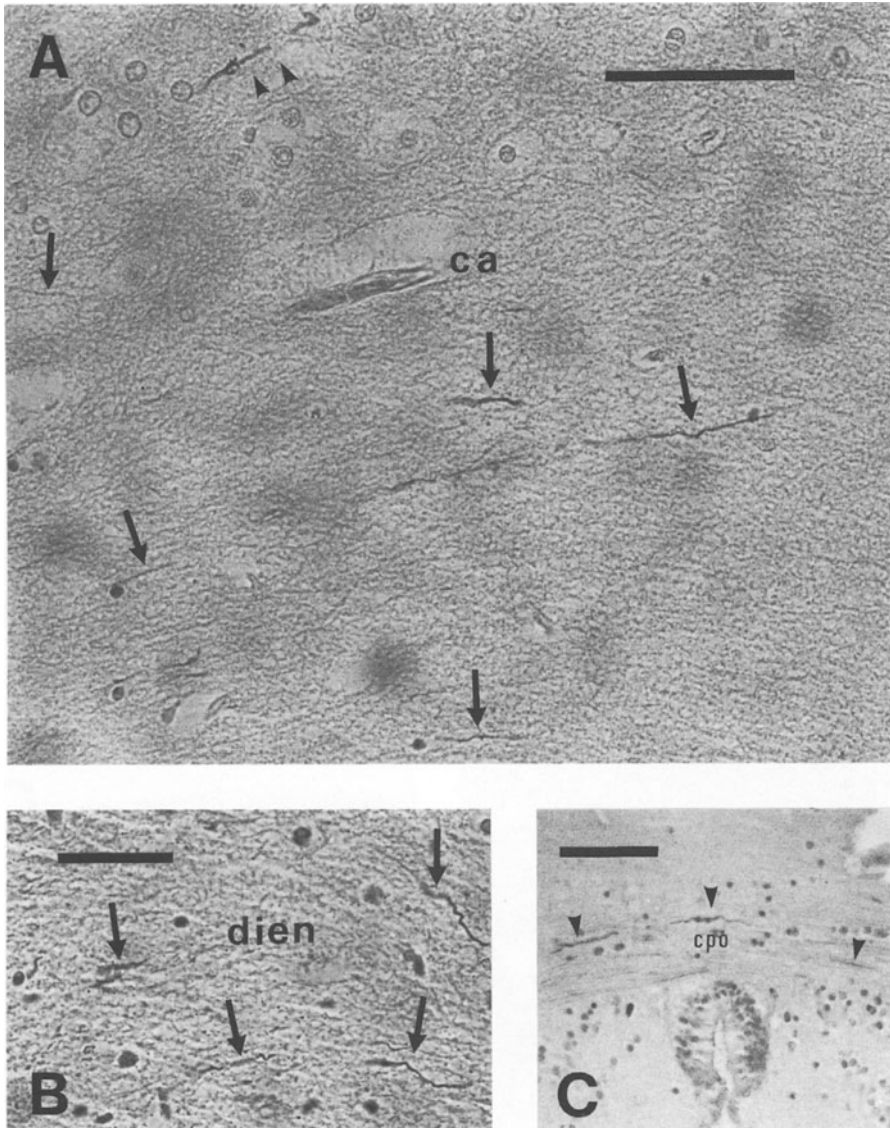
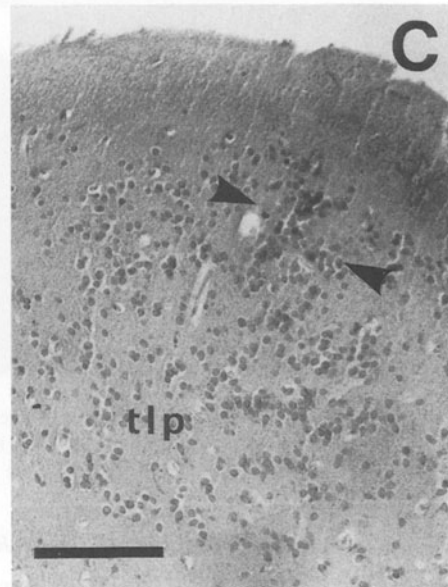
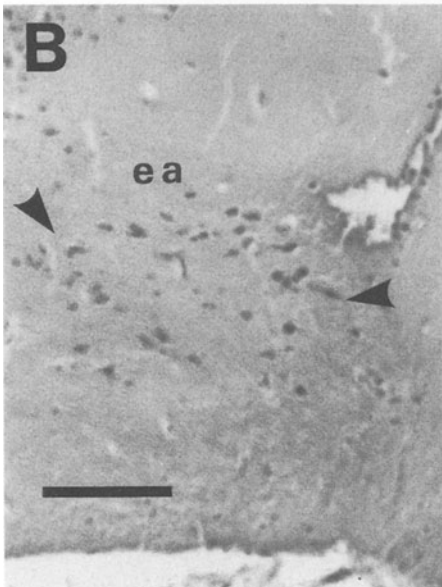
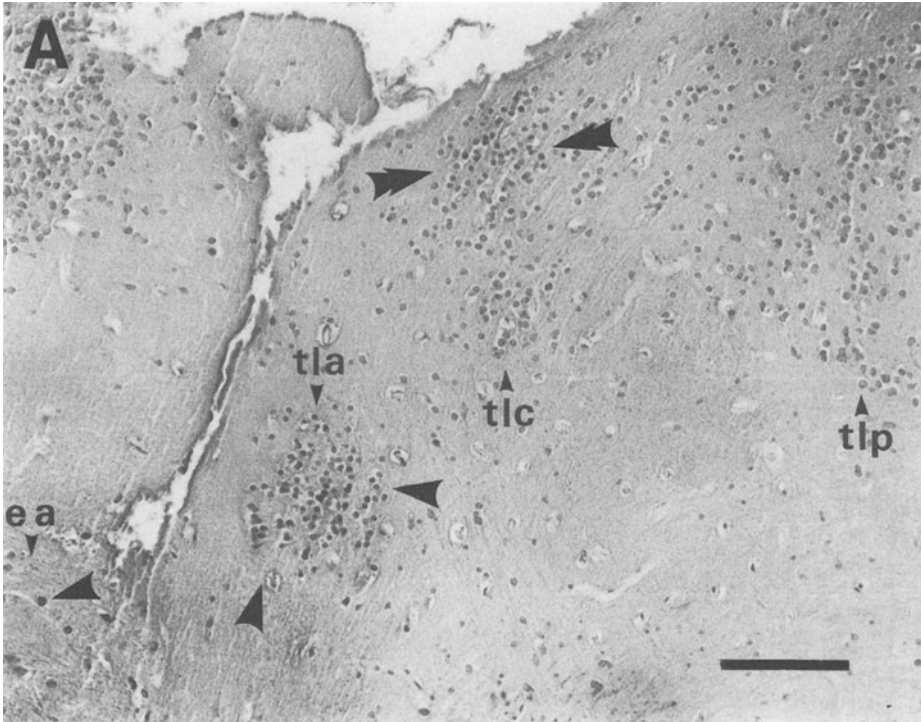


Fig. 48A–C. Cross sections. *HRP* injection 18 (see Fig. 46). **A** Fibers (arrows) in *ca* for *ea* and toward *s* (double arrowheads). Bar, 50 μ m. **B** Labeled fibers in the contralateral ventromedial *dien*. Bar, 50 μ m. **C** Fibers in *cpo*. Bar, 100 μ m. For abbreviations see list

20. Horseradish Peroxidase Injection Rostrally in the Optic Tectum

This was a whole mount incubation. The injection site is rostrally in the optic tectum. Labeled cells are found in the posterior lateral thalamic nucleus (Fig. 50A) and a field of labeled cells appears in the ipsilateral optic tectum as well as in the lamina covering the torus semicircularis (Fig. 50B). The brown haze covers the same area. Labeled fibers can be traced into and next to the optic tract (Fig. 51D) and to descend into the brain stem.



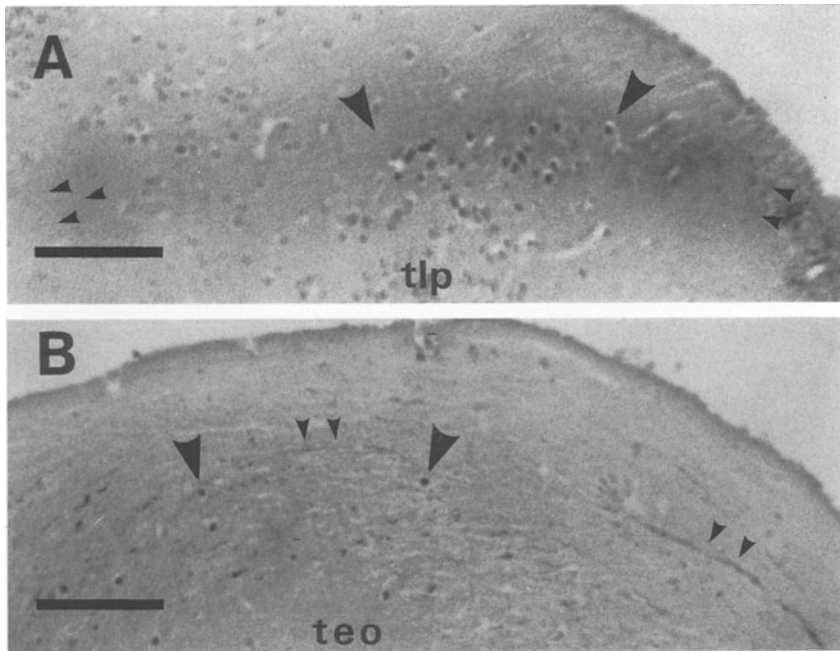
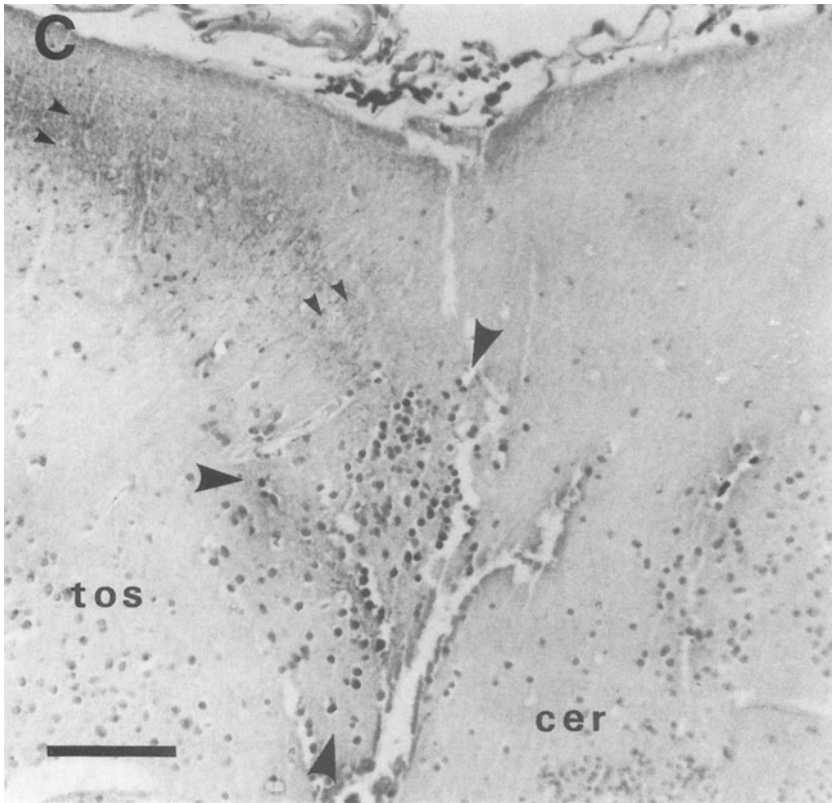


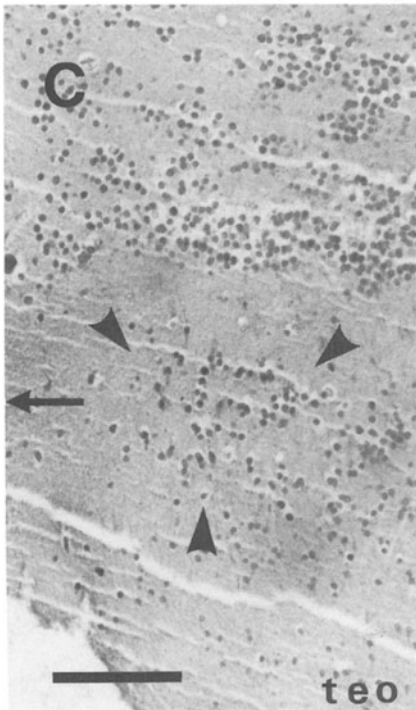
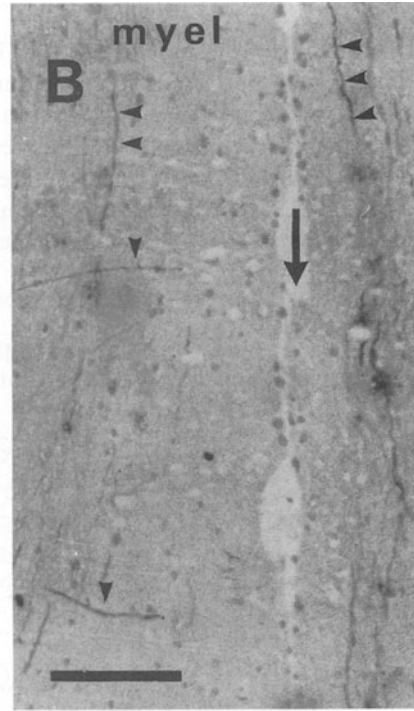
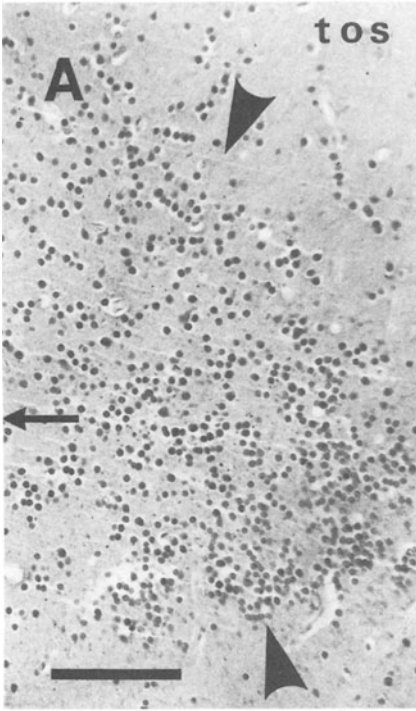
Fig. 50A–C. Horseradish peroxidase injections 20 (A,B) and 21 (C) in the tectum (see Fig. 10). **A** Sagittal section. A haze stretching through the dorsolateral thalamus (arrowheads). Labeled neurons (large arrowheads) in *tlp*. **B** Sagittal section. Labeled fibers (small arrowheads) and neurons (large arrowheads) in *teo* over *tos*. **C** see P. 54

◁ **Fig. 49A–C.** Sagittal sections. *HRP* injection 19 (see Fig. 10) in the caudal lateral thalamus. **A** Labeled neurons in *ea* (single large arrowhead), in *tla* (two large arrowheads), and in *tlc* (two large double arrowheads). Compare with Fig. 8B. **B** Labeled neurons in *ea* (arrowheads). **C** A haze over *tlp* with labeled neurons (arrowheads) in *tlp*. Bars are 100 μ m. For abbreviations see list



C Quasi horizontal section. Fine labeled fibers (*small arrowheads*) stretching past *tos*. Labeled neurons (*large arrowheads*) in the brain stem in between *tos* and *cer*. *Bar*, 100 μ m. For *abbreviations* see list

Fig. 51A–D. Horseradish peroxidase injections 20 (**D**, sagittal section) and 21 (**A**, **B**, **C**, quasi horizontal sections) in the tectum (see Fig. 50). **A** Population of labeled neurons (*arrowheads*) contralateral in *tos*. The *arrow* marks the midline. **B** Labeled axons descending ipsilaterally (*double arrowheads*) and contralaterally (*triple arrowheads*), and crossing over (*single arrowheads*) at the level of the fourth ventricle (*arrow*). **C** Labeled neurons (*arrowheads*) contralateral in *teo*. The *arrow* marks the midline. **D** Labeled fibers (*double arrowheads*) and haze (*triple arrowheads*) stretching through the ventral *dien* to reach the contralateral tectum. For **A–D** the tops are caudal. *Bars*, 100 μ m. For *abbreviations* see list



21. *Horseradish Peroxidase Injection in the Optic Tectum*

This was a whole mount incubation. The injection site is lateral at the border of the optic tectum and the torus semicircularis. Labeled cells appear bilaterally in the torus semicircularis and optic tectum (Fig. 51A, C), and ipsilaterally ventrolateral to the caudal border of the torus semicircularis (Fig. 50C) and in the posterior lateral thalamic nucleus rostral to the border of the tectum (not shown). Ipsilaterally, labeled fibers enter the thalamus, and others descend into the brain stem, where a number cross the midline below the fourth ventricle (Fig. 51B).

