The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones

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The study of synaptic connections in the electron microscope has established an 'elementary' circuit for the neostriatum which consists of a pathway from cortical areas (neocortex, hippocampus, amygdala) to medium spiny neurones of the striatum that also receive converging synaptic input from midbrain dopamine neurones. The striatal medium spiny neurones are projection neurones and they form synaptic contacts with output neurones in the globus pallidus and substantia nigra reticulata. In this way, dopaminergic afferents can directly modulate the flow of information from cortical areas through the striatum to the 'premotor' areas of the brainstem and to the thalamus. It is proposed that certain parts of the striatum can themselves control the activity of midbrain dopamine neurones and so one part of the striatum can 'gate' the flow of information through another part.

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Studies of the fibre connections of the basal ganglia[1,2] have shown that the neostriatum (caudate nucleus, putamen, nucleus accumbens and olfactory tubercle) receives input from the entire cortical mantle, including the allocortex, but that its major output is to just two regions – the substantia nigra and pallidum. The recognition that information originating in different parts of the cortex may remain segregated in several parallel pathways that pass through the striatum to the pallidum or substantia nigra[3,4] (see also article by G. Alexander and M. D. Crutcher, this issue) has challenged the traditional view that the striatum serves as a kind of funnel through which information from the cortex converges onto a limited number of output targets. Accordingly, when we consider the organization of connections at the synaptic level within the striatum, we no longer have to look for a network that leads to a high degree of convergence. Instead, we can ask the question, is there a fundamental neural network that occurs in each of the parallel channels? In other words, is the striatum organized as a number of parallel 'central processing units', each of which carries out essentially the same operations on information from different parts of the cortex? We shall see how far it is possible to answer this question from ultrastructural studies on the synaptic connections of identified neurones and will go on to develop a working hypothesis that goes beyond current knowledge of synaptic connections.

Importance of the study of identified neurones

It is nearly two decades since the publication of a series of papers by Kemp and Powell that have become a landmark in our knowledge about the basal ganglia[5]. In these papers, the organization of the striatum was described on the basis of studies at the light microscopic level by the Golgi method and at the synaptic level by electron microscopy. The commonest cell type in cat striatum, also described by Ramón y Cajal in 1911, was a medium-sized neurone whose dendrites were densely covered in spines (medium spiny neurone); this neurone comprised 96% of all Golgi-impregnated neurones in the caudate nucleus of the cat (Fig. 1). Because the Golgi procedure led to impregnation of extensive local axon arbors of these neurones but did not reveal any axons leaving the striatum, Kemp and Powell considered that the medium spiny neurone was a local-circuit neurone in the striatum and that the main projecting neurones were larger in size and comprised less than 3% of the total population of impregnated neurones. On the other hand, their electron microscopic studies, in which anterograde degeneration was used to

