Review

Evolution of the basal ganglia: new perspectives through a comparative approach

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ABSTRACT

The basal ganglia (BG) have received much attention during the last 3 decades mainly because of their clinical relevance. Our understanding of their structure, organisation and function in terms of chemoarchitecture, compartmentalisation, connections and receptor localisation has increased equally. Most of the research has been focused on the mammalian BG, but a considerable number of studies have been carried out in nonmammalian vertebrates, in particular reptiles and birds. The BG of the latter 2 classes of vertebrates, which together with mammals constitute the amniotic vertebrates, have been thoroughly studied by means of tract-tracing and immunohistochemical techniques. The terminology used for amniotic BG structures has frequently been adopted to indicate putative corresponding structures in the brain of anamniotes, i.e. amphibians and fishes, but data for such a comparison were, until recently, almost totally lacking. It has been proposed several times that the occurrence of well developed BG structures probably constitutes a landmark in the anamniote-amniote transition. However, our recent studies of connections, chemoarchitecture and development of the basal forebrain of amphibians have revealed that tetrapod vertebrates share a common pattern of BG organisation. This pattern includes the existence of dorsal and ventral striatopallidal systems, reciprocal connections between the striatopallidal complex and the diencephalic and mesencephalic basal plate (striatonigral and nigrostriatal projections), and descending pathways from the striatopallidal system to the midbrain tectum and reticular formation. The connectional similarities are paralleled by similarities in the distribution of chemical markers of striatal and pallidal structures such as dopamine, substance P and enkephalin, as well as by similarities in development and expression of homeobox genes. On the other hand, a major evolutionary trend is the progressive involvement of the cortex in the processing of the thalamic sensory information relayed to the BG of tetrapods. By using the comparative approach, new insights have been gained with respect to certain features of the BG of vertebrates in general, such as the segmental organisation of the midbrain dopaminergic cell groups, the occurrence of large numbers of dopaminergic cell bodies within the telencephalon itself and the variability in, among others, connectivity and chemoarchitecture. However, the intriguing question whether the basal forebrain organisation of nontetrapods differs essentially from that observed in tetrapods still needs to be answered.

Key words: Chemoarchitecture; comparative neuroanatomy; dorsal and ventral striatopallidal systems.

INTRODUCTION

The basal ganglia (BG) constitute key brain structures that play a prominent role in motor functions, in particular in the planning, initiation and execution of movement (Albin et al. 1989). The term basal ganglia, however, has no precise limitations or definitions, and it has been used in many different ways through the years. From a developmental point of view, the term refers to the striatal and pallidal components of the

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basal telencephalon that evolve from the lateral and medial ganglionic eminences. In mammals, these structures include the caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, globus pallidus and ventral pallidum. Frequently other forebrain and midbrain structures, such as the subthalamic nucleus, ventral tegmental area (VTA, A10) and substantia nigra (SN, A9), are also included, merely because they are closely related to the striatopallidal circuitry. Most of our current knowledge about the involvement of the BG in motor function has been gained from studies of human disorders, in particular Parkinson's and Huntington's diseases, and from animal (mammalian) models mimicking these diseases (Alexander & Crutcher, 1990; DeLong, 1990; Marsden & Obeso, 1994; Heimer et al. 1995; Parent & Hazrati, 1995*a*, *b*). Moreover, it is now generally accepted that the BG are involved in a variety of nonmotor functions, including those related to incentive and motivated behaviours (McDonald & White, 1993; Redgrave et al. 1999).

Research during the last 2 decades has revealed that there are many similarities in the organisation of the BG among reptiles, birds and mammals (for reviews see Parent, 1986; Russchen et al. 1987*a*, *b*; Anderson & Reiner, 1990; Smeets, 1991; Medina & Reiner, 1995; Veenman et al. 1997). Features that are shared by all amniotes studied so far are: (1) the presence of dorsal and ventral striatopallidal systems; (2) the presence of 2 chemically and hodologically distinct populations of striatal projection neurons; (3) intrinsic striatal neurons; (4) a strong dopaminergic input originating from the midbrain tegmentum; (5) corticostriatal and thalamostriatal connections; (6) striatal and pallidal projections to the midbrain tegmentum; and (7) BG projections to mesencephalic and isthmic premotor centres. These similarities have led to the conclusion that a comparable BG organisation was already present in the ancestors of amniotes. Conversely, it has been pointed out that major differences in the organisation of the BG between living amniotes and anamniotes (i.e. fish and amphibians) might exist, suggesting that well-developed BG evolved only at the anamniote-amniote transition during evolution (Parent, 1986).

Recent studies of BG organisation in amphibians have provided evidence that most of the features shared by amniotes are already present in the basal forebrain of anurans and urodeles (for reviews, see Marín et al. 1998*b*, *c*), thus supporting the notion that a general plan of BG organisation was already present in the brain of ancestral tetrapods. In this survey, we present first the evidence derived from the recent studies in amphibians that prompted us to reconsider the evolution of the BG. Subsequently, an attempt will be made to answer the question whether this general plan also holds for other anamniotes. Finally, some less known aspects of BG organisation will be discussed that might be of great interest for a better understanding of BG organisation and functioning in vertebrates in general.

GENERAL FEATURES OF TETRAPOD BG ORGANISATION

Striatopallidal systems

As shown in Figure 1, the BG of mammals are subdivided into 2 distinct components, both comprising striatal and pallidal structures, that is, the dorsal and the ventral striatopallidal systems (Heimer et al. 1995). The *dorsal striatopallidal system* consists of the dorsal striatum or striatum proper (caudate nucleus and putamen in primates and felines, caudate-putamen in other mammals) and the dorsal pallidum. The latter structure is subdivided into 2 parts with distinct chemoarchitecture and connectivity, i.e. the external segment of the globus pallidus (Gpe; primates) or merely the globus pallidus (GP; nonprimates), and the internal segment of the globus pallidus (Gpi; primates) or entopeduncular nucleus (EP; nonprimates). The *ventral striatopallidal system* is constituted by the ventral striatum (nucleus accumbens and part of the olfactory tubercle) and the ventral pallidum (Fig. 1). Comparative studies have revealed that the BG of birds and reptiles also consist of dorsal and ventral striatopallidal systems (Russchen et al. 1987*a*, *b*; Medina & Reiner, 1995, 1997), although in the literature different names have been given to homologous structures (Fig.1). Of note is the fact that the dorsal pallidum in nonmammalian vertebrates does not possess anatomical subdivisions. As in mammals, the dorsal and ventral striatopallidal systems of reptiles and birds have distinct connections with the forebrain, midbrain and isthmus, suggesting that both systems are involved in partially segregated circuits in all amniotes.

Early studies dealing with the connectivity of the basal forebrain in amphibians, based on degeneration or horseradish peroxidase (HRP) transport, did not support the existence of distinct dorsal and ventral striatopallidal systems. However, the development of antibodies against a great variety of neurotransmitters or their synthesising enzymes, some of which are now considered as general markers of BG structures, as well as the introduction of a new generation of tracers have given new impetus to the search for BG

