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Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of nigral dopaminergic neurons innervating the striatum, the main input structure of the basal ganglia. This creates an imbalance between dopaminergic inputs and cholinergic interneurons (ChIs) within the striatum. The efficacy of anticholinergic drugs, one of the earliest therapy for PD before the discovery of L-3,4-dihydroxyphenylalanine (L-DOPA) suggests an increased cholinergic tone in this disease. The dopamine (DA)-acetylcholine (ACh) balance hypothesis is now revisited with the use of novel cutting-edge techniques (optogenetics, pharmacogenetics, new electrophysiological recordings). This review will provide the background of the specific contribution of ChIs to striatal microcircuit organization in physiological and pathological conditions. The second goal of this review is to delve into the respective contributions of nicotinic and muscarinic receptor cholinergic subunits to the control of striatal afferent and efferent neuronal systems. Special attention will be given to the role played by muscarinic acetylcholine receptors (mAChRs) in the regulation of striatal network which may have important implications in the development of novel therapeutic strategies for motor and cognitive impairment in PD.

1. Introduction

The striatum is the most prominent nucleus of the basal ganglia circuitry controlling goal-directed action selection, habit learning and motivational processes (Pisani et al., 2007; Schultz, 2002). Striatal activity is mainly driven by excitatory glutamatergic cortical and thalamic afferents as well as modulatory dopaminergic (DA) afferents from the midbrain (Bolam et al., 2000; Gerfen and Surmeier, 2011; Kreitzer and Malenka, 2008; Tepper et al., 2007). Progressive degeneration of DA neurons in the substantia nigra *pars compacta* (SNc) is known to be the major neuropathological characteristic of Parkinson's disease (PD), although recent studies highlight the degeneration of serotonergic, noradrenergic, cholinergic and glutamatergic neuronal systems during the course of the disease (Brichta et al., 2013; Hung and Schwarzschild, 2014; Moghaddam et al., 2017). This produces major changes in the striatal microcircuits and in the projection neurons of the striatum, named medium spiny neurons (MSNs), representing 90–95% of the striatal neuronal population. The remaining 5–10% of striatal neurons are interneurons, which are crucial regulators of MSNs and afferents to the striatum. Among them, cholinergic interneurons (ChIs) closely interact with the midbrain DA afferents in a dynamic balance. Despite being few in numbers, ChIs modulate MSNs activity and control neuronal afferents by extensive ramifications and widespread projections throughout the striatum (Phelps et al., 1985). Disruption of ChIs activity often leads to the basal ganglia-related movement disorders such as PD, dystonia and Tourette syndrome (Deffains and Bergman, 2015; Gonzales and Smith, 2015; Pisani et al., 2007; Tanimura et al., 2018). PD is well-characterized by its motor symptomatology (akinesia, rigidity and tremor at rest), but may also be associated with mood disorders and cognitive impairment (Chaudhuri et al., 2006; Obeso et al., 2000). Striatal ChIs appear to be important contributors to affective, attentional, motivational, synaptic plasticity and cognitive functions mediated by the dorsal striatum (Aarsland, 2016; Bohnen and Albin, 2011; Calabresi et al., 2006; Chaudhuri et al., 2006; Deffains and Bergman, 2015; Owen et al., 1993). Considering that ChIs, in close interaction with the dopaminergic system, play a key regulatory role in motor function, in physiological and pathological conditions (Acquas and Di Chiara, 2002; Aosaki et al., 2010; Di Chiara et al., 1994; Gittis and Kreitzer, 2012; Lester et al., 2010; Rizzi and Tan, 2017), their involvement in non-motor symptoms of PD remains an important

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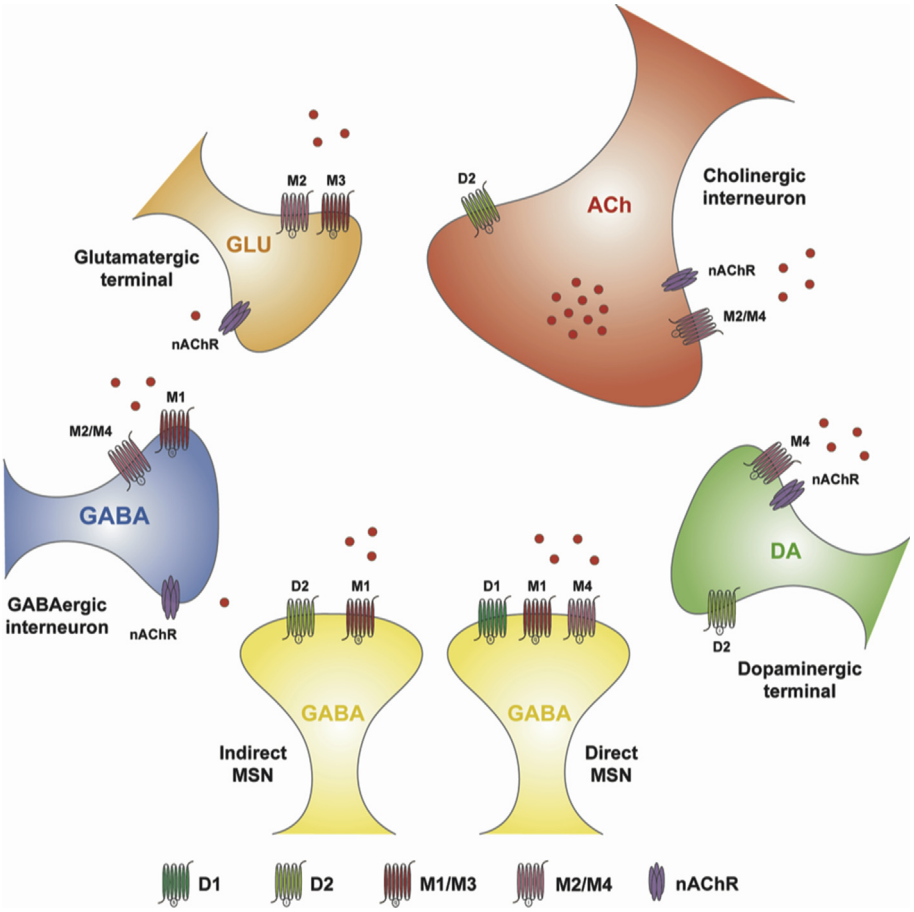

