J. Anat. (2000) **196**, pp. 527–542, with 4 figures Printed in the United Kingdom

Review

Synaptic organisation of the basal ganglia

J. P. BOLAM, J. J. HANLEY, P. A. C. BOOTH AND M. D. BEVAN

MRC Anatomical Neuropharmacology Unit, Department of Pharmacology, Oxford, UK

(*Accepted 5 November 1999*)

ABSTRACT

The basal ganglia are a group of subcortical nuclei involved in a variety of processes including motor, cognitive and mnemonic functions. One of their major roles is to integrate sensorimotor, associative and limbic information in the production of context-dependent behaviours. These roles are exemplified by the clinical manifestations of neurological disorders of the basal ganglia. Recent advances in many fields, including pharmacology, anatomy, physiology and pathophysiology have provided converging data that have led to unifying hypotheses concerning the functional organisation of the basal ganglia in health and disease. The major input to the basal ganglia is derived from the cerebral cortex. Virtually the whole of the cortical mantle projects in a topographic manner onto the striatum, this cortical information is 'processed' within the striatum and passed via the so-called *direct* and *indirect* pathways to the output nuclei of the basal ganglia, the internal segment of the globus pallidus and the substantia nigra pars reticulata. The basal ganglia influence behaviour by the projections of these output nuclei to the thalamus and thence back to the cortex, or to subcortical 'premotor' regions. Recent studies have demonstrated that the organisation of these pathways is more complex than previously suggested. Thus the cortical input to the basal ganglia, in addition to innervating the spiny projection neurons, also innervates GABA interneurons, which in turn provide a feed-forward inhibition of the spiny output neurons. Individual neurons of the globus pallidus innervate basal ganglia output nuclei as well as the subthalamic nucleus and substantia nigra pars compacta. About one quarter of them also innervate the striatum and are in a position to control the output of the striatum powerfully as they preferentially contact GABA interneurons. Neurons of the pallidal complex also provide an anatomical substrate, within the basal ganglia, for the synaptic integration of functionally diverse information derived from the cortex. It is concluded that the essential concept of the direct and indirect pathways of information flow through the basal ganglia remains intact but that the role of the indirect pathway is more complex than previously suggested and that neurons of the globus pallidus are in a position to control the activity of virtually the whole of the basal ganglia.

Key words: Striatum; globus pallidus; corticostriatal; pallidostriatal; GABA interneurons; substantia nigra; synaptic convergence.

INTRODUCTION

The basal ganglia are a group of subcortical nuclei involved in a variety of processes including motor, associative, cognitive and mnemonic functions. The dorsal division of the basal ganglia consists of the striatum (or caudate-putamen), the globus pallidus (GP, external segment of the globus pallidus in primates), entopeduncular nucleus (EP, internal segment of globus pallidus in primates, GPi), the subthalamic nucleus (STN) and the substantia nigra (SN). The latter structure is divided into 2 main parts, the dorsal pars compacta (SNc) in which the dopaminergic nigrostriatal neurons are located and the more ventral pars reticulata (SNr). In addition to these structures which are associated with motor and associative functions there is a ventral division of the basal ganglia (ventral striatum or nucleus accumbens; ventral pallidum and ventral tegemental area) that is associated with limbic functions.

The major input to the basal ganglia is derived from the cortex; virtually the whole of the cortical mantle

Correspondence to Dr J. P. Bolam, MRC Anatomical Neuropharmacology Unit, Department of Pharmacology, Mansfield Road, Oxford OX1 3TH, UK. Tel: +44 (0) 1865 271 869; fax: +44 (0) 1865 271 647; e-mail: paul.bolam@pharmacology.ox.ac.uk

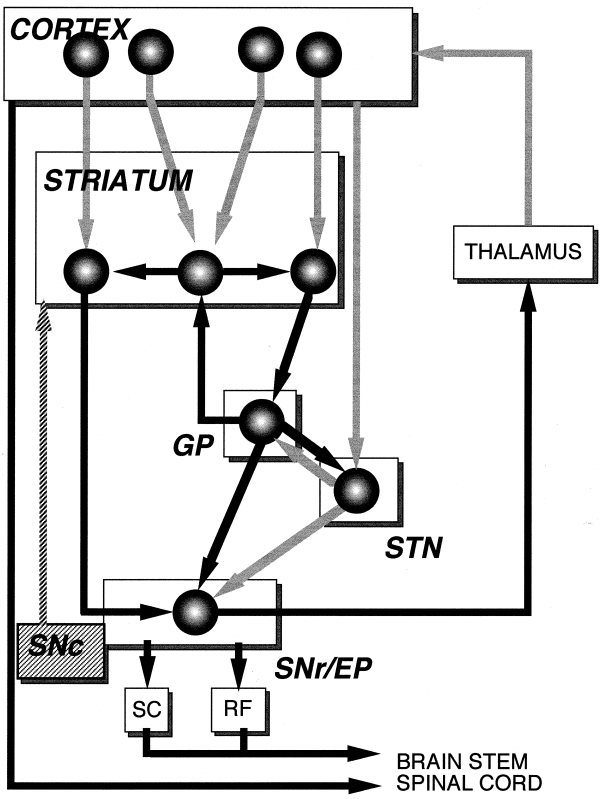

Fig. 1. Simplified block diagram of the circuitry of the basal ganglia. Inhibitory projections are shown by mottled lines, excitatory projections by dotted lines. Cortical information that reaches the striatum is conveyed to the basal ganglia output structures (SNr/EP, substantia nigra pars reticulata/entopeduncular nucleus) via 2 pathways, a direct inhibitory projection from the striatum to SNr/EP and an indirect pathway, which involves an inhibitory projection from the striatum to globus pallidus (GP), an inhibitory projection from the GP to the subthalamic nucleus (STN) and to the output nuclei and an excitatory projection from the STN to SNr/EP. The information is then transmitted back to the cerebral cortex via the thalamus or conveyed to various brainstem structures including the superior colliculus (SC) and the parvicellular reticular formation (RF). Dopaminergic neurons of the SNc provide a massive feedback projection to the striatum (hatched line) and modulate the flow of cortical information. A proportion of GP neurons also feedback to the striatum where they innervate interneurons which also receive cortical input. Cortical information can also reach the basal ganglia via the cortico-subthalamic projection.

projects onto the basal ganglia in a highly topographical manner. The main point of entry of this cortical information to the basal ganglia is the striatum although there are significant cortical projections to the STN. The corticostriatal projection imparts functionality on to the striatum and consequently other divisions of the basal ganglia. In what is now considered the classic view of basal ganglia circuitry (Albin et al. 1989; DeLong, 1990; Smith et al. 1998), the functional organisation is such that cortical information carried by the corticostriatal projection is processed within the striatum, integrated with the many other inputs to the basal ganglia (e.g. intralaminar thalamic nuclei, amygdala, hippocampus, dorsal raphe) which primarily innervate the striatum, and then the 'processed information' is transmitted to the output nuclei of the basal ganglia, the EP and the SNR. The basal ganglia influence behaviour by these output nuclei projecting to the ventral thalamus and then back to the cortex or by projecting to subcortical 'premotor' regions including the superior colliculus, the pedunculopontine nucleus or the reticular formation (Fig. 1) (see Albin et al. 1989; DeLong, 1990; Bolam & Bennett, 1995; Gerfen & Wilson, 1996; Smith et al. 1998 for recent reviews).

The transmission of cortical information through the basal ganglia occurs through 2 routes, the 'direct' and 'indirect' pathways (Albin et al. 1989; DeLong, 1990). In the *direct pathway* corticostriatal information is transmitted directly from the striatum to the output nuclei. In the *indirect pathway* corticostriatal information is transmitted indirectly to the output nuclei via the complex network interconnecting the GP and STN (Shink et al. 1996; Fig. 1). Data from a variety of disciplines, but particularly the pioneering work of Deniau and colleagues (Chevalier & Deniau, 1990), Albin and colleagues (Albin et al. 1989) and DeLong (DeLong, 1990), has shown that the output signal of the basal ganglia under resting conditions is one of inhibition, and that there is a loss of inhibition during a basal ganglia associated behaviour. This is brought about by the neurochemical nature of neurons in the pathways and their basal activity. Striatal projection neurons are GABAergic and quiescent under resting conditions; basal ganglia output neurons are also GABAergic but have a high discharge rate, tonically inhibiting the targets of the basal ganglia, i.e. neurons in the ventral thalamus or subcortical premotor regions. When the system is activated by the firing of corticostriatal glutamatergic neurons, striatal neurons discharge, which in turn causes inhibition of basal ganglia output neurons in the SNR and EP. This reduction in firing of basal ganglia output neurons leads to release from inhibition, or disinhibition, of neurons in the targets of the basal ganglia and is associated with 'basal ganglia behaviour'. In contrast to this, activation of the indirect pathway or network leads to the opposite physiological effect, i.e. increased firing of output neurons and increased inhibition of basal ganglia targets. It has been suggested that tonic activity of STN neurons is the driving force for the resting activity in basal ganglia output nuclei (Bevan & Wilson, 1999; Nakanishi et al. 1987). Under normal conditions during basal ganglia associated behaviour, the output of the basal ganglia is a complex

spatiotemporal pattern of increased and decreased firing, i.e. inhibition and disinhibition. It has been suggested that the indirect pathway acts to attenuate or terminate a basal ganglia associated movement or to suppress unwanted sequences of movement (Mink & Thach, 1993).

Overlying this 'feed-forward' organisation of the basal ganglia are many feedback pathways. The major one of these is the dopaminergic projection from the SNC to the striatum. This projection modulates the flow of cortical information through the basal ganglia. Loss of these neurons in Parkinson's disease leads to an imbalance of the flow of cortical information through the basal ganglia in favour of the indirect pathway and hence the akinetic behaviour associated with this disorder (Albin et al. 1989; DeLong, 1990).

