CHAPTER 3

Functional neuroanatomy of the basal ganglia

Chapter contents

Introduction

The basal ganglia comprise a collection of nuclear structures deep in the brain and have been defined anatomically and functionally. Anatomically, the basal ganglia are the deep nuclei in the telencephalon. Functionally, three closely associated structures, the subthalamic nucleus (STN) (in the diencephalon), the substantia nigra (SN), and pedunculopontine nucleus (PPN) (both in the mesencephalon), are also included as part of the motor part of the basal ganglia. The definition of which structures are included has varied over the years and depends also in part on a preconceived notion of their function. Most of the time, and for the purposes of the study of movement disorders, the basal ganglia are viewed as having primarily a motor function. Indeed, the early movement disorders included in the concept, such as Parkinson disease (PD) (see Table 3.1 for all abbreviations in this chapter) and Huntington disease (HD), were primarily basal ganglia related, and interested neuroscientists would meet at "basal ganglia clubs." It is now clear, however, that the basal ganglia also play a role in cognitive, behavioral, and emotional functions. For example, the limbic system interacts extensively with the basal ganglia, and some components of the basal ganglia, such as the amygdala (archistriatum), nucleus accumbens, and ventral pallidum, serve these functions (Haber and Knutson, 2010; Tremblay et al., 2015).

The core motor structures of the basal ganglia include the caudate and putamen, collectively called the neostriatum (commonly abbreviated as the striatum), the globus pallidus (GP) (paleostriatum), the STN, the SN, and the PPN (Figs. 3.1–3.3). The putamen and GP together are sometimes called the lenticular nucleus. The main informational processing loop of the basal ganglia, as described in Chapter 2, comes from the cortex and goes back to the cortex via the thalamus. The substantia nigra pars compacta (SNc) is largely a modulator of this main loop, with dopamine as its neurotransmitter. Other modulators are the locus coeruleus (LC), with norepinephrine (NE) as neurotransmitter, and the median raphe nucleus (MRN), which uses serotonin as neurotransmitter. The notion that the basal ganglia provide an "extrapyramidal" control of movement separate from the cortical-pyramidal control is not correct because the main output of the basal ganglia projects to the cortex. Therefore, the term *extrapyramidal disorders* for disorders arising from dysfunction of the basal ganglia is a misnomer.

In this chapter, we will first consider the neurotransmitters and their receptors that are involved in basal ganglia circuitry (Table 3.2). Next, we will consider the main components of the basal ganglia and the way that they interact with each other. At the end, we will review some features of the physiologic activity and consider what the main functions of the basal ganglia might be. As an introductory comment to the section on neurotransmitters, it is important to note that although we generally discuss neurons as if they had a single neurotransmitter, typically neurons may have more than one. For example, dopaminergic neurons may also contain glutamate (El Mestikawy et al., 2011) and striatal medium spiny neurons contain protein neurotransmitters in addition to gamma-aminobutyric acid (GABA).

Neurotransmitters

Dopamine

It is appropriate to start out the discussion of neurotransmitters with a consideration of dopamine, the most "prominent" neurotransmitter because it is depleted in PD and because we have the means to manipulate this transmitter in therapeutics. The main sources of dopamine are the lateral SNc (A9), the medial ventral tegmental area (VTA, A10), and the retrorubral area (A8) (see Fig. 3.2). The SNc innervates the striatum via the nigrostriatal pathway, and the VTA and retrorubal areas give rise to the mesolimbic innervation of the

Table 3.1 Abbreviations

AADC	Aromatic L-amino acid decarboxylase	L-dopa	Levodopa
ACh	Acetylcholine	LFP	Local field potential
AChE	Acetylcholinesterase	M1	Primary motor cortex
ADP	Adenosine diphosphate	MAO	Monoamine oxidase
2-AG	2-Arachidonoylglycerol	mAChR	Muscarinic acetylcholine receptor
AMPA	α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate	mGluR	Metabotropic glutamate receptor
ATP	Adenosine triphosphate	MEA	Midbrain extrapyramidal area
BuChE	Butyrylcholinesterase (pseudocholinesterase)	MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
cAMP	Cyclic adenosine monophosphate	MRN	Median raphe nucleus
ChAT	Choline acetyltransferase	MSN	Medium spiny neuron
CM	Centrum medianum nucleus of the thalamus	3-MT	3-Methoxytyramine (3-O-methydopamine)
CoA	Coenzyme A	nAChR	Nicotinic acetylcholine receptor
COMT	Catechol-O-methyltransferase	NE	Norepinephrine
DA	Dopamine	NMDA	N-methyl-D-aspartic acid
DAG	Diacylglycerol	PD	Parkinson disease
DAT	Dopamine transporter	Pf	Parafascicular nucleus of the thalamus
DBH	Dopamine beta-hydroxylase	PMv	Premotor cortex, ventral division
DBS	Deep brain stimulation	PPN	Pedunculopontine nucleus
DOPAC	3,4-Dihydroxyphenylacetic acid	PPNc	Pedunculopontine nucleus, pars compacta
EAAT	Excitatory amino acid transporter	PPNd	Pedunculopontine nucleus, pars dissipatus
GABA	Gamma-amino butyric acid	SERT	Serotonin transporter
GABA-T	GABA-transaminase	SMA	Supplementary motor area
GAD	Glutamic acid decarboxylase	SN	Substantia nigra
GAT	GABA transporter	SNc	Substantia nigra, pars compacta
Glu	Glutamate	SNr	Substantia nigra, pars reticulata
GP	Globus pallidus	STN	Subthalamic nucleus
GPe	Globus pallidus externa	TANs	Tonically active neurons
GPi	Globus pallidus interna	TH	Tyrosine hydroxylase
HD	Huntington disease	$TRVP_1$	Transient receptor potential vanilloid type1
5-HT	5-Hydroxytryptamine, serotonin	VA	Ventral anterior nucleus of thalamus
5-HTP	5-Hydroxytryptophan	VAChT	Vesicular ACh transporter
HVA	Homovanillic acid	VL	Ventral lateral nucleus of thalamus
IP3	Inositol triphosphate	VMAT2	Vesicular monoamine transporter 2
KA	Kainate	VTA	Ventral tegmental area
LC	Locus coeruleus	ZI	Zona incerta

ventral striatum (nucleus accumbens) and the mesocortical innervation of the dorsolateral and ventromedial prefrontal cortex regions (Fig. 3.4) (Van den Heuvel and Pasterkamp, 2008). Less appreciated is that the SNc also innervates the globus pallidus and subthalamic nucleus (Smith and Kieval, 2000), and that the thalamus also received dopamine input from a variety of sources (Sanchez-Gonzalez et al., 2005).

Dopamine is formed from levodopa (L-dopa) by the enzyme aromatic L-amino acid decarboxylase (AADC), which has been commonly called dopa decarboxylase (Fig. 3.5) (Stahl, 2013). Once synthesized, dopamine is taken up into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2). In vivo, levodopa is synthesized from L-tyrosine by the enzyme tyrosine hydroxylase (TH). L-tyrosine is an essential amino acid in the brain, because it cannot be synthesized from L-phenylalanine, as it can in the rest of the body. Dopamine can be metabolized by monoamine oxidase (MAO) to 3,4-dihydroxyphenylacetic