structures in the brain of urodeles and anurans. In particular, dopamine, substance P (SP) and enkephalin (ENK) have been used to delineate striatal and pallidal compartments within the basal forebrain of amniotes and amphibians. Furthermore, the newly developed tracers such as dextran amines, either biotinylated or conjugated to fluorescent compounds (Glover et al. 1986; Veenman et al. 1992; Fritzsch, 1993), could be delivered to restricted sites in the brain and were sensitive enough to enable a selective study of the connections of the various subdivisons within the basal telencephalon of anuran (*Rana perezi*, *Xenopus laevis*) and urodele (*Pleurodeles waltl*) amphibians. As a first step, the location of dorsal and ventral striatal components, i.e. the striatum proper and the nucleus accumbens, was identified histochemically primarily by means of antibodies against dopamine and tyrosine hydroxylase, the rate limiting enzyme in catecholamine synthesis (González & Smeets, 1991, 1994). It was found that the striatum proper and the nucleus accumbens occupy a large portion of the ventrolateral and ventromedial walls, respectively, of the telencephalic hemispheres in anuran amphibians (Fig.1). The nucleus accumbens is restricted to the rostral one-third of the telencephalic wall and is clearly distinguished from the lateral adjacent striatum by marked differences in catecholamine and neuropeptide immunoreactivities (Marín et al. 1998*a*). It is worth mentioning that the nucleus accumbens of urodeles lies within the ventrolateral telencephalic wall, occupying a position more lateral than the corresponding structure in anurans. The striatum proper extends throughout the ventrolateral telencephalic wall from a level just caudal to the olfactory bulb to the level of the lamina terminalis. The degree of cell migration within the ventromedial aspect of the striatal cell plate increases as the striatum expands caudally. Pallidal areas are not noticeable in Nissl-stained sections through the amphibian forebrain, but can be clearly delineated in sections stained immunohistochemically for SP and ENK (Marín et al. 1998*a*). As in amniotes (Haber & Elde, 1982; Russchen et al. 1987*a*), ventral and dorsal pallidal regions are distinguished on the basis of their relative staining for SP and ENK. Whereas the dorsal pallidum contains a prominent plexus of ENK immunoreactive fibres and a less conspicuous SP fibre plexus, the ventral pallidum exhibits the reverse condition, i.e. a strong SP but only a moderate ENK fibre plexus. Another difference between the dorsal and ventral pallidum is that the latter also receives a prominent catecholaminergic innervation, which is primarily noradrenergic (González & Smeets, 1993; Marín et al. 1998*a*), a condition similar to that observed in reptiles (Smeets & Steinbusch, 1989; Smeets, 1994) and birds (Reiner et al. 1994).

The existence of dorsal and ventral striatopallidal systems in the brain of all tetrapods has a major implication for the understanding of the organisation of the basal telencephalon. Thus the striatal and pallidal components of the BG comprise 2 distinct rostrocaudally adjacent compartments in the basal telencephalon. The existence of such compartments in all tetrapods is supported by the pattern of expression of different sets of homeobox genes, which appear to play an important role in the regional specification of the telencephalon. For example, genes of the *dlx* class delineate the BG anlage during the early development of the basal telencephalon in mammals, birds and amphibians (Puelles & Rubenstein, 1993; Puelles et al. 1999) and are essential for the differentiation of the striatum (Anderson et al. 1997). In addition, the expression of the *nkx-2.1* gene specifically demarcates the medial ganglionic eminence, which is thought to give rise to the globus pallidus, among other structures.

Striatal projection neurons

Two main populations of projection neurons have been found in the dorsal and ventral striatal regions of all amniotes studied so far. Both types of projection neurons are medium-sized, spiny, and contain the neurotransmitter γ-aminobutyric acid (GABA), but differ in their content in neuropeptides (Albin et al. 1989; Graybiel, 1990; Reiner & Anderson, 1990; Parent et al. 1995; Reiner et al. 1999). Thus one type of striatal projection neuron contains SP and dynorphin, whereas the other possesses ENK. Since the SP immunoreactive striatal neurons of mammals project directly to the BG output structures (GPi/SNr) and the ENK immunoreactive striatal neurons reach the latter structures indirectly via the globus pallidus (GPe) and/or the subthalamic nucleus, they are referred to as the direct and indirect pathways of the BG, respectively (Albin et al. 1989; Smith et al. 1998). In reptiles and birds, the pallidum is not divided into internal and external segments and it receives both SP and ENK immunoreactive fibres throughout its entire extent (Reiner et al. 1998). A similar condition seems to exist in amphibians suggesting that in all non-mammalian tetrapods, the parcellation of pallidal neurons into 2 separate fields has not yet taken place (Reiner et al. 1998).

