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RESEARCH ARTICLE

ANATOMY AND RELEVANCE IN PHARMACOTHERAPY OF DISEASES RELATED TO BASAL GANGLIA

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ABSTRACT

Basal ganglia are group of subcortical nuclei which are components of modular circuits involving cerebral cortex, thalamus and brain stem related with cortical functions. Basal ganglia includes four to five distinct loop which is responsible for parallel processing of information and grouped into two distinct direct and indirect pathways. Thus, this dual system provides a motor centre exhibiting both excitatory and inhibitory effect. These circuits are involved in movement disorders categorized as Hyperkinetic and Hypokinetic movement disorder. In recent year, with the upcoming studies it has been clear that functions of basal ganglia not only focuses motor disturbances but also involves cognitive and emotional functions as well.

INTRODUCTION

Basal ganglia: The word basal originates from the fact that this structure is located at the base of forebrain. Ganglia has been termed as a misnomer as the neural network in peripheral nervous system is called "GANGLIA" but in central nervous system, these neural clusters are called nuclei. Basal ganglia acts as a functional network and forms a major centre in extrapyramidal motor system and is known for the motor function. Basal ganglia is involved in many neuronal pathways along with the cortex is responsible for emotion, motivation motor, cognitive functions and limbic behaviour. The Striatum receives cortical input through thalamus and projects to frontal lobe areas involved in motor planning. The circuits through which processing of information takes place:-

- Regulates cortex having automatic and voluntary motor response to pyramidal system.
- Reinforce wanted behaviour and suppress unwanted behaviour.
- This is involved in initiating movement and spatial working memory.

These circuit plays an important role in attention, learning and potentiation of behaviour.

Basal ganglia in regulation of motor activity have been demonstrated in animal studies. Several studies revealed that Basal ganglia are involved both in motor planning, motor execution and sensory-motor integration. Though, the role of basal ganglia in movement has been clear but the function of Basal ganglia has been dramatically modified from sensory-motor network to more complex and complicated network mediating functions like emotion, motivation and cognition.

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Different regions of Basal ganglia nuclei not only serves sensory motor function but also limbic and cognitive activity. Ventral area of Basal ganglia is responsible for reward and reinforcement and is responsible for development of addiction and habits. Central area of Basal ganglia helps in cognitive functions like learning and working memory tasks .The pathology of Basal ganglia has been linked with schizophrenia, drug addiction, and obsessive compulsive disorder affects the ventral area of Basal ganglia where as dorsal area of Basal ganglia is affected by disease impairing motor control. Though studies has been conducted to understand anatomy, physiology and pharmacology of Basal ganglia but their exact motor function is still debated. The recent study shows that sub cortical nuclei along with frontal cortex through complex corticobasal ganglia network carry out complex behaviour. This review summarises the basal ganglia organisation associated with cortical function directed to carry out other physiological and behavioural actions.

Anatomy of Basal Ganglia

The nervous system is classified based on three primitive vesicles. The primary vesicle form neural tube of foetus which includes prosencephalon, mesencephalon and rhombencephalon. During the process of development, Basal ganglia is formed by tangential migration of cells which is directed by lateral and medial ganglionic eminences. Basal ganglia forms a functional component of telencephalon (forebrain) (Fig.1).

According to the classical anatomists basal ganglia is defined as large deep collection of grey masses embedded in white matter of each cerebral hemisphere. Basal ganglia was described according to the topographic classifications. In 1786, thalamus was regarded as part of basal ganglia in work of vicq d' Azyr.

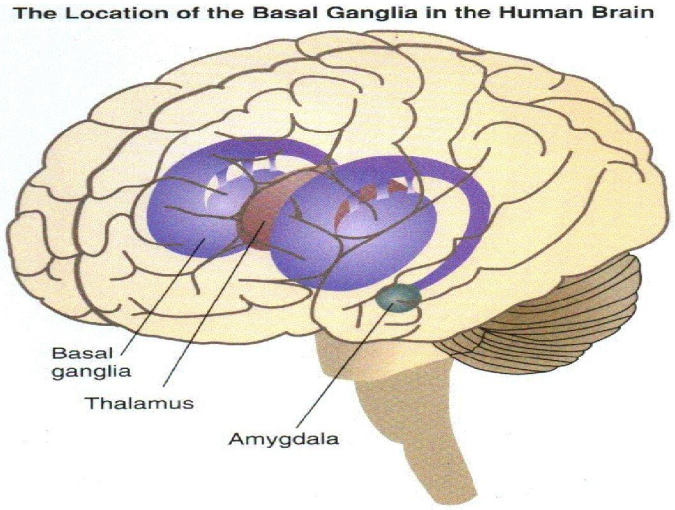


Fig.1. Location of Basal ganglia

Components of Basal Ganglia

The components of Basal ganglia (Fig.2 and Fig.3) includes caudate nucleus, lentiform nucleus, putamen, Globus pallidus along with substantia nigra (SN) and Subthalamic nucleus (STh). The Caudate nucleus and the putamen forms the neostriatum. 'Striatum' word is used to describe the striated appearance due to arrangement of corticofugal, striatofugal and corticopetal axons. This region is also defined as dorsal striatum. The largest of the structure is corpus striatum. Neostriatum is well developed in human beings which involves both caudate nucleus and putamen. Caudate nucleus is a shaped as comet along lateral side of lateral ventricle.It has a large head at front with narrow dorsal body and thin tail passing ventrally along temporal horn of the ventricle and ending at the amygdaloid body. The inferior part of head is attached to the putamen at ventral part at nucleus acumbens level. Head of caudate nucleus and putamen are connected by thin bridges of grey matter. Putamen is a shell shaped structure located medially to the cortex of insula and surrounded laterally by external capsule, medially by lateral medullary lamina of the globus pallidus and superiorly by white matter of corona radiata. The globus pallidus (paleostriatum) has two segments medial (internal) and lateral (external). Both are located medially to putamen.The putamen and globus pallidus are shaped like lens and are referred as lenticular nucleus. The lateral globus pallidus is separated from the putamen by lateral medullary lamina and the medial globus pallidus is separated from the lateral by medial medullary lamina.

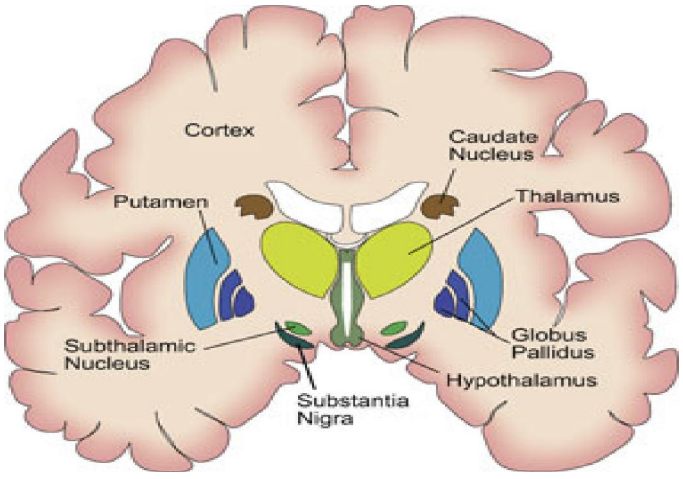
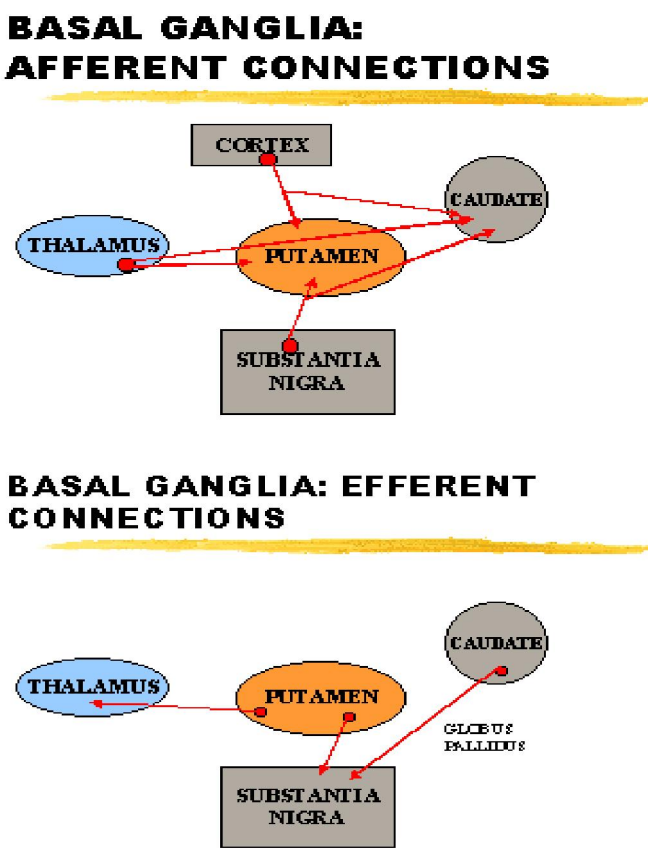


