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COMMENTARY

MICROCIRCUITRY OF THE DIRECT AND INDIRECT PATHWAYS OF THE BASAL GANGLIA

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Abstract—Our understanding of the organization of the basal ganglia has advanced markedly over the last 10 years, mainly due to increased knowledge of their anatomical, neurochemical and physiological organization. These developments have led to a unifying model of the functional organization of the basal ganglia in both health and disease. The hypothesis is based on the so-called "direct" and "indirect" pathways of the flow of cortical information through the basal ganglia and has profoundly influenced the field of basal ganglia research, providing a framework for anatomical, physiological and clinical studies. The recent introduction of powerful techniques for the analysis of neuronal networks has led to further developments in our understanding of the basal ganglia. The objective of this commentary is to build upon the established model of the basal ganglia connectivity and review new anatomical findings that lead to the refinement of some aspects of the model. Four issues will be discussed. (1) The existence of several routes for the flow of cortical information along "indirect" pathways. (2) The synaptic convergence of information flowing through the "direct" and "indirect" pathways at the single-cell level in the basal ganglia output structures. (3) The convergence of functionally diverse information from the globus pallidus and the ventral pallidum at different levels of the basal ganglia. (4) The interconnections between the two divisions of the pallidal complex and the subthalamic nucleus and the characterization of the neuronal network underlying the indirect pathways.

The findings summarized in this commentary confirm and elaborate the models of the direct and indirect pathways of information flow through the basal ganglia and provide a morphological framework for future studies. © 1998 IBRO. Published by Elsevier Science Ltd.

Key words: globus pallidus, subthalamic nucleus, substantia nigra, entopeduncular nucleus, striatum, synaptic organization.

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Abbreviations: BDA, biotinylated dextran amine; EP, entopeduncular nucleus; GP, globus pallidus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; NADPH, reduced nicotinamide adenine dinucleotide phosphate; PHA-L, *Phaseolus vulgaris* leucoagglutinin; PPN, pedunculopontine nucleus; RTN, reticular nucleus of the thalamus; SN, substantia nigra; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VP, ventral pallidum.

1. INTRODUCTION

The basal ganglia are a group of subcortical nuclei of the vertebrate brain that are intimately involved in the control of movement. The basal ganglia include the striatum (or caudate–putamen), the globus pallidus (GP) and its equivalent in primates, the external segment of the globus pallidus (GPe), the entopeduncular nucleus (EP) and its equivalent in primates, the internal segment of the globus pallidus (GPi), the subthalamic nucleus (STN) and the substantia nigra (SN). They are a complex and highly interconnected group of nuclei that have been the subject of intensive study over many decades, primarily because of their clear involvement in neurological disorders that are associated with abnormal motor activities. Indeed, one of the first descriptions of the basal ganglia by Willis in the 17th Century intimated a role of the basal ganglia in the control of movement and in neurological disorders: "To the corpus callosum are attached the corpora striata connecting the cerebrum to the legs of the medulla oblongata. In these corpora there are some striae passing upwards and others downwards and through them the spirits and images of sensible things pass from the medulla oblongata into the cerebrum, while spirits initiating movement descend into the medulla oblongata. In those who suffer or have died from paralysis, I have often observed that these corpora are affected: they became flaccid and their striae are almost obliterated" (Willis, *c.* 1664, from lecture notes by Locke translated by Dewhurst[83]).

The role of the basal ganglia in the control of movement is more subtle and complex than simply a direct influence on muscle contraction. On the basis of extensive anatomical studies, Nauta proposed that the basal ganglia act as an interface between limbic and motor systems, i.e. the basal ganglia subserve an integrative role in the manifestation of motor behaviour.[233] Since that time, many functional analyses, as well as anatomical studies, have expanded this concept and it is now clear that the basal ganglia are involved in a variety of cognitive and mnemonic functions in the generation and execution of context-dependent behaviours (see, for instance, Refs 123, 273, 274 and 339). Despite intensive studies of the anatomical and functional organization of the basal ganglia and the large amount of data gathered about the pathophysiology of motor disorders associated with neurodegenerative diseases that affect the basal ganglia (e.g., Parkinson's disease, Huntington's disease, hemiballismus), unifying hypotheses of basal ganglia function that take into account data derived from different disciplines remained elusive for many years (see review by DeLong and Georgopoulos[79]). However, several key advances in the knowledge of the anatomical, neurochemical and physiological organization, as well as data from *post mortem* studies, led Albin *et al.*[5] to formulate their unifying model of the functional organization of the basal ganglia that accounts for both normal and abnormal function. This model, which has been expanded and elaborated by other groups,[7,65,74–76,113–115,118] is based on the so-called "direct" and "indirect" pathways of the flow of cortical information through the basal ganglia (Fig. 1). According to this model, cortical information impinging on the striatum is processed and transmitted to the output nuclei of the basal ganglia via two routes: either directly from the striatum to the output nuclei or indirectly via the GP and STN (Fig. 1). The consequences of activation of the direct and indirect pathways are functionally opposite in the target regions of the basal ganglia.[7,76] Thus, activation of the direct pathway leads to a

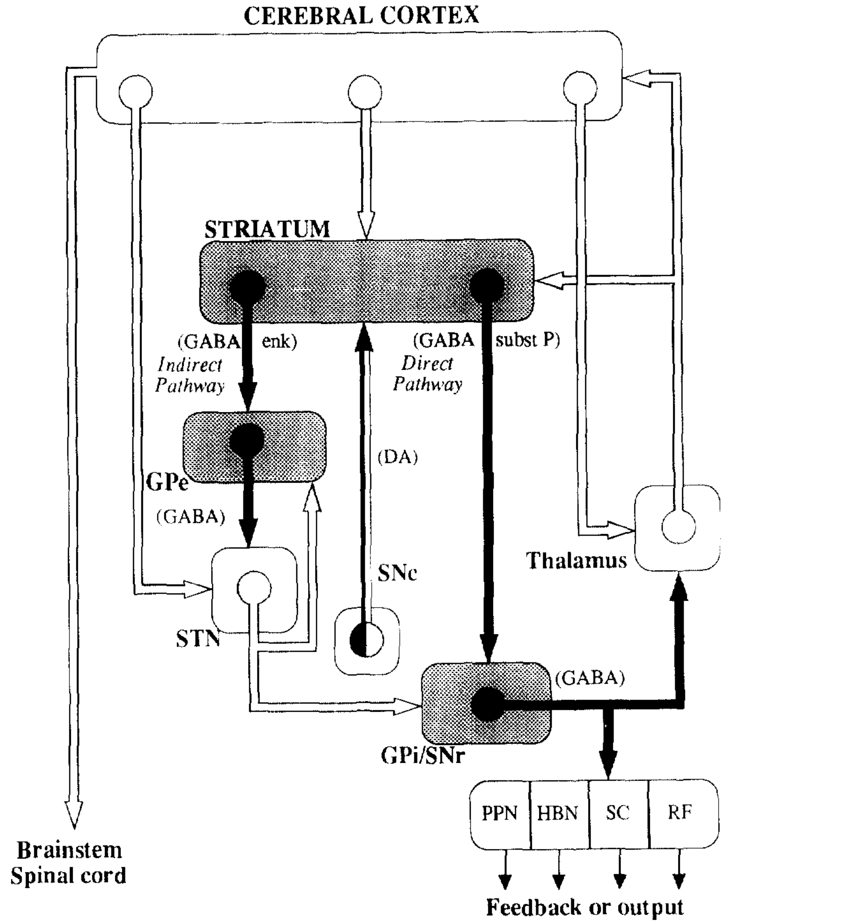

Fig. 1. The circuitry of the basal ganglia in primates as proposed in 1990.[5,7,76] Inhibitory projections are shown as filled arrows, excitatory projections as open arrows. According to this model, cortical information that reaches the striatum is conveyed to the basal ganglia output structures (GPi/SNr) via two pathways, a direct inhibitory projection from the striatum to the GPi/SNr and an indirect pathway, which involves an inhibitory projection from the striatum to the GPe, an inhibitory projection from the GPe to the STN and an excitatory projection from the STN to the GPi/SNr. The information is then transmitted back to the cerebral cortex via a relay in the thalamus or conveyed to various brain stem structures. The GPi projects to the pedunculopontine nucleus (PPN) and the lateral habenular nucleus (HBN), whereas the SNr innervates the PPN, the superior colliculus (SC) and the parvicellular reticular formation (RF). The direct and indirect pathways largely arise from different populations of striatal spiny neurons that contain different peptides and preferentially express different subclasses of dopamine receptors. The dopaminergic neurons of the substantia nigra pars compacta (SNc) exert a net excitatory effect on spiny neurons giving rise to the direct pathway by the activation of D_1 receptors, whereas they exert a net inhibitory effect on spiny neurons giving rise to the indirect pathway by activation of D_2 receptors. Cortical information can also reach the basal ganglia via the corticosubthalamic projection. Other abbreviations: DA, dopamine; enk, enkephalin; subst P, substance P. Modified from Fig. 2 in Alexander and Crutcher.[7]

disinhibition of neurons in the target regions of the basal ganglia, whereas activation of the indirect pathway leads to an inhibition of neurons in the target regions (see below). The development of this concept has had a profound influence on basal ganglia research, providing a stimulus and rationale for anatomical, functional and clinical studies and, indeed, has led to the development of new therapies and the resurgence of surgical approaches (see Laitinen *et al.*[195a]) for the treatment of Parkinson's disease.[16,18,22,23,28,39,55,125,189,195,206,208,235,313,313a,329,330]

The introduction of powerful techniques for the analysis of neuronal networks has led to many advances in our knowledge and understanding of the anatomical and synaptic organization of the basal ganglia. The objective of this commentary is to review these new anatomical data concerning the connections, synaptic organization and neurochemistry of the neurons in the basal ganglia that underlie the direct and indirect pathways. Our aim is to illustrate how these new data support and expand the concept of the direct and indirect pathways and how they provide clues to the functional organization of the basal ganglia. For more details about the overall organization of the basal ganglia, the reader is referred to recent comprehensive reviews.[7,27a,41,65,67,113,114,118,122,127,128,130,157a,166–168,204,217a,238,242,285,332] The discussion will be almost exclusively confined to the "dorsal" aspects of the basal ganglia, except for some of the connections of the ventral pallidum (Section 2.6). The reader is referred to recent reviews dealing with the circuitry of the ventral components of the basal ganglia.[9,9a,127,130,156,157a,344]

In order to provide a basic framework for the interpretation of the new data within the functional organization of the basal ganglia, we will begin with a brief discussion of the concept of direct and indirect pathways as introduced by Albin *et al.*[5] and elaborated by DeLong and colleagues[7,76] (Fig. 1). This will be followed by a brief description of the technical developments that have led to the elucidation of the pathways and synapses that mediate the interaction between different neurons and different nuclei of the basal ganglia. We will then summarize recent data relating to the synaptology of the direct and indirect pathways and present a revised version of the circuitry of the basal ganglia.

1.1. *Terminology*

The terminology applied to the divisions of the basal ganglia is particularly confusing because the nomenclature is based on the anatomical location and gross appearance of individual nuclei, and because of differences in the gross anatomy of primate and rodent brains. For the purposes of this commentary, we will endeavour to use the simplest terminology. Thus, the term "basal ganglia output nuclei" will refer to the entopeduncular nucleus or the primate equivalent, the internal segment of the globus pallidus (EP/GPi), and the substantia nigra pars reticulata (SNr). In using the term "globus pallidus" (GP), we will not only refer to that structure in non-primates but include the primate equivalent, the external segment of the globus pallidus (GPe). Only when referring to particular experiments in a single species will we use the terms GP and EP or GPe and GPi. The term "targets of the basal ganglia" refers to the main structures innervated by the basal ganglia, i.e. the ventral tier of the thalamus, the lateral habenula, the superior colliculus, the mesopontine tegmentum and the reticular formation.