22. *Horseradish Peroxidase Injection in the Caudal Mesencephalon (Fig. 52)*

This was on the slide incubation. The penetration tract centers at 0.75 with a dump in the torus semicircularis and a dump in the ventral caudal mesencephalon.

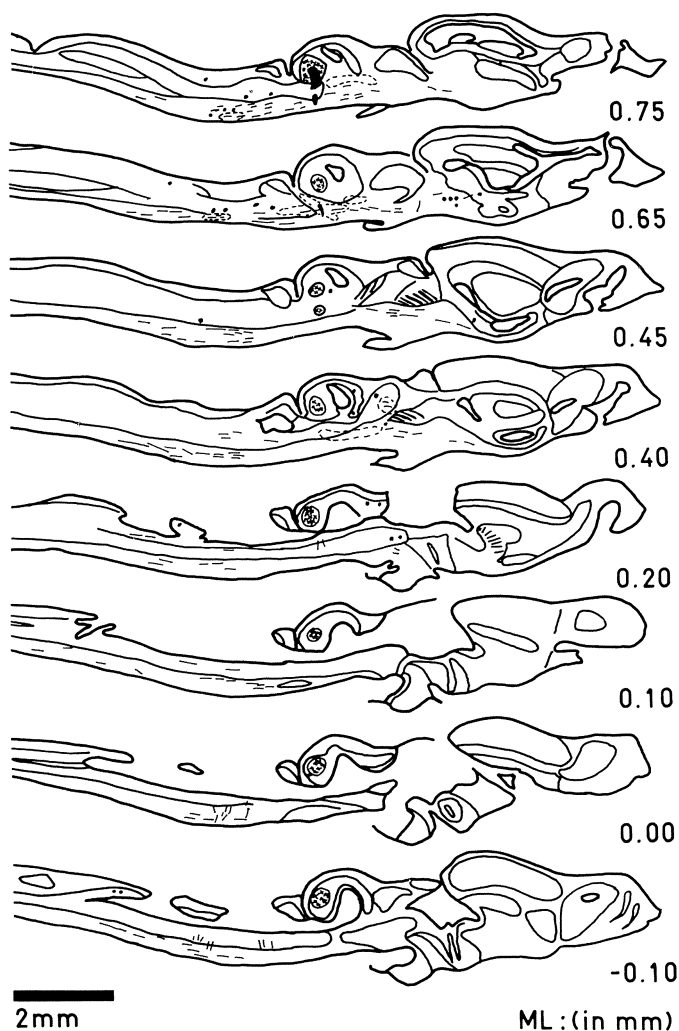


Fig. 52. Horseradish peroxidase injection 22. Sagittal sections showing *HRP* transport. See text and description of format

Ipsilaterally, labeled cells are found laterally in the dorsal and ventral regions of the rostral half of the myelencephalon (0.75–0.45), in the optic tectum and caudal thalamus (0.40–0.20), in the anterior entopeduncular nucleus (0.65), in the amygdaloid complex (0.65), and in the striatum (0.45). Bilaterally, labeled cells occur close to the wall of the fourth ventricle (0.20–0.10) and in the torus semicircularis (0.75, 0.45, 0.00). Labeled fibers are found around the ipsilateral amygdaloid complex and striatum (0.75–0.40) and to reach bilaterally through the brain stem (0.75–0.10) until beyond the obex (0.10). A terminal field occurs bilaterally through the tori semicirculari (encircled crosses, 0.75–0.10). A small terminal field appears ventrally at the level of the eighth nerve (small area encircled with a broken line 0.75–0.65); others are ventral to the cerebellum (0.65), ventral to the torus semicircularis and optic tectum (0.75–0.40), and in the caudal thalamus (0.40) (all surrounded by broken lines).

The left top view (Fig. 53) shows the afferents to the caudal mesencephalon: ipsilaterally, from (in a rostral to caudal sequence) the striatum and amygdaloid complex, anterior entopeduncular nucleus, caudal thalamus, optic tectum, and rostral lateral region of the myelencephalon; contralaterally from the torus semicircularis; and bilaterally from adjacent regions to the fourth ventricle. The right top view (Fig. 53) shows the efferents from the caudal mesencephalon (in a rostral to caudal sequence): to the caudal regions of the amygdaloid complex and striatum, caudal thalamic nuclei, rostral mesencephalon, contralateral torus semicircularis, and in various bundles down the brain stem to the spinal cord with fibers crossing the midline below the fourth ventricle.

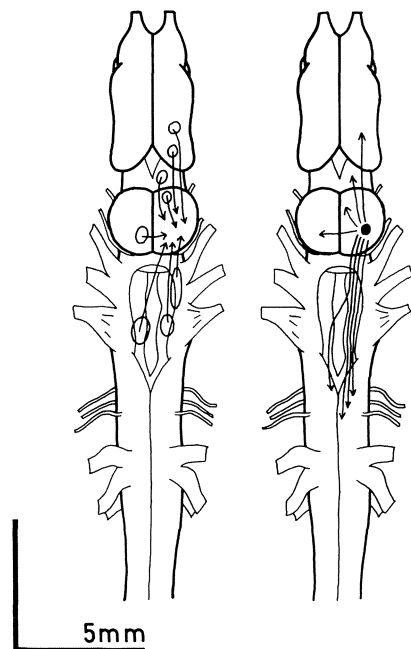


Fig. 53. Horseradish peroxidase injection 22. Top views with reconstruction of *connectivity*. Afferents (*left*) to, and efferents (*right*), from the injection site. See text and description of format

3 Methods and Results: Electron Microscopic Study of HRP-Labeled Elements

C.L. Veenman, H. Kern, and M. Rickmann

3.1 Preparation of the Electron Microscopic Material

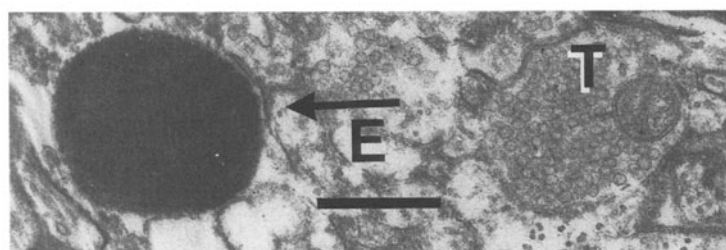
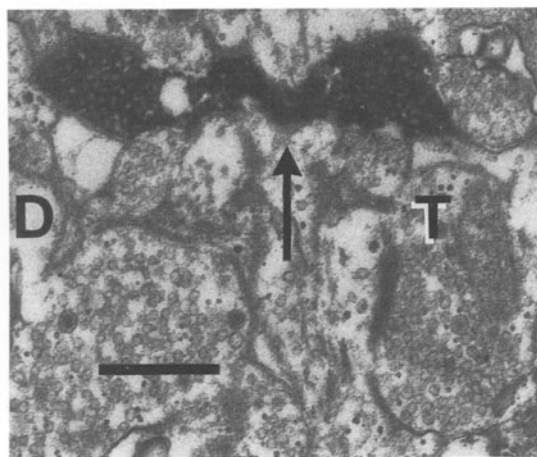
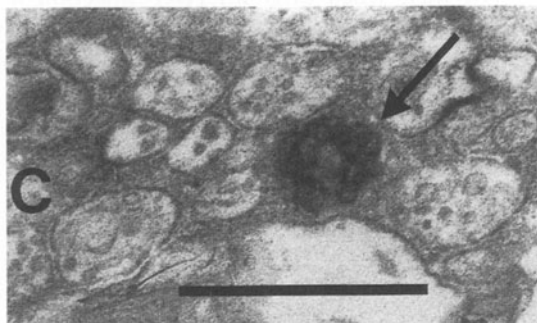
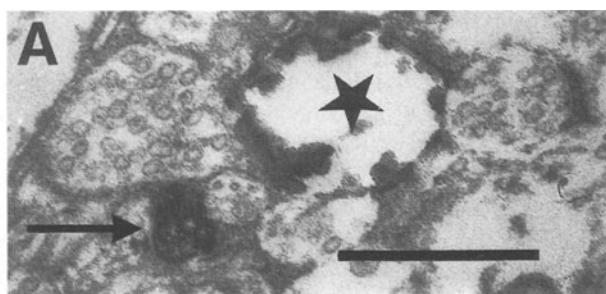
To see whether in the areas with an even brown haze (Sect. 2) neuronal elements with diameters less than 1 μm were labeled, the brains of two adult male *Xenopus laevis*, with HRP injected in the amygdaloid complex, were processed for electron microscopy.

The procedure deviated little from the normal whole mount method used to determine HRP transport (Sect. 2). The animals were perfused with 1.25% glutaraldehyde and 2% paraformaldehyde in phosphate buffer (pH 7.4, 0.1 *M*). Methanol was omitted from the incubation solutions. The brains were sectioned in 1-mm-thick slices. The slices were postfixed in 0.4% OsO_4 and 4.8% $\text{K}_2\text{Cr}_2\text{O}_7$ and flat embedded in Spurr's medium (Spurr 1969). Sections where labeling was anticipated were cut on a Ultracut microtome (Reichert and Jung) for semithin sections (2 μm). These sections were studied under the light microscope. Ultrathin sections were cut from regions containing HRP reaction product. These sections were stained with uranyl acetate and lead citrate (Venable and Coggeshall 1965). The occurrence of labeled neuronal elements was determined with an electron microscope (EM 10, Zeiss) and representative structures were photographed.

3.2 Electron Microscopic Material

Light microscopically, labeling was seen to radiate from the injection sites in the amygdaloid complex. One brain was fixated well enough to allow for processing for electron microscopy. In the areas with an even brown haze, labeled axons and terminals smaller than 1 μm occurred (Fig. 54), farther away even clearer than close to the injection site. In the region directly around the injection site labeled axons appeared damaged (Fig. 54A, B); those farther away were smooth, showing neurotubuli (Fig. 54C). The labeled boutons can be recognized by having vesicles and synaptic densities (Fig. 54D) or suspected, when the internal structure is obscured by reaction product, by being as large and having the same shape as unlabeled terminals (Fig. 54E).

Fig. 54A–E. Electron microscopy, HRP transport. **A** Large (*star*) and small (*arrow*) HRP-labeled axonal elements together with similar unlabeled axonal elements. **B** Detonated labeled axon (*arrow*). **C** Small labeled axon (*arrow*) in a bundle of unlabeled axons. **D** Labeled axon (*arrow*) with boutons en passant and unlabeled terminal (*T*) with synaps. **E** Unlabeled terminals (*T*) and similar sized labeled element (*arrow*). Bars, 0.5 μm



3.3 Conclusions

The brown haze is related to the occurrence of neuronal elements smaller than 1 μm . Of course, to become visible at the light microscopic level, there should be enough of these small labeled neuronal elements. Thus it may be possible that an anterograde projection from the injection site is labeled but does not become visible. This can have happened with the wheatgerm agglutinin conjugated HRP injections, because here the reaction product possibly remains confined to small vesicles and does not fill out complete neuronal elements, or when injections are so small that not enough fibers are filled.

Anyway, when after an HRP injection a haze occurs at a relatively long distance from the injection site and with an asymmetrical distribution, it can be concluded that this haze most likely stems from labeled neuronal elements with diameters less than 1 μm .

4 Methods and Results: Distributions of Opioids, Substance P, and Serotonin

C.L. Veenman, P. Wahle, and P. van Mier

4.1 Immunohistochemistry

In order to obtain more parameters to understand the organization of *Xenopus laevis* telencephalon, the distributions of opioids, substance P, and serotonin were determined.

Four adult male *Xenopus laevis* were used to demonstrate opioid- and substance P-like immunoreactivity in the forebrain. The animals were perfused through the heart under deep MS222 anesthesia with 0.9% NaCl and 1% sucrose in 0.05 M phosphate buffer pH 7.4 followed by a mixture of 4% paraformaldehyde, 1% sucrose, 0.1%–0.2% picric acid in 0.1 M phosphate buffer. Brains were postfixed in fixative without picric acid for 1–2 h, and subsequently soaked in 20% buffered sucrose overnight at 4°C. Sections were cut on a freezing microtome into 50- μ m-thick sections. Two brains were used for cross sections and two for sagittal sections. From each brain two series of alternating sections were collected in 0.1 M phosphate buffer. Sections were rinsed in 0.05 M Tris buffer pH 7.6, then in 0.05 M Tris-buffered 125 mM NaCl pH 7.6, containing 1% sucrose and 0.1% bovine serum albumin (TBS), followed by an incubation in 0.5% Triton in TBS for 30 min, to enhance penetration of the antisera, which was finished with a rinse in TBS. Unspecific binding was blocked by an incubation in 3% normal swine serum (NSWS, DAKO) in TBS for 1 h. The series of sections were incubated in the primary antisera overnight at room temperature. All antisera were diluted in 3% NSWS in TBS. We have used a polyclonal antisubstance P antiserum raised in rabbit [a gift from Dr. M. Tohyama; for specification of the antiserum see Inagaki et al. (1981)] at a dilution of 1/1000, and a monoclonal antibody 3E7 raised against β -endorphin [a gift from Drs. A. Herz and C. Gramsch; for specification see Gramsch et al. (1983)] at a dilution of 1/500. The anti- β -endorphin antibody 3E7 is specific for the N-terminus of opioid peptides. It recognizes a variety of opioid peptides derived from the three precursors and shows a 100% cross-reactivity with enkephalins [for review see Höllt (1983)]. For the substance P antiserum the peroxidase-antiperoxidase (PAP) method (Sternberger et al. 1970) was applied. Swine-anti-rabbit antiserum (DAKO) diluted 1/20 was used as bridge antiserum for 3 h, followed by a rabbit PAP complex (DAKO) diluted 1/50 for 2 h. For the anti- β -endorphin antibody we used a peroxidase-labeled rabbit anti-mouse serum diluted 1/10 for 2 h. Peroxidase activity was developed in 0.002% DAB and 0.0001% H₂O₂ in Tris buffer. Sections were mounted on gelatin-coated slides and dried. The reaction product was intensified with 1% OsO₄ in 0.1 M phosphate buffer pH 7.4 for 1 min. Sections were dehydrated in graded alcohols, cleared in xylene, and coverslipped.

The distribution of serotonergic fibers and neurons was studied in four females 6–8 months of age. Before fixation the animals were deeply anesthetized in tap water containing an overdose of MS222 (Sandoz; 250 mg/100 ml) and perfused transcardially with 0.1 M phosphate buffer containing 4% paraformaldehyde (pH 7.2–7.4). The CNS was dissected and postfixed for 4–8 h at 4°C. The meninges were removed and the CNS washed in several changes of 0.1 M phosphate-buffered saline (PBS, pH 7.2) with 5% sucrose in the last wash. Serotonin immunoreactivity was studied using the PAP method (Sternberger 1979; Sternberger et al. 1970). The sections were incubated in: (a) rabbit serotonin antiserum diluted 1:400 in PBS containing 0.1% Triton X-100 at 4°C for 18 h, (b) goat antirabbit IgG serum (F_c specific, Nordic, Tilburg, the Netherlands) diluted 1:20 at a room temperature for 2 h, (c) PAP complex (Dakopatts, Copenhagen, Denmark) diluted 1:200 for 1 h, and (d) 0.025% diaminobenzidine with 0.01% H₂O₂ in 0.05 M Tris buffer for 15 min in the dark. Subsequently the sections were dehydrated through an alcohol series and coverslipped with DPX-mounting medium (Gurr). The preparation and specificity of the antisera against serotonin were described by Steinbusch et al. (1978, 1983).

The immunohistochemically prepared material was studied and photographed with a Wild photomicroscope and a Leitz photomicroscope.