Fig.2. The basal ganglia comprise several interconnected brain areas deep in the cerebral cortex



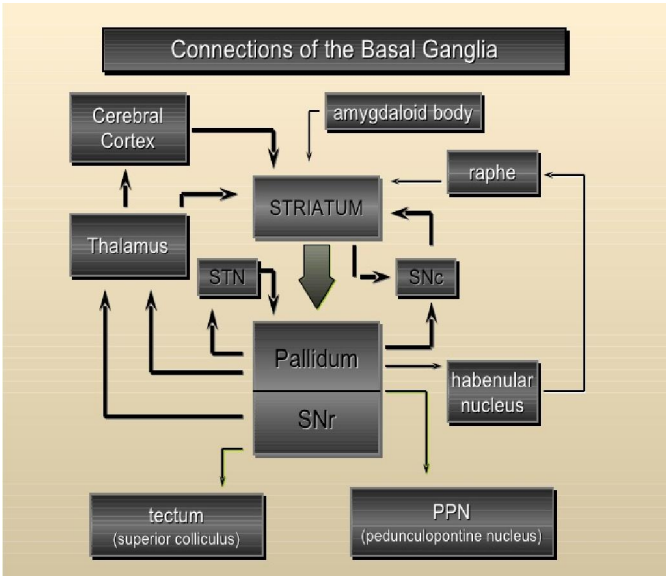


Fig. 3. Connections of basal ganglia including afferent and efferent connections

Sub thalamic nucleus is a small lenti form nucleus situated at border between midbrain and diencephalon. This is surrounded medially by posterior limb of the internal capsule, dorsally by the lenticular fasciculus and ventrally by the zona incerta. T1- and T2-weighted MR images easily demarcated the subthalamic nucleus which is surrounded by white fibres. The substantia nigra is located at the ventral tegmentum of midbrain and the pars compacta is the largest part. In order to understand the motor and cognitive functions of normal as well as diseased brain, understanding the anatomical and functional organisation of basal ganglia is needed. The complex extrapyramidal motor system is governed by basal ganglia, opposite to pyramidal motor system which is governed by corticobulbar and corticospinal pathways. Since the end of the 19th century, basal ganglia is considered as a motor centre: Motor centres guiding

automatic or sub-voluntary activities located at corpus striatum which is responsible for organisation of habitual or automatic movements [1].Basal ganglia do not make any direct output connections to spinal cord[2] due to which pyramidal system mediates motor action[3]. Basal ganglia participated in many neuronal pathways where it has motor, emotional, motivational, associative and cognitive functions[4,5,6,7,8,9,10].Striatum is a central selection device[11] where basal ganglia was found to have a role in error connection mechanisms[12]. Research in human and nonhuman primates took place to introduce new concepts [13,14] as well as ex vivo method of learning was demonstrated to study functional basal ganglia anatomy[15]. In the year 1960, striato-pallido-nigral-network ("Nauta-Mehler loop") came into picture [16]. Neo cortex is the place where transmission circuit of basal ganglia originates [17,18]. Inputs from associative areas of the neo cortex and sensorimotor cortex (dorsal basal ganglia circuit) were received by the caudate and putamen, where as inputs from the orbitofrontal cortex and other limbic cortical areas as well as from the hippocampus and the amygdale (ventral basal ganglia circuit) [19,20], were received by nucleus acumbens. Both the dorsal and ventral basal ganglia circuits started in cerebral cortex and extended throughout the neostriatum, paleostriatum and the ventral thalamic nuclei. These circuits reached both motor and premotor area of frontal lobe concerned with the motor planning as well as associative and limbic cortical areas of the frontal lobe [21]. Symptoms in basal ganglia disease was due to five parallel and largely segregated loops which has convergent and integrative mechanism [20,21]. These parallel loops pertaining to motor, oculomotor, cognitive, associative and limbic function is related to major cortical area, which is responsible for maintaining segregated parallel pathways through [4,5,22]

1. Striatum
2. Both segments of the globus pallidus
3. Sub thalamic nucleus
4. Substantia nigra pars reticulata

The convergence of information has been found

- At level of globus pallidus and substantia nigra pars reticulate [23,24,25]
- At level of thalamus[26]
- At axonal collateral within the different nuclei [27]

It was later found that this parallel processing of information which is convergent as well as integrative mechanisms are the reason for various symptoms in basal ganglia disease.

Recently, models based on three main categories were proposed.

- Models of serial processing
- Models of action selection
- Models of reinforcement learning

In the first category, this model includes role of basal ganglia in generation of sequences involving activity pattern. Second category involves model which exerts tonic inhibitory activity by basal ganglia output (Gurney, Prescott and Ridgrave, 2001). Schultz and Dickinson, 2000; Schultz, Tremblay and Hollerman, 2000 provided experimental evidence which suggests that reinforcement learning plays an important role in basal ganglia processing. The dopaminergic (DA) neurons activity was recorded during the performance of behavioural tasks. Schultz and group demonstrated that DA neurons respond to primary rewards and with the progress of experiment, neuron responses shifted from primary reward to reward predicting stimuli. This provided information about the firing of DA neurons and timing of delayed rewards. This model is similar to the temporal difference models.

Multiple neurotransmitters in the basal ganglia

The basal ganglia consists of neurotransmitters which modulates the transfer of information in basal ganglia. GABA- is predominant intrinsic transmitter of basal ganglia. The two most important modes of information transfer are inhibition and disinhibition. 95 % of the neurons in striatum are GABAergic medium spiny neurons. Medium spiny neurons give rise to indirect pathway which contains enkephalin as a co-transmitter. Most of the striatal interneurons as well as neurons in GPe (external pallidal segment), GPi (internal pallidal segment) and SNr (substantia nigra pars reticulata) are also GABAergic which is present in high concentration because striatal and GPe (external pallidal segment) efferents end in the SNr, GPe and GPi. Two types of GABA receptors are GABA-A and GABA-B. GABA-A receptors are inhibitory ionotropic receptors receptors found in postsynaptic membrane mostly. GABA-B receptors are pre- and postsynaptic G-protein coupled receptors. Glutamate- Glutamate is utilized as a neurotransmitter from cortex, pedunculopontine nucleus (PPN) and Centro median nucleus of the thalamus/pf (as inputs to the basal ganglia) as well as intrinsic projections from STN (sub thalamic nucleus).Glutamate receptors are categorised into ionotropic and metabotropic receptors (mGluRs). Ionotropic glutamate receptors i.e NMDA, Kainate and AMPA receptors located postsynaptically throughout the basal ganglia. These are primary receptors used for transfer of information from cortex to striatum and STN, these receptors are involved in learning through long -term depression (LTD) and long-term potentiation (LTP). There are 8 types of ionotropic glutamate receptors which are classified into three groups based on genetic and pharmacological properties. These receptors are located at striatal and extrastriatal site.

Acetylcholine-Most of the acetylcholine is present as neurotransmitters of large spiny interneurons found in basal ganglia. Both muscarinic and nicotinic cholinergic receptors are found in the striatum. Postsynaptic muscarinic receptors inhibit transmitter release from glutaminergic terminals whereas nicotinic receptor activation enhance transmitter release. Dopamine-Dopamine is present in high concentration striatum in dense arborized terminals of projections which originates in SNc (substantia nigra pars compacta). Neurons in the ventral tegmental area contribute to the dopamine supply to the ventral striatum as well as cortex. The important site of extrastriatal dopamine release is SNr where transmitter is released from dendrites of SNc neurons. Dopamine synthesis takes place in dopaminergic terminals which require tyrosine hydroxylase in presence of iron and tetrahydropteridine oxidising tyrosine to 3,4-dihydroxy phenylalanine (Levodopa, L-DOPA). Levodopa is decarboxylated to dopamine by aromatic amino acid decarboxylase (AADC) enzyme which requires pyridoxyl phosphate as a coenzyme. Dopamine acts on G-protein coupled receptors belonging to the D1-family of receptors (comprised of D1- and D5- receptors) and the D2- family of receptors (D2-like receptors, comprised of D2-, D3-, D4- receptors). D1LRs (D1 like receptors) stimulate adenylate cyclase activity and also phosphoinositide hydrolysis, while D2LRs (D2 like receptors) reduce adenylate cyclase activity. In striatum, D1LRs are associated with medium spiny neurons of direct pathway while D2LRs are found as autoreceptors on dopaminergic terminals, as heteroreceptors on cholinergic interneurons and on neurons of indirect pathway.

Actions of dopamine are terminated through presynaptic reuptake. Most of the dopamine is re-incorporated into vesicles while rest is metabolised. Dopamine and its O-methyl derivatives are subjected to action of monoamine oxidase (MAO). MAO is a flavor protein present in the outer membrane of mitochondria.MAO exists in two forms:-

MAO type A- present in catecholaminergic neurons.