The subject of this communication is first, to briefly review the synaptology underlying the pathways of information flow through the basal ganglia, secondly, to demonstrate how new knowledge of the connections of individual neurons in the basal is leading to modifications or an elaboration of the classical models of the circuits and thirdly, to demonstrate one of the sites of integration of functionally diverse information in the basal ganglia.

SYNAPTIC TARGETS OF THE CORTICOSTRIATAL PROJECTION

The striatum contains both projection neurons and several populations of interneurons (Bolam & Bennett, 1995; Kawaguchi et al. 1995; Kawaguchi, 1997). The major type of projection neuron is the medium size densely spiny neuron (spiny neuron; Fig. 2*A*). They account for 90–95% of the total population of striatal neurons (Kemp & Powell, 1971*a*), utilise GABA as their major neurotransmitter and are subdivided into 2 major populations on the basis of their projection region, pattern of axonal collateralisation and their neurochemical content (for reviews see Smith & Bolam, 1990; Bolam & Bennett, 1995; Gerfen & Wilson, 1996; Kawaguchi, 1997; Smith et al. 1998). One subpopulation projects preferentially to the output nuclei of the basal ganglia and expresses, in addition to GABA, the neuropeptides substance P and dynorphin and the D1 subtype of dopamine receptors. The second subpopulation projects almost exclusively to the GP and expresses enkephalin and the D2 subtype of dopamine receptors. Evidence from morphological studies, including intracellular filling of neurons (see Chang & Wilson, 1990) or Golgi impregnation (see Pasik et al. 1979) have demonstrated that spiny neurons also give rise to extensive local axon collaterals, one of the major synaptic targets of which are other spiny neurons (Wilson & Groves, 1980; Somogyi et al. 1981). This is supported by the findings that terminals that display immunoreactivity for the neuropeptides expressed by spiny neurons, i.e. enkephalin or substance P, and possess the morphological features of spiny neuron terminals, make symmetric synaptic contact with the dendrites, spines and perikarya of spiny neurons (Pickel et al. 1980, 1992; Aronin et al. 1981; DiFiglia et al. 1982; Somogyi et al. 1982; Bolam et al. 1983; Bouyer et al. 1984*b*; Bolam & Izzo, 1988).

The early anterograde degeneration studies demonstrated that corticostriatal terminals form asymmetric synapses primarily with dendritic spines (Kemp & Powell, 1971*b*, *c*). The fact that spiny projection neurons are the major spine-bearing neurons in the striatum indicates that these cells are likely to be the major targets of the corticostriatal projection (Kemp & Powell, 1971*b*, *c*). Indeed, the result of direct analysis has demonstrated that corticostriatal terminals make synaptic contact with the heads of spines of spiny projection neurons which give rise both to the direct and indirect pathways (Frotscher et al. 1981; Somogyi et al. 1981; Dube et al. 1988; Hersch et al. 1995; Fig. 2*B*). Wilson and colleagues (Kincaid et al. 1998) have proposed that an individual cortical neuron makes very few synaptic contacts with an individual striatal neuron, that there is a high degree of convergence of corticostriatal neurons onto individual striatal neurons but close neighbours do not share common cortical inputs. The activation of corticostriatal neurons leads to the release of glutamate, activation of both AMPA and NMDA receptors that are localised almost exclusively within the synapse (Ber-nard et al. 1997; Bernard & Bolam, 1998; Fig. 2*C*) which leads to depolarisation of the neuron (Wilson, 1993; Kita, 1996); a volley of action potentials follows if there is sufficient convergent excitatory input to an individual spiny neuron (Wilson, 1993; Stern et al. 1997, 1998).

The excitatory cortical input to spiny neurons is modulated by the many other inputs to spiny neurons, including those from extrinsic sources and from local interneurons (see Smith & Bolam, 1990; Bolam & Bennett, 1995; Kawaguchi, 1997 for reviews of the synaptology of spiny neurons). Of particular importance is the input from the dopaminergic terminals derived from the SNC which degenerate in Parkinson's disease. These terminals form symmetric synaptic contacts mainly with the necks of dendritic spines of spiny projection neurons (Bouyer et al. 1984; Freund et al. 1984; Smith et al. 1994; Hanley &

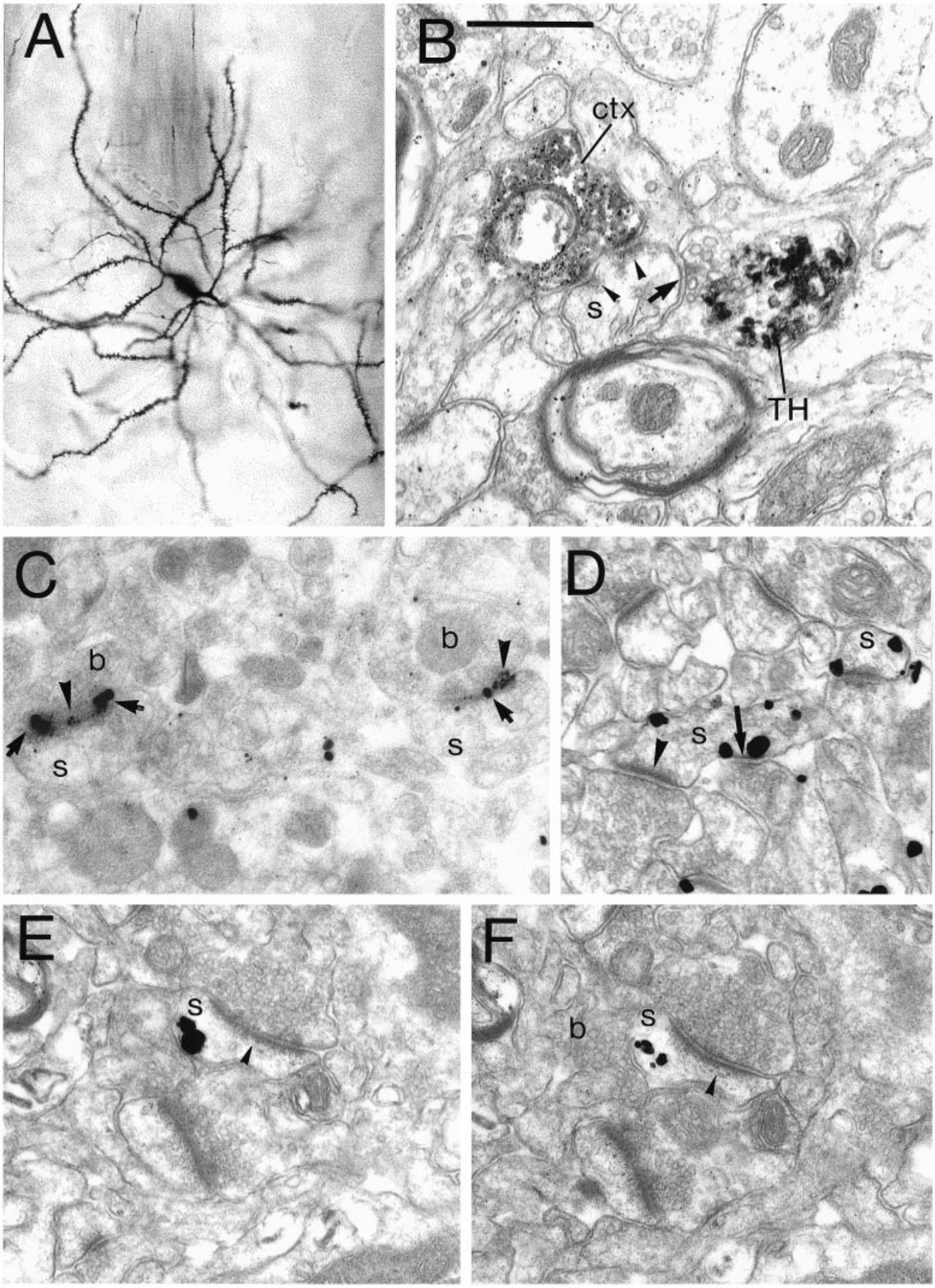

Fig. 2. For legend see opposite.

Bolam, 1997). The head of spines that receive the dopaminergic input invariably receive input from terminals forming asymmetric synapses (Freund et al. 1984) which are generally derived from the cortex (Fig. 2*B*; Bouyer et al. 1984; Smith et al. 1994). This anatomical arrangement is ideally suited for the dopamine released from the nigrostriatal terminal, which is likely to act on dopamine receptors localised both within the synapse and at extrasynaptic sites (Fig. 2*D–F*; Yung et al. 1995), to very selectively modulate the response to the excitatory input at the head of the spine. Other inputs to spiny neurons, e.g. cholinergic input, exhibit a similar anatomical organisation (Izzo & Bolam, 1988; Pickel & Chan, 1990) and GABAergic terminals are also observed in contact with the necks of spines (Bolam et al. 1985).

