The basal ganglia and its role in Parkinson's disease.

Author: *Maria Pia Tabone*

Supervisor: *Professor Richard Muscat B.Sc.(Hons)(Liv.),M.Sc.(Lond.),Ph.D.(Lond.)*

Abstract

The basal ganglia consist of a collection of subcortical nuclei that play an essential role in the control of motor function but also too in cognition. These nuclei can in turn be divided according to their projections into input, output and intrinsic nuclei. The classical basal ganglia model was developed to explain the circuits within this structure. It consists of a direct pathway that promotes movement, an indirect pathway that inhibits movement and a dopaminergic pathway that modulates movement. Disorders are seen to arise due to a dysfunction in a part of the circuit. Such can be arranged in a spectrum that consists of hyperkinetic disorders on one side and hypokinetic disorders on the other. By identifying which parts of the circuit is dysregulated, one would be able to design therapies to elevate these symptoms.

Keywords: Basal ganglia, Parkinson's disease, movement disorders

Introduction

The basal ganglia can be defined as a series of nuclei that are located deep within the telencephalon (1,2). They are primarily involved in voluntary motor control. This collection of structures are also seen to be involved in other processes, such as those motivational, cognitive and emotional that eventually lead to movement being carried out. (3,4). In fact the associate, limbic, motor and orbitofrontal cortico- basal ganglia-thalamo-cortical loops have all been identified. For the purpose of this review emphasis will be made on the motor cortico-basal ganglia-thalamo-cortical loop, due to it being the most relevant in motor pathophysiology (5).

The classical model of Parkinson's disease

The classic basal ganglia model was developed in 1980's and is based on the cortico- basal ganglia- thalamo- cortical loop. It can be simplified as follow; projections arise from the motor and association cortex and terminate on the striatum (Figure 1). From here, impulses move to the pallidum that is the internal segment of the Globus pallidus (GPi) and the substantia nigra pars recticularis (SNpr). These in turn project onto the thalamus which then sends neurons back to the motor cortex (3). This model states that cortical activation, as a result of the intention to carry out a desired movement, leads to glutamate release on the striatal neurons. This results in the activation of the medium spiny neurons (MSN). Being inhibitory due to

GABA release, MSN result in SNpr and the GPi deactivation. Since now the SNpr and GPi have been inhibited, the GABA release from the SNpr and GPi is reduced and thus inhibition of subsequent structures, which include the thalamus, is lost. This allows for activation of venterolateral and venteroanterior thalamus. Hence these neurons can now activate the primary motor cortex, the premotor and supplementary motor cortex. This is known as the direct pathway. Furthermore, MSNs that project from the striatum to the pallidum also project onto the external segment of the Globus pallidus (GPe) via the indirect pathway. MSNs release GABA onto the GPe and result in its deactivation. Hence now the subthalamic nucleus (STN) which was previously inhibited by the GPe will be activated. This leads to the activation of the GPi because of glutamate release from the STN. The STN also activates the SNpr through glutamate release. Both the SNpr and the GPi contain inhibitory GABA releasing neurons, hence once activated they will inhibit the superior colliculus and the thalamic nuclei respectively. As a result, excitatory impulses arising from the thalamus and projecting to the motor cortex are abolished. Hence, the thalamus will no longer be able to stimulate the cortex and thus movement is revoked. (6-8) The direct and indirect pathway are theorised to work simultaneously so as to select intended movement and supress the undesired ones (9). This model also states that dopamine released from the substantia nigra pars compacta (SNpc) plays a major role in providing modulation of the inputs of the cortex from the striatum. The modulation depends on whether dopamine binds to D1 receptors located on neurons participating in the direct pathway causing excitation or to D2 receptors located on neurons in the indirect pathway, causing inhibition (10).

It should be noted that the STN receives additional projections that arise directly from the cerebral cortex, these are excitatory impulses that form part of the hyperdirect pathway. Activation of this pathway leads to inhibition of the thalamus via the activation of the SNpr as previously described and hence no movement occurs (6)

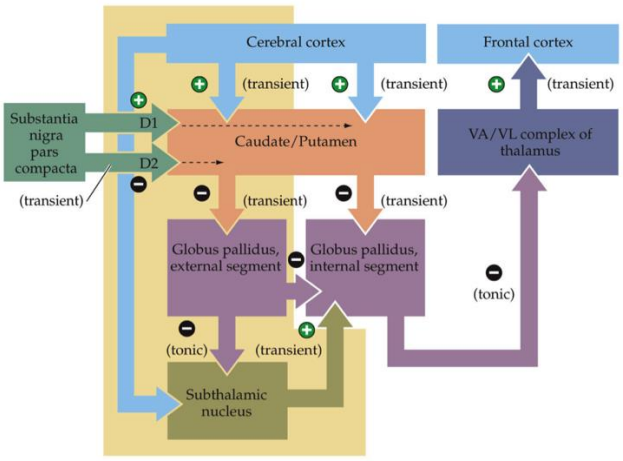


Figure 1: The classical basal ganglia model demonstrating the direct, indirect pathway and hyper-direct pathways. Retrieved from White *et al.,* 2001.

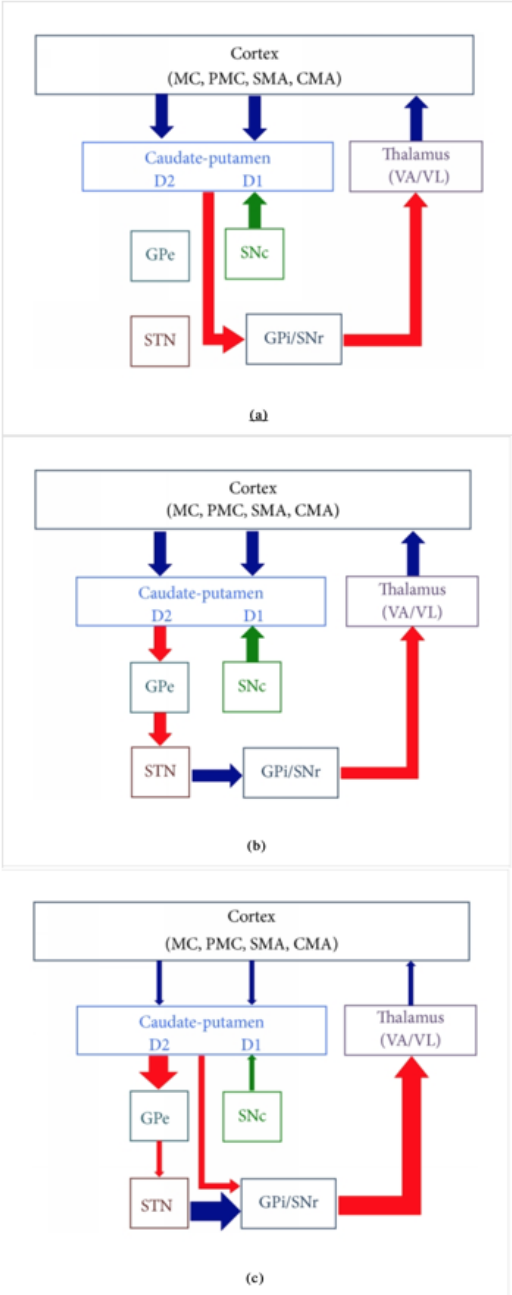
Overview of basal ganglia movement disorders

In terms of disorders that can arise, one can compose a spectrum with two opposing ends; hyperkinetic disorders, characterised by involuntary movement, like Huntington's disorder on one side and hypokinetic disorders, characterised by a diminished motor activity (excluding the resting tremor), like Parkinson's disease on the other side. It is suggested that involuntary movements seen in hyperkinetic disorders are a result of a diminished inhibitory output from the basal ganglia. This results in a decreased suppression of fronto-cortical areas which in turn initiate movement. The reversal of this is observed in hypokinetic disorders (11).

Parkinson's disease

Parkinson's disease (PD) collectively refers to neurodegenerative conditions that affect different parts of the brain. Parkinsonism in turn refers to the motor impairments experienced such as akinesia, bradykinesia, rigidity and resting tremors. These motor impairments are largely attributed to a diminished dopamine in the basal ganglia. It has been shown that parkinsonism is a complex connectivity disorder that arises as a result of dysfunctional activity in a group of neurons mainly in substantia nigra. These neurons in turn alter the synchrony, excitation, oscillatory activity and also sensory response of regions in the cerebral cortex that are involved in movement planning and execution. Signs, including both motor and non-motor will start to appear once substantial loss of nigrostriatal neurons has taken place. (12)

Degeneration of the dopaminergic neurons in the SNpc is observed, while some of these neurons take decades to degenerate, neurons that project to the putamen do so at a faster rate. (12). Dopamine loss results in the reduction in post synaptic potential facilitation in the direct pathway and a reduction in the post synaptic potential inhibition in the indirect pathway, allowing for the latter to take over (Figure 2). This results in an abnormally high inhibition arising from the basal ganglia reducing the thalamic activation of upper motor neurons within the cortex hence resulting in the hypokinesia experienced (6). Thus, dopaminergic neuron loss leads to GPe neurons firing less and GPi, STN and SNpr cells with a greater spontaneous discharge and increased response to cortical stimulation. Studies have shown that there is also a change in their firing patterns as well as firing rates. An increased tendency to fire in a burst of action potentials was observed in the striatum and STN as well as enhanced



rhythmic/oscillatory activity. In addition, there was also increased synchrony between neighbouring neurons. Burst activity of the Globus pallidus and STN was seen to be more prolonged **Figure 1:** A simple representation of the direct pathway in (a), indirect pathway in (b) and the alteration observed in Parkinson's Disease (**blue arrows**: excitatory glutaminergic pathways; **red arrows**: inhibitory Gabaergic pathways; **green arrows**: dopaminergic pathways). Retrieved from Magrinelli *et al.,* 2016.

in terms of its duration, as well as in the length of the individual burst (Figure 3). The

presence of abnormal oscillatory activity within each nucleus and among structures in Parkinson's disease has also been recognised. This may in turn contribute to the development of parkinsonism. This is because the oscillatory activity in a single cell in the basal ganglia is reflected in the cerebral cortex. (12,15).

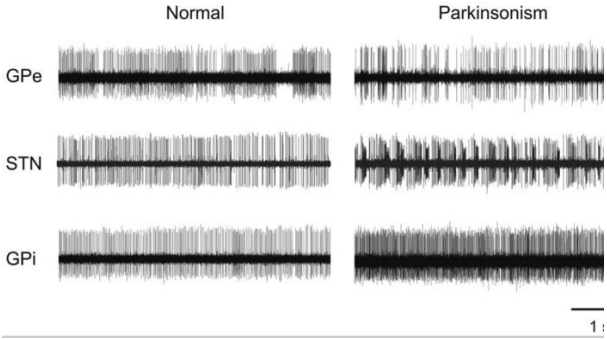


Figure 3: *A figure that illustrates the change in single cell activity as observed in normal and MPTP treated monkeys (to represent parkinsonian patients). Each segment represents a 5s duration. Retreived from Galvan and Wichmann, 2008.*

In addition to this, dopamine loss also results in other secondary changes such as the reduction in dendritic spine density of the MSNs, especially those present in the putamen. This would have major pathophysiological significance as it results in major alterations in the corticostraital and the thalamostriatal projections as it may account for diminished glutamatergic input (Figure 4). Studies have shown that D2 receptor expressing MSNs are affected to a greater extent and loss of spines may be a result of calcium channel dysregulation. Furthermore, dopamine reduction also leads to changes in both sensitivity and density of dopamine receptors (12,15). A study was conducted by by Gerfen and his colleagues using rats with lesions nigrostriatal dopamine pathway induced by 6-hydroxydopamine to serve as Parkinson's disease models. The latter showed that D1 receptor mRNA was reduced in the MSNs participating in the direct pathway and D2 receptor mRNA was increased in MSNs participating in the indirect pathway (16).

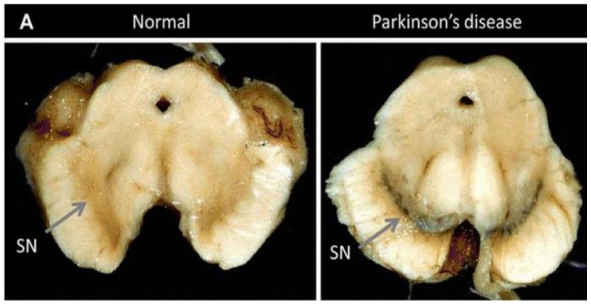


Figure 4: Anatomical changes observed a result of substantia nigra (SN) dopaminergic neuron degeneration Retrieved from Mandel *et al.,* 2010.

Since the pathophysiology underlying Parkinson's disease is dopamine depletion, indicated treatment is to provide pharmaceutical products that replace this dopamine loss. In fact, L- DOPA (levodopa) a dopamine precursor has been shown to be quite successful and more to the point, is considered to be the gold standard for PD patients. This precursor encourages dopamine synthesis by midbrain neurons (17). Additional drugs can be added to L – DOPA so as to increase L- DOPA's half-life, hence allowing for a reduced dose to be prescribed. An example of the latter is Carbidopa, a dopamine decarboxylase inhibitor. This block peripheral breakdown of L- DOPA, as it is unable to cross the blood brain barrier. Hence, increasing the amount of L- DOPA delivered to the brain, without an increase in L- DOPA dose (18). None the less, some patients also experienced dramatic side effects when taking L- DOPA like emotional disturbances and dyskinesia (17). In fact, L-DOPA dyskinesia is one of the most denilitating side-efects faced by patients suffering from this disease who are taking this particular treatment. This occurs when antiparkinsonian effects of this drug are maximal (19). The on and off phenomenon can be used to describe the effects of L- DOPA after long term use. In the off-phase, patients experience negative symptoms such as rigidity due to the lack of drug efficacy. In contrast, the on phase describes positive symptoms which can range from normal

movement to abnormal movement. Sometimes the term intermediate is used to describe normal movement (24). This phenomenon is thought to arise due to pulsatile administration of L –DOPA (23). This leads to an increased gene expression of the neurotransmitter in the direct pathway while failing to normalise the pathogenic upregulation of gene expression in the indirect pathway .Recent studies have indicated that dyskinesia experienced with this treatment is a result of these neurotransmitter changes (20,21).

Another way of targeting this disease is by increasing the activity of the ventrolateral and ventroanterior nuclei of the thalamus. This can be done by reducing the activity of the GPi. In addition, one can also aim to reduce STN activity which would also result in a reduction in GPi impulse generation. This can be done through deep brain stimulation, a recent advancement of neuro-medicine in the last two decades that involves the delivery of adjustable stimulation which in turn can offer a therapeutic effect for disorders related to an abnormal circuitry, which allows for neuromodulation of these targets described. This technique is actually applied to modulate the activity of the STN and GPi that are hyper activated. Improvements in the quality of life of patients that underwent this procedure were reported even in those with advanced PD. When deep brain stimulation is used along with L-DOPA treatment, potentiation of their beneficial outcomes occurs resulting in decreased PD symptoms (17,24).

PD arises from dopamine producing cell degeneration in the substantia nigra pars compacta, hence replacement of these cells can also be a way of increasing dopamine production. Treatments have been developed to target this by providing nigral cell transplantation. This method utilises embryonic midbrain neurons which are then transplanted into adult brains. These neurons are then able to form axons in the scar tissue present resulting in the innervation to be resorted (17). A somewhat similar approach was also devised using genetically modified cells that contain the necessary genes to produces tyrosine hydroxylase, an enzyme utilised in the dopamine production (6).

Conclusion

Despite information with regards to the core structure within the basal ganglia being available for some years, the actual role of these structures as well as its projections to both cortical and subcortical structures is still in a process of development, with more circuits both intrinsic and extrinsic being discovered. Thus, more research is required in this grey area. This allows for the ability to link clinical observations to those modelled in the laboratory to be able to devise new treatments hence potentially increasing the life expectancy and quality of life of patients who have both physical and cognitive impairments as a result of a dysfunction in this major core structure.

Declarations

Conflict of interest: N.A.

Ethical statement: N.A.

References

1. Graybiel AM. The basal ganglia. Current biology 2000 Jul 13;10(14): R509-R511.
2. Mas NG, Said HM, Tosun M, Yonguc N, Soysal Y, Karabekir HS. Anatomical, Biological, and Surgical Features of Basal Ganglia [Internet]. InTech; 2017. Available from: https://www.intechopen.com/books/human-anatomy-reviews-and-medical-advances/anatomical-biological-and-surgical-features-of-basal-ganglia

3. Lanciego JL, Luquin N, Obeso JA. Functional Neuroanatomy of the Basal Ganglia. 2012 Dec 1;2(12): a009621. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23071379
4. Haber SN. The basal ganglia. Nestor GJ, editor. CRC Press; 2013. (Scientific basis for treatment of Parkinson's disease)
5. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Arbizu J, Gimenez-Amaya JM. The Basal Ganglia and Disorders of Movement: Pathophysiological Mechanisms. 2002 Apr 1;17(2):51–5. Available from: https://journals.physiology.org/doi/full/10.1152/nips.01363.2001
6. White Leonard E, Hall William C. Modulation of movement by the basal ganglia. United States of America: Oxford university press; 2001. 17 p. (Neuroscience).
7. Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Direct and indirect pathways of basal ganglia: a critical reappraisal. 2014 Aug;17(8):1022–30. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25065439
8. PhD H John E., MS H Michael E.MD. Cerebellum and Basal Ganglia Contributions to Overall Motor Control [Internet]. Elsevier; 2021. 16 p. (Guyton and Hall Textbook of Medical Physiology). Available from: https://www.clinicalkey.es/playcontent/3-s2.0-B9780323597128000576
9. Yin HH. The Basal Ganglia in Action [Internet]. Los Angeles, CA: SAGE Publications; 2017. p. 299–313. (The Neuroscientist; vol. 23). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6500733/
10. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, et al. Pathophysiology of the basal ganglia in Parkinson's disease. 2000;23(10): S8–19. Available from: http://dx.doi.org/10.1016/S1471-1931(00)00028-8
11. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis [Internet]. New York, NY: Elsevier Inc; 2001. p. 190–8. (Paediatric Neurology; vol. 25). Available from: http://dx.doi.org/10.1016/S0887-8994(01)00262-4
12. Galvan A, Wichmann T. Pathophysiology of Parkinsonism. 2008;119(7):1459–74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2467461/
13. Francesca M, Alessandro P, Pierluigi T, Angela F, Laura R, Nicola S, et al. Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. 2016;2016:18. Available from: https://doi.org/10.1155/2016/9832839
14. Mandel S, Morelli M, Halperin I, Korczyn A. Biomarkers for prediction and targeted prevention of Alzheimer's and Parkinson's diseases: evaluation of drug clinical efficacy. 2010 Jun;1(2):273–92. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23199065
15. Galvan A, Devergnas A, Wichmann T. Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state. 2015; 9:5. Available from: https://www.frontiersin.org/articles/10.3389/fnana.2015.00005/full
16. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Jr M FJ, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. 1990 Dec 7;250(4986):1429–32. Available from: http://www.sciencemag.org/cgi/content/abstract/250/4986/1429
17. Iarkov A, Barreto GE, Grizzell JA, Echeverria V. Strategies for the Treatment of Parkinson's Disease: Beyond Dopamine. 2020;12:4. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2020.00004/full
18. Emily L, Prasanna T. Carbidopa. StatPearls; 2021
19. Lee Chong S. Levodopa-induced dyskinesias; mechanisms and management. 2001; 43:206–9. Available from: https://bcmj.org/articles/levodopa-induced-dyskinesia-mechanisms-and-management
20. Henry B, Crossman AR, Brotchie JM. Effect of repeated L-DOPA, bromocriptine, or lisuride administration on preproenkephalin-A and preproenkephalin-B mRNA levels in the striatum of the 6-hydroxydopamine-lesioned rat. Exp Neurol 1999;155:204-220.[PubMed Abstract]
21. Lee CS, Cenci MA, Schulzer M, et al. Embryonic ventral mesencephalic grafts improve levodopa-induced dyskinesia in a rat model of Parkinson's disease. Brain 2000;123:1365-1379.[PubMed Abstract]
22. Dubuis R. 'On-Off' Phenomenon: Description, Incidence and Management. 1987;27(Suppl 1):3–8. Available from: https://www.karger.com/Article/FullText/116169
23. Fahn S. Parkinson Disease, the Effect of Levodopa, and the ELLDOPA Trial. 1999 May 1;56(5):529–35. Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/774960
24. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. 2019 Mar;15(3):148–60. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397644/