MAO type B- present in serotonin containing neurons and in astrocytes.

Reaction with MAO leads to aldehyde corresponding to the amine substrate, H_2O_2 and NH_3. Aldehyde undergo further dehydrogenation to form DOPA, which is the substrate for catechol-O-methyl transferase (COMT) to generate homovanillic acid (HVA).

Intrinsic connections of Basal ganglia

The intrinsic pathways interconnect various basal ganglia structure (Fig. 3 and Fig.4):-

- Striatopallidal pathway- GABAergic inhibitory connection between the striatum and both segments of globus pallidus.
- Striatonigral pathway – GABAergic inhibitory connection between the striatum and the SNr (substantia nigra pars reticulata).
- The globus pallidus external segments is a GABAergic and exerts inhibitory connection to the subthalamic nucleus.
- The subthalamic nucleus is glutaminergic and exerts excitatory connections to both segments of globus pallidus and SNr (substantia nigra pars reticulata).This is the only excitatory pathway.
- The nigrostriatal pathway makes dopaminergic synapse onto striatal neurons.This is known to be a mixed pathway with excitatory effects on some striatal neurons where as inhibitory effects on others.

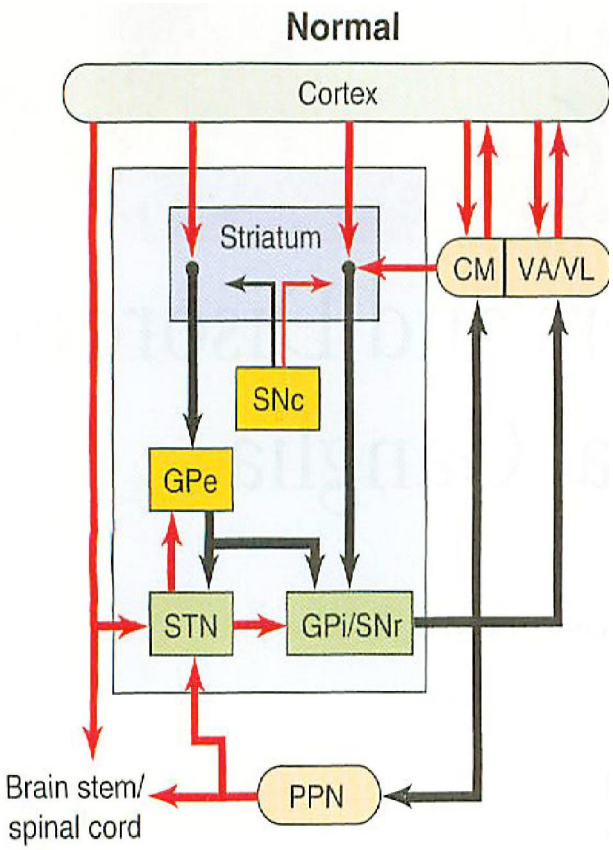


Fig. 4. Anatomical connections within the basal ganglia circuit. GPe, external pallidal segment; STN, subthalamic nucleus; GPi, internal pallidal segment; SNr, substantia nigra pars reticulata; PPN, pedunculo pontine nucleus; CM, centromedian nucleus of the thalamus; VA, ventral anterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; Red arrows denote excitatory connections; black arrows denote inhibitory (GABAergic)connections

Two basic pathways in basal ganglia

The efferent neurons are medium spiny neurons in the striatum has dendritic organization and GABAergic. It has been found that there are some segregation of projections. These efferent neurons from striatum are divided into dual striatal output, part of the neurons projecting to the internal globus pallidus and the substantia nigra pars reticulata (striatal direct output pathway) and part of neurons to external globus pallidus (striatal indirect output pathway) [28]. These dense fibre connections form four to five distinct loops or circuits which is responsible for allowing parallel processing of information through them. There are two distinct pathways in the loop: direct and indirect pathway (Fig. 5).

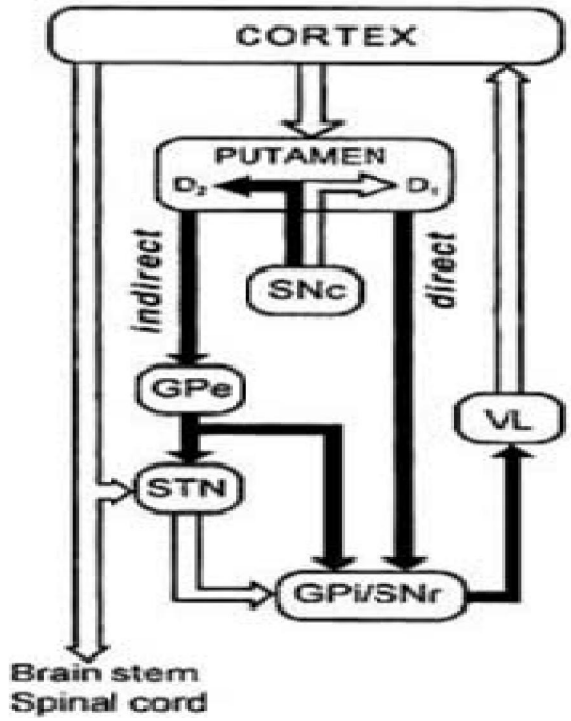


Fig. 5. Overview of motor loop allowing parallel processing of information through direct and indirect pathway. GPe,external pallidal segment; STN, subthalamic nucleus; GPi, internal pallidal segment; SNr, substantia nigra pars reticulata; PPN,pedunculopontine nucleus; CM, centromedian nucleus of the thalamus; VA, ventral anterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus.

Direct pathway- This is directed by dopaminergic D1 receptors (substance P and dynorphin containing neurons) disinhibits the powerful inhibition of GPi/SNr upon VL thalamus which facilitate the influence on motor cortex. Indirect pathway- The indirect pathway is driven by D2-dopamine receptors and enkephalin-containing neurons which exert net inhibitory influence. This dual projection system form a centre-surround mechanisms to focus its effects on selected cortical neurons. The GABAergic output neurons of external globus pallidus exert inhibitory effect on subthalamic glutaminergic neurons which sends excitatory projections to both output nuclei (internal globus pallidus and substantia nigra pars reticulata) of basal ganglia. This duality of projection which is found in the output nuclei of basal ganglia which is projected further to the different nuclei of thalamus which is arranged in parallel and somatotopically[22,23] while thalamic neurons send convergent inputs to same cortical area but different laminae[29]. Striatal and extrastriatal dopaminergic innervations are responsible for modulating the function of basal ganglia [30,31]. Excitatory inputs from cortex modulates dopamine in striatal spiny neurons giving rise to synapses at dendritic spines [32]. In this case, striatal spiny neurons are supervised by dopamine-mediated reinforcement signal to recognise the state useful in guiding behavior [33].

Pathophysiological changes in basal ganglia

The pathophysiological changes that occurs in disorder of basal ganglia has been demonstrated by experimental evidences using MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of parkinsonism in non human primates. MPTPis a neurotoxin including dopaminergic degeneration resulting in parkinsonian syndrome[34,35]. The nigrostriatal denervation results in overactivity of internal globus pallidus and the substantia nigra pars reticulate [36,37]. The pathophysiological hyperactivity of both these nuclei and subthalamic nucleus [38] has been found due to reduced inhibitory input from the

striatum to the direct pathway [39] and increased activity of the indirect pathway [40]. The activity and function of external globus pallidus is needs to have a further extended study in order to understand the mechanism fully [41]. The clinical symptoms and pathologies are not fully explained by the current models of basal ganglia [42,43].

240 cases with lesion in the basal ganglia ere studied [44]. This indicated that syndrome of abulia and dystonia which are manifested as both behavioural and motor disturbances which are common disturbances in basal ganglia. The symptoms were different depending on the location of the lesion

- Lesion affecting caudate nucleus even unilateral lesion caused abulia, rarely caused disinhibited behaviour and occasionally caused motor disorders (did not cause parkinsonism ,but caused chorea or dystonia sometimes).
- Lesions of lentiform nucleus caused dystonia and rarely caused chorea.
- Lesions involving putamen are more prone to cause dystonia and rarely cause chorea.
- Lesions involving globus pallidus causes abulia or disinhibition.
- Bilateral lesions involving the globus pallidus do not cause parkinsonism but commonly causes behavioural disturbances.

Functions of basal ganglia

Motor functions- The motor functions of basal ganglia is not understood fully. Basal ganglia is involved in initiation of voluntary movements by modulating motor programs stored in cortex[45].The voluntary movements are interacted in the cortex.