SYNAPTOLOGY OF THE DIRECT AND INDIRECT PATHWAYS

The synaptology of the direct and indirect pathways downstream of the striatum is essentially as indicated in Figure 1 (see Smith et al. 1998 for a detailed bibliography). Thus spiny neurons giving rise to the direct pathway make direct synaptic contact with neurons of the EP (or GPi; Moriizumi et al. 1987; Bolam & Smith, 1992; Bevan et al. 1994; Shink & Smith, 1995), the majority of which are output neurons (Carter & Fibiger, 1978), and output neurons of the substantia nigra reticulata (Somogyi et al. 1979; Williams & Faull, 1985; Smith & Bolam, 1991; Bolam et al. 1993). The release of GABA following their stimulation will therefore lead to an inhibition of the output neurons of the basal ganglia and thus a disinhibition of the targets of the basal ganglia. Similarly, spiny neurons giving rise to the indirect pathway make direct synaptic contact with neurons of the GP (Chang et al. 1981; Totterdell et al. 1984), these neurons make synaptic contact with the neurons of the STN (Smith et al. 1990; Shink et al. 1996) which in turn innervate neurons of the output nuclei (Bevan et al. 1994; Bevan & Bolam, 1995; Shink & Smith, 1995). Neurons of the GP also directly contact the output neurons of the basal ganglia (Smith & Bolam, 1989; Kincaid et al. 1991). Thus inhibition of neurons of the GP, which themselves are also GABAergic, by the increased activity of striatal spiny neurons will lead to increased firing of the output neurons by 2 mechanisms. First, the loss of inhibitory input to the excitatory neurons of the STN will lead to increased activity and hence increased excitation of the output neurons. Secondly, the inhibition of GP neurons will have a direct disinhibitory effect on the output neurons. The consequence of the increased firing of the output neurons will be increased inhibition of neurons in the targets of the basal ganglia. Thus, in this greatly simplified scheme of the functional organisation of the basal ganglia, the synaptic organisation of the cortico–striato–fugal pathways are such that it offers simple possible explanations for

Fig. 2. (*A*) Light micrograph of a Golgi impregnated medium size spiny neuron in the striatum of a rat. Note the medium sized perikaryon (approximately 15 μm in diameter), the spine-free proximal dendrites and the densely spiny secondary and higher order dendrites. (*B*) Convergence of cortical and dopaminergic terminals at the level of an individual spine in the striatum. Electron micrograph of a dendritic spine (s) in the putamen of a squirrel monkey. The spine is postsynaptic to a terminal that forms an asymmetric specialisation (arrowheads) and is anterogradely labelled from the motor cortex (ctx) (anterograde tracer: biocytin, revealed using the peroxidase method and diaminobenzidine (DAB) as the chromogen). The terminal contains the characteristic electron dense and amorphous DAB reaction product. The spine is also postsynaptic to a terminal (TH) that forms symmetric specialisations (arrow) and is immunoreactive for tyrosine hydroxylase thus identifying it as a nigrostriatal dopaminergic terminal. The tyrosine hydroxylase immunoreactive sites were identified by an immunoperoxidase method using benzidine dihydrochloride as the chromogen which produces an irregular and more electron dense reaction product. (Data from Smith et al. 1994). (*C*) Colocalisation of the NR1 subunit of the NMDA receptor and the GluR2/3 subunit of the AMPA receptor at synapses in the striatum. Immunoreactive sites were revealed by a postembedding immunogold method with silver intensification on freeze-substituted Lowicryl-embedded sections. The NR1 subunit was detected using a monoclonal antibody NR1 and secondary antibody coupled to 10 nm diameter colloidal gold (large immunoparticles; arrows). The GluR2/3 subunits were identified with a rabbit antibody and a secondary antibody coupled to 1.4 nm diameter colloidal gold (small immunoparticles; arrowheads). The 2 asymmetric axospinous synapses illustrated (which are probably derived from the cortex) are positive for both the AMPA and NMDA receptor subunits. b, boutons; s, spine. (Data from Bernard & Bolam, 1998). (*D*) Localisation of the D1 subtype of the dopamine receptor in the striatum. Immunoreactive sites were identified by the pre-embedding immunogold method (with silver enhancement). Two D1-immunolabelled spines (s) both of which receive asymmetric synaptic input at the head (indicated by an arrowhead in the one on the left) from a terminal that is probably derived from the cortex. One of the spines also receives input (arrow) from a bouton that forms a symmetric synapse that is associated with immunogold labelling denoting D1 receptor. This bouton has the morphological characteristics of a dopaminergic nigrostriatal terminal. (Data from Yung et al. 1995). (*E*, *F*) Localisation of the D2 subtype of the dopamine receptor in the striatum. Immunoreactive sites were identified by the pre-embedding immunogold method (with silver enhancement). Serial sections of a spine (s) that receives synaptic input from a terminal forming an asymmetric synaptic specialisation (arrowheads) (probably derived from the cortex). A second bouton that similar in morphological characteristics to a dopaminergic nigrostriatal bouton (labelled b in *F*) closely apposes the spine but a synaptic specialisation was not observed. Immunogold particles are associated with the membrane apposed to the bouton indicating the presence of D2 receptor. Note that in *F* the silver-intensified immunogold particles are at their periphery and no longer touching the membrane. (Data from Yung et al. 1995). Bar in *B* applies to all electron micrographs: 0.5 μm.

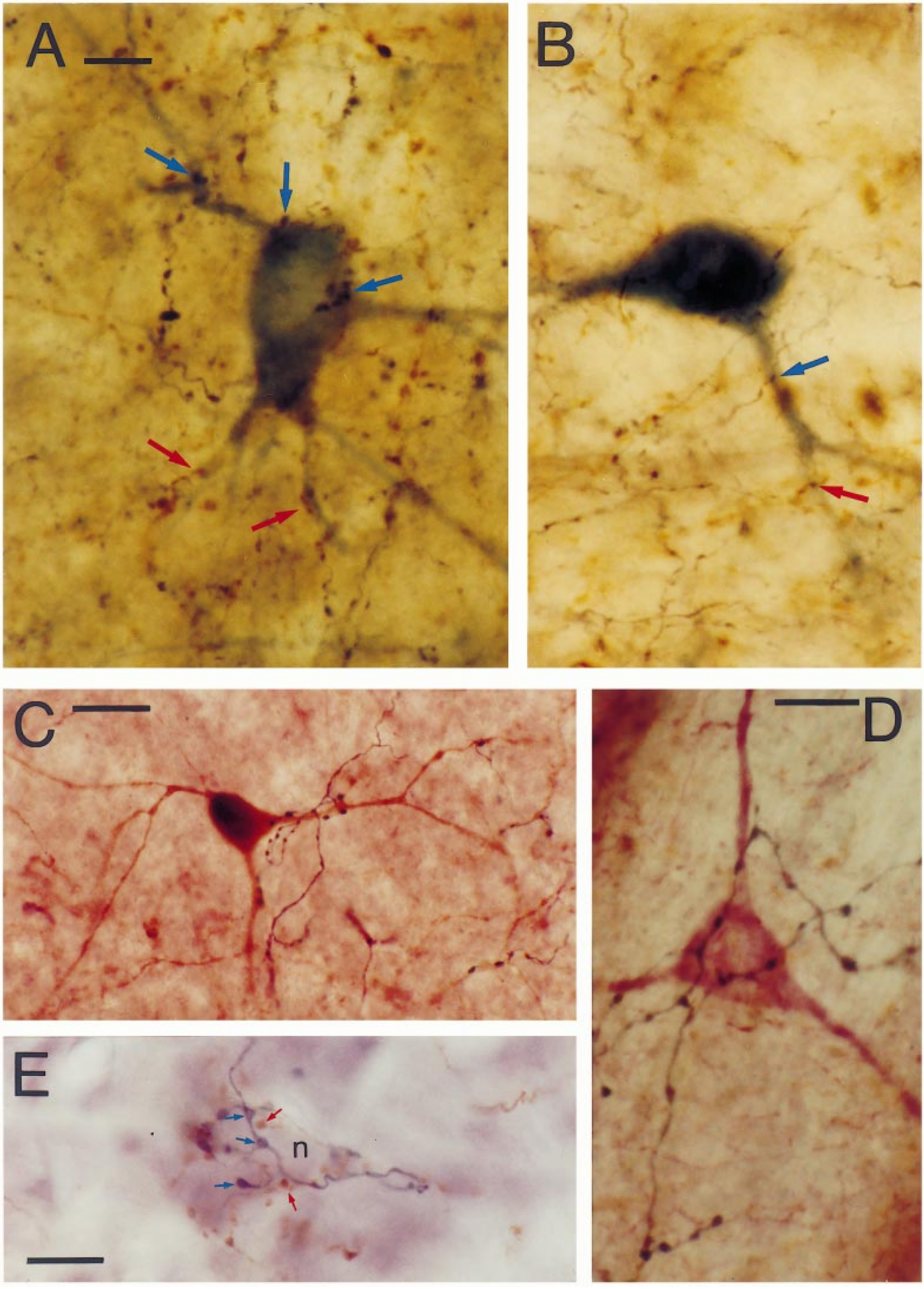

Fig. 3. For legend see opposite.

the increased and/or decreased firing of the output neurons of the basal ganglia and the neurons in the targets of basal ganglia. (For detailed discussions of the anatomical and functional organisation of the basal ganglia see reviews by Gerfen & Wilson, 1996 and Smith et al. 1998).

In the following sections, recently discovered anatomical features of the organisation of the basal ganglia that are likely to have a bearing on our understanding of the transmission of cortical information will be discussed.

GABA INTERNEURONS IN THE STRIATUM

Striatal GABAergic interneurons were originally identified on the basis of the selective uptake of exogenous [^{3}H]GABA (Iversen & Schon, 1973; Bolam et al. 1983) and glutamate decarboxylase immunocytochemistry (Ribak et al. 1979; Bolam et al. 1985; Kita & Kitai, 1988). There are several subtypes of GABA interneurons (Kubota et al. 1993; Kawaguchi, 1997) but the largest population is characterised by the presence of calcium binding protein, parvalbumin (PV) (Fig. 3 *A–C*; Cowan et al. 1990; Kita et al. 1990; Kita, 1993). These neurons account for only a small proportion of the total population of striatal neurons, possess smooth spine-free dendrites, have the ability to fire at high rates (Kawaguchi, 1993) and are interconnected by gap junctions (Kita, 1993; Koos & Tepper, 1999). Electron microscopic analysis has revealed that these cells receive synaptic input from many terminals that form asymmetric synaptic specialisations (Kita et al. 1990; Bolam et al. 1983, 1985), i.e. the type of synapses associated with the corticostriatal projection (see above). Indeed, anterograde tracing studies have demonstrated that one of the major inputs to PV-positive, GABA interneurons is from the cortex (Lapper et al. 1992; Bennett & Bolam, 1994). As with the cortical input to spiny neurons the input to GABA interneurons is associated with AMPA receptors localised within the synaptic specialisation (Bernard et al. 1997). It is interesting to note that following cortical stimulation these neurons increase expression of Fos over a larger area of striatum than do spiny neurons (Parthasarathy & Graybiel, 1997). Furthermore, these neurons may subserve some role in the integration of cortical afferents from different functional territories as preliminary light microscopic analyses in double anterograde tracing studies suggest that an individual neuron may receive input from both motor and sensory regions of cortex (Fig. 3 *A*, *B*; J. J. Hanley, J.-M. Deniau and J. P. Bolam, unpublished observations). Indeed, in individual sections up to 25% of all PV-positive interneurons were found to be apposed by boutons derived from both motor and sensory regions of cortex. Furthermore, up to 50% of those interneurons that were identified as receiving cortical input were apposed by terminals from both the motor and sensory regions of cortex.