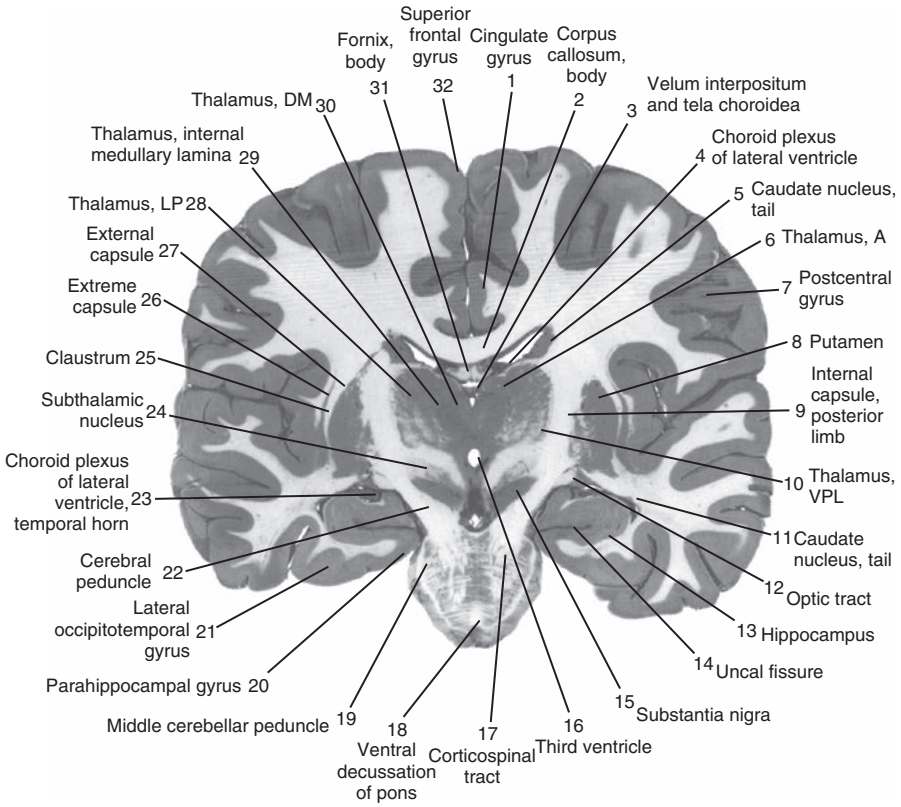

Fig. 3.1 Anatomy of the basal ganglia. A coronal section of the brain showing most of the basal ganglia nuclei. *A,* Anterior nucleus; *DM,* dorsomedial nucleus; *LP,* lateral posterior nucleus; *VPL,* ventral posterior lateral nucleus. (*From Woolsey TA, Hanaway J, Gado MH. The Brain Atlas: A Visual Guide to the Human Central Nervous System. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2008.*)

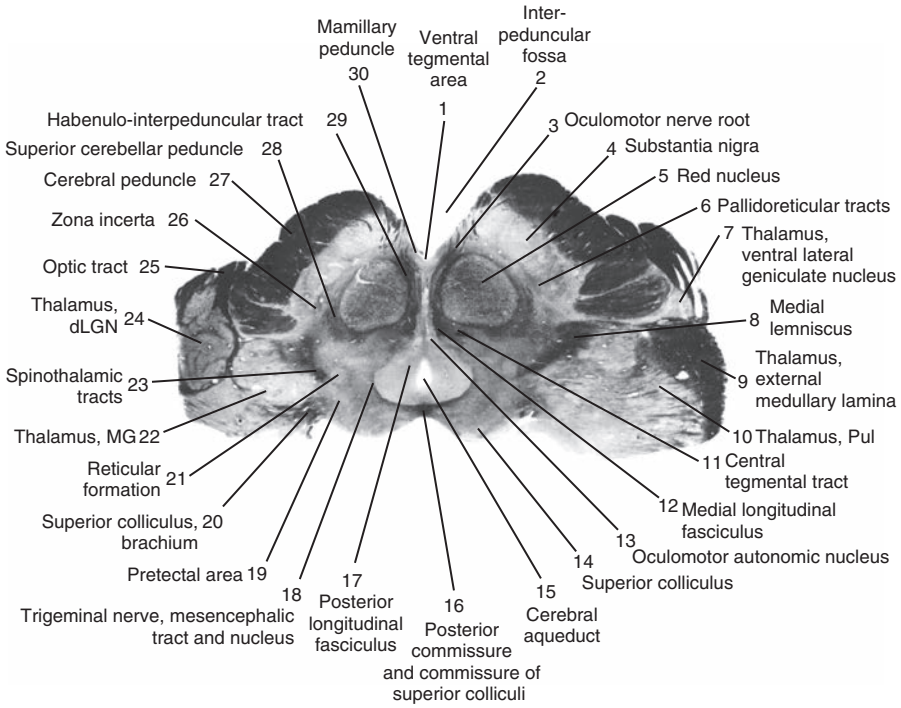

Fig. 3.2 An axial section at the midbrain level showing the principal nuclei for the origin of dopamine projections, the substantia nigra, and the ventral tegmental area. *dLGN,* Dorsal lateral geniculate nucleus; *MG,* medial geniculate nucleus; *Pul,* pulvinar. (*From Woolsey TA, Hanaway J, Gado MH. The Brain Atlas: A Visual Guide to the Human Central Nervous System. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2008.*)

acid (DOPAC), by catechol-O-methyltransferase (COMT) to 3-methoxytyramine (3-MT) (also called 3-O-methydopamine), and by both enzymes serially to homovanillic acid (HVA). MAO exists in two forms, MAO-A and MAO-B, both found in the mitochondria of neurons and glia (Bortolato et al., 2008). COMT is a membrane-bound enzyme (Bonifacio et al., 2007). Physiologically, dopamine action is terminated by reuptake into the dopaminergic nerve terminal by action of the dopamine transporter (DAT). Once in the cytosol, it can be taken back up into synaptic vesicles by VMAT2. Dopamine neurons have MAO-A (not MAO-B) (Demarest et al., 1980), but virtually no COMT. Dopamine not taken up into vesicles will therefore be metabolized to DOPAC. If dopamine remains nonmetabolized in the cytosol, it might contribute to oxidative stress, as discussed in Chapter 5.

DOPAC can diffuse out of the presynaptic terminal, where it might confront COMT on the postsynaptic neuron, endothelial cells, or possibly glial cells and be converted to HVA. MAO-B is prominent in the basal ganglia and is largely in glial cells. Any dopamine not taken up in the presynaptic terminal might diffuse into glial cells (DAT is not necessary in nondopaminergic cells), where it would be converted to HVA. HVA and DOPAC eventually will diffuse out of cells and either into the circulation or into the cerebrospinal fluid via the choroid plexus.

The exact biology of dopamine differs in different parts of the body and even different parts of the brain. For example, in the cerebral cortex there is not much DAT so that after dopamine release, COMT is much more important in terminating dopamine action (Matsumoto et al., 2003).

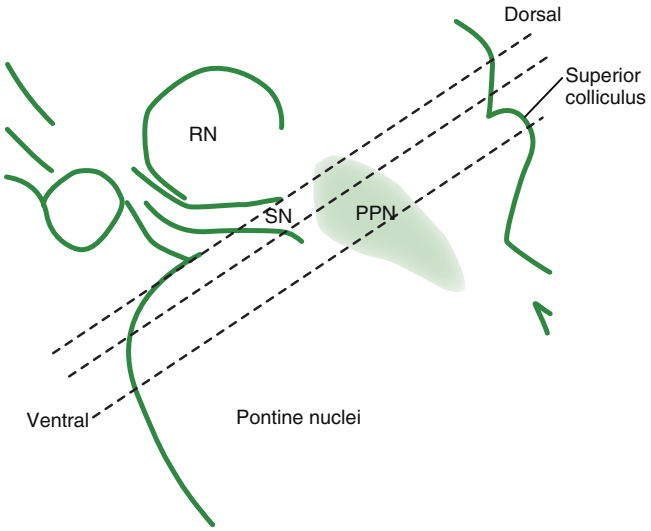

Fig. 3.3 Location of the pedunculopontine nucleus (PPN) with respect to the red nucleus (RN) and the substantia nigra (SN). (*From Jenkinson N, Nandi D, Muthusamy K, et al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord. 2009;24[3]:319–328.*)

There are five subtypes of dopamine receptors, D1 to D5, in two families, D1-like and D2-like (Missale et al., 1998; Beaulieu and Gainetdinov, 2011; Klein et al., 2019). The D1-like family, composed of D1 and D5, activates adenyl cyclase and causes conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Raising the concentration of cAMP is typically excitatory. The D2-like family, composed of D2, D3, and D4, inhibits adenyl cyclase and reduces the concentration of cAMP. Lowering cAMP is typically inhibitory. Some D2 receptors, called autoreceptors, are on the presynaptic side of dopamine synapses, regulating release by negative feedback. The dopamine receptors are G protein coupled and give rise to downstream effects in the postsynaptic cell in addition to modulating adenyl cyclase (Klein et al., 2019).