It was demonstrated that whenever necrosis of the caudate nucleus and putamen is present for long period of time, retrograde degeneration of the cortico-striate fibres both in the subcallosal, fasciculus and in the external capsul[46].The basal ganglia-thalamocortical circuits acts as a pyramidal motor system which maintain somatotopic organisation of movement related neurons throughout the circuit[22,47]through the putamen mainly. Neurons related to the active and / or passive movements of the lower extremity are found in rostrocaudal extension of dorsolateral putamen, neurons relating to orofacial movements are situated ventromedially and movement of upper extremity neurons are located at an intermediate position.Both the segments of the globus pallidus follows somatotopical distribution.Extrapyramidal system interruption seems to be responsible for muscle spasticity and hyperactive deep reflexes. Basal ganglia involvement along with ventrobasal nuclei of the thalamus is linked to the voluntary and stereotyped movements without involving motor function.The disease of basal ganglia which involve extrapyramidal pathology leads to profound movement disorder which affects the motor function.

a. Spontaneous Hyperkinetic disorders which is seen in Huntington's disease [48,49] or Tourette's syndrome.
b. Akinesia or hypokinesia which results in diminished movement seen in parkinson's disease [50] and progressive supranuclear palsy [51].
c. Motor stereotypies[52]

Basal ganglia lesions bring about changes in muscle tone (muscular rigidity), fine resting tremor, postural disorders and athetosis (vermicular movement of the distal extremities). Hyperactivity, dyskinesia or hemiballism are other involuntary movement disorders depending on the position of lesion in the basal ganglia. Chorea and dementia with neostriatal neuronal loss and gliosis (vascular chorea) has been documented [53]. Wilson's disease which is associated with variable tremor and rigidity along with the degeneration of lenticular nucleus (putamen and globus pallidus) results in the copper metabolic disorders [54]. Complex stereotypies [55], dystonia after head trauma [56,57,58], involuntary movements of choreiform type, athetoid type Movements [57] or ballism [59] are known movement disorders associated with other degenerative changes in the basal ganglia. Hemiballism is the best pathological correlation: uncontrollable sudden, flailing gross movement of the proximal limb musculature of one of both limbs on the contralateral side of the lesion [60]. Hemiballism is associated with lesion in of the contralateral subthalamic nucleus of Luys[61] or its connections but it has also been reported that Hemiballism was found without subthalamic lesion but with lenticular lacunae infarct with internal globus pallidus involvement[62,63]. The important pacemakers of basal ganglia are subthalamic nucleus and internal globus pallidus [64]. The degeneration of the substantia nigra pars compacta [65] results in loss of dopaminergic input to the striatum which is responsible for the cardinal motor signs found in parkinson's disease (akinesia, rigidity and resting tremors). Dyskinesia or hypokinesis [50] were the unacceptable side effects which was found due to the chronic treatment with levodopa and /or dopaminergic agonists. The reversal of symptoms is due to the imbalance between direct and indirect basal ganglia pathways required for coordinated movements[66,67].Recently, new therapeutic approaches have been added:-

a) Pharmacological approaches with different dopamine receptor agonists [43] and new surgical approaches.
b) Dopaminergic neuron transplantation [68].
c) Lesions or deep brain stimulation (DBS) of the subthalamic nucleus or of the internal globus pallidus [69,70].

Cognitive functions or behavioural disturbances- Basal ganglia and adjacent structures predicts future events by reinforcing wanted behaviour and suppressing unwanted behaviour[10] and shifts attentional sets and initiates movement of high order processes [71] as well as spatial working memory[72].Function of basal ganglia includes cognitive and emotional functions along with psychological ,mood and thought disturbances, including depression, schizophrenia and obsessive compulsive disorder[73,74,75,76]. The functional subdivisions of oculomotor ,prefrontal and cingulated circuits by basal ganglia-thalamocortical circuit performs an important role in attention, learning and potentiation of behaviour-guiding rules[9,77,78] which is comparable to somatotopic channel within motor circuit, performing programming and control of movement. A study was conducted by Bhatia and Marsden [44] on 240 patients with basal ganglia lesion. Out of 240 patients, 111 had behavioural disorder with aphasic and dysarthric dysfunction, abulia, depression, disinhibited behaviour and acute confusional states after hemorrhage into the caudate. When lesions are located in the caudate nucleus, aphasia was found without hemorrhagic lesions[79,80,81,82]. Bilateral lesions was established with frontal lobe syndrome, psychic akinesia [81] and obsessive compulsive disorder[82], memory[77], learning[6,7], cognitive[9,11] and behavioural functions [10] were contributed by the caudate nucleus. Apathy, decreased recent memory and reduced initiative and spontaneity [83,84] were seen with the bilateral damage of caudate nucleus.

Sensory function of basal ganglia- Although the basal ganglia is regarded as a motor control centre, the benefit of external sensory cues in parkinson's disease and the sensory trick in dystonia throw some light on the sensory aspects implicated in these basal ganglia disorders. Animal studies demonstrated the sensory input reaching the basal ganglia differ from lemniscal exteroceptive system which showed encoding of information in motor control [85]. Thus, the basal ganglia appears as 'gate' sensory inputs at various levels[86,87].Basal ganglia stimulation inhibits auditory and visual cortical evoked responses, lemniscal and extralemniscal components of the somatosensory system which is modified by basal ganglia. Automatic movement is affected by the lesion of the basal ganglia which need sensory guidance. Basal ganglia control automatic or highly trained movement in relation to sensory inputs [88,89]. Head control and blinking are examples of automatic movements which is impaired in spasmodic torticollis or blepharospasm. These motor program are associated with fixed sensory input and a motor output [5].

Anatomy of basal ganglia disorders

Model of basal ganglia disease

A model of basal ganglia function was developed to explain the pharmacology of parkinsonism and Huntington disease. Here, in this model, the basal ganglia participated in a corticocortical feedback loop to control sequencing of motor programs. The afferents from the cortex excited the striatal neurons which inhibited the neurons of the pallidum and nigra. Increased activity by thalamocortical neurons of the VA/VL/MD/CM-pf nuclei (VA/VL, ventral-anterior and ventral-lateral thalamic nuclei; MD, mediodorsal thalamic nuclei; CM-pf nuclei, centromedian-parafascicular nuclei) was seen during the inhibition of GABAergic and inhibitory output neurons of basal ganglia. This circuit was modified by DA by inhibiting cholinergic striatal projection neurons. In parkinson's disease, absence of dopamine left the cholinergic interneurons during the striatal projection neurons which resulted in supranormal thalamocortical neuron activity which in turn excite the premotor cortex and executes motor program. On the contrary, Huntington's disease is marked by striatal projection neuron degeneration. The loss of striatal output resulted in disinhibition of the MGP and SNr (MGP; medial globus pallidus, SNr; substantia nigra pars reticulata) and inhibition of the VA/VL/MD/CM-pf nuclei (VA/VL, ventral-anterior and ventral-lateral thalamic nuclei; MD, mediodorsal thalamic nuclei; CM-pf nuclei, centromedian-parafascicular nuclei). Loss of activity of thalamocortical projections resulted in decreased drive to execute the ongoing motor programs.

This model predicted that adventitious movements should result from striatal destruction. When striatal lesions in both man and other mammals do not produce a hyperkinetic movement disorder .The model failed to explain the fact that hyperkinetic movement disorder is produced in man by lesions of the STN (sub thalamic nucleus). Thus, the model suffered this defect.

Other additional predictions derived from this model are as follows:-

- Striatal lesions in animals produced GABA receptor upregulation in pallidum and SNr (substantia nigra pars reticulata) due to loss of GABAergic afferents to this nuclei. This prediction proved to be true ([90,91]).
- Destruction of nigrostriatal dopaminergic projection was predicted in this model which resulted in down regulation of pallidal and SNr (substantia nigra pars reticulate) GABA receptors due to excessive activity of GABAergic striatal output neurons.

Rats with unilateral 6-hydroxy-dopamine lesions of median forebrain bundle were used to perform this experiment which showed decreased receptor density in globus pallidus (GP) but in contrast to this predictions, increased GABA receptors densities were seen in the EP (entopeduncular nucleus) and SNr (substantia nigra pars reticulata)[[49]]. This studies implicated that dopamine functionally inhibited the striatal projections to EP/SNr (EP, entopeduncular nucleus; SNr, substantia nigra pars reticulata). The result obtained from this study appeared inconsistent as afferent striatal axons to the GP (globus pallidus) and SNr (substantia nigra pars reticulata) in rodents were thought to be collaterals [[10]]. The elctrophysiological studies gave conflicting results about the effects of dopamine on striatal neurons [[92-94]]. In some studies dopamine (DA) appeared inhibitory but in other studies it excited striatal neurons. This model was a failure which suggested shortcomings in the anatomical and physiological study on which this model was based.