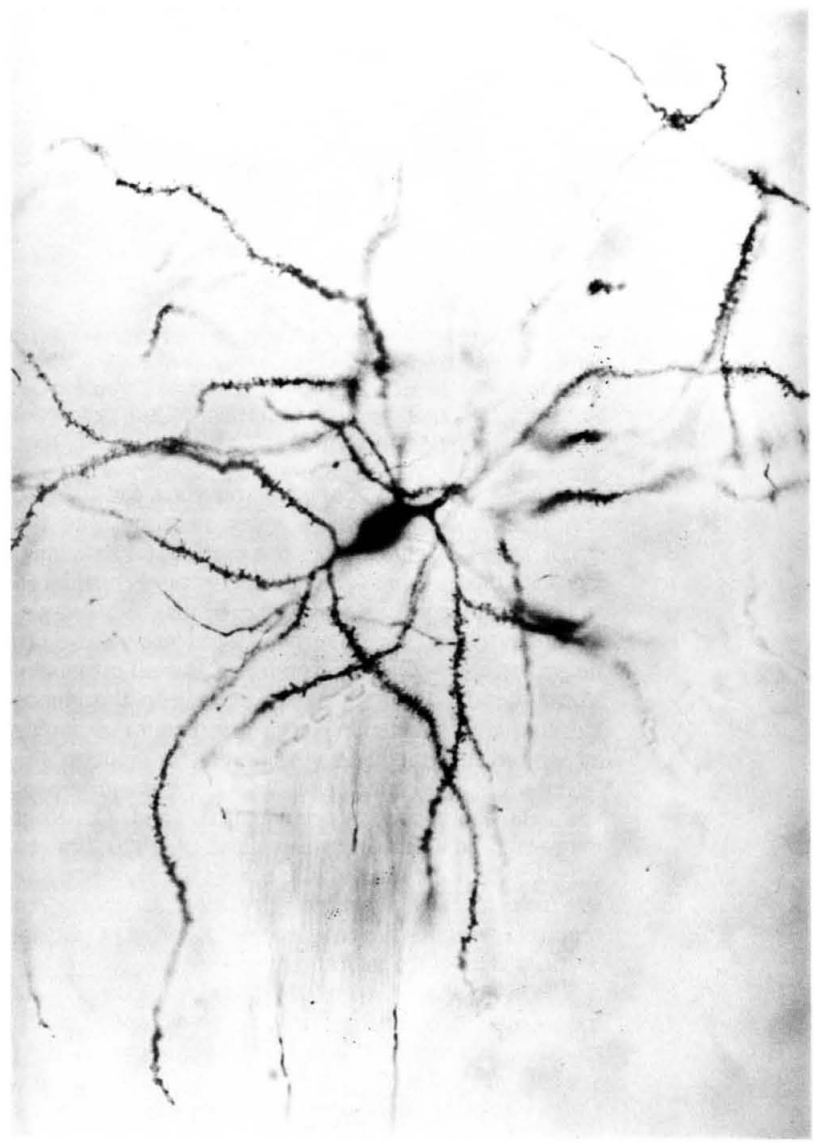

Fig. 1. *A typical medium-sized, densely spiny neurone of the neostriatum as revealed by Golgi impregnation in the rat. This example shows the more common type of very densely spiny neurone that has been shown to project to the substantia nigra and to receive synaptic input from the cortex and from dopaminergic terminals. A second type of less densely spiny neurone receives input from the parafascicular nucleus of the thalamus in the rat.*

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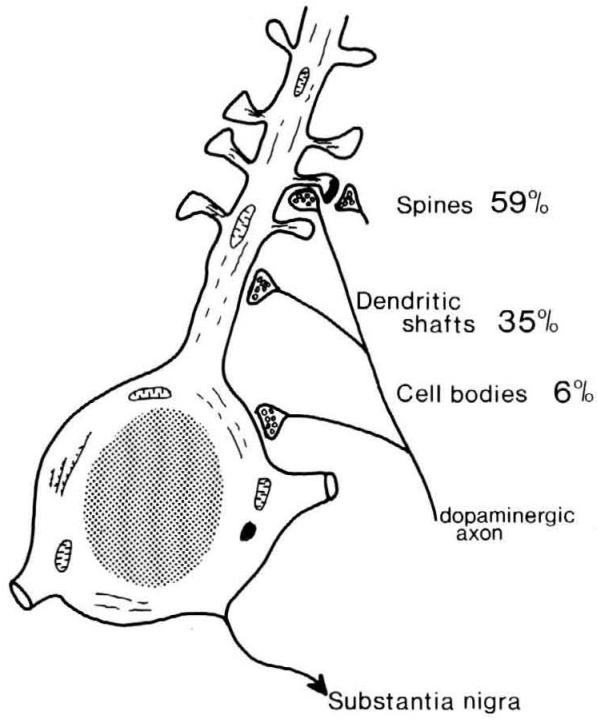

Fig. 2. *The distribution of tyrosine hydroxylase-immunoreactive synaptic boutons in contact with identified striatonigral medium spiny neurones in the rat. It can be assumed that these terminals, which form symmetrical synaptic contacts, originate from midbrain dopaminergic neurones, and so the results indicate that one of the main functions of dopamine in the striatum is to influence the flow of information from neurones that terminate with asymmetrical contacts on the same dendritic spines. It has been shown that such terminals originate in cortical areas, including the neocortex and hippocampus.* (Data from Ref. 17.)

determine the origin of synaptic boutons, led them to conclude that the medium spiny neurone was the major target of inputs from the cortex and thalamus. Because the medium spiny neurones were considered to be interneurones, it was assumed that they relayed this input to the larger neurones that were believed to be projecting neurones. Kemp and Powell concluded 'consequently, the information passing to the globus pallidus and substantia nigra represents a highly integrated and modified version of the input to the [striatum]'. This conclusion was fully in agreement with the authoritative view of C. and O. Vogt expressed in their *magnum opus* of 1920 (for an excellent historical review see Ref. 6). However, as we have already indicated, this view is difficult to reconcile with the new evidence of a series of parallel corticostriato-pallidonigral pathways.

The conclusion reached by Kemp and Powell[5] was based upon a comparison of the results of electron microscopic studies with the results of separate Golgi studies; at that time, it was not possible to examine Golgi-impregnated neurones in the electron microscope. Another problem, common to most contemporary studies of synaptic contacts in the electron microscope, was that the identity of the postsynaptic target neurone could only be deduced by analogy with the appearance of neurones in the light microscope. Two technical advances have now made it possible to reveal which type of Golgi-impregnated neurone projects from a brain area and to study these identified neurones in the electron microscope (for reviews see Refs 7,8). Application of these methods has established that the medium spiny neurone is the major projecting neurone of the striatum: a combination of retrograde transport of HRP and Golgi impregnation in the same material showed that almost all striatonigral neurones are of medium size and have dendrites densely covered in spines[9,10]. A similar conclusion was reached for the striatopallidal pathway by application of a different method – tracing individual axons after the intracellular injection of HRP into striatal neurones[11]. The finding that the commonest cell type in the striatum is the major projecting neurone is much easier to reconcile with multiple parallel pathways and allows us to begin to formulate the basic circuit of the neostriatum.