Fig. 1. Cholinergic modulation of the striatal microcircuitry. Simplified diagram of the interactions among the different types of striatal neurons – cholinergic interneuron (red), direct/indirect MSNs (yellow), GABAergic interneuron (blue) – and glutamatergic (orange) and dopaminergic (green) afferents to the striatum. The illustration reports the widespread distribution of muscarinic acetylcholine receptors (mAChRs: M1, M2, M3, M4), nicotinic acetylcholine receptors (nAChRs), and dopamine receptor subtypes (D1, D2). G protein-coupled receptors are displayed with their associated G-protein: Gs, Gi, or Gq. The diversity of mAChRs and nAChRs and their localization highlight the complexity of cholinergic modulation in the striatum. Abbreviations: ACh, acetylcholine; DA, dopamine; GABA, Gamma-aminobutyric acid, Glu, glutamate; MSN, medium spiny neuron.

question.

The prevailing view of DA-ACh interactions in the striatum supports the idea that the cholinergic and dopamine systems exert opposing actions to produce movement, and that unbalanced interactions are observed in pathological condition (Aosaki et al., 2010). This was supported by preclinical studies in PD models demonstrating that striatal dopamine depletion leads to increased ChIs excitability *in vitro* (Fino et al., 2007; Maurice et al., 2015), synaptic reorganization of striatal ChIs within the striatum (Salin et al., 2009; Tozzi et al., 2016) and increased release of striatal ACh (Bonsi et al., 2011; DeBoer et al., 1993; Pisani et al., 2007). The DA-ACh balance hypothesis was also supported by clinical evidence showing improvement of parkinsonian tremor and rigidity by both DA agonists and anticholinergic drugs (Barbeau, 1962). Within the striatum, these two neurotransmitters exhibit coincident changes in their activity during behavior (Apicella, 2007; Morris et al., 2004) and exert reciprocal control on their release (Cragg, 2006; DeBoer and Abercrombie, 1996; Pisani et al., 2000; Threlfell et al., 2012). However, this competition, and sometimes cooperation, between the two systems has been revisited in light of the major role played by thalamostriatal connections on striatal microcircuits and synaptic rearrangements in PD and the complexity of the receptors involved in these regulations (Parker et al., 2016; Surmeier and Graybiel, 2012; Threlfell et al., 2012). Although cholinergic tone increases as striatal DA level decline, the mechanisms underlying this alteration are still unclear. This review will focus on the specific interaction between striatal ChIs and DA systems and the mechanisms underlying the regulation of striatal and basal ganglia function in physiological and pathophysiological state, in light of the recent results obtained with novel technologies and selective cholinergic receptor subtypes drugs, with a specific emphasis on muscarinic acetylcholine receptors (mAChRs) subtypes. The complexity of the mechanisms by which ACh modulates striatal microcircuit in physiological condition and its implication for PD has been recently addressed in different reviews (Abudukeyoumu et al., 2018; Conti et al., 2018; Girasole and Nelson, 2018; Tanimura et al., 2018).

2. Cholinergic interneurons in the striatal microcircuitry

ChIs represent approximately 1–2% of striatal neurons (Bolam et al., 1984; Kemp and Powell, 1971; Phelps et al., 1985) and were first identified in 1896 by Kölliker on the basis of choline acetyltransferase immunolabeling (ChAT, the ACh synthesizing enzyme) and acetylcholinesterase (AChE, the ACh degrading enzyme). Despite a recent tract tracing and electron microscopy study reporting an external cholinergic projection from the brainstem into the striatum (Dautan et al., 2014), ChIs are still considered the main source of acetylcholine (ACh) within the striatum (Phelps et al., 1985; Satoh et al., 1983; Woolf and Butcher, 1981). Anatomically, they are easily characterized from other striatal cell types by their large spherical soma (20–50 μm of diameter) and widespread dendritic and axonal arborizations (Bolam et al., 1984). ChIs are heterogeneously distributed within the striatum with a preferential distribution at the border between striosomes and extra-striosomal matrix (van Vulpen and van der Kooy, 1998).

Referred to as giant aspiny interneurons, striatal ChIs send projections widely throughout the striatum, leading to high levels of cholinergic markers (ChAT and AChE) in the striatum. ChIs axons are characterized by small varicosities; it is estimated that each ChI possesses an average of 500,000 varicosities (Contant et al., 1996). In contrast to the dense striatal cholinergic innervation, few cholinergic synapses have been found (Aznavour et al., 2003; Contant et al., 1996), suggesting that ACh, in addition to synaptic transmission, acts also via non-synaptic transmission (volumetric transmission) released by these

varicosities (Descarries et al., 1997; Havekes et al., 2011).

Electrophysiological characteristics of ChIs are distinct from MSNs and GABAergic interneurons during *in vivo* recordings. In contrast to other striatal neuronal populations, ChIs fire spontaneously even in the absence of synaptic activity. This particular autonomous pacemaker activity led them to be referred to 'tonically active neurons' (TANs) (Aosaki et al., 1995; Tepper and Bolam, 2004; Wilson et al., 1990). *In vitro* electrophysiological recordings show that ChIs display tonic action potential firing (2–10 Hz) (Bennett and Wilson, 1999), depolarized resting membrane potential (−60 mV) (Lee et al., 1998), long-lasting action potential (Kawaguchi, 1993), high input resistance (200 MΩ), slow spike afterhyperpolarization current (Goldberg and Wilson, 2005), and prominent hyperpolarization-activated cation current (I_h) (Deng et al., 2007).

ChIs have a wide range of effects in the striatum mediated by two types of receptors, metabotropic muscarinic ACh receptors (mAChRs) and ionotropic nicotinic ACh receptors (nAChRs). These two types of receptors are expressed by ChIs, MSNs, as well as corticostriatal and thalamostriatal glutamatergic terminals, and nigrostriatal dopaminergic terminals. As illustrated in Fig. 1, the diversity of mAChRs and nAChRs and their localization highlights the complexity of striatal connectivity (Bonsi et al., 2011; Conti et al., 2018; Kreitzer, 2009; Lim et al., 2014; Pisani et al., 2007).

Five distinct G-protein-coupled mAChRs (M1-M5) are divided into two main classes according to their pharmacological properties and transduction mechanisms (Wess et al., 2007): M1-like (M1, M3, and M5) and M2-like (M2 and M4). M1-like receptors are coupled to Gq/11 proteins, intracellular Ca^{2+} mobilization, phospholipase C and protein kinase C activation, whereas M2-like receptors are coupled to Gi/o proteins, reduce cAMP formation and inhibit Ca^{2+} channels (Kreitzer, 2009). Interestingly, the activation of mAChRs has been shown to result in both excitation and inhibition of cholinergic, dopaminergic, GABAergic and glutamatergic activities in the striatum, suggesting a complex modulatory role of mAChRs involving numerous subtypes at multiple pre- or postsynaptic levels (Conti et al., 2018; Pisani et al., 2007). Several receptor localization studies in rodents report a predominant expression of M4 mAChRs within the striatum (45% of total striatal mAChRs) whereas M1 and M2 mAChRs are expressed at 30% and 20% of total striatal mAChRs, respectively (Chapman et al., 2011; Volpicelli and Levey, 2004; Waelbroeck et al., 1990; Yasuda et al., 1993). M3 mAChRs are clearly less abundant and M5 mAChRs are expressed at a very low level (Chapman et al., 2011; Hersch and Levey, 1995; Weiner et al., 1990; Yasuda et al., 1993).

nAChRs constitute the second type of cholinergic receptors. They are ligand-gated ion channels composed of five subunits that are assembled into homomeric or heteromeric subunits combinations, which determine pharmacological characteristics and biophysical properties of the receptors (Dani, 2001). Different subtypes of nAChRs composed of α4, α6, α7, β2, and β3 subunits are the most expressed in the striatum, with a predominant expression of α4β2 and α6β2 subunits combination, with other subunits present at lower levels (Quik et al., 2007; Quik and Wonnacott, 2011; Zhou et al., 2002). nAChRs are expressed on glutamatergic and dopaminergic neuron terminals, fast-spiking GABAergic interneurons (English et al., 2011; Nelson et al., 2014) and ChIs, but are absent from MSNs (Quik et al., 2007). They can be expressed both pre- and post-synaptically, where they induce depolarization and increase excitability and thus glutamate, DA and GABA release (Brichta et al., 2013; Koós and Tepper, 2002; Rice et al., 2011; Zhou et al., 2001).

Despite that both types of acetylcholine receptors transduce ACh signals, mAChRs are highly expressed by axon terminals of all major afferents to the striatum (glutamatergic and dopaminergic terminals) and by all striatal neurons examined so far, primarily in ChIs and in MSNs (Goldberg et al., 2012; Kreitzer, 2009; Zhou et al., 2003) as illustrated in Fig. 1. Activation of mAChRs results in a slower, but potentially more sustained response (Lester et al., 2010). The part played by mAChRs in the regulation of striatal network is the main focus of this review. Excellent reviews about the involvement of nAChRs in the regulation of striatal circuit complement the topics broached here (Abudukeyoumu et al., 2018; Conti et al., 2018; Cragg, 2006; Gonzales and Smith, 2015; Threlfell and Cragg, 2011; Zhou et al., 2003, 2002).

2.1. Muscarinic modulation of cholinergic interneurons

M2 and M4 mAChRs, coupled to Gi/o proteins, are expressed presynaptically in ChIs where they act as autoreceptors which exert a negative feedback control on ACh release (Calabresi et al., 2000, 1998a; J. J. Ding et al., 2006; Oldenburg and Ding, 2011; Pisani et al., 2007; Yan and Surmeier, 1996). A relatively selective antagonist of M2 mAChRs, AF-DX 116, induces a net increase of ACh release in the striatum by blocking negative feedback control (Galarraga et al., 1999). Using M2 or M4 mAChRs-knockout mice or even double M2/M4-knockout mice, a study showed that deletion of M2 mAChRs does not affect ACh release whereas deletion of M4 mAChRs completely suppresses the inhibitory control on ACh release in the striatum (Zhang et al., 2002). These data indicate that M4 mAChRs expressed in ChIs rather than M2 mAChRs play a critical role in the negative feedback control of ACh release within the striatum.

2.2. Muscarinic modulation of MSNs

M1 mAChRs are expressed in both direct and indirect MSNs, while M4 mAChRs are mainly expressed in direct MSNs (Bonsi et al., 2011; Ince et al., 1997; Pisani et al., 2007). Indeed, a study investigated their distribution and reported that M4 mAChRs are found in 86% of direct MSNs and 14% of indirect MSNs (Santiago and Potter, 2001). M1 mAChRs are coupled to Gq proteins that activate phospholipase C resulting in activation of inositol trisphosphatase and diacyl-glycerol, ultimately increasing intracellular Ca^{2+} (Pisani et al., 2007). The pharmacological blockade of M1 mAChRs with the selective antagonist, telenzepine, thus produces a reduction of activity in the two striatal output pathways (Ztaou et al., 2016). Several studies suggest that the activation of M1 mAChRs enhances NMDA-receptor mediated currents, promoting MSNs depolarization and corticostriatal long-term potentiation (Bonsi et al., 2011; Calabresi et al., 1999, 1998b; Oldenburg and Ding, 2011).

M4 mAChRs activate Gi/o proteins and their activation results, among other mechanisms, in Cav2 channel inhibition and therefore shapes the spiking of direct MSNs (Santiago and Potter, 2001; Pisani et al., 2007).

2.3. Muscarinic modulation of GABAergic interneurons

GABAergic interneurons express predominantly M1 mAChRs and to a lesser extent M2 and M4 mAChRs (Kreitzer, 2009). Electrophysiological data show that the nonselective mAChRs agonist, muscarine, decreases GABA release, suggesting that M2 and M4 mAChRs are predominantly expressed by GABAergic interneurons and involved in inhibition of GABA release (Kreitzer, 2009).

2.4. Muscarinic modulation of glutamatergic terminals

M2 and M3 mAChRs are both expressed on glutamatergic corticostriatal afferents where they exert opposite effects either by inhibiting or facilitating glutamate release, respectively (Alcantara et al., 2001; Higley et al., 2009; Pisani et al., 2007). Overall, scopolamine, a nonselective mAChRs antagonist, has been shown to increase the extracellular glutamate concentration within the striatum (Rawls and McGinty, 1998). The contribution of mAChRs to the regulation of the glutamatergic thalamostriatal connections remains unknown and will greatly benefit from delineation of the respective contributions of corticostriatal and thalamostriatal inputs to the synaptic rearrangements in

pathological condition.

2.5. Muscarinic modulation of dopaminergic terminals

Dopaminergic nerve terminals express M4 mAChRs and their activation induces a decrease of DA release. *In vitro* studies using striatal slices or striatal synaptosomes show that activation of mAChRs from dopaminergic terminals increases ACh release (Bonanno et al., 1985; Lehmann and Langer, 1982). Conversely, *in vivo* microdialysis studies revealing that local injection of mAChRs agonists and antagonists may either increase, decrease, or have no effect on DA release (Meltzer et al., 1994; Smolders et al., 1997; Westerink et al., 1990; Whitehead et al., 2001; Xu et al., 1989). These data are contradictory, however the diversity of cholinergic receptors subtypes could be partially responsible for the different effects on DA release. This also might be explained by the fact that muscarinic modulation of dopaminergic terminals is only a minor contribution to the cholinergic regulation of striatal activity compared to nicotinic receptor modulation.

3. Functional dysregulation of cholinergic interneurons in Parkinson's disease

The classical view of basal ganglia functional organization posits that two pathways control basal ganglia output structures. Direct pathway MSNs project to globus pallidus internal segment (GPi) and substantia nigra *pars reticulata* (SNr), and preferentially express DA D1 receptors. Indirect pathway MSNs that project indirectly to GPi/SNr via the globus pallidus external segment (GPe) and the subthalamic nucleus (STN) and preferentially express the DA D2 receptors (Albin et al., 1989; Alexander and Crutcher, 1990; Bolam et al., 2000; DeLong, 1990; Gerfen et al., 1990; A. D. Smith and Bolam, 1990). The direct pathway promotes the initiation of movement by transiently interrupting the tonic inhibitory GPi/SNr effect on the thalamocortical pathway and brainstem targets while the indirect pathway inhibits movement. However, recent studies challenge this view by showing that both pathways may be concurrently active during movements (Calabresi et al., 2014; Tecuapetla et al., 2014).

In PD, the degeneration of DA neurons in the SNc induces a reduction of DA levels within the striatum and creates an imbalance between the activity in the direct and indirect pathways. The prevailing view is that the progressive loss of DA activation of D1 and D2 receptors leads to hypoactivity of direct MSNs and hyperactivity of indirect MSNs. Decreased activity of the direct pathway results in the disinhibition of basal ganglia output structures GPi/SNr. Meanwhile, increased activity of the indirect pathway causes GPe inhibition, resulting in STN disinhibition, which exacerbates basal ganglia output structures GPi/SNr signaling (Albin et al., 1989; DeLong, 1990). The overall effect leads to an overstimulation of the inhibitory GPi/SNr control of the thalamocortical pathway and the brainstem targets, which is presumably responsible for motor symptoms expressed by akinesia and bradykinesia in PD patients.

Previous clinical observations showing that antimuscarinic drugs were the first symptomatic treatment of PD patients before the discovery of L-DOPA (Charcot, 1879; Fahn, 1989) led to the hypothesis that both cholinergic and dopaminergic signaling systems had to be in balance to allow the striatum to function normally to control movement (Barbeau, 1962; McGeer et al., 1961). In PD, anticholinergic drugs presumably would reduce the increased striatal cholinergic tone caused by the loss of DA and thus partially restore the balance between these two signaling systems (Conti et al., 2018; Langmead et al., 2008; Ztaou et al., 2018, 2016). Indeed, it has long been reported that DA and ACh exert opposing effects on striatal circuitry (Aosaki et al., 2010; Bonsi et al., 2011; Conti et al., 2018; Lester et al., 2010; Lim et al., 2014; Perez-Lloret and Barrantes, 2016; Pisani et al., 2007; Rizzi and Tan, 2017). However, whether and how the cholinergic disruption of striatal properties contributes to motor and non-motor symptoms as DA level falls and affects basal ganglia circuitry remain open questions. Moreover, this classical view has been challenged recently in a review reporting that these two neurotransmitters could also work in concert with one another to create patterns of activity in the striatum crucial for the control of movement (Tanimura et al., 2018).

4. Dopamine-acetylcholine balance in physiological condition

The balance between dopaminergic and cholinergic systems is crucial to modulate the striatal circuitry for the control of movement in the physiological state. Indeed, ChIs activity is modulated by DA projections originating from the SNc and ventral tegmental area (VTA). Direct MSNs are activated by DA action on D1 receptors and inhibited by ACh action on M4 mAChRs. In contrast, indirect MSNs are inhibited by DA action on D2 receptors but activated by ACh action on M1 mAChRs (Bonsi et al., 2011; Gerfen and Surmeier, 2011; Goldberg et al., 2012; Kreitzer, 2009; Oldenburg and Ding, 2011; Pisani et al., 2007; Rizzi and Tan, 2017). Hence, dopaminergic and cholinergic transmissions modulate the functional balance between the direct and indirect pathways and consequently the correct execution of movement.

Dopaminergic control of ACh release depends on dopaminergic receptors expressed by ChIs. All ChIs express D2 receptors while only a small proportion of them express D1 receptors (Gonzales and Smith, 2015; Lim et al., 2014). Several *in vitro* and *in vivo* studies show that DA exerts an inhibitory control on ChIs via D2 receptors and induces a decrease of ACh release (Consolo et al., 1993; DeBoer and Abercrombie, 1996; Lehmann and Langer, 1983; Pisani et al., 2000; Stoof et al., 1992; Yan et al., 1997). On the contrary, in absence of D2 receptors, DA acts on D1 receptors and increases ACh release (Acquas and Di Chiara, 1999; Damsma et al., 1991; DeBoer and Abercrombie, 1996; Di Chiara et al., 1994; Steinberg et al., 1998).

Cholinergic control of DA release is dependent upon the activation of presynaptic nAChRs and mAChRs modulation (Acquas and Di Chiara, 2002; Aosaki et al., 2010; Exley and Cragg, 2008; Goldberg et al., 2012; Kreitzer, 2009; Oldenburg and Ding, 2011; Threlfell and Cragg, 2011). Recent studies showed that optogenetic activation of ChIs generates a local release of DA in the striatum, via the activation of presynaptic nAChRs expressed on dopaminergic terminals (Threlfell et al., 2012; Wang et al., 2014). Cachope et al. reported that the effect of ChIs activation on DA release is only partially mediated by the activation of nAChRs (Cachope et al., 2012). Indeed, the combination of optogenetic and pharmacological *in vitro* approaches demonstrate a concomitant action of ACh on β2-containing nAChRs and mAChRs, together with an inactivation of AMPA receptors.

There is evidence of a predominant expression of mAChRs in the ventral striatum in comparison to the dorsal striatum in rodents (Tayebati et al., 2004; Threlfell and Cragg, 2011). In the dorsolateral striatum, both types of cholinergic receptors are involved in the regulation of DA release, whereas in the dorsomedial striatum mAChRs have a predominant role (Gauchy et al., 1991). M1 mAChRs-knockout mice exhibit increased DA release in the striatum (Gerber et al., 2001). As dopaminergic terminals do not express M1 mAChRs, cholinergic modulation has been suggested to indirectly affect DA transmission in the striatum by an action on M1 mAChRs expressed on a subset of MSNs that project directly to the SNc and inhibit dopaminergic neurons. In the absence of M1 receptors, the loss of this inhibitory control of dopaminergic neurons produces greater discharge activity and elevation of striatal DA release (Gerber et al., 2001). Other studies using M2 mAChRs-knockout mice or M4 mAChRs-knockout mice suggest that they are involved in the DA-ACh balance in the striatum and are crucial in motor control (Gomeza et al., 1999a, 1999b; Salamone et al., 2001; Wess et al., 2007). In these mutant mice, an exacerbated dopaminergic transmission is also observed. The loss of autoreceptors function on ACh release results in a net increase in striatal ACh, which then activates nAChRs expressed in the dopaminergic terminals (Pisani et al., 2007; Wess et al., 2007).

In the striatum, neuropeptides such as tachykinins (substance P, neurokinins A and B) and opioids (enkephalins and dynorphins) expressed by MSNs play also a crucial role in the DA-ACh balance. When these peptides are released by MSNs collaterals, they regulate dopaminergic (Di Chiara and Imperato, 1988; Dourmap et al., 1997; Kemel et al., 1992; Krebs et al., 1994; Li et al., 2002; Tremblay et al., 1992) and cholinergic transmission in the striatum (Arenas et al., 1991; Blanchet et al., 1998; Jabourian et al., 2004; Steinberg et al., 1998). Indeed, direct MSNs co-express substance P with GABA and form synaptic connections with ChIs. By stimulation of NK1 receptors expressed in ChIs, Substance P induces a release of ACh (Lim et al., 2014). In contrast, enkephalins co-expressed with GABA in indirect MSNs exert an inhibitory control of ACh release via μ opioid receptors (MORs) expressed in ChIs. Inhibition of ACh, via MORs activation, induces a decrease of DA release in the striatum, presumably by limiting presynaptic activation of nAChRs (Britt and McGehee, 2008).

Electrophysiological recordings in non-human primates display distinct but coincident reward-related activity in DA neurons and ChIs during performance on an instrumental conditioning task (Cragg, 2006). DA neurons signal reward-predicting or unexpected events by a phasic burst or pause in firing rate associated with reward presentation or omission, respectively, while ChIs always display a pause in firing rate following reward-related events (Aosaki et al., 2010, 1994; Apicella et al., 1997; Morris et al., 2004; Zhang and Cragg, 2017). The pause response of ChIs actually consists of triphasic response which begins with an initial excitation, followed by a pause and a rebound excitation (Aosaki et al., 2010; Morris et al., 2004). DA neurons and ChIs responses are 'time-locked': when DA neurons are recorded in the same learning conditioning task, their reward-related bursts occur with similar latency and duration than ChIs response (Morris et al., 2004). Although the precise mechanisms contributing to the pause response of ChIs are still being investigated, it requires both the nigrostriatal dopaminergic projections and the thalamostriatal glutamatergic projections to occur, as the pause response disappears if either projection is interrupted (Aosaki et al., 1994; Reynolds and Wickens, 2004; Zhang and Cragg, 2017).

5. Disruption of the dopamine-acetylcholine balance in Parkinson's disease

In non-human primates, unilaterally injected with a selective neurotoxin of dopamine neurons 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and trained in a classical conditioning task, responsive TANs were dramatically decreased in the depleted striatum, whereas cells in the intact side remained responsive (Aosaki et al., 2010, 1994). This evidence suggests that there is close relationship between ChIs activity and DA neuronal firing, ultimately altered in parkinsonian state.

In the 6-hydroxydopamine (6-OHDA) lesion model of PD, microdialysis studies showed that striatal ACh levels are elevated in the DA-depleted rat striatum (DeBoer et al., 1993), indicating a deregulation of ChIs excitability *in vitro* (Fino et al., 2007; Maurice et al., 2015). The increased striatal ACh level was attributed to the loss of inhibitory control mediated by D2 receptors on ChIs (Maurice et al., 2004). However another study indicates that it could also be due to a reduction in the efficacy of M4 mAChRs autoreceptors (through downregulation of RGS4 expression, an autoreceptor-associated, GTPase-accelerating protein) and this would consequently increase ACh signaling (J. J. Ding et al., 2006). Given the therapeutic effects of anticholinergic drugs in PD mentioned above, and the physiological changes in ChIs seen in animals models of the disease, it is evident that DA-ACh imbalance is crucial to the expression of parkinsonian-like symptoms (Brichta et al., 2013; Kalia et al., 2013; Langmead et al., 2008; Maurice et al., 2015; Ztaou et al., 2018, 2016).

In DA-depleted rats, there is also evidence of synaptic reorganization of striatal ChIs within the striatum following intranigral 6-OHDA injection (Salin et al., 2009). Salin et al. used retrograde transynaptic spread of rabies virus injected into the GPe or SNr to identify the strength of ChIs connection onto either direct or indirect MSNs. In normal condition, ChIs provide equivalent input onto direct or indirect MSNs. In parkinsonian state, however, there is a switch of cholinergic innervation onto indirect MSNs, which could contribute to the imbalanced striatal outflow. Recent studies using optogenetics support the central role of striatal ChIs activity in the reorganization of striatal microcircuitry and the production of motor symptoms in PD condition (Conti et al., 2018; Lester et al., 2010; Pisani et al., 2007; Rizzi and Tan, 2017). Indeed, optogenetic photoinhibition of ChIs in DA-depleted mice following unilateral 6-OHDA lesions improves PD-like motor symptomatology by reducing akinesia, bradykinesia, and sensorimotor neglect (Maurice et al., 2015; Ztaou et al., 2016). Interestingly, positive effects of ChIs photoinhibition are also observed on cognitive and affective alterations (anxiety, visuospatial short-term memory) induced by partial striatal DA depletion, mimicking the premotor phase of PD (Ztaou et al., 2018), suggesting that the DA-ACh imbalance may also be present in the early stages of the disease. In addition, striatal ChIs appear to be crucial to the expression of L-DOPA-induced dyskinesia and optogenetic activation of striatal ChIs regulates their expression (Bordia and Perez, 2018; Bordia et al., 2016).

Dopaminergic depletion also induces an alteration of neuropeptide expression (tachykinins, opioids) in the striatum and thus of striatal cholinergic transmission leading to an imbalance of the DA-ACh interaction. In DA-depleted rats, tachykinin increases cholinergic transmission in the sensorimotor (Kemel et al., 2002) and limbic (Pérez et al., 2007) territories of the striatum. Moreover, in the absence of dopaminergic transmission, enkephalins via μ opioid receptors (MORs) expressed by ChIs inhibit ACh release in the limbic regions of the striatum (Jabourian et al., 2007). Hence, an alteration of the regulation of cholinergic transmission, via enkephalins and MORs, play a role in cognitive and motivational deficits associated with PD in rodent parkinsonian model.

In addition to alteration in ChIs signaling, M2 and M4 mAChR subtypes, and nAChRs expression are also affected in PD (Aubert et al., 1992; Bohnen and Albin, 2011; Brown and Marsden, 1990; Lang and Lozano, 1998a, 1998b; Müller and Bohnen, 2013). A loss of M2 mAChRs has been shown in a genetic model for PD, the *Pitx3*$^{ak/ak}$ mice (Cremer et al., 2015). Conflicting studies show that M4 mAChRs expression may be either decreased or enhanced in parkinsonian states. The loss of DA innervation has been reported to attenuate M4 mAChRs expression in ChIs, which might be a main factor in the elevated striatal ACh signaling after DA depletion (J. J. Ding et al., 2006). On the other hand, other studies indicate that M4 mAChRs activation contributes to PD symptoms. Salamone et al. showed that central-acting M4 mAChRs antagonist and M4 mAChRs-knockout mice reduce tremulous jaw movements in a pharmacological rat model of dyskinesia in PD (Salamone et al., 2001). M4 mAChRs antagonism also alleviate motor deficits such as akinesia, bradykinesia, and sensorimotor neglect in the 6-OHDA mice model of PD (Ztaou et al., 2016). The anti-parkinsonian effects of the M4 mAChRs antagonist tropicamide have been shown to be almost completely abolished in mutant 6-OHDA-lesioned mice lacking M4 mAChRs specifically in direct MSNs (D1-M4-knockout mice). This suggests that the beneficial effects of M4 mAChRs antagonism on motor symptoms is the consequence of a postsynaptic M4 mAChRs expressed on direct MSNs blockade rather than a presynaptic blockade of M4 mAChRs located on ChIs (Ztaou et al., 2016).

The loss of dopamine is associated with a widespread loss of nAChRs expression in PD (Aubert et al., 1992; Bohnen and Albin, 2011; Müller and Bohnen, 2013). An estimated 50–90% loss of nigrostriatal nAChRs expression is observed after DA depletion in experimental models and clinical populations (Conti et al., 2018). A post-mortem *in vitro* study using a nAChRs ligand demonstrated a loss of nAChRs specifically in the striatum concomitantly to the loss of nigrostriatal dopaminergic markers (Pimlott et al., 2004). *In vivo* imaging studies of PD patients have

also reported a reduction of α4β2 nAChRs expression in the striatum (Fujita et al., 2006; Kas et al., 2009). The loss of nAChRs containing α6β2 tends to be more severe than that of those containing α4β2 since α6β2-containing nAChRs are selectively located on nigrostriatal terminals (Conti et al., 2018; Perez, 2015; Perez et al., 2010).

Whether these impairments are the cause or the consequence of DA loss in PD, targeting cholinergic receptors offers potential therapeutic application to normalize the striatal DA-ACh balance and thus, treat parkinsonian symptoms.

6. Potential targets for Parkinson's disease treatment

As mentioned above, as striatal DA levels fall in PD, the cholinergic tone rises (Barbeau, 1962; Duvoisin, 1967; Hornykiewicz and Kish, 1987). This elevation is clinically important, as antagonizing mAChRs – which appears to be the highest concentration of cholinergic receptors found in the striatum (Cortes and Palacios, 1986; Cortes et al., 1986) – might effectively reverses many motor (and non-motor) symptoms of PD (Bonsi et al., 2011; Ferreira et al., 2013; Langmead et al., 2008; Pisani et al., 2007; Rascol et al., 2011; Rezak, 2007; Y. Smith et al., 2012).

Charcot was the first, in 1879, to note the beneficial effects of belladonna alkaloids (agents with potent anticholinergic properties) containing atropine on the parkinsonian motor signs. They were effective on rigidity and tremor, potentially exerting their effects by preventing ChIs overactivity (Barbeau, 1962; Hornykiewicz and Kish, 1987). However, anticholinergic drugs do not alleviate akinesia or bradykinesia. Moreover, they produce side-effects including urinary retention, nausea, falls, and drowsiness. Cognitive impairment affecting learning and memory processes, as well as cognitive flexibility may also be produced by anticholinergic drugs presumably caused by the decrease of ACh tone in frontal cortical areas during the course of the disease (Ferreira et al., 2013; Rascol et al., 2011; Rezak, 2007). Anticholinergics remained the only drugs available for the symptomatic treatment of PD for nearly a century until the introduction of L-DOPA. Nowadays, anticholinergics drugs are prescribed if tremor persists (Ferreira et al., 2013) and only to relatively young patients in the early stages of PD or for those who do not respond to DA replacement therapy (Yamada et al., 2002).

Despite the fact that anticholinergic drugs are accompanied by troublesome side effects, impairment of striatal ChIs activity could be pharmacologically manipulated by targeting the multitude of cholinergic receptor subtypes expressed in the striatal circuitry. Thus, their potential therapeutic relevance warrants further research to obtain more selective agents (Pisani et al., 2007). Whether the discovery of selective antagonists, more precisely targeting a mAChRs subtype, will provide better treatment for parkinsonian rigidity and tremor without the side effects remains to be investigated (Langmead et al., 2008).