Recent basal ganglia anatomy

In this model, striatum was assumed to be a uniform structure and striatal afferents had a uniform effect on striatal projection neurons. Over the past 15 years, striatum has been discovered to be richly heterogenous. In the year 1972, Olson *et al.* [[95]] demonstrated that dopamine terminals are heterogeneously distributed in neonatal and adult rats. Grabiel and colleague showed that striatum is divided into two broad compartments; the striasomes and the matrix. These compartments are defined by intensity of histochemical staining for acetylcholinesterase in cats and primates [[96,97]] and by heterogenous distribution of μ-opioid receptor in rodents [[98-100]].The striasomes receives cortical afferents from primary motor and somatosensory cortex as well as frontal, parietal, and occipital cortex. The two striatal compartments are linked functionally by inter neurons that contain both somatostatin and neuropeptide Y ([101,103]). Along with the compartment segregation, striatal projection neurons are differentiated by neuropeptides they contain and the target zone which they target upon. Recent tract-tracing studies done in cats and primates showed that projecting striatal neurons to a given striatal target zone have few collateral to other target nuclei ([104-106]). On contrary to the classical view, the striatum seems to consist of discrete population of projection neurons with restricted input and output. These studies suggested that dopamine (DA) exert its effect directly on striatal projection neurons.

Revised model of basal ganglia disorders

A new model of basal ganglia function was constructed based on new anatomical, pharmacological and physiological data that accounts for the clinical phenomenon of movement disorders. Two fundamental

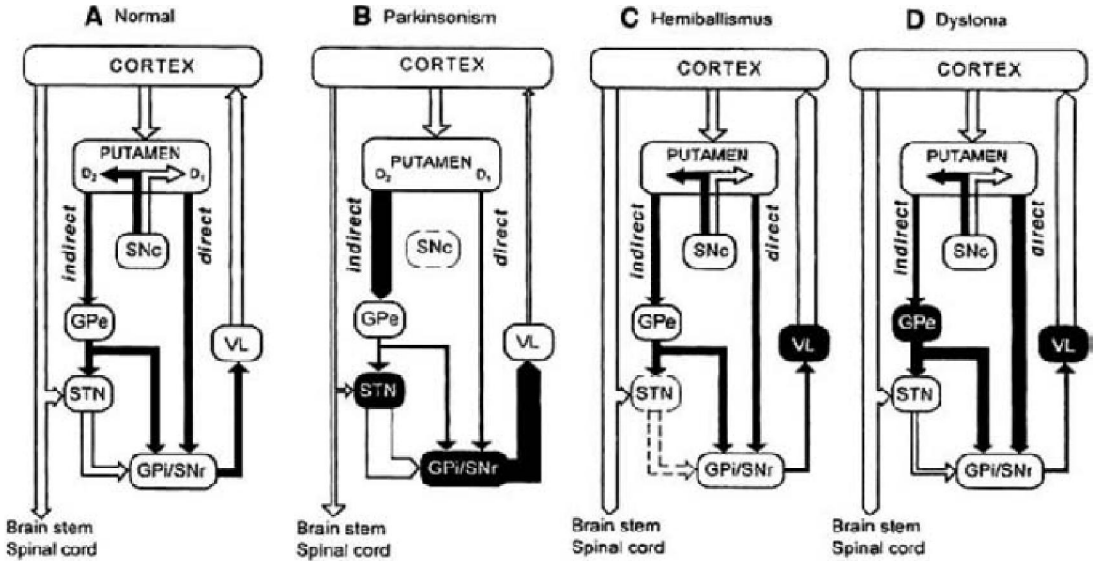


Fig.6. Motor loop showing Alexander and Crutcher model

attributes of this revised model are : existence of subpopulations of striatal projection neurons with different projection target and DA has different effects on these subpopulations of striatal projection neurons. LGP-STN-MGP/nigra (LGP; lateral globus pallidus, STN; subthalamic nucleus, MGP; median globus pallidus) pathway was incorporated into the revised model, thalamocortical projections which are affected by the disease states are different from those predicted by the prior model. Through this model, we were made to believe that basal ganglia are regulators of cortical function via influence on thalamocortical projections. This revised model demonstrated how functional anatomy explains the understanding movement disorders.

Movement disorders

Movement disorders are the spectrum of abnormal movements which is caused due to disorder of basal ganglia. These movement disorders are group of neurological symptoms, signs or diseases manifested as either slowness or paucity of movement (hypokinesis: parkinson's disease) or by excessive, abnormal involuntary movement (hyperkinesias).

These abnormal movement are classified on the basis of their clinical appearance. Two categories of movement disorders

1) Hyperkinetic
2) Hypo kinetic

Hyperkinetic movement disorder

Anatomy of Hyperkinetic movement disorder

Ballism is the only hyperkinetic movement disorder with a well established anatomical localization. Crossman and colleagues have exploited this non-human primate model in recent years to study the pathophysiology of hyperkinetic movement disorders [[107]]. They demonstrated that when activity of the sub thalamic nucleus (STN) or output to the medial globus pallid s(MGP) is blocked, produces a movement disorder seen in human hyperkinetic movement disorder[[107,108]]. Previous studies of pallidal and nigral GABA receptors in rats with 6-hydroxydopamine lesions predicted that facilitation of the major inhibitory input to the STN (subthalamic nucleus) produced a hyperkinetic movement disorder from decrease in activity of STN neurons[[109]].Crossman's group produced hyperkinetic movement by infusing bicuculline (GABA receptor antagonist) into the lateral globus pallidus (LGP). The GABAergic input from the striatum is blocked and activity of the GABAergic LGP (lateral globus pallidus) neurons projecting to STN (subthalamic nucleus) is potentiated. Anton Reiner and Keith D. Anderson demonstrated that in the early stages of Huntington's disease (HD), chorea is most prominent where there selective loss of striatal neurons projecting to the lateral globus pallidus[[110]]. In early-stage Huntington disease (HD) specimens, selective loss of enkephalin-immunoreactive striatal terminals in the LGP (lateral globus pallidus) was demonstrated. Until the late stages of HD (Huntington's disease), substance P –immunoreactive striatal terminals in the MGP (medial globus pallidus) were found to be well preserved when they too become depleted. The temporal gradient of cell loss in HD was inferred,in which enkephalinergic neurons projecting to LGP (lateral globus pallidus) were lost early and substance P- containing neurons projecting to MGP (medial globus pallidus) are lost late in the course of the disease.

The selective involvement of specific striatal projection neurons explains effectiveness of D_2 receptor antagonists in alleviating hyperkinetic movement disorders. It is now clear that DA (dopamine) antagonists do not have uniform effects on the various subpopulations of striatal projection neurons. When study was conducted with striatal neuropeptides, administration of D_2 antagonists increase the synthesis of enkephalins and pre-proenkephalins mRNA in the striatum. Enkephalin levels in LGP (lateral globuspallidus) also rise indicating increased synthesis of enkephalin in striatal neurons projecting to LGP (lateral globus pallidus)[[111-113]]. D_2 receptor antagonists effects were blocked by the co-administration of antimuscarinic cholinergic agent scopolamine. This lead to increase in enkephalin levels and mRNA increases the neuronal activity and indicated that D_2 receptor antagonist potentiate activity of striatal neurons projecting to the LGP (lateral globus pallidus). DA agonists was shown to produce the opposite effect. Hyperkinetic movement was induced when dopamine agonists were administered in monkeys, decrease in the activity of striatal-LGP projection was also seen. In Huntington's disease (HD), administration of D_2 antagonists resulted in the stimulation of remaining striatal-LGP neurons and overcame the defect created by the degeneration of projection neurons. In ballism, administration of D_2 antagonists resulted in inhibition of LGP neurons projecting to the STN (sub thalamic nucleus) due to which sub thalamic nucleus function was potentiated. Anticholinergics was found to antagonize the effect of DA blockade and explained the fact that chorea worsens with administration of anticholinergic drugs.

The distribution of neuropeptides was studied in case of Tourette's syndrome specimen and decrease in dynorphin like immunoreactivity in the LGP (lateral globus pallidus) was seen. This reflected impaired function of enkephalinergic striatal neurons projecting to the LGP, because of antibody used in this study cross-reacted with enkephalins and few striatal neurons projecting to the GP (globus pallidus) in rats and other species contain dynorphin[[114-116]]. Thus, decreased activity of the STN (sub thalamic nucleus), either due to STN (sub thalamic nucleus) destruction or because of selective dysfunction of a subpopulation of striatal neurons projecting to the LGP (lateral globus pallidus) was responsible for hyperkinetic movement disorder of choreoathetosis, ballism and tics. Loss of STN-derived excitation to the MGP (medial globus pallidus) and SNr (substantia nigra pars reticulata) and disinhibition of the VA/VL/MD/CM-pf (VA/VL, ventral-anterior and ventral-lateral thalamic nuclei; MD, mediodorsal thalamic nuclei; CM-pf nuclei, centromedian-parafascicular nuclei) thalamocortical projections were the ultimate effect.

Classification of Hyperkinetic movement disorders

Tremor – is defined as rhythmical oscillatory movement of a body part.