The medium spiny neurone as the target of striatal inputs

Kemp and Powell[5] showed that terminals in cat striatum that degenerated after placement of lesions in the neocortex formed asymmetric synaptic contacts mainly with dendritic spines, and they suggested that these spines belonged to the medium spiny neurone. Direct evidence of such an input was provided by the demonstration of degenerating boutons in contact with the dendritic spines of Golgi-impregnated

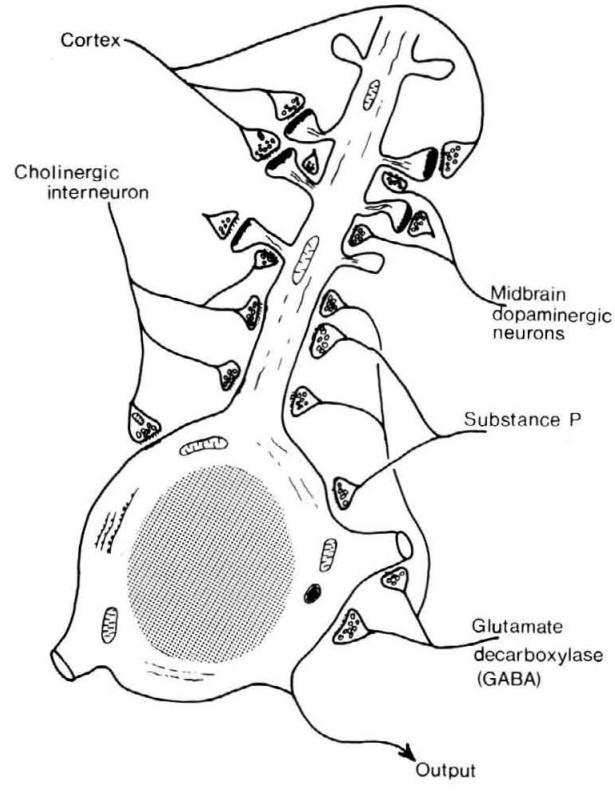

Fig. 3. *Topography of synaptic inputs to the medium spiny neurone. The distribution of inputs on the striatal medium spiny neurone is far from being random. On the whole, inputs from outside the striatum terminate on more distal parts of the dendritic tree and in particular on the dendritic spines, while inputs from local neurones (probably other medium spiny neurones) that contain substance P and GABA, terminate on proximal parts of the dendritic shaft and on the cell body. Inputs from the large cholinergic interneurones terminate in an intermediate position.*

medium spiny neurones in cat striatum after unilateral ablation of the cortex[12]. Application of a combination of three procedures in the same material (anterograde degeneration, Golgi impregnation and retrograde transport of HRP) made it possible to show synaptic input from rat sensorimotor cortex to the dendritic spines of identified medium spiny neurones that project to the substantia nigra[13]. The latter result could only have been obtained by using a procedure that revealed the distal dendrites of the projecting striatonigral neurones because synaptic input from the cortex was only found on distal dendrites. These two examples show that input from the neocortex terminates mainly on the dendritic spines of medium spiny neurones located in the dorsal striatum; the synaptic contacts are invariably of the asymmetric type. If such a connection forms part of a basic striatal circuit, it should also be found in the ventral striatum through which pass parallel pathways from limbic regions. This type of synaptic contact has now been demonstrated in rat medial nucleus accumbens after destruction of hippocampal efferent fibres in the fimbria-fornix: degenerating boutons were found in asymmetric synaptic contact with dendritic spines of Golgi-impregnated medium spiny neurones[14].