Intrinsic striatal neurons

Apart from the spiny projection neurons, which

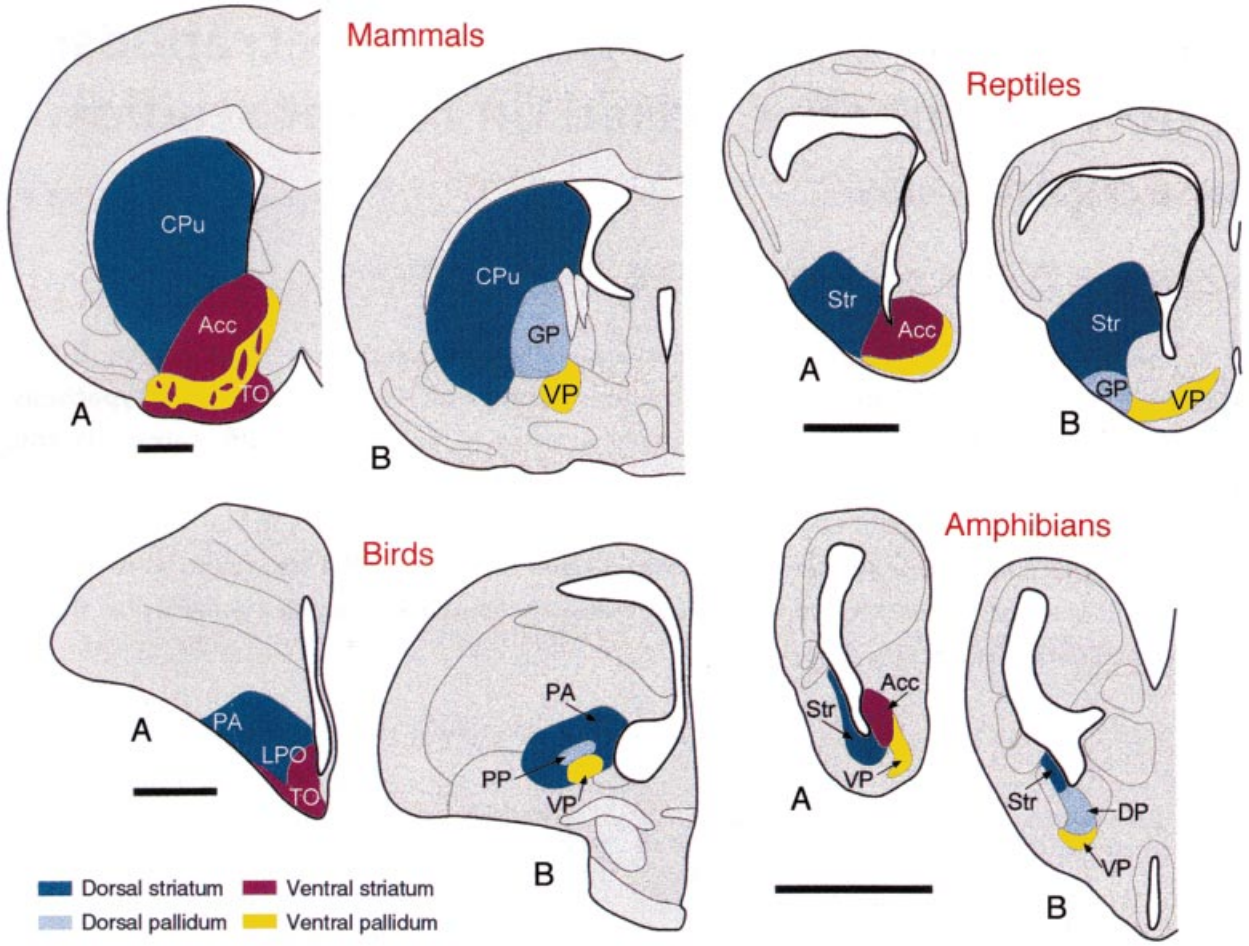


Fig. 1. The dorsal and ventral striatopallidal systems. The basal ganglia are organised into dorsal and ventral striatopallidal systems in all tetrapods. For each vertebrate class, 2 representative transverse sections at a rostral (*A*) and caudal (*B*) telencephalic level illustrate the relative position of striatal and pallidal structures. Although in the literature different names have been given to homologous structures, the same colours have been used for comparable regions in each tetrapod to simplify identification. Abbreviations: A8, retrorubral cell group; A9, substantia nigra pars compacta; A10, ventral tegmental area; Acc, nucleus accumbens; Ad, anterodorsal tegmental nucleus; Amy, amygdala; apvl, area periventricularis ventrolateralis; asb, area superficialis basalis; Av, anteroventral tegmental nucleus; BG, basal ganglia; cDTh, caudal dorsal thalamic nuclei; Cpu, caudate-putamen; DARPP-32, dopamine- and cAMP-regulated phosphoprotein, Mr 32000; DP, dorsal pallidum; DVR, dorsal ventricular ridge; EP, entopeduncular nucleus; GP, globus pallidus; Hb, habenula; HYP, hypothalamus; IN/M, intralaminar midline-like nuclei; Ist, isthmic segment; Jc, uxtacommissural pretectal nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LPO, lobus parolfactorius; M, mesencephalic segment; Mp, medial pallium; Ncp, nucleus of the posterior commissure; nPT, nucleus pretectalis; oc, optic chiasm; p1–p3, prosomere 1–3; PA, paleostriatum augmentatum; Pb, parabrachial nucleus; PP, paleostriatum primitivum; PPN, pedunculopontine nucleus; PT, pretectal region; rDTh, rostral dorsal thalamic nuclei; RF, raphé nuclei; SC, superior colliculus; SN, substantia nigra; SNc, substantia nigra pars compacta; SNL, substantia nigra lateralis; SNr, substantia nigra pars reticulata; SpL, nucleus spiriformis lateralis; SPr, secondary prosencephalon; STh, subthalamus; Str, striatum; T, tectum mesencephali; TO, olfactory tubercle; Tor, torus semicircularis; VP, ventral pallidum; Vth, ventral thalamus.

constitute about 90% of striatal neurons, the dorsal and ventral striatum of amniotes contains several types of local circuit neurons. A first type is constituted by aspiny, cholinergic neurons which are present in amniotes and at least in some amphibians (Vincent & Reiner, 1987; Hoogland & Vermeulen-VanderZee, 1990; Woolf, 1991; Medina et al. 1993; Medina & Reiner, 1994; Marín et al. 1997*c*). However, although the presence of cholinergic neurons in the striatum and the nucleus accumbens appears to be a common feature of tetrapods, substantial differences between species exist in the number, location and physiological features of these cells (Hoogland & Vermeulen-VanderZee, 1990; Henselmans et al. 1991; Medina et al, 1993; Marín et al. 1997*c*). Nevertheless, the demonstration of cholinergic neurons in at least some amphibians implies that already in early tetrapods dopamine-acetylcholine interactions may have taken place within the striatum. In mammals, the remaining striatal interneurons contain the neurotransmitter GABA. Generally, 3 different populations of GABAergic interneurons are distinguishable on the

basis of their chemical content: (1) GABAergic cells containing parvalbumin; (2) GABAergic cells containing calretinin; and (3) GABAergic cells cocontaining somatostatin, nitric oxide synthase and neuropeptide Y (Kawaguchi et al. 1995; Figueredo-Cardenas et al. 1996*a*, *b*). The striatum of amphibians, reptiles and birds also contains cells that are immunoreactive to several of those substances (Marín et al. 1998*a*; Reiner et al. 1998), but it is largely unknown yet whether they coexist with striatal GABAergic interneurons. Despite the lack of direct evidence by means of double labelling studies, it may be postulated that local circuit neurons were already present in the brain of early tetrapods and that the number of striatal cell populations seems to have increased markedly during evolution.

Cortical and thalamic inputs to the striatum

The striatum is the major receptive structure of the BG in all tetrapods and receives its main inputs from the cortex (or pallium), the thalamus and the dopaminergic neurons of the VTA-SN complex. Afferents from the cortex (or pallium) and the thalamus provide the striatum with a direct access to diverse and multimodal information, although substantial differences exist in the extent and degree of organisation of these projections among tetrapods. In mammals, virtually all cortical areas contribute to the innervation of the striatal territories, giving rise to a complex representation of the functional cortical map at the striatal level (Parent & Hazrati, 1995*a*). In reptiles and birds, the major source of cortical/pallial inputs to the striatum is the dorsal ventricular ridge (DVR), a telencephalic structure that is embryologically derived from the pallium. Although some authors consider this structure comparable, to some extent, to the isocortex of mammals (Butler, 1994; Reiner et al. 1998), its true nature is still a matter of debate (for reviews, see Lohman & Smeets, 1991; Striedter, 1997). In addition, the striatum of reptiles and birds receives projections from other pallial regions, such as the dorsal cortex and the Wulst, respectively. Recently, it has been shown that palliostriatal connections are also present in amphibians (Marín et al. 1997*a*), thus underscoring the notion that the existence of striatal afferents from the telencephalic mantle is a feature shared by all tetrapods (Fig. 2). Nevertheless, it is obvious that a dramatic increase in the number and complexity of the cortico/palliostriatal projections characterises the anamniote-amniote as well as the nonmammalian-mammalian transitions.

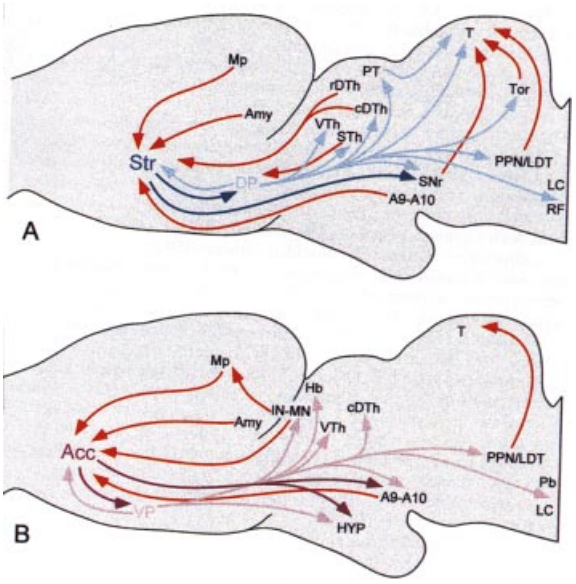


Fig. 2. Basal ganglia connections in ancestral tetrapods. The putative connections of the dorsal (*A*) and ventral (*B*) striatopallidal systems in the ancestral tetrapods can be inferred from a comparative analysis of the basal ganglia organisation in extant tetrapods. See Fig. 1 caption for abbreviations.

The evolution of thalamic afferents to the striatum has been related to the expansion of the cortex and, consequently, to the elaboration of the corticostriatal system. In mammals, direct thalamic afferents to the striatum originate primarily in the midline and intralaminar nuclear complex that relays diverse multimodal ('nonspecific') information to specific parts of the striatum and the cortex (Groenewegen & Berendse, 1994). Specific sensory information, on the contrary, reaches the BG primarily via thalamocorticostriatal connections, although striatal afferents from certain specific relay nuclei in the thalamus do exist (Heimer et al. 1995). In sharp contrast, projections from specific sensory thalamic nuclei are the main afferents of the striatum in living amphibians (Marín et al. 1997*a*) and, therefore, sensory information of different modalities is essentially relayed to the amphibian BG without involvement of the telencephalic pallium. Multimodal sensory and limbic information is relayed to the amphibian striatum and pallium by the anterior thalamic region. An intermediate condition is found in reptiles and birds, where specific sensory thalamic nuclei project to the dorsal cortex and the DVR, but also to the striatal components of the BG (González et al. 1990; Veenman et al. 1997). Furthermore, a region of the dorsal thalamus of birds and reptiles appears to be largely comparable to the entire intralaminar, mediodorsal and midline nuclear complex of mammals, providing widespread projections to the striatum and

the pallium (Veenman et al. 1997). In conclusion, the existence of direct sensory inputs from the thalamus to the striatum seems to be a primitive feature of the BG in tetrapods (Fig. 2). A major evolutionary trend is, however, the progressive involvement of the cortex or cortical-like structures in the processing of the thalamic sensory information relayed to the BG of tetrapods. It also seems likely that the striatum of the common ancestors of tetrapods has been the target of the projections of a dorsal thalamic nuclear complex that receives inputs of diverse and multimodal nature (Fig. 2). In contrast to the specific sensory thalamic nuclei, the midline intralaminar nuclei are involved in nondiscriminative or affective aspects of the information, which might be required to prevent the organism from potentially dangerous situations and, therefore, possess an obvious adaptive value (Groenewegen & Berendse, 1994).