Types of tremors:-

- Rest tremor- when the body part is supported against gravity and not actively contracting, it is defined as rest tremor. This movement is absent during sleep and suggests nigrostriatal dopaminergic deficiency. Though rest tremors usually respond to levodopa therapy, some rest tremors such as rubral tremor (Holme's tremor associated with lesions in the cerebellar-outflow pathway.
- Essential or Dystonic tremor-occurs even in the absence of parkinsonian features and response to dopaminergic drugs is less predictable. It can also be seen when moving the body part to and from a target (example-finger to nose).
- Action tremor- is present during maintenance of posture.
- Postural tremor-this tremor is seen when arms are extended horizontally and perpendicular to the body.
- Kinetic or intention tremor- It is seen in patients with cerebellar-outflow lesions.
- Primary writing tremor-is the most common type of task specific tremor.
- Orthostatic tremor- this is the position-specific tremor which is less common and often unrecognised tremor characterised by high frequency (16 Hz) tremor, predominantly involving the legs and trunk. When the patients stand for certain period of time. This can also occur when patient is in supine position .This tremor can be easily detected by palpation, auscultation or electromyography.

Therapeutic options for tremor

Medical therapy- The first step in the treatment of essential tremor is to minimise or eliminate factors like stress and various tremorogenic drugs. Alcohol reduces the amplitude of essential tremor in about two-third of the patients. A glass of wine (blood level as low as 0.30 %) is offered as prophylactic treatment. Alcohol act centrally as infusion of alcohol into brachial artery of tremulous arm is ineffective in controlling the tremors. Alcohol affect several neurotransmitters and stabilise neuronal membranes by potentiating GABA-receptor-mediated chloride influx. A food additive, 1-octanol suppresses harmaline-induced tremor in animal models of essential tremor and reduces the amplitude of essential tremor for about 90 minutes ([117]). Pharmacological therapy- propranolol, a β- adrenergic blocker and primidone, an anticonvulsant is used for the treatment of essential tremor. This exerts a central mechanism of action, some exert potent anti-tremor activity even though they are not lipid soluble and hence do not cross the BBB. The therapeutic effect of β-adrenergic blockers is mediated by peripheral β-adrenergic receptor. The major side effect of propranolol and other β-blocker include fatigue, sedation, depression and erectile dysfunction. Primidone is started at a low dose (< 25 mg at bed time) and increasing this dose slowly over several weeks, the acute toxic side effects (nausea, vomiting, sedation, confusion and ataxia) can be prevented. The anti-tremor effect of primidone is attributed to the parent compound rather than its metabolites, phenylethyl-malonamide or Phenobarbital. In addition to β-blockers, primidone and benzodiazepines drugs such as diazepam, lorazepam, clonazepam, alprazolam and barbiturates have ameliorating effects on essential tremors ([118]).

Topiramate was an effective anti-tremor drug in a multicentre, double-blind, placebo-controlled trial of 208 patients with essential tremor ([119]). Topiramate showed greater improvement in function and disability than placebo. The most common adverse events reported were paresthesias, weight loss, taste perversion, other side effects include nausea, difficulty in concentration, attention and somnolence. Levetiracetam is another antiepileptic drug which had significant anti-tremor effect in one double-blind, placebo-controlled trial at a single dose of 1000 mg ([120]). Mirtazapine, clozapine, sodium oxybate, dimethoxymethyl-diphenyl-barbituric and carisbamate ([118]) are other drugs which reported beneficial effect in patients with essential tremor. Drugs such as gabapentin, clonazepam, levodopa, primidone, Phenobarbital and amantadine is effective in treating orthostatic tremor. Botulinum toxin therapy- Botulinum toxin injection into muscles is involved in the production of the oscillatory movement, particularly the forearm wrist flexors which provide decrease in the amplitude of the hand tremor for about 3 months. Injections of this toxin is beneficial in patients with essential tremor invoving head [[121]] and voice [[122]]. Botulinum toxin is also effective in primary writing tremor though a specifically designed writing device might be a simple treatment [[123]]. Surgical therapy- Many studies have indicated beneficial effects for tremor produced by deep brain stimulation (DBS) targeting the ventral intermediate (Vim) nucleus of the thalamus([124]) and other nuclei such as sub thalamic nucleus([125,126]) and the caudal zona incerta nucleus ([127]). Vim DBS reduces mainly contralateral but lesser extent ipsilateral tremor ([128]) as well as head tremor, rest and task-specific hand tremor ([129]) and cerebellar-outflow tremors ([124]). Long term studies found that bilateral vim DBS is associated with dysarthria, loss of balance, and loss of coordination([130]).The quality standards subcommittee of the American academy of neurology reviewed the studies in essential tremors and concluded that there was level A evidence that Propranolol and primidone reduce limb tremor, but level B evidence to support the effectiveness of alprazolam, atenolol, gabapentin, sotalol and topiramate for reducing hand tremor and propranolol for reducing head tremor ([131]). The effective treatment had reduced only level C support: clonazepam, clozapine, nadolol, and voice tremor, and chronic DBS and thalamotomy. The low level of support for botulinum toxin and DBS, in spite of their efficacy in reducing the amplitude of tremor was due to high occurrence of adverse events.

Dystonia

is defined as a neurological disorder followed by sustained muscle contractions which cause twisting, repetitive, patterned movements or abnormal postures ([132]). Dystonic movements can be slow, manifested by prolonged tonic spasms resulting in abnormal postures which can be rapid and jerk-like movement. Dystonia also present as a rhythmical movement. When the patient attempts to correct underlying abnormal dystonic posture. This dystonic tremor is not seen when the patient is asked to relax and body is allowed to move in the direction of the dystonic pull (null position).

Two types of dystonia:-

- The idiopathic adult-onset dystonias are usually focal or segmental. Exampes include cranial dystonia, cervical dystonia, laryngeal dystonia, and dystonic writer's cramp. Dystonic writer's cramp is example of a group of focal dystonias referred to as occupational spasms which consists of task-specific or position-specific dystonias, such as musician dystonias([133]) and dystonia that affect athletes, artists and other profession in which skilled movement is a key feature.
- Childhood-onset dystonias-They usually start distally and progress to a more generalised dystonia. Primary dystonias, such as autosomal-dominant dystonia caused by mutation in gene that encodes torsin A (TOR1A; also known as DYT1)([132]),are not associated with any other neurological disorders, whereas secondary dystonias occur in parkinson's disease or other form of parkinsonism and various other neurological sporadic and genetic disorders([134]).The genetic disorders associated with dystonia and other hyperkinesias are syndromes of neurodegeneration with brain iron accumulation which include pantothenate kinase-associated neurodegenration (Hallervorden-spatz syndrome), neuroferritinopathy, infantile neuroaxonal dystrophy, aceruloplasminaemia, and PLA2G6-associated neurodegenration ([135,136]). Iron chelators similar to copper chelation in wilson's disease is used in the future to treat these neurodegenerative disorders ([137]).

Therapeutic options for Dystonia

Medical therapy- The treatment of primary dystonia involves symptomatic treatment in order to relieve involuntary movement, correct abnormal posture, prevent contracture, reduce pain and embarrassment and improve function ([138,139]). Small number of patients were diagnosed with secondary dystonia and responded to treatments such as levodopa in dopa-responsive dystonia, withdrawing causative treatment in drug-induced dystonia or copper chelation in wilson's disease. Physical and well fitted braces improve posture and prevent contractures. In peripherally induced dystonia ([140]), casting of affected limb was a potential treatment. It has not been clear whether constraint-induced movement therapy can be used in rehabilitation of some patients with spasticity after stroke ([133]). Another non-pharmacologic treatment includes repetitive use of transcranial magnetic stimulation at low frequencies (< 1 Hz) for 20 min ([141]). Therapeutic strategies were modified according to the need of individual patient with which includes chemodenervation with botulinum toxin injections in patients with focal or segmental dystonia and pharmacological therapy or DBS in patients with generalised dystonia.

Pharmacological therapy-Pharmacological treatment of dystonia is based on empirical studies. Dose-responsive dystonia in which the biochemical and genetic mechanisms have been elucidated ([142]). Mutation in gene that encodes GTP-cyclohydrolase 1(GCH1) are important genetic cause of dopa-responsive dystonia but other genetic mutations such as those in the genes that encode tyrosine hydroxylase (TH) and parkin (PARK2) which accounts for dystonia. Dopa-responsive dystonia present in childhood is often confused with cerebral palsy. As the Dopa-responsive dystonia is not easily diagnosed that is why therapeutic trial of levodopa is recommended

for patients with childhood-onset dystonia which is the most reliable diagnostic test. Most of the patients with dopa-responsive dystonia improve even with small doses of levodopa (100 mg of levodopa plus 25 mg of a decarboxylase inhibitor) but some may respond to levodopa as high as 1000 mg per day. Patients with dopa-responsive dystonia also improve with dopamine agonists and anticholinergic drugs in addition to levodopa. Antidopaminergic drugs is beneficial in the treatment of dystonia but the potential clinical benefit is limited by side effects. Dopamine depleting drugs such as tetrabenazine are useful in the treatment of tardive dystonia ([143]). Anticholinergic medications are most beneficial in treatment of generalised and segmental dystonia in early double-blind, placebo-controlled trial ([144]). This is started at low dose and increased slowly started with 1 mg of trihexyphenidyl and the dose was increased upto 12 mg/day for 4 weeks. Some patient require 60-100 mg/day but dose related drowsiness, confusion, memory difficulty, blurring of vision, hallucinations and urinary retention limits its usefulness. These side effects are common in children than in children and managed by pyridostigmine for constipation, pilocarpine eye drops for blurring of vision, cholinergic drugs such as bethanechol for urinary retention and synthetic saliva for dry mouth.