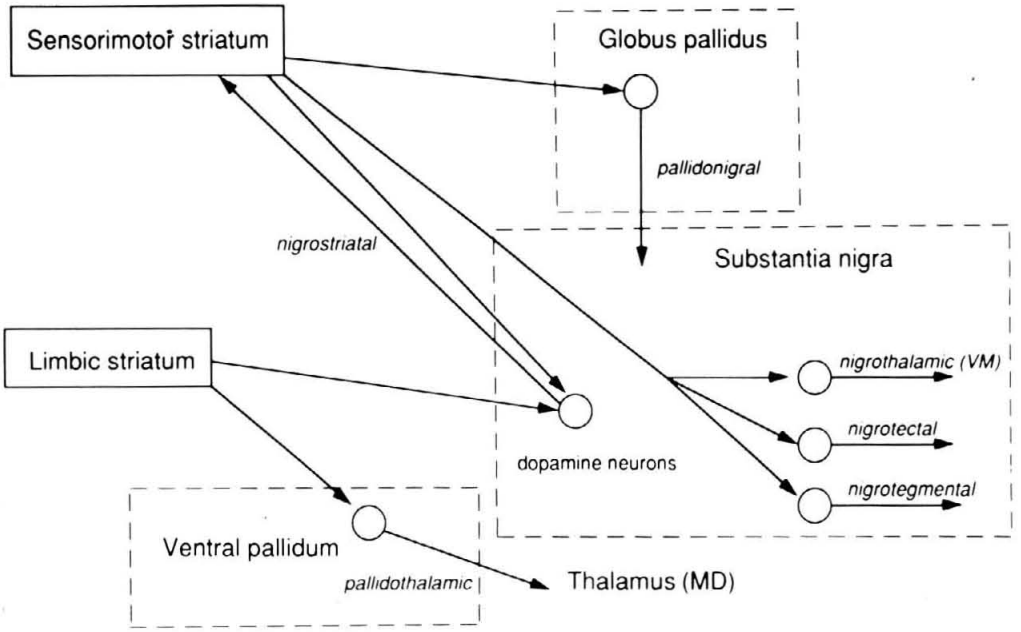

Fig. 4. *Identified targets of striatal output neurones. The targets of the projection neurones of the neostriatum have been identified mainly by looking for degenerating terminals in synaptic contact with characterized neurones in the target zones. In some cases, anterograde transport of HRP has been used (e.g. in the demonstration of a striato-nigrostriatal loop[35]). There are four classes of extrinsic neurone that receive input from the medium spiny neurones of the striatum: those projecting to the thalamus; those projecting to subcortical 'pre-motor' areas such as the tectum and tegmentum; those projecting from the external segment of the pallidum to the substantia nigra; and, lastly, nigrostriatal dopaminergic neurones. Abbreviations: MD, mediodorsal nucleus of the thalamus; VM, ventromedial nucleus of the thalamus.*

Kemp and Powell[5] described degenerating boutons in asymmetric synaptic contact with dendritic spines in the striatum after placement of large lesions in cat thalamus; they also argued, on the basis of Golgi studies, that such inputs converge on the same dendrites as cortical inputs. In the rat, a different result was found after injection of HRP–WGA (wheat germ agglutinin) in the parafascicular nucleus: anterogradely labelled boutons were found in asymmetric contact with the dendritic shafts of a distinct type of Golgi-impregnated medium spiny striatal neurone that had a lower density of spines than the more common type[15]. In the same study, anterograde degeneration was used to identify boutons originating from neurones in the sensorimotor cortex and these were found to terminate on the more common type of densely spiny neurone; no evidence of convergence of cortical and thalamic input onto the same medium spiny neurone could be found.

There is no direct evidence, by anterograde tracing from the substantia nigra or ventral tegmental area, about the nature of the target neurone of these mesencephalic inputs to the striatum. However, use of antibodies to tyrosine hydroxylase to reveal catecholaminergic boutons gives strong evidence that such inputs terminate extensively on medium spiny neurones. A technique for combining Golgi impregnation with immunocytochemistry has been devised[16], and application of this procedure reveals a striking distribution of tyrosine hydroxylase-immunoreactive boutons on Golgi-impregnated medium spiny neurones that have also been retrogradely labelled from the substantia nigra (Fig. 2). The major targets of these boutons, which form symmetrical synaptic contacts, are distal dendritic spines of striatonigral neurones, but only those spines that also receive input from another, non-immunoreactive, bouton receive dopaminergic input[17]. Such an anatomical arrangement implies that one of the main functions of the dopaminergic input is to interact with the other input received by the same spine. The non-dopaminergic boutons form asymmetrical synaptic contacts and so probably derive from neurones in the cortex. Evidence of convergence of input in the striatum from the cortex[18] or from the hippocampus[14] onto dendritic spines that also receive dopaminergic synaptic input has been obtained. In the nucleus accumbens, identified Golgi-impregnated medium spiny neurones have been shown to receive hippocampal input on spines arising from dendritic shafts that also receive dopaminergic input[14]. It is likely, therefore, that circuits through the dorsal (sensorimotor) striatum and those through the ventral (limbic) striatum are basically similar with regard to the organization of dopaminergic input.

We can conclude that a fundamental striatal circuit will probably include a densely spiny medium-sized neurone that projects from the striatum and that receives input on its distal dendritic spines from the cortex and input on its distal dendritic spines and shafts from dopaminergic terminals. A second class of medium-sized spiny neurone, with a lower density of spines[6], may form part of another circuit; this type of neurone receives input on its dendritic shafts from the parafascicular nucleus of the thalamus and may also be a projecting neurone and also receive dopaminergic input (see discussion in Ref. 15).