4.2 Distributions

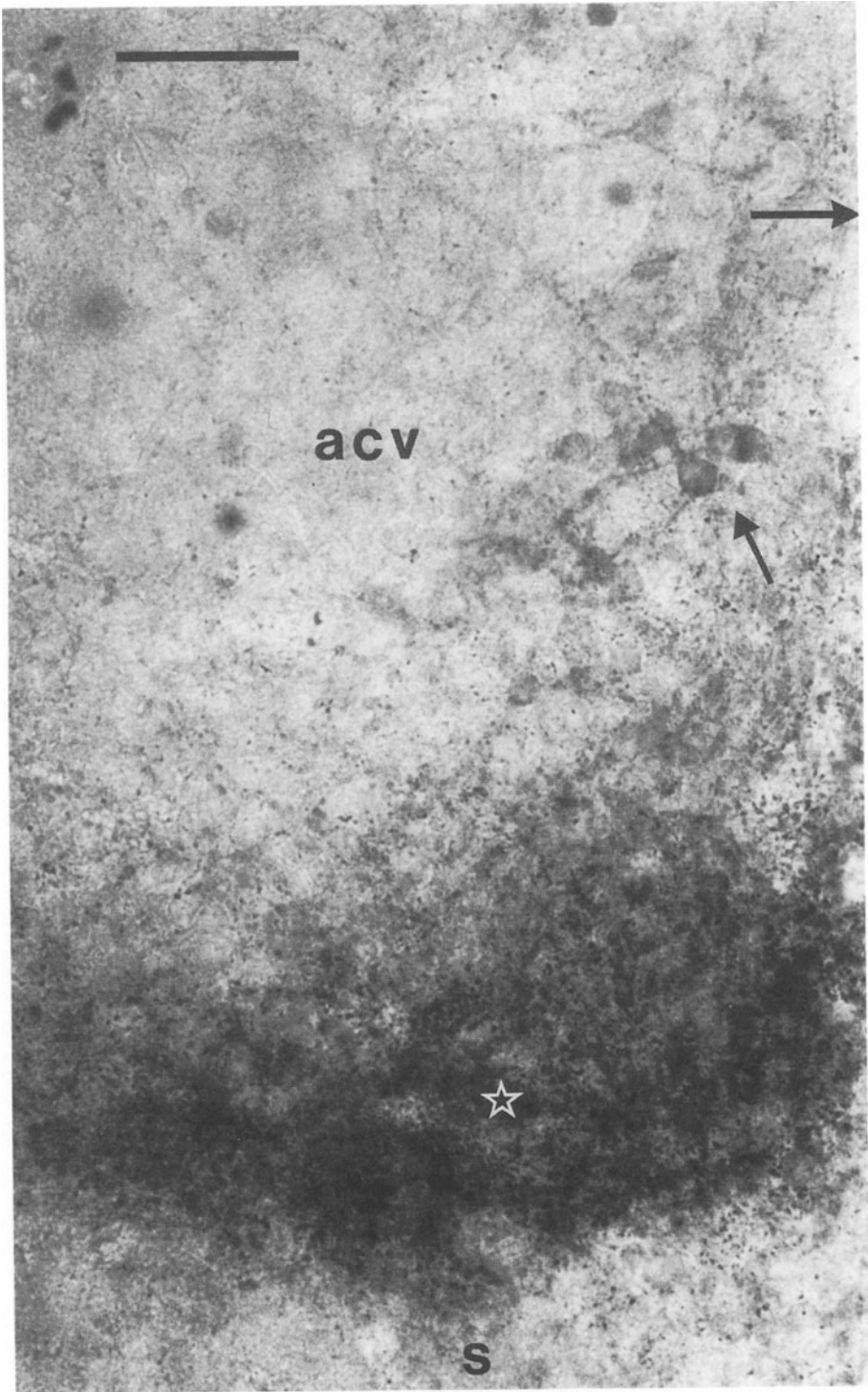
4.2.1 Substance P and Opioids

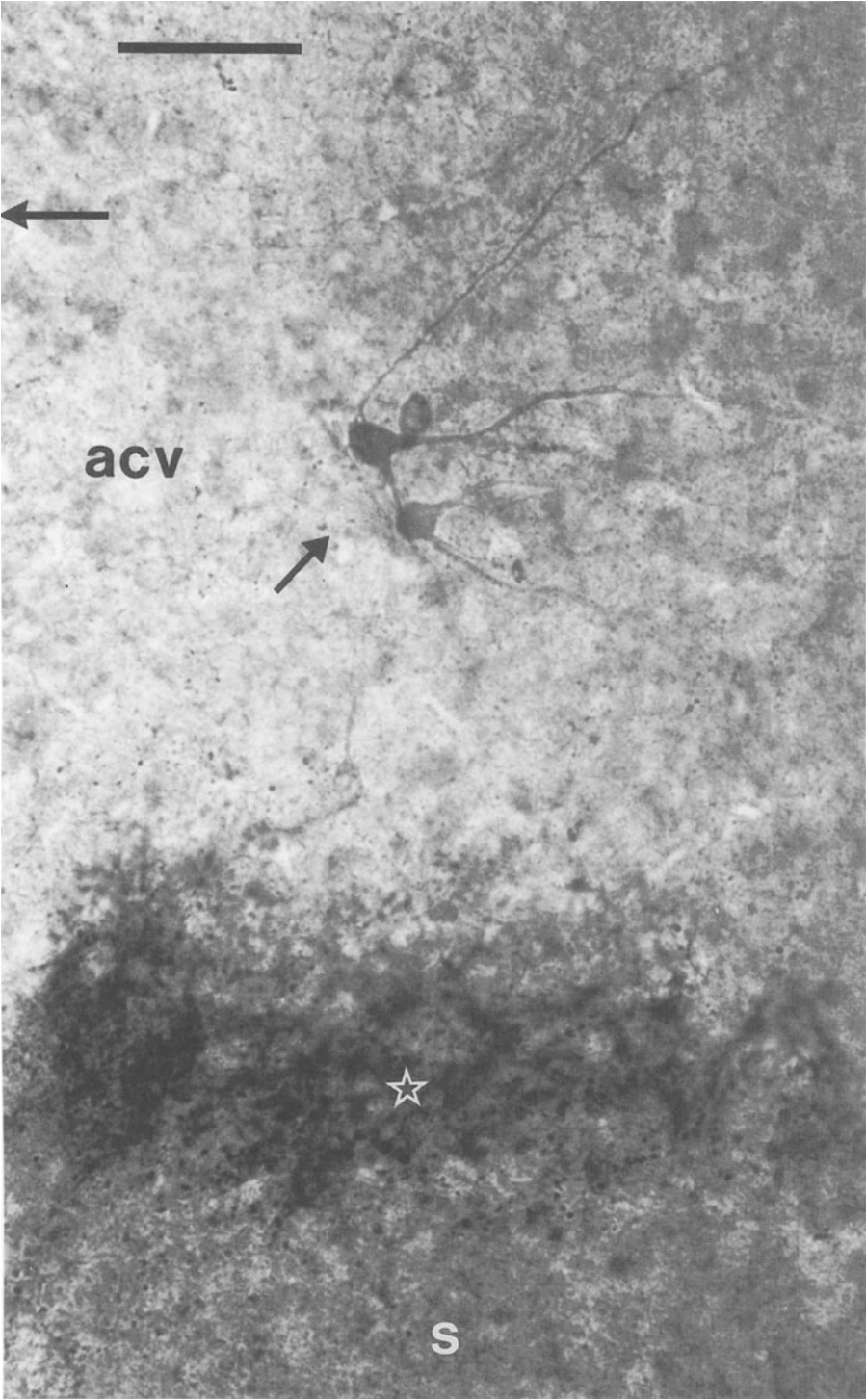
Cells showing immunoreactivity for the antisubstance P and the antiopioid antibodies were found throughout the lengths of the amygdaloid complex and the striatum. Throughout the length of the septum substance P-ergic immunoreactive cells also appeared. Coherent groups of cells with substance P-ergic and opioidergic immunoreactivity were found rostrally in the amygdaloid complex together with the rostral beginning of a field of fibers and terminals showing in immunoreactivity for both antibodies (Figs. 55, 56). This plexus of fibers and terminals stretches along the whole length of the amygdaloid complex. Rostrally, the group of opioidergic cells appears more peripherally in the amygdaloid complex than the substance P-ergic group (Figs. 55, 56). As seen with Golgi preparations (Fig. 61) and with HRP injections (Fig. 2) most dendrites and axons point to the periphery.

The distribution of opioidergic and substance P-ergic immunoreactivity shows both striking differences and similarities to those already mentioned in the first paragraph. A dense opioidergic terminal field unifies the pallial part of the telencephalic hemisphere (Fig. 58). It is narrow in the cellular region of the lateral pallium, widening over the dorsal pallium, to fill out the cell mass of the medial pallium. This field is most dense in the dorsal pallium and shows a gradient by intensifying from rostral to caudal. In contrast, the pallial substance P-ergic immunoreactivity seems to rise from the amygdaloid complex (Fig. 57), appearing as a haze in which no elements visible at the light microscopic level can be recognized; it remains restricted to the intermediate layer and becomes indistinct at the border of the dorsal and medial pallium. Also the pallial substance P-ergic immunoreactivity shows a rostrocaudal gradient, the caudal regions being most densely labeled.

The neuropil and white matter of the striatum is filled out with an opioidergic fiber plexus (Fig. 56). In this region substance P-ergic immunoreactivity only appears caudally (Fig. 57). Both a substance P-ergic and opioidergic fiber plexus fills out a well-circumscribed border region between the rostral striatum and septum. This plexus is continuous with the one mentioned with the amygdaloid complex (Figs. 55, 56). The septum contains loose arrays of fibers and terminals reactive to both sets of antibodies. The diencephalon stains intensely dark from both (Figs. 57, 58). Substance P-ergic and opioidergic cells in the diencephalon are confined to the ventricle walls of the preoptic recess, the ventral part of the main ventricle, and the infundibular recess (not indicated).

Fig. 55. *Substance P.* Cross section through the rostral telencephalic hemisphere. Labeled neurons (arrowhead) in *acv* and a fiber plexus (star) between *acv* and *s*. The arrow points medially. Bar, 50 μ m. For abbreviations see list





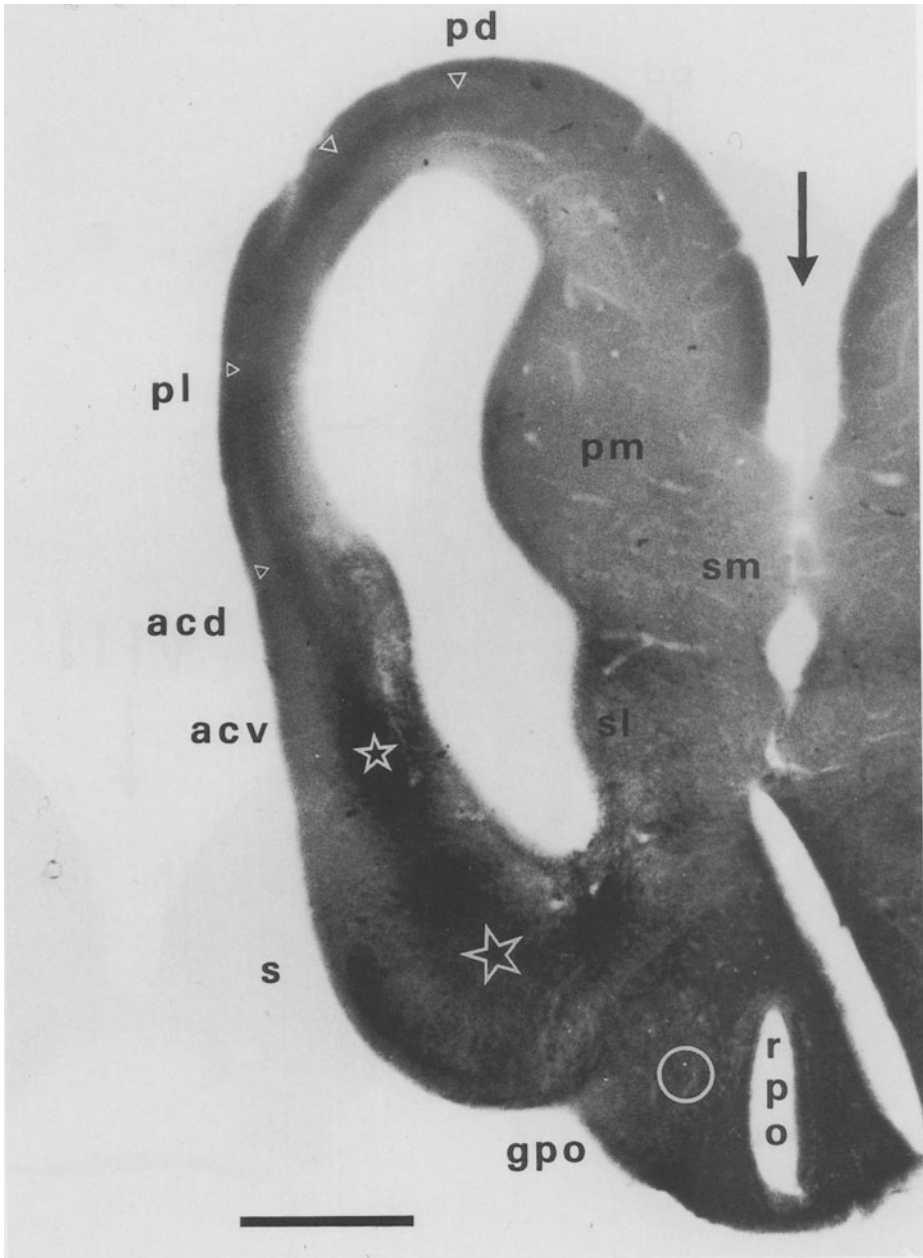


Fig. 57. *Substance P*. Cross section through the caudal half of the telencephalon. The diencephalic part (circle) is heavily stained. *Fiber plexus* appear in: *s* (large star), in *acv*, *acd* (small star), and as a haze in *pl* and *pd* (triangles). Scattered *fibers* appear in *sl*, *sm*. Arrow marks the midline. Bar, 0.5 mm. For abbreviations see list.

◁ **Fig. 56.** *Opioids*. Cross section through the rostral telencephalic hemisphere. Labeled *neurons* (arrow-head) in *acv* and a *fiber plexus* (star) between *acv* and *s* and a less-dense *fiber plexus* in *s* itself. The arrow points medially. Bar, 50 μ m. For abbreviations see list

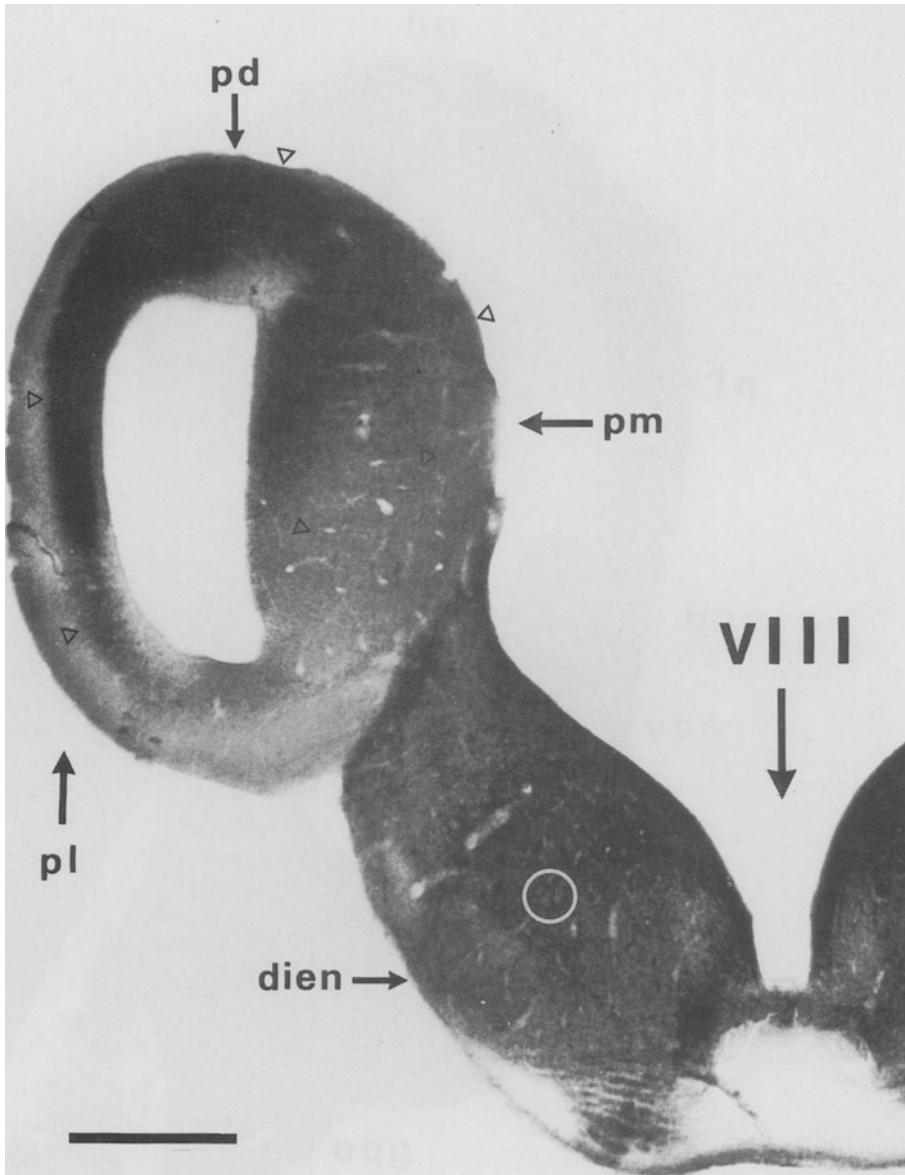


Fig. 58. *Opioids*. Cross section through the caudal pole of the telencephalon. The diencephalic part (circle) is intensely stained. A fiber plexus unifies *pl*, *pd*, and *pm* (triangles). Large arrow marks the midline. Bar, 0.5 mm. For abbreviations see list