Other ancillary treatment in addition to anticholinergic drugs in patients with generalised dystonia include muscle relaxants such as benzodiazepines, tizanidine, cyclobenzaprine, and baclofen. Intrathecal infusion of baclofen helpful in patients with truncal and leg dystonia associated with spasticity seen in cerebral palsy ([145,146]). Other medications in the treatment of dystonia include slow release morphine sulphate, sodium oxybate, levetiracetam and zonisamide. Local electromyographically guided injection of phenol used as the treatment is painful with inconsistent results. The kinesigenic paroxysmal dystonia is controlled by anticonvulsants (carbamazepine, phenytoin, levetiracetam, topiramate) ([147]). The non kinesigenic paroxysmal dystonia is responsive to pharmacological treatment though clonazepam and acetazolamide may be beneficial ([148]). Patient suffering from exercise-induced dystonia can overlap with epilepsy and has been associated with mutations in SLC2A1 (encodes glucose transporter (GLUT1) successfully treated with ketogenic diet ([149]). Sometimes dystonia can be so severe that along with the abnormal postures, dystonic movement is disabled which compromises respiration and causes muscle breakdown, life-threatening hyperthermia, rhabdomyolysis, myoglobinuria([150]).37 patients with status dystonicus (dystonic storm) were studied and following treatment approach was used. They were admitted to ICU, monitored for myoglobinuria, respiratory and renal compromise were avoided, sedation with intravenous midaolam (10μg/kg/min and subsequently at 30-100 μg/kg/h). Treatment with possible barbiturate anaesthesia combined with endotracheal intubation and mechanical ventilation, continous intrathecal baclofen, and bilateral globus pallidus interna (GPi) DBS or pallidotomy ([150]). Botulinum toxin therapy- Botulinum toxin was introduced in the late 1980s for the treatment of dystonia. Botulinum toxin is the most potent biological toxin and is a very powerful tool in the treatment of neurological, opthalamic, oro-laryngeal, urological, autonomic, dermatological and cosmetic disorders ([151,152]). In the year 1989, US FDA (Food and drug administration) approved botulinum toxin A (Botox) as a therapeutic drug in patients with blepharospasm and other facial nerve disorders such as hemifacial spasm. Botulinum and toxin B (Myobloc) in 2000 was approved for treatment of cervical dystonia. The European medicines agency has approved three botulinum toxin A preparations; Botox, Dysport and Xeomin and one botulinum toxin B preparation. Neurobloc is used for the treatment of several dystonia and other therapeutic and cosmetic uses. The various neurotoxins are antigenically different ad contain a common subunit structure and cross-reactive epitopes which cause cross-neutralization of antibodies ([153]). Patients who has developed blocking antibodies respond to an immunologically distinct botulinum toxin still has the risk of developing antibodies to second toxin and are likely to develop resistance towards alternative type of botulinum toxin ([154]).

The therapeutic and technology assessment committee of the American academy of Neurology recommended that: botulinum toxin should be used as a treatment option for cervical dystonia (level A evidence), used as a treatment in blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia and upper extremity essential tremor (level B) and used for hemifacial spasm, focal lower limb dystonia and motor tics (level C) ([155]). Surgical therapy- Patients who continues to experience discomfort through disabling symptoms from dystonia despite physical and pharmacological therapy, chemodenervation with botulinum toxin are subjects for surgical treatment. Understanding of functional anatomy of basal ganglia and physiological mechanisms responsible for movement disorders coupled with imaging and surgical techniques has led to the resurgence of surgery, particularly GPi DBS, as a treatment option for patients with disabling dystonia ([156-158]). Many studies have revealed that patients with a phasic form of dystonia has improved more than those with tonic contractions and posturing. Peripheral denervation procedures have been used before the introduction of botulinum toxin but is now used rarely and restricted to patients with botulinum toxin-resistant blepharospasm or cervical dystonia ([159]).

Tics and Tourette's syndrome

Tic is another hyperkinetic movement disorder which are abrupt, often repetitive and stereotyped movements which vary in intensity and are repeated at irregular intervals ([160])

Types of Tics-

- Clonic tics-movements are jerky
- Dystonic tics- movements are slower and more prolonged movements
- Tonic tics- isometric muscle tensing.

Tics can persist for several weeks or months .Patients with childhood-onset tics develop tourette's syndrome, a genetic disorder which is characterised by wide array of chronic, fluctuating, simple as well as complex motor and phonic (vocal) tics. This syndrome is associated with comorbidities such as attention-deficit disorder and impulse control disorder. For example-Gillesde la Tourette's syndrome in which person utter whole words and obcene phrases uncontrollably which are supressed by D_2 receptor antagonists. Motor and phonic tics persist during all stages of sleep ([160]).

Therapeutic options for Tic and Tourette's syndrome-

Medical therapy- The first step in the management of patient's with Tourette's syndrome is to educate the patients, relatives and other individuals who interact with the patients about the nature of tics ad comorbidities of Tourette's syndrome([161,162]). Medications are given at low doses, titrated to lowest effective dosage and tapered during less stressful periods. Giving medications and maintaining regimen is an important principle of therapy in tourette's syndrome.

Pharmacological therapy- The drugs used for tic suppression are the neuroleptic drugs which includes dopamine receptor-blocking drugs and monoamine-depleting drugs ([162]). Fluphenazine,of the neuroleptic drug found to have lower side effects associated with neuroleptic drugs such as sedation, depression, eight gain and school phobia ([161]).The potential side effect of fluphenazine include tardive dyskinesia(tardive stereotypy and tardive dystonia) which has not been documented in patients (> 1000) treated with this drug. When a double-blind placebo-controlled study was conducted for 8 weeks where 24 patients received risperidone in doses of 0.5 to 6 mg per day and 24 patient were assigned placebo. Risperidone showed significant improvement and prove superior to placebo on the global severity rating of the tourette's syndrome severity scale ([163]). Fatigue and somnolence are the two most common associated adverse effects of risperidone.

Atypical neuroleptics such as aripiprazole, clozapine, olanzapine, quetiapine or ziprasidone were not found effective in the treatment of tics. These drugs can prolong the QT interval and associate with other side effects attributing to the classical neuroleptics including tardive dyskinesia. Tetrabenazine, a monoamine-depleting drug is a powerful anti-tic drug which has not been linked with tardive dyskinesia and can be considered as first line treatment for the patients with troublesome tics([164]). Tetrabenazine is associated with less weight gain than typical neuroleptics ([165]). Topiramate was found safe and effective for treatment of moderately severe tourette's syndrome ([166]). Antidopaminergic drugs seems to have beneficial effects in tics. In view of this finding, dopamine agonists improving tics seems ironical.The observed effects of dopamine agonists can be mediated by their action on dopamine D_2 autoreceptors, thus reducing endogenous dopamine turnover. Pramipexole, a D_2 and D_3 receptor agonist is studied in a double-blind, placebo-controlled trial ([167,168]).

Other drugs effective in the treatment of tics are clonazepam, flutamide, ondansetron, baclofen, donepezil, nicotine and cannabinoids. Attention-deficit hyperactivity, one of the comorbidity associated with Tics ,is treated with atomoxetine, modafinil, and armodafinil along with CNS stimulants. Behavioural Comorbidities are treated with guanfacine and clonidine. Though, clonidine has been used to treat tics in children, but this presynaptic α2-adrenergic agonist is not considered as an effective anti-tic drug. Botulinum toxin therapy- Localised motor tics are treated with botulinum toxin injections in the affected muscles ([169,170]).The focal chemodenervation alleviates involuntary movements, vocalisations and also the premonitory sensory component. Botulinum toxin can be used to control life-threatening tics, such as dystonic cervical tics ("whiplash" tics) which could cause compressive myelopathy or radiculopathy ([171,172]). Surgical therapy - Surgical treatment of Tourette's syndrome is an effective treatment in patients with disabling (malignant) Tourette's syndrome associated with self-injurious behaviours ([171]). DBS targeting thalamus, globus pallidus and other brain regions are effective strategies to treat uncontrollable and life-threatening tics ([173-176]) and obsessive-compulsive disorder associated with it ([177]).