1.2. *The direct and indirect pathways of information flow through the basal ganglia*

The direct and indirect pathways of information flow through the basal ganglia, as originally introduced, are summarized in Fig. 1.[5,7,28,76] Virtually all regions of the cerebral cortex provide a topographical projection to the striatum and, indeed, the cortical input imposes functionality upon different territories of the striatum. The cortical information, together with information from local neurons and other extrinsic afferents, is integrated within the striatum primarily by the spiny projection neurons. These neurons account for up to 90% of neurons in the striatum, they are recipients of most of the afferent synaptic input to the striatum and they are the main output neurons.[118,122,171–173,285] Once "processed", the cortical information is transmitted to the output nuclei of the basal ganglia either by a subpopulation of spiny neurons that projects directly to the output nuclei, or a separate population of spiny neurons that conveys the "processed information" to the output nuclei by an indirect route. The neurons that give rise to the indirect pathway project to the GP,[21,99,113,115,119,200,201] which, in turn, projects to the STN and then to output nuclei of the basal ganglia (Fig. 1). The subpopulations of spiny neurons that give rise to the direct and indirect pathways are further characterized by their selective expression of neuropeptides and dopamine receptor subtypes. Thus, although all striatal spiny neurons use GABA as their main neurotransmitter, the subpopulation that gives rise to the direct pathway contains the neuropeptides substance P and dynorphin, and preferentially expresses the D_1 subtype of dopamine receptors, and the subpopulation that gives rise to the indirect pathway contains enkephalin and preferentially expresses the D_2 subtype of dopamine receptors.[5,113,115,118,119,200,201] A small population of striatal neurons express both D_1 and D_2 receptors.[315a,b] It has been shown in the rat that single spiny neurons in the striatum do not exclusively innervate the GP or the output nuclei, but the density of the axonal arbor is greater in only one of the targets.[169] Thus, neurons that arborize profusely in the GP give rise to minor axon collaterals with only few terminals in the EP and SNr, whereas neurons that project massively to the EP and SNr emit more sparse axon collaterals in the GP.[169] These features have recently been confirmed in monkeys.[239]

By virtue of the neurotransmitters and basal activity of neurons in these networks, activation of the direct and indirect pathways produces functionally opposite effects in neurons of the target nuclei of the basal ganglia. Corticostriatal neurons and neurons of the STN are excitatory, utilizing glutamate as a neurotransmitter. All other neurons in the network, including neurons of the output nuclei, are GABAergic. Under resting conditions, the activity of the spiny output neurons is low compared to that of the tonically active neurons in the GP and the STN. Activation of the corticostriatal pathway leads to increased firing of striatal neurons. Increased activity of neurons that give rise to the direct pathway leads, by virtue of their GABAergic nature, to the inhibition of neurons in the output nuclei. A reduction in the tonic activity of neurons in the output nuclei leads to a reduction in the inhibition of, or a disinhibition of, neurons in the target nuclei of the basal ganglia.[7,76] The phenomenon of reduced inhibition or disinhibition of the targets of the basal ganglia is

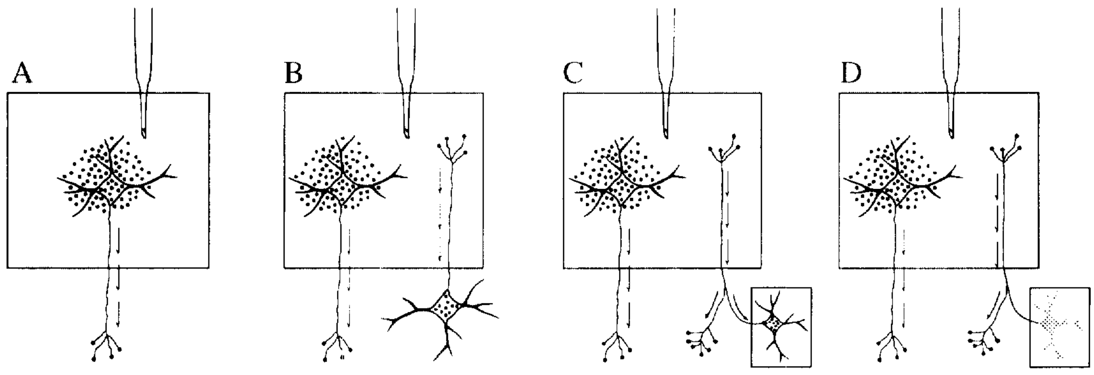

Fig. 2. Multimodal transport of neuronal tract-tracers. Diagram illustrating the multimodal transport of some neuronal tract-tracers that are commonly considered as exclusively anterograde tracers (biocytin, PHA-L, BDA). In addition to being transported in an anterograde fashion (A), many anterograde tracers are also transported retrogradely, i.e. from the terminal field of a neuron back to its cell body (B). Tracers that have been retrogradely transported may subsequently be transported in an anterograde fashion along axon collaterals (C). In some cases, tracers may be retrogradely transported to the branch point of an axon and then preferentially transported along the collaterals with only minimal labelling of the perikaryon (D).

central to the physiology of the basal ganglia and may underlie many basal ganglia-associated functions.[67,68,81,339] In contrast to this, activation of those spiny neurons that project to the GP, i.e. neurons that give rise to the indirect pathway, leads to the opposite functional effect in the targets of the basal ganglia. This is brought about in the following manner. Activation of corticostriatal fibres leads to increased activity of striatal neurons which, in turn, inhibit the tonically active neurons in the GP. Inhibition of these neurons disinhibits neurons in the STN. Since neurons in the STN are excitatory, their increased activity leads to increased firing of neurons in the output nuclei and, hence, because neurons in the output nuclei are GABAergic, leads to a greater inhibition of neurons in the target nuclei. The increased inhibition of neurons in the target nuclei is likely to be associated with the cessation of selected movements and possibly the suppression of non-selected movements.[7,76] The tonic activity of neurons in the GP and STN in the resting animal may also shape the tonic firing patterns of basal ganglia output neurons and thus the inhibition of neurons in the targets of the basal ganglia.

The model also serves as a basis for understanding the pathophysiology of disorders of movement associated with diseases of the basal ganglia.[5,27a,28,76] Since the increased activity of the direct pathway is associated with facilitation of movement and increased activity of the indirect pathway is associated with inhibition of movement, it has been suggested that akinetic motor disorders, of which Parkinson's disease is the archetype, are the result of an imbalance in the activity of the direct and indirect pathways in favour of the indirect pathway.[28,76] On the other hand, dyskinetic or hyperkinetic motor disorders, of which Huntington's chorea is the archetype, are associated with an imbalance in favour of the direct pathway. In keeping with these suggestions, data obtained from experimental animals[17,28,29,55,57,95,115,144,145,217,329] have implicated a relative over-activity of the indirect pathways in Parkinson's disease and a relative under-activity in Huntington's disease. Furthermore, pharmacological manipulation or surgical interventions that restore the balance between the two pathways alleviate the abnormal motor activity.[16,28,55,125,189] The value of the model is further exemplified by the application of this type of intervention to the treatment of Parkinson's disease.[22,23,94,195,206,208,235]

1.3. *Technical developments in the elucidation of neuronal networks*

The elucidation of the neuronal networks of the basal ganglia at both light and electron microscopic levels has posed particular problems because of the complex nature of the interconnections between these nuclei. Several technical advances have been important in the elucidation of these neuronal networks. First, the availability of new sensitive anterograde tracers that result in a high resolution of labelling of axons and terminal fields has helped our ability to trace connections between populations of neurons and between individual neurons in the CNS. The first of these tracers to be introduced was the lectin, *Phaseolus vulgaris* leucoagglutinin (PHA-L).[117] Two further markers have also proved to be valuable tools in tracing neuronal connections at both light and electron microscopic levels, biocytin or biotinylated lysine[160,176] and biotinylated dextran amine (BDA).[54,323] The availability of more than one high-resolution neuronal tracer and the ability to perform double peroxidase staining for light[148,337] and electron microscopy[203,207] has allowed us to develop double anterograde tracing techniques for the elucidation of convergence of different pathways at the synaptic level.[287,292,293] The combined anatomical approaches to the study of synaptic interactions, especially the ability to characterize neuronal structures postsynaptic to anterogradely labelled terminals on the basis of connectivity and the ability to identify the presence of amino acid transmitters in individual anterogradely labelled terminals, have been particularly important in the elucidation of neuronal microcircuits.[30,31,42,46,70,103,105,262,289,291,293,294,303,304,324]

The application of these techniques has led to major advances in our knowledge and understanding of the neuronal networks of the basal ganglia. However, these technical advances have not been without their drawbacks. The main drawback is that the anterograde tract-tracers, although being transported preferentially in the anterograde direction, may also be transported retrogradely (Fig. 2A, B).[32,33,34,64a,89,132,177,237,257,259,277,282,284,294,338] Furthermore, retrogradely transported tracers may then be transported anterogradely along axon collaterals (Fig. 2C; see, for instance, Refs 64a, 89, 177, 237, 259 and 277) The factors that dictate whether an "anterograde" tracer will be transported retrogradely are unknown, but may relate to, the density of the axonal arborization, the activity of the neuron[164] or the effect of damage caused at the injection site. The retrograde transport of anterograde tracers is a particular problem in the basal ganglia. The interpretation of data from anterograde tracing studies is complicated because the basal ganglia are heavily interconnected and individual neurons frequently give rise to axon collaterals that innervate multiple target areas. Thus, in the use of anterograde tracers it is necessary to incubate and analyse sections, not only from the proposed region of anterograde labelling, but also from any region of the brain that may have retrogradely transported the tracers and then anterogradely transported them via axon collaterals. Data from tracing studies may sometimes be even more difficult to assess as tracers may be retrogradely transported to the branch point of an axon and then be preferentially transported along the collateral with only minimal retrograde labelling of the perikaryon (Fig. 2D).[64a,237]

The phenomenon of retrograde and then anterograde transport of tracers, which can be referred to as multimodal transport, is best illustrated with an example. In analyses of the synaptic organization of the projections of the STN to the output nuclei of the basal ganglia in rats and primates,[32,34,298,299] deposits of either PHA-L or biocytin were made in the STN. As predicted from the known projections of the STN, both the EP/GPi and the SNr were rich in populations of anterogradely labelled terminals. However, light microscopy in primates,[154] and combined light and electron microscopy in rats and primates,[32,34,298,299] revealed that the anterogradely labelled terminals were heterogeneous in their morphology. In each of these experiments, two populations of terminals were labelled. Electron microscopy in the rat revealed that the major type of terminal possessed the typical characteristics of terminals from the STN (see Section 1.4.3), i.e. they were medium-sized boutons that contained round synaptic vesicles and formed asymmetric synapses with perikarya and dendrites.[32,34,298,299] The same class of terminals, anterogradely labelled from the STN, has been shown to be enriched in immunoreactivity for glutamate.[262] The second class of terminals, in contrast, were large, contained pleomorphic vesicles that congregated at the active zone, usually contained several mitochondria, formed symmetric synapses and were immunoreactive for GABA. Furthermore, the distribution of this second class of terminals on the postsynaptic neurons was different to that of the major type, i.e. they were predominantly located on the cell body and proximal dendrites. Since all neurons of the STN are believed to be glutamatergic,[4,297] it is unlikely that the second class of terminals were labelled by direct anterograde transport from the STN. The morphological characteristics, the presence of GABA and the pattern of innervation of the postsynaptic neurons are features typical of terminals derived from the GP (see Section 1.4.2.). Furthermore, retrogradely labelled neurons were observed in the GP. It can be concluded, therefore, that in addition to being anterogradely transported by subthalamofugal neurons, the tracers were also retrogradely transported along the axons of neurons of the GP that project to the STN and then anterogradely transported along their axon collaterals to the output nuclei (Fig. 2C; see discussions in Refs 32, 34, 298 and 299).

The multimodal transport of neuronal tracers in experiments designed to elucidate neuronal networks means that the data obtained require careful interpretation. It is essential to have a thorough knowledge of the connections between the regions under investigation and the findings must be supported by ultrastructural analysis and the characterization of the endogenous transmitters of the anterogradely labelled boutons. However, the ability of tracers to be transported in a multimodal fashion can have advantages in the study of neuronal networks, since the collateralization of axons and topographical relationships can be identified (see below; Figs 9–11).

1.4. *Characteristics of synaptic terminals underlying the direct and indirect pathways of information flow through the basal ganglia*

1.4.1. *Axon terminals of projection neurons of the striatum.* The first data relating to the ultrastructural features and synaptic organization of striatal afferents to the pallidal complex and the SN were obtained by means of anterograde degeneration methods.[1,134,141,170,302,327,331] These observations have since been confirmed and extended in different species using modern tract-tracing methods, intracellular labelling or immunohistochemical localization of peptides known to be present in striatal neurons.[32,34,46–48,63,64,86,209,254,292,306,307,324] In each of the targets of the striatum, i.e. the GP, the output nuclei of the basal ganglia and the substantia nigra pars compacta (SNc), terminals of striatal neurons have a similar morphology. Furthermore, the terminals of the local axon collaterals of striatal neurons identified by intracellular labelling,[334] Golgi impregnation,[301] or by immunocytochemistry for substance P, enkephalin or glutamate decarboxylase[11,40,43,44,45,50–52,87,210,248,260] are indistinguishable from terminals in the targets of the striatum.

The terminals of striatal neurons are small- to medium-sized (0.5–1.5 μm in diameter), they are densely packed with ovoid, electron-lucent vesicles and contain only an occasional mitochondrion. They form symmetrical synaptic contacts with their targets (Figs 3A, 4A, B, 5A–C). In some strains of rat, a proportion of striatal boutons in basal ganglia output nuclei have an irregular shape and are pierced, or interdigitated, by unmyelinated axons and terminals (Fig. 4B).[32,34,160] The combination of the anterograde labelling with post-embedding immunogold labelling utilizing antibodies against GABA has demonstrated that striatal terminals in the EP/GPi and SNr are GABAergic (Figs 3A, 5A, B).[46–49,324]

1.4.2. *Axon terminals of neurons of the globus pallidus*. Following deposits of tracers in the GP, the morphology, the ultrastructural features and the neurochemistry of anterogradely labelled pallidal terminals have been characterized in the EP/GPi,[48,49,298,299] the STN[33,281,294] and the SN.[36,289,291,292,324] In each region, terminals derived from the GP have a characteristic morphology and neurochemistry (Figs 3B, C, 5A–C, 7) that is uniform across species. The terminals are large (1.0–4.5 μm in diameter), contain small pleomorphic synaptic vesicles that form clusters close to the active zones and usually contain several mitochondria (Figs 3B, C, 5A–C, 7). They form short symmetrical synaptic contacts most frequently with the proximal regions of their postsynaptic neuron.[49,291] Individual boutons often possess more than one active zone making multiple synaptic contacts with a single postsynaptic structure. Post-embedding immunogold labelling has revealed that anterogradely labelled pallidal outons[33,48,49,289,291,294,299,324] or boutons with similar ultrastructural features[30,31,70,280] are strongly immunoreactive for GABA (Figs 3C, 5A, B).