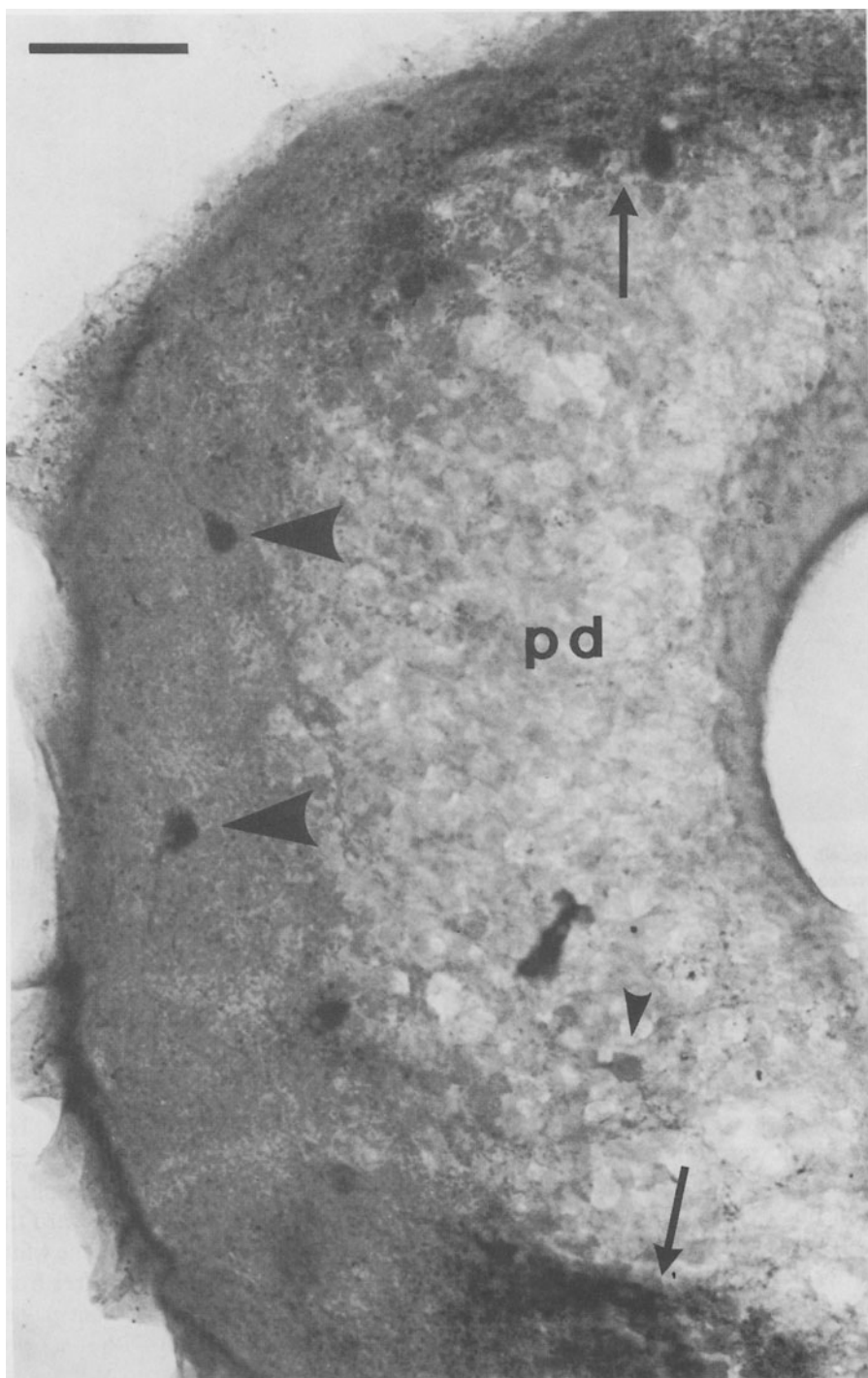


Fig. 59. Serotonergic labeling in the rostral *pd*. Arrowheads point at stained neurons. Arrows point at fiber plexus which separate *pm* (top) and *pl* (bottom) from *pd*. Labeled terminals are scattered throughout *sa* whereas *sgs* and *sgp* remain relatively free from labeling. Bar, 50 μ m. For abbreviations see list

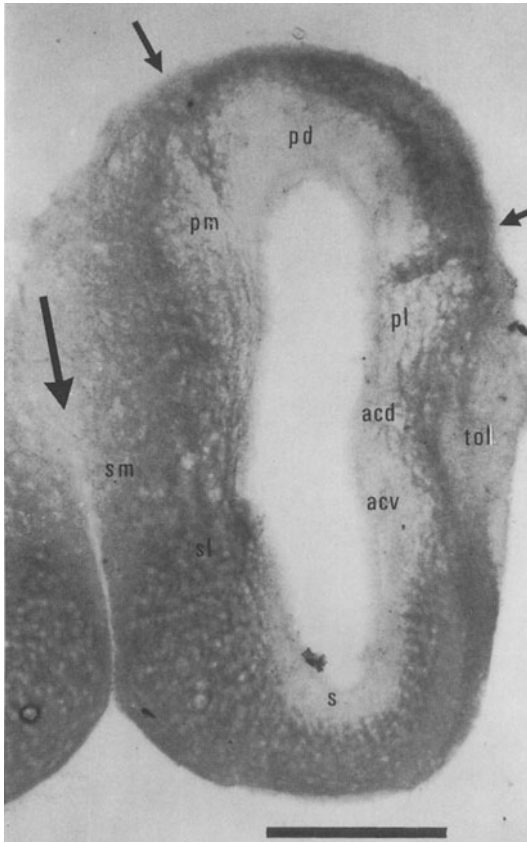


Fig. 60. *Serotonin.* Cross section through the rostral telencephalic hemisphere. The whole circumference of the hemisphere contains labeling. The *small arrows* point at *plexus* dividing *pm*, *pd*, and *pl*. The *large arrow* marks the midline.

4.2.2 Serotonin

The immunoreactivity for serotonin forms a pattern quite different from the patterns seen for antibodies against opioids and substance P. It must be borne in mind, however, that the serotonin experiments are performed on juveniles. Telencephalic serotonergic cells were only found in the rostral pallium (Fig. 59). Plexus of serotonergic fibers and terminals stretch throughout the telencephalic hemispheres (Fig. 60). Serotonergic plexus reaching from the periphery toward the ventricle seem to separate the medial, dorsal, and lateral pallium (Fig. 60). The white matter most peripheral from the amygdaloid complex remains relatively free from serotonergic labeling (Fig. 60), possibly because the lateral olfactory tract passes here (Figs. 34–36). The medial wall of the hemisphere is filled out with a serotonergic fiber and terminal plexus, giving no hint of borders between the medial pallium, septal regions, and striatum (Fig. 60).

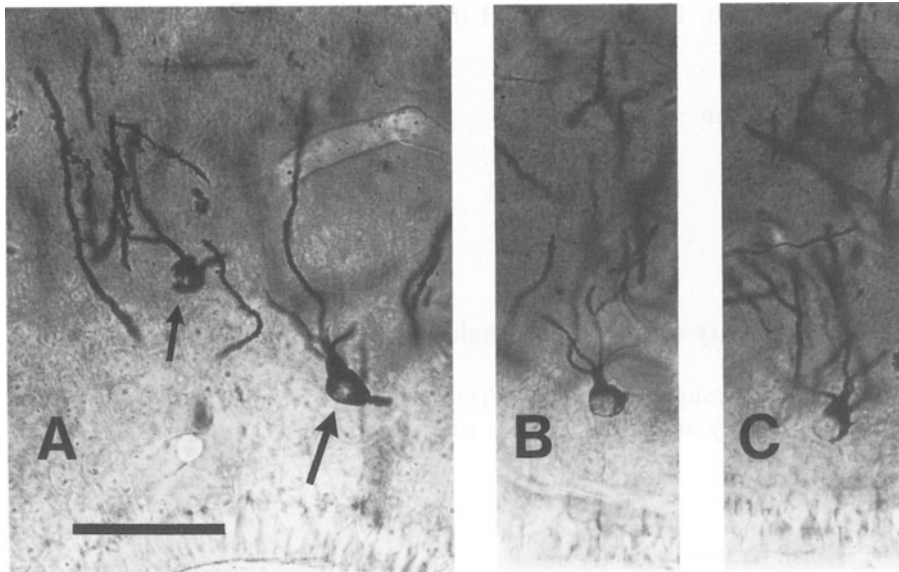


Fig. 61A–C. Golgi stain. Neurons with *dendrites* pointing to the periphery in *dp*. At the bottom is *ependym* bordering the ventricle. Bar, 50 μ m. For abbreviation see list

4.3 Conclusions

The described parameters can be compared with those found for mammals (Nieuwenhuys 1985). The distributions of substance P-ergic and opioidergic immunoreactivity make it possible to consider a longitudinal band between the pallium and striatum as the amygdaloid complex (Veenman et al. 1987). This is in congruence with the hodological parameters (Sect. 5) and leaves the striatum, septum, and pallium to be compared with their traditional equivalents.

The immunohistochemistry also allows for subdividing the pallium. It can be considered a coherent entity on the basis of its opioidergic fiber plexus, but can be divided into a rostral and a caudal part on the basis of the distribution of serotonergic cells, and into a medial, dorsal, and lateral part on the basis of dividing serotonergic fiber plexus. Both the substance P-ergic and opioidergic plexus show a density increase from rostral to caudal through the pallium. Substance P-ergic immunoreactivity is more prominent in the lateral pallium and opioidergic immunoreactivity is more prominent in the dorsal pallium.

5 Discussion: Hodological, Functional, and Comparative Concepts

C.L. Veenman

5.1 Connectivity of the Telencephalon

In this section the suggested structuralization of the forebrain (Sect. 1, Fig. 1A) will be tested step by step on the basis of the connections found with the HRP experiments.

5.1.1 Input Systems to the Pallium

Our results showed that in *Xenopus laevis* the rostral third of the pallium appears to be the recipient for afferents from the olfactory bulb and from the dorsal thalamus (Fig. 62). HRP injections in the caudal two-thirds of the pallium did not show retrograde labeling in the thalamus or olfactory bulb. Of the rostral pallial areas the dorsal pallium appears to be most strongly connected with the thalamus. The afferents come mainly from rostral dorsal thalamic regions. There is a topological ordering in the thalamopallial connectivity: input from medial to lateral thalamic regions connects correspondingly with medial to lateral regions in the rostral pallium.

Especially the lateral nuclei of the dorsal thalamus are reciprocally connected with the tectum. Both anatomically and physiologically it is determined that in *Xenopus laevis* the tectum opticum and torus semicircularis receive input from: the lateral line system, auditory system, and visual system (Levine 1980; Fritsch et al. 1984; Will et al. 1985a, b; Lowe 1986, 1987; Zittlau et al. 1987). Visual input also enters the dorsal thalamus directly (Levine 1980). Thus at least via the tectum the dorsal thalamus receives multimodal sensory input. This means that the rostral pallium is the pallial entrance structure for multimodal input which is relayed via a thalamopallial pathway together with an olfactopallial pathway. Additional input to the pallium comes from the habenula into the lateral pallium. Apparently the pallium is accessible for any information, a postulated prerequisite for telencephalic function (Sect. 1, Fig. 1A).

5.1.2 Intrinsic Connections of the Pallium

The medial, dorsal, and lateral pallium were each subdivided into a rostral, central, and caudal area. For this no special experimentally derived parameters were used, just location. Each area received a number of HRP injections. The sum of connections determined for the different areas added up to a connectivity pattern

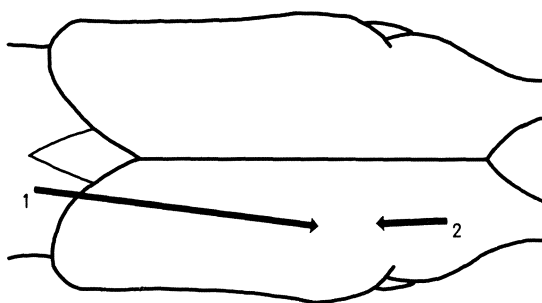


Fig. 62. Thalamic (1) and olfactory (2) *afferents* to the rostral pallium

spreading over the pallium (Fig. 63). From the complex pattern constructed in this way several elements can be extracted (Figs. 64, 65).

Our results showed that the connections between all the rostral pallial areas are completely reciprocal. The connections from the central medial pallium to the central lateral pallium and from the caudal lateral pallium to the caudal medial pallium are unidirectional. The connections between the medial and the dorsal pallium, and between the lateral and the dorsal pallium, are reciprocal throughout the length of the telencephalon. This means that within the rostral pallial areas themselves, which form the input station of the pallium, neuronal activity can be transferred through two opposing, noninterrupted, circular sequences. In the central pallial areas and in the caudal pallial areas, the two separated sequences can form the basis for two unidirectional circular transfers of neuronal activity, or for a combination underlying a unidirectional circular transfer of neuronal activity throughout the caudal two-thirds of the pallium. Thus, also in this respect of connectivity the caudal two-thirds of the pallium are different from the rostral third.

The reciprocal and unidirectional connections between the chosen pallial areas are displayed in different diagrams (Figs. 64, 65) to see whether additional clues to pallial organization can be discerned. The reciprocal connections (Fig. 64) appear to be mainly between adjacent areas, and to occur predominantly in rostral pallial areas. The rostrocaudal gradient of reciprocity gives the impression of two different patterns, namely, the rostromedial half of the pallium appears to be covered by a network in which activity can run in any direction, and the caudolateral half of the pallium appears to be surrounded by a circular chain through which information can run back and forth. Apart from this, the caudal two-thirds of the pallium is covered by a network of reciprocal connections which are shorter than the extent of the chosen subdivisions. So it is possible that information is processed relatively crudely in the rostral pallium and more refined in the microcircuitry of the caudal pallium.

(Note: and additional reciprocal connection exists between the caudal lateral pallium and the central medial pallium. The reason why this is not included within the diagram of reciprocal connections, but as two unidirectional projections, is that the projection from caudolateral to centromedial runs around the caudal pole of the hemisphere, whereas the returning projection runs over the dorsal surface of the hemisphere.)