Transmitters of striatal medium spiny neurones

The chemical nature of the transmitters used by medium spiny neurones has been difficult to establish by rigorous techniques that include identification of the neurone by a method that reveals its dendritic arbor. Combination of Golgi impregnation with immunocytochemistry has shown that medium spiny neurones contain substance P and enkephalin-like peptides[19]. There is much evidence that GABA is present in striatal output pathways (see Ref. 20 for review) and also in medium-sized neurones within the striatum[21], and a preliminary report has described GABA immunoreactivity in Golgi-impregnated medium spiny striatonigral neurones[22]. On the other hand, uptake of radiolabelled taurine has been demonstrated in identified striatonigral neurones[23] and in Golgi-impregnated medium spiny neurones[24]. We can conclude that likely transmitters of medium spiny neurones as a class are a tachykinin, opiate peptides, GABA and taurine. There is evidence that in individual striatal neurones GABA co-exists with either substance P or an opiate peptide[21], but such co-existence has not yet been demonstrated in identified medium spiny neurones. No distinction has yet been made between the transmitters of the common densely spiny type of neurone and the less densely spiny type that receives input from the thalamus.

The striatal medium spiny neurone as a target of chemically defined local circuits

The medium spiny neurone has extensive local axon collaterals within the striatum and, indeed, these have been directly demonstrated for identified medium spiny striatonigral neurones that receive cortical input[13]. Although the synaptic contacts (symmetrical) of local axon collaterals of medium spiny neurones have been demonstrated[13,25], there is no direct evidence that other identified medium spiny neurones are one of the targets, although this is very likely.

Immunocytochemistry has been used to characterize the synaptic inputs of Golgi-impregnated medium spiny neurones: boutons immunoreactive for either substance P[26] or glutamic acid decarboxylase (GAD)[27] have been found in symmetric synaptic contact with the proximal dendritic shaft. Although the major target is the dendritic shaft, occasional boutons are found on cell bodies. Any, or all, of the above boutons could originate from other medium spiny neurones but additional sources are possible. Thus, the striatum contains a local GABAergic aspiny interneurone that has an extensive axon field[27,28], and a small population of substance P-containing neurones may be interneurones[29]. Another striatal interneurone, the large aspiny neurone that contains choline acetyltransferase[30], is the likely source of the ChAT-immunoreactive boutons found in symmetrical synaptic contact with the dendritic shafts and spines of Golgi-impregnated medium spiny neurones[31].

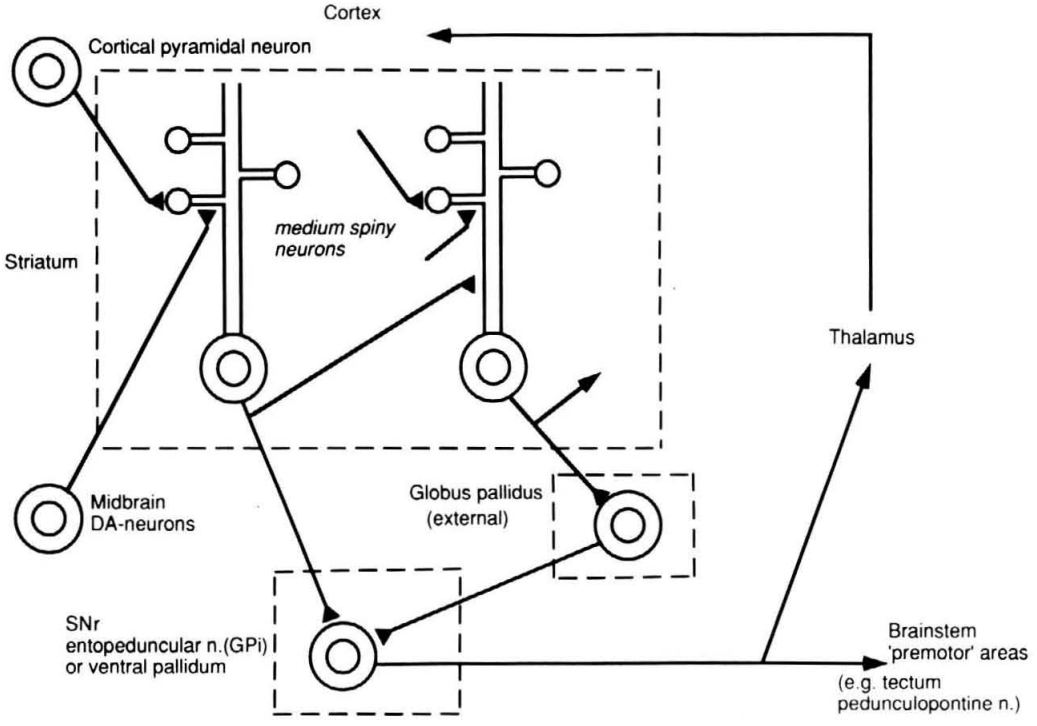

Fig. 5. *The fundamental circuit of the basal ganglia is shown here in a highly simplified form. The key features are the monosynaptic link from cortical areas (neocortex, hippocampus and amygdala) through striatal medium spiny neurones to the main output zones of the basal ganglia (pallidum and substantia nigra). The operation of this monosynaptic link is likely to be strongly and specifically influenced by the input from dopaminergic midbrain neurones that terminates on the same dendritic spines. Note that distinct medium spiny neurones project from the striatum to the substantia nigra and to the external segment of the globus pallidus and that it is suggested that these neurones are laterally connected through axon collaterals of medium spiny neurones. It is also suggested that the striatopallidal neurones receive input from the cortex and from midbrain dopamine neurones. (There is no evidence of these connections as yet.) Note that output neurones in the substantia nigra reticulata may receive converging input directly from the striatum and indirectly via the striato-pallidonigral loop. We have omitted from this scheme another similar circuit originating in the parafascicular nucleus of the thalamus that terminates on another type of medium spiny neurone (see text). We have also omitted the subthalamic nucleus, which probably plays an important role in the control of output neurones in the globus pallidus and substantia nigra[49]. Abbreviations: DA, dopaminergic; GPi, internal segment of the globus pallidus; SNr, substantia nigra pars reticulata.*

Topography of synaptic inputs to the medium spiny neurone

A notable feature of the distribution of synaptic inputs on different parts of the medium spiny neurone is the preponderance of extrinsic inputs on the distal dendrites and the concentration of intrinsic inputs on the proximal dendrites and cell body (Fig. 3). Two types of local afferent input can be distinguished – that presumably from other medium spiny neurones, which terminates proximally on the cell body and proximal dendrites, and that from the large cholinergic interneurone, which terminates rather more distally on the dendritic shaft and on some spines. The afferent synaptic 'topography' of the medium spiny neurone provides an anatomical basis for several possible levels of interaction or integration of afferent information. Level one can be defined as the distal dendritic

spine, of which two types have been identified, a spine that has a single synaptic bouton in asymmetric contact, comprising 53% of the total in the study of Freund *et al.*[17] and a second type that receives dual input, i.e. from one bouton forming an asymmetric contact and from another forming symmetric contact (47% of the total). The first type of spine presumably allows input from the bouton to reach the dendritic shaft unimpeded, while the second type of spine, as pointed out by Kemp and Powell[5], might form the anatomical substrate for interaction between the two types of input. Since by far the largest proportion of such 'dual-input' spines receives input from dopaminergic terminals, these spines provide a site for the interaction of dopaminergic input with that from cortical regions[17]. The second level of interaction between inputs occurs on the distal dendritic shaft, where the changes in the electrical properties of the membrane induced by the inputs from both types of spine will interact with each other and with synaptic input directly onto the shaft, such as that from dopaminergic or cholinergic afferents. The third level of interaction is the proximal part of the dendritic shaft and the cell body, where the inputs originating from within the striatum can interact with each other and also influence the propagation of the information from the distal dendrites. In principle, it seems very likely that the actions of transmitters released from boutons in contact with the proximal dendritic shafts and cell body will be modulatory in character, setting the level of excitability of the neurone and so altering its response to inputs arriving more distally on the dendritic tree.

Many questions remain to be answered about the significance and the operation of the topographically specific inputs to the medium spiny neurone. For example, we have not considered the functional significance of the lateral interactions between medium spiny neurones that involve synaptic actions on the proximal part of the neurone: Groves[32] has suggested that one function of these interactions is to provide lateral inhibition. We have not considered the question of what

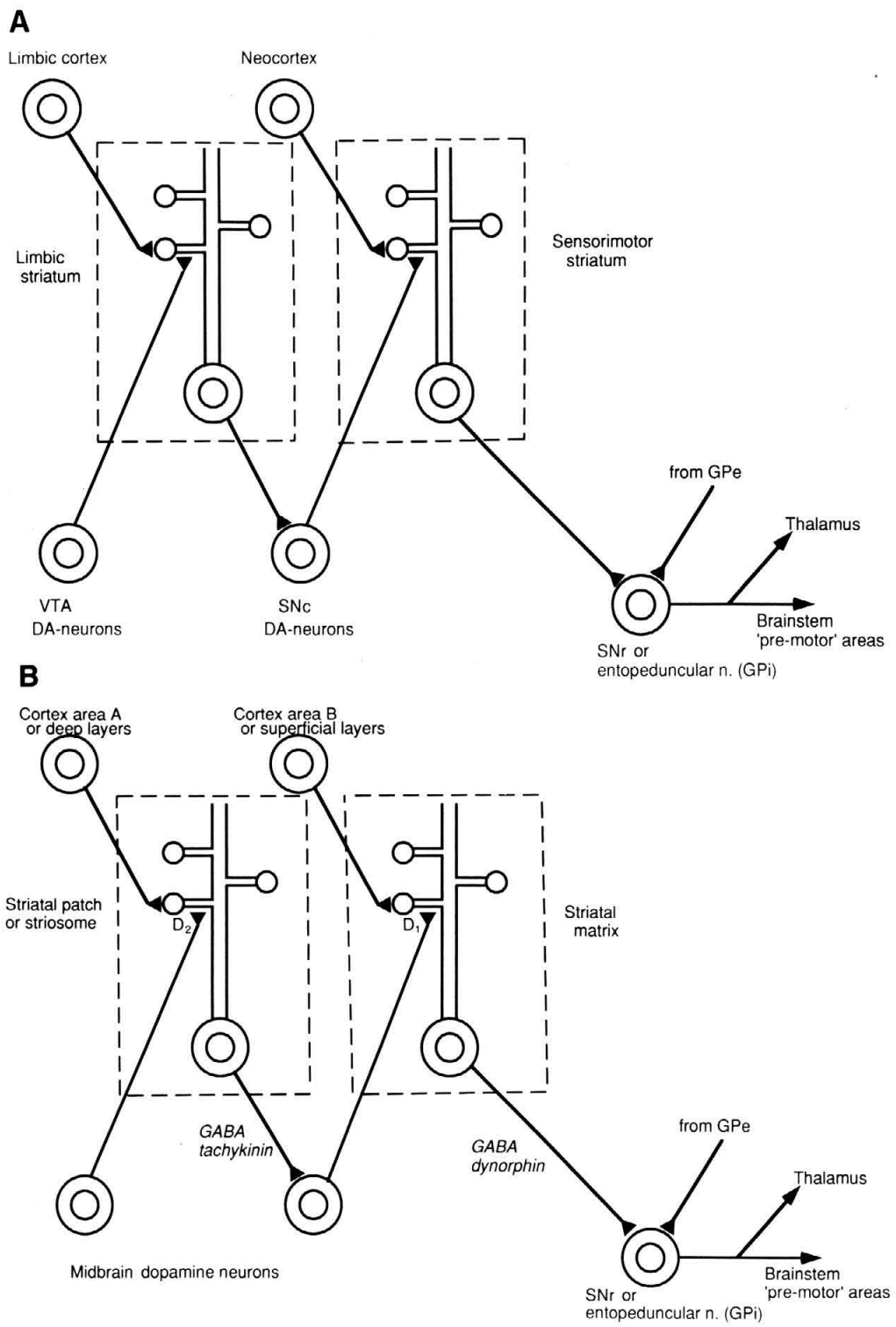

Fig. 6. *Circuits that link one part of the striatum with another through midbrain dopamine neurones. The right-hand sides of (A) and (B) are simplified versions of the circuit shown in Fig. 5, and the striato-pallidonigral loop is not shown in full.* **(A)** *The limbic striatum might be able to 'gate' the flow of information through the sensorimotor striatum because some of the output from the limbic striatum terminates on nigrostriatal neurones that innervate the sensorimotor striatum[35]. In this way, areas of the brain concerned with emotion and motivation could influence the motor functions of the striatum.* **(B)** *Illustrates a hypothesis in which the scheme shown in (A) is generalized to show how information flow through the patch (striosome) compartment of the striatum can influence the flow of information through the matrix compartment via a dopaminergic pathway originating in the substantia nigra. In this way, particular striosomal compartments might be able to 'gate' the flow of information through particular matrix compartments. Inputs to the respective patch and matrix compartments may either originate in distinct parts of the cortex or from different layers of the same cortical area. Abbreviations: D_1 and D_2, different classes of dopamine receptor; GPe and GPi, external and internal segments of globus pallidus, respectively; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area.*

controls the activity of the striatal interneurones that innervate the proximal region of the medium spiny neurone (see Ref. 20 for review). We will consider the important question of what controls the dopaminergic influence on the distal parts of the medium spiny neurone at the end of this article.

Output function of the striatal medium spiny neurone

As we have already indicated, there is now direct evidence that the medium spiny neurones carry the major output from the striatum to the substantia nigra and external segment of the globus pallidus. It is very likely that medium spiny neurones will be found to be the origin of the striatopallidal output to the internal segment of the globus pallidus as well. However, the chemical nature of some of the transmitters in these distinct output pathways appears to be different. Thus, the striatonigral pathway in the rat contains GABA, a tachykinin, and dynorphin, while the striatopallidal pathway contains GABA and enkephalin, and the striato-entopeduncular pathway contains GABA and a tachykinin[20].

If we are to define the output function of the striatum we must identify the nature of the neurones that are targets of the medium spiny neurone in the pallidum and substantia nigra. Ultrastructural studies have established that striatonigral neurones terminate on identified nigrothalamic[10], nigrotectal[33], nigrotegmental[34], and nigrostriatal[35] neurones, and on identified nigral dopaminergic neurones[36]. Striatopallidal neurones terminate on pallidonigral neurones[37], while one target of striato-entopeduncular neurones is the entopedunculo-thalamic neurone[38]. Finally, neurones in the striatal part of the olfactory tubercle have been shown to form synaptic contacts with neurones in the ventral pallidum that project to the thalamus[39] (see also A. Parent, this issue). It can be seen that four distinct types of remote neurone receive input from the medium spiny neurones of the striatum (Fig. 4): (1) those projecting to the thalamus, which presumably form part of the return loop to the cortex (see G. Alexander and M. D. Crutcher, this issue); those projecting to subcortical premotor areas (tectum, tegmentum); those projecting from the external segment of the pallidum to the substantia nigra; and the dopaminergic neurones that project back to the striatum. It will clearly be crucial to determine if different types of medium spiny neurone (defined chemically or morphologically) participate in these different pathways and to identify the postsynaptic responses in the different target neurones. For example, the direct striatonigral pathway using GABA as transmitter could mediate the inhibitory response of nigrotectal neurones to striatal stimulation (see article by G. Chevalier and J. M. Deniau, this issue), whereas the indirect striato-pallidonigral pathway could mediate disinhibition of nigrotectal neurones, since it has been shown that the pallidonigral pathway is GABAergic[40].

Towards the fundamental neural network

We have shown how the study of the synaptic connections of identified neurones allows us to postulate a basic network for the operation of the striatum (Fig. 5). Such a network could operate in each of the major subdivisions of the striatum, the limbic striatum and the sensorimotor striatum, and it could operate for each of the many segregated parallel pathways that pass through both parts of the striatum. For each pathway the operation of the network will be the same: its functions appear to be to allow information from different parts of the cortex to influence subcortical premotor areas and also to return to the cortex in a loop circuit. However, the operation of this network is likely to be crucially dependent upon the gating or modulation exerted by the dopaminergic input from the midbrain[41,42]. It is thus particularly significant that output from the striatum can itself influence the dopaminergic neurones of the substantia nigra. We would like to conclude by suggesting that control of the dopaminergic neurones by the striatum is exerted by anatomically, and perhaps chemically, distinct parts of the striatum (Fig. 6).

Nauta *et al.*[43] discovered that a prominent output from the nucleus accumbens terminates in the medial pars compacta of the substantia nigra. Subsequently, this pathway was confirmed at the ultrastructural level where it was shown that terminals from neurones in the nucleus accumbens form symmetric synaptic contacts on identified nigrostriatal neurones[35]. Since the nucleus accumbens is part of the limbic striatum and receives input from hippocampus, amygdala and prefrontal cortex, this monosynaptic pathway provides a way in which information passing through the networks in the limbic striatum could influence the dopaminergic modulation of information passing through the networks in the more dorsal, sensorimotor striatum (Fig. 6A). As pointed out by Nauta and Domesick[44], this pathway might provide an interface between areas of the brain concerned with 'motivation' and those concerned with motor behaviour.

The control of nigrostriatal neurones by the nucleus accumbens could be just one example of a more general type of control exerted by those striatonigral neurones that terminate on dopaminergic neurones (Fig. 6B). The striatonigral projection originating in striosomes (see article by A. M. Graybiel, this issue) preferentially innervates the pars compacta[45]: the medium spiny neurones in the striosomes, which contain a tachykinin as well as GABA[19], might preferentially terminate on nigrostriatal neurones while the dynorphin-containing striatonigral neurones in the matrix might preferentially terminate on output neurones in the pars reticulata.

It has been reported that inputs to the striosomes and the matrix arise either from different parts of the cortex or from different layers of the same cortical area (see A. M. Graybiel, this issue and also Ref. 46). The fundamental network of the basal ganglia might therefore be extended to include a striatonigrostriatal loop that would permit particular cortical areas or layers to influence the flow of information through the basal ganglia from other cortical areas or layers (Fig. 6B). Such an arrangement means that the operations of the basal ganglia might be even more intimately linked with those of the cortex than hitherto suspected. The proposed circuit also highlights the role of dopamine, which is involved at two stages in the circuit, and of the two major classes of dopamine receptor (D_1 and D_2; see article by G. Sedvall, this issue). It is suggested that dopamine operates in the first stage within striosomes via D_2 receptors and in

the second stage within the matrix via D_1 receptors. Such a complex role for dopamine in the functioning of the basal ganglia is consistent with many studies suggesting that motor behaviour requires the synergistic activation of both D_1 and D_2 receptors (see, for example, reviews in Refs 47,48) and might provide a basis for understanding why the type of movement most affected in Parkinson's disease is that with a motivational or cognitive element.

The circuit proposed in Fig. 6B, which provides a mechanism for lateral interaction between the patch (striosome) and matrix compartments of the striatum via a monosynaptic link in the substantia nigra, is put forward as a working hypothesis; further work will be required to establish whether or not such synaptic connections exist.

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