1.4.3. *Axon terminals of neurons of the subthalamic nucleus*. The morphology and ultrastructural features of terminals anterogradely labelled from neurons in the STN have been characterized in the GPe,[277,280,299] in the EP/GPi[34,226,299] and in the SN.[32,182,262] As with terminals derived from the striatum and the GP, the morphology and type of synaptic specialization are similar in each of the targets of the STN and in different species. They are of medium size (0.7–2.5 μm in diameter), often contain two or three mitochondria and numerous round or slightly pleomorphic vesicles. The most characteristic feature of terminals derived from the STN is that they form asymmetric synapses associated with a thick postsynaptic density and sometimes subjunctional dense bodies (Figs 3D–F, 4).[32,34,182,226,262,277,280,299] The use of anterograde transport methods combined with post-embedding immunogold labelling has revealed that subthalamic terminals[262] or terminals with similar ultrastructural features[70,280] are enriched in glutamate immunoreactivity.

2. SYNAPTOLOGY OF THE DIRECT AND INDIRECT PATHWAYS

2.1. *Cortical inputs to striatal neurons giving rise to the direct and indirect pathways*

In primates, the somatosensory, motor and premotor cortices project somatotopically to the postcommissural region of the putamen,[98,100,191a,192,205] the associative cortical areas project to the caudate nucleus and the rostral putamen,[121,275,341,342] and the limbic cortices, the amygdala and hippocampus, terminate preferentially in the ventral striatum.[9,9a,138,191,265] This functional segregation of the cortical inputs in the striatum is also maintained in rats and cats.[26,127,131,156,157a,214] The neurons that give rise to the corticostriatal projection are divided into at least three major types based on their intracortical connections, laminar origin and pattern of striatal aborization.[73,118,175] Striatal neurons are believed to receive inputs from a large number of cortical fibres, suggesting that a striatal neuron may increase its firing rate only if there is activation of convergent input from many different cortical neurons.[73,332,332a]

Cortical terminals form asymmetric synapses primarily with dendritic spines[171–173,285,301] of the medium-sized densely spiny projection neurons and also with the dendrites of interneurons.[41,285] In the rat, it has been shown that striatal projection neurons giving rise to the direct[157,301] and those giving rise to the indirect[157] pathways both receive synaptic input from motor cortical areas.

Striatal projection neurons are also the major recipient of other afferents of the striatum, including the dopaminergic input from the SNc,[51,53,104,190a,288] the serotonergic input from the dorsal raphe,[300] and the excitatory, probably glutamatergic, inputs from the thalamus[91,108,173,270,284,288,340] and amygdala.[108,183,212,213] Furthermore, they are also the major recipients of terminals derived from local GABAergic interneurons,[11,25,45,186,260] cholinergic interneurons[84,161,251,252] and somatostatin-positive interneurons.[85,317] Each of these afferents gives rise to a specific pattern of innervation of the spiny

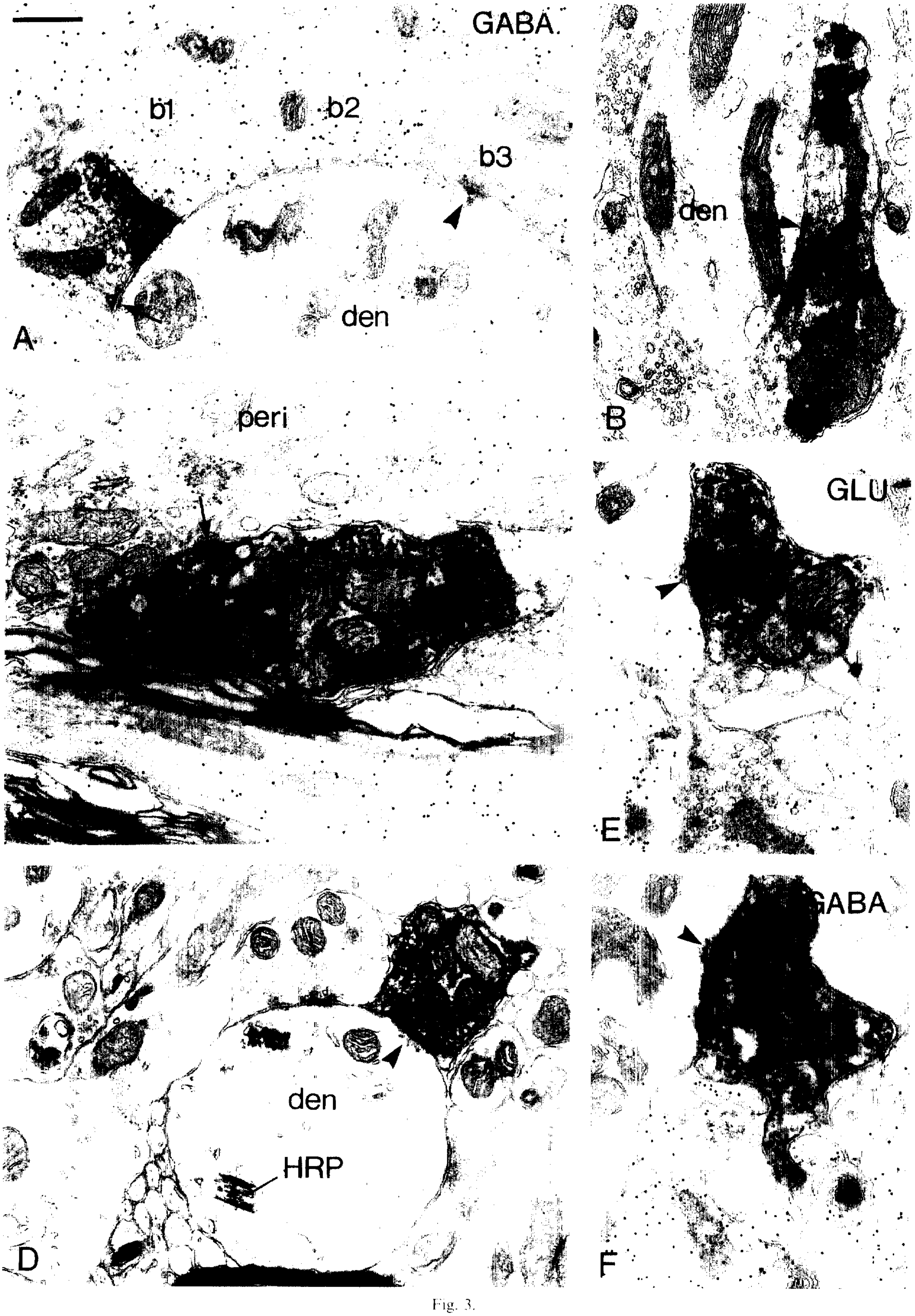

Fig. 3.

neurons[41,285] and contribute to the modulation of the excitatory cortical input to these neurons.[58,59,234,271]

Although it is clear that the majority of cortical terminals form synapses with spiny neurons, anatomical data indicate that striatal interneurons immunoreactive for parvalbumin (i.e. GABA interneurons)[25,29a,197,246a] or neuropeptide Y[325] also receive cortical input. Although anatomical evidence has not been forthcoming,[196] electrophysiological and pharmacological evidence suggests that cholinergic neurons also receive cortical afferents,[71,333] but this input is likely to be sparse and terminate on the distal dendrites. Each of these classes of neurons is likely to feed-forward the cortical information to spiny projection neurons.[25,41,161,168,178]

2.2. *Synaptic connections between striatal neurons giving rise to the direct and indirect pathways*

Evidence from morphological studies, including the intracellular filling of neurons[38,64,169,188,334] and Golgi impregnation,[247,301] has shown that spiny neurons give rise to extensive local axon collaterals that arborize within, or close to, their dendritic field and form symmetric synapses with dendrites and spines.[301,334] Evidence from immunohistochemical data suggests that spiny neurons that give rise to the direct pathways are synaptically interconnected, as are those that give rise to the indirect pathway.[11,44,50,52,87,253,255,307] Furthermore, evidence from striatal tissue double immunostained with markers of the neurons giving rise to the direct and indirect pathways indicates that the two populations are synaptically interconnected.[11,343] Since all spiny neurons are GABAergic, these interconnections have been traditionally ascribed as the substrate for mutual inhibition between spiny neurons;[135] however, little evidence has been found for surround inhibition arising from their collaterals.[162] One possibility, therefore, is that the interactions between spiny neurons are mediated predominantly by neuropeptide transmission and that GABA interneurons are the main source of inhibitory influences on spiny neurons.[25,167a,178,186]

2.3. *Synaptic organization of the direct pathway*

The terminals of striatal neurons that give rise to the direct pathway account for the majority of boutons in contact with neurons in the EP/GPi and SNr, and it has been suggested that individual striatal axons establish multiple contacts with their targets, although there is still debate over this issue.[64,101,112,140,156] In the GPi of squirrel monkeys, it has been estimated that striatal terminals account for more than 80% of the afferent input to dendrites and 32% of the input to perikarya (Fig. 8),[280] and a similar pattern of innervation is likely to occur in both the EP and SN of rats.[46,48,141,292,302]

Combined tracing and immunocytochemical studies have shown that striatal terminals in the EP and SNr are immunoreactive for GABA,[46,48,324] and make symmetrical synaptic contacts with EP neurons that project to the thalamus,[34,226] and with neurons in the SNr that project to the thalamus,[32,305] the superior colliculus,[292,331] the region of the mesopontine tegmentum[318] and the reticular formation.[324]

There is likely to be a high degree of convergence in the direct projections from the striatum to neurons in the output nuclei, as it has been estimated that the EP and SNr of the rat contain 3200 and 26300 neurons respectively, whereas the striatum contains

Fig. 3. Characteristic features of synaptic boutons of the direct and indirect pathways. Micrographs illustrating typical ultrastructural features, synaptic specializations and neurochemistry of synaptic terminals derived from the neostriatum (A), the globus pallidus (B, C) and the subthalamic nucleus (D–F). The sections illustrated in A, C and F were labelled by the post-embedding immunogold method to reveal GABA immunoreactivity, and the section illustrated in E was processed to reveal glutamate immunoreactivity. (A) A striatal bouton in the GPi anterogradely labelled following an injection of BDA in the putamen of a squirrel monkey. The bouton is in symmetric synaptic contact (arrow) with a dendrite (den) and is immunoreactive for GABA. Two neighbouring boutons (b1 and b2), which possess the morphological features of striatal terminals, are also immunoreactive for GABA. In contrast, the bouton b3 forms an asymmetric synapse (arrowhead) and does not display GABA immunoreactivity. This bouton possesses morphological features of a terminal derived from the STN. (B, C) Terminals derived from the GP forming symmetrical synaptic contacts (arrows) with a dendritic shaft (den) in B and a perikaryon (peri) in C. The bouton in B is in the EP and was labelled after an injection of PHA-L in the GP of the rat (revealed using benzidine dihydrochloride). The bouton in C is in the STN and was labelled after an injection of BDA in the GPe of the squirrel monkey. This labelled bouton displays a high level of GABA immunoreactivity. Note the similarity in the morphological characteristics of the pallidal boutons, despite the fact that they are from different species and in different nuclei. (D) A terminal derived from the STN. This terminal is in the rat SNr and was anterogradely labelled following the injection of biocytin in the STN. It forms an asymmetric synapse (arrowhead) with a dendrite (den) that contains retrogradely transported horseradish peroxidase (HRP) from the ventromedial thalamic nucleus. (E, F) Adjacent sections of the same STN bouton in the GPe that forms an asymmetric synapse (arrowheads). The bouton was labelled by multimodal transport following injection of BDA in the GPi of the squirrel monkey. The BDA was transported retrogradely to neurons in the STN and then anterogradely, via axon collaterals, to the GPe. The bouton is enriched in glutamate (E), but is not immunoreactive for GABA (F). Note the similarity in the morphological features of the subthalamic terminals in different species and in different nuclei. Scale bar in A = 0.5 µm (valid for B–F).