The major synaptic target of the GABA interneurons are spiny output neurons (Kita et al. 1990; Bennett & Bolam, 1994). Individual spiny neurons receive a basket-like innervation around their perikarya from PV-positive terminals, the majority of which are likely to be derived from the PV-positive GABA interneurons. On the basis of this anatomical organisation and the failure to detect inhibitory signals mediated by the collaterals of spiny neurons (Jaeger et al. 1994) despite the presence of synapses (Wilson & Groves, 1980; Somogyi et al. 1981*a*; Yung et al. 1996), it has been proposed that the GABA interneurons are the principal mediators of lateral

Fig. 3. (*A*, *B*) Convergence of motor and sensory corticostriatal fibres on GABA interneurons in the rat striatum. Animals received injections of *Phaseolus vulgaris*-leucoagglutinin in the motor cortex (M1) and biotinylated dextran amine in the sensory cortex (S1). The striatum was then processed to reveal the anterogradely corticostriatal fibres with different reaction products (blue/black nickel enhanced DAB for motor cortical fibres (blue arrows) and brown DAB for sensory cortical fibres (red arrows)) and PV immunoreactive neurons (using Vector SG as the chromogen). Parvalbumin is a marker for the major population of GABA interneurons in the striatum. The GABA neurons are located in a region of striatum where there is overlap between the motor cortical and sensory cortical fibres, and are closely apposed by terminals derived from both regions of cortex (arrows). (Unpublished data, J. J. Hanley, J.-M. Deniau and J. P. Bolam). Bar, 20 μm. (*C*) Selective innervation of GABA interneurons by pallidostriatal neurons. A parvalbumin-positive GABA interneuron in the striatum revealed by the brown reaction product formed by using DAB as the chromogen for the peroxidase reaction. A pallidostriatal axon arising from the neuron in Fig. 4 *B* revealed by blue/black reaction product (nickel-enhanced DAB) forms many contacts with the proximal dendrites of the interneuron. Bar, 20 μm. (Data from Bevan et al. 1998). (*D*) Selective innervation of nitric oxide-positive interneurons by pallidostriatal neurons. A nitric oxide-positive interneuron in the striatum revealed by the purple reaction product formed by using Vector VIP as the chromogen for the peroxidase reaction. A pallidostriatal axon arising from the neuron in Fig. 4 *B* revealed by blue/black reaction product (nickel-enhanced DAB) forms many contacts with the perikaryon of the interneuron. Bar, 10 μm. (Data from Bevan et al. 1998). (*E*) Convergence of afferents from the globus pallidus and ventral pallidum on basal ganglia output neurons. An unlabelled neuron in the substantia nigra pars reticulata apposed by boutons labelled with PHA-L which was anterogradely transported from the ventral pallidum and revealed using nickel-enhanced DAB as the chromogen for the peroxidase reaction (blue-black boutons, indicated by blue arrows) and boutons labelled with BDA which was anterogradely transported from the globus pallidus and visualised using DAB as the chromogen (brown boutons indicated by red arrows). Bar, 10 μm. (Data from Bevan et al. 1996).

inhibition in the striatum and provide a feed-forward inhibition of cortical information to spiny neurons (Pennartz & Kitai, 1991; Jaeger et al. 1994; Plenz & Kitai, 1998). Indeed, paired recordings in vitro have shown that GABA interneurons produce large unitary IPSPs in spiny neurons (Koos & Tepper, 1999). Although the precise role of this inhibition is unknown, there are several possibilities. First, the effect may simply be to shunt coincident cortical excitation and limit the duration of excitation. Secondly, depending on their pattern of connectivity, the interneurons may underlie surround inhibition thereby focusing cortical excitation (Parthasarathy & Graybiel, 1997). Thirdly, by their dense local axonal arbors they might synchronise sub- and supra-threshold activity of groups of neighbouring spiny output neurons (Koos & Tepper, 1999).

It is thus evident that the PV-positive GABA interneurons receive cortical input and, despite their relatively low numbers, are in a position to powerfully control the activity of neurons giving rise to the direct and indirect pathways and thus the output of the striatum.

NEURONS OF THE GLOBUS PALLIDUS

The main synaptic targets of spiny neurons that give rise to the indirect pathway are the GABAergic neurons of the GP; they are thus key structures of the circuitry underlying the indirect pathway. The GP in turn projects to the STN, the output nuclei of the basal ganglia and the SNC. The results of tracing studies at the electron microscope level combined with postembedding immunolabelling for glutamate and GABA, suggest that *individual* neurons of the GP innervate the STN and output structures of the basal ganglia (see Bolam et al. 1993; Smith et al. 1998). Tracing and physiological studies have also indicated that the GP in addition, provides a feedback to the striatum (for references see Bevan et al. 1998). Single cell filling studies have confirmed these suggestions (Fig. 4; Kita & Kitai, 1994; Bevan et al. 1998). All pallidal neurons give rise to local axon collaterals within the GP and collalteral projections to the STN, EP and SN. About a quarter of pallidal neurons also give rise to collateral projections to the striatum (Fig. 4; Kita & Kitai, 1994; Bevan et al. 1998). On average, pallidostriatal neurons give rise to 790.6 boutons within the striatum. From the known number of neurons in the striatum and GP (2.79×10^6 and 4.6×10^4 respectively; Oorschot, 1996) and the proportion of pallidal neurons giving rise to striatal collaterals, it can be calculated that on average a striatal neuron will receive input from 3.3 pallidal boutons. It is unlikely that such a small number of synapses in a projection can impart significant information on, or significantly affect, the function of the striatum. However, combination of single-cell filling with immunolabelling for subpopulations of striatal neurons has revealed that pallidostriatal axons *selectively* innervate striatal interneurons (Bevan et al. 1998). Up to 60% (mean $\pm$ S.D.: 43.7 ± 17.8) of the striatal terminals of an individual pallidostriatal neuron make contact with PV-positive GABA interneurons (Fig. 3*C*). An individual PV-positive neuron receives on average 6.7 boutons from an individual pallidal axon and these make contact primarily in the proximal regions of the neurons. In addition, 3–32% of terminals of a single pallidal neuron make contact with nitric oxide synthase (NOS)-positive interneurons (Fig. 3*D*). The synaptic target of the remainder of the pallidal boutons is at present unknown. A quantitative model of the connectivity between pallidal neurons and GABA interneurons, assuming similar patterns of connectivity, suggests that each GABA interneuron receives input on average from 7.1 pallidal neurons that give rise to a total of 47.6 synaptic boutons (Table).

Thus despite the relatively small number of neurons and boutons that comprise the pallidostriatal pathway, pallidostriatal neurons are in a position to powerfully control the activity of the striatum by selective innervation of PV-positive GABA interneurons which in turn control the activity of the output neurons of the striatum. Since GP neurons receive monosynaptic and/or rapid disynaptic activation (via the STN; Tremblay & Filion, 1989; Ryan & Clark, 1991; Kita, 1992; Naito & Kita, 1994; Plenz & Kitai, 1998), following cortical activation they are well placed to modulate the cortical activation of PV interneurons (Pennartz & Kitai, 1991; Plenz & Kitai, 1998) through shunting of coincidental cortical excitatory postsynaptic potentials and/or phase-lock action potential generation (see Pennartz & Kitai, 1991; Cobb et al. 1995). The total number and placement of GP terminals on PV-positive GABA interneurons when compared with studies of similar unitary inhibitory connections suggest that they might powerfully shunt excitatory inputs, phase-lock or prevent action potential generation (Cobb et al. 1995). The same pallidostriatal neurons that innervate PV interneurons also provide a major input to NOS interneurons which themselves are likely to regulate striatal activity through the release of GABA (Kubota et al. 1993), nitric oxide (Hanbauer et al. 1992;

Table 1. *Quantitative model of the connectivity between pallidostriatal neurons and GABA interneurons in the striatum*

1.	Number of striatal boutons arising from pallidostriatal neurons	790.6 ± 404.2
2.	Average proportion of pallidal boutons in contact with GABA interneurons	43.7 ± 17.8 %
3.	Number of boutons of 1 pallidal neuron in contact with GABA interneurons (43.7 % of 790.6)	345.5
4.	Number of boutons of 1 pallidal neuron contacting 1 GABA interneuron	6.7
5.	Number of GABA interneurons innervated by 1 pallidal neuron (3 divided by 4)	51.6
6.	Total number GP neurons projecting to striatum (25 % of neurons in GP)	11 500
7.	Theoretical total number of GABA interneurons innervated by pallidostriatal neurons (5 multiplied by 6)	593 400
8.	Number of GABA interneurons in striatum (3 % of total number of neurons in striatum*)	83 700
9.	Number of pallidostriatal neurons innervating one GABA interneuron (7 divided 8)	7.1
10.	Number of pallidostriatal boutons in contact with one GABA interneuron (8 multiplied by 4)	47.6

The values in 1, 2 and 3 are from Bevan et al. (1998). The total number of neurons in the GP (4.6×10^4) and total number in the striatum (2.79×10^6) are from Oorschot (1996).
* Estimate from Kita et al. (1990).

