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Review Article

The role of neurotransmitters and neuropeptides in Parkinson's disease: implications for therapy

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Abstract

Parkinson's disease is a progressive neurodegenerative disease of the basal ganglia. Pathologically, it is characterized by continuous dopaminergic cell loss in the nigrostriatal system. The classic triad of signs comprises resting tremor, rigidity and bradykinesia. The decrease of dopamine content in the substantia nigra pars compacta in Parkinson's disease disrupts the delicate balance between neurotransmitters, *e.g.*, noradrenaline, serotonin (5-HT), acetylcholine, GABA and glutamate, and also neuropeptides, *e.g.*, enkephalins and substance P, in the brain, especially within the basal ganglia circuit. This causes a variety of neurotransmission changes that eventually influence the motor cortex, and as a result affect movement control and autonomic functions. In addition, levodopa and dopamine agonists might also alter mRNA transcripts of neurotransmitters and neuropeptides in the basal ganglia, thus contributing to the imbalance in neurotransmission. An understanding of the complex relationships among neurotransmitters, neuropeptides and their receptors may enable manipulation of the system with new drugs or microsurgical techniques. The aim of these novel therapies would be to reduce the problems associated with levodopa therapy, such as dyskinesias, and to improve the quality of life of Parkinson's patients.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease of the basal ganglia, which contain a remarkable diversity of neuroactive substances organized into functional subsystems. Pathologically, it is characterized by continuous dopaminergic cell loss in the nigrostriatal system, and also in other dopaminergic systems that are found outside the basal ganglia, and the main classic triad of signs consists of resting tremor, rigidity and bradykinesia (1, 2). Furthermore, due to changes in dopaminergic receptors, mainly D2 receptors, there are also alterations in other neurotransmitters and neuropeptides in the basal ganglia circuit, which determine the severity of parkinsonian signs (3). These include changes in the cholinergic muscarinic receptors in the striatum and muscarinic receptor supersensitivity in cortical areas (4), as well as increased activity of the inhibitory γ-aminobutyric acid (GABA) output nuclei in the basal ganglia, the internal segment of the globus pallidus and the substantia nigra pars reticulata (5). In addition, there are also changes in neuropeptides, which are small neuromodulatory substances, and their receptors within the basal ganglia (6). For example, there is supersensitivity of delta and loss of mu opioid receptors in the striatum and the limbic system, and a decrease in the Met-enkephalin, somatostatin and substance P content in PD patients (7). This review summarizes the multiple neuronal alterations in the parkinsonian brain, especially those in the nigrostriatal system, and addresses the importance of understanding the complex relationships between neurotransmitters and other neuromodulators in basal ganglia for designing better therapies and technologies for the treatment of PD.

Neurotransmitters and neuropeptides in the brain

Neurotransmitter receptors

The neurotransmitter receptors in the brain play an important role in motor and sensory functions and in other

complex systems, including memory and other cognitive processes. The neurotransmitter receptors can be divided into direct receptors and indirect receptors (8). The direct receptors are also referred to as ionotropic, as they are linked to ion channels. They are either excitatory (*e.g.*, Na^+ channels) or inhibitory (*e.g.*, Cl^- channels). Indirect receptors are referred to as metabotropic due to their effect on metabolic processes in the cell body beyond the synapse. Their response is longer than direct receptors, lasting from whole seconds to hours. These indirect receptors activate G-proteins on the inner membrane surface, which in turn increase activity of the enzymes adenylyl cyclase and phospholipase C (PLC). Adenylyl cyclase converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA). This enzyme phosphorylates cellular proteins, thereby changing their shape and activity (9). Phospholipase C hydrolyzes membrane phospholipid to form other secondary messengers. These cause the release or uptake of Ca^{2+} within the cell cytosol, which may regulate rhythmic responses within these neurons (10).

Families and subfamilies of neurotransmitters

Neurotransmitters are classified into two major groups: the amines and the peptides, and each group includes multiple classes of receptors with different functions.

Dopamine

Dopamine is a catecholamine neurotransmitter found in large concentrations in the nigrostriatal pathway. This neurotransmitter is also found in the mesocortical (from the ventral tegmental area [VTA] to the frontal cortex) and in the mesolimbic (from the VTA to the nucleus accumbens of the limbic system) pathways (11).

Dopamine is mostly an inhibitory neurotransmitter. For example, in the nigrostriatal pathway, dopamine causes inhibition of excessive muscle tone. A lack of dopamine in this pathway is seen in PD, resulting in a marked increase in muscle tone. Dopamine in the mesocortical and mesolimbic pathways causes arousal of the brain and of the whole individual. In the hypothalamus, dopamine inhibits the release of prolactin from the anterior pituitary gland, a system that is deactivated by breast-feeding. Dopamine is thus a prolactin-inhibitory factor (PIF) (12).

Dopamine is derived from the dietary amino acid tyrosine, which is first converted to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (tyrosine 3-monooxygenase), and then to dopamine by aromatic-L-amino-acid decarboxylase. Dopamine is released by presynaptic vesicles in the synaptic bulb into the synaptic cleft. There is some dopamine reuptake into the presynaptic bulb; however, catabolism takes place in both the synaptic cleft and the bulb. The enzyme catechol *O*-methyltransferase (COMT) partially inactivates the dopamine molecule, which can be repackaged in the vesicles or degraded further. Mitochondrial-bound monoamine oxidase (MAO) and other oxidases or reductases further degrade the molecule, completing deactivation. The end product is homovanillic acid (HVA, 4-hydroxy-3-methoxyphenyl acetate), which is excreted via the cerebrospinal fluid (CSF) (9).

Dopamine receptors are classified as members of one of two families based on the relatedness of protein and gene sequences and the coupling to similar signal-transducing systems. Dopamine receptors of the D1 family (D1 and D5 receptors) couple to the membrane-associated G-protein Gs, resulting in the stimulation of adenylyl cyclase activity and the formation of cAMP. Dopamine receptors of the D2 family (D2, D3 and D4 receptors) couple to the G-protein Gi, resulting in inhibition of adenylyl cyclase (and decreased cAMP formation) and/or direct modulation of ion channel activity. Dopamine can modify neuronal excitability, metabolism and/or gene expression, depending on the cellular context of receptor activation. In addition to postsynaptic expression of dopamine receptors, D2 (and perhaps D3) receptors are also expressed on dopaminergic cell bodies and nerve terminals, providing the dopaminergic cell with immediate feedback regarding the level of extracellular dopamine. The D1 and D2 receptors are by far the most prevalent receptors in the brain (9). Therefore, the balance of activity between D1 and D2 is thought to be very important in the regulation of neuronal activity, and this concept of balance may be found to extend to the remaining three receptors (D3 to D5) as well (13).

Noradrenaline

Noradrenaline (or norepinephrine) is a catecholamine neurotransmitter responsible for arousal and the level of activity within the whole human being, probably through inhibition of a postsynaptic inhibitory neuron (*i.e.*, inhibiting the inhibitor) or disinhibition. As such, it is most active during the day. High concentrations of noradrenaline occur in the locus coeruleus, a nucleus of the medulla which is involved in anxiety, learning and pleasure (*i.e.*, psychological arousal) (10).

Noradrenaline is produced from dopamine by dopamine β-hydroxylase (dopamine-β-monooxygenase), and it is degraded, similar to dopamine, via COMT, MAO and other reductase enzymes. The result is the end product 4-hydroxy-3-methoxyphenyl ethyl glycol (MHPG), which is excreted in the urine (9).

Adrenergic receptors occur as both synaptic autoreceptors and postsynaptic receptors. The known adrenergic receptors are designated α_1, α_2, β_1 and β_2. They are all metabotropic, having a long-term action by activating intracellular enzymes. The α_1-adrenoceptor activates PLC, which affects changes in cell metabolism, including enzyme activity, gene expression and protein synthesis. Most noradrenaline autoreceptors are of the α_2 type, which are associated with inhibition of adenylyl cyclase

via the inhibitory G-protein, reducing cAMP production. They also cause an increase in K^+ and a decrease in Ca^{2+} permeability into the cell. The β_1-adrenoceptor increases adenylyl cyclase activity, which increases cAMP production. Postsynaptic noradrenaline receptors are mostly β_2-adrenoceptors, which increase cAMP, but in some cases this may have a poorly understood inhibitory effect on action potentials, possibly disinhibition (9).

Serotonin

Serotonin (5-hydroxytryptamine, or 5-HT) is an indoleamine neurotransmitter that is important for mood, behavior, movement, pain appreciation, sexual activity, appetite, endocrine secretions, cardiac functions and the sleep-wake cycle. Most of the brain's serotonin is found in nine raphe nuclei strung out along the midline of the pons and medulla. From here, a wide pattern of fibers extends to many parts of the brain, including the cerebral cortex and the limbic areas. These fibers form part of the "diffuse modulatory systems". Serotonin is also produced within the pathway from the medulla to the hypothalamus, which conveys the stimulus for breast-feeding. Activation of this pathway blocks the hypothalamic dopamine inhibition of prolactin, which can then be released from the anterior pituitary gland and stimulate breast milk production. Some serotonin is converted to melatonin, the "sleep" hormone in the pineal gland, which has neural connections with the retina and therefore responds to light intensity (14).

Serotonin projections from the dorsal raphe nuclei innervate all components of the basal ganglia circuitry (15). It is thus likely that serotonin plays a role in regulating the appropriate selection of voluntary movements by basal ganglia.

Serotonin is produced from the dietary amino acid tryptophan, which is transported across the blood-brain barrier into the neuron by the large neutral amino acid transporter (LNAA), which also transports other amino acids, notably, tyrosine, valine, leucine and isoleucine. Tryptophan must compete with these for transport into the brain, and therefore levels in the brain are dependent on both its concentration and the concentration of the other amino acids in the blood. Inside the neuron, the enzyme tryptophan hydroxylase (tryptophan 5-monooxygenase) converts tryptophan to 5-hydroxytryptophan, which is the substrate for another enzyme called aromatic-L-amino-acid decarboxylase. This enzyme converts 5-hydroxytryptophan to serotonin, supported by vitamin B_6 (pyridoxine). Serotonin is degraded by MAO and aldehyde oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted via the CSF and the blood (9).

It is now possible to categorize at least 14 serotonin receptors into 7 distinct families (5-HT_1-5-HT_7), several of which are subdivided, *e.g.,* 5-$HT_{1A,B,C,D,E,F}$ and 5-$HT_{2A,B,C}$, on the basis of their molecular biology, signal transduction mechanisms and pharmacology (16).

Acetylcholine

Acetylcholine (ACh) is the only low-molecular-weight transmitter that is not derived directly from amino acids. Its main actions are related to arousal, learning and motor control.

Acetylcholine is synthesized within the nerve terminals from choline, most of which is taken up into the nerve terminal by a special choline transport system. Free choline within the nerve terminals is acetylated by a cytosolic enzyme, choline *O*-acetyltransferase, the source of the acetyl groups being acetyl-CoA. Acetylcholinesterase, the ACh-catalyzing enzyme, is present in the presynaptic nerve terminals and ACh is continuously hydrolyzed and resynthesized. Acetylcholine is very widely distributed in the brain, occurring in all parts of the forebrain, midbrain and brainstem, although rather little is present in the cerebellum. The striatum and nucleus accumbens are exceptionally rich in ACh, where it produces excitatory effects, as opposed to dopamine which has mainly inhibitory effects (17, 18).

The main subdivisions of ACh receptors include nicotinic receptors (nAChR), which are directly coupled to cation channels and mediate fast excitatory synaptic transmission in the CNS and periphery, and muscarinic receptors (mAChR), which are G-protein-coupled receptors that mediate ACh effects at postganglionic parasympathetic synapses and contribute to ganglionic excitation. The three main types of mAChR are: 1) M_1 receptors, which are found mainly on CNS and peripheral neurons and therefore referred to as "neural", producing slow excitation of ganglia; 2) M_2 receptors, which are found mainly in the heart, and also on presynaptic terminals of peripheral and central neurons, and are therefore referred to as "cardiac"; and 3) M_3 receptors, which are referred to as "glandular". The cloned M_4 receptor does not occur in the periphery, but is confined to certain regions of the CNS (19, 20).

Amino acids

Amino acids released as excitatory neurotransmitters in the CNS include glutamate, which is the major excitatory neurotransmitter, aspartate, and possibly homocysteine. The main source of glutamate and aspartate is from Krebs cycle intermediates, although glutamine also serves as a source.

In addition to its central role in excitatory neurotransmission and its involvement in learning and memory acquisition processes, glutamate can also be neurotoxic. Indeed, overactivation of its receptors, mainly the *N*-methyl-D-aspartate (NMDA) receptor, by high levels of glutamate*, i.e.*, excitotoxicity, causes a massive influx of extracellular Ca^{2+} into the cytoplasm, leading to activation of Ca^{2+}-dependent enzymes and necrotic cell death (21-23).

Glutamate exerts its neurotransmitter actions via ionotropic receptors, namely the NMDA, α-amino-3-hydroxy-

5-methyl-4-isoazolepropionic acid (AMPA) and kainate (KA) receptors. It also stimulates metabotropic receptors, which are linked to G-proteins, and produces changes in cyclic nucleotides or phosphoinositol metabolism (24, 25). The metabotropic receptor family comprises 8 subtypes ($mGluR_1$-$mGluR_8$), which are subdivided into 3 groups. Further molecular biology studies have demonstrated that NMDA, AMPA and KA receptors are composed of subunits encoded by different gene families, *e.g.*, the 2 subunits of the NMDA receptor NR1 and NR2, the 4 subunits of the AMPA receptor GluR1-GluR4, and the 5 subunits of the KA receptor GluR5, GluR6, GluR7, KA1 and KA2 (24, 25).

GABA

γ-Aminobutyric acid, or GABA, is the main inhibitory neurotransmitter, with the exception of glycine, in the mammalian CNS, especially in the nigrostriatal system. Most of the neurons in the striatum and globus pallidus are GABAergic, as are neurons of the substantia nigra pars reticulata. The GABAergic neurons of the striatum project to the GABAergic neurons of the globus pallidus and substantia nigra pars reticulata, which in turn project out of the basal ganglia to the thalamus and brainstem (or into the subthalamic loop). This arrangement, considered in conventional terms, means that the excitatory drive from the cortex disinhibits the thalamus and brainstem. As thalamocortical connections are thought to excite the cortex, the end result of the cortex-basal ganglia-thalamus-cortex circuit would be excitation of the cortex (26).

GABA is converted from glutamic acid by the action of glutamic acid decarboxylase. GABA is then broken down both within the cell and in the synaptic cleft by GABA transaminase (4-aminobutyrate transaminase) to form succinic semialdehyde. In turn, succinic semialdehyde is converted either to succinic acid by succinic semialdehyde dehydrogenase, or to γ-hydroxybutyric acid by succinic semialdehyde reductase (27).

GABAergic neurotransmission can be divided into fast and slow components. Fast inhibitory neurotransmission is mediated by the $GABA_A$ receptor and the $GABA_C$ receptor, both of which are ligand-gated Cl^- channels. Slow inhibitory neurotransmission is mediated by the G-protein-coupled $GABA_B$ receptor. $GABA_A$ and $GABA_B$ receptor-mediated mechanisms contribute significantly to long-term inhibition of synaptic transmission, and their inappropriate function may be implicated in several diseases of the CNS. GABAergic neurons, including $GABA_A$ and $GABA_B$ receptors, can also be found in the human basal ganglia (28).

Histamine

Histamine (2-[4-imidazolyl]ethylamine) is formed from histidine by the biosynthetic enzyme histidine decarboxylase, which is present mainly in neurons. Its main actions in humans involve stimulation of gastric secretion, smooth muscle contraction, cardiac stimulation, vasodilatation and increased vascular permeability, all produced by H_1-H_2 activation (see below).

Histamine has been proposed as a possible neurotransmitter for many years, with objective findings supporting this hypothesis (29). Its levels in the brain are much lower compared to other tissues and it is synthesized mainly by mast cells rather than neurons. Histamine-containing neurons originate mainly from a small region of the hypothalamus and their axons run in the medial forebrain bundle, which carries a variety of monoamine-containing projections to the cortex and midbrain. Histamine may be excitatory or inhibitory, depending on the type of receptor activated (29).

Histamine produces its actions by an effect on specific histamine receptors, which are of three main types: H_1 and H_2, which appear mainly in the periphery, and H_3, which appears mainly in neural tissue, predominantly at presynaptic sites. H_3 receptor activation results in inhibition of the release of a variety of transmitters (29).

Other neurotransmitters

The purine nucleotides adenosine and ATP produce a wide range of pharmacological effects that are not directly related to their role in energy metabolism, including bradycardia, hypotension, vasodilatation, inhibition of intestinal movements and neurotransmission

Adenosine is known to be a mediator in the CNS (30), and among other things, it is responsible for presynaptic inhibition and is thought to have a neuroprotective effect. It is released not only from neurons, but also from glia and other cells, by a membrane transport mechanism.

ATP is known to be a transmitter in the periphery, both as a primary mediator and as a co-transmitter in noradrenergic nerve terminals (31). ATP is contained in synaptic vesicles of both noradrenergic and cholinergic neurons, and may stimulate autonomic nerves by itself. In addition, ATP has been shown to serve as a conventional "fast" neurotransmitter in the CNS and in autonomic ganglia (31). ATP acts through activation of two types of purine P2 receptors: P2X, which is a ligand-gated ion channel responsible for fast synaptic responses, and P2Y, which is coupled to various secondary messengers (31).

Adenosine acts through specific receptors, classified as A_1 or A_2, the activation of which is associated with inhibition (A_1) or stimulation (A_2) of adenylyl cyclase. Four distinct adenosine receptor subtypes have been cloned so far: A_1, A_{2A}, A_{2B} and A_3 (32). Adenosine receptors are highly expressed in the basal ganglia, particularly in the striatum, where they appear to co-localize with dopamine receptors. In particular, A_1 receptors are co-expressed with D1 receptors on striatal neurons projecting to the substantia nigra pars reticulata and the medial globus pallidus, while A_{2A} receptors are co-expressed with D2 receptors on striatal neurons projecting to the internal

globus pallidus (33). Strict functional interactions characterize the co-localization of adenosine and dopamine receptors on the same striatal neuron, which are based on their opposite effects on adenylyl cyclase activity, and also on a direct intramembrane "receptor-receptor" cross-talk ensuing from the interactions between macromolecules involved in signal recognition and transduction. As a result, adenosine modulates the responses of striatal projection neurons to dopaminergic stimulation, by counteracting the effects of dopamine (33).

Families of neuropeptides

The last decade has witnessed the discovery of a variety of neuropeptides which may act as neurotransmitters or neuromodulators (*e.g.*, enkephalin, substance P, neuropeptide Y [NPY]) in the brain, especially in the basal ganglia, distinguished by their potential for prolonged actions. These substances are co-released with other neurotransmitters (*e.g.*, vasoactive intestinal peptide [VIP] with ACh; NPY, somatostatin, enkephalin and neurotensin with noradrenaline; somatostatin and NPY with GABA; and cholecystokinin and enkephalin with dopamine). They have been grouped into families based upon different criteria, such as their anatomical localization, biological function, *e.g.*, hormones such as angiotensin, sequence homology and derivation from a common precursor (34).

More than 30 regulatory peptides are now recognized and it is likely that more will be discovered. Neuropeptides are derived from the processing of secretory proteins that are formed in the cell body on polyribosomes that attach to the endoplasmatic reticulum. These peptides cause inhibition, excitation, or both, when applied iontophoretically to target neurons.

Neuropeptides may represent a different mode of intercellular communication from the fast and point-to-point action of amino acids such as GABA and glutamate: they have a slower time course, less precise spatial connections and a wider range of chemical messengers (34).

One of the major groups of neuropeptides are the opioids, which are coded for by three distinct genes: preproopiomelanocortin (POMC), preproenkephalin (or preproenkephalin A) and preprodynorphin (or preproenkephalin B). The α-, β- and γ-endorphins are other peptides with morphine-like actions. The expression of the precursor proteins varies in brain areas, *e.g.*, POMC and its derivatives are found mainly in the pituitary and hypothalamus, whereas enkephalins are found in the central and peripheral nervous system. Opioids function by activating three distinct types of receptors: mu, delta and kappa, and play a role mainly in pain and analgesia, but probably also in movement control (34).

Another major group of neuropeptides are the tachykinins, which comprise three related peptides: substance P, neurokinin A (NKA) and neurokinin B (NKB). Substance P and NKA are found especially in the substantia nigra and striatum, suggesting a function in the motor system. In addition, they also occur in nociceptive sensory neurons, enteric neurons and other regions of the brain. Tachykinins exert mainly excitatory effects on neurons, secretory cells and smooth muscles, and they also cause vasodilatation and increase vascular permeability. They work by activation of three distinct types of receptors —NK_1, NK_2 and NK_3—, which are selective for the three endogenous tachykinins (35).

Normal and pathological anatomy of the basal ganglia

In the classic model of basal ganglia function, the basal ganglia are viewed as part of a neural circuit that arises from the cortex, passes through the striatum, pallidum and the thalamus, and projects back to the frontal cortex (36). The striatum serves as the recipient of efferents from most cortical areas and projects by means of a direct and indirect pathway to both basal ganglia output nuclei, the internal segment of the globus pallidus and the substantia nigra pars reticulata. In the direct pathway, striatal GABAergic neurons project directly onto and inhibit the output nuclei. In the indirect pathway, activation of the striatal neurons that project to the external globus pallidus causes inhibition of the latter and subsequent disinhibition of the subthalamic nucleus. The activation of the subthalamic nucleus, which is glutamatergic, increases the activity of the output nuclei.

Neurons from the internal globus pallidus and substantia nigra pars reticulata project to the ventral motor nuclei of the thalamus, which in turn project back to the frontal cortex. Dopamine released from endings of neurons located in the substantia nigra pars compacta modulates the activity of striatal cells and therefore of the whole circuit (37).

A major assumption of the model is that different dopamine receptors (D1 or D2) are localized on the different striatal populations that give rise to either the direct or the indirect pathways (37). Under normal conditions, striatal neurons projecting directly to the internal globus pallidus appear to be facilitated by dopamine actions on D1 receptors, whereas neurons projecting to the external globus pallidus are inhibited by dopamine actions on D2 receptors. According to this model, the dopamine depletion in the striatum that occurs in PD leads to both a reduction of activity in the direct inhibitory pathway and an increase of activity in the indirect excitatory pathway, synergistically leading to an increase in internal globus pallidus activity. Because the internal globus pallidus-thalamic projection is inhibitory, an increased globus pallidus discharge leads to inhibition of thalamocortical neurons. The resulting reduction of cortical activation would then account for the hypokinetic signs of PD.

However, in recent years new experimental data and clinical observations have unraveled quite a number of inadequacies of the original model. For example, the classic model cannot explain the antidyskinetic effect of pallidotomy (38) or the minor negative effects of basal

Table I: Neurotransmitters, neuropeptides and their effects.

Family and subfamily	Neurotransmitters and neuropeptides	Major effects	Alterations in PD
Amines			
Quaternary amines	Acetylcholine (ACh)	Generally excitatory	Increase
Monoamines	*Catecholamines*	Generally excitatory	Decrease
	Noradrenaline		Decrease
	Adrenaline		
	Dopamine (DA)	Inhibitory/excitatory	Decrease
	Indoleamines	Inhibitory	
	Serotonin (5-HT)		Decrease
	Melatonin		Increase
Amino acids	Glutamate	Excitatory	Increase
	Glycine	Inhibitory	Increase
	γ-Aminobutyric acid (GABA)	Inhibitory	Increase
	Histamine	Inhibitory/excitatory	Increase
Purine neurotransmitters	Adenosine and ATP	Excitatory	Increase
Neuropeptides			
Opioid peptides	*Enkephalins*	Inhibitory	Increase/decrease
	Met-enkephalin		
	Leu-enkephalin		
	Endorphins	Inhibitory	Unchanged
	β-Endorphin		
	Dynorphins	Inhibitory	Unchanged
	Dynorphin A		
Other relevant peptides	Vasoactive intestinal peptide (VIP)	Modulatory	Unchanged
	Tachykinins (*e.g.*, substance P)	"	Decrease
	Somatostatin	"	Decrease
	Cholecystokinin (CCK)	"	Decrease/unchanged
	Neuropeptide Y (NPY)	"	Increase

ganglia lesions (*i.e.*, thalamotomy, pallidotomy and subthalamotomy) on motor function (39). Therefore, our understanding of the basal ganglia has departed from the strictly parallel anatomic organization and neuron firing rate transmission of information implicit in the classic model (5, 40), to incorporate newer physiological and anatomic features. Of particular note is the increasing recognition of the relevance of discharge patterns and oscillatory activity (41) in basal ganglia output nuclei, the description of profuse collateral branching throughout the basal ganglia in the so-called indirect circuit (42), and the existence of several internal circuits (*i.e.*, external globus pallidus/internal globus pallidus-subthalamic nucleus or thalamo-striatum/subthalamic nucleus-internal globus pallidus-thalamus) that play a critical homeostatic role in maintaining stable basal ganglia output activity (3).

Despite the problems with the classic model of the basal ganglia and PD, the basal ganglia are the primary locus of pathology in PD. Therefore, it is logical to assume that PD symptoms are due to neurotransmission abnormalities (*e.g.*, alterations in the levels of neurotransmitters and their receptors that might change discharge rate and pattern) within this circuit.

Neurotransmitters in Parkinson's disease

The drastic degeneration of the dopaminergic system in the substantia nigra and the striatum in PD patients is well documented and accompanied by alterations in other ascending subcortical neurotransmitter systems, although it is not clear which of these events is primary. These include the noradrenergic system (locus coeruleus), the serotonergic system (dorsal raphe nucleus), the cholinergic system (nucleus basalis of Meynert) (43) and other systems (Table I). The complex interactions of the various neurotransmitter systems affected lead to a variety of motor, *e.g.*, bradykinesia, and nonmotor, *e.g.*, cognition and mood problems, abnormalities that affect the quality of life of PD patients.

The symptom that is the most clearly related to dopamine deficiency is bradykinesia, which occurs immediately and invariably in lesioned animals. However, rigidity and tremor involve more complex neurochemical disturbances of other transmitters (particularly ACh, noradrenaline, serotonin and GABA), as well as dopamine (3).

Noradrenaline and adrenaline

The CSF levels of noradrenaline and adrenaline (or epinephrine) are significantly decreased in PD patients compared to controls (44, 45). The decrease was found to be correlated with the clinical severity, *i.e.*, dopamine content in the substantia nigra (44).

Serotonin

Biochemical evidence suggests that 5-HT transmission is abnormal in the basal ganglia of patients with PD (46), including changes in 5-HT_{1A} (47), 5-HT_{2C} (48) and 5-HT_{1B} (49) receptors. These data suggest that 5-HT and its receptors play a key role in the control of movement by the basal ganglia and are involved in the pathogenesis of PD and levodopa-induced dyskinesia.

In addition, it was found that the circadian secretion pattern of melatonin, a metabolite of 5-HT, is modified in patients with levodopa-related motor complications (50) and that the levels of melatonin are increased in PD (51), thus supporting the notion that serotonin levels are decreased in PD.

Acetylcholine

The loss of striatal dopaminergic terminals that occurs in PD removes the tonic dopaminergic inhibitory tone on ACh release. This imbalance leads to hyperactivity of cholinergic interneurons, the source of striatal ACh, and in turn, to an abnormal influence on medium spiny neurons projecting to the output structures of the basal ganglia.

The striatal cholinergic interneurons establish reciprocal synaptic connections with both medium spiny neurons and other GABAergic interneurons, which influence synaptic activity and plasticity of projection neurons (52). Endogenous ACh has been shown to increase the excitability of medium spiny projection neurons via M_1-like muscarinic receptors, which exert a facilitatory action both on the amplitude of corticostriatal excitatory postsynaptic potentials (EPSPs) and on the induction of striatal long-term potentiation (LTP) (53). This long-lasting increase in GABAergic transmission would occur both at D1 and D2 receptor-containing medium spiny projection neurons. Thus, in a parkinsonian state, this equilibrium is lost: following dopaminergic denervation, cholinergic facilitation would now occur preferentially in medium spiny neurons of the indirect pathway where the D2-dependent inhibition is lost, leading to an increased inhibitory drive to the external globus pallidus (see above) (54-56). This state might cause cognitive deficits and may progress to dementia, in association with other forms of cognitive impairment and psychotic symptoms (57).

Glutamate

Ionotropic glutamate receptors represent a target for pharmacological research in PD (58, 59) due to overactivity of glutamate, *i.e.*, excitotoxicity, in the basal ganglia. The physiological role of these receptors has been extensively documented in several brain areas, demonstrating their deep involvement in the modulation of ion channel activity and cell excitability and in the control of synaptic transmission, serving both as autoreceptors and heteroreceptors and thereby regulating transmitter release (60, 61).

GABA

Upregulation of the $GABA_A$ receptor in the internal globus pallidus correlates with the development of dyskinesias induced by the D1/D2 agonist MPTP in monkeys (62, 63) and in dyskinetic patients (64). In contrast, no significant increase in $GABA_B$ receptors was found in the internal globus pallidus of dyskinetic MPTP-treated monkeys (65) or in dyskinetic levodopa-treated PD patients (64).

Increased $GABA_A$ receptors in the internal globus pallidus suggests that neurons in the internal globus pallidus may be supersensitive to GABAergic input from the striatum and the external globus pallidus in dyskinetic subjects (65, 66). Increased response of internal globus pallidus neurons to the inhibitory effect of GABA may favor the underactivity of these neurons, which was shown to be related to the process of dyskinesias induced by dopaminomimetics (67-70). In this view, low activity of internal globus pallidus neurons may cause disinhibition of their target neurons in the thalamus, resulting in dysregulation of the thalamocortical circuit, which may contribute to the development of dyskinesias. However, this interpretation must be accepted with caution, since there is probably no simple relationship between average internal globus pallidus neuron activity and dyskinesias (38, 66, 69, 71).

Histamine

Histamine concentrations in *post mortem* brain samples of patients with PD were found to be significantly increased in the putamen, substantia nigra pars compacta, internal and external globus pallidus (72, 73). Histamine H_3 receptors were also found to be increased in the substantia nigra and striatum of PD patients (74), while H_2 receptors were unchanged (75). These results indicate that the concentration of histamine, but not its metabolism, is increased in PD.

Adenosine

Adenosine A_{2A} receptor mRNA levels were found to increase in the putamen (lateral and medial) of dyskinetic PD patients compared with controls and in the lateral putamen compared with nondyskinetic patients. Moreover, A_{2A} receptors were found to increase in the external globus pallidus of PD patients compared with controls, regardless of the dyskinetic response to levodopa (76).

Neuropeptides

Along with changes in neurotransmitters in PD, there are also alterations in the levels of neuropeptides in the brain, especially within the basal ganglia (Table I). The striatal and nigral expression of substance P and Met-enkephalin were found to be similar in *post mortem* studies of controls and PD patients (77, 78). In addition, substance P and Met-enkephalin levels were found to be reduced in the internal globus pallidus only, which was dependent on dopamine degeneration in the caudate nucleus (79). The density of neurotensin and opioid receptors was decreased in the globus pallidus and putamen of PD patients (78). These findings contrast with animal models of PD, where the expression of substance P is decreased and Met-enkephalin mRNA increased. A possible explanation for this difference may be that compensatory mechanisms develop during the long-term evolution of PD, and that chronic L-DOPA therapy may result in normalized expression of the two genes.

The mRNA levels of NPY (80) and somatostatin (81) were found to be elevated compared to control individuals in the basal ganglia, especially in the nucleus accumbens, the ventral part of the caudate nucleus and the globus pallidus. In other brain areas, *e.g.*, the cortex (82) and the CSF (83), the levels of NPY and somatostatin were found to be reduced. The increase in NPY mRNA in the basal ganglia may reflect the loss of dopaminergic tone on striatal NPY-containing interneurons, although a role for chronic L-DOPA therapy cannot be ruled out (80).

Cholecystokinin, one of the most abundant neuropeptides in the human CNS, modulates central motor effects of dopamine through nigral or striatal CCK_1 (CCK_A; excitatory) and CCK_2 (CCK_B; inhibitory) receptors (84). Cholecystokinin was found to decrease in the substantia nigra of patients with PD, and CCK_1 antagonist binding is reduced in hemiparkinsonian monkeys (85).

The measurement of neurotensin (NT) levels and NT receptors in the striatum and both segments of the globus pallidus in PD patients compared to controls revealed a slight reduction (78, 86) or no change (87), while there was a twofold increase in the substantia nigra of PD patients. Degeneration of the nigrostriatal pathway and/or prolonged antiparkinsonian treatment in PD appears to alter NT levels in an attempt to activate the dopaminergic nigrostriatal pathway (87).

Levodopa adverse events and levodopa-induced dyskinesia

Levodopa, which is the main treatment for PD, is associated with unwanted effects, including nausea and anorexia, hypotension and psychological effects, *e.g.*, confusion, disorientation, insomnia and nightmares. However, the most well-known side effect in PD is levodopa-induced dyskinesia, which appears in 50% of all patients treated with levodopa for 5 years or more (88-90). The exact pathophysiology of levodopa-induced dyskinesia is not fully understood, but is probably related to striatal dopamine receptor changes following dopaminergic denervation and chronic exposure to levodopa. These receptor alterations include changes of sensitivity, alterations of the relative balance between different dopamine receptor subtypes and different translational and neuromodulatory system responses (88, 90-92). It is assumed that other neurotransmitters are involved in this phenomenon, either as the result of striatal dopamine receptor changes or as the primary cause of levodopa-induced dyskinesia. Thus, it is rational to use, together with dopaminergic therapies, nondopaminergic therapies for the treatment or alleviation of levodopa-induced dyskinesia (3).

Conclusions and future directions

In light of the above, the decrease in dopamine content in the substantia nigra pars compacta in PD appears to disrupt the delicate balance between neurotransmitters and other neuromodulators, *e.g.*, neuropeptides, in the basal ganglia. However, it is not always clear whether there is an increase or decrease in a specific neurotransmitter/neuropeptide in the basal ganglia, and how this change correlates to PD severity. In addition, levels of neuromodulators, especially neuropeptides, in the brain and in the CSF may not be correlated. Clearly, there are nondopaminergic neurotransmission changes that also influence the motor cortex and affect movement and autonomic functions.

Several nondopaminergic drugs have been introduced for the alleviation of PD symptoms and nonmotor complications, including dementia, psychosis, depression, autonomic dysfunction, somnolence, insomnia and others (*e.g.*, falls). These include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and benzodiazepines for depression and psychosis, and also anticholinergic drugs, which mainly affect tremor and rigidity (93, 94) through muscarinic blockade. In addition, several antiglutamate agents are used in PD, including amantadine (95), dextromethorphan and riluzole (96-98). Other agents include gabapentin for periodic limb movement during sleep, adrenergic agonists and peripheral dopamine inhibitors, such as midodrine and domperidone, for orthostatic hypotension, and adrenergic antagonists, such as yohimbine, for falls (99).

However, due to unwanted side effects of these drugs, novel therapies based on recent experimental work have been proposed. These novel drugs include the ionotropic glutamate receptor antagonists (100), group II metabotropic glutamate receptor agonists (101-103), adenosine A_1 and A_{2A} receptor antagonists (104, 105), 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C} receptor antagonists (16) and neuropeptides such as VIP (106, 107).

A better understanding of the complex relationships among neurotransmitters, neuromodulators and their receptors, especially within the basal ganglia, and their modulation by dopaminergic drugs would enable a

synchronization of the system, using either novel drugs with better bioavailability and maximal selectivity, or novel microsurgical manipulations. The aim of these new therapies would be to provide relief of symptoms, improve the quality of life of PD patients and reduce the side effects associated with levodopa therapy (*e.g.*, levodopa-induced dyskinesia).

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