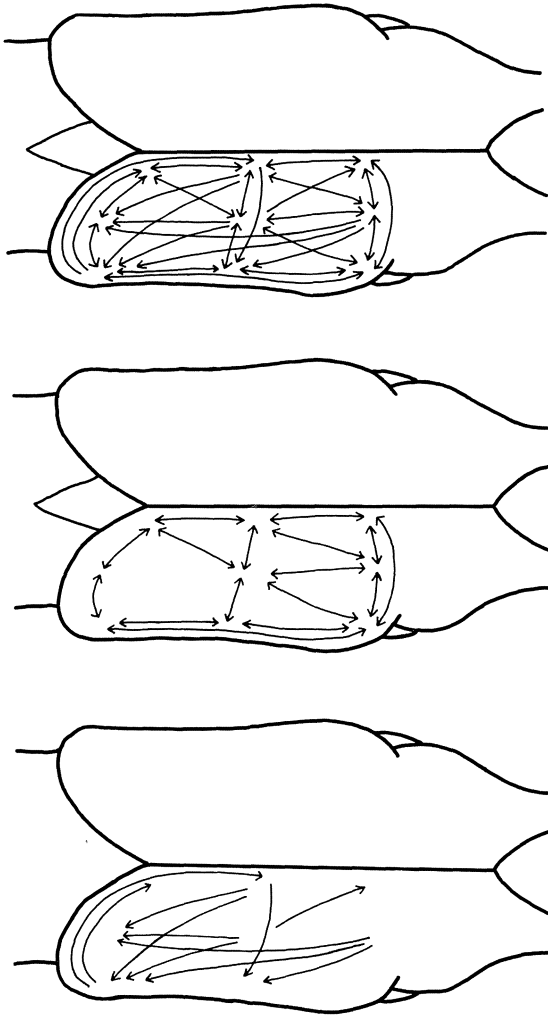


Fig. 63. (above) *Intrinsic connections of the pallium*

Fig. 64. (middle) *Intrinsic reciprocal connections of the pallium*

Fig. 65. (below) *Intrinsic unidirectional connections of the pallium*

The unidirectional connections (Fig. 65) generally cover greater distances than the reciprocal connections. Most of the unidirectional connections are located in the caudal half of the pallium. The main direction of the projections is rostral-caudal, with a few projections running in lateromedial directions. These relatively long unidirectional fiber systems can form the basis for the projection of neuronal activity, arising over the whole of the pallium, into the caudal pole of the hemisphere, and more specifically from the rostral third of the pallium into the caudal two-thirds of the pallium. In a similar way the caudolateral pole of the medial pallium can be a target for activity arising in the caudolateral pole of the hemisphere. The central medial pallium in turn projects backwards into the caudal two-thirds of the dorsal and lateral pallium. A comparable pattern of returning

projections can be recognized in the rostral pallium. Thus, also the unidirectional projections through the pallium give parameters to distinguish and separate rostral and caudal pallial areas.

The immunohistochemistry (Sect. 4) gave additional parameters to distinguish the rostral pallium from the caudal pallium.

Summarizing: The rostral input area of the pallium is linked up to a network of reciprocal connections which becomes more refined in caudal pallial areas, suggesting the existence of differentiated processing systems. The network of reciprocal connections can be considered to be a system over which any information entering the rostral pallium can be processed in any combination via sequences of nonlinear relationships (Sect. 1, Fig. 1A). The main direction of the intrapallial unidirectional projections is caudad, together with lateromedial and mediolateral projections. The processing within the pallium, together with the processing in the amygdaloid complex and the septum with which the pallium is reciprocally connected (see Sect. 5.1.5.3), might form the basis for internal control (Sect. 1, Fig. 1A).

5.1.3 Efferents of the Pallium

Since the pallium was supposed to play a role in the selection of behavior and since the caudal pole of the hemisphere was a target for long unidirectional intrapallial connections (see Sect. 5.1.2), it was expected that the caudalmost pallium would be the major output area of the pallium. However, HRP injections in this area never revealed anterograde labeling of fibers leaving the telencephalon. From the caudal pole of the telencephalon fibers were only seen to reach the caudal lateral pallium. From here anterograde labeling could only be followed as far as the rostral dorsal thalamus, and into the ventrocaudal telencephalon. In looking at descending systems, ten Donkelaar et al. (1981) also did not see pallial sources for telencephalic efferents reaching the spinal cord.

Therefore, the possibilities of alternative pathways of the pallium to influence motor centers in the medulla were looked into. In a first postulation, the rostral pallium was considered as an input-output system. Apart from receiving thalamic and olfactory input, the rostral pallium has projections to virtually all of the telencephalic areas; and to the habenula, ventral thalamus, and hypothalamus. In this concept, the caudal two-thirds of the pallium are linked up as an information-processing system to the input-output system constituted by the rostral third of the pallium. Information enters the rostral pallium, runs through the caudal pallium, reenters the rostral pallium, and is then fed into the striatum and diencephalic regions from where the motor systems in the medulla are reached. The rostral pallium is also connected to the septum and amygdaloid complex, other areas which project out of the telencephalon.

A second postulation for the ability of the pallium to influence lower brain parts was that, while information is processed throughout the pallium, several entities in the diencephalon are driven as a result of this processing (Fig. 66): the hypothalamus from the medial pallium (1), the habenula, ventral thalamus, and hypothalamus from the rostral pallium (2), and the medial thalamus and habenula from the caudal lateral pallium (3). The medial pallium also projects into the

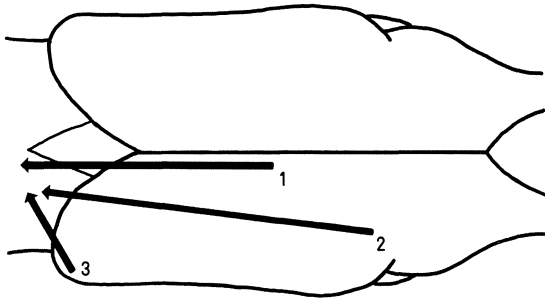


Fig. 66. Efferents of the pallium: from the medial (1), rostral dorsal (2), and caudal lateral (3) pallium to the diencephalon

septum, which projects into the hypothalamus. The lateral pallium also projects into the amygdaloid complex, which projects into several systems in the diencephalon and the lower brain stem (see Sect. 5.5.2).

Finally, however, it was found that after horseradish peroxidase injection in the caudal hypothalamus labeled cells do appear in the caudal pole of the telencephalon. Thus, the pallium can be considered to be a structure where multimodal input enters rostrally, is processed in a rostral to caudal sequence, and the resulting output leaves caudally. But this then should not be considered the sole possibility for the pallium to influence behavior. The other elucidated possibilities doubtlessly will play a role. So, the whole of the pallium can be considered to be a versatile system where any information (see Sect. 5.1.1) can be associated in any combination (see Sect. 5.1.2), with possibilities for internal control (see Sects. 5.1.2, 5.1.5.3), and, via the hypothalamus, external selection (see Sect. 5.1.5.3). (See also Fig. 1A.)

5.1.4 Efferents and Afferents of the Striatum

Horseradish peroxidase injection in the caudal mesencephalon showed that the anterior entopeduncular nucleus and the striatum project into the brain stem. The injections in the tectum and in the caudal thalamus showed that the anterior entopeduncular nucleus projects into the caudal thalamus. Injection in the anterior entopeduncular nucleus labeled fibers reaching into the caudal thalamus and the midbrain. Thus, the anterior entopeduncular nucleus in *Xenopus laevis* appears to be an output structure of the telencephalon. Other work on *Xenopus laevis* shows the caudal striatum as an output system reaching the cervical part of the medulla (ten Donkelaar et al. 1981). Work on *Rana catesbeiana* mentions that the striatum projects into the anterior entopeduncular nucleus (Wilczynski and Northcutt 1983b). Our injection in the anterior entopeduncular nucleus caused a haze of labeling stretching from the caudal lateral pallium throughout the length of the striatum; this suggests that the anterior entopeduncular nucleus and the striatum form a complex.

Injection in the olfactory bulb labeled fibers entering the striatum. Injection in the anterior entopeduncular nucleus showed labeled cells in the caudal thalamic

regions and in the accessory olfactory bulb. The lack of this labeling after injections hitting the preoptic region, septum, amygdaloid complex, and caudal lateral pallium makes it likely that the anterior entopeduncular nucleus and possibly the striatum are recipients for the projections from the caudal thalamus and from the accessory olfactory bulb. This type of connectivity is not only seen in *Xenopus laevis* but also in other amphibians (Wilczynski and Northcutt 1983a; Wicht and Himstedt 1986; Zittlau et al. 1987). Our injection in the caudal lateral thalamus labeled fibers in the lateral forebrain bundle, but we could not determine terminal fields in the anterior entopeduncular nucleus or in the striatum.

So, our results and those of others show the striatum with the anterior entopeduncular nucleus (striatum complex) as a system accessible for multimodal sensory input and having direct access to motor centers in the medulla (see Fig. 67). This means that the striatum complex has the properties needed for the postulated sensorimotor system (Sect. 1, Fig. 1A).

5.1.5 Dual Information Processing System of the Telencephalon

5.1.5.1 Pallium and Striatum Complex

As described in the previous sections the rostral pallium and the striatum complex (striatum and anterior entopeduncular nucleus) are marked as telencephalic input-output systems (Fig. 67). They receive input from the thalamus and from the olfactory system. The rostral pallium receives input from rostral thalamic areas and the olfactory bulb. The striatum complex receives input from caudal thalamic areas and the accessory olfactory bulb. The rostral pallium has efferents to the ventral thalamus; the striatum complex has efferents to the brain stem and cervical spinal cord. Between the rostral pallium and the striatum are reciprocal connections. This simplified diagram (Fig. 67) shows that the telencephalon can be subdivided into two parallel, but interacting, input-output systems.

The cytoarchitectonic differences between the pallium and striatum make it likely that they process information differently. The compact, uniform appearance of the striatum together with its relatively simple input-output relations give reason

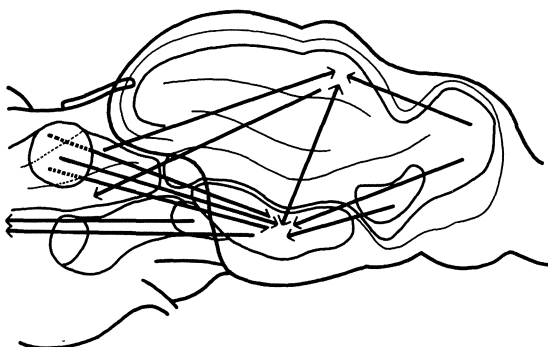


Fig. 67. Afferents and efferents of the rostral pallium and the striatum complex. For orientation see reconstructions of Fig. 8B,C

to assume that via this system sensory information is transformed to motor programs in a straightforward way. The differentiated appearance of the pallium together with its complex but relatively short efferent system gives the impression that this is a versatile controlling system. Thus it appears that the striatum and pallium have properties in concordance with the postulated prerequisites for the sensorimotor and selection system (Sect. 1, Fig. 1A) (see also Sect. 5.1.3).

However, the efferents from the striatum complex are not restricted to motor centers, but also reach the dorsal thalamus and tectum, and the efferents from the pallium also reach targets which can influence motor performance directly, for example the habenula with its fasciculus retroflexus (Herrick 1948; Clairambault et al. 1986). The meaning of these, not postulated, pathways will be discussed more in Sects. 5.3 and 5.4.

5.1.5.2 Amygdaloid Complex

In addition to the above mentioned connections (Sect. 5.1.5.1) the pallium and striatum can interact via the amygdaloid complex.

In a separate study (Veenman et al. 1987, see also Sects. 1–4) the amygdaloid complex was defined according to topological, hodological, and immunohistochemical criteria, and considered a likely equivalent to the mammalian amygdala.

Clues to the role of the amygdaloid complex in telencephalic function can be based on its connectivity (Fig. 68). The amygdaloid complex itself is a major recipient for olfactory input. It has reciprocal connections with the rostral and lateral pallium, and it sends fibers to the caudal pallium. The injections in the lateral pallium showed a terminal field at the caudal aspect of the ventral telencephalon. It was concluded that this was adjacent to the amygdaloid complex, but it must be borne in mind that especially in this region in sagittal sections it is difficult to distinguish the neuropil of the amygdaloid complex from the neuropil of the striatum. The injection in the amygdaloid complex itself showed a reciprocal connectivity with the striatum, but mainly efferents; and a widespread efferentation to regions in more caudal brain parts, namely, the habenula, dorsal thalamus, preoptic region, ventral hypothalamus, and ventral brain stem.

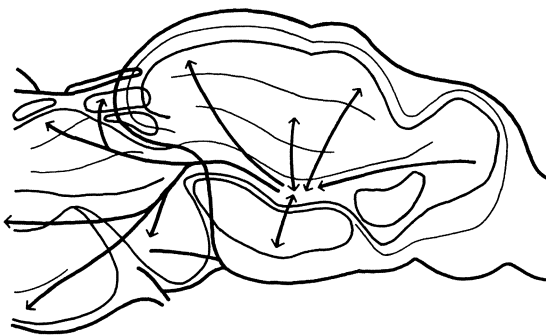


Fig. 68. *Afferents and efferents of the amygdaloid complex. For orientation see reconstructions of Fig. 8B, C*

Quite in contrast to the labeling of cells in the caudal pole of the telencephalon after the injection in the caudal hypothalamus, what was not anticipated since no anterograde labeling leaving the telencephalon was found from this area, the anticipated labeled cells in the amygdaloid complex did not appear. However, labeled cells do appear in the amygdaloid complex after the injection in the caudal mesencephalon, but not after injections in the tectum, which confirms the amygdaloid brain stem projection. And labeled cells appear in the amygdaloid complex after the injection in the septum and preoptic region, but not after injections in the medial pallium, which supports the amygdaloid hypothalamic projection.

Conclusions. Since it is situated between the pallium and striatum complex, the amygdaloid complex can be considered a system via which these two can communicate, or it can be considered a system which correlates the information processed in both and subsequently influences the regions in the lower brain stem as a controlling factor for determining the motor output of the telencephalon, with the olfactory input being the sensory dominator. The differentiated appearance of the amygdaloid complex is a property it shares with the mammalian amygdala (Nieuwenhuys et al. 1980) and suggests that it is subdivided into subsystems specialized for different functions. At present we can only speculate about the possible specific functions of the subdivisions of the amygdaloid complex.

5.1.5.3 Position of the Pallium in Relation to Other Prosencephalic Structures

So far we have described two multimodal input-output systems –the pallium and striatum complex– and an olfactory input-output system –the amygdaloid complex– intermediate between the first two. Still these systems do not cover the complete telencephalon, nor are all their interactive connections discussed. Another telencephalic system is the septum. The injection in the olfactory bulb labeled fibers entering the septum. Injections in the pallium showed reciprocal connections with the septum. The injection in the caudal hypothalamus showed labeled cells in the caudal septum.

So, the amygdaloid complex, medial pallium, and septum have in common that they receive olfactory input, project into the hypothalamus and through reciprocal connections are intimately related with the dorsal and lateral pallium. The injections in the hypothalamus showed that it projects into the anterior entopeduncular nucleus and into the striatum. In Fig. 69 the relationship of this system (pallium, septum, amygdaloid complex, and hypothalamus) with the striatum complex is shown.

Via these pathways several aspects resulting from the information processing in the pallium can be selectively projected into the hypothalamus. In the hypothalamus these aspects can be weighed. In fishes it was shown that the preoptic region is under the influence of different telencephalic regions (Hallowitz et al. 1971). “It was particularly interesting that preoptic units behaved as though they were activated by unique combinations of telencephalic input” (Pearson and Pearson 1976, p. 490). The outcome of this weighing can determine the output of the striatum complex, i.e., what behavior will be performed, simultaneously with a determination of the output of the hypophyseal system, i.e., the hormonal system

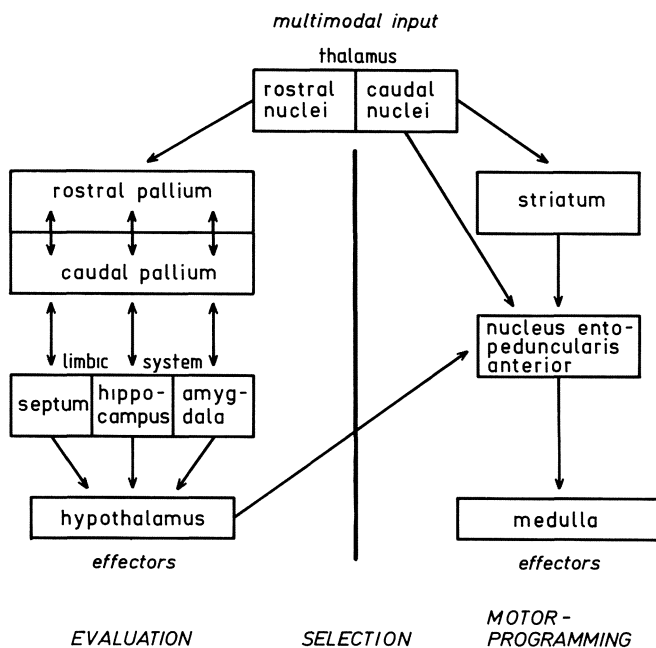


Fig. 69. Prosencephalic organization of *Xenopus laevis*. See also Figs. 1, 74. *Top: Multimodal input.* This is input to the thalamus plus olfactory input to the telencephalon. *Left:* The rostral thalamic nuclei project to the rostral third of the pallium, which is reciprocally connected with the rest of the pallium. The pallium has reciprocal connections with the septum, hippocampus (medial pallium), and amygdala (amygdaloid complex), which generally are reckoned to be part of the limbic system. The septum, hippocampus, and amygdala project to the hypothalamus (preoptic region, ventral and dorsal hypothalamus). *Bottom left: Effectors.* The hypothalamus plays a behavioral role by setting the humoral system and influencing medullar units. *Right:* The caudal thalamic nuclei project to the striatum complex (striatum and anterior entopeduncular nucleus). The hypothalamus projects into the striatum complex. The striatum projects to the medulla oblongata and to the cervical part of the medulla spinalis. *Bottom right: Effectors.* The neurons in the medulla play a behavioral role by driving the muscles and the endocrine system. *Bottom: Evaluation.* It is thought that via the pallium and its auxiliary structures the relevance of sensory information is determined. *Selection.* It is thought that via weighing of processed sensory information in the hypothalamus adequate output from the striatum complex is chosen. *Motor programming.* It is thought that complex sensory information is transformed via the striatum into neuronal activity which drives the motor centers in the medulla. Note: the diagram is simplified; several more interactions between the palliolimbic system and the striatum complex are possible

will operate in concordance with what behavior will be performed. As with much research on the hypothalamus, its role in reproductive processes and development is taken as a topic in *Xenopus* (Roy et al. 1986). However, via its output into the endocrine system and directly into the CNS the hypothalamus can, and probably does, influence all kinds of behavior.