Dopaminergic input to the striatum

The dopaminergic innervation of the dorsal and ventral components of the striatum is one of the most conservative features of the BG in tetrapods. However, essential differences in the localisation and development of the dopaminergic cell groups that project to the basal forebrain have been thought to exist between amniotes and anamniotes (Parent, 1986). In amniotes, the BG receive a strong dopaminergic input primarily from the substantia nigra pars compacta (A9) and the ventral tegmental area (A10). The ventromedially located A10 cell group as well as the dorsolaterally extending A9 cell group are considered classically to be located in the mesencephalic tegmentum. In contrast, the dopaminergic neurons projecting to the basal forebrain of amphibians constitute a continuous field along the rostrocaudal axis of the diencephalic-mesencephalic basal plate, extending from the retromammillary region to the level of the exit of the oculomotor nerve. The apparent differences in topography of these cell groups in amniotes and amphibians have traditionally constituted a strong argument against their homology. However, when a segmental approach is applied to the localisation of the dopaminergic cell groups in the brain of vertebrates, a different conclusion can be reached (Fig. 3A). Apparently, the distribution of the dopaminergic cells in the A10 and A9 of amniotes is not restricted to the mesencephalic segment. In fact, the A10 complex of amniotes stretches across several segments and consists of diencephalic (prosomeres 1–3), mesencephalic and isthmic segments. In addition, a multisegmental origin also holds for the substantia nigra pars compacta of mammals, the neurons of which appear to be generated in the floor plate and adjacent basal plate of at least 3 different segments (mesencephalic, p1, p2). In birds and reptiles, the A9 cell group seems to have a more restricted distribution. In amphibians, the dopaminergic cell field corresponding to the paramedian A9–A10 cell complex of amniotes is present almost in its entirety, although they lack a laterally migrated substantia nigra and retrorubral (A8) field, as well as the isthmic portion of the A10 complex (Fig. 3*A*). Developmental studies using the segmental approach have demonstrated that the dopaminergic cells of the diencephalic prosomeres (p1–p3) of amphibians, like the corresponding cell groups in birds and mammals, develop earlier than those in the midbrain and isthmic segments (Fig. 3*B*). Accordingly, the first dopaminergic cell bodies projecting to the basal telencephalon are found in the rostrolateral portion of the developing A9–A10 complex and reach the striatum before the nucleus accumbens (Puelles & Medina, 1994; Marín et al. 1997*c*). The segmental approach as well as the development of the A9–A10 cell groups give further support to the notion that the organisation of the dopaminergic innervation of the BG of tetrapods is highly conservative. The amphibian homologues of the A9–A10 cell groups might therefore exemplify an early stage in the evolution of these structures, which most probably have evolved further in amniotes by increasing their number of cells and expanding caudally and laterally, in parallel with the increase of the striatal territories (Fig. 3*B*). The presence of organised dopaminergic projections to the dorsal and ventral striatum in all tetrapods points to a remarkably conserved modulatory mechanism of the striatal functioning. In mammals, one of the main functions of the dopaminergic innervation is to modulate the cortical or thalamic inputs directly on the striatal projection neurons (Smith & Bolam, 1990). It seems conceivable that, independently of the origin and nature of other striatal afferents, the dopaminergic input to the striatum might play a similar role in other tetrapods. Depletion of dopaminergic input to the BG modifies the normal motor behaviour in all tetrapods (Goodman et al. 1983; Barbeau et al. 1986: Greenberg et al. 1988; Reiner, 1994), suggesting that dopamine can have a fundamental effect on striatal function.

BG projections to the midbrain tegmentum

The mammalian substantia nigra is a highly heterogeneous structure that comprises at least 2 distinct

components, the pars compacta (SNc) and the pars reticulata (SNr). The SNc contains the majority of the dopaminergic cell that project to the striatum, whereas the SNr is the main recipient of the striatonigral pathway. The SNr contains GABAergic neurons and is characterised by a dense plexus of fibres which are immunoreactive for both substance P and dynorphin (Reiner et al. 1999). The mesencephalic tegmentum of nonmammlian tetrapods also contains a population of GABAergic neurons in the place where striatal projections form a conspicuous network, which is therefore considered homologous to the mammalian SNr. However, the topographic relationship between the SNc and the SNr varies substantially among tetrapods (Fig. 4). Two different patterns are found, one with little overlap between dopaminergic cells and SP immunoreactive fibres (frogs, lizards, turtles, rats) and another with extensive overlap (crocodiles, snakes, pigeons and primates, including humans (Haber & Groenewegen, 1989; Smeets, 1991). The close topographic relationship between the SNr and the SNc reached in some tetrapods might confer a number of advantages. For example, it allows simultaneous influence of the striatonigral projections on both components of the SN, as well as a dopaminergic control of the striatal inputs to the SNr through dendritically released dopamine from the SNc (Fallon & Loughlin, 1995). On the basis of these data, it seems likely that the SN is not only a functionally dual structure in all tetrapods, but also that both components of the SN have evolved separately, converging only in some tetrapods. Recent developmental studies indicate that the SN in all tetrapods might consist of a floor or basal-plate-derived cell group (SNc) and an alar-plate-derived cell group (SNr). In that perspective, the differences found in the pattern of organisation of the SN among tetrapods could be attibuted to the degree of migration of each component. As suggested for other brain regions, the modifications of the general plan of organisation of homologous structures are most probably generated by a limited set of developmental mechanisms.

BG projections to midbrain and isthmic premotor centres

Although the cortico-BG-thalamo-cortical loops constitute the main route for information processing in mammals and, most likely, in birds, the output structures of the BG also reach brainstem regions in all tetrapods studied. These projections arise mainly from the dorsal pallidum and the SNr, and terminate in the superior colliculus (tectum in nonmammalian vertebrates) and the reticular formation. In the light of recent anatomical findings, the BG involvement in visuomotor behaviour in tetrapods appears to be far more complex than previously thought. Diverse descending pathways from the BG to the midbrain tectum have been demonstrated in amphibians (Marín et al. 1997*b*, *e*), reptiles (Medina & Smeets, 1991), birds (Medina & Reiner, 1997), and mammals (Faull & Mehler, 1978; Redgrave et al. 1992), suggesting that the existence of several BG-tectal pathways is the primitive condition in tetrapods (Fig. 5). In all tetrapods, the SNr mediates output from the BG to the tectum and this constitutes the basic route by which the BG influence tectal activity involved in specific motor functions such as orientation and defensive behaviours, gaze shifting and fixation, and saccadic movements. In mammals, these pathways represent additional routes to lower motor centres besides the well-established striato-pallidal-thalamo-cortical pathway. Conversely, in nonmammalian tetrapods the BG-tectal pathways constitute the main anatomical basis for the involvement of the BG in motor control. Classically, 2 major BG-tectal pathways have been recognised in tetrapods, that is, a *ventral route* via the SNr and a *dorsal route* via a pretectal relay (Medina & Smeets, 1991). Since both the striatonigral and nigrotectal neurons contain the inhibitory neurotransmitter GABA, activation of the ventral route results in disinhibition of tectofugal neurons (Chevalier & Deniau, 1990). The striatum can also modulate the activity of nigrotectal neurons via the globus pallidus (Fig. 5). Pallidal inputs to the SNr are also GABAergic and therefore stimulation of a particular set of dorsal striatal neurons can cause either inhibition or excitation (or a combination of both effects) on nigrotectal neurons and, ultimately, on tectal projection neurons (Smith & Bolam, 1991).