Chorea and Huntington's disease

Chorea consists of irregular, abrupt, rapid, brief, jerky, unsustained movements that flow randomly from one part of the body to another. "Choreoathetosis" term describes the combination of chorea and athetosis, defined as a slow form of chorea manifested by writhing movements involving distal extremities. Ballism, a severe form of chorea, comprises wide amplitude, flinging movements involves the proximal limbs and affects only one side of the body (hemiballism). Ballism is caused by a lesion in the contralateral subthalamic nucleus, but may be associated with pathology in other subcortical areas. Most of the patients with ballism also have distal choreic movements and as recovery occurs, hemiballism gradually transforms into hemichorea and hemidystonia. Huntington's disease, an autosomal-dominant neurodegenerative disorder which is one of the common causes of chorea, but other genetic causes include dentatorubral-pallidoluysian atrophy, neuroacanthocytosis, benign hereditary chorea, spinocerebellar atrophies types 2, 3, and 17 and neurodegeneration with brain iron accumulation, neuroferritinopathy, and ataxia telangiectasia. Non-genetic causes of chorea include cerebral palsy, systemic lupus erythematosus, Sydenham's chorea, chorea gravidarum, hyperthyroidism, vasculitis, antiphospholipid syndrome, Moyamoya disease, and several other drug-induced and metabolic disorders ([178]).

Stereotypy, akathisia and tardive dyskinesia

Stereotypies are involuntary, patterned, repetitive, continuous, coordinated and ritualistic movements, postures, or utterances. This movement can be exemplified by a repetitive tongue protrusion, chewing, or body-rocking movements, or can be complex such as crossing and uncrossing of legs. Akathisia, is of tardive origin which consists of the combination of complex stereotypic movements and feeling of restlessness. Tardive dyskinesia is caused by exposure to dopamine receptor-blocking drugs such as antipsychotics or antiemetics. Other causes of stereotypy movement include mental retardation, autism, Rett syndrome, schizophrenia, and automatisms in patients with seizures ([179,180]).

Therapeutic options for chorea

Medical therapy- Though Huntington's disease has been considered as an excellent model for evaluation of early neuroprotective treatments [[181,182]] but still currently there is no treatment that stops or slows the progression of Huntington's disease. Coenzyme Q10, creatine, dimebon, ethyl eicosapentaenoate and minocycline [[181,182]] are treatment approaches investigated in clinical trials for disease-modifying effects.

Pharmacological therapy - Dopamine receptor-blocking drugs (neuroleptics) are used as the main treatment of chorea but the use has been limited because of its serious side-effects, including parkinsonism and tardive dyskinesia. Chorea which is primary target symptom in all studies, has been improved with haloperidol and fluphenazine, with less evidence for olanzapine. A double-blind, randomised crossover study was conducted which showed a decrease in dyskinesia scores after both intravenous and using oral administration of amantadine [[183]]. In the year 2008, FDA approved tetrabenazine as the first drug for the treatment of chorea associated with Huntington's disease. Tetrabenazine which is potent and selective depletor of dopamine from nerve terminals, and depletor of norepinephrine and serotonin as well to a lesser extent is effective in the treatment of several hyperkinetic movement disorders[[143]]. Tetrabenazine impairs uptake of monoamines into synaptic vesicles by inhibiting the brain synaptic vesicular monoamine transporter type 2 (VMAT2) and, caused them to remain in the cytoplasm, where they are degraded rapidly by monoamine oxidases. VMAT2 is expressed in CNS neurons, whereas VMAT1 is expressed in peripheral nerve terminals. Tetrabenazine mainly inhibits VMAT2, whereas reserpine binds irreversibly to both VMAT1 (peripheral) and VMAT2 (central). This pharmacological difference is responsible for the absence of hypotension and gastrointestinal side-effects with tetrabenazine as compared with reserpine. Tetrabenazine can exacerbate depression, sedation, akathisia, and parkinsonism. Thus, this drug is an effective anti-chorea drug which has an advantage over the other neuroleptics as it does not cause tardive dyskinesia [[184-186]].

An observational, longitudinal study was conducted at Baylor College of Medicine. In this study, 448 patients suffering from hyperkinetic movement disorders were treated with tetrabenazine for up to 21.6 years and were evaluated with a clinical response scale. The dose-related side effects were drowsiness (112 patients) parkinsonism (69 patients), depression (34 patients), and akathisia (34 patients),with less common side-effects including nausea or vomiting, nervousness or anxiety, and insomnia. Many patients were ready to tolerate side-effects such as parkinsonism (treated with amantadine, levodopa, and dopamine agonists) because of beneficial effect of tetrabenazine on hyperkinetic movement disorder.This was supported by another double blind study at Baylor college of medicine which showed re-emergence of chorea when 30 patients with Huntington's disease were treated with stable dose of tetrabenazine were assigned staged withdrawal [[187]]. Modifications in pharmacological therapy of tetrabenazine was done by slow, careful dose titration and monitoring for depression or suicidality and other potential adverse events such as sedation, parkinsonism and akathisia. Surgical therapy- Palliative surgery (pallidotomy and DBS) has been investigated in patients with severe chorea associated with Huntington's disease. Low-frequency (40 Hz) GPi DBS was associated with reduced chorea, but no improvement was seen in motor function and quality of life [[188]]. Animal studies and clinical trials results are still awaited for the use of foetal cells or intrastriatal implantations of genetically engineered cells designed to produce trophic factors useful in the treatment of

Huntington's disease [189,190]. RNA interference provided a promising therapeutic strategy, but extended work has to be done in this field to find out whether this method only suppress the expression of the mutated form, or the normal gene which encodes the huntingtin protein[191].

Hypokinetic movement disorders

Parkinson's Disease

This is categorised as hypokinetic movement disorder as well as degenerative disorder which primarily affects nigrostriatal dopaminergic neurons. This clinical condition was first described by James Parkinson from Queen square, London who reported the triad features of akinesia, rigidity and tremor in 1817[192].There was extensive loss of the dopaminergic cell body in the substantia nigra particularly in the zona compacta and dopaminergic fibres in the striatum. The etiology was obscure but recent discovery of a neurotoxin MPTP raised the possibility of chronic toxication. In early 1980s, a synthetic drug, 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) was sold in the market to drug addicts as the drug was not listed as a controlled drug in the United States. A contaminant MPTP was produced due to lack of stringent purification procedures in young addicts. Several studies were conducted which led to the discovery of MPTP in the year 1983 [193].When MPTP was given to monkey, it caused parkinsonian features and destruction of dopaminergic neurons in the substantia nigra and the striatum.

Classification of Parkinsonism

- Primary parkinsonism, Parkinson's disease (78%)
- Secondary parkinsonism (8%)

a) Vascular: multiple infarctions
b) Drugs: reserpine, lithium, phenothiazines
c) Infections: postencephalitic
d) Toxins: manganese, carbon dioxide, MPTP
e) Trauma: pugilistic encephalopathy (boxing)

- Hereditary parkinsonism (1 %)

a) Huntington's disease
b) Olivopontocerebellar and spinocerebellar degenerations
c) Halleworden-Spatz disease
d) Wilson's disease

- Parkinsonism-plus syndromes (multiple systems degeneration) (12%)

a) Progressive supranuclear palsy
b) Shy-Drager syndrome
c) Striatonigral degeneration
d) Lewy body disease

Clinical presentation of Parkinson's disease

- The initial presentation of Parkinson's disease may vary but at initial diagnosis tremor is present in 70% of patients. The tremor begins unilaterally affecting the hand and upper extremity. The tremor is described as a slow (4-7 Hz), pillrolling, resting tremor.
- Muscular rigidity - is a disabling symptom of Parkinson's disease and affects proximal appendicular muscles at an early stage including axial structures [194,195]. The facial muscles are also involved leads to diminished expression called "poker stare."
- Bradykinesia, - is defined as slowness of movement and develops along with rigidity ([195]).In Parkinson's disease, the ability to initiate and execute a movement was impaired. Akinesia ("without movement") is defined as the extreme of bradykinesia [196,197].
- Motor planning involved execution of simultaneous or sequential motor programs. Motor planning was impaired so that reflex movements that usually occur with little or no conscious effort (eg, blinking, facial movements) now required concentrated effort [198,199].
- Postural instability refers to the loss of balance which was a direct consequence of neurotransmitter imbalance in Parkinson's disease.
- Tremor, rigidity, bradykinesia, and postural instability occurs as "direct effects" of Parkinson's disease [200]. These direct effects leads to the indirect secondary musculoskeletal effects of the disease like stooped posture, kyphosis, head flexion, shoulder protraction, and knee or elbow contractures which impaired physical performance [200,201]. Other symptoms and signs of Parkinson's disease involve muscle aches or cramps, depression, dementia, dysarthria, dysphagia, orthostatic hypotension, