

Nigrostriatal interaction in the aging brain: new therapeutic target for Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder of unclear etiology and pathogenesis. Research results gathered to date support the hypothesis that the motor symptoms of the disease result from the gradual loss of midbrain dopamine neurons residing in the substantia nigra pars compacta (SNpc). Recent discoveries, however, significantly expand this knowledge indicating that the primary source of the PD pathogenesis may be located both in the SNpc as well as in the GABAergic striatum. Newly discovered striatal neurogenesis – normally a lifelong process – determines the efficiency of nigrostriatal interaction. Deficient neurogenesis within the striatum followed by a decline in the GABAergic/dopaminergic interaction results in progressive disconnection of the dopaminergic input, which initiates a 'vicious circle' cascade of neuronal damage. Effects of both deficient striatal neurogenesis and age-related neurodegeneration within the striatum accumulate, resulting in a progressive decline in the control functions of the basal ganglia, loss of dopaminergic neurons, and occurrence of PD clinical symptoms. Functional and pharmacological control of these dynamic relationships may result in treatments that are more effective with fewer side-effects.

Key words: Parkinson's disease, striatum, nigrostriatal interaction, neurodegeneration, neurogenesis, GABA collapse, cellular turnover

Nigrostriatal interaction and neurodegenerative disorders

Neurodegenerative diseases constitute a heterogeneous group of age-related disorders that are characterized by a slow but irreversible deterioration of brain functions. Parkinson's disease (PD) represents the second most common neurodegenerative disorder that is clinically characterized by non-motor and motor symptoms (Błaszczyk 1998, Chaudhuri et al. 2006, Pellicano et al. 2007, Schapira 2008, Yadav and Li 2015). The etiology and pathogenesis of PD still remains unclear, but it is thought that it may be caused by a combination of genetic and environmental factors (Braak et al. 2004, Schapira 2007, Mosharov et al. 2009, Brichta and Greengard 2014, Yadav and Li 2015, Goedert 2015). It is well documented that the cardinal features of PD motor symptoms including bradykinesia, muscular rigidity, rest tremor, and postural and gait instability can be entirely explained by degeneration of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) (Cenci 2007, Pellicano et al. 2007, Fahn 2008, Brichta and Greengard 2014, Yadav and Li 2015). Consequently, treatment for PD has classically involved supplementation of endogenous dopamine (DA) with medicinal options that either replace

dopamine or augment the nigrostriatal dopaminergic pathway (Schapira 2007, Fahn 2008, Yadav and Li 2015). Surprisingly, all current pharmacological therapies and surgical treatments, including deep brain stimulation and stem cell therapy, are oriented towards symptomatic relief and do not cure disease (Schapira 2007, Yadav and Li 2015). Our current knowledge why the SNpc dopaminergic neurons are particularly vulnerable to degeneration is still extremely limited (Pissadaki and Bolam 2013, Brichta and Greengard 2014, Dopeso-Reyes et al. 2014), and without this knowledge, development of a promising neuroprotective treatment strategy is not possible. For instance, intracellular calbindin content in addition to the relatively high energy cost of neuronal activity may be clues to the susceptibility of midbrain DA neurons to neurodegeneration (Pissadaki and Bolam 2013, Brichta and Greengard 2014, Dopeso-Reyes et al. 2014). The latter factor, i.e. the neuronal activity is strongly controlled by the GABAergic system (Błaszczyk et al. 2016). That is why decline in GABA inhibitory function may initiate/escalate neurodegenerative processes both in the striatum and the SNpc, thus leading to the development of pathologies such as Parkinson's disease (Błaszczyk 2016). In particular, GABAergic input of the striatum with its fragile and

sophisticated nigrostriatal interaction may be a primary locus for the pathology.

The striatum is a major portion of the basal ganglia that forms their GABAergic input (Cicchetti et al. 2000, Grillner et al. 2005, Brichta and Greengard 2014, Ernst et al. 2014). It is functionally subdivided into ventral and dorsal areas which participate in different aspects of motor control (Koós and Tepper 1999, Rodrigo et al. 2002, Grillner et al. 2005, Wesson and Wilson 2011, Brichta and Greengard 2014). The ventral striatum functions as part of the reward system and is mostly involved in the motivational/emotional modulation of motor behavior. Here, dopaminergic projections from the nucleus accumbens and the SNpc are used to integrate the emotional and motivational salience of multi-sensory input with reinforcement and to reward perception related to motor activity (Grillner et al. 2005). Dysfunction of the ventral striatum is probably responsible for PD premotor symptoms (Chaudhuri et al. 2006).

The second part, the dorsal striatum is directly involved in the main aspects of motor control including motor program selection, activation, and execution (Cicchetti et al. 2000, Grillner et al. 2005, Cenci 2007). Neural processes involved in selection and activation of a context-specific motor program are based upon the integration of motivational/emotional signaling with sensory-motor inputs (Wesson and Willson 2011, Yager et al. 2015). In order to execute a relevant motor program, it must be released from the pallidal inhibition through activation of the nigrostriatal input. For this purpose, the SNpc dopaminergic neurons provide the massive excitatory projection to the dorsal striatum (Grillner et al. 2005, Ibáñez and Andressoo 2017). Axons of this pathway synapse onto GABAergic striatal medium spiny neurons (MSNs) and thus gain access to the main functions of motor control. This unique synaptic junction between the GABAergic and dopaminergic systems, results in a close and specific functional interaction between both systems, including the process of nigrostriatal synaptogenesis and continuous cellular turnover of striatal interneurons (Dayer et al. 2005, Curtis et al. 2011, Wang et al. 2011, Ernst et al. 2014, Adlaf et al. 2016). Consequently, the motor symptoms of Parkinson's disease may be due both to the dysfunction of dopaminergic SNpc or to the GABAergic striatum. In particular, parkinsonian akinesia may be attributed to an imbalance between movement-suppressing and movement-promoting pathways within the basal ganglia (Damodaran et al. 2014). To verify this claim, we must look closer at the phenomena of nigrostriatal interaction and particularly their striatal contributions.

The MSNs make up 75–80% of the striatal input neuronal cells, and the four subtypes of interneurons together represent 20–25% of the striatum (Cicchetti et al. 2000, Tepper and Bolam 2004). Both the neurons and the interneurons of the striatum are inhibitory and use GABA

as their main neurotransmitter. It has been documented that the medium spiny neurons do not degenerate and their population in the adult human brain is not renewed to a significant level (Cenci 2007, Curtis et al. 2011, Ernst et al. 2014). On the contrary, the GABAergic interneurons, although in the minority, appear to play a fundamental role in the physiology and pathophysiology of the nigrostriatal input (Wang et al. 2011, Ernst et al. 2014, Adlaf et al. 2016). In order to function correctly, the striatal input must be protected against unwanted, accidental activation (Grillner et al. 2005). During resting conditions that are characterized by a mild tonic dopaminergic activation (Brichta and Greengard 2014), the medium spiny neurons must be kept in a silent 'hyperpolarized state' until they receive a robust excitatory dopaminergic input (Domodaran et al. 2014, Hu et al. 2014).

It has been documented that nigrostriatal-projecting neurons express a lower level of calbindin and thus are particularly prone to degeneration due to neurotoxins, excitotoxicity or aging (Brichta and Greengard 2014, Dopeso-Reyes et al. 2014). The dopaminergic neuron activity is driven by calcium channels (Brichta and Greengard 2014). In such conditions, both the level and the threshold of striatal input is effectively controlled just by the network of GABAergic interneurons (Damodaran et al. 2014). As depicted graphically in Fig. 1, sparsely represented parvalbumin-expressing fast-spiking interneurons (FSI), constituting only about 0.7% of striatal neurons exert a powerful and decisive impact on the nigrostriatal input (Cicchetti et al. 2000, Hu et al. 2014). The FSIs synapse on the striatal MSNs, projecting mainly to their somas and proximal dendrites (Koós and Tepper 2002, Cicchetti et al. 2000, Yager et al. 2015). In this way, fast-spiking interneurons can efficiently control the excitability of the MSNs (Damodaran et al. 2014). Moreover, a single FSI can block or delay the firing of more than 100 medium spiny projection neurons (Koós and Tepper 2002).

Each MSN receives a vast amount of input from different incoming DA axons. It is estimated that a single medium spiny GABAergic neuron may receive synaptic input from more than 200 SNpc dopaminergic cells (Ibáñez and Andressoo 2017). Consequently, the axonal tree of each individual SNpc dopaminergic neuron branches extensively onto the GABAergic medium spiny neurons covering on average, 1.5% of the total striatal volume (Ibáñez and Andressoo 2017). This redundancy explains the remarkable compensatory capacity of the nigrostriatal control and the fact that motor deficits of PD do not become symptomatic until more than 30–40% of SNpc neurons are lost. It should be mentioned here, that acetylcholine is also one of the main modulators of striatal fast-spiking interneurons, contributing greatly to the powerful modulation of GABAergic synaptic transmission between FSIs and spiny projection neurons (Koós and Tepper 2002).

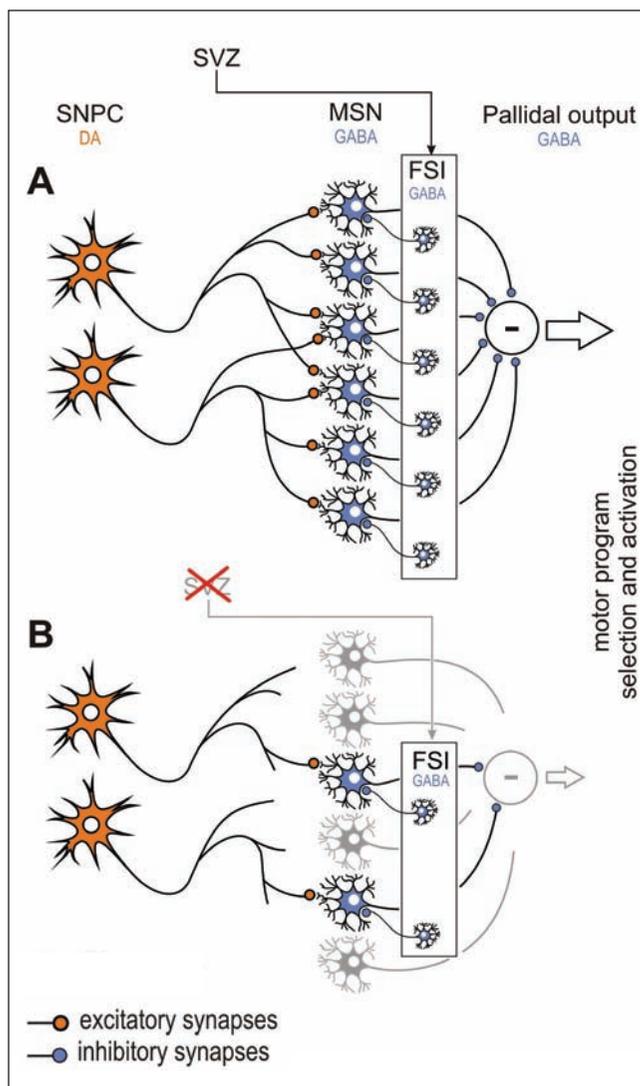


Fig. 1. Heuristic model of the nigrostriatal interaction showing the physiology (A) and pathophysiology (B) of the striatum that may cause Parkinson's disease. In physiological conditions, the interaction is determined by the activity-dependent continuous turnover of GABAergic interneurons of the striatum. The parvalbumin expressing fast-spiking interneurons (FSI) are susceptible to apoptosis thus physiological function of the striatum requires rapid and continuous exchange of these interneurons. Normal activity of the striatum that is characterized by an elevated level of neurotransmitters (mostly GABA) and the glia-derived neurotrophic factor (GDNF) intensifies proliferation and migration of stem cells to the striatum. The subventricular (SVZ) is a specialized brain area containing self-renewing GFAP+ astrocytes functioning as neural stem cells that generate new FSIs in the striatum throughout life. Deficient neurogenesis within the striatum followed by a decline in the nigrostriatal interaction results in progressive withdrawal and eventually disconnection of the dopaminergic input from the substantia nigra pars compacta (SNpc). This initiates a 'vicious circle' cascade of pathological events resulting in a devastating decline of nigrostriatal interaction that leads to a fatal damage of the FSI turnover and neurodegeneration of the DOPA neurons of the SNpc. In this pathological state, the striatum loses its control over the pallidal output and clinical symptoms of full-blown Parkinson's disease (including the bradykinesia, tremor, rigidity) are observed.

The emergent properties of the nigrostriatum are determined by multi-level and multi-functional interaction between the dopaminergic and GABAergic systems. Most importantly, impairment and progressive decline of the nigrostriatal interaction can be initiated from either systems: dopaminergic or GABAergic. In the former case, the DA neuron degeneration may be triggered by mitochondrial neurotoxins such as MPP⁺ or rotenone that results in parkinsonism (Brichta and Greengard 2014). Also, reliance of SNpc dopaminergic neurons on calcium for their spontaneous activity in combination with a relatively lower level of intracellular calbindin makes them extremely prone to age-related degeneration (Brichta and Greengard 2014, Pisadaki and Bolam 2013). In this case, the elevated oxidative stress and formation of Lewy bodies could initiate a 'vicious circle' of DA neuronal insult and progressive neurodegeneration. Importantly, the process of DA neurodegeneration may be triggered, as well, by the decline of GABA neuron turnover in the striatum.

Fragile balance between neurodegeneration and neurogenesis in the striatum

Two fundamental properties of the nigrostriatal input: its adaptivity and synaptic plasticity, allow continuous adjustment of the threshold, sensitivity and selectivity of the input depending on the behavioral context including individual motor experience and learning. These properties are fundamentally determined by the anatomy of the nigrostriatal input and its propensity to adaptive remodeling (Ernst et al. 2014, Adlaf et al. 2016, Ibáñez and Andressoo 2017). In contrast to the medium spiny projection neurons, the GABA interneurons and their supportive, non-neuronal cells (a subset of short-lived oligodendrocytes), are prone to neurodegeneration (Ernst et al. 2014). However, lost interneurons and oligodendrocytes are constantly replaced with new ones in the process of striatal cell turnover (Bédard et al. 2002, Brazel et al. 2003, Dayer et al. 2005, Wang et al. 2011, Ernst et al. 2014, Adlaf et al. 2016). In humans, the subventricular zone (SVZ) is a specialized area containing self-renewing GFAP+ astrocytes functioning as neural stem cells that generate new GABA fast-spiking interneurons in the striatum throughout life (Brazel et al. 2003, Adlaf et al. 2016). In the adult human striatum, the median turnover rate of interneurons is comparable to the turnover rate of neurons within the hippocampus (Ernst et al. 2014).

The aging of the brain appears, among other to be related to a decline of striatal cell turnover (Strömberg et al. 1993, Koós and Tepper 2002). GABA interneuron turnover is fundamental for motor control and its deficiency due to aging is probably the main cause for the development

of PD clinical symptoms (Androutsellis-Theotokis et al. 2009, Zachrisson et al. 2011, Ibáñez and Andressoo 2017). In fact, it became evident recently that deficient neurogenesis within the striatum followed by a decline in the nigrostriatal interaction results in progressive withdrawal and eventual disconnection of the dopaminergic synapses. A deficient nigrostriatal input, in turn, results in progressive neuronal damage (Ibáñez and Andressoo 2017). The striatal input network (structured from MSNs) deprived from FSI inhibition, initially becomes overactive. This impairs its function (i.e. selective control of the pallidal output). It also makes the MSNs more susceptible to neurodegeneration (likely due to energy deficiency, as suggested by Pissadaki and Bolam 2013) that, in a longer perspective, leads to damage of the basal ganglia.

Early effects of neurodegeneration within the nigrostriatal input are, at least partially, compensated by the process of synaptic reorganization that usually requires an enforced activity of the medium spiny neurons (Adlaf et al. 2016). For instance, it has been documented in the PD rodent models that the axonal trees of the surviving dopaminergic axons can re-innervate the nigrostriatal synapses left vacant by the degenerating GABA neurons (Ibáñez and Andressoo 2017).

Striatal neurogenesis in humans appears to be a productive lifelong process whose understanding may provide the opportunity to manage neurodegenerative disorders (Wei et al. 2011, Zachrisson et al. 2011, Göritz and Frisé 2012). In the process of striatal cell turnover, the glial cell-derived neurotrophic factor (GDNF) seems to play a pivotal role (Lin et al. 1993, Strömberg et al. 1993, Lapchak et al. 1996, 1997, Cohen et al. 2003, Ibáñez and Andressoo 2017). In the striatum, the GDNF is predominantly expressed by GABA interneurons.

In the process of neurogenesis, GDNF promotes the functional and morphological differentiation of GABAergic neurons (Ibáñez and Andressoo 2017, Marsh and Blurton-Jones 2017). GDNF also functions as a chemoattractant, stimulating both (i) the proliferative stem cells of the SVZ to migrate and form interneurons in the adjacent striatum, and (ii) the synaptogenesis and DOPA/GABA re-innervation (Adlaf et al. 2016, Ibáñez and Andressoo 2017).

A growing body of evidence suggests that SVZ neural stem cell proliferation and migration is controlled by both neurotransmitters (DA and GABA) that determine striatal neuronal activity (Zachrisson et al. 2011, Adlaf et al. 2016). They are both dependent on the overall motor activity of a patient. Importantly, it seems well-documented that cytokines from apoptotic neurons may initiate the process of striatal cell turnover. Thus, an increased SVZ proliferation follows striatal neuron death (Brazel et al. 2003, Adlaf et al. 2016). In the other words, neurodegeneration of

striatal GABA interneurons initiates neurogenesis that compensates for the loss of fast-firing interneurons.

Neurogenesis in the adult brain serves to maintain a pool of striatal interneurons with unique properties that are present for a limited time and enable specific types of neural processing (Ernst et al. 2014). We can currently only speculate about the aspects of continuous striatal neurogenesis in humans, and the functional integration of the new neurons into existing neuronal circuits (Borel and Götz 2014). This process requires further research but data gathered so far allows us to posit that dysfunction of the striatum may be a primary cause of Parkinson's disease. We should remember, however, that brain aging and related neurodegenerative processes are very complex and may result from the interaction of various, seemingly unrelated, physiological mechanisms. For instance, virtually all PD patients develop sleep disturbances at the early stage of the disease (Chaudhuri et al. 2006). The disturbances have a multifactorial etiology, but early degeneration of the locus coeruleus noradrenergic system (Samuels and Szabadi 2008) and the serotonergic system related to the dorsal raphe nucleus (Grosch et al. 2016) may be of particular importance for the pathology. Their dysfunctions result in a decline of the restorative function of sleep that may cause accumulation of potentially neurotoxic waste products within the CNS (Xie et al. 2013). This, in turn, may escalate neurodegeneration and limit neurogenesis within the aging brain.

Can we cure Parkinson's disease?

Therapeutic interventions that slow the progressive neurodegeneration within the nigrostriatal system or restore its normal function (neurorescue) depend on a clear understanding of the etiology and pathogenesis of PD (Schapiro 2007). Recognizing the existence of striatal neurogenesis and identifying factors that promote the renewal of striatal neurons may facilitate the development of new therapeutic strategies. Finding that neurons are added continuously in the adult human striatum poses the question of whether this process can be utilized therapeutically in Parkinson's disease. Studies in rodents confirmed that promoting cell proliferation in the subventricular zone can have a positive effect in models of Parkinson's disease, likely mediated by the new cells having a neurotrophic effect on the nigro-striatal system (Androutsellis-Theotokis et al. 2009, Zachrisson et al. 2011).

It has been shown recently that the neural stem cells within the striatum respond directly to GABA (Adlaf et al. 2016). Consequently, inserting glutamic acid decarboxylase (GAD) gene into the subthalamic nucleus seems to offer an alternative therapeutic strategy (LeWitt

et al. 2011). In the brain, GAD synthesizes GABA using the active form of vitamin B6 as a cofactor. Therefore, this therapeutic strategy restores local GABA transmission within the subthalamic nucleus and normalizes output from the nucleus by adding an inhibitory GABA outflow, thereby reducing excessive excitatory glutamate output to key targets such as the globus pallidus interna and the substantia nigra pars reticulata (LeWitt et al. 2011).

As mentioned above, GDNF has regenerative properties for brain cells showing potential in the treatment of PD (Lapchak et al. 1996, 1997, Cohen et al. 2003, Kirik et al. 2004, Eserian 2013, Marsh and Blurton-Jones 2017). GDNF was discovered while searching for a neurotrophic factor for substantia nigra dopamine neurons (Lin et al. 1993). So far, it has been well documented that GDNF is involved in the development of the dopaminergic pathways and regulates DA cells apoptosis in the substantia nigra (Mosharov et al. 2009). Dopaminergic neurons of the SNpc express both GDNF receptors: tyrosine kinase RET and GDNF Family Receptor alfa1 (GFR α 1) (Ibáñez and Andressoo 2017). RET is the main GDNF receptor in the midbrain dopaminergic neurons that project to the striatum.

In the striatum, GDNF is predominantly expressed by parvalbumin positive interneurons. Interestingly, GDNF delivery into the striatum, but not to the SNpc, results in functional recovery in rodent PD models, underlying the importance of GDNF delivery to its physiological site of expression for the treatment of PD (Kirik et al. 2004). *In vitro* studies demonstrated that GDNF can promote the functional and morphological differentiation of GABAergic neurons and function as a chemoattractant for GABAergic cells in explants from the subventricular zone (Paratcha et al. 2006). Thus GDNF signaling through RET is fundamental for long-term maintenance of the dopaminergic nigrostriatal projection. Additionally, GDNF/GFR α 1 signaling is involved in axonal outgrowth and promotes synapse formation within the striatal input (Ernst et al. 2014). Recent studies confirm a role for GDNF/GFR α 1 signaling in the development and function of multiple classes of GABAergic neurons in the mammalian brain. In particular, the GFR α 1 contributes to the development and allocation of parvalbumin expressing fast-spiking GABAergic interneurons (Ibáñez and Andressoo 2017). Unfortunately, progress in the development of the new GDNF pharmacotherapy is progressing slowly because GDNF does not cross the blood-brain barrier.

There is growing evidence that vitamin D increases the levels of tyrosine hydroxylase expression, suggesting that it might modulate dopaminergic processes (Eserian 2013). Vitamin D is a potent inducer of endogenous GDNF, and the most prominent feature of GDNF is its ability to support the survival of dopaminergic neurons. Thus, supportive therapy with vitamin D may prove to be useful in PD (Eserian 2013).

Another therapeutic aspect of adult GDNF expression and function is the possibility of its regulation with physical activity (Brazel et al. 2003, Cohen et al. 2003, Adlaf et al. 2016). Studies in rodents have shown upregulated GDNF expression in several CNS structures following increased motor activity. In particular, striatal GDNF level was found to be dramatically increased (Cohen et al. 2003). This implies simply that GDNF expression leading to intrinsic neuroprotective and neuroregenerative outcomes may be therapeutically regulated by physical activity. Because GDNF potentiates and attracts striatal dopamine input, it is tempting to hypothesize that physiologically (e.g. by physical activity) or pharmacologically enforced neurogenesis of GDNF-expressing interneurons in the striatum will induce re-growth of the degenerating dopaminergic system in the aging brain (Ibáñez and Andressoo 2017).

Finally, we should mention here recent studies suggesting the important functions of the GDNF/RET signaling system in the integrity and function of the blood-brain barrier (Ibáñez and Andressoo 2017). The results indicate that GDNF may be an important up-regulator of microglial activation and suggest that GDNF may offer protection from neurodegeneration through the inhibition of neuroinflammation (Morale et al. 2006, Ibáñez and Andressoo 2017).

CONCLUSIONS

The results of research on the pathogenesis of idiopathic Parkinson's disease gathered so far, allow one to posit that the initial locus of the pathology is decline of the nigrostriatal interaction that may be triggered among others by faulty turnover of the striatal GABA interneurons. Adult striatal neurogenesis in humans appears to be a productive lifelong process. It has been retained during human evolution, to provide movement adaptability. Continuous turnover of GABA-interneurons seems essential for activity-dependent adaptive remodeling of the striatal system. Firstly, it contribute to functional adjustment of the striatal input: it controls its gain, the input threshold and selectivity. Secondly, it determines efficiency of network remodeling and adaptability during motor learning. In this context the striatum should be considered as a part of 'movement memory system'. It adjusts functioning of the nigrostriatal input to individual's motor behavior. Unfortunately, the latter interaction seems to be an additional factor that makes the nigrostriatal system more vulnerable to neurodegeneration. It initiates a 'vicious circle' cascade of neurodegenerative processes, including progressive withdrawal of dopaminergic synaptic input to the striatum, leading

inevitably to decreased motor activity. This, in turn, decreases GDNF expression within the striatum that results in progressive damage to both the striatal neuronal turnover and the dopaminergic input. This process is manifested initially by non-motor symptoms and then spreads into the dorsal striatum, resulting in the appearance of motor symptoms. Therefore, the search for new therapies in PD should now focus on the GABAergic striatum. In the light of the present knowledge, however, it would be rather naive to posit that we can stop or totally reverse the ageing and all neurodegenerative processes within the brain. However, if we manage to slow down functional decline of the nigrostriatal interaction we will be able to improve quality of life of millions patients with idiopathic PD.

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REFERENCES

- Adlaf EW, Mitchell-Dick A, Kuo CT (2016) Discerning neurogenic vs. non-neurogenic postnatal lateral ventricular astrocytes via activity-dependent input. *Front Neurosci* 10: 111. doi: 10.3389/fnins.2016.00111.
- Androutsellis-Theotokis A, Rueger MA, Park DM, Mkhikian H, Korb E, Poser SW, Walbridge S, Munasinghe J, Koretsky AP, Lonser RR, McKay RD (2009) Targeting neural precursors in the adult brain rescues injured dopamine neurons. *Proc Natl Acad Sci U S A* 106: 13570–13575.
- Bédard A, Cossette M, Lévesque M, Parent A (2002) Proliferating cells can differentiate into neurons in the striatum of normal adult monkey. *Neurosci Lett* 328: 213–216.
- Błaszczak JW (1998) Motor deficiency in Parkinson's disease. *Acta Neurobiol Exp (Wars)* 58: 79–93.
- Błaszczak JW (2016) Parkinson's disease and neurodegeneration: GABA-collapse hypothesis. *Front Neurosci* 10: 269. doi: 10.3389/fnins.2016.00269.
- Borel V, Götz M (2014) Role of radial glial cells in cerebral cortex folding. *Curr Opin Neurobiol* 27: 39–46. doi: 10.1016/j.conb.2014.02.007.
- Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K (2004) Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 318: 121–134.
- Brazel CY, Romanko MJ, Rothstein RP, Levison SW (2003) Roles of the mammalian subventricular zone in brain development. *Prog Neurobiol* 69: 49–69. doi: 10.1016/S0301-0082(03)00002-9.
- Brichta L, Greengard P (2014) Molecular determinants of selective dopaminergic vulnerability in Parkinson's disease: an update. *Front Neuroanat* 8: 152. doi: 10.3389/fnana.2014.00152.
- Cenci MA (2007) Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia. *Trends Neurosci* 30: 236–243. doi: 10.1016/j.tins.2007.03.005.
- Chaudhuri KR, Healy DG, Schapira AHV (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 5: 235–245.
- Cicchetti F, Prensa L, Wu Y, Parent A (2000) Chemical anatomy of striatal interneurons in normal individuals and in patients with Huntington's disease. *Brain Res Brain Res Rev* 34: 80–101.
- Cohen AD, Tillerson JL, Smith AD, Schallert T, Zigmond MJ (2003) Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF. *J Neurochem* 85: 299–305.
- Curtis MA, Kam M, Faull RL (2011) Neurogenesis in humans. *Eur J Neurosci* 33: 1170–1174. doi: 10.1111/j.1460-9568.2011.07616.x.
- Damodaran S, Evans RC, Blackwell KT (2014) Synchronized firing of fast-spiking interneurons is critical to maintain balanced firing between direct and indirect pathway neurons of the striatum. *J Neurophysiol* 111: 836–848. doi: 10.1152/jn.00382.2013.
- Dayer AG, Cleaver KM, Abouantoun T, Cameron HA (2005) New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. *J Cell Biol* 168: 415–427.
- Doposo-Reyes IG, Rico AJ, Roda E, Sierra S, Pignataro D, Lanz M, Sucunza D, Chang-Azancot L, Lanciego JL (2014) Calbindin content and differential vulnerability of midbrain efferent dopaminergic neurons in macaques. *Front Neuroanat* 8: 146. doi: 10.3389/fnana.2014.00146.
- Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, Possnert G, Druid H, Frisén J (2014) Neurogenesis in the striatum of the adult human brain. *Cell* 156: 1072–1083.
- Eserian JK (2013) Vitamin D as an effective treatment approach for drug abuse and addiction. *J Med Hypotheses Ideas* 7: 35–39. doi:10.1016/j.jmhi.2014.02.002.
- Fahn S (2008) The history of dopamine and levodopa in the treatment of Parkinson's disease. *Movement Disord* 23(Suppl 3): S497–S508.
- Goedert M (2015) Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Ab, tau, and a-synuclein. *Science* 349: 1255555. doi: 10.1126/science.1255555.
- Göritz C, Frisén J (2012) Neural stem cells and neurogenesis in the adult. *Cell Stem Cell* 10: 657–659.
- Grillner S, Hegglin J, Ménard A, Saitoh K, Wikström MA (2005) Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. *Trends Neurosci* 28: 364–370.
- Grosch J, Winkler J, Kohl Z (2016) Early degeneration of both dopaminergic and serotonergic axons – a common mechanism in Parkinson's Disease. *Front Cell Neurosci* 10: 293. doi: 10.3389/fncel.2016.00293.
- Hu H, Gan J, Jonas P (2014) Fast-spiking, parvalbumin⁺ GABAergic interneurons: from cellular design to microcircuit function. *Science* 345(6196): 1255263. doi: 10.1126/science.1255263.
- Ibáñez CF, Andressoo JO (2017) Biology of GDNF and its receptors – Relevance for disorders of the central nervous system. *Neurobiol Dis* 97: 80–89. doi: 10.1016/j.nbd.2016.01.021.
- Kirik D, Georgievska B, Björklund A (2004) Localized striatal delivery of GDNF as a treatment for Parkinson disease. *Nat Neurosci* 7(2): 105–110.
- Koós T, Tepper JM (1999) Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nat Neurosci* 2: 467–472. doi: 10.1038/8138.
- Koós T, Tepper JM (2002) Dual cholinergic control of fast-spiking interneurons in the neostriatum. *J Neurosci* 22: 529–535.
- Lapchak PA, Gash DM, Collins F, Hilt D, Miller PJ, Araujo DM (1997) Pharmacological activities of glial cell line-derived neurotrophic factor (GDNF): preclinical development and application to the treatment of Parkinson's disease. *Exp Neurol* 145: 309–321. doi:10.1006/exnr.1997.6501.
- Lapchak PA, Miller PJ, Jiao S, Araujo DM, Hilt D, Collins F (1996) Biology of glial cell line-derived neurotrophic factor (GDNF): implications for the use of GDNF to treat Parkinson's disease. *Neurodegeneration* 5: 197–205.
- Lin LF, Doherty DH, Lile JD, Bektess S, Collins F (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* 260: 1130–1132.

- LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, Kostyk SK, Thomas K, Sarkar A, Siddiqui MS, Tatter SB, Schwalb JM, Poston KL, Henderson JM, Kurlan RM, Richard IH, Van Meter L, Sapan CV, Doring MJ, Kaplitt MG, Feigin A (2011) AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol* 10: 309–319.
- Marsh SE, and Blurton-Jones M (2017) Neural stem cell therapy for neurodegenerative disorders: The role of neurotrophic support. *Neurochem Int* 2017. doi: 10.1016/j.neuint.2017.02.006.
- Morale MC, Serra PA, L'Episcopo F, Tirolo C, Caniglia S, Testa N, Gennuso F, Giaquinta G, Rocchitta G, Desole MS, Miele E, Marchetti B (2006) Estrogen, neuroinflammation and neuroprotection in Parkinson's disease: glia dictates resistance versus vulnerability to neurodegeneration. *Neuroscience* 138: 869–878.
- Mosharov EV, Larsen KE, Kanter E, Phillips KA, Wilson K, Schmitz Y, Krantz DE, Kobayashi K, Edwards RH, Sulzer D (2009) Interplay between cytosolic dopamine, calcium, and alpha-synuclein causes selective death of substantia nigra neurons. *Neuron* 62: 218–229.
- Paratcha G, Ibáñez CF, Ledda F (2006) GDNF is a chemoattractant factor for neuronal precursor cells in the rostral migratory stream. *Mol Cell Neurosci* 31(3): 505–514. doi: 10.1016/j.mcn.2005.11.007.
- Pellicano C, Benincasa D, Pisani V, Buttarelli FR, Giovannelli M, Pontieri FE (2007) Prodromal non-motor symptoms of Parkinson's disease. *Neuropsychiat Dis Treat* 3: 145–152.
- Pissadaki EK, Bolam JP (2013) The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease. *Front Comput Neurosci* 7: 13. doi: 10.3389/fncom.2013.00013.
- Rodrigo J, Alonso D, Bentura ML, Castro-Blanco S, Encinas JM, Fernández AP, Fernández-Vizarra P, Richart A, Santacana M, Serrano J, Martínez A (2002) Physiology and pathophysiology of nitric oxide in the nervous system, with special mention of the islands of Calleja and the circumventricular organs. *Histol Histopathol* 17: 973–1003.
- Samuels ER, Szabadi E (2008) Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function. Part I: principle of functional organisation. *Curr Neuropharmacol* 6: 235–253.
- Schapira AHV (2007) Future directions in the treatment of Parkinson's disease. *Mov Disord* 22(Suppl 17): S385–S391.
- Schapira AHV (2008) Progress in neuroprotection in Parkinson's disease. *Eur J Neurol* 15(Suppl 1): 5–13.
- Strömberg I, Björklund L, Johansson M, Tomac A, Collins F, Olson L, Hoffer B, Humpel C (1993) Glial cell line-derived neurotrophic factor is expressed in the developing but not adult striatum and stimulates developing dopamine neurons in vivo. *Exp Neurol* 124: 401–412.
- Tepper JM, and Bolam JP (2004) Functional diversity and specificity of neostriatal interneurons. *Curr Opin Neurobiol* 14: 685–692.
- Wang C, Liu F, Liu YY, Zhao CH, You Y, Wang L, Zhang J, Wei B, Ma T, Zhang Q, Zhang Y, Chen R, Song H, Yang Z (2011) Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. *Cell Res* 21: 1534–1550.
- Wei B, Nie Y, Li X, Wang C, Ma T, Huang Z, Tian M, Sun C, Cai Y, You Y, Liu F, Yang Z (2011) Emx1-expressing neural stem cells in the subventricular zone give rise to new interneurons in the ischemic injured striatum. *Eur J Neurosci* 33: 819–830.
- Wesson DW, Wilson DA (2011) Sniffing out the contributions of the olfactory tubercle to the sense of smell: hedonics, sensory integration, and more?. *Neurosci Biobehav Rev* 35: 655–668.
- Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M (2013) Sleep drives metabolite clearance from the adult brain. *Science* 342(6156): 373–377. doi: 10.1126/science.1241224.
- Yadav HP, Li Y (2015) The development of treatment for Parkinson's disease. *Advances in Parkinson's Disease* 4: 59–78. doi: 10.4236/apd.2015.43008.
- Yager LM, Garcia AF, Wunsch AM, Ferguson SM (2015) The ins and outs of the striatum: role in drug addiction. *Neuroscience* 301: 529–541. doi: 10.1016/j.neuroscience.2015.06.033.
- Zachrisson O, Zhao M, Andersson A, Dannaeus K, Häggblad J, Isacson R, Nielsen E, Patrone C, Rönnholm H, Wikström L, Delfani K, McCormack AL, Palmer T, Di Monte DA, Hill MP, Janson Lang AM, Haegerstrand A (2011) Restorative Effects of Platelet Derived Growth Factor-BB in Rodent Models of Parkinson's Disease. *J Parkinsons Dis* 1: 49–63.