Guevara-Guzman et al. 1994; Lonart & Johnson, 1994; Stewart et al. 1996) and neuropeptides (Radke et al. 1993).

SITES OF INTEGRATION OF FUNCTIONALLY DIVERSE CORTICAL INFORMATION IN THE BASAL GANGLIA

The classic view of the organisation of the basal ganglia is that the functionally diverse information arising from the cerebral cortex is processed in the striatum and subsequent divisions of the basal ganglia by parallel and segregated cortical-basal ganglia-thalamocortical loops (Alexander et al. 1986; Alexander & Crutcher, 1990; Hoover & Strick, 1993; Groenewegen & Berendse, 1994; Joel & Weiner, 1994, 1997). However, it is clear that the basal ganglia integrate functionally diverse information derived from different cortical regions to generate context dependent, goal-directed patterns of behaviour (Wurtz & Hikosaka, 1986; Graybiel et al. 1994; Aosaki et al. 1995; Schultz et al. 1995, 1997). Anatomical analyses have identified several neuronal elements or systems which could provide the morphological basis of such integration within the basal ganglia. These include the local circuit neurons of the striatum (Gerfen, 1984; Chesselet & Graybiel, 1986; Kubota & Kawaguchi, 1993; Bolam & Bennett, 1995; Kawaguchi et al. 1995), the ascending projections of midbrain dopamine neurons (Somogyi et al. 1981*b*; Nauta & Domesick, 1984; Gerfen et al. 1987; Jimenez-Castellanos & Graybiel, 1987), the GPi output to the pedunculopontine nucleus (Shink et al. 1997) and open-interconnected cortico-basal ganglia-thalamocortical loops (Joel & Weiner, 1994, 1997). It has recently been demonstrated that the circuitry of the indirect pathway may underlie this type of integration at the synaptic level and in particular the synaptic organisation of the descending projections of neurons of the GP and its ventral equivalent the ventral pallidum (VP; Bevan et al. 1996, 1997). In the output nuclei, pallidal neurons give rise to large synaptic boutons that selectively innervate the proximal regions of basal ganglia output neurons, often in a basket-like manner (see Smith et al. 1998). This is also the case in the subthalamic nucleus although the terminals are more distributed across the somatodendritic trees of STN neurons. The descending projections of the VP, which largely receive limbic cortical information via the nucleus accumbens (Alexander et al. 1986; Alexander & Crutcher, 1990; Groenewegen & Berendse, 1994) and the GP, which receives mostly sensorimotor and associative cortical information via the striatum (Alexander et al. 1986; Alexander & Crutcher, 1990; Hoover & Strick, 1993; Groenewegen & Berendse, 1994; Joel & Weiner, 1994, 1997) give rise to topographically segregated fields of anterogradely labelled terminals in the output nuclei and the STN. However, double anterograde tracing from the 2 divisions of the pallidal complex in individual animals has revealed, in addition to topographically segregated projections, zones of overlap of the 2 projections (Bevan et al. 1996, 1997). Electron microscopy demonstrated that in the regions of overlap in each nucleus the proximal parts of many neurons, including tyrosine hydroxylase-immunopositive neurons (i.e. dopaminergic) in the SNc, receive convergent synaptic input from both the VP and GP (Bevan et al. 1996, 1997; Fig. 3*E*). Thus individual output neurons of the basal ganglia as well as neurons of the STN and dopaminergic neurons receive convergent input from pallidal afferents carrying motor/associative information and limbic information. Another way by which basal ganglia output neurons and STN neurons may integrate functionally diverse information from the pallidal complex is via their dendrites as they also

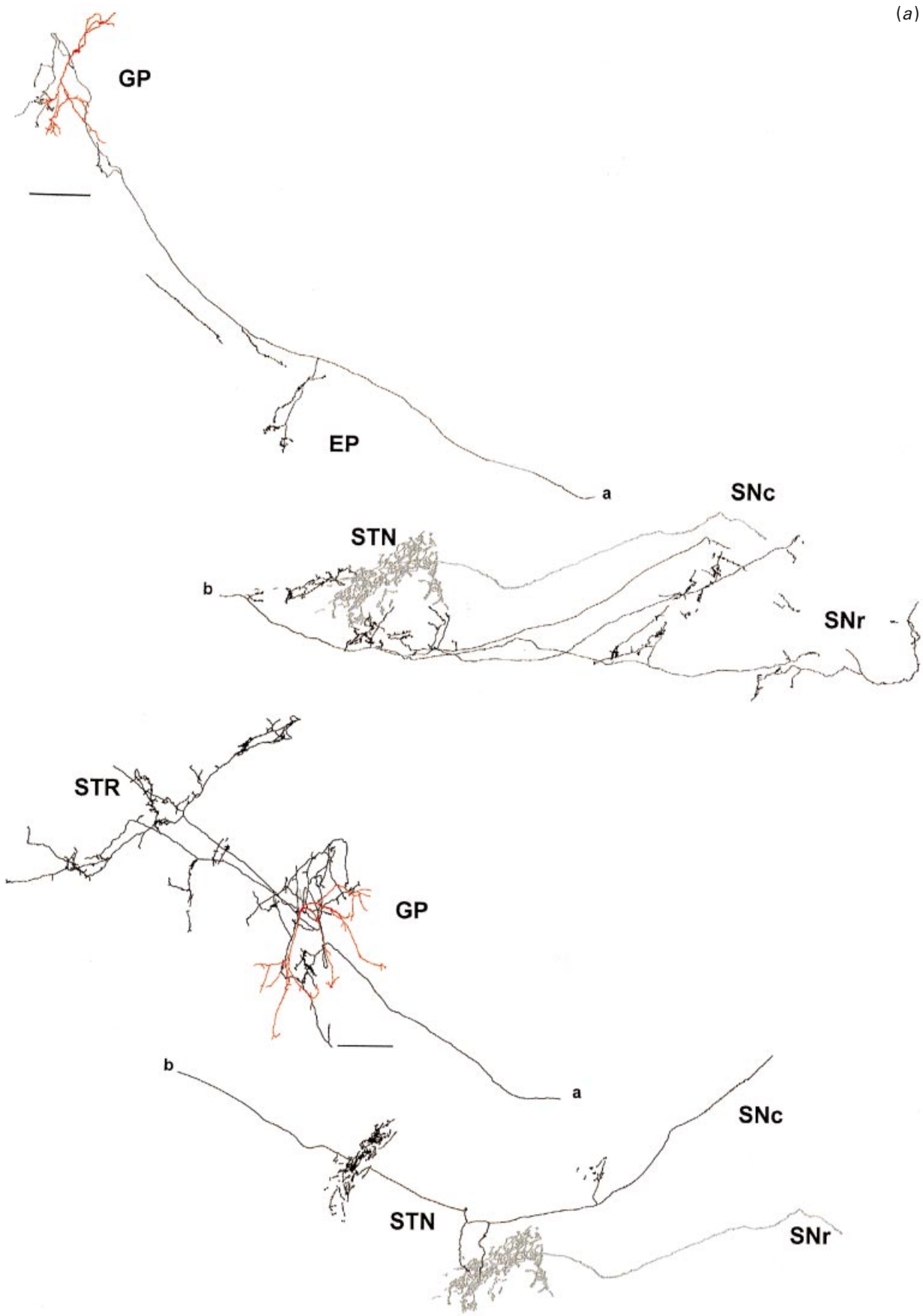

Fig. 4*A*. For legend see page 538.

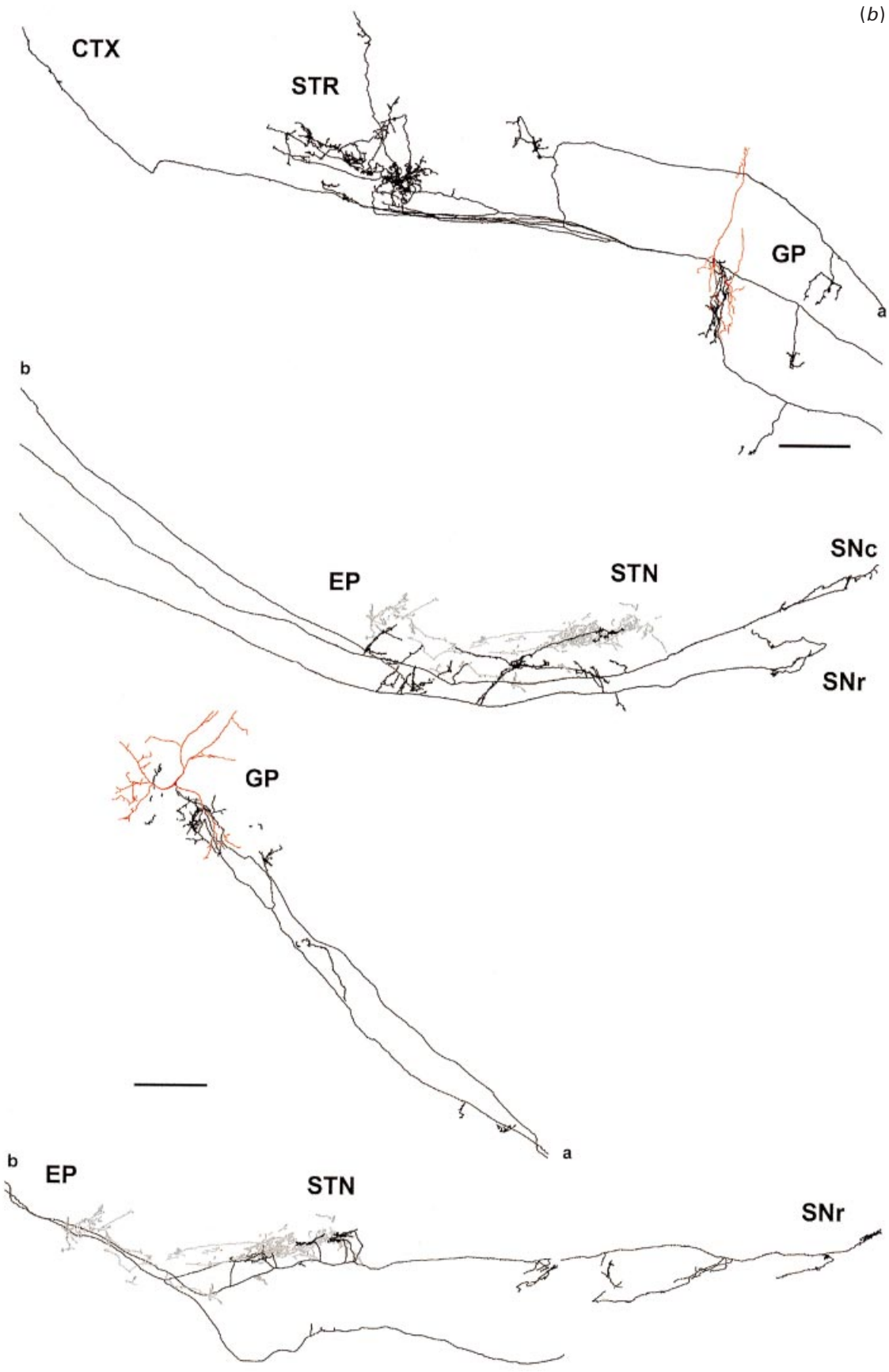

Fig. 4*B*. For legend see page 538.

receive pallidal inputs (Smith & Bolam, 1989; Bolam & Smith, 1992; Bevan et al. 1996, 1997) and are often oriented to cross the functional boundaries defined by inputs from different functional divisions of the pallidal complex (Grofova et al. 1982; Kita et al. 1983; Nakanishi et al. 1991; Bevan et al. 1997).

SUMMARY AND CONCLUSIONS

1. Cortical input to the basal ganglia, carried by the corticostriatal pathway, imparts functionality on the basal ganglia.

2. The cortical information is received primarily by the spiny projection neurons whose function is to transmit the information via 2 pathways through the basal ganglia to the output nuclei.

3. The basal ganglia influence behaviour by the output nuclei projecting to the ventral thalamus and thence motor and premotor regions of cortex or by projecting to subcortical premotor regions.

4. Cortical input is also received by GABA interneurons which provide feed-forward inhibition of spiny neurons. These neurons may 'limit' cortical excitation of spiny neurons, may 'focus' the cortical input to the striatum and/or may synchronise the activity of spiny neurons.

5. A subpopulation of neurons of the GP, in addition to being key components of the indirect pathway and innervating the STN, EP and SN, also provide a powerful inhibitory feedback to the striatum that is in a position to modify the flow of cortical information through the basal ganglia.

6. The 'power' of the pallidostriatal pathway lies in the fact that pallidostriatal neurons selectively innervate GABA interneurons which in turn, innervate spiny neurons. Thus by inhibiting or synchronising the activity of GABA interneurons which in turn inhibit or synchronise the activity of spiny neurons, they are in the position to modulate the flow of cortical information through the basal ganglia.

7. Neurons of different functional territories of the pallidal complex may subserve an integrative role by making convergent synaptic contacts with individual neurons to the output nuclei of the basal ganglia and the STN and SNC.

8. Finally, although the essential concept of the direct and indirect pathways remains intact, the findings summarised here suggest that the indirect pathway is much more complex than previously described and is likely to profoundly influence the flow of cortical information through the basal ganglia.

ACKNOWLEDGEMENTS

The author's work described in this review was supported by the Medical Research Council UK; the Wellcome Trust (MDB; Wellcome Trust Advanced Training Fellowship 046613/Z/96/Z) and The European Community (JPB and JJH; BIOMED 2 Project: BMH4-CT-97-2215). The authors thank Caroline Francis, Liz Norman and Paul Jays for technical assistance.

REFERENCES

ALBIN RL, YOUNG AB, PENNEY JB (1989) The functional anatomy of basal ganglia disorders. *Trends in Neurosciences* **12**, 366–375.

ALEXANDER GE, DELONG MR, STRICK PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience* **9**, 357–381.

ALEXANDER GE, CRUTCHER ME (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences* **13**, 266–271.

AOSAKI T, KIMURA M, GRAYBIEL AM (1995) Temporal and spatial characteristics of tonically active neurons of the primate's striatum. *Journal of Neurophysiology* **73**, 1234–1252.

ARONIN N, DIFIGLIA M, LIOTTA AS, MARTIN JB (1981)

Fig. 4. (*A*) Drawing tube reconstructions of 2 neurons in the GP of a rat (animal no. 9665) that were labelled in vivo with neurobiotin by the juxtacellular method and revealed by the peroxidase method using DAB as the chromogen (Bevan et al. 1998). The cells have been reconstructed along the rostrocaudal axis but the drawings have been bisected approximately at the level of the internal capsule (a connects to b). The cell bodies and dendrites are shown in red, the axon and boutons in black and regions of the axonal arbors in the STN (484 boutons) and SNr (50 boutons) that could not be unequivocally ascribed to one or other of the neurons are shown in grey. The upper of the 2 neurons did not give rise to a projection to the striatum but gave rise to local terminations in the GP (92 boutons) and projected to all caudal basal ganglia nuclei: EP (108 boutons), STN (184 boutons), SNr (209 boutons) and SNc (16 boutons). The lower of the 2 neurons gave rise to a projection to the striatum (478 boutons) as well as local collaterals in the GP (233 boutons), the STN (274 boutons), the SNc (11 boutons) and probably also the SNr. (*B*) Two pallidal cells from another animal (no. 9671) reconstructed and represented as above. The area of overlap of the arbors are shown in grey and contain 407 boutons in the STN and 157 in the EP. The upper cell gave rise to a projection to the STR (851 boutons; see Figs 3*C*, *D*), the other nulcei of the basal ganglia, EP (130 boutons), STN (41 boutons), SNr (36 boutons), SNc (28 boutons) as well as local collaterals in the GP (140 boutons). The lower cell did not innervate the striatum but gave rise to local collaterals in the GP (294 boutons) and projected to caudal basal ganglia nuclei (STN; 60 boutons; SNr; 159 boutons), except the SNc. It showed no clear projection to the EP, this however cannot be ruled out, as the undertermined projection (grey axon) to the EP could be from this cell. (Unpublished data, M. D. Bevan, P. A. C. Booth and J. P. Bolam and from Bevan et al. 1998). Bars, 300 μm.

Ultrastructural localization and biochemical features of immunoreactive leu-enkephalin in monkey dorsal horn. *Journal of Neuroscience* **1**, 561–577.

BENNETT BD, BOLAM JP (1994) Synaptic input and output of parvalbumin-immunoreactive neurones in the neostriatum of the rat. *Neuroscience* **62**, 707–719.

BERNARD V, SOMOGYI P, BOLAM JP (1997) Cellular, subcellular, and subsynaptic distribution of AMPA-type glutamate receptor subunits in the neostriatum of the rat. *Journal of Neuroscience* **17**, 819–833.

BERNARD V, BOLAM JP (1998) Subcellular and subsynaptic distribution of the NR1 subunit of the NMDA receptor in the neostriatum and globus pallidus of the rat: co-localization at synapses with the GluR2/3 subunit of the AMPA receptor. *European Journal of Neuroscience* **10**, 3721–3736.

BEVAN MD, BOLAM JP (1995) Cholinergic, GABAergic and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in monkeys. *Journal of Neuroscience* **15**, 7105–7120.

BEVAN MD, CROSSMAN AR, BOLAM JP (1994) Neurons projecting from the entopeduncular nucleus to the thalamus receive convergent synaptic inputs from the subthalamic nucleus and the neostriatum. *Brain Research* **659**, 99–109.

BEVAN MD, SMITH AD, BOLAM JP (1996) The substantia nigra as a site of synaptic integration of functionally diverse information arising from the ventral pallidum and the globus pallidus in the rat. *Neuroscience* **75**, 5–12.

BEVAN MD, CLARKE NP, BOLAM JP (1997) Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. *Journal of Neuroscience* **17**, 308–324.

BEVAN MD, BOOTH PAC, EATON SA, BOLAM JP (1998) Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. *Journal of Neuroscience* **18**, 9438–9452.

BEVAN MD, WILSON CJ (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. *Journal of Neuroscience* **19**, 7617–7628.

BOLAM JP, CLARKE DJ, SMITH AD, SOMOGYI P (1983) A type of aspiny neuron in the rat neostriatum accumulates (^{3}H) γ aminobutyric acid: combination of Golgi-staining, autoradiography and electron microscopy. *Journal of Comparative Neurology* **213**, 121–134.

BOLAM JP, SOMOGYI P, TAKAGI H, FODOR I, SMITH AD (1983) Localization of substance P-like immunoreactivity in neurons and nerve terminals in the neostriatum of the rat: a correlated light and electron microscopic study. *Journal of Neurocytology* **12**, 325–344.

BOLAM JP, POWELL JF, WU J-Y, SMITH AD (1985) Glutamate decarboxylase-immunoreactive structures in the rat neostriatum. A correlated light and electron microscopic study including a combination of Golgi-impregnation with immunocytochemistry. *Journal of Comparative Neurology* **237**, 1–20.

BOLAM JP, IZZO PN (1988) The postsynaptic targets of substance P-immunoreactive terminals in the rat neostriatum with particular reference to identified spiny striatonigral neurons. *Experimental Brain Research* **70**, 361–377.

BOLAM JP, SMITH Y (1992) The striatum and the globus pallidus send convergent synaptic inputs onto single cells in the entopeduncular nucleus of the rat: a double anterograde labeling study combined with post-embedding immunocytochemistry for GABA. *Journal of Comparative Neurology* **321**, 456–476.

BOLAM JP, SMITH Y, INGHAM CA, VON-KROSIGK M & SMITH AD (1993) Convergence of synaptic terminals from the striatum and the globus pallidus onto single neurones in the substantia nigra and the entopeduncular nucleus. In *Chemical Signalling in the Basal Ganglia* (ed. Arbuthnott GW, Emson PC). *Progress in Brain Research* **99**, 73–88. Oxford: Elsevier.

BOLAM JP, BENNETT B (1995) The microcircuitry of the neostriatum. In *Molecular and Cellular Mechanisms of Neostriatal Functions* (ed. Ariano M, Surmeier DJ), pp. 1–19. Austin, TX: R. G. Landes.

BOUYER JJ, MILLER RJ, PICKEL VM (1984*a*) Ultrastructural relation between cortical efferents and terminals containing enkephalin-like innunoreactivity in rat neostriatum. *Regulatory Peptides* **8**, 105–115.

BOUYER JJ, PARK DH, JOH TH, PICKEL VM (1984*b*) Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. *Brain Research* **302**, 267–275.

CARTER DA, FIBIGER HC (1978) The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. *Journal of Comparative Neurology* **177**, 113–121.

CHANG HT, WILSON CJ, KITAI ST (1981) Single neostriatal efferent axons in the globus pallidus: a light and electron microscopic study. *Science* **213**, 915–918.

CHANG HT, WILSON CJ (1990) Anatomical analysis of electrophysiologically characterized in the rat strio-pallidal system. In *Analysis of Neuronal Microcircuits and Synaptic Interactions* (ed. Björklund A, Hökfelt T, Wouterlood F, van den Pol A). *Handbook of Chemical Neuroanatomy* **8**, 351–402. Amsterdam: Elsevier Biomedical

CHESSELET MF, GRAYBIEL AM (1986) Striatal neurons expressing somatostatin-like immunoreactivity: evidence for a peptidergic interneuronal system in the cat. *Neuroscience* **17**, 547–571.

CHEVALIER G, DENIAU J-M (1990) Disinhibition as a basic process in the expression of striatal functions. *Trends in Neuroscience* **13**, 277–280.

COBB SR, BUHL EH, HALASY K, PAULSEN O, SOMOGYI P (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* **378**, 75–78.

COWAN RL, WILSON CJ, EMSON PC, HEIZMANN CW (1990) Parvalbumin-containing GABAergic interneurons in the rat neostriatum. *Journal of Comparative Neurology* **302**, 197–205.

DELONG MR (1990) Primate models of movement disorders of basal ganglia origin. *Trends in Neuroscience* **13**, 281–285.

DIFIGLIA M, ARONIN N, MARTIN JB (1982) Light and electron microscopic localization of immunoreactive leu-enkephalin in the monkey basal ganglia. *Journal of Neuroscience* **2**, 303–320.

DUBÉ L, SMITH AD, BOLAM JP (1988) Identification of synaptic terminals of thalamic or cortical origin in contact with distinct medium size spiny neurons in the rat neostriatum. *Journal of Comparative Neurology* **267**, 455–471.

FREUND TF, POWELL J, SMITH AD (1984) Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience* **13**, 1189–1215.

FROTSCHER M, RINNE U, HASSLER R, WAGNER A (1981) Termination of cortical afferents on identified neurons in the caudate nucleus of the cat. A combined Golgi-EM degeneration study. *Experimental Brain Research* **41**, 329–337.

GERFEN CR (1984) The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. *Nature* **311**, 461–464.

GERFEN CR, HERKENHAM M, THIBAULT J (1987) The neostriatal mosaic: II. patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *Journal of Neuroscience* **7**, 3915–3934.

GERFEN CR, WILSON CJ (1996). In *The Basal Ganglia* (ed. Björklund A, Hökfelt T, Swanson L). *Handbook of Chemical Neuroanatomy*, *Integrated Systems of the CNS*, Part III, pp. 369–466. Amsterdam: Elsevier Science.

GRAYBIEL AM, AOSAKI T, FLAHERTY AW, KIMURA M

(1994) The basal ganglia and adaptive motor control. *Science* **265**, 1826–1831.

GROENEWEGEN HJ, BERENDSE HW (1994) Anatomical relationships between the prefrontal cortex and the basal ganglia in the rat. In *Motor and Cognitive Functions of the Prefrontal Cortex* (ed. Thierry A-M, Glowinski J, Goldman-Rakic PS, Christen Y), pp. 52–76. Berlin: Springer.

GROFOVA I, DENIAU JM, KITAI ST (1982) Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP. *Journal of Comparative Neurology* **208**, 352–368.

GUEVARA-GUZMAN R, EMSON PC, KENDRICK KM (1994) Modulation of in vivo striatal transmitter release by nitric oxide and cyclic GMP. *Journal of Neurochemistry* **62**, 807–810.

HANBAUER I, WINK D, OSAWA Y, EDELMAN GM, GALLY JA (1992) Role of nitric oxide in NMDA-evoked release of [^{3}H]-dopamine from striatal slices. *NeuroReport* **3**, 409–412.

HANLEY JJ, BOLAM JP (1997) Synaptology of the nigrostriatal projection in relation to the compartmental organization of the neostriatum in the rat. *Neuroscience* **81**, 353–370.

HERSCH SM, CILIAX BJ, GUTEKUNST CA, REES HD, HEILMAN CJ, YUNG KKL et al. (1995) Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *Journal of Neuroscience* **15**, 5222–5237.

HOOVER JE, STRICK PL (1993) Multiple output channels in the basal ganglia. *Science* **259**, 819–821.

IVERSEN LL, SCHON FE (1973) The use of autoradiographic techniques for the identification and mapping of transmitter-specific neurones in CNS. In *New Concepts in Neurotransmitter Regulation* (ed. Mandell AJ), pp. 153–193. New York: Plenum Press.

IZZO PN, BOLAM JP (1988) Cholinergic synaptic input to different parts of spiny striatonigral neurons in the rat. *Journal of Comparative Neurology* **269**, 219–234.

JAEGER D, KITA H, WILSON C J (1994) Surround inhibition among projection neurons is weak or nonexistent in the rat neostriatum. *Journal of Neurophysiology* **72**, 2555–2558.

JIMENEZ-CASTELLANOS J, GRAYBIEL AM (1987) Subdivisions of the dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix. *Neuroscience* **23**, 223–242.

JOEL D, WEINER I (1994) The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. *Neuroscience* **63**, 363–379.

JOEL D, WEINER I (1997) The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. *Brain Research Reviews* **23**, 62–78.

KAWAGUCHI Y (1993) Physiological, morphological, and histochemical characterization of three classes of interneurons in rat neostriatum. *Journal of Neuroscience* **13**, 4908–4923.

KAWAGUCHI Y (1997) Neostriatal cell subtypes and their functional roles. *Neuroscience Research* **27**, 1–8.

KAWAGUCHI Y, WILSON CJ, AUGOOD SJ, EMSON PC (1995) Striatal interneurones: chemical, physiological and morphological characterization. *Trends in Neurosciences* **18**, 527–535.

KEMP JM, POWELL TPS (1971*a*) The structure of the caudate nucleus of the cat: light and electron microscopy. *Philosophical Transactions of the Royal Society of London* **B 262**, 383–401.

KEMP JM, POWELL TPS (1971*b*) The site of termination of afferent fibres in the caudate nucleus. *Philosophical Transactions of the Royal Society of London* **B 262**, 413–427.

KEMP JM, POWELL TPS (1971*c*) The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi mehod. *Philosophical Transactions of the Royal Society of London* **B 262**, 429–439.

KINCAID AE, PENNEY JB, YOUNG AB, NEWMAN SW (1991) Evidence for a projection from the globus pallidus to the entopeduncular nucleus in the rat. *Neuroscience Letters* **128**, 121–125.

KINCAID AE, ZHENG T, WILSON CJ (1998) Connectivity and convergence of single corticostriatal axons. *Journal of Neuroscience* **18**, 4722–4731.

KITA H (1992) Responses of globus pallidus neurons to cortical stimulation: intracellular study in the rat. *Brain Research* **589**, 84–90.

KITA H (1993) GABAergic circuits of the striatum. In *Chemical Signalling in the Basal Ganglia* (ed. Arbuthnott GW, Emson PC). *Progress in Brain Research* **99**, 51–72. Oxford: Elsevier.

KITA H (1996) Glutamatergic and GABAergic postsynaptic responses of striatal spiny neurons to intrastriatal and cortical stimulation recorded in slice preparations. *Neuroscience* **70**, 925–940.

KITA H, CHANG HT, KITAI ST (1983) Pallidal inputs to subthalamus: intracellular analysis. *Brain Research* **264**, 255–265.

KITA H, KITAI ST (1988) Glutamate decarboxylase immunoreactive neurons in rat neostriatum: their morphological types and populations. *Brain Research* **447**, 346–352.

KITA H, KOSAKA T, HEIZMANN CW (1990) Parvalbumin-immunoreactive neurons in the rat neostriatum: a light and electron microscopic study. *Brain Research* **536**, 1–15.

KITA H, KITAI ST (1994) The morphology of globus pallidus projection neurons in the rat: an intracellular staining study. *Brain Research* **636**, 308–319.

KOOS T, TEPPER JM (1999) Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nature Neuroscience* **2**, 467–472.

KUBOTA Y, KAWAGUCHI Y (1993) Spatial distribution of chemically identified intrinsic neurons in relation to path and matrix compartments of rat neostriatum. *Journal of Comparative Neurology* **332**, 499–513.

KUBOTA Y, MIKAWA S, KAWAGUCHI Y (1993) Neostriatal GABAergic interneurones contain NOS, calretinin or parvalbumin. *NeuroReport* **5**, 205–208.

LAPPER SR, SMITH Y, SADIKOT AF, PARENT A, BOLAM JP (1992) Cortical input to parvalbumin-immunoreactive neurones in the putamen of the squirrel monkey. *Brain Research* **580**, 215–224.

LONART G, JOHNSON KM (1994) Inhibitory effects of nitric oxide on the uptake of [^{3}H]dopamine and [^{3}H]glutamate by striatal synaptosomes. *Journal of Neurochemistry* **63**, 2108–2117.

MINK JW, THACH WT (1993) Basal ganglia intrinsic circuits and their role in behavior. *Current Opinion in Neurobiology* **3**, 950–957.

MORIIZUMI T, NAKAMURA Y, OKOYAMA S, KITAO Y (1987) Synaptic organization of the cat entopeduncular nucleus with special reference to the relationship between the afferents to entopedunculothalamic projection neurons: an electron microscope study by a combined degeneration and horseradish peroxidase tracing technique. *Neuroscience* **20**, 797–816.

NAITO A, KITA H (1994) The cortico-pallidal projection in the rat: an anterograde tracing study with biotinylated dextran amine. *Brain Research* **653**, 251–257.

NAKANISHI H, KITA H, KITAI ST (1987) Intracellular study of rat substantia nigra pars reticulata neurons in an in vitro slice preparation: electrical membrane properties and response characteristics to subthalamic stimulation. *Brain Research* **437**, 45–55.

NAKANISHI H, KITA H, KITAI ST (1991) Intracellular study of rat entopeduncular nucleus neurons in an in vitro slice preparation: response to subthalamic stimulation. *Brain Research* **549**, 285–291.

NAUTA WJH, DOMESICK VB (1984) Afferent and efferent relationships of the basal ganglia. In *Functions of the Basal Ganglia* (ed. Evered D, O'Connor M). *Ciba Foundation Symposium* **107**, 3–23. London: Pitman.

OORSCHOT DE (1996) Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical dissector methods. *Journal of Comparative Neurology* **366**, 580–599.

PARTHASARATHY HB, GRAYBIEL AM (1997) Cortically driven immediate-early gene expression reflects modular influence of sensorimotor cortex on identified striatal neurons in the squirrel monkey. *Journal of Neuroscience* **17**, 2477–2491.

PASIK P, PASIK T, DIFIGLIA M (1979) The internal organization of the neostriatum in mammals. In *The Neostriatum* (ed. Divac I, Oberg FGE), pp. 5–36. Oxford: Pergamon Press.

PENNARTZ CM, KITAI ST (1991) Hippocampal inputs to identified neurons in an in vitro slice preparation of the rat nucleus accumbens: evidence for feed-forward inhibition. *Journal of Neuroscience* **11**, 2838–2847.

PICKEL VM, SUMAL KK, BECKLEY SC, MILLER RJ, REIS DJ (1980) Immunocytochemical localization of enkephalin in the neostriatum of rat brain: a light and electron microscopic study. *Journal of Comparative Neurology* **189**, 721–740.

PICKEL VM, CHAN J (1990) Spiny neurons lacking choline acetyltransferase immunoreactivity are major targets of cholinergic and catecholaminergic terminals in rat striatum. *Journal of Neuroscience Research* **25**, 263–280.

PICKEL VM, CHAN J, SESACK SR (1992) Cellular basis for interactions between catecholaminergic afferents and neurons containing leu-enkephalin-like immunoreactivity in rat caudate-putamen nuclei. *Journal of Neuroscience Research* **31**, 212–230.

PLENZ D, KITAI ST (1998) Up and down states in striatal medium spiny neurons simultaneously recorded with spontaneous activity in fast-spiking interneurons studied in cortex-sriatum-substantia nigra organotypic cultures. *Journal of Neuroscience* **18**, 266–283.

RADKE JM, SPYRAKI C, THERMOS K (1993) Neuronal release of somatostatin in the rat striatum – an in vivo microdialysis study. *Neuroscience* **54**, 493–498.

RIBAK CE, VAUGHN JE, ROBERTS E (1979) The GABA neurons and their axon terminals in rat corpus striatum as demonstrated by GAD immunocytochemistry. *Journal of Comparative Neurology* **187**, 261–284.

RYAN LJ, CLARK KB (1991) The role of the subthalamic nucleus in the response of globus pallidus neurons to stimulation of the prelimbic and agranular frontal cortices in rats. *Experimental Brain Research* **86**, 641–651.

SCHULTZ W, APICELLA P, ROMO R, SCARNATI E (1995) Context-dependent activity in primate striatum reflecting past and future behavioral events. In *Models of Information Processing in the Basal Ganglia* (ed. Houk JC, Davis JL, Beiser DG), pp. 11–28. Massachusetts: MIT Press.

SCHULTZ W, DAYAN P, MONTAGUE PR (1997) A neural substrate of prediction and reward. *Science* **275**, 1593–1599.

SHINK E, SMITH Y (1995) Differential synaptic innervation of neurons in the internal and external segments of the globus pallidus by the GABA- and glutamate-containing terminals in the squirrel monkey. *Journal of Comparative Neurology* **358**, 119–141.

SHINK E, BEVAN MD, BOLAM JP, SMITH Y (1996) The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. *Neuroscience* **73**, 335–357.

SHINK E, SIDIBE M, SMITH Y (1997) Efferent connections of the internal globus pallidus in the squirrel monkey. II. Topography and synaptic organization of pallidal efferents to the pedunculopontine nucleus. *Journal of Comparative Neurology* **382**, 348–363.

SMITH AD, BOLAM JP (1990) The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. *Trends in Neurosciences* **13**, 259–265.

SMITH Y, BENNETT BD, BOLAM JP, PARENT A, SADIKOT AF (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *Journal of Comparative Neurology* **344**, 1–19.

SMITH Y, BOLAM JP (1989) Neurons of the substantia nigra reticulata receive a dense GABA-containing input from the globus pallidus in the rat. *Brain Research* **493**, 160–167.

SMITH Y, BOLAM JP (1990) The output neurons and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat. *Journal of Comparative Neurology* **296**, 47–64.

SMITH Y, BOLAM JP, VON KROSIGK M (1990) Topographical and synaptic organization of the GABA-containing pallido-subthalamic projection in the rat. *European Journal of Neuroscience* **2**, 500–511.

SMITH Y, BOLAM JP (1991) Convergence of synaptic inputs from the striatum and the globus pallidus onto identified nigrocollicular cells in the rat: a double anterograde labelling study. *Neuroscience* **44**, 45–73.

SMITH Y, BEVAN MD, SHINK E, BOLAM JP (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* **86**, 353–387.

SOMOGYI P, HODGSON AJ, SMITH AD (1979) An approach to tracing neuron networks in the cerebral cortex and basal ganglia. Combination of Golgi staining, rerograde transport of horseradish peroxidase and anterograde degeneration of synaptic boutons in the same material. *Neuroscience* **4**, 1805–1852.

SOMOGYI P, BOLAM JP, SMITH AD (1981*a*) Monosynaptic cortical input and local axon collaterals of identified striatonigral neurons. A light and electron microscopic study using the Golgi-peroxidase transport-degeneration procedure. *Journal of Comparative Neurology* **195**, 567–584.

SOMOGYI P, BOLAM JP, TOTTERDELL S, SMITH AD (1981*b*) Monosynaptic input from the nucleus accumbens-ventral striatum region to retrogradely labelled nigrostriatal neurones. *Brain Research* **217**, 245–263.

SOMOGYI P, PRIESTLEY JV, CUELLO AC, SMITH AD, TAKAGI H (1982) Synaptic connections of enkephalin-immunoreactive nerve terminals in the neostriatum: a correlated light and electron microscopic study. *Journal of Neurocytology* **11**, 779–807.

STERN EA, KINCAID AE, WILSON CJ (1997) Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal and striatal neurons in vivo. *Journal of Neurophysiology* **77**, 1697–1715.

STERN EA, JAEGER D, WILSON CJ (1998) Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo. *Nature* **394**, 475–478.

STEWART TL, MICHEL AD, BLACK MD, HUMPHREY PPA (1996) Evidence that nitric oxide causes calcium-independent release of [^{3}H]dopamine from rat striatum in vitro. *Journal of Neurochemistry* **66**, 131–137.

TOTTERDELL S, BOLAM JP, SMITH AD (1984) Characterization of pallidonigral neurons in the rat by a combination of Golgi-impregnation and retrograde transport of horseradish peroxidase: their monosynaptic input from the neostriatum. *Journal of Neurocytology* **13**, 593–616.

TREMBLAY L, FILION M (1989) Responses of pallidal neurons to striatal stimulation in intact waking monkeys. *Brain Research* **498**, 1–16.

WILLIAMS MN, FAULL RLM (1985) The striatonigral projection and nigrotectal neurons in the rat. A correlated light and electron microscopic study demonstrating a monosynaptic striatal input to identified nigrotectal neurons using a combined degeneration and horseradish peroxidase procedure. *Neuroscience* **14**, 991–1010.

WILSON CJ (1993) The generation of natural firing patterns in

neostriatal neurons. In *Chemical Signalling in the Basal Ganglia* (ed. Arbuthnott GW, Emson PC). *Progress in Brain Research* **99**, 277–297. Oxford: Elsevier.

WILSON CJ, GROVES PM (1980) Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum: a study employing intracellular injection of horseradish peroxidase. *Journal of Comparative Neurology* **194**, 599–615.

WURTZ RH, HIKOSAKA O (1986) Role of the basal ganglia in the initiation of saccadic eye movements. *Progress in Brain Research* **64**, 175–190.

YUNG KKL, BOLAM JP, SMITH AD, HERSCH SM, CILIAX BJ, LEVEY AI (1995) Ultrastructural localisation of D1 and D2 dopamine receptors in the basal ganglia of the rat by light and electron microscopic immunocytochemistry. *Neuroscience* **65**, 709–730.

YUNG KKL, SMITH AD, LEVEY AI, BOLAM JP (1996) Synaptic connections between spiny neurons of the direct and indirect pathways in the neostriatum of the rat: evidence from dopamine receptor and neuropeptide immunostaining. *European Journal of Neuroscience* **8**, 861–869.