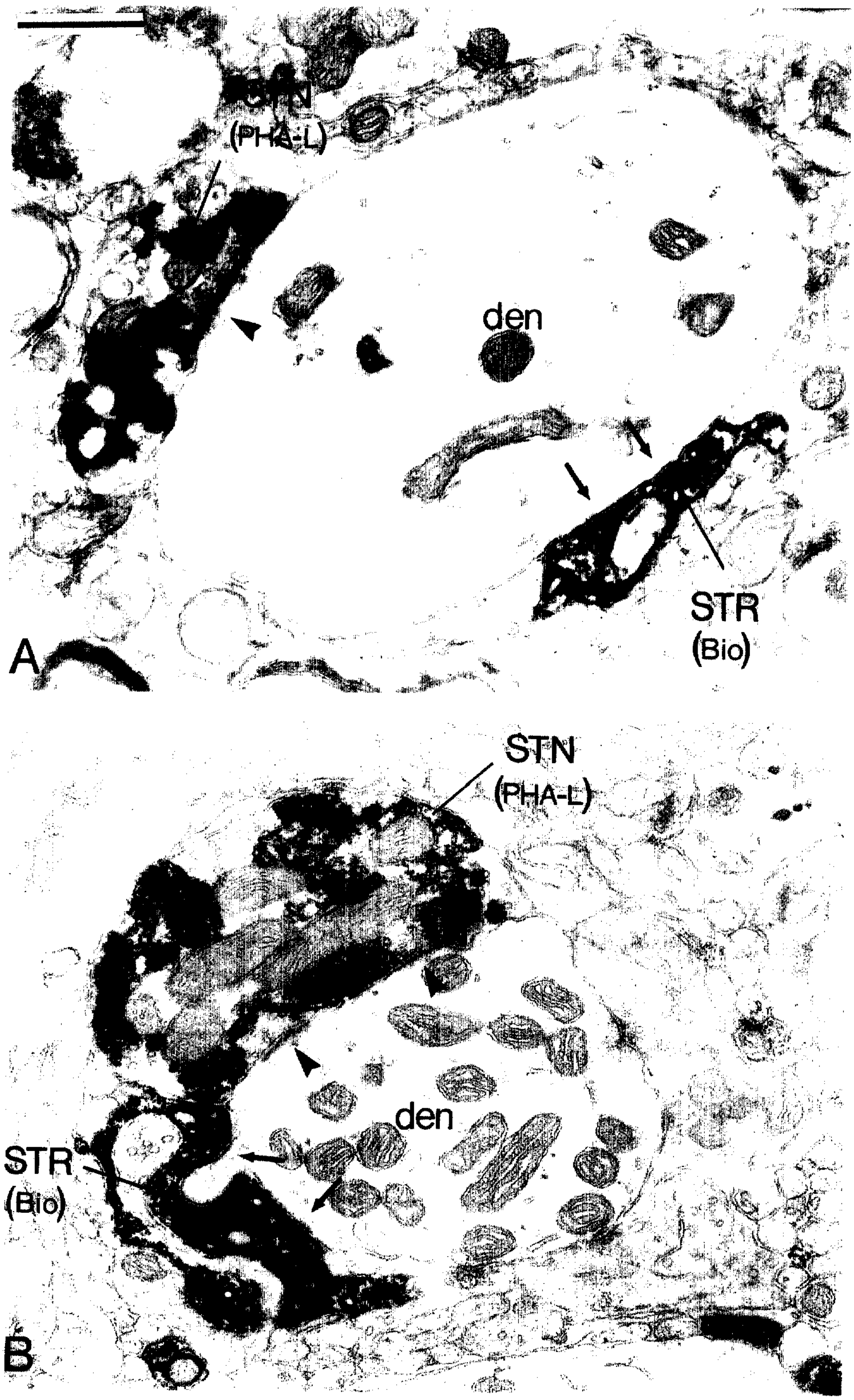

Fig. 4. Synaptic convergence of direct and indirect pathways. These micrographs illustrate synaptic convergence of striatal and subthalamic terminals at the level of single dendrites (den) in the EP (A) and the SNr (B) of the rat. In these experiments, double anterograde tracing was performed by the injections of PHA-L in the STN (localized with benzidine dihydrochloride) and biocytin (Bio) in the striatum (STR) (localized with diaminobenzidine). The terminals derived from the STN form asymmetric synaptic contacts (arrowheads) with the dendrites, whereas the terminals derived from the striatum establish symmetric synapses (arrows). Note that the striatal bouton in B has an irregular shape and is pierced by an unlabelled vesicle-filled process. Scale bar in A=0.5 μm (valid for B). Data derived from Bevan et al.[32,34]

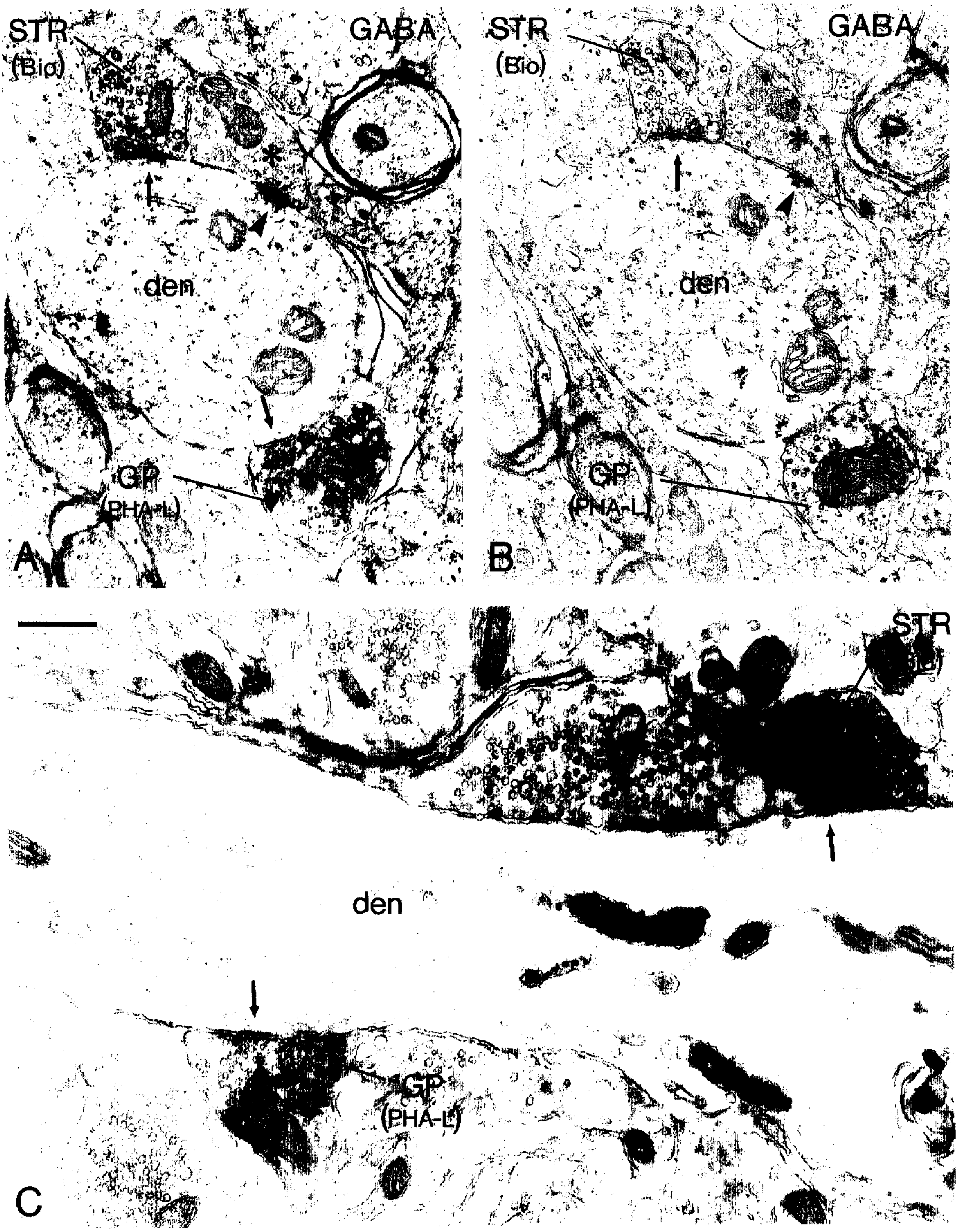

Fig. 5. Synaptic convergence of direct and indirect pathways. These micrographs illustrate the synaptic convergence of terminals derived from the striatum (STR) and the GP at the level of individual dendrites (den) in the EP (A, B) and the SNr (C) of the rat. In these experiments, biocytin (Bio) was injected in the striatum and localized with diaminobenzidine, whereas PHA-L was deposited in the GP and localized with benzidine dihydrochloride. A and B are adjacent sections that have been immunolabelled to reveal GABA by the post-embedding immunogold method. Both the striatal terminal and the GP terminal form symmetric synapses (arrows) with the dendrite and display GABA immunoreactivity. The dendrite is also postsynaptic to an unlabelled bouton (asterisk) that forms an asymmetric synapse (arrowheads) and is not immunoreactive for GABA. The features of this terminal are typical of those derived from the STN. Scale bar in C=0.5 μm (valid for A, B). Data derived from Bolam and Smith[48] and Smith and Bolam.[292]

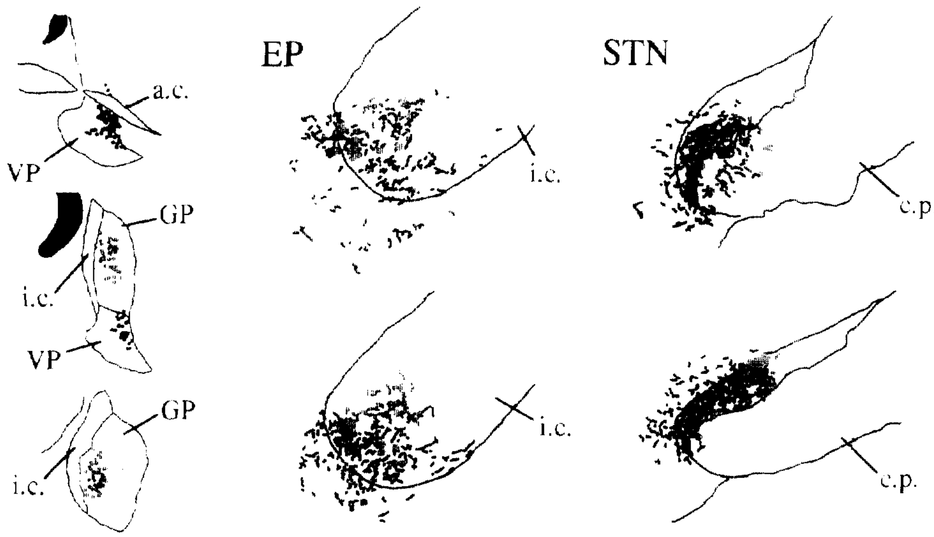

Fig. 6. Convergence of functionally diverse pallidal efferents in the EP and the STN. Schematic representations of the rostrocaudal extent of the injection sites of PHA-L in the ventral pallidum (VP; blue dots, left column) and BDA in the GP (red dots, left column). The middle and right columns show the resulting anterograde labelling (blue and red stippling) in the EP and STN at two different rostrocaudal levels. The green dots identify neurons that were apposed by varicosities derived from both the VP and the GP. Other abbreviations: a.c., anterior commissure; i.c., internal capsule; c.p., cerebral peduncle. Data derived from Bevan et al.[33]

2.79×10^6 neurons.[236] Assuming that 90% of neurons in the striatum are spiny neurons[172] and 50% of spiny neurons give rise to the direct pathway to the EP/SNr,[118] then 1.26×10^6 striatal neurons directly innervate the output nuclei. This gives a ratio of 392 striatal neurons to one EP neuron and 48 striatal neurons to one SNr neuron. Since it is likely that an individual striatal neuron makes synaptic contact with many neurons in the EP and SNr,[169,239] then the degree of convergence of the direct pathway at the level of the output nuclei is likely to be much higher. However, it remains to be established whether the converging striatal input to an individual neuron in the output nuclei arises from functionally related neurons in the striatum or whether this convergence represents a mechanism for the integration of functionally diverse information.[6,8,249,250]

2.4. *Synaptic organization of the indirect pathways*

2.4.1. *The projection from the striatum to the globus pallidus.* The first neuronal link in the indirect pathway is the projection from the striatum to the GP. Three features characterize this projection: the dual pattern of arborization, the high degree of specificity and the high density of innervation. In the rat, axons of single or groups of striatal cells that enter the GP arborize profusely and form two distinct bands of anterograde labelling that are interconnected by thick varicose axons.[64,112,335] There is an indication that

Fig. 7. Synaptic convergence of terminals derived from different functional domains of the pallidal complex in the EP (A) and the STN (B–D). (A) Electron micrograph of part of a proximal dendrite of a neuron in the entopeduncular nucleus (EPn). The neuron is apposed by three anterogradely labelled boutons, each of which forms symmetric synapses with the neuron (arrows). Two of the boutons (VP) contain the benzidine dihydrochloride reaction product that was used to localize PHA-L anterogradely transported from the ventral pallidum (VP). The third bouton (GP) contains the diaminobenzidine reaction product that was used to localize the BDA anterogradely transported from the GP. Note that the benzidine dihydrochloride reaction product has an irregular appearance and occupies only part of the labelled terminals. In contrast, the diaminobenzidine reaction product is amorphous and occupies the whole of the labelled structures. (B–D) Part of a neuronal perikaryon in the subthalamic nucleus (STNn) that is apposed by three anterogradely labelled terminals (VP, GP). Two of them are shown at higher magnification in C and D. In this animal, the injections were reversed, i.e. the PHA-L (localized with benzidine dihydrochloride) was injected in, and anterogradely transported from, the GP and the BDA (localized with diaminobenzidine) was injected in, and anterogradely transported from, the VP. One of the boutons (C) contains the amorphous diaminobenzidine reaction product, identifying it as arising from the VP, whereas the other two boutons are strongly labelled with the crystalline benzidine dihydrochloride reaction product, indicating that they arise from the GP (the one on the left is illustrated at high magnification in D). The three labelled terminals form symmetric synaptic contacts with the neuron (arrows). Scale bars = 1 μm (A), 2 μm (B), 1 μm (D; valid for C). Data derived from Bevan et al.[33]

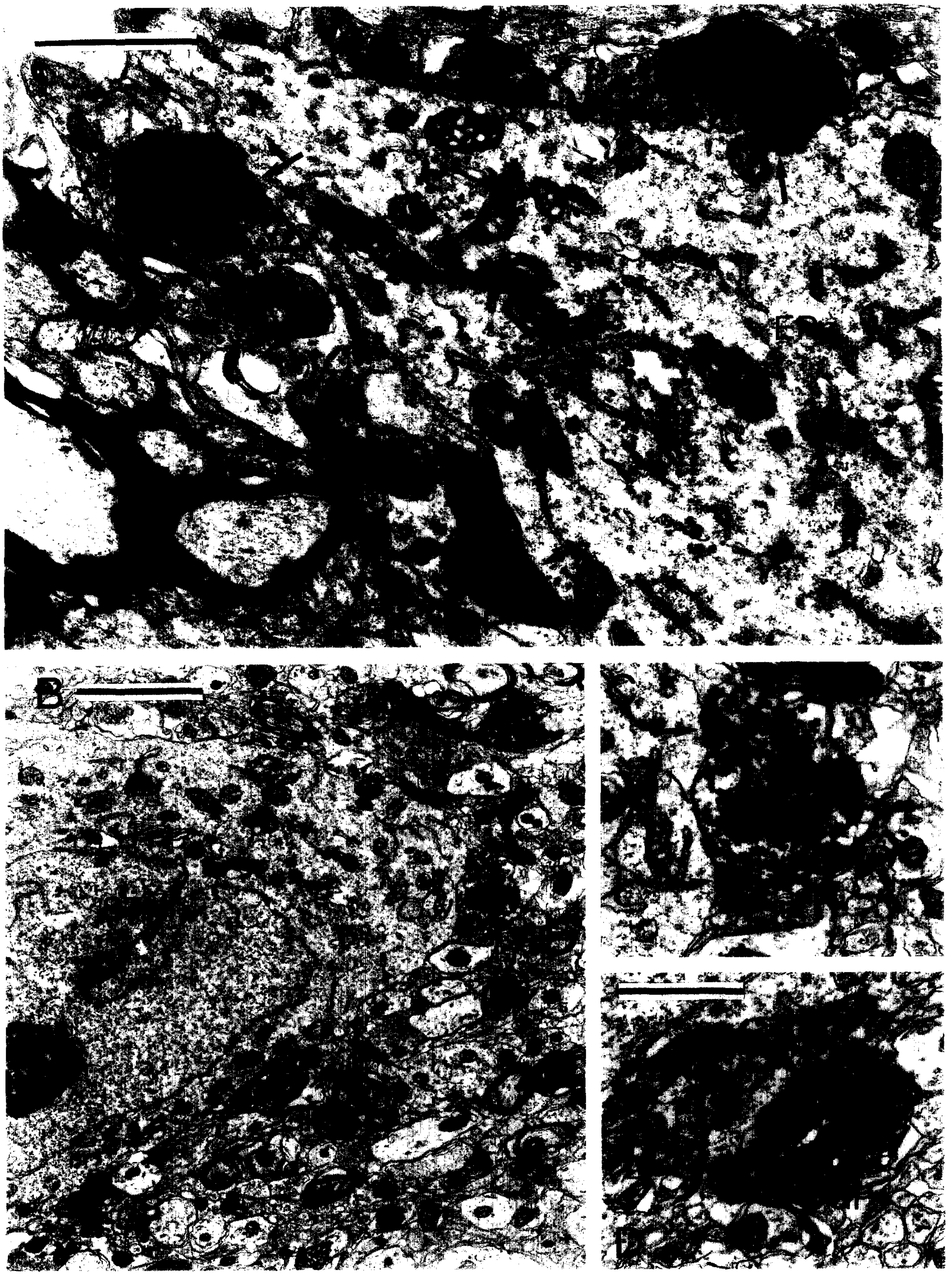

Fig. 7.

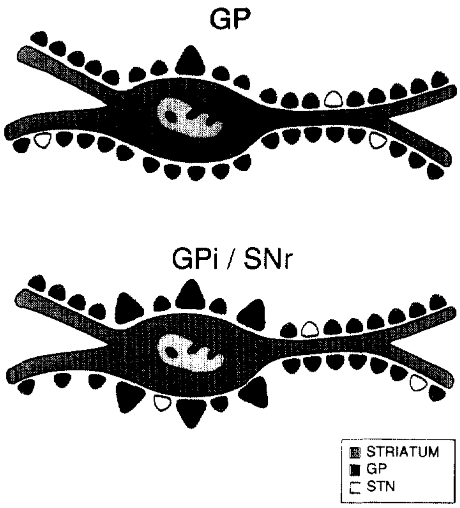

Fig. 8. Diagrams summarizing the overall pattern of innervation of projection neurons in the GPe and the GPi. These diagrams are based on data obtained in the squirrel monkey by means of anterograde tracing and post-embedding immunogold labelling for GABA or glutamate.[277,280,298,299] Evidence indicates that it is likely that neurons of the GP and the SNr of non-primates also receive a similar pattern of innervation (see text for more details). The relative sizes and proportions of each category of terminal are represented in the diagrams. The major difference between the innervation of neurons of the GPe and GPi is that the latter receive a high proportion of their input at the level of the perikaryon from the GPe, whereas terminals derived from the striatum and the STN are relatively evenly distributed on GPe and GPi neurons. Although not indicated in this diagram, terminals derived from the GPe also make synaptic contact with proximal dendrites and, albeit to a lesser extent, distal dendrites. For the sake of clarity, the less well characterized inputs from the raphe, PPN, SNc and thalamus have not been included. Data derived from Shink and Smith.[280]

this is also the case in primates.[239] Although it appears to be more complex, a similar pattern of organization has been observed in the SNr.[112,118] The high degree of specificity of the striatofugal projections has been demonstrated in experiments that involved small injections of two anterograde tracers in close, but non-overlapping, regions of the striatum.[112,155] The anterogradely labelled fibres that arise from these injections form dense bands of staining that are largely segregated in the GP and also in the output nuclei of the basal ganglia. These findings suggest that the information arising from small pools of striatal neurons is transferred with a high degree of specificity to restricted parts of the GP. However, there is probably a high degree of synaptic convergence in the GP, as the ratio of striatal neurons to neurons of the GP is about 27:1.[236]

Striatal terminals form symmetrical synaptic contacts with all parts of neurons in the GP, as shown by immunostaining for enkephalin, and account for the majority of boutons in contact with them.[87,307] In the GPe of the squirrel monkey, striatal terminals have been estimated to represent over 80% of terminals in contact with perikarya and dendrites[280] (Fig. 8). The ultrastructural features of the striatal terminals in the GP are typical of those in other nuclei (see above): they are GABA immunoreactive[46] and have been shown in the rat to make synaptic contact with pallidonigral neurons.[319]

2.4.2. *The projection from the globus pallidus to the subthalamic nucleus.* The projection from the GP to the STN represents part of the "classical" indirect pathway. Both the GP and the ventral pallidum (VP) give rise to massive topographically organized projections that terminate throughout the entire extent of the STN. In the rat, the terminals arising from neurons in the GP are distributed according to a mediolateral and rostrocaudal topography.[294] On the other hand, the dorsolateral part of the VP projects to the dorsomedial part of the STN, whereas the ventral part of the VP is connected with the adjacent lateral hypothalamic area.[126,129] Similar relationships have been described in monkeys.[136] The pallidosubthalamic fibres characteristically possess large varicosities, which are sometimes grouped to ensheath the perikarya and dendrites of STN neurons.[33,294] Single GP axons may give rise to several varicosities apposed to the surface of a single neuron in the STN.[294] Pallidosubthalamic varicosities have the typical ultrastructural appearance of pallidal terminals (see above), are GABA positive and form synapses with all parts of STN neurons.[33,281,294] In the rat, it has been estimated that 31% of pallidal terminals form synapses with perikarya, 39% with large dendrites and 30% with small dendrites.[294] Preliminary findings indicate that terminals arising from the GPe in the squirrel monkey display a similar pattern of distribution in the STN.[281] Some of the GPe terminals form synapses with vesicle-containing profiles in monkeys[281] and cats,[225] but this type of synapse has not been observed in the rat.[30,294] Many of the STN neurons that receive pallidal inputs project back to the GP,[126,225,277] indicating that the relationship between neurons of the STN and the GP is, at least in part, reciprocal (see Section 3). Convergence and divergence is likely to exist in the system as in the rat, the ratio of the number of neurons in the GP to the number in the STN is approximately 3:1,[236] and an individual neuron may contact multiple subthalamic neurons.[35,185]

2.4.3 *The projection from the subthalamic nucleus to basal ganglia output nuclei.* The major projection sites of the STN are to the two output nuclei of the basal ganglia, i.e. the EP/GPi and the SNr, as well as the GP. Additional projections to the striatum,[20,182,244,295,296] the SNc,[126,182,221,264,286,295] the pedunculopontine nucleus (PPN)[146,182,244] and the spinal cord[316] have also been described, but will not be considered further here.

In the rat, STN neurons are highly collateralized.[82,147,181,322] Intracellular labelling,[147,181] electrophysiological analyses[82,146] and tracing experiments in which the tracers were transported in a multimodal fashion[32,34,48,49] indicate that single STN neurons send axon collaterals to the GP, EP and SNr. The situation has been proposed to be different in primates, primarily on the basis of retrograde double labelling methods.[243,244,245] Thus, neurons projecting to the GPe and those projecting to the SN were found to be spatially separate populations within the STN of squirrel monkeys.[244] Similarly, STN neurons projecting to the GPe have been proposed to be segregated from those projecting to the GPi.[243,245] However, in the latter case the conclusion was based on injections of fluorescent tracers in different functional domains of the GPe and GPi which would result in the retrograde labelling of different regions of the STN. Indeed, the results of tract-tracing experiments, in which the multimodal transport of BDA was utilized (see Section 1.3), indicate that in primates as well, single neurons in the STN project to both the GPe and GPi, and do so primarily to related functional domains[277] (see Section 3). It remains to be established whether neurons in the primate STN project to both the GPe and SNr.

Axon terminals in the basal ganglia output nuclei and the GP that are derived from the STN display common ultrastructural features (Fig. 3D–F), are enriched in glutamate immunoreactivity and form asymmetrical synaptic contacts (see above). In primates, they account for approximately 10% of the total population of terminals in the GPe and GPi, and are evenly spread over perikarya and dendrites[280] (Fig. 8); a similar distribution has been observed in the rat.[32,34] Combined tracing studies have demonstrated that they make direct synaptic contact with neurons in the EP and SNr that project to the thalamus.[32,34]

2.4.4. *The projection from the globus pallidus to the entopeduncular nucleus/internal pallidum.* In addition to the "classical" indirect pathway, consisting of projections from the striatum to the GP, the GP to the STN and then the STN to output nuclei, cortical information may also influence the output of the basal ganglia by the projection directly from the GP to the output nuclei. A direct projection from the GP to the EP or GPi has been described in both rat[48,49,174,185,290] and monkey.[154,277,280,298,299] In the monkey, this projection is organized according to a strict dorsoventral and rostrocaudal topography.[277,299] In the rostrocaudal plane, the GPe cells are located 0.5–1.0 mm more rostral than their termination area in the GPi.[277] The principles of organization of the projection from the GP to the EP/GPi are discussed in Section 3 (Fig. 11).

Terminals from the GP that make synaptic contact with EP/GPi neurons display the typical ultrastructural features of pallidal boutons, forming symmetrical synaptic contacts and displaying GABA immunoreactivity. In the monkey, they form short symmetric synapses predominantly with the proximal part of GPi neurons,[277,280,299] and have been estimated to account for 48% of the total number of terminals in contact with the perikarya of GPi cells and 5% of the axodendritic synapses[280] (Fig. 8). In the rat, they are more evenly distributed on neurons of the EP.[48,49] Single neuronal perikarya in the EP/GPi are tightly surrounded by dense aggregates of pallidal terminals that often arise from single pallidal axons.[48,154,299] It is clear from single cell labelling studies that individual GP neurons may contact multiple neurons in the EP.[35,185] Small neurons in the GPi of monkeys, which are presumed to be interneurons,[88,101] do not appear to receive input from the GPe.[280]

2.4.5. *The projection from the globus pallidus to the substantia nigra.* Analogous to the projection from the GP to the EP/GPi, the existence of a projection from the GP (or GPe) to the SN has been demonstrated in various species by means of both retrograde[137,151,240,272,309,311,319] and anterograde tracing.[36,136,289,291,292,324] Filling of single neurons in the GP of the rat has shown that the axons reaching the SN are collaterals of the pallidosubthalamic projection.[35,185] Anterograde tracing studies have revealed that the pallidonigral projection is organized according to an inverted dorsoventral topography.[49,129,137,289,291,292,324] and cell-filling studies indicate that individual GP cells terminate over a large rostrocaudal extent of the SN.[35,185]

Pallidonigral terminals display ultrastructural features typical of boutons derived from the GP, they form symmetrical synapses and are rich in GABA immunoreactivity. They make contact predominantly with the perikarya (59%) and proximal dendrites (37%) of SNr neurons, but much less frequently (4%) with distal dendrites.[49,289,291] They display a basket-like innervation of their target neurons, with a single axon sometimes forming many contacts with the cell body and proximal dendrites of individual SNR neurons. The neurons postsynaptic to the pallidal terminals have been characterized as projecting to the thalamus, tectum, PPN and reticular formation.[49,291,324]

2.4.6. *The projection from the globus pallidus to the reticular nucleus of the thalamus.* The existence of a projection from the GP to the reticular nucleus of the thalamus (RTN) was first proposed in cats on the basis of the anterograde transport of tritiated amino acids from the GP.[232] More recent findings obtained by means of retrograde and anterograde tracing techniques confirmed that the RTN receives an input from the GP in rat,[12,15,72,109,276] cat[37] and monkey.[13,14,152] The projection is organized according to a rostrocaudal topography[14,15,37,72] and uses GABA as a neurotransmitter.[13,15,37] Anterogradely labelled pallidoreticular boutons display the typical ultrastructural features of pallidal terminals, form symmetric synapses with the perikarya and proximal dendrites of RTN neurons,[13,15,37] and are immunoreactive for GABA.[13,37] A small proportion of labelled terminals form asymmetric synapses with distal dendrites.[15] These terminals probably arise from the cholinergic neurons of the basal forebrain which, in the rat and cat, are intermixed with the GABAergic neurons of the GP.[37,215] Indeed, the ultrastructure of these terminals is similar to that of cholinergic boutons described in other studies.[143]

These findings suggest that the information from the basal ganglia can reach thalamocortical cells, not only via the EP/GPi and SNr, but also via the pallidoreticular projection. Whether or not the information flowing through the EP/GPi–dorsal thalamus and GP–RTN–thalamus pathways converges on common populations of dorsal thalamic neurons remains to be established.

2.4.7. *Intrinsic axon collaterals of globus pallidus neurons.* The majority of neurons in the GP possess local axon collaterals.[35,92,102,185,230,246] The axons may innervate widespread or more restricted regions of the nucleus and form dense clusters of terminals on the proximal regions of a small number of neurons.[35,185] Boutons presumed to be derived from local collaterals display ultrastructural features of pallidal terminals and have been estimated to represent 10% of the terminals in contact with the perikarya of GPe neurons in the squirrel monkey[280] (Fig. 8).

2.4.8. *Other efferent projections of the globus pallidus.* The existence of a topographically organized GABAergic projection from the GP to the dorsal striatum or from the VP to the ventral striatum has been described in retrograde and anterograde tracing studies in rat,[54a,69,129,258,282,310,326] cat[19,97,163] and monkey.[19,240,296,308] Some of the pallidal cells projecting to the striatum send axon collaterals to the SN,[35,311] the STN[35,185] or the cerebral cortex.[97] Boutons in the striatum that are derived from the VP have been shown to mainly form symmetric synapses predominantly with dendrites and less frequently with somata of projection neurons in the rat.[194] In line with these findings, light microscopic observations[129,258,296] and electrophysiological data[142] suggest that striatopallidal and pallidostriatal projections are reciprocal. Preliminary findings indicate that the NADPH-diaphorase-containing interneurons as well as spiny neurons receive pallidal inputs in the rat.[24,41,312] Furthermore, a single cell-filling study suggests that GP terminals in the striatum preferentially innervate the parvalbumin-positive and nitric oxide synthase-positive interneurons.[35]

Although the bulk of basal ganglia afferents to the mesopontine tegmentum arises from the EP/GPi and SNr (Fig. 1), a minor projection from the GP has also been described.[224,272] In the rat, this projection is GABAergic and arises from the caudal part of the GP.[224,276] Those GP neurons that project to the PPN send axon collaterals to the STN and the SNr, but do not project to the auditory cortex.[224,272]

2.5. *Synaptic convergence of direct and indirect pathways on basal ganglia output neurons*

The response of output neurons of the basal ganglia to striatal stimulation is not simply decreased firing due to activation of the direct pathway or increased firing due to activation of the indirect pathway, but rather individual neurons respond with increased and/or decreased firing depending on the site of stimulation in the striatum or cortex.[67,106,180,267,268,320] Indeed, in behaving animals, output neurons exhibit complex patterns of increased and decreased firing.[56,110,218,222] These findings, together with observations concerning the topographical organization of the direct and indirect pathways, raise the possibility that individual neurons in the output nuclei receive convergent synaptic input from both the direct and indirect pathways.

2.5.1. *Convergence of subthalamic and striatal terminals on individual basal ganglia output neurons.* Double anterograde tracing has demonstrated that neurons of the striatum (direct pathway) and STN (indirect pathway) innervate common regions of the EP/GPi or SNr.[32,34,153] Electron microscopic analyses (Fig. 4) have demonstrated that the terminals derived from the striatum and the STN form convergent synaptic contacts with individual dendrites and perikarya in both the EP and the SNr, and at least some of these neurons have been identified as projecting to the ventral medial nucleus of the thalamus.[32,34]

2.5.2. *Convergence of pallidal and striatal terminals on individual basal ganglia output neurons.* In addition to the indirect pathway that includes the STN, synaptic convergence between the direct and indirect pathways mediated by the projection from the GP to the output nuclei has been demonstrated in the rat.[48,49,292,324] Thus, deposits of tracers in the striatum and GP lead to largely overlapping fields of anterograde labelling in the EP and SNr. Electron microscopic analysis has demonstrated that both striatal and pallidal terminals make convergent synaptic contact with the perikarya and dendrites of individual neurons in the EP and SNr[48,49,292,324] (Fig. 5). Some of the postsynaptic neurons in the SNr have been further characterized as projecting to the superior colliculus or the reticular formation.[292,324]

2.5.3. *Convergence of subthalamic, pallidal and striatal terminals on individual basal ganglia output neurons.* In simple ultrastructural analyses of basal ganglia output neurons in the EP/GPi or SNr. individual neurons are seen to receive synaptic input from terminals that have the morphological features of all three classes of terminals that mediate the direct and indirect pathways. i.e. striatal, subthalamic and pallidal terminals. On the basis of data from double anterograde tracing studies in which the multimodal transport of tracers injected in the GP or the STN has occurred (see Section 3), it is evident that individual output neurons in the EP or SNr that receive synaptic input from the striatum also receive synaptic input from terminals derived from the STN and the GP[32,34,48,49,292,324] (Figs 4, 5). These findings indicate that groups of neurons, in the GP, STN and output nuclei, are likely to be reciprocally connected.

2.6. *Synaptic convergence of descending functionally diverse information arising from the globus pallidus and ventral pallidum*

It has been suggested that functionally diverse information arising from the cerebral cortex is processed in the basal ganglia by parallel and segregated cortical–basal ganglia thalamocortical loops.[6,8,128,158,166,167] 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.[10,124,273,274,339] Anatomical analyses of the basal ganglia have identified several neuronal elements or systems which could provide the morphological basis of such integration. These include the local circuit neurons of the neostriatum,[41,66,111,168,190] the ascending projections of midbrain dopamine neurons,[116,165,233,285,302] the GPi output to the PPN[278,279] and open-interconnected cortico-basal ganglia–thalamocortical loops.[166,167]

It has recently been demonstrated[33,36] that the descending projections of the VP, which largely receives limbic cortical afferents via the nucleus accumbens,[6,8,128] and the GP, which receives mostly sensorimotor and associative afferents via the neostriatum,[6,8,112,128,158,166,167] may provide a morphological basis for the synaptic integration of functionally diverse information in the basal ganglia. Thus, double anterograde tracing from the two divisions of the pallidal complex in individual animals revealed. in addition to the well established topographically segregated fields of anterogradely labelled terminals in the EP, STN and SN. zones of overlap of the two projections (Fig. 6). Electron microscopy demonstrated that in the regions of overlap in each nucleus the proximal parts of many neurons. including tyrosine hydroxylase-immunopositive neurons in the SNc. received convergent synaptic input from both the VP and GP[33,36] (Fig. 7).

Another way by which EP, STN and SN neurons may integrate functionally diverse information from the pallidal complex is via their dendrites, as they also receive pallidal inputs[33,36,48,289,291] and are often oriented to cross the functional boundaries defined by pallidal inputs.[33,133,181,229,281]

In monkeys, projections arising from the associative and limbic territories of the GPi converge on common regions of the thalamus. lateral habenular nucleus and PPN.[278,279,283] This may also underlie a mechanism for the synaptic convergence of functionally diverse information in the output regions of the basal ganglia.

2.7. *The corticosubthalamic projection: an additional indirect pathway*

Although the striatum is commonly seen as the main entrance of cortical information to the circuitry of the basal ganglia, the STN also receives excitatory glutamatergic projections from the cerebral cortex.[31,149,187] Anatomical evidence indicates that the corticosubthalamic projection is exclusively ipsilateral.[3,61,62,149] In contrast to the corticostriatal projection which arises from the entire cortical mantle, the corticosubthalamic projection is largely derived from the primary motor cortex, with a minor contribution from the prefrontal and premotor cortices.[3,149,193,231] but not somatosensory or visual cortical areas.[3,149] In both rat and monkey, the corticosubthalamic projection is topographically organized, so that afferents from the primary motor cortex are confined to the dorsolateral part of the STN; the premotor area, the supplementary motor area and adjacent frontal cortical areas innervate mainly the medial third of the nucleus, whereas the prefrontal limbic cortices project to its medial-most tip.[3,27,149,231] Like the cortical input to the striatum. the corticosubthalamic projection from the primary motor cortex is somatotopically organized: the face area lies laterally, the arm area centrally and the leg area medially.[149,231] In line with these anatomical findings, neurons in the dorsolateral part of the STN respond somatotopically, with increases in discharge to sensory stimulation or active movements of different body parts.[78,328] In contrast, neurons located more medially are not affected by somatosensory stimulation and skeletal movements, but some respond to visuooculomotor tasks, which implies that they may be involved in the control of visual saccades.[211]

The exact cellular origin and degree of collateralization of the corticosubthalamic projection are still poorly understood. Double retrograde labelling in the rat[93] has shown that the corticosubthalamic neurons are mainly located in layer V and that many of them send axon collaterals to the striatum. Other findings in cats suggest that the corticosubthalamic axons detach from the pyramidal tract.[120] which indicates that the STN, as is the case for the striatum,[73,90,202] is directly influenced by copies of cortical signals descending to the spinal motor centres.

Corticosubthalamic terminals are small boutons packed with round electron-lucent vesicles, and form asymmetric synapses with the distal dendrites and spines of STN neurons.[31,263] In primates[263,281] and cats,[225] but not in rats,[31] about 10% of the cortical terminals form synapses with vesicle-filled structures. The corticosubthalamic terminals are enriched in glutamate immunoreactivity.[31] The same postsynaptic structures that receive cortical input also receive synaptic afferents from boutons that have the morphological and neurochemical characteristics of pallidal terminals.[31]

The intralaminar nuclei of the thalamus,[31,93,227,228,269,315] the dorsal raphe,[159,198] the mesopontine tegmentum[30,199,216,223,314,336] and the dopaminergic cells in the SNc[60,61,150,189a,261] also innervate the STN.

The projection sites of STN neurons that receive cortical input still remain to be established, although it is likely that in the rat, both subthalamopallidal and subthalamonigral neurons receive common cortical inputs, since single STN neurons send axon collaterals to the GP, EP and SNr (see Section 2.4.3.). In line with these anatomical observations, stimulation of the sensorimotor cortex induces short-latency excitatory postsynaptic potentials in the different targets of STN neurons in this species.[180] A characteristic of the corticosubthalamic projection in the rat is the widespread excitatory influence generated in the STN following stimulation of a single site in the sensorimotor cortex.[107] Although it is clear that inputs from different cortical areas are largely segregated in the STN,[3,149] the existence of intranuclear axon collaterals[181] and the large extent of the dendritic tree of single STN neurons[2,33,147,181,256] are features that may account for the generalized effect of cortical excitation.[107,180] Whether similar responses occur in primates remains to be established (see below). The recent data showing that single STN neurons innervate interconnected territories of the GPe and GPi[277] suggest that common cortical inputs may be conveyed to both pallidal segments (see Section 3).

3. NEURONAL NETWORK UNDERLYING THE INDIRECT PATHWAYS

3.1. *Basic circuit underlying the indirect pathways*

The synaptology and tract-tracing data summarized above confirm the existence of the "indirect pathway" of information flow through the basal ganglia and, furthermore, demonstrate its existence at the synaptic level. The data also indicate that there are several routes by which cortical information may be transmitted through the basal ganglia which, on a hypothetical basis, may give rise to increased firing of basal ganglia output neurons and hence to inhibition of the targets of the basal ganglia. It is clear from the extensive studies of the synaptology of this system that each indirect pathway converges, at the synaptic level, on to individual output neurons of the basal ganglia and that terminals of striatal neurons that give rise to the direct pathway make convergent synaptic contact with the same output neurons. Thus, individual output neurons of the GPi or EP and SNr are the common targets of the direct and indirect pathways.

The existence of multiple indirect pathways through the basal ganglia, however, does not imply the existence of multiple, unrelated, parallel pathways but, rather, the findings summarized above indicate that the multiple indirect pathways are intimately interlinked. Data derived from the tracing and synaptology studies in the rat (see above for references) and the squirrel monkey[277] lead to the conclusion that the multiple indirect pathways are in fact components of a highly interconnected system and should be considered as an "indirect network". The findings in the rat that lead to this conclusion are as follows. (1) Two components of the indirect pathways, namely neurons of the GP and neurons of the STN, make convergent synaptic contact with basal ganglia output neurons in the EP and SNr. (2) The multimodal transport of the tracers has demonstrated that the groups of neurons in the GP and STN that give rise to the convergent projection in the output nuclei are themselves reciprocally interconnected.

Fig. 9. Neuronal network underlying the interconnections between the STN and the two segments of the GP in monkeys. Schematic drawings of the GPe and GPi (A–D) and the STN (E–F) of the squirrel monkey illustrating the distribution of labelled fibres (sinuous lines) and perikarya (red dots) following injections of BDA in interconnected regions of the sensorimotor territory in the GPi (A, C, E) and GPe (B, D, F). The deposits of BDA in the GPi (C) led to the retrograde labelling of cell bodies in both the GPe (A) and STN (E) by retrograde transport of the BDA and, by multimodal transport, led to the labelling of terminal fields in both regions. Thus, the terminal field in the GPe was derived from neurons in the STN that had retrogradely transported the tracer and then anterogradely transported it, and the terminal field in the STN was derived from retrogradely labelled neurons in the GPe. The deposits of BDA in the GPe (B) led to retrograde and anterograde labelling in the STN (F), and to labelling of terminal fields in the GPi (D) by anterograde and multimodal transport. The location of the injection site in the GPe corresponds to the position where the retrogradely labelled cells are found after injection in the GPi (compare A and B). As predicted from functional topography, the labelling in the GPi (D) after injection in the GPe (B) occurred in the same region as the injection site in the GPi (C). Similarly, the retrograde and anterograde labelling that resulted from injections in the GPi and GPe are in register in corresponding regions of the STN (E–F) (see for details). The anteroposterior coordinates for each section are indicated in parentheses. Data derived from Shink et al.[277]

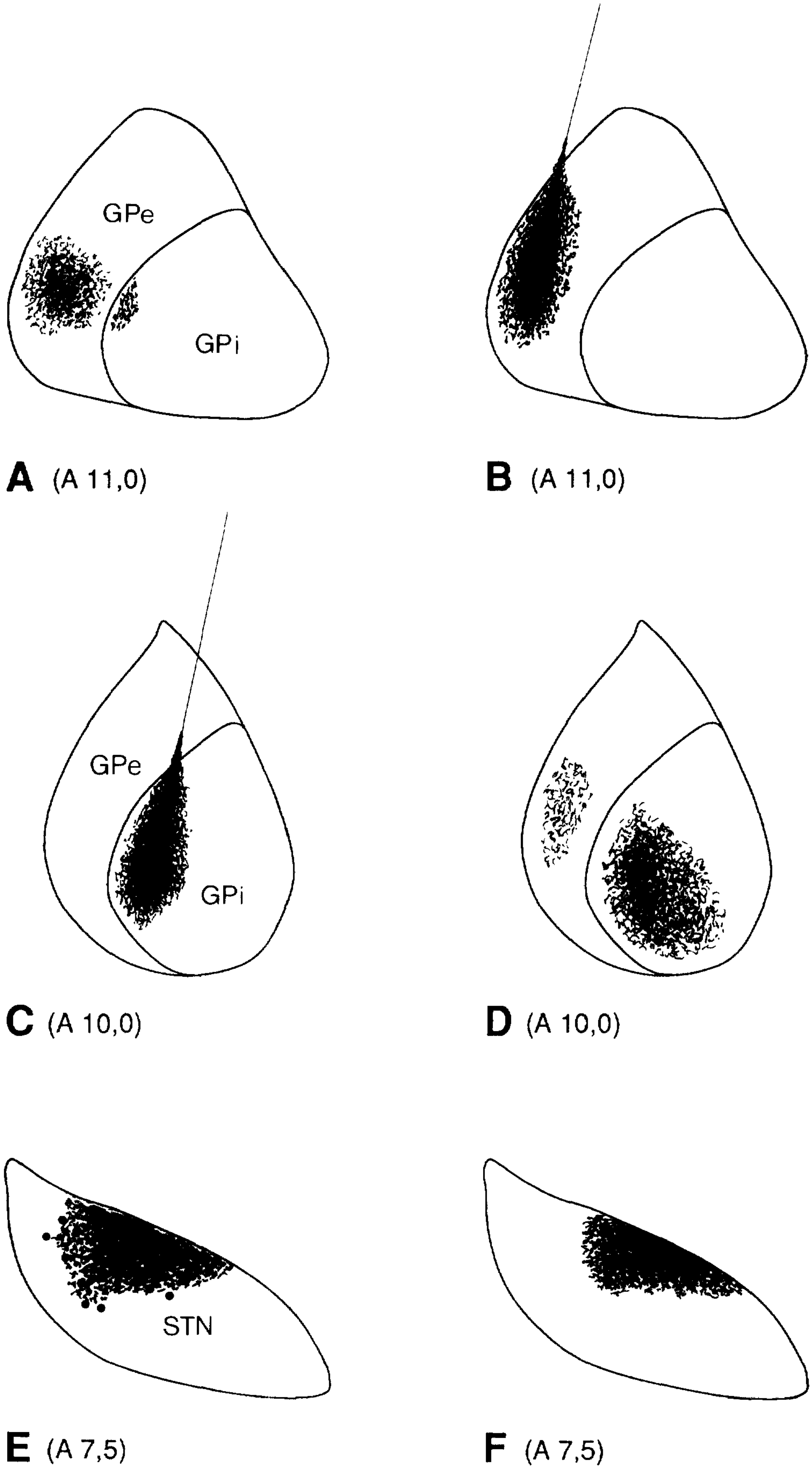

Fig. 9.

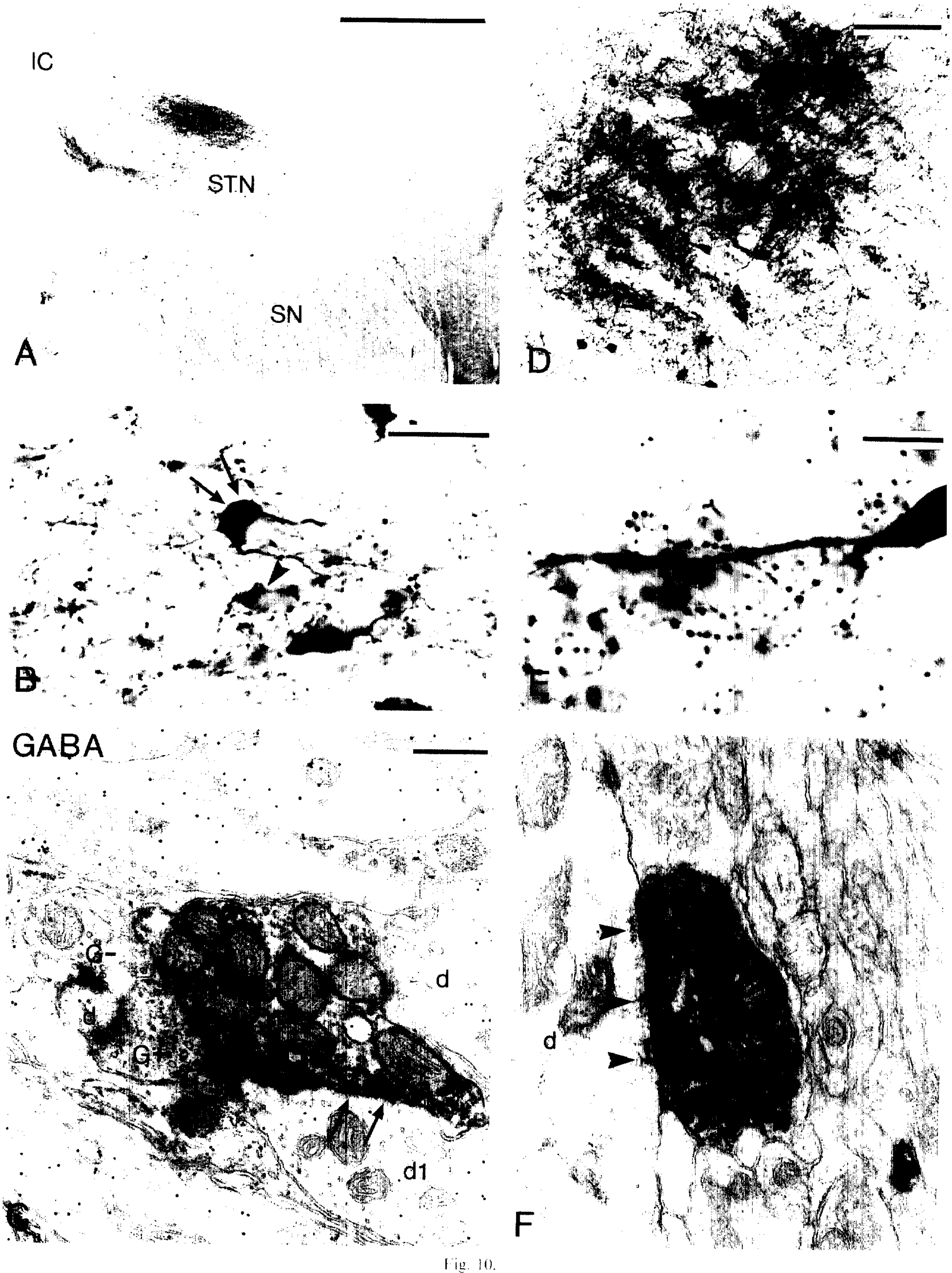

Fig. 10.

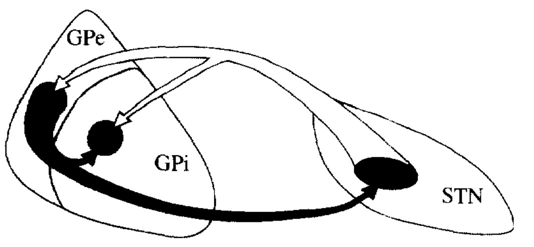

Fig. 11. Neuronal network underlying the interconnections between the STN and the two segments of the GP in monkeys. Summary of the relationships between the GPe, STN and the basal ganglia output nucleus, the GPi, as revealed by injections of BDA in functionally related regions of the GPi and GPe in squirrel monkeys.[277] Groups of neurons in homologous functional zones of the GPe and STN are reciprocally connected and innervate, via axon collaterals, common, functionally homologous regions in the GPi. In addition to this system, there is also evidence for connections between functionally non-homologous regions of the pallidal complex and the STN (see text). Furthermore, when considering topographical relationships it should be remembered that the dendrites of neurons in the pallidal complex and STN are very long and often oriented to cross functional boundaries. The black arrow indicates the inhibitory connections of the GPe and the white arrow indicates the excitatory connections of the STN. Redrawn from Shink *et al.*[277]

The findings in the squirrel monkey that support the notion of an indirect network are derived from the tracing study of Shink *et al.*,[277] in which the connections between the two segments of the pallidal complex and the STN were examined. The key findings are as follows. (1) Tracer deposits in the GPi led to clusters of retrogradely labelled neurons in both the GPe and the STN (Figs 9A, C, E, 10A, B, D, E). (2) The retrogradely labelled neurons were co-distributed with clusters of labelled terminals (Figs 9A, E, 10). (3) Electron microscopy and post-embedding immunocytochemistry identified the majority of terminals in the GPe as having arisen, by multimodal transport, from neurons of the STN (Fig. 10F), whereas the majority of labelled terminals in the STN were derived from neurons in the GPe (Fig. 10C). (4) Tracer deposits in the GPe led to retrograde labelling of neurons in the STN that were co-distributed with anterogradely labelled terminals derived from the same region of the GPe (Fig. 9B, D, F). (5) The same deposits of tracer in the GPe gave rise to a cluster of terminals in the GPi (Fig. 9D) that were derived from both the GPe and, by multimodal transport, from the STN (Fig. 9). Thus, in the squirrel monkey, as in the rat, reciprocally interconnected regions of the GPe and STN converge on the same region (and probably the same neurons) in the GPi. Furthermore, this organizational principle largely maintains the functional topography of both segments of the pallidal complex and the STN (Fig. 11). Thus, groups of neurons of the GPe are reciprocally connected to functionally related groups of neurons in the STN and both sets of neurons innervate common groups of functionally related neurons in the output nuclei of the basal ganglia.

Although there is clearly much to learn about the intrinsic physiological properties of cells in the GPe, STN and output nuclei and their responses to afferent synaptic activity, these data may partly provide the anatomical substrate for the complex sequences of inhibition and excitation that are observed in individual GPe, STN and output neurons following electrical or pharmacological stimulation of the cortex or striatum and normal movement behaviour.[67,77,78,80,106,107,179,184,187,266,267,320,328,329] Studies by several groups have demonstrated that the first response of GPe, STN and output neurons to cortical stimulation or stimulation of corticofugal fibres is a brief period of excitation.[106,107,179,187,266,267,320] This effect appears to be mediated by the corticosubthalamic pathway, which excites subthalamic neurons, and these, in turn, excite GP/GPe neurons and neurons in the output nuclei.[106,107,179,187,266,267,320] The conduction speeds of this system are faster than those of the pathways flowing from the cortex through the striatum.[106,107,179,187,266,267,320] This brief period of excitation is terminated and followed by a longer period of inhibition, which is mediated in part, by the

Fig. 10. Neuronal network underlying the interconnections between the STN and the two segments of the GP in monkeys. Retrograde and anterograde labelling in the STN (A–C) and GPe (D–F) following injections of BDA in the sensorimotor territory of the GPi. (A) Cluster of labelling in the dorsolateral part of the STN. At higher magnification (B), this cluster is seen to contain both labelled (arrows) and unlabelled (arrowhead) neurons in a field of varicosities which became labelled by retrograde transport of the tracer to the GPe and then anterograde transport to the STN. (C) An example of the major type of terminal that was labelled in the STN following injection of BDA in the GPi. The bouton displays the ultrastructural features of terminals derived from the GPe (see Fig. 3B, C), it is in symmetrical synaptic contact (arrows) with a dendrite (d1) and displays GABA immunoreactivity. The terminal labelled G+ is also immunoreactive for GABA, whereas the terminal indicated by G− and the dendritic shafts (d) do not display GABA immunoreactivity. (D, E) Cluster of labelling in the central part of the GPe that occurred following the tracer deposit in the GPi. The cluster contains both retrogradely labelled perikarya and a population of varicosities that became labelled following retrograde transport to the STN and then anterograde transport to the GPe. (F) Electron micrograph of the major type of terminal labelled in the GPe after injection of BDA in the GPi. The bouton displays the ultrastructural features typical of terminals derived from the STN (see Fig. 3D–F) and forms an asymmetric synapse with a dendrite (d). Scale bars = 1.0 mm (A), 100 μm (B), 0.5 μm (C; valid for F), 250 μm (D), 20 μm (E). Data derived from Shink *et al.*[277]

activated population of GP/GPe neurons that provide feedback inhibition to the activated population of subthalamic neurons, in turn leading to reduced excitation of neurons of the GP/GPe and the output nuclei.[106,107,179,187,266,267,320] Since the activated GP/GPe neurons that provide feedback inhibition to the STN also project to the population of activated neurons in the output nuclei, they may also contribute to the inhibition of neurons in the output nuclei.

Of course, the major route of cortical influence on the basal ganglia is through the striatum, and it has been shown that the long periods of inhibition of the GP/GPe and neurons in the output nuclei that occur following corticostriatal activation and follow the initial period of excitation (see above) are a result of striatal-mediated inhibition.[67,106,179,267,320] Synchronous inhibition of GP/GPe and output neurons would hypothetically result in a period of decreased firing of GP/GPe and neurons in the output nuclei. This period of inhibition of output neuron firing is associated with the disinhibition of basal ganglia targets and movement.[5,7,67,68,76,81,339] Since the indirect pathways are likely to terminate on functionally homologous populations of output neurons that are targeted by the direct pathway[32,34,48,292] and are likely to exert their effects after the direct pathway,[67,106,107,184,266,267,320] then the final period of facilitation of firing that is observed in the STN and output neurons following cortical activation might be mediated by inhibition of GP/GPe neurons (see above; indirect pathway). This inhibition would act to disinhibit neurons in the output nuclei and STN neurons. Presumably, disinhibition of the STN would further supplement the facilitation of basal ganglia output neurons by increased excitatory drive. The increased firing of neurons in the output nuclei, and the consequent inhibition of basal ganglia targets, may then act to terminate or inhibit the behaviour associated with the activation of the direct pathway. The restoration of firing patterns and rates in the GP/GPe, STN and output nuclei that are associated with resting animals are likely to result from the reciprocal interaction of populations of GP/GPe and STN neurons, which may tend towards equilibrium following the perturbation caused by cortical activation.

3.2. *Functional specificity of the indirect network*

The degree to which the interconnections of the STN and pallidal complex respect the functional divisions of these regions is critical to our understanding of the indirect network and of the functional organization of the basal ganglia. It has recently been proposed,[243] on the basis of double retrograde fluorescent labelling,[245] that neurons of the STN that project to the GPi are distinct from those neurons that project to the GPe. Furthermore, it has been suggested, on the basis of anterograde labelling, that the GPe innervates mainly the dorsolateral part of the STN, i.e. that region of the STN that is proposed to provide a reciprocal innervation of the GPe.[243] These suggestions raise questions about the position of the STN in the functional organization of the basal ganglia and call into question the existence of the indirect pathway. However, the tracer deposits that led to this interpretation were located in different functional territories of the GPe and GPi, and it is likely that the positions of the retrogradely labelled neurons and anterograde labelling in the STN simply respected the known topographical relationships of this system. From the observations of Shink *et al.*,[277] it appears that (i) all regions of the STN project to both the GPe and GPi in a topographical manner, (ii) that the GPe innervates all regions of the STN in a topographical manner, and (iii) that interconnected regions of the STN and GPe innervate common, functionally related, regions of the GPi. Furthermore, many of the individual neurons that contribute to the reciprocal connections between the STN and GPe also project, via axon collaterals, to a common region of the GPi. Thus, the indirect pathway, as originally proposed,[5,7,76] is supported by the experimental data and, indeed, exhibits a high degree of specificity.

The interconnections between the GPe, the STN and output neurons of the basal ganglia in the GPi are thus capable of a greater degree of specificity than suggested previously.[241,243] However, in addition to this highly specific organization in which functionally homologous zones of the GPe, STN and GPi are interconnected, Joel and Weiner[167] have suggested, on the basis of topographical studies, that an additional component of the GPe–STN projection terminates in a functionally non-homologous region of the STN. They proposed that the associative GPe projects mainly to the associative STN, but also to the motor and limbic territories of the nucleus. In addition, they raised the possibility that although the STN projects to functionally homologous regions of the GPe and GPi, it is also likely to innervate functionally non-homologous zones (also see Ref. 139). Experimental data demonstrating both functionally homologous and non-homologous connections arise from the work of Shink *et al.*[277] Thus, the deposits of BDA in the GPe or GPi, which gave rise to clusters of retrogradely labelled neurons in register with anterogradely labelled GPe terminals, also led to retrograde labelling of STN neurons outside the fields of anterogradely labelled GPe terminals. It is possible that these neurons are reciprocally connected with functionally non-corresponding regions of the GPe. Furthermore, in the same experiments, it was noted that there were many STN neurons within the anterogradely labelled GPe terminal fields that were not retrogradely labelled. The possibility that these neurons project to functionally non-corresponding regions of the pallidal complex should be considered. However, they may also innervate only the GPe

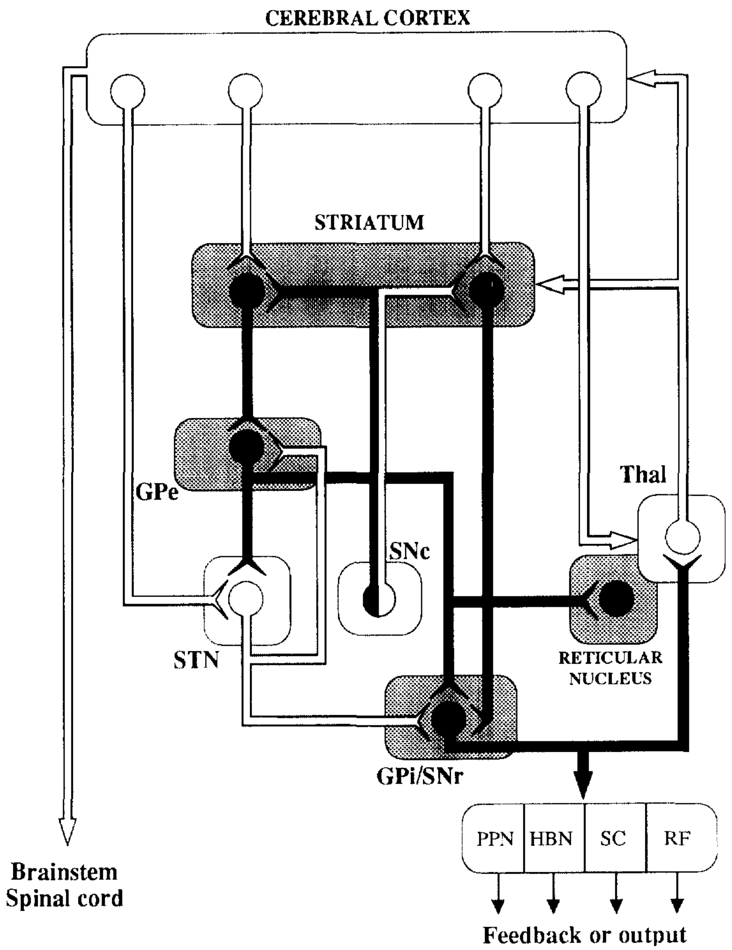

Fig. 12. Updated model of the circuitry of the basal ganglia in the light of new anatomical data on the connectivity of the GPe. The major difference between this model and that outlined in Fig. 1 is the existence of multiple "indirect" pathways through the GPe. In addition to a massive projection to the STN, the GPe projects directly to the output structures of the basal ganglia (GPi/SNr) and to the RTN. In the basal ganglia output structures, the direct and indirect pathways through the GPe and the STN converge at the single-cell level. The transmitters used by the different pathways are indicated in Fig. 1. It should be noted that the diagram is still a simplification, as many connections have not been indicated. Modified from Fig. 2 in Alexander and Crutcher.[7]

or GPi, or may project to targets other than the pallidal complex.

It should be noted that the findings of most topographical studies relate to the location of neuronal perikarya. However, it is evident from work in both the rat and primate that the dendrites of neurons in the STN are oriented in such a manner to traverse functionally heterogeneous regions defined by pallidal inputs.[33,281] Thus, considerable convergence of functionally diverse pallidal information is likely to occur at the level of dendrites in the STN.[33]

These data paint a confusing picture of the topographical relationships of the GPe, GPi and STN. It is clear that these nuclei are not simply connected to each other with a point-to-point, functionally homologous organization. The projections are also distributed to such an extent that even different functional streams converge on to individual neurons (for references, see above). The precise details of the connectivity of neural networks in these nuclei remain to be determined, but one promising approach is likely to be the three-dimensional reconstruction and analysis of the connections of single filled neurons.

The functional implications of this system are apparent from the responses of output neurons to the indirect and direct pathways that are engaged following stimulation of the cortex. Thus, individual neurons appear to respond with any combination of early excitation, late inhibition and late excitation depending on the site and intensity of cortical stimulation.[106] The spatial arrangement of output neurons responding in a similar manner to cortical stimulation is highly complex and does not appear to conform to any simple geometrical pattern.[106] One possibility is that output neurons that only respond with excitation during behaviour (see Refs 219 and

321, and references therein), or to stimulation of a specific region of striatum or cortex,[68,81,106,320] are targeted by indirect pathways that do not conform to functionally specific topographic rules. This system might act to excite and/or disinhibit output neurons that mediate non-selected motor programmes and thus prevent the execution of inappropriate motor behaviour.[217a,220] Conversely, the functionally homologous component of the indirect network is likely to be more directly involved in the motor behaviour by terminating it or by mediating a selective inhibition of groups of muscles that is an integral component of the behaviour.

4. AN UPDATED VERSION OF THE SCHEME OF THE BASAL GANGLIA CIRCUITRY

Five major conclusions summarize the new anatomical findings presented in this commentary. (1) There are several routes for the flow of cortical information along functionally defined "indirect" pathways, i.e. those pathways that hypothetically result in increased firing of the output neurons of the basal ganglia. Thus, information carried by neurons in the GP can reach the output structures of the basal ganglia, not only via the STN, but also directly via massive inhibitory projections that terminate on the proximal parts of EP/GPi and SNr neurons. The GP also innervates the RTN, which provides a route by which a copy of the information flowing along the indirect pathways reaches thalamocortical neurons and, in view of the GABAergic nature of neurons in the RTN, activation of this projection will produce the same effect on thalamocortical neurons as activation of other indirect pathways. An updated version of the basal ganglia–thalamocortical circuitry, which takes into account the connections of the GP, is presented in Fig. 12 (see also Ref. 65). (2) Information flowing through the direct pathway and the indirect pathways interacts at several levels within the basal ganglia, including the output neurons in the EP/GPi and SNr. Thus, striatal neurons giving rise to the direct pathway are synaptically interconnected to neurons giving rise to the indirect pathways, and the direct and indirect pathways converge at the synaptic level on single output neurons of the basal ganglia. Furthermore, synaptic terminals derived from the GP and terminals derived from the cerebral cortex converge at the single-cell level in the STN. (3) Functionally diverse information carried by the descending projections of the pallidal complex is synaptically integrated by individual neurons in the EP, STN and SN. (4) A major component of the interconnections between the STN and the two divisions of the pallidal complex are highly specific and follow a strict functional topography in primates. The basic circuit in both the rat and primates is such that reciprocally interconnected groups of neurons in the GPe and the STN innervate, via axon collaterals, the same population of neurons in the EP/GPi. (5) The interconnections between the GPe, GPi and STN are also likely to exhibit additional levels of organization that facilitate the communication between functionally non-homologous regions.

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