The amygdaloid complex, medial pallium, and septum are not just considered as relay stations for the pallium to the hypothalamus, but also as three information-processing systems which coordinate their activities via the pallium. This entity – pallium with septum and amygdaloid complex – might have the capacity for internal control (Sect. 1, Fig. 1A). Output from the septum enters the

amygdaloid complex by way of the pallium and vice versa. The internal control could work in the following way: as an animal is subject to a multifaceted stimulus configuration, several components of the configuration can be laid down in the septum, medial pallium, and amygdaloid complex, (e.g., (a) social interactions, (b) spacial information, and (c) specific clues). When these components operate in congruence (e.g., (a) a female (b) within reach, without the appearance of (c) the shadow of a potential predator) the resulting neuronal activities can mutually amplify each other over the pallium. When these components do not operate in congruence they will mutually extinguish their resulting neuronal activity projecting into the pallium. These interactions can be the basis for a harmonized activity pattern spreading over the septum, pallium, and amygdaloid complex. Hereafter, the hypothalamus is a target for this harmonized activity and can be used as a gate for external selection (Sect. 1, Fig. 1A).

5.2 Midline Crossing Connections

5.2.1 Basis for Left-Right Interactions

A question was how the left and right halves of the forebrain can communicate. Therefore it was determined what kind of connections cross the midline.

5.2.2 Commissures

Commissural fibers are abundant between the halves of the telencephalon, diencephalon, and mesencephalon (Fig. 70).

The telencephalic commissural connections are mostly not so much between bilateral counterparts, but rather projections from one entity to entities neighboring the contralateral counterpart. Fibers mingle in their pathways to the contralateral hemisphere and care has to be taken in pinpointing the relations

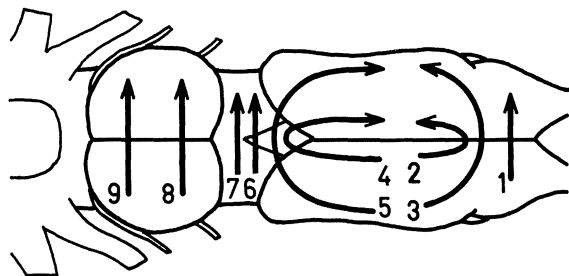


Fig. 70. *Commissural connections between the telencephalic halves: 1 over the dorsal surface of the olfactory bulbs, 2 over the rostral dorsal commissure between the rostral medial pallia, 3 over the rostral dorsal commissure between the lateral walls, 4 over the pallial commissure between the medial walls, and 5 over the habenular commissure and the anterior commissure between the lateral walls. Commissural connections between the di- and mesencephalic halves: 6 from the thalamus, 7 from the hypothalamus, 8 from the optic tectum, and 9 from the torus semicircularis*

between sources and targets. The quantitative differences seen make it possible to state that all telencephalic entities, except perhaps the striatum, project to different regions in the contralateral hemisphere. That the dorsal pallium does not communicate directly with contralateral brain parts might support the idea that this area serves mainly as a communicator between the septum, medial pallium, and amygdaloid complex. In the bullfrog, commissural connections between the different parts of the striatum complex are determined (Wilczynski and Northcutt 1983a, b). Also the thalamus and hypothalamus appear to project to widespread areas of the contralateral di- and mesencephalon. These commissures can also be seen with Gallyas impregnations (see Fig. 3). The optic tectum and torus semicircularis project to their contralateral counterparts.

Conclusion. Commissural connections form one substrate for interactions between the two brain halves in *Xenopus laevis*.

5.2.3 Bilateral Projections

No pure contralateral ascending or descending projections from tel-, di, or mesencephalic regions were observed; contralaterality was always part of more or less bilateral symmetry within ascending and descending projections (Figs. 71, 72).

Not explicitly indicated are bilateral projections from the caudal pallial areas to the hypothalamus, and from the raphe nuclei and the hypothalamus into the telencephalon. The habenulas are possibly also a source of bilateral projections into the telencephalon.

Notably absent are contralateral thalamopallial and thalamostriatal projections. We also have no indication for contralateral striatal projections into diencephalic and mesencephalic areas, and no evidence for telencephalic contralateral projections beyond that. Ten Donkelaar et al. (1981) also only found an ipsilateral striatal projection into the spinal cord. In *Urodeles* a clear bilateral projection from the thalamus to the rostral pallium can be determined (Wicht and Himstedt, 1986).

Conclusion. Bilateral projection systems also play a role in left-right interactions in *Xenopus laevis* brain.

5.2.4 Conclusions

Both commissures and bilateral projections can form the basis for left-right interactions in *Xenopus laevis* forebrain. But especially the thalamic input to the telencephalon and the telencephalic output to the spinal cord are unilateral; so, here telencephalic and diencephalic commissures play a major part in bilateral synchronization.

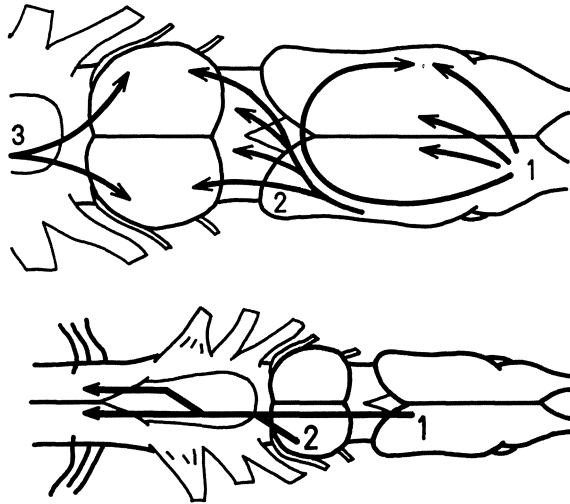


Fig. 71. (top) *Bilateral projections:* 1 The olfactory bulb projects to the rostral medial septa, and along the ipsilateral lateral wall, over the habenular and anterior commissures, to the contralateral amygdaloid complex. 2 The amygdaloid complex projects into the di- and mesencephalon, 3 Brain-stem neurons project into the caudal mesencephalon

Fig. 72. (bottom) *Bilateral projections:* 1 The preoptic region (perhaps also septum) and 2 the caudal mesencephalon (possibly torus semicircularis) project into the spinal cord.

5.3 Function of the Pallium

5.3.1 Mechanism of Association

How is an animal able to choose from different behaviors? Like changing preferences in particular situations after the simultaneous encounter of stimuli from previous nonrelated situations, as described by Farr and Savage (1978).

In Sect.1 it is mentioned that the telencephalon plays a major role in making decisions in new situations. The way the extrinsic and intrinsic connections of the pallium are organized led to suggestions about how this telencephalic function of choosing the right behavior is performed. The multimodal input to the pallium implies that the pallium has access to any information (Fig. 1A) the animal can get about its outside world and perhaps also about its milieu interieur.

The original repertoire of behaviors to information from the outside world consists of unconditioned reflexes. This behavior can probably be performed without the pallium. But still, when this behavior occurs, an activity pattern can be generated in the pallium over different channels. However, once this activity pattern in the pallium is established, it will be directly correlated with this behavior, which means that when this activity pattern occurs it in turn can again determine the original behavior via the pallial output channels. In this way, any behavior can be related to an activity pattern in the pallium. When another stimulus appears simultaneously with the stimulus for the unconditioned reflex, two patterns of activity will run through the pallium. When the new stimulus in itself does not cause an unconditioned reflex, its resulting activity pattern in the

pallium will not be deterministic in any way. However, the activity pattern from the unconditioned reflex stimulus and from the new stimulus will interfere.

We think that the interference runs the following course: When the two activity patterns hit the same unit, the first will facilitate the transmission of the second (Fig. 73). Several mechanisms can be imagined which suppress transmissions of nonmatching activity, for example center-surround inhibition which is specific, or a general inhibition for newly active terminals causing a high threshold for transmission. In this concept, activity in and from neighboring synapses will be amplified and activity in and from nonneighboring synapses will be inhibited. This interference of the two activity patterns will finally result in the second pattern becoming identical to the first. Then the activity pattern resulting from the second stimulus can cause the original behavior.

A prerequisite for coupling different sensory inputs is that the original and new stimulus occur simultaneously often enough to allow the resulting activity patterns to match. The circular sequences of connections in the pallium can form a substrate for stabilizing matching activity patterns, since a circular information flow allows for repetitious events in synapses. And, since any pairing of different stimulus combinations should be possible, a network where any information can enter and subsequently can run free is also necessary. The pallium fulfils these conditions, it receives multimodal input, and it builds a network consisting of many reciprocal connections. A network consisting of reciprocal connections processes information in a nonpredictable way (Johannesma et al. 1986). This network spreading through the pallium makes it likely that activity starting at one point can reach any point in this network. This makes the pallium a likely substrate for any combination of any information (Fig. 1A).

When indeed a new stimulus can cause an activity pattern identical to that following from a previous stimulus, then this is a possible basis for memory (accessibility for past events). When such activity reenters the system via a loop, a past sensory image can be restructured. Reentrant systems are considered to be the basis for consciousness (Edelman 1978). Here, however, we only talk about choosing behaviors, consciously or not.

5.3.2 Synaptic Triad

The simplest unit where above mentioned interactions can occur is the synaptic triad. Several interactions in a synaptic triad can be imagined (Fig. 73). As can be expected, our electron microscopy showed labeled and unlabeled fibers within the same bundles, and labeled and unlabeled terminals adjacent to the same dendritic elements. This means that probably afferents from different sources synapse on the same postsynaptic element, which is needed for the association of previously unrelated events.

The reason for assuming that synaptic triads play a role in the modulation of synaptic transmission is, firstly, that they form a basis for a close apposition of different terminals and dendritic elements and, secondly, that they are common in vertebrate CNS (Ribeiro-da-Silva et al. 1985; So et al. 1985; Moriizumi et al. 1987).

For associative learning, spatial and temporal convergence of synaptic activity is necessary (Kandel 1985). Long-term modification of transmission efficacy at synapses is the cellular basis for memory and learning (Kano and Kato 1987). The

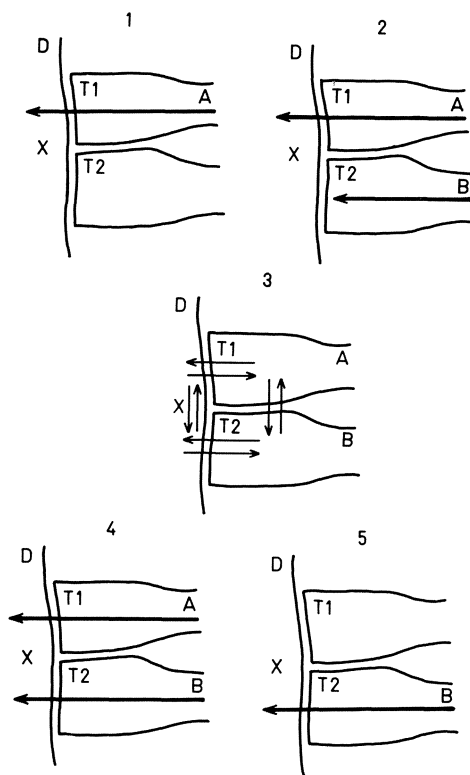


Fig. 73. Postulated interactions in a synaptic triad. 1 Activity A (presynaptic potential) in the terminal element T1 results in activity X (postsynaptic potential) in the dendritic element D. A and X take part in a pallial activity pattern related to, for example, an unconditioned reflex. In this activity pattern the terminal element T2 is silent. 2 Simultaneously with the activity pattern described in diagram 1 appears a second stimulus. This stimulus causes activity in T2 but this activity is not strong enough to drive a postsynaptic potential in D. 3 In the triad of simultaneous active terminal elements T1 and T2 and dendritic element D several interactions can take place. T1 can, through its activity like ion and transmitter release, stimulate ion release of T2 and accelerate the production and/or release of neurotransmitters in T2. The activity in D from T1, together with T2's activity, can cause a multiplication of neurotransmitter receptors and/or ion channels in the membrane of D opposing T2. Finally, enough ion channels are present in T2 and in D opposing T2, and enough neurotransmitter is produced and released from T2 together with the presence of enough receptors in D opposing T2. The summation of these positive feedback and feedforward loops then results in a sufficiently potent presynaptic potential in T2 together with a sufficiently receptive postsynaptic membrane in D to allow a presynaptic potential in T2 to cause a postsynaptic potential in D. 4 Both the activity A and B in T1 and T2 result in activity X in D. 5 As a result of the foregoing, activity B in T2 by itself can cause activity X in D also when T1 is silent. As A and X took part in a pallial activity pattern related to an unconditioned reflex, B and X take part in an activity pattern related to a conditioned reflex

neuropeptide arginine vasotocin modulates synaptic transmission in *Aplysia* (Goldberg et al. 1987) and can be found in amphibian hypothalamus, pallium, amygdaloid complex, and striatum (Zoeller and Moore 1986). Apart from extracellular neuropeptide receptor interactions (Fossier et al. 1987; Kaulen et al. 1985), protein structures can also interact within the framework of the cellular wall (Ijzerman and Timmerman 1986) and external events can influence the intracellular events in neurons (Lach et al. 1984; Fukuda et al. 1987).

The number of synapses in vertebrate CNS structures remains fairly constant throughout adult life (Bertoni-Freddari et al. 1985, 1986; Huttenlocher and de Courten 1987), hinting at the possibility that learning in adults takes place through the modification of existing synapses. Bear et al. (1987) gave a review and a hypothesis for synaptic modification which is very useful for the understanding of cellular processes underlying associative learning. They emphasize that postsynaptic and excitatory presynaptic activity have to occur simultaneously for the modulation of synaptic efficacy. They take as a condition that the presynaptic element a priori must be able to activate the postsynaptic element; this might be so, but when one includes converging synapses this is not inductively necessary (Fig. 73). Disinhibiting networks have long been recognized as a potential substrate underlying the process of learning (Hirai 1980). Others emphasize the involvement of inhibition in the modulation of synaptic efficacy (Stelzer et al. 1987; Kano and Kato 1987). Electrophysiological research indicates that it is possible that synaptic elements have to be active before they can be inhibited (Veenman 1984; Gottschaldt et al. 1983), and facilitated before they can be excited (Amassian et al. 1987).

Thus, the synaptic interactions supposedly needed for the transmission of matching activity patterns as mentioned in Fig. 73 do take place in the CNS. The postulation that association takes place through pre- *and* postsynaptic changes at converging nerve endings needs further electrophysiological testing and determinations of processes at a molecular biological level.

5.3.3 Pallial-Striatal Interactions

The efferents from the striatum complex to the dorsal thalamic nuclei, which form relays to the pallium, possibly allow striatal output to determine activity patterns in the pallium. In this way the pallial activity can be correlated with the striatal activity. The striatal output probably plays a role in the determination of the activity of the motor centers in the medulla (Hutchison and Poynton 1963/1964; ten Donkelaar et al. 1981; K.E. Zittlau personal communication). Activity patterns in the pallium can probably determine the output of the striatum complex via its efferents into the amygdaloid complex, medial pallium, and septum, which in turn project into the hypothalamus from where projections run into the striatum complex (Fig. 69). We think that the striatum complex and pallium interfere in each other's input and output pathways in a way similar to that proposed for the intrapallial interactions, i.e., simultaneously active and conjunct terminals will be functionally coupled.