Acetylcholine

Cholinergic neurons have two different types of roles (Pisani et al., 2007; Eskow Jaunarajs et al., 2015). One is as an interneuron, and the "giant aspiny interneuron" of the striatum is cholinergic (Girasole and Nelson, 2015). A second role is as a projection neuron. There are two prominent cholinergic projection systems in the brain. The best known are the neurons of the basal forebrain, such as the nucleus basalis of Meynert, which innervate wide areas of cortex, are involved with

Table 3.2 Neurotransmitters relevant to basal ganglia function

Dopamine
Acetylcholine
Glutamate
Gamma-aminobutyric acid (GABA)
Norepinephrine
Serotonin
Adenosine
Endogenous opioids
Neuropeptides
Endocannabinoids

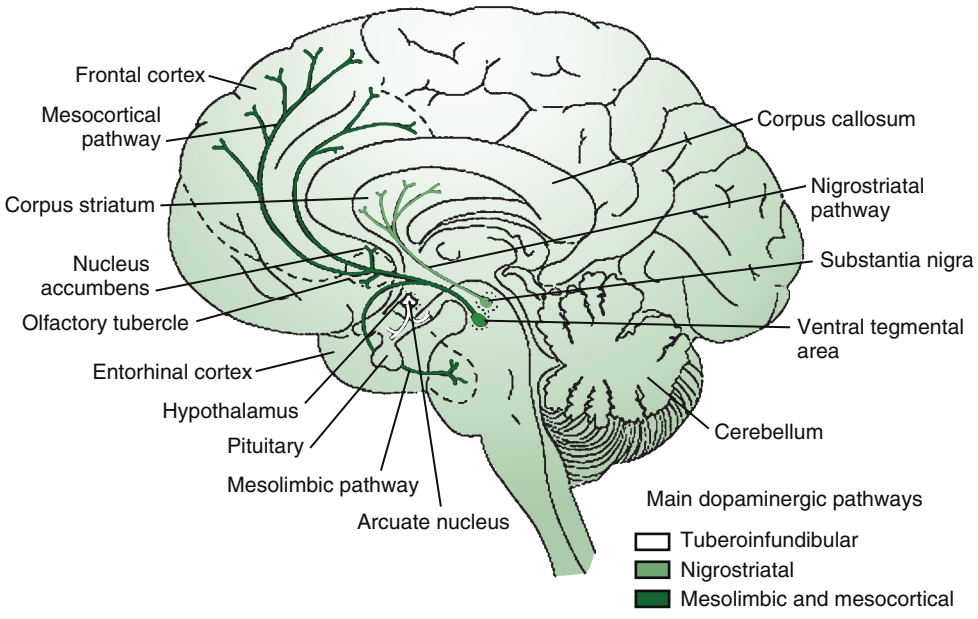

Fig. 3.4 The dopamine projection systems in the brain. The nigrostriatal pathway begins in the substantia nigra (light green), the mesolimbic and mesocortical pathways begin in the ventral tegmental area (dark green), and the tuberoinfundibular pathway begins in the arcuate nucleus (white). (*From* http://www.australianprescriber.com.)

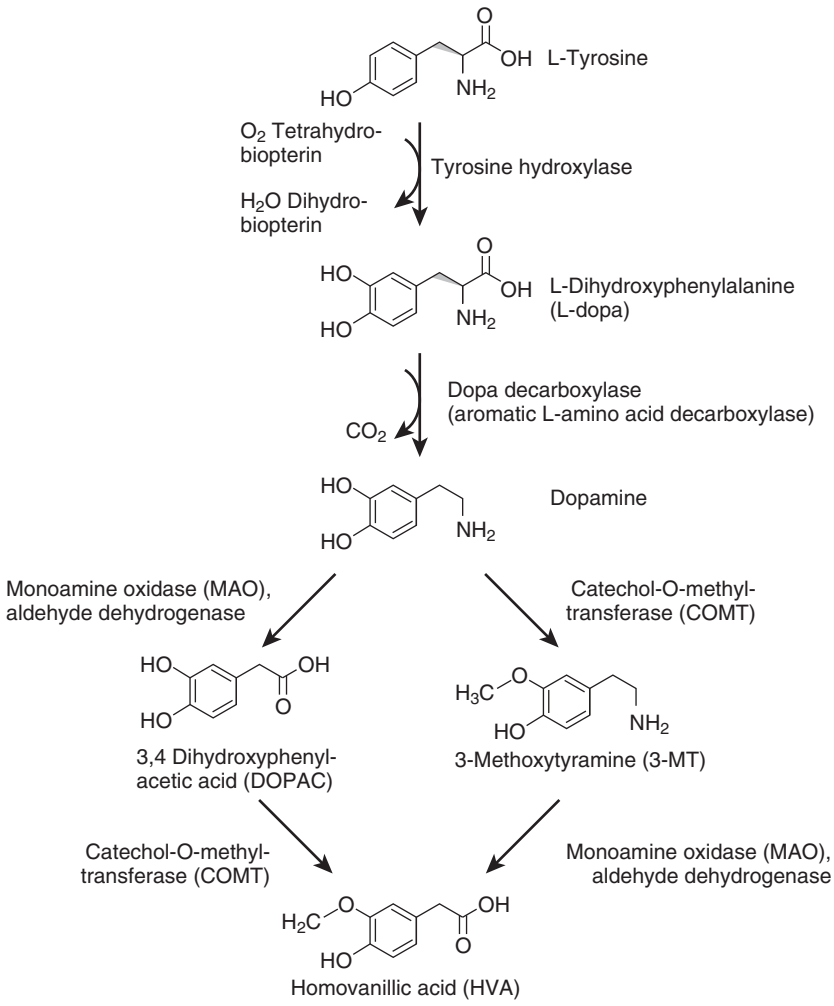

Fig. 3.5 Metabolism of dopamine. (*From* http://en.wikipedia.org/wiki/Dopamine.)

functions such as memory, and are deficient in Alzheimer disease. The other is the set of projections from the mesopontine tegmental complex, which includes the PPN. These are importantly involved in the basal ganglia motor system.

Acetylcholine (ACh) is synthesized in neurons from choline and acetyl-coenzyme A (acetyl-CoA) by the enzyme choline acetyltransferase (ChAT). After synthesis it is collected into vesicles by the enzyme vesicular ACh transporter (VAChT). Once released from the nerve terminals it is broken down by acetylcholinesterase (AChE), which is both presynaptic and postsynaptic, and butyrylcholinesterase (BuChE), also called pseudocholinesterase, that resides in glia (Cooper et al., 2003; Siegel et al., 2006). The resultant choline is taken back up into the presynaptic cell by a choline transporter (Stahl, 2013).

The two broad classes of ACh receptors are nicotinic and muscarinic. Nicotinic receptors (nAChR) are ionotropic and are prominent outside the brain at the neuromuscular junction and autonomic ganglia, but are also in the brain (Albuquerque et al., 2009). Activation at an nAChR will open a nonselective cation channel allowing flow of sodium, potassium, and sometimes calcium. Muscarinic receptors (mAChR) are metabotropic and also found both inside and outside the brain. Activation at an mAChR couples to a variety of types of G proteins (Eglen, 2005, 2006). There are many types of nAChR, and these are generally described by their subunit composition (Liu and Su, 2018). Designations of M_1 to M_5 are given to the mAChRs. Both nAChR and mAChR are found in the basal ganglia, and there are both excitatory and inhibitory effects.

Glutamate

Glutamate (Glu) is the primary excitatory neurotransmitter in the brain, and as such it has a prominent role in the excitatory cortical-striatal input and in the excitatory projection from the STN to the globus pallidus interna (GPi). Glu is a central molecule in many cellular processes and is also the precursor for the most important inhibitory neurotransmitter in the brain, GABA. Glu is made from glutamine in mitochondria by glutaminase. It is then taken up into synaptic vesicles by the vesicular glutamate transporter. On release, its action is terminated by its being taken up into glial cells via an excitatory amino acid transporter (EAAT) and then converted to glutamine by glutamine synthetase. Glutamine transporters then move the glutamine from the glial cell into the neuron (Siegel et al., 2006; Stahl, 2013).

Glu receptor biology is very complex, and the details are well beyond this chapter (Willard and Koochekpour, 2013; Reiner and Levitz, 2018). There are three groups of metabotropic glutamate receptors (mGluR), groups I, II, and III, depending on mGluR composition. There are also three classes of ionotropic receptors, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), N-methyl-D-aspartic acid (NMDA)

(Hansen et al., 2017), and the kainate (KA) receptors. Hence, glutamate not only transmits an excitatory signal by opening calcium channels, but also sets many metabolic processes in action, such as creating short- and long-term changes in synaptic excitability. Such changes are thought to be fundamental in brain plasticity (Lovinger, 2010; Reiner and Levitz, 2018).

Gamma-amino butyric acid

GABA is the main inhibitory neurotransmitter in the brain, and this includes the major inhibitory connections in the basal ganglia. It is synthesized by glutamic acid decarboxylase (GAD) from glutamate. Once synthesized, it is collected into synaptic vesicles by vesicular inhibitory amino acid transporters. After release, its action is terminated by its being taken back into the presynaptic cell by the GABA transporter (GAT). If the nerve ending has too much GABA in it, it can be broken down by GABA transaminase (GABA-T).

There are three classes of GABA receptors: A, B, and C (Stahl, 2013; Siucinska, 2019). GABA-A and GABA-C are ionotropic and have inhibitory action by opening chloride and potassium channels. Much is known about GABA-A, but only little about GABA-C. GABA-A channels have many subclasses depending on the subunit makeup. An important distinction between subclasses is whether they are sensitive to benzodiazepines, depending on whether the benzodiazepines bind to them. In the sensitive channels, benzodiazepines can increase the inhibitory action of a GABA-A synapse. GABA-B is a metabotropic receptor (Filip and Frankowska, 2008) and produces a longer duration inhibition than GABA-A by promoting potassium channels and inhibiting calcium channels.

Norepinephrine

NE influence on the basal ganglia comes from the strong projection to it from the LC (Sasaki et al., 2008). NE is made from dopamine (in noradrenergic neurons) by the action of dopamine beta-hydroxylase (DBH). After synthesis, it is stored in vesicles by action of VMAT2 (similar to dopamine). After release, it is taken back up presynaptically by the NE transporter. Like dopamine, it can be metabolized by MAO-A, MAO-B, or COMT, but similar to dopamine, the main enzyme in the presynaptic terminal is MAO-A.

There are a large number of NE receptors; the different classes are alpha 1A, 1B, 1D, alpha 2A, 2B, 2C, and beta 1, 2, and 3 (Stahl, 2013). All can be postsynaptic, and the alpha 2 receptors also can be presynaptic. Activation of the presynaptic receptors inhibits further NE release. The alpha 1 receptors are G protein coupled, and increase levels of phospholipase C, inositol trisphosphate (IP3), and calcium. The alpha 2 receptors are G protein coupled, with an action to inactivate adenylate cyclase and reduce concentrations of cAMP. The beta receptors couple to G proteins that activate adenylate cyclase and increase cAMP.

Serotonin (5-hydroxytryptamine)

Serotonin (5-HT) influence on the basal ganglia comes from the MRN (Sasaki et al., 2008). 5-HT is synthesized from the amino acid tryptophan. Tryptophan is converted to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase, and then 5-HTP is converted to 5-HT by aromatic amino acid decarboxylase (AADC). As with dopamine and NE, after synthesis, 5-HT is taken up into vesicles by the action of VMAT2. After release, it is metabolized by MAO-A or taken back up into the serotonergic neuron by the serotonin transporter (SERT). Serotonergic neurons contain both MAO-A and MAO-B.

There are many subtypes of 5-HT receptors (Sarkar et al., 2020), categorized into seven families, 5-HT_1 to 5-HT_7. 5-HT_3 is a ligand-gated sodium (Na^+) and potassium (K^+) channel that depolarizes membranes. The other family members are G protein coupled. 5-HT_1 and 5-HT_{5A} decrease cAMP; 5-HT_4, 5-HT_6, and 5-HT_7 increase cAMP; 5-HT_2 increases IP3 and diacylglycerol (DAG). 5-HT_{1A} and 5-$HT_{1B/D}$ receptors are presynaptic and act to reduce 5-HT release, a negative feedback influence. Postsynaptic receptors include 5-HT_{1A}, 5-$HT_{1B/D}$, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7. Serotonin actions are complex. Activation of the 5-HT_{1A} receptor is generally inhibitory but also increases dopamine release. Activation of the 5-HT_{2A} receptor is generally excitatory but also inhibits dopamine release (Stahl, 2013). Monoamine interactions in general are very complex; for example, NE can influence 5-HT release and 5-HT can influence NE release.

Adenosine

Adenosine is a purine nucleoside and is an endogenous molecule in the brain (Benarroch, 2008a). Part of ATP, adenosine diphosphate (ADP), and cAMP, adenosine is a critical molecule in cellular energy metabolism, but it also plays a role as a neurotransmitter. Adenosine is found both intracellularly and extracellularly, and the concentration in the synaptic area is regulated by adenosine transporters (Hasko et al., 2008). There are four subtypes of adenosine receptors, A1, A2A, A2B, and A3, all G protein coupled. Caffeine is an important antagonist at the adenosine receptors. The A1 receptor is generally inhibitory, and the A2 receptors are excitatory, increasing levels of cAMP. Adenosine A2A receptors are colocalized with striatal dopamine D2 receptors on GABAergic medium spiny neurons (MSNs) that project via the "indirect" striatopallidal pathway to the globus pallidus externa (GPe) (Fuxe et al., 2007; Mori, 2020). Adenosine at the A2A receptor reduces binding of dopamine to the D2 receptor, and an antagonist of adenosine, such as caffeine, therefore enhances dopamine binding (Simola et al., 2008; Stahl, 2013).

Endogenous opioids

There are a variety of subclasses of these neurotransmitters, including dynorphins, enkephalins, endorphins, endomorphins, and nociceptin. Although these neurotransmitters play an important role in pain, they also have a direct influence on other functions in the basal ganglia, importantly in the limbic part of the circuitry. They act on the G protein–coupled opioid receptors (Faouzi et al., 2020); delta, kappa, mu, and the nociceptin receptor; delta and kappa are the most prominent in the basal ganglia (Benarroch, 2012). Opioids facilitate dopamine release. GABA receptors on the presynaptic dopamine terminal act to inhibit dopamine release. Opioids act to inhibit GABA release, which will then in turn reduce the amount of inhibition on dopamine release.

Neuropeptides

The opioids are examples of neuropeptide neurotransmitters, but there are approximately 100 of them. Typically, they are coreleased with other neurotransmitters. A neuropeptide important in the basal ganglia that is not an opioid is substance P. The MSNs in the striatum that have D1 receptors have the cotransmitters substance P and dynorphin, and those with D2 receptors have encephalin.

Endocannabinoids

Although much of the interest in cannabinoids originated with exogenous substances, there is an endogenous system (Morera-Herreras et al., 2012). The principal receptor in the central nervous system and abundant in the basal ganglia is the CB1 receptor (Davis et al., 2018). Transient receptor potential vanilloid type1 ($TRVP_1$) receptors also respond to cannabinoids. Natural ligands for the receptor are anandamide and 2-arachidonoylglycerol (2-AG). The evidence is that the cannabinoids modulate dopaminergic effects (Garcia et al., 2016; Covey et al., 2017; Behl et al., 2020) and in many circumstances diminish dopamine release and slow behavior (Kluger et al., 2015). The data are limited, however, and more work is needed.

Components of the basal ganglia

Striatum

The striatum is composed of the caudate, putamen, and ventral striatum. As will be discussed later, when dealing with circuitry, the different parts of the striatum have different functions related to different patterns of connectivity with the rest of the brain. In general, the putamen is the motor part; the caudate is the associative or cognitive part; and the ventral striatum, which includes the nucleus accumbens, is the limbic part.

A large majority of cells in the striatum (80%–95%) are MSNs, primarily affected in HD (Reiner and Deng, 2018). These are GABAergic cells that project out of the striatum to the GP. They receive glutamatergic input from the cortex and the thalamus. The centrum medianum (CM) nucleus of the thalamus projects to the putamen and the parafascicular (Pf) nucleus to the caudate. These cells also receive important dopaminergic input from the SNc. Additional input from the LC is noradrenergic and from the MRN is serotonergic. The glutamatergic input comes to the dendritic spines on these cells, and the dopaminergic input comes to the neck of these spines (Fig. 3.6). It certainly appears that dopamine regulates the glutamatergic influence on these cells. There are two types of MSNs that are differentiated by the dopamine receptors on their surface. Those that have D1 receptors, in addition to GABA, also contain the polypeptide neurotransmitters substance P and dynorphin. These cells project to the GPi in what is called the direct pathway. Those that have D2 receptors, in addition to GABA, also contain the polypeptide neurotransmitter enkephalin. These cells project to the GPe, as the first step of the circuit to the GPi, known as the indirect pathway.

The striatum also contains interneurons, which are aspiny and do not project outside the striatum. There are at least

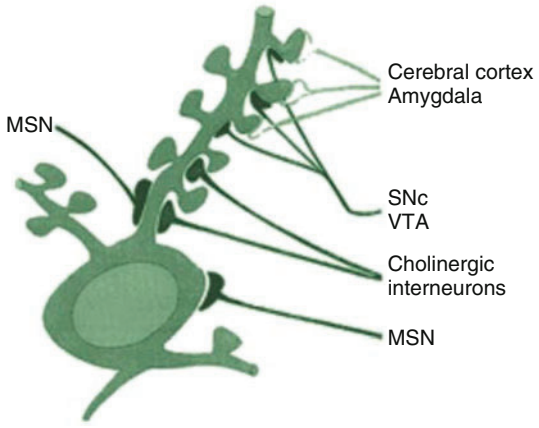

Fig. 3.6 Sites of synaptic input onto medium spiny neurons (MSNs) in the striatum. Note in particular that the cortical input is on the head of the spine and the dopaminergic input, from both substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), are on the neck of the spine. (*From Groenewegen HJ. The basal ganglia and motor control. Neural Plast. 2003;10[1–2]:107–120.*)

four classes of these cells. One of these neurons is the giant aspiny cholinergic cell that has axons with large terminal fields (Pisani et al., 2007; Eskow Jaunarajs et al., 2015). These cells receive their principal input from the cortex (glutamate) and the SNc (dopamine). The cortical input activates the cells and the nigral input inhibits them. The cells have autonomous spontaneous activity and are also known as the tonically active neurons (TANs). This spontaneous action means that there is a tonic release of ACh in the striatum. The extracellular level of ACh will be modulated by AChE and by negative feedback mediated by presynaptic mAChRs. These interneurons are also influenced by adenosine, GABA, NE, and 5-HT (Pisani et al., 2007). The cells play a role in reward processing and modulation of dopamine-dependent neuroplasticity (Deffains and Bergman, 2015).

There are three classes of GABAergic interneurons in the striatum. These are identified by their containing parvalbumin, calretin, or somatostatin/nitric oxide/neuropeptide Y. All these cells are obviously inhibitory in nature. More detailed studies have been identifying more interneuron types, making the situation rather complex (Silberberg and Bolam, 2015).

Staining of the striatum for AChE revealed an interesting organization of the cells, which had not been anticipated by simple histology. There are regions called striosomes or patches that are AChE-poor, embedded in a matrix that is AChE-rich (Prager and Plotkin, 2019) (Fig. 3.7). This organization presumably comes from segregated influences of the cholinergic interneurons or the cholinergic projection neurons from the PPN. The matrix appears to receive more sensorimotor and associative input, and the striosomes receive more limbic input (Eblen and Graybiel, 1995; Crittenden and Graybiel, 2011). Interneurons span the two compartments, perhaps allowing for limbic influence on other functions. The output of the two compartments also differs (Crittenden and Graybiel, 2011; Fujiyama et al., 2011). The matrix projects mainly to the GP, and the striosomes provide the only projection to the SNc and a smaller contribution to the GP (Crittenden and Graybiel, 2011). Neurons in the striosomes also provide the major input to the pallido-(lateral)habenular circuit (Hong et al., 2019).

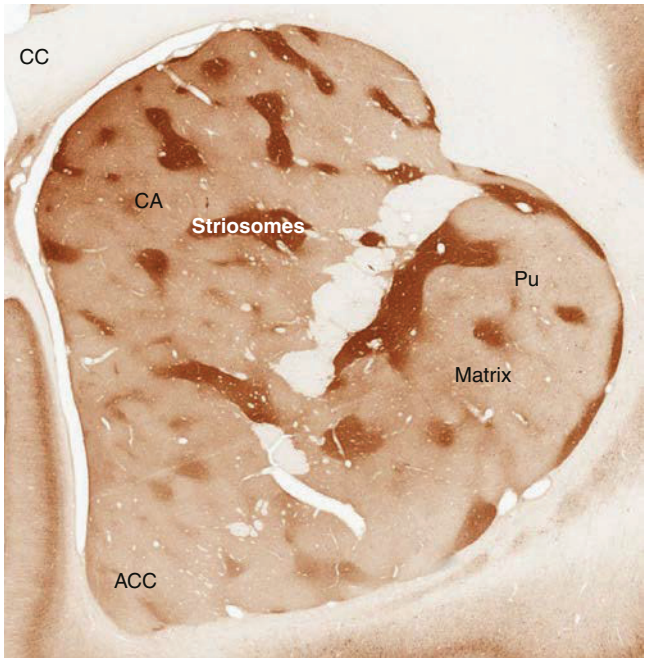

Fig. 3.7 Striosomes in the striatum of *Macaca fascicularis*. The striosomes are stained against potassium voltage-gated channel-interacting protein 1. *ACC*, Nucleus accumbens; *CA*, caudate; *CC*, corpus callosum; *Pu*, putamen. (*From* http://www.BrainMaps.org, *copyright UC Regents, Davis.*)

Globus pallidus

The GP is divided into the dorsal part and the ventral part (ventral striatum) and into the internal and external divisions, GPi and GPe, respectively, which are separated by the medial medullary lamina. There are only a few interneurons because most neurons are large, parvalbumin-positive, GABAergic neurons with large arbors of dendrites. The cells are shaped as flat disks that are parallel to each other (Yelnik et al., 1984). The GP gets input from all parts of the striatum, and the motor part is posterolateral (Nambu, 2011; Iwamuro et al., 2017). The pars reticulata of the SN (SNr) is similar in histology and connectivity to the GPi, from which it is separated by the internal capsule.

Subthalamic nucleus

The main neurons of the STN are glutamatergic with long dendrites (Yelnik and Percheron, 1979; Hamani et al., 2004). There are about 7.5% GABAergic interneurons (Levesque and Parent, 2005). The dorsolateral part of STN is motor (Nambu, 2011; Iwamuro et al., 2017), whereas the ventral part is associative and the medial part projects to limbic areas (Benarroch, 2008a).

Substantia nigra

The two parts of the SN are rather different from each other and will be described separately.

Substantia nigra pars compacta

The majority of the neurons of the SNc are dopaminergic and are the cells of origin of the nigrostriatal projection. It is clear that the SNc facilitates movement, and there is good evidence as well for a role of dopamine in facilitating specific reward behaviors. Indeed, it is possible to identify rapid signaling of dopaminergic neurons for specific movements (da Silva et al., 2018) and for indicating reward (Howe and Dombeck, 2016). These neurons also have tonic release of dopamine and phasic release. The cells contain neuromelanin, which makes them dark, giving rise to the name of the nucleus ("nigra"). Because the death of these cells gives rise to the motor symptoms in PD, their cell biology has been studied extensively. Neuromelanin is derived from conjugation of dopamine-quinone, an oxyradical, thereby protecting the dopaminergic neurons from oxidative stress (Sulzer et al., 2000). Neuromelanin can chelate iron and can bind a variety of toxins (Zecca et al., 2001). Some of the dendrites of the dopaminergic cells extend into the SNr, where they have GABAergic receptors. About 15% of cells are interneurons, at least some of which are GABAergic (Hebb and Robertson, 2000).

Substantia nigra pars reticulata

The SNr is similar to the GPi in its histology, connectivity, and even pattern of degeneration in neurologic disorders. Hence, it is often considered a part of the GPi that has been separated by anatomic accident. In addition to connectivity similar to that of the GPi, it has an important output to the superior colliculus, which plays an important role in the control of saccadic eye movements.

Pedunculopontine nucleus

The PPN has important reciprocal connections with other parts of the basal ganglia, and it is crucial to understand its role. It appears to be a critical component in the midbrain locomotor area, among other functional activities. The PPN region is rather complex and is composed of a number of subregions that are not always completely distinct from each other. Many of the details of the subregions, their exact localization in humans, their connectivities, and their neurotransmitters are still being worked out (Karachi et al., 2012; Fournier-Gosselin et al., 2013; Hamani et al., 2016; Snijders et al., 2016; Garcia-Rill et al., 2019). The PPN can be divided into the compacta (PPNc) and dissipatus (PPNd) (Pahapill and Lozano, 2000; Hamani et al., 2007; Zrinzo et al., 2008; Jenkinson et al., 2009; Benarroch, 2013). Other nuclei in the vicinity include the midbrain extrapyramidal area (MEA) (Steininger et al., 1992), the peripeduncular nucleus (Zrinzo and Hariz, 2007), the laterodorsal tegmental nucleus (Benarroch, 2013), and the cuneiform and subcuneiform nuclei (Piallat et al., 2009).

The PPNc is composed mainly of cholinergic cells. The PPNd may be mostly glutamatergic cells but has also cholinergic cells.

Lateral habenula

As we learn more about the basal ganglia, it becomes apparent that there are many structures with important influence on their function. There has been increasing interest in the lateral habenula (Hikosaka et al., 2008; Nair et al., 2013; Yang et al., 2018). The habenula is located above the

posterior thalamus near the midline. The cells have a mixture of neurotransmitters. The lateral part of the habenula has a strong inhibitory influence on the SNc (via the rostromedial tegmental nucleus) (Haber, 2014) and the MRN. There are also reciprocal connections with the VTA (Stamatakis et al., 2013). It appears to exert its inhibition when there is a negative result from action, thus inhibiting a possible favorable effect of dopamine in facilitating rewarded behavior (Bromberg-Martin et al., 2010) or directly promoting aversion (Lammel et al., 2012). It is also implicated in depression (Hu et al., 2020). The main inputs to the lateral habenula come from forebrain areas, the lateral hypothalamus and the perifornical area, and from the GPi (Haber, 2014).

Zona incerta

The zona incerta (ZI) is a distinct nucleus, which appears to be an extension of the reticular nucleus of the thalamus, sitting ventral to the thalamus and between the fields of Forel, the fiber tracts conveying the pallidal output to the thalamus (Plaha et al., 2008; Chou et al., 2018; Lau et al., 2020). It receives input from the GPi and SNr, the ascending reticular activating system, the cerebellum, and different regions of the cerebral cortex. Its output cells are GABAergic and go to the centrum medianum/parafascicular (CM/Pf) and the ventral anterior nucleus of thalamus (VA)/VL thalamic nuclei, MEA, medial reticular formation, and reciprocal connections to the cerebellum, GPi/SNr, and cerebral cortex. The ZI may act to help synchronize activity across the many regions that it contacts (Plaha et al., 2008) and function as an integrative node for behavior and physiological state (Wang et al., 2020).

Other nuclei

The LC is the source of noradrenergic input to the basal ganglia (Fig. 3.8). The MRN is the source of serotonergic input. The thalamus, although not part of the basal ganglia itself, is a main relay station for output from the GPi and SNr to the cortex. There are two important nuclear target regions, the VA/VL nuclei, which are the classic relay nuclei, and the CM/Pf nuclei, which are midline thalamic nuclei and serve as internal feedback to the basal ganglia. These thalamic neurons are all glutamatergic.

Circuitry of the basal ganglia

General circuitry

The connectivity of the basal ganglia is clearly crucial in carrying out its functions. The connections are complex, and it is necessary to have some general model for how they are organized. Such a model was proposed about two decades ago independently by three groups of investigators, each using a different technique: Crossman (1987); Albin Young, and Penney (1989); and DeLong (1990). This model has been extremely helpful in organizing thinking, planning pharmaceutical strategies for basal ganglia disorders, and even developing surgical approaches to patients. However, there were always difficulties with the model, and in more recent years it has become apparent that this model is not sufficient to explain what we now know. Hence, a new model is emerging that takes into account many more of the known connections and basal ganglia functions. It is worthwhile to present the older, "classic" model first, because it does form a foundation for the new model and much current thinking is still based on it.

The classic model is shown in Chapter 2, Fig. 2.2A, and is a part of the model shown in Fig. 3.9. In this model, described also in Chapter 2, there are two parallel loops from the cortex through the basal ganglia and back to the cortex and the direct and indirect pathway. The direct pathway starts with cortical glutamatergic input to the striatal cells bearing D1 receptors. These GABAergic neurons project directly to the GPi. The GABAergic neurons of the GPi project to the VA/VL nuclei of the thalamus, and the thalamic cells return glutamatergic input to the cortex. This four-neuron circuit has two inhibitory neurons and would be net excitatory. The indirect pathway starts with cortical glutamatergic input to the striatal cells bearing D2 receptors. These GABAergic cells project to the GPe, which has a GABAergic projection to the STN, which has a glutamatergic projection to the GPi. The final part of the path from GPi through thalamus to cortex is the same as the direct pathway. This is a six-neuron pathway with three inhibitory neurons, and therefore this would be net inhibitory. The SNc is a modulator of both direct and indirect pathways. By its influence on D1 and D2 receptors, it will facilitate those striatal neurons of the direct pathway

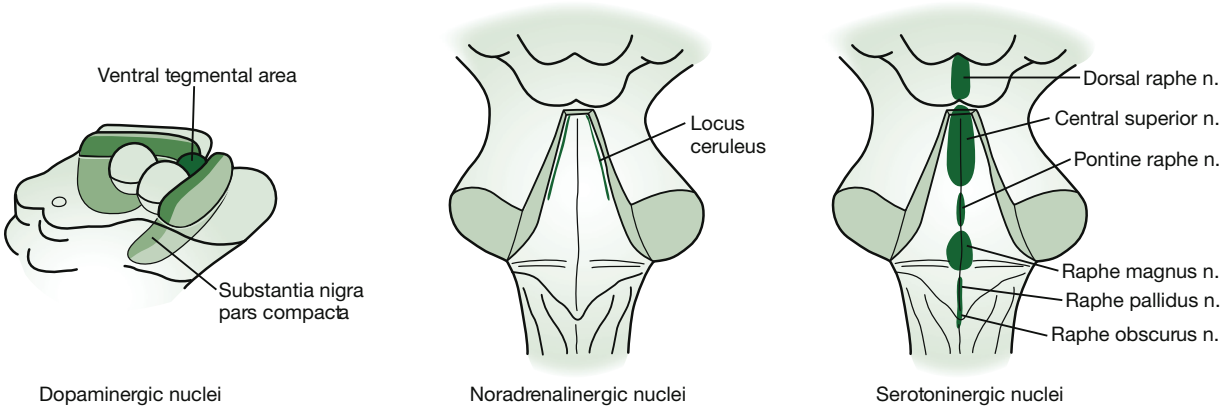

Fig. 3.8 Anatomy of the dopaminergic, noradrenergic, and serotonergic nuclei in the brainstem. Dopamine comes from the substantia nigra pars compacta and ventral tegmental areas, noradrenaline from the locus ceruleus, and serotonin from the median raphe nuclei. (*From Sasaki M, Shibata E, Tohyama K, Kudo K, Endoh J, Otsuka K, Sakai A. Monoamine neurons in the human brain stem: Anatomy, magnetic resonance imaging findings, and clinical implications. NeuroReport. 2008;19:1649–1654.*)

and inhibit those striatal neurons of the indirect pathway. Thus, the influence of the SNc is to facilitate the facilitatory pathway and inhibit the inhibitory pathway. Although it is not the role of this chapter to discuss pathophysiology, it is immediately apparent why dysfunction of the SNc should give rise to bradykinesia as seen in PD. Other movement disorders appear superficially to be similarly easily explained.

Many connections are left out of the classic model, and it appears that many of them are rather important. Fig. 3.9 (and Chapter 2, Fig. 2.4B) shows the connections of a more complete model. This model does not dispute any of the old connection; it adds new, apparently important connections. There is a strong connection from the cortex directly to the STN; this is called the hyperdirect pathway and appears to be a very important component (Pan et al., 2014; Coude et al., 2018; Miocinovic et al., 2018). Like the indirect pathway, its influence should be net inhibition. The cortex also has a strong projection directly to the thalamus (Crandall et al., 2015). A missing node in the older network is the CM/Pf nucleus of the thalamus. The GPi projects to it and to VA/VL, and the CM/Pf in turn projects back both to striatum and STN. CM projects mainly to the putamen and Pf to caudate and ventral pallidum. CM/Pf also has reciprocal connections to the cortex.

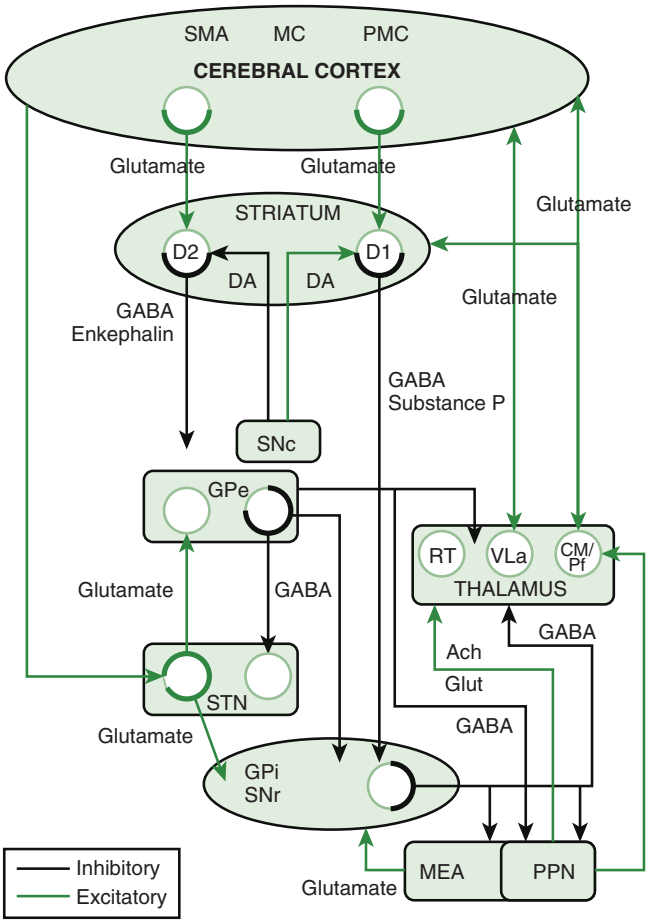

Fig. 3.9 Basal ganglia circuitry. Abbreviations are standard for this chapter except for *MC,* motor cortex; *PMC,* premotor cortex; *RT,* reticular nucleus of thalamus; *VLa,* anterior part of VL nucleus of thalamus. (*From Kopell BH, Rezai AR, Chang JW, Vitek JL. Anatomy and physiology of the basal ganglia: Implications for deep brain stimulation for Parkinson's disease. Mov Disord. 2006;21[Suppl. 14]:S238–S246.*)

Additionally, the SNc projects to STN and the STN projects back to the GPe as a reciprocal connection to what was in the classic model. The GPe itself plays a more critical role, now not only getting input from the striatum, but also from STN and SNc. The major new aspects are increased importance of STN and GPe as integrative nodes, and more widespread direct influence of SNc (Obeso et al., 2008; Gittis et al., 2014).

Increasingly more connections are being described. Some may be quite important, and new physiologic schemes will have to be developed to take all this new information into account. Bridging collaterals connect the direct and indirect pathways (Cazorla et al., 2015). The direct pathway neuron from striatum to GPi has a collateral to GPe, and the indirect pathway neuron from GPe to STN has a collateral back to the striatum. There might even be a direct cortico-pallidal pathway as suggested by human magnetic resonance imaging studies (Milardi et al., 2015) and physiologic studies (Ni et al., 2018); however, there is also physiologic evidence against such a pathway (Miocinovic et al., 2018).

Even these newer models, discussed in the last paragraphs, do not include the brainstem influences. These come from the LC (NE), the MRN (5-HT), the ZI, the lateral habenula, and the PPN. The lateral habenula and the PPN have several different neurotransmitters, but the PPN is the main source of cholinergic input to the basal ganglia. The PPN has reciprocal connections with virtually every part of the basal ganglia circuitry (Fig. 3.10). The most important inputs come from GPi and STN, and the most important outputs go to STN, GPi, SNc, thalamus, and brainstem. The latter output to the brainstem is now thought to be the major directly

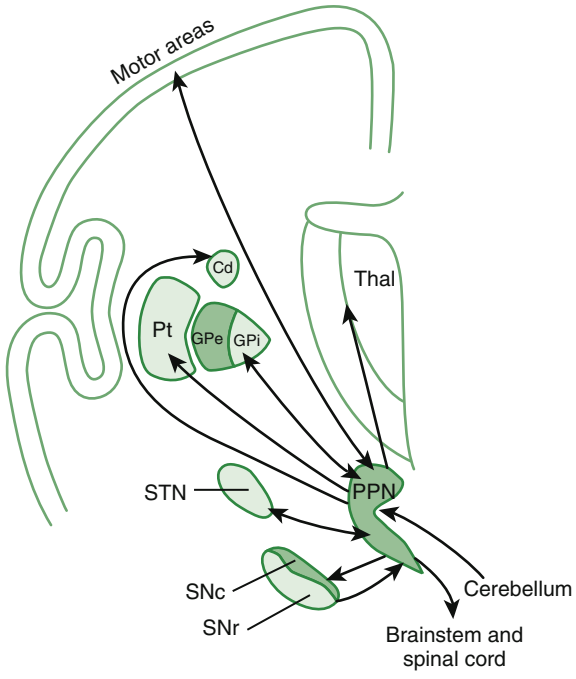

Fig. 3.10 Connections of the pedunculopontine nucleus (PPN). *Cd,* Caudate nucleus; *GPe,* external division of the globus pallidus; *GPi,* internal division of the globus pallidus; *Pt,* putamen; *SNc,* substantia nigra pars compacta; *SNr,* substantia nigra pars reticulata; *STN,* subthalamic nucleus; *Thal,* thalamus. (*From Jenkinson N, Nandi D, Muthusamy K, et al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord. 2009;24[3]:319–328.*)

descending motor influence from the basal ganglia. The PPN is also reciprocally connected directly to the cortex.

Parallel pathways

Another important principle of basal ganglia circuitry is its parallel organization (Alexander et al., 1986; Rodriguez-Oroz et al., 2009). Each part of the cortex has a separate pathway through the whole circuit (Fig. 3.11). In broad brush, the motor loop would run from motor cortex, to putamen, to lateral GPi, to VL, and back to cortex. An executive or cognitive loop would run from dorsolateral prefrontal cortex, to dorsolateral caudate, to medial GPi, to medial dorsal and VA nuclei of the thalamus, and back to cortex. A limbic loop, which plays an important part in reward (Haber and Knutson, 2010) and emotion, would run from anterior cingulate cortex, to ventral striatum, to ventral pallidum, to medial dorsal nucleus of thalamus, and back to cortex. These loops are generally separate, but there is some overlap allowing integration (Haynes and Haber, 2013; Averbeck et al., 2014; Jarbo and Verstynen, 2015). The loops are even more fine-grained, so that, for example, in the motor system, different parts of the motor system have different loops and somatotopy of different body parts is maintained throughout the loop (Middleton and Strick, 2000). For example, the primary motor area (M1), the supplementary motor area (SMA), and the ventral premotor area (PMv) will have separate loops. The cerebellum has similar isolated loops, and whereas it had been thought that the cerebellar and basal ganglia loops did not interact, it is now clear that there are important reciprocal connections (Bostan and Strick, 2010, 2018; Bostan et al., 2010, 2018).

Physiology

Cellular activity

Most information about normal cellular activity comes from recordings in animals. There are considerable data from primates. Human information comes largely from recordings when placing electrodes for deep brain stimulation (DBS) surgery and thus is pathologic rather than normal. By comparing human pathologic data with animal models, such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD, it has been generally concluded that primate information is likely quite similar to that of humans (Wichmann et al., 2018).

The MSNs in the striatum have a low firing rate, on average 0.5 to 2 Hz (van Albada and Robinson, 2009). Cells are often in a hyperpolarized, or down, state because of an intrinsic inwardly rectifying K^+ current (Hammond et al., 2007). Cells will fire largely only when there is a convergence of inputs onto the cell. Excitatory inputs come mainly from cortex and thalamus. The excitatory input will be modulated by the striatal interneurons and the nigrostriatal dopamine neurons that have input at the base of the dendritic spine and on the shaft of the dendrite itself (see Fig. 3.6). The cholinergic interneurons, the TANs, appear to be the most spontaneously active neurons in the striatum. They fire at 2 to 10 Hz and are modulated to some extent during learning (Aosaki et al., 1995).

Cellular activity in the GPi is the opposite of the striatum; cells are tonically active at 60 to 90 Hz (van Albada and Robinson, 2009). Activity in the GPe shows two types of behavior. Approximately 85% of cells have high-frequency bursts together with long intervals of silence for up to several seconds and an average firing rate of 55 Hz. The other 15% have a slower average rate of about 10 Hz, with occasional bursts (van Albada and Robinson, 2009). Cells in the STN also show spontaneous activity, at about 20 to 30 Hz, and spikes may be in pairs or triplets (van Albada and Robinson, 2009). Cells in the VA/VL of the thalamus fire at about 18 to 19 Hz (van Albada and Robinson, 2009).

Circuit physiology

Exactly what the basal ganglia ordinarily contribute to brain processing is not certain. However, the cellular processing should give some insight into this. Inputs from cortex (and thalamus) come to the striatum, and, as noted previously, only a strong, convergent input will activate neurons. Activity of MSNs of the direct pathway will then suppress the tonically rapid firing cells in the GPi, which will release a

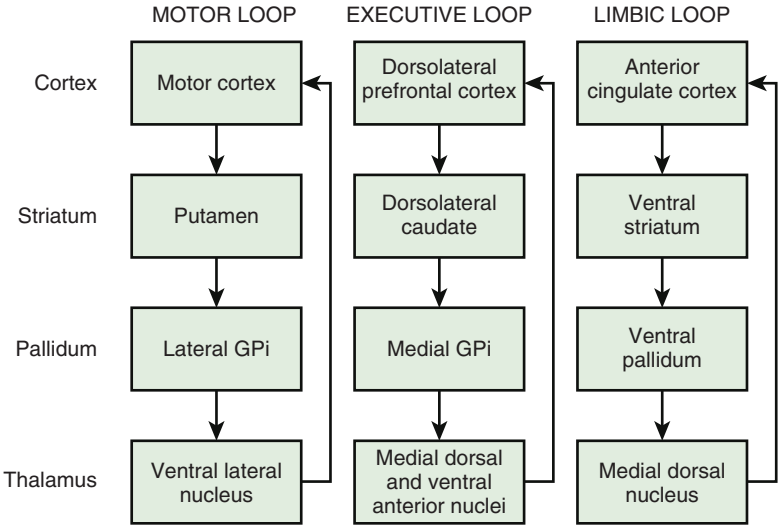

Fig. 3.11 Segregated loops through the basal ganglia. (*Redrawn from Purves D, Augustine GJ, Fitzpatrick D, et al. Neuroscience. 2nd ed. Sunderland, MA: Sinauer Associates; 2001.*)

region of the thalamus from tonic inhibition. This should be a net facilitation back to the cortex. At the same time that the GPi is inhibited by the direct pathway, there are a number of sources of excitation (or lessened inhibition). The GPe delivers less inhibition. Other inputs arrive via the STN, which gets less inhibition via the classic indirect pathway and excitation via the hyperdirect pathway. Thus, the output of the STN on the GPi is to excite it. The GPi therefore has to integrate its opposing inputs for a properly balanced output. This notion of how the direct and indirect pathways influence GPi cellular activity has been verified in mice using optogenetic techniques (in mice the SNr is used as the analog of the GPi in humans) (Freeze et al., 2013). As noted in Chapter 2, one possible function of the facilitation and inhibition is movement focusing and selection with a surround inhibition mechanism.

The basal ganglia clearly provide important signal processing, but there is strong evidence that they are also involved in motor learning (Obeso et al., 2017). The basal ganglia show significant plasticity of synaptic connections. Dopamine plays an important role in this plasticity, conveying reward signals that indicate the importance of what should be learned (Schultz, 2010; Steinberg et al., 2013; Kim and Hikosaka, 2015).

Another measure of cellular activity is called a local field potential (LFP). LFPs summate large numbers of neurons and synaptic activity, similar to the electroencephalograph (EEG). Like the EEG, LFPs can sometimes show rhythmic behavior in different frequency ranges (if cellular activity is analyzed, similar rhythmic activity can be appreciated [Du et al., 2018]). Cellular activity in the basal ganglia nuclei is not typically synchronized, and LFPs do not show prominent oscillations. In PD, there is synchronization and oscillations in both STN and GPi in the 10- to 30-Hz (beta) range (Brown, 2007; Galvan and Wichmann, 2008; Israel and Bergman, 2008; Alavi et al., 2013; Stein and Bar-Gad, 2013; Wichmann, 2018). The origin of this beta rhythm is not completely clear, but it appears to correlate with bradykinesia (Chen et al., 2010; Tass et al., 2010; Little et al., 2012). There is evidence that the beta oscillations may be more in the striatal neurons of the indirect pathway than the direct pathway, and that might be part of the explanation of why the oscillations are antikinetic (Sharott et al., 2017). The beta rhythm also may be coupled to even higher frequency oscillations (Lopez-Azcarate et al., 2010). There are also oscillations in alpha frequency range that correlate with tremor.

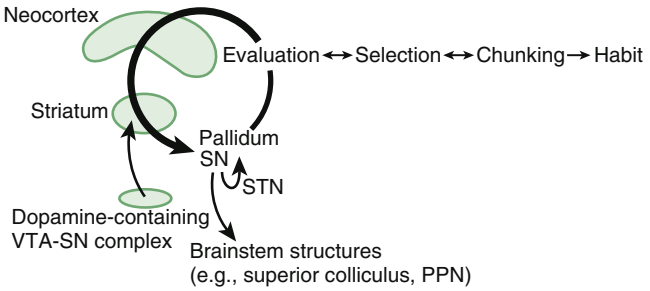

Fig. 3.12 Proposed basal ganglia function of making movements automatic and habitual by iterative cycling through the basal ganglia. PPN, Pedunculopontine nucleus; SN, substantia nigra; STN, subthalamic nucleus; VTA, ventral tegmental area. (*From Graybiel AM. Habits, rituals, and the evaluative brain. Annu Rev Neurosci. 2008;31:359–387.*)

There are a number of theories as to what the basal ganglia contribute to movement processing, and by analogy to processing of cognitive and limbic information. One such theory is movement selection, wherein the direct pathway selects a movement to be facilitated, and the indirect and hyperdirect pathways inhibit undesired movements. Other concepts include the automatic running of motor programs (Marsden, 1982) and learning and release of habits (Graybiel, 2008). The latter idea is that certain behaviors that get rewarded and get repeated, eventually become automatic (Fig. 3.12). It also appears that the basal ganglia help speed up brain processes, both motor and nonmotor (Hanakawa et al., 2017). As is abundantly clear in this book, considering all the hyperkinetic and hypokinetic disorders that derive from basal ganglia dysfunction, the basal ganglia must have something to do with the regulation of amount of motor output. It seems also to be the case that the function of the basal ganglia must be to some extent a parallel pathway of brain function, because a large stroke destroying most of the basal ganglia or an ablative lesion of the GPi, such as performed with pallidotomy in PD, results in a patient performing reasonably well on most tasks.

References available on Expert Consult: www.expertconsult.com