In pharmacology, it is generally considered easier to develop subtype selective antagonists than agonists. In animal models and early stage of PD, blocking mAChRs, more precisely M1 and M4 mAChRs, has been shown to improve parkinsonian motor deficits (Betz et al., 2007; Xiang et al., 2012; Ztaou et al., 2016). Mice lacking M1 mAChRs (M1 mAChRs-knockout mice) exhibit an elevated locomotor activity and an exacerbated dopaminergic transmission in the striatum, suggesting that blocking M1 mAChRs might be an alternative strategy for alleviating motor symptoms (Gerber et al., 2001). However, M1 mAChRs blockade has been associated with puzzling effects on non-motor symptoms in PD. Studies show that antagonizing M1 mAChRs impairs working memory, memory consolidation and behavioral flexibility (Anagnostaras et al., 2003; Ragozzino et al., 2002; Tzavos et al., 2004). On the contrary, the selective M1 mAChRs antagonist, telenzepine, injected at low dosage reduce mood disorders such as anxiety-like behavior (Ztaou et al., 2018).

M4 mAChRs antagonists may also be used to restore the DA-ACh balance in PD and thus improve motor symptoms. Studies show that M4 mAChRs antagonists could be potential antiparkinsonian agents to alleviate pilocarpine-induced tremulous jaw movements in rats (Mayorga et al., 1999) and akinesia/bradykinesia in 6-OHDA mice (Ztaou et al., 2016). Gomeza et al. show that mice lacking M4 mAChRs (M4 mAChRs-knockout mice) exhibit an elevated basal locomotor activity (Gomeza et al., 1999b). A review describing recent progress made in mAChRs drug discovery promotes the use of selective M4 mAChRs antagonists to address the parkinsonian tremor and rigidity and M1 mAChRs agonists to treat cognitive deficits (Langmead et al., 2008).

In summary, investigation of highly selective components and translation into clinical use remains a challenge. Normalizing ChIs signaling, by targeting cholinergic receptors, is a crucial therapeutic goal for a multisystem disorder like PD. However modulating striatal ACh to alleviate either motor symptoms or non-motor symptoms of PD across the disease progression may require multi-faceted treatment across the disease progression.

7. Concluding remarks

The advances in the experimental tools (optogenetic and chemogenetic techniques, new recording techniques, highly selective mAChRs compounds) have shed light on the function of ChIs in physiological and pathological conditions.

The ability of ChIs to release other neurotransmitters like glutamate, in addition to ACh itself, has been increasingly described in recent reviews (Kljakic et al., 2017; Mestikawy et al., 2011; Trudeau and Mestikawy, 2018). A study shows that glutamate via the vesicular glutamate transporter type 3 (VGLUT3) plays also an important role in the development of L-DOPA-induced dyskinesia (Gangarossa et al., 2016). Furthermore, these two co-transmitters exert opposing effects on DA release. DA efflux is stimulated by nAChRs and inhibited by VGLUT3-dependent glutamate (through metabotropic glutamate receptors, mGluRs, most likely located on DA terminals) (Sakae et al., 2015). Although the co-release ACh/glutamate and the nAChRs regulation are not central in this review, these two points need to be considered in the regulation of striatal network.

Moreover, DA inputs regulate ChIs differently across dorsal striatal regions. Two recents studies reported that DA neurons drive pauses in the firing of dorsomedial ChIs but bursts in dorsolateral ChIs (Cai and Ford, 2018; Chuhma et al., 2018). These variations are due to different actions of DA/glutamate cotransmission and encompass once more the complexity of DA-ACh balance regulation in the striatum.

In this review, we discuss the long-standing model that DA and ACh oppose one another. There are still compelling evidence of opposite effects of these two neurotransmitters in striatal microcircuitry regulation. However, this view has been revised also suggesting a cooperation between DA and ACh, that indicates a more complex interaction between these two neuronal systems (Surmeier and Graybiel, 2012; Threlfell et al., 2012).

It is clear that cholinergic signaling plays a major role in modulation of striatal microcircuitry and basal ganglia output. ChIs undergo major changes during PD that will be more and more investigated in the future years, as well as in other basal ganglia diseases (*e.g.* dystonia, Tourette syndrome, Huntington's disease). The development of novel anticholinergic drugs, more selective of mAChR subtypes, may help to avoid the major side-effects associated with classical anticholinergic treatment. Novel wireless implantable micro-scale devices will allow the use of optogenetics to target specific neural circuits, like ChIs, in experimental models of these diseases and probably in the future will provide new therapeutic strategies.

Conflicts of interest

None of the authors have a conflict of interest, scientific or financial.

Author contributions

All authors contributed to drafting and editing the manuscript.

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Abbreviations

6-OHDA	6-hydroxydopamine
ACh	acetylcholine
AChE	acetylcholinesterase
ChAT	choline acetyltransferase
ChIs	cholinergic interneurons
DA	dopamine
GABA	Gamma-aminobutyric acid
L-DOPA	Levodopa or L-3,4-dihydroxyphenylalanine
GPe/i	globus pallidus external/internal segment
mGLURs	metabotropic glutamate receptors
m/nAChRs	muscarinic/nicotinic acetylcholine receptors
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSNs	medium spiny neurons
PD	Parkinson's disease
SNc/r	substantia nigra *pars compacta/pars reticulata*
STN	subthalamic nucleus
TANs	tonically active neurons
VGLUT3	vesicular glutamate transporter type 3

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