One can imagine the following overall sequence for pallial-striatal interactions (see Sect.1, Fig. 1A; Fig. 69): sensory input (accessibility for present events) determines the output of the striatum complex (sensorimotor system); this output determines the thalamic input to, and thereby activity in, the pallium (accessibility for past events). Via its direct and indirect access to the striatum complex the pallial output will become positively related to the sensory input to the striatum complex and to the striatal output (a prerequisite for external selection). New information can be matched with old information in the pallium (any combination). Septo-pallio-amygdaloid interactions can function to weed out nonrelevant

activity patterns and stabilize adequate activity patterns (internal control). Directly, and via septal, amygdaloid, and hypothalamic channels, the pallial activity pattern resulting from the new information can select the same output from the striatum complex as did the old information (external selection). When this has happened often enough the new information by itself can determine the output of the striatum complex (conditioned reflex).

In short: the striatum complex determines the input of the pallium, and the pallium associates different kinds of information and determines the input *and* the output of striatum complex.

5.3.4 Conclusions and Implications

The anatomical data obtained indicate that the requirements for the selection system mentioned in the Sect. 1 are fulfilled in *Xenopus laevis* forebrain, namely, the accessibility for present and past events (any information), the capacity to process this information in a nondetermined way (any combination) with the possibility of ordering (internal control), and the access (external selection) to motor-affecting systems (the sensorimotor system).

From the foregoing one would expect that lesions of the pallium impair associative and reversal learning and cause animals to be slow to react to unknown stimuli which remain below the fear-eliciting level, since an important possibility to link new information with old patterns is lost. Lesions of the anterior entopeduncular nucleus should be even more dramatic, since then input, output, and interaction pathways of the selection system and the sensorimotor system are interrupted.

The described concept is developed at least partly a posteriori to effects found after telencephalic lesions and ablations. One control to see whether the described pattern indeed is needed for telencephalic function is to determine whether such a pattern also appears in other vertebrates. This is done in the following sections.

5.4 Comparisons with Other Vertebrates

5.4.1 Comparison with Other Amphibians

Supportive and additional anatomical and physiological information from other amphibians for the presented model is abundant. In Table 1 the data obtained with *Xenopus laevis* are compared with similar data obtained with other amphibians. These data are in congruence with the diagram of Fig. 69. Two different thalamo-telencephalic pathways reach the pallium and striatum. The striatum and pallium are parts of different systems. The striatum projects into the medulla. The pallium and septum project into the hypothalamus. The hypothalamus projects back into the telencephalon and plays an important role in determining behavior. Telencephalic ablations impair reactivity to new situations and stimuli. It is only a pity that little work other than ours has been done on the intrinsic and efferent connections of the amphibian pallium.

At this point it should be mentioned that the hypothalamus appears to be a conservative structure, i.e., that many characteristics are shared throughout the

Table 1. Comparison of data obtained from *Xenopus laevis* with data obtained from other amphibians

<i>Xenopus laevis</i>	<i>Rana pipiens</i>	<i>Rana catesbeiana</i>	<i>Rana ridibunda</i> <i>Rana temporaria</i>	<i>Bufo bufo</i> <i>Bufo japonicus</i> <i>Bufo marinus</i>	<i>Urodeles</i>
Dual multimodal pathway to the pallium and the striatum	Wilczynski and Northcutt 1977 Kicliter 1979 Comer and Grobstein 1981 Hall and Feng 1987	Neary and Northcutt 1983 Wilczynski and Northcutt 1983a Neary 1984 Neary and Wilczynski 1986		Carlile and Pettigrew 1984 Pettigrew and Carlile 1984	Finkenstädt et al. 1983 Wicht and Himstedt 1986
Striatal output to the medulla	Kicliter 1979	Wilczynski and Northcutt 1983b			Kokoros and Northcutt 1977
Intrinsic pallial connections					Herrick 1927, 1948
Pallioseptal connections				Jokura and Urano 1986	
Pallioamygdaloid connections		Wilczynski and Northcutt 1983a (dorsal striatum is acv + acd)			
(a) Pallial, (b) septal, and (c) amygdaloid output to the hypothalamus	Kicliter 1979 Chang and Dellman 1984 (preoptic region to infundibulum)	McCreery 1984 (a, b)		Jokura and Urano 1985b	

Hypothalamo-striatal connections	Kiehlter 1979 Lechago et al. 1984	Sotowska-Brochocka 1983 Benyamina et al. 1986 Vullings and Diederer 1986	
Hypothalamic involvement in behavior	Schmidt 1976	Crim 1984, 1985 Whalen and Crim 1985	Miyakawa et al. 1984 Takami and Urano 1984 Fasolo et al. 1984 Rodicio and Anadon 1984, Mazzi et al. 1985, Moore and Zoeller 1985, Vellano et al. 1985
Telencephalic ablation results in: "Lack of responsiveness"		Stehouwer 1987 "Lack of the typical behavior elicited by unfamiliar situations"	Laming et al. 1984 "Effects on the processing of sensory information in the tectum"

different vertebrate classes (Fuller and Hemrick-Luecke 1983; Sano et al. 1983; Shimizu et al. 1983; Yui 1983; Hall and Chadwick 1984; Crawshaw et al. 1985; Tonon et al. 1985; Zoeller and Moore 1985, 1986; Licht 1986). Most often the hypothalamic involvement in reproduction and development is stressed. However, the hypothalamus is also involved in the day-to-day cueing of the body of an organism to its environment; this includes behavior, and then again cueing the bodily state to the behavior (Luiten et al. 1987; Reis and Ledoux 1987).

Our opinion on the position of the amygdala (Sects. 1–4) deviates from what is normally believed. Herrick in his book on the brain of *Ambystoma* (1948) determined the prevailing opinion on the position of the amygdala. He, however, did not show the data which he claimed that substantiated his idea. P. Clairambault agrees with our opinion about the position and extension of the amygdala in amphibians (personal communication). Other workers have opinions similar to ours for the amygdala in lungfish (Schnitzlein and Crosby 1967), and it is also mentioned that one could include the reptilian nucleus of the lateral olfactory tract in the amygdaloid complex (Pearson and Pearson 1976, p. 527).

Not included in our scheme is another important output system for the telencephalon in amphibians, namely, the habenula with its tractus retroflexus (Herrick 1948; Kemali and Guglielmotti 1984; Clairambault et al. 1986).

5.4.2 Comparison with Fishes

An immunohistochemical study on the telencephalon of the African lungfish (Reiner and Northcutt 1987) shows that it is remarkably similar to the amphibian telencephalon. Cross sections through the central telencephalon of lungfish are indistinguishable from cross sections at the same location in amphibians. Our immunohistochemical work shows distributions of opioids, substance P, and serotonin in *Xenopus laevis* telencephalon which are remarkably similar to the distributions in the African lungfish. On the basis of topology, morphology, and immunohistochemistry the following homologies can be assumed: intercalated nucleus is amygdaloid complex, pars ventralis of medial pallium is septum, subpallium is striatum, and the rest is pallium. As mentioned, Schnitzlein and Crosby (1967) also consider the amygdala to be a longitudinal zone in the lungfish telencephalon.

Research done on cartilaginous and ray-finned fish telencephalon gives some hints for possible analogies considering connections (compare with Fig. 69). Ebbesson (1980) determined ascending sensory systems entering the telencephalon in cartilaginous fishes. Smeets and Boord (1985) determined connections between the telencephalon and hypothalamus for a cartilaginous fish. Telencephalohypothalamic connections in ray-finned fishes are recognized (Nieuwenhuys 1963; Shiga et al. 1985). In the carp different diencephalotelencephalic pathways can be seen (Murakami et al. 1986b). In the goldfish there is an acetylcholinergic telencephalo-habenulo-interpeduncular system (Villani et al. 1987) but no telencephalospinal pathway was determined (Prasada et al. 1987).

A thorough investigation into the intrinsic and extrinsic connections of the telencephalon of a bony fish, *Sebasticus marmoratus*, was performed by Murakami et al. (1983, 1986a, b) and Ito et al. (1986). (Note: We use their abbreviations. The

abbreviations refer to relative positions: *d*, dorsal; *v*, ventral; *c*, central; *m*, medial; *l*, lateral; *p*, posterior; *s*, supracommissural.) The following comparisons can be made: The telencephalon receives multimodal input via different pathways; Dd and Dm receive afferents from the thalamic nucleus glomerulosis, Dc, Dd, Dm, and Vs from the thalamic nucleus ventromedialis; together with their relative positions this makes it possible to consider Dd and Dm as pallial regions, and Dc and Vs as striatal regions; the medial structures vDM, Vd, Vs, Vp have septal properties (midline structures having olfactory input and output to the hypothalamus); the lateral and central structures Dl, Dp, and Dc combine amygdaloid and striatal properties (ventrolateral position and olfactory input, hypothalamic output, and other descending fiber systems). The dorsal structures dDm and Dd have medial pallial properties (dorsal position and output to the hypothalamus). Dc again also has dorsal pallial properties in that it is strategically positioned as a relay in between septal, medial pallial, and amygdaloid equivalents.

Conclusion. Although the extrinsic and intrinsic telencephalic connections of *Sebasticus marmoratus* and *Xenopus laevis* possess similar properties, their telencephalic subdivisions cannot be compared in one-to-one equations. The prosencephalic structural and connective elements encountered in *Xenopus laevis* appear in fishes but in a different ordering. So, it seems that not so much the arrangements of the components is essential for telencephalic function, but rather the components themselves. These components are: a dual input-output system and a system where different entities do not communicate directly but via an intermediate structure. Further it becomes clear that homology is not the tool to determine homologies between crossopterigians and actinopterigians; for this, developmental studies should be carried out.

5.4.3 Comparison with Reptiles

In reptiles it is easier to discern a pattern equivalent to that of amphibians (Fig. 69) than in fishes. Septo-, amygdalo-, and pallio-hypothalamic connections exist (Stoll and Hoogland 1984; Stoll et al. 1983; Martinez-Garcia et al. 1986; Smeets et al. 1986) as well as ascending sensory pathways to pallial derivatives—cortex and dorsal ventricular ridge (Pritz 1980; Pritz and Northcutt 1980; Bruce and Buttler 1984a, b; Belekova et al. 1985; Ouimet et al. 1985). The paleostriatum is an important output system of the telencephalon (Reiner et al. 1980, 1984a; Brauth et al. 1983) and also receives thalamic input (Brauth and Kitt 1980; Pritz and Northcutt 1980). There are hypothalamic projections into the telencephalon (Bruce and Buttler 1984a, b). A reckless postulation might be that the enkephalinergic and substance P-ergic fiber systems found in the telencephalon (Brauth et al. 1983; Reiner 1987; Russchen et al. 1987b) find their origin in the hypothalamus.

The reptilian forebrain deserves more investigation to get a better insight into the intrinsic pallial connections, hypothalamic efferents, striatal afferents, and parameters for the amygdaloid and pallial equivalents. The different groups of reptiles take intermediate positions between amphibians and the radiations of birds and mammals in regard to the level of telencephalic organization (Ariens-Kappers et al. 1936; Kuhlenbeck 1967; 1978; Pearson and Pearson 1976, Bruce and

Butler 1984a, b; Reiner et al. 1984a; Kriegstein et al. 1986). So, more knowledge about this class can give a better understanding of the evolutionary pathways of telencephalic development.

5.4.4 Comparison with Birds

Research performed on birds originally led to the postulation that the telencephalon can be differentiated into a sensorimotor system and a decision-making system (Veenman and Gottschaldt 1986) (see Sect. 1). Pigeons were subject to research projects covering much of the forebrain, which makes it possible to assemble a pattern as was seen in amphibians (Fig. 69). The archistriatum (amygdala) and the dorsal hyperstriatum (medial pallium) project into the hypothalamus (Zeier and Karten 1971; Casini et al. 1986). The neostriatum and ventral hyperstriatum form a relay between the archistriatum and the dorsal hyperstriatum (Ritchie 1979; Wild et al. 1985). The paleostriatum complex forms an input-output system separate from the neostriatum and its related structures (Wallenberg 1903; Karten and Dubbeldam 1973; Wild et al. 1985; Berk 1987). The hypothalamus projects back into several telencephalic structures (Berk and Hawkin 1985) (own preliminary results with fluorogold injections in the paleostriatum complex and the caudal neostriatum of the pigeon are in concordance with this). Work on other birds suggests that this pattern can be generalized (Bradley et al. 1985; Veenman and Gottschaldt 1986; Dubbeldam and Visser 1987). So, the paleostriatum complex would be the sensorimotor system, while the neostriatal, hyperstriatal, archistriatal and probably septal areas would be part of the selection system.

5.4.5 Comparison with Mammals

Although a mass of anatomical, physiological, and behavioral data are available from mammals, at present no overall scheme has been given which involves all of the telencephalic structures and explains the function of the telencephalon as a whole, while fitting in the subdivisions and their subfunctions. Our questions were whether the scheme determined for amphibians (Fig. 69) fits the telencephalic organization of mammals, and whether the behavioral and physiological data found for mammals fit with the concept developed from our work on *Anser anser* (Veenman and Gottschaldt 1986) and *Xenopus laevis* (presented in this volume).

On the basis of different reviews (Creutzfeldt 1983; Carpenter 1976; Grofova 1979; Webster 1979; Nieuwenhuys et al. 1980; Heimer 1983), a scheme comparable to that of amphibians could be devised (Fig. 74). Reciprocal connections are not taken into account to simplify the mammalian scheme. Direct cortical interconnections are excluded since the cortex does not function without external input (Creutzfeldt 1983). In the following sections recent works highlighting aspects of the scheme and others giving new data are summarized.

Apart from receiving unspecific thalamic input and frontal lobe input, and projecting back into the cortex via the thalamus, the corpus striatum receives input from specific thalamic nuclei (Takada et al. 1985; Smith and Parent 1986) and

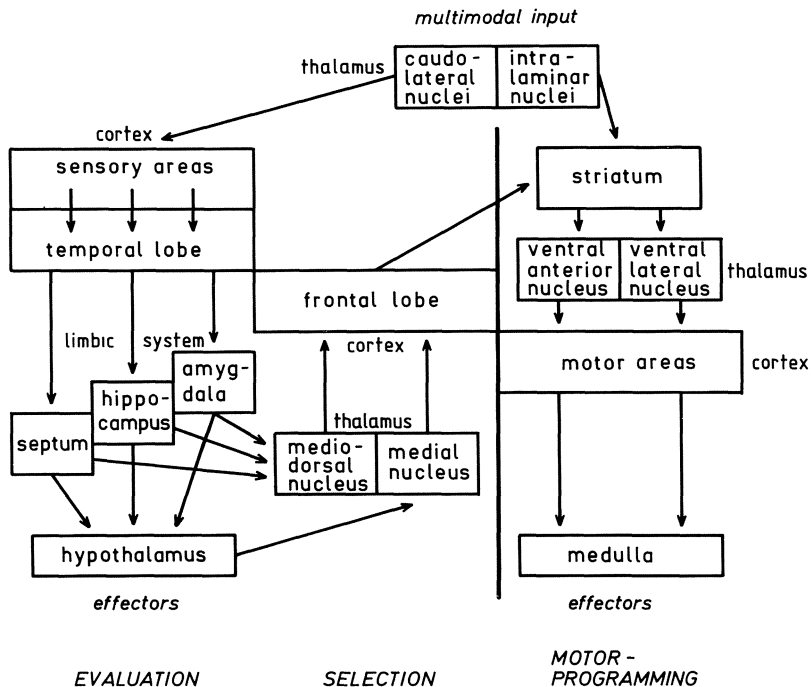


Fig. 74. Prosencephalic organization in mammals. See also Figs. 1, 69. *Top: Multimodal input.* This is input to the thalamus plus olfactory input to the telencephalon. *Left: The specific thalamic nuclei* project to the sensory areas of the cortex, which are connected with temporal lobe. The temporal lobe is connected with the septum, hippocampus, and amygdala, which are generally reckoned to be part of the limbic system. The septum, hippocampus, and amygdala project to the hypothalamus and the mediodorsal thalamic nucleus. The hypothalamus projects to the medial thalamic nucleus. The thalamic mediodorsal and medial nuclei project to the frontal lobe. *Bottom left: Effectors.* The hypothalamus plays a role in behavior by setting the humoral system and influencing medullar units. *Right: The unspecific thalamic nuclei* project into the striatum (corpus striatum). The frontal lobe projects into the striatum. The striatum projects into ventral thalamic nuclei. The ventral thalamic nuclei project into the motor cortex. The motor cortex projects into the medulla. *Bottom right: Effectors.* The neurons in the medulla play a behavioral role by driving the muscles and the endocrine system. *Bottom: Evaluation.* It is thought that via the sensory and association cortices and their limbic follow-up structures the relevance of sensory information is determined. *Selection.* It is thought that via weighing of processed sensory information in the hypothalamus and the thalamofrontal lobe system adequate output from the striatum is chosen. *Motor programming.* It is thought that the striatum transforms sensory information into neuronal activity driving the motor centers in the medulla. The thalamomotor cortical system is relayed after the striatum to process the commands from the striatum for refined movements. Note: The diagram is simplified, reciprocity is omitted, and several more interactions between the corticolimbic system and striatum are possible

projects farther into the brain stem than into thalamic and basal ganglionic nuclei (Harnois and Fillion 1982). Thus, the corpus striatum in mammals can also be considered a sensorimotor system, like the striatum complex in amphibians (compare Fig. 74 with Fig. 69).

The projections from specific and nonspecific thalamic nuclei into primary, secondary, and associational sensory cortices are well known (Nieuwenhuys et al. 1980; Creutzfeldt 1983; Heimer 1983), as well as the cortical connections with

the temporal lobe including the parahippocampal cortex (Campbell et al. 1984; Markowitsch et al. 1985; Room et al. 1985; Friedman et al. 1986; van Groen and Lopez da Silva 1986; Room and Groenewegen 1986a, b, Witter and Groenewegen 1986; Weller and Kaas 1987; Yasui et al. 1987). Via their connections these cortices are a relay to, and a switchboard in between, the septum, hippocampus, and amygdala (Fig. 74), a situation as described for *Xenopus laevis* pallium in relation to the septum, medial pallium and amygdaloid complex (Fig. 69). Thus, both the striatal and pallial systems of mammals and amphibians are organized in a similar fashion. Interesting in this respect is that in mammals prenatally the sensory cortices are less parceled than in adults (Ben Hamida 1985; Clarke and Innocenti 1986), i.e., more like the amphibian rostral pallium.

Problems were, firstly, that the mammalian motor cortex and frontal lobe do not fit readily into the scheme drawn for amphibians, and, secondly, that in mammals no tracer studies show a projection from the hypothalamus to the striatum. These three points are discussed as follows (compare also Fig. 74 with Fig. 69):

1. Going from the striatum, the motor cortex can be considered a downstream relay specialized for fast reactions to complex stimuli and for fine movements (Wiesendanger 1969; Porter 1985; Gould et al. 1986; Amassian et al. 1987). Apart from this, not all movements need cortical involvement, and the pyramidal system also plays its role via sensory systems (Wiesendanger 1969; Nieuwenhuys et al. 1980; Infante et al. 1983; He and Wu 1985; Sciabassi et al. 1986; Rampin and Morain 1987). And, the pyramidal and extrapyramidal systems have similar effects on alpha and gamma motoneurons (Wiesendanger 1969). So, the pyramidal and extrapyramidal systems are rather parts of one system than two different systems, and their combination gives an appearance similar to that of the connectivity of amphibian striatum complex.

2. The frontal lobe can be considered to be a relay in between the striatum and the "sensory" cortices. It is involved in a loop which runs from the "sensory" cortices, via the septum, hippocampus, and amygdala (see above) through the mediodorsal thalamic nucleus (Creutzfeldt 1983; van Eden 1986; Russchen et al. 1987a) to the frontal lobe, which projects into the striatum (Arqueros et al. 1985; Dauth et al. 1985; Haug et al. 1984; Peinado and Mora 1986; Walker and Fonnum 1983). An additional pathway runs via the hypothalamus and medial thalamic nucleus (Nieuwenhuys et al. 1980; Creutzfeldt 1983). So, in mammals the frontal lobe forms a link between the limbic and striatal system, whereas in *Xenopus laevis* the hypothalamus projects directly into the striatum complex.

3. Data which allow a closer anatomical match between the amphibian and mammalian prosencephalon have become available recently. The preoptic medial basal forebrain region in mammals seems to be organized like the amphibian preoptic-hypothalamic region. The nucleus basalis of Meynert, diagonal band of Broca, substantia innominata, and "limbic" ventral pallidum are connected with cortical, hypothalamic, and striatal regions in a way similar to that of the amphibian preoptic region (Pearson et al. 1984; Haber et al. 1985; Russchen et al. 1985; Irle and Markowitsch 1986; Room and Groenewegen 1986b; Mogenson et al. 1987). Also a projection from the hypothalamus to the striatum in mammals has been made likely, immunohistochemical work reviewed by Nieuwenhuys (1985) shows a histamine projection from the caudal hypothalamus into the

caudate/putamen, and similar neurotensin and somatostatin pathways can be postulated.

Thus, a pallio-hypothalamo-striatal pathway appears to exist in mammals as well as in amphibians. In addition, both in *Xenopus laevis* and in mammals an amygdaloid striatal pathway exists (Royce and Laine 1984; Turner and Zimmer 1984; Jayaraman 1985). Also, the corticostriatal connections in mammals do have a counterpart in *Xenopus laevis*, namely, in the projection from the rostral dorsal pallium into the striatum. The latter means that the cortico-limbo-thalamo-cortico-striatal pathway in mammals is paralleled in *Xenopus laevis* in the pathway from the pallium to the amygdaloid complex, and then via the rostral mediodorsal thalamic region to the rostral pallium, which projects into the striatum. Conclusion: all the pathways connecting the pallium with the striatum complex seen in *Xenopus laevis* were also determined in mammals, and vice versa.

A few important mammalian telencephalic areas are not included in the scheme of Fig. 74: the claustrum and the gyrus cinguli. The claustrum, like the adjacent amygdala, is connected with widespread areas of the cerebral cortex (Sripanidkulchai et al. 1984; Turner and Zimmer 1984; Guldin et al. 1986; Sloniewski et al. 1986). The gyrus cinguli is closely related to adjacent cortical regions and to the hippocampus (Cavada and Reinoso-Suarez 1985; Vogt et al. 1986) and part of a well-known limbic feedback loop (Nieuwenhuys et al. 1980; Heimer 1983). We would like to consider the claustrum and the gyrus cinguli as extensions of the amygdala and hippocampus, respectively.

Behavioral data observed after telencephalic lesions are in concordance with the scheme (Fig. 74) given for mammals. On the one hand the cortex can be considered as one entity with overlapping functions of motor, sensory, and associational cortices; on the other hand lesions in different places of the brain permit differentiation on the basis of function (Poeck 1982; Creutzfeldt 1983; Heimer 1983). Damage to the sensory areas and the associational parietal lobe results in impairments in dealing with sensory information as such (sensory deficits, agnosia). Damage to the temporal lobe, including the hippocampus and amygdala, results in problems fitting information into a context (Klüver-Bucy syndrome). Damage to the frontal lobe impairs the ability to choose a behavior (frontal lobectomy syndromes). Infliction of the striatum impairs the initiation of motor programs (basal ganglia syndromes). Damage to the motor cortex impairs motor performance (deficits in refined digital movements and fast reactions). The subcortical connections explain why separation of cortical fields does not have so much effect (Creutzfeldt 1983). As a whole the scheme explains the fact that a "limbic" phenomenon – depression – influences "motor" symptoms – tremors – of the parkinsonian basal ganglia syndrome (Rosse and Peters 1986/1987), namely, by connecting the limbic system via the hypothalamus and thalamus with the frontal lobe, which has efferents to the striatum. An alternative would be a more direct connection, namely, limbic system–hypothalamus–basal ganglia, as in amphibians (Fig. 69).

Restricted ablations of different cortical areas have different effects. Anterior temporal lobectomy impairs cognition in humans (Ivnik et al. 1987). In *Macaca mulata* ablation of only rhinal cortex or in combination with hippocampal ablation gives a recognition deficit as severe as with only a hippocampal ablation. Combining rhinal cortex ablation with amygdala ablation gives a recognition deficit as

severe as a combined amygdala–hippocampus ablation (Murray and Mishkin 1986). This indicates that amygdala–cortex–hippocampus interactions play an important role in recognition. The inferior temporal cortex is important for pattern discrimination (Optican and Richmond 1987). The neocortical polysensory areas may be necessary for generating new visual representations during learning a performance which requires cross-modal recognition of unfamiliar objects, whereas the amygdala seems to be involved in the cross-modal recognition of familiar objects (Streicher and Ettlinger 1987). In rats damage to the sensory association zone results in a deficit on a task requiring the association of two spatially discontinuous cues (Kolb and Walkey 1987). These behavioral effects related to the ability to associate occur in regions anatomically related to the temporal pole: hippocampus, amygdala, and associational cortices, and fit the role postulated for the caudal pallium in *Xenopus* (Sects. 5.1.5.3, 5.3.1).

In the same way the well-known primary sensory cortices (Nieuwenhuys et al. 1980; Creutzfeldt 1983; Heimer 1983) can be related to the input system of the rostral pallium in *Xenopus*. For the mammalian motor cortex no amphibian pallial counterpart is at hand.

Reis and Ledoux (1987) suggest that, by way of the amygdala–hypothalamus–brain stem and spinal cord, blood pressure and blood flow are coupled to behavior. In the rat, lesions of the mediodorsal nucleus and caudate/putamen cause a decrease in self-stimulation of the medial frontal cortex and lesion of the caudate/putamen causes a decrease in spontaneous motor activity. These effects are temporal (Vives et al. 1986). Similarly, unilateral ablations of the frontal cortex, rostral striatum, nucleus accumbens, septal area, and olfactory tubercle temporarily decrease ipsilateral hypothalamic self-stimulation (Colle and Wise 1987). The effects as such can be expected from lesions of systems involved in the selection of behavior and more directly in motor performance. That they are only temporal implies that there are parallel pathways, for example, the peripeduncular area in the rat is a relay between sensory, hypothalamic, and motor areas (Arnault and Roger 1987).

In a freely moving human, bilateral lesion of the basal medial frontal lobe had the following effects: inability to make a decision (choose a restaurant), to get something done (dressed), and to cease unsatisfactory habits (keeping a large number of nonfunctioning televisions), contrasting with outstanding performances on recognizing complex relationships in, for example, moral, ethical, and political topics (Esslinger and Damasio 1985). The structural concept predicts that interruption of the connection between the selection system and the sensorimotor system will impair decision making but not the associational processes leading to decision making. Rats with medial frontal lobe lesions perform sporadically and are impaired in reversal learning but not in acquisition (Wolf et al. 1987) and are impaired on a reinforced alternation task (Kesslak et al. 1986a, b). In *Macaca mulata* the frontal lobe is involved in the intention to act (Valenstein et al. 1987) and in the performance of spatial delayed reactions (Naneishvili et al. 1987). These are all elements necessary to choose a reaction, also observed by Rosenkilde (1983). These reactions can be: not reacting, doing something immediately, waiting for the right stimulus to appear, just doing what comes to mind, and changing habitual reactions. Thus, on the basis of its connectivity and its specific functions,

the frontal lobe can be considered a link in the cortico-limbo-striatal system, although alternative pathways cannot and should not be excluded.

Summarizing: The anatomical data found in *Xenopus* (Fig. 69) 'match those found for mammals (Fig. 74). The described sequences of the anatomical connections and the structural concept given in Sect. 1 (Fig. 1) and discussed in Sect. 5.3 give an explanation for common neurological and experimentally inflicted disorders.

The scheme does not explain the fact that no differences in memory disturbances occur after frontofrontal or temporoparietal electroconvulsive therapy (Widepalm 1987). An unsatisfactory explanation is that this therapy goes far beyond the normal processing capacity of the interacting cortices and causes an overall effect via association fibers. From a comparative point of view it would be nice to consider the mammalian cortex as an entity like the amphibian pallium, with an entrance part and a part forming a relay between the limbic structures of the septum, hippocampus, and amygdala, and to emphasize the pallio-limbo-hypothalamo-striatal connection, but this again does not explain the different functions of the different cortical areas.

5.5 Conclusions

The amphibian forebrain is a fairly simple structure which can be studied as whole and allows relatively easy comparisons with reptiles, birds, and mammals, and even with fishes. The structural and connective components constructing a dual sensorimotor and selection system needed for telencephalic function (decision making in new situations) as postulated in Sect.1 were determined in *Xenopus laevis* and can also be seen in other vertebrates. In tetrapods a general pattern for the arrangement of these components can be recognized. In actinopterygians the same components can be distinguished, but in another configuration. This might mean that the components are needed but that the way they are assembled is free. Important is that the behavioral effects of forebrain lesions described for mammals at least are in concordance with the developed structural concept.

The position of the tetrapod pallium in between the limbic structures, whereby especially the amygdala and hippocampus are not directly interconnected and have to communicate via the pallium, logically forces us to the conclusion that the pallium with the limbic system forms one entity, namely, the selection system. The proposed palliolimbic entity is also in concordance with the opinion that rational analysis is based on, driven by, and leads to preconceptions and emotions.

6 Summary

The basic thesis for this study was that the telencephalon is needed to make decisions in new situations. Subsidiary hypotheses were that the telencephalon consists of: (a) a sensorimotor system which generates motor activity from sensory input and (b) a selection system which makes choices from possible motor programs. It was postulated that the selection system should fulfil the following requirements: be accessible for past and present events, have the capacity to process this information in a nondetermined way with a possibility for ordering, and have access to motor-affecting systems (the sensorimotor system). The ability of the selection system to correlate information in a nonpredetermined way was considered most important. In short: The selection system should be able to associate any information in any combination, and have the capability for internal control of neuronal activity and external selection of motor programs (see Fig. 1A.)

Xenopus laevis was chosen as a subject, since it has a relatively simple telencephalon, with characteristics that it shares with “primitive” species of different vertebrate classes, and because it is easy to maintain as a laboratory animal. The main method used was the determination of connections with HRP. The pallium was in the focus of attention, since it was considered to be the core of the selection system. Immunohistochemistry was used as an additional parameter to compare *Xenopus laevis* forebrain with those of other vertebrates.

The results showed that the pallium can be subdivided into a rostral (third) and a caudal (two-thirds) entity. The rostral third is the main recipient for thalamic and olfactory input. The caudal two-thirds are linked up to the rostral third and have a refined microcircuitry. Efferents from the pallium remain restricted to the forebrain. The entire pallium consists of a network of intrinsic reciprocal connections and can be considered to be positioned between the medial pallium (hippocampus), septum, and amygdaloid complex (amygdala). As a whole this system targets the hypothalamus. The hypothalamus in turn projects into the striatum complex (striatum with anterior entopeduncular nucleus). The rostral dorsal pallium and the amygdaloid complex also project into the striatum complex. The striatum is positioned between the sensory input from the thalamus and olfactory bulbs, and the motor output to the medulla.

It is concluded, on the basis of its straightforward input-output relations and uniform appearance, that the striatum complex fulfils the requirements for a sensorimotor system. The pallium together with the septum, amygdaloid complex, and hypothalamus fulfils the requirements for a selection system. Because of its multimodal input and network of reciprocal connections forming the basis of functions assembled from nonlinear relationships, the pallium can associate any

information in any combination. Because of their arrangement and connections, the septum, pallium, and amygdaloid complex can perform the function of internal control, possibly by mutually enhancing and excluding their activities. This combined system can, probably via the hypothalamus but also directly, externally select which output from the striatum complex will reach the motor centers in the medulla. The indifferentiated striatum complex has access to the input systems of the pallium. The pallium with its sophisticated neuronal network, and its auxiliary structures, has access to the input and output systems of the striatum complex. Thus the striatum complex and the overlying system of septum, pallium, and amygdaloid complex can mutually influence each other.

The distribution of opioid- and substance P-like immunoreactivity enabled the amygdaloid complex to be equated with the mammalian amygdala, and the striatum and septum to be equated with their mammalian counterparts, leaving the pallial regions to be compared with cortical regions. Serotonin-like immunoreactivity supported the differentiation of the pallium into rostral and caudal as well as medial, dorsal, and lateral parts.

The pattern of prosencephalic connectivity in *Xenopus laevis* determined in this study is paralleled in mammals. Two basic differences appear: the mammalian counterparts are enlarged and parceled into subunits, and a counterpart to the mammalian corticomedullar projection system is missing in *Xenopus laevis*. In *Xenopus laevis* the striatum complex projects into the spinal cord.

The elements of the connectivity pattern as seen in *Xenopus laevis* are also met in other tetrapods and in the same configuration. In actinopterygians similar elements can be encountered but the configuration seems to be quite different.

General Conclusions. The prerequisites for a combined sensorimotor–selection system; which is considered to be essential for making decisions in new situations, can be determined in the prosencephalon of a single species. The emerging pattern can be generalized to all tetrapods and the separate elements can be distinguished in fishes. From the latter it can be concluded that the elements in themselves, and not so much the configuration, are needed for telencephalic function. The pallium and the limbic system should be considered as a coherent entity, namely, the selection system, and the striatum complex as the sensorimotor system.

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