The striato-pallido-pretecto-tectal or dorsal route forms the second major route by which the BG influence tectal functioning, but this route is not equally developed in all tetrapods. It is well developed in anurans, some lizards (*Gallotia*, *Podarcis*), crocodiles, turtles and birds, but weak or even absent in urodeles, other lizards (*Gekko*, *Varanus*), snakes and mammals (Fig. 5). Striatal stimulation would lead to inhibition of tectofugal neurons through this pathway, because both pallidal and pretectal neurons are inhibitory. The final outcome, however, is further complicated by the existence of direct striatopretectal (amphibians, birds) and pallidotectal (amphibians, reptiles, mammals) pathways, which would result in disinhibition of tectofugal neurons. Moreover, in amphibians a direct striatotectal connection has been

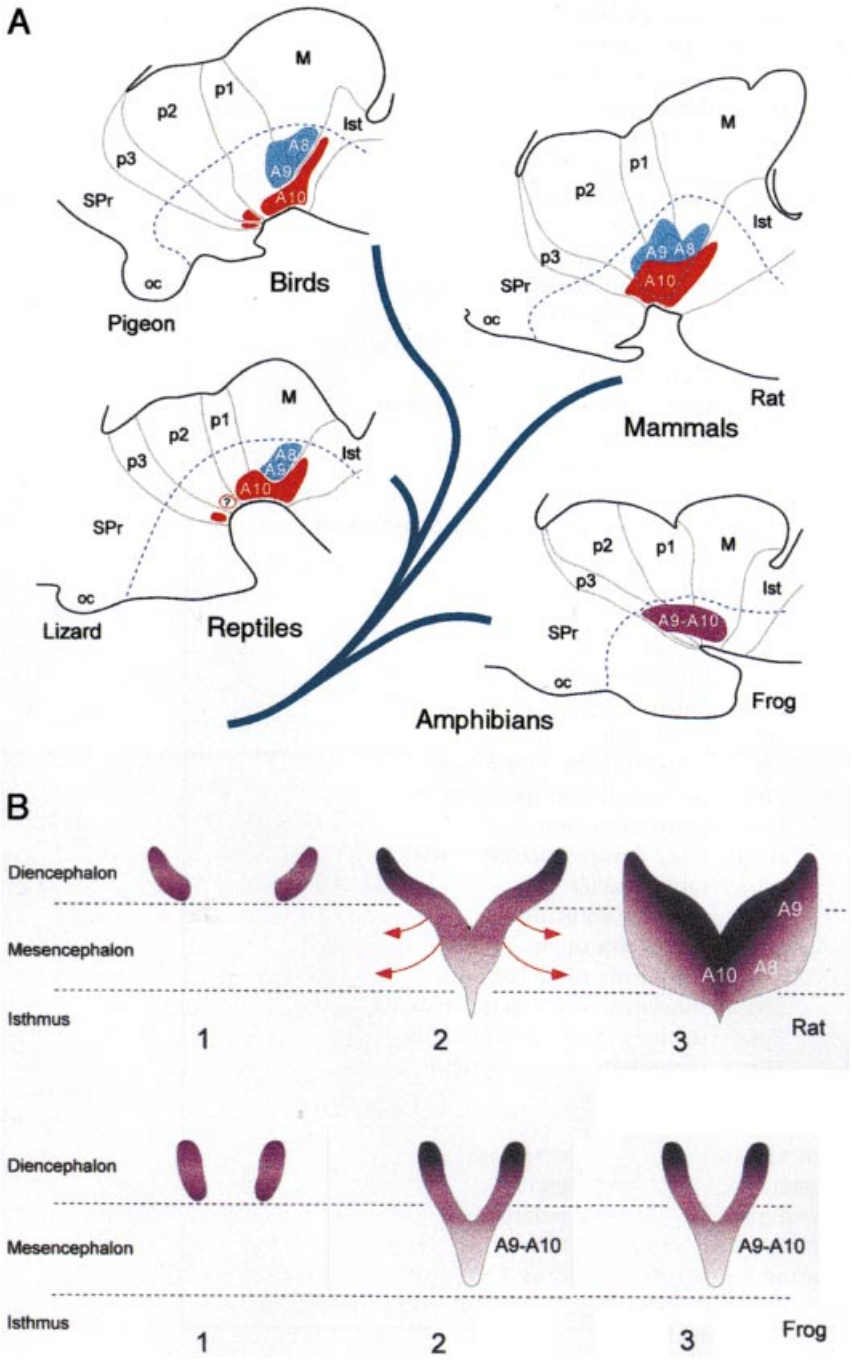


Fig. 3. Localisation and development of the dopaminergic A8–A10 cell groups in tetrapods. (*A*) Schematic drawings of midsagittal sections of representative brains belonging to the 4 classes of vertebrate tetrapods showing the segmental concurrence of the dopaminergic cells in the ventral tegmental area (A10), the substantia nigra pars compacta (A9) and retrorubral field (A8). The segmental boundaries are marked by solid lines, whereas the interrupted line indicates the boundary between basal and alar plates. (*B*) Comparison of the development of the A9–A10 cell groups in mammals and amphibians suggests a common process for the generation of the dopaminergic neurons along the rostrocaudal brain axis (steps 1 and 2). On the other hand, the migration of cells into the lateral zone of the A8–A9 cell groups , as observed in mammals (red arrows), does not occur in amphibians (step 3).

demonstrated (Marín et al. 1997*b*, *e*), which would account for a direct inhibition. The presence of multiple routes that relate the BG and tectal neurons in all tetrapods reflects a complicated system by which the motor behaviour elicited by the tectum can be influenced. This seems to hold true in particular for amphibians, which is in sharp contrast with previous views (Ewert, 1997). It is still unknown how the different BG-tectal routes modulate the output of tectal neurons. It is possible that different BG-tectal pathways control distinct sets of movements or, alternatively, that the BG could modulate the tem-

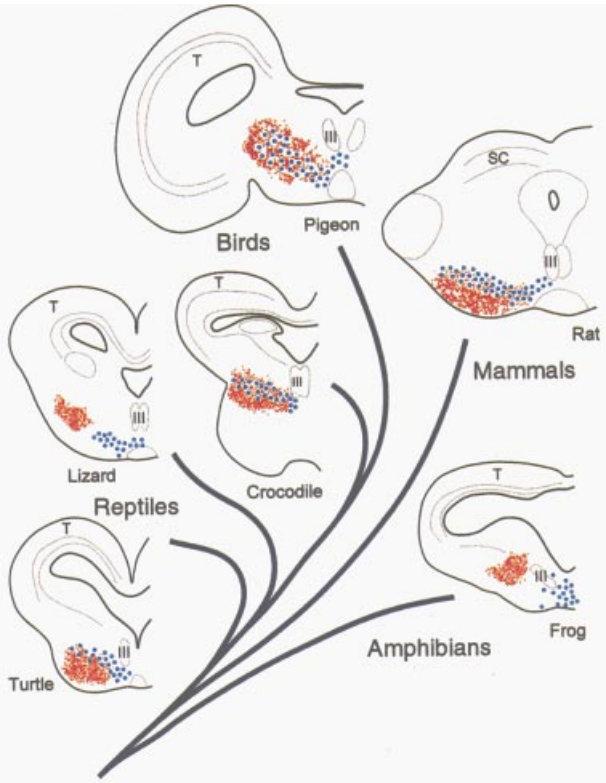
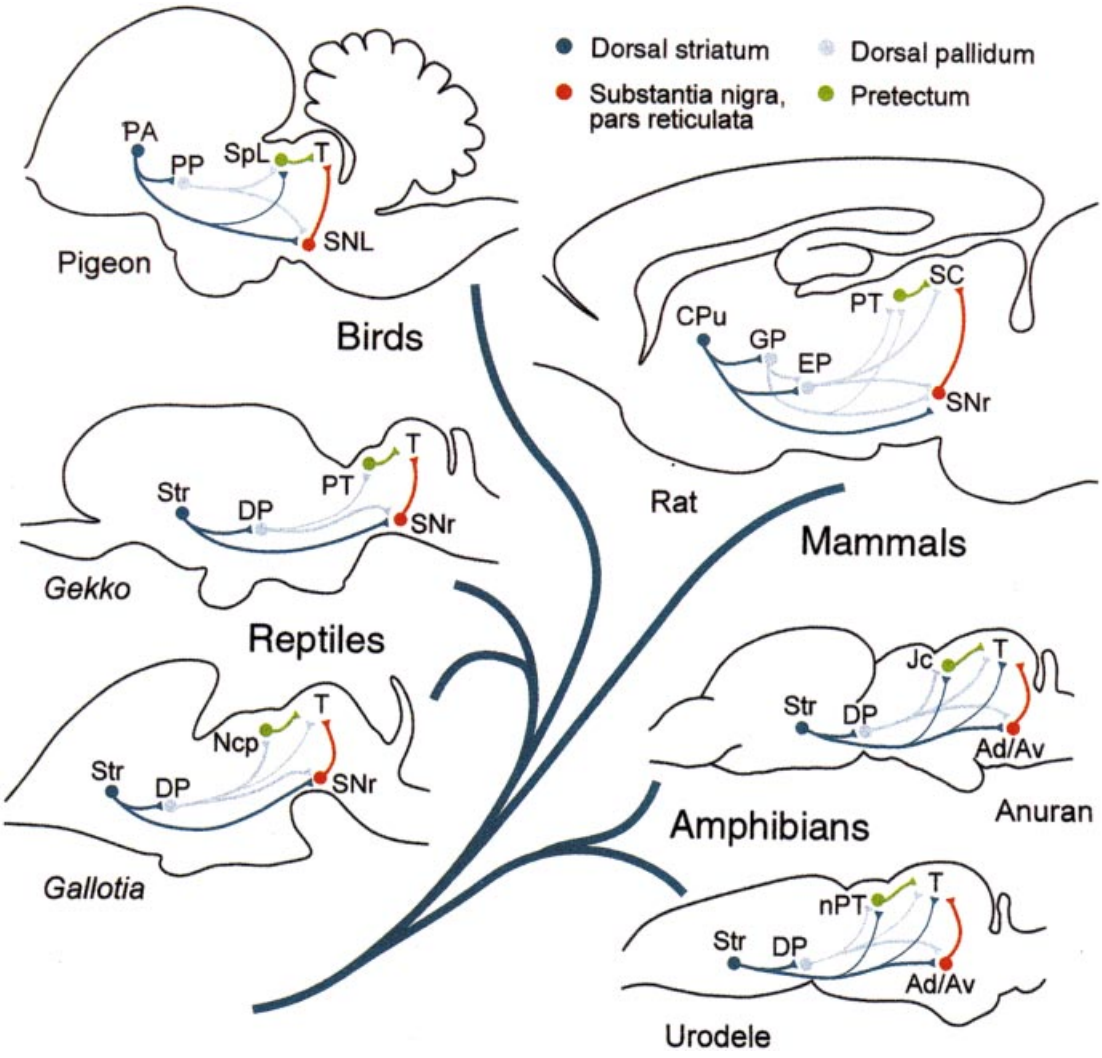


Fig. 4. Evolution of the striatonigral pathway in tetrapods. Phylogenetic tree of transverse sections of representatives of the 4 classes of tetrapods showing the different conditions observed in the topographical relationship between the terminal field of the striatonigral projection (red dashes) and the dopaminergic cell bodies of the substantia nigra pars compacta and the ventral tegmental area (blue dots). See Fig. 1 caption for abbreviations.

Fig. 5. Basal ganglia-tectal connections in tetrapods. Phylogenetic tree showing schematic drawings of the various ways by which the striatopallidal system can influence the superior colliculus or tectum of tetrapods. Predominant pathways are indicated by thick lines and less prominent projections by thin lines. In the light of recent anatomical findings, the basal ganglia involvement in visuomotor behavior in tetrapods appears to be far more complex than previously thought. See Fig. 1 caption for abbreviations.



poral coding of movements elicited in the tectum by convergence of the multiple pathways on a particular set of tectofugal neurons.

In mammals, it is known that outflow from the striatopallidal sytem relays not only to the cortex via a series of striato-pallido-thalamo-cortical loops and superior colliculus, but also to several pontine and medullary centres (Parent & Hazrati, 1995*a*, *b*). Thus dorsal and ventral pallidal efferents terminate in the mesopontine tegmentum, in close relation to the cholinergic neurons of the pedunculopontine tegmental nucleus (Rye et al. 1987; Groenewegen et al. 1993). In reptlies and birds, BG projections terminate in the isthmic tegmentum close to the cholinergic cell group that has been considered homologous to the mammalian pedunculopontine tegmental nucleus (Medina et al. 1993; Medina & Reiner, 1994). Recently, a similar projection has been demonstrated in amphibians (Marín et al. 1997*c*, *e*, 1999), suggesting that a BG projection to a cholinergic cell group in the isthmic tegmentum is a conservative feature of BG organisation of tetrapods that might already have been present in their ancestors (Fig. 2). It has been proven that these isthmic cell groups provide a cholinergic input to the midbrain tectum (Inglis & Winn, 1995; Takakusaki et al. 1996; Marín et al. 1999), probably exerting an excitatory influence on tectal neurons (Inglis & Winn, 1995).

NONTETRAPOD BG ORGANISATION

Because of the apparently conservative nature of BG organisation in the brains of tetrapods, the intriguing question that arises now is whether a similar organisation might exist in nontetrapod vertebrates. In other words, do cyclostomes and fishes display traits that are comparable to BG structures in tetrapods? Unfortunately, little information is available about structures in the forebrain of fishes that could be homologous to the BG structures of tetrapods. So far, hypotheses about BG in nontetrapods are primarily based on histochemical criteria such as staining for TH, substance P, and enkephalin. Connectional studies, on the contrary, are largely missing, as are developmental studies. A comparison is further complicated by the fact that in teleost fish the telencephalon is not evaginated but everted, which results in an unusual topography of the telencephalon (Meek & Nieuwenhuys, 1998). The comparison is also hampered by the fact that in many elasmobranchs the telencephalic ventricle is largely reduced resulting in a massive forebrain even with no clear demarcation between pallial and subpallial regions. The same holds for hagfishes, which possess a very peculiar forebrain, also lacking ventricles and being very compact in structure (Wicht & Northcutt, 1992). It is therefore not surprising that some authors have tried to define BG structures by using antibodies against TH, substance P and enkephalin. Such an approach has not led to an unequivocally accepted delineation of striatal and pallidal structures, although that has sometimes been claimed (Reiner et al. 1998).

Striatopallidal systems

The periventricular ventrolateral area (apvl, Fig. 6*A*) of dogfishes has been considered homologous to the striatum (Northcutt et al. 1988; Reiner et al. 1998), primarily based on the presence of cells immunoreactive for substance P and enkephalin and TH-immunoreactive fibres. However, we found the densest plexus of TH immunoreactive fibres in a more lateral position (Fig. 6*B*), which has been labelled previously as striatum (Smeets et al. 1983). Conversely, the densest dopaminergic innervation of the basal forebrain of skates is located more medially, internal to the area superficialis basalis (Meredith & Smeets, 1987). The latter structure has been considered homologous to the pallidum because of its relative high content of fibres immunoreactive for substance P and enkephalin (Northcutt et al. 1988). Remarkably, the same structure is also densely innervated by putative dopaminergic fibres. Similar observations have been made in the brain of lampreys (Pombal et al. 1997) and bony fishes (for refs, see Reiner et al. 1998). However, it is obvious that other criteria such as connections and development have to be considered before final conclusions about the presence of BG structures equivalent to the dorsal and ventral striatopallidal systems of tetrapods can be drawn.

Nigrostriatal and striatonigral connections

In all anamniotes studied so far, a dopaminergic cell group is located at the level of the diencephalic-mesencephalic transition (posterior tubercle) and appears to give rise to the dopaminergic innervation of the basal forebrain. In cyclostomes and bony fishes, this cell group is restricted to prosomeres 1–3, lacking a mesencephalic portion. In some bony fishes, e.g. *Polypterus* and the stickleback, they are found only in prosomere 3 (see Reiner et al. 1998 for discussion). In lungfishes and, in particular, sharks and skates (elasmobranchs), a distinct mesencephalic dopa-

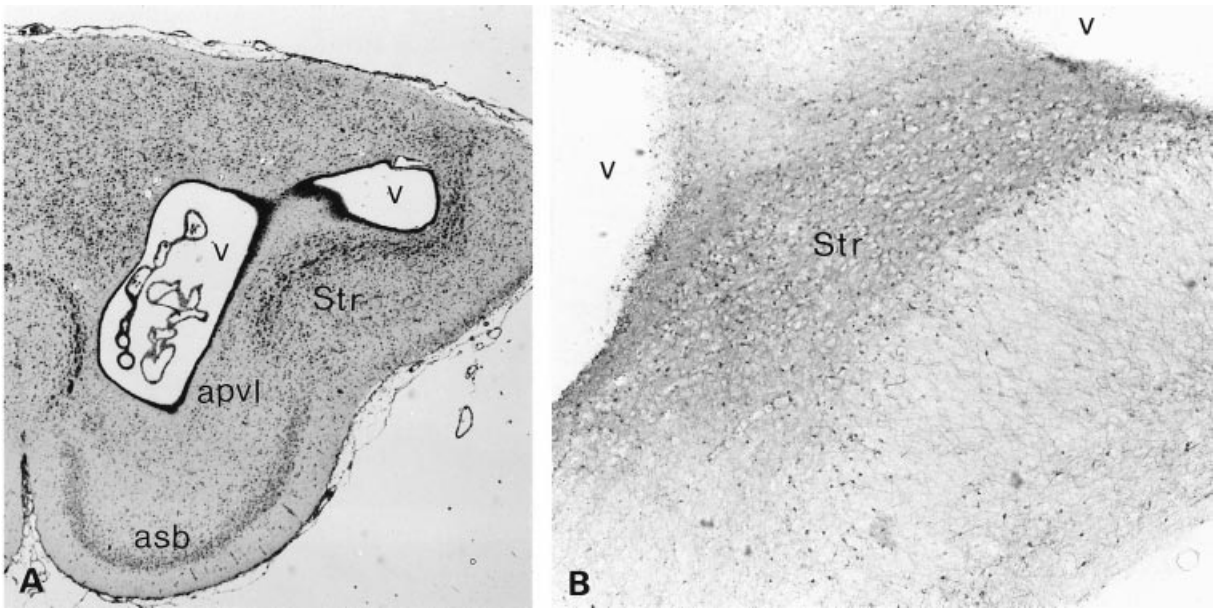


Fig. 6. (*A*) Transverse (hemi)section through the rostral telencephalon of the dogfish *Scyliorhinus canicula* showing the position of the area periventricularis ventrolateralis (apvl), the area superficialis basalis (asb) and the striatum (str) as depicted by Smeets et al. (1983). (*B*) Higher magnification of a corresponding transverse section stained immunohistochemically for TH, showing a higher immunoreactivity in the presumed striatum. Note also the numerous TH-immunoreactive cell bodies.

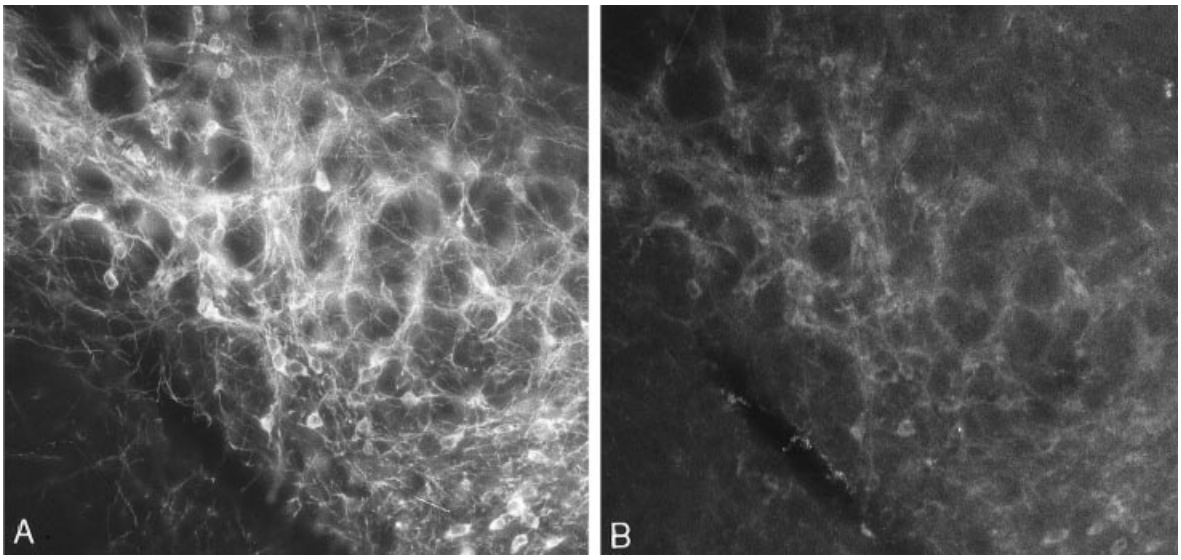


Fig. 7. Photomicrographs of transverse sections of the substantia nigra of the lizard *Gekko gecko*, showing cell bodies that are immunofluorescent for TH (*A*) and NOS (*B*). Lateral is to the left, medial to the right. Note that almost every NOS immunoreactive cell stains for TH.

minergic cell group is recognised. In elasmobranchs, medial and lateral subdivisions of this group are found, resembling in position the VTA and SN, respectively, of amniotes. The mesencephalic part of the VTA-SN dopaminergic cell group, however, is lacking in the sister group of the elasmobranchs, i.e. the Holocephali (ratfishes). Thus considerable differences in the extent of the VTA-SN dopaminergic cell group are noted even between species belonging to the same class of vertebrates. Whether such differences have consequences for the innervation of specific brain regions is still unknown, since detailed information about the connections of these dopaminergic cells is not available.

On the basis of the distribution of substance P and enkephalin immunoreactive fibres, it is assumed that in all vertebrates, striatonigral projections containing these transmitters, are present. For example, dense

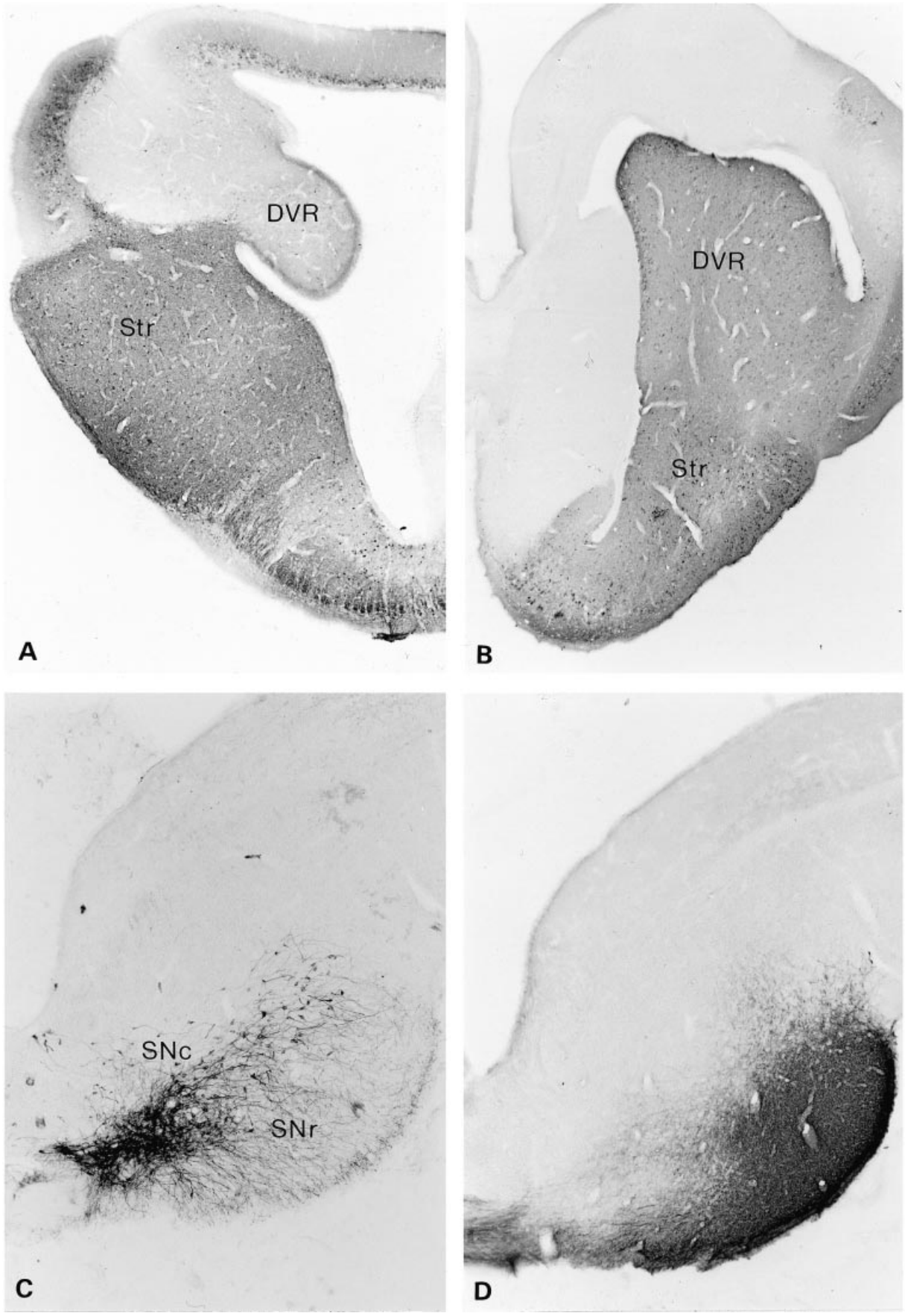


Fig. 8. For legend see opposite.

substance P fibre plexuses are found adjacent to dopaminergic cells in the posterior tubercle and the midbrain tegmentum as experimentally confirmed for amphibians. Similar conditions hold for sharks as can be inferred from the study by Northcutt et al. (1988).

NEW VISTAS THROUGH A COMPARATIVE APPROACH

Apart from more insight in the evolution of BG organisation, the comparative approach has revealed several features that may be of great interest for a better understanding of the functioning or dysfunctioning of these structures.

A remarkable feature of the forebrain of elasmobranch fish are the numerous TH-immunoreactive cell bodies in subpallial and, in particular, pallial regions (Fig. 6*B*; Stuesse et al. 1994). The first evidence that these cell bodies might be dopaminergic was provided by Meredith & Smeets (1987) using antibodies that were specifically raised against dopamine. Later, such neurons have also been noted in lampreys (Pombal et al. 1997), and bony fish (Meek, 1994), but not in amphibians (González & Smeets, 1994) and birds (Reiner et al. 1994). In reptiles, a limited number of TH-immunopositive, but dopamine-immunonegative cell bodies occur in pallial forebrain regions (Smeets, 1994). TH immunoreactive cells have also been reported in the forebrain of mammals. Initially, it was thought that, in rats, these cells transiently expressed TH immunoreactivity during development (Specht et al. 1981). More recent studies have revealed that such neurons also occur in the brains of adult rats, but primarily in cortical regions (Tashiro et al. 1989). However, striatal TH-immunoreactive neurons are particularly numerous in primates (Dubach et al. 1987; Dubach, 1994; Ikemoto et al. 1998). The reason why these neurons have not received much attention may be related to their paucity in rats and to the widespread belief that dopaminergic innervation of the striatum is exclusively extrinsinc. This view is challenged by recent studies in monkeys showing changes in number and/or morphology of striatal TH immunoreactive cells after MPTP treatment suggesting an upregulation of dopamine synthesis in these intrinsic striatal neurons (Dubach, 1994; Betarbet et al., 1997). This upregulation lasted at least for 2 y after the treatment (Betarbet et al. 1997), but it is unknown whether L-DOPA treatment has an effect on it. Given that a similar condition may be present in humans, it might be one of the reasons why the first symptoms of Parkinson's disease are recognised only when the majority of the midbrain dopaminergic cells are already lost. It is obvious that these intrinsic striatal dopaminergic cells are of tremendous potential interest, in particular when such cells can be recruited to produce and release dopamine within the striatum of patients suffering from Parkinson's disease. The TH/DA immunoreactive cells in the forebrain of cartilaginous fishes may perhaps serve as a model for studying functional aspects of such cells.

Another aspect that deserves some attention is the distribution of nitric oxide synthase (NOS) in relation to catecholaminergic structures. By means of a double fluorescence technique in a lizard (*Gekko gecko*), we found a substantial number of cells in the VTA and, in particular, the SNc (Fig. 7) that display double fluorescence (Smeets et al. 1997). The general impression was that almost all NOS-immunoreactive cells in the SNc and retrorubral (A8) cell group also stain with the TH antiserum. A similar extensive colocalisation has been reported for birds (Panzica et al. 1996), but seems to be absent or limited in amphibians and mammals (Johnson & Ma, 1993; González et al. 1996). Less than 1% of the TH immunoreactive cells in the VTA appear also to contain NOS, as demonstrated with the NADPH-diaphorase staining technique (Johnson & Ma, 1993). No colocalisation was found in the SNc or any other catecholaminergic cell group of mammals. It is noteworthy that NOS/NADPH-diaphorase positive cell bodies have been found to be more resistant to the noxious effects of excitatory amino acids and hypoxia, and to be spared during degenerative processes which occur in Huntington's disease and Alzheimer's disease (for references, see Smeets et al. 1997). It would be of great interest to know whether such a neuroprotective role for nitric oxide holds also for the dopaminergic midbrain cell groups of reptiles and birds.

Fig. 8. (*A*, *B*) Photomicrographs showing the distribution of DARPP-32 immunoreactivity in transverse sections through the forebrain of the turtle, *Pseudemys scripta elegans* (*A*) and the lizard *Gekko gecko* (*B*). Note the dense staining of the striatum, including cellular and fibre staining, and the striking difference in staining in the dorsal ventricular ridge (DVR). (*C*, *D*) Photographs of adjacent transverse sections through the midbrain tegmentum of the turtle stained for TH (*C*) and DARPP-32 (*D*) illustrating the relationship between the descending striatonigral pathway and the dopaminergic cell bodies in the substantia nigra.

CONCLUDING REMARKS

From the previous account it is clear that BG structures of amniotes and tetrapod anamniotes (amphibians) share many features. Some of those features may also be shared with nontetrapod anamniotes, but for the latter group of vertebrates, we are in desperate need for detailed information about connections, chemoarchitecture and development, such as the pattern of homeobox genes. In order not to confuse the reader, we have tried to stay to the main lines of BG organisation, emphasising the common features so as to discover general rules about how these structures function and change. Another aim of the comparative approach is to relate the BG organisation to physiology and behaviour. It is obvious that there are considerable qualitative and quantitative differences in BG structures among vertebrates, even between species belonging to the same class or even order. Such differences may reflect differences in certain aspects of behaviour, but we are still far away from answering such questions. To exemplify the difficult task of the comparative neurobiologist, we refer to the distribution of the phosphoprotein DARPP-32, which is known to be localised on dopaminoceptive cells that possess dopamine-sensitive adenylate cyclase (D1 dopamine receptors). In mammals, DARPP-32 is primarily found in the caudate-putamen, nucleus accumbens and olfactory tubercle (Greengard et al. 1998). Since this phosphoprotein is located not only on the soma and dendrites, but also on the axons and axon terminals of striatal projection neurons, dense staining for DARPP-32 is found in the globus pallidus and the SNr. Similar conditions have been found in reptiles (Fig. 8; Smeets & González, unpublished observations) and birds (Anderson & Reiner, 1991), but in amphibians, only very weak DARPP-32 immunoreactivity was observed in the basal forebrain (González, unpublished observations). The latter finding suggests a major quantitative difference in signal transduction between amphibians and amniotes. On the other hand, the same study has shown that, contrary to what has been stated before (Hemmings & Greengard, 1996), DARPP-32 is present in the CNS of anamniotes, and is even very distinct in the midbrain tectum, as in reptiles. Figure 8 also makes clear that chemoarchitectonic criteria alone are not conclusive for defining the nature of brain regions. In *Gekko*, the DVR resembles more the striatum with respect to its staining for DARPP-32, whereas in *Pseudemys* the corresponding structure shows more similarity with cortical areas. This finding fits well with the previously reported difference in the degree of dopaminergic innervation of the DVR in both reptilian species and contributes to the ongoing discussion about the true nature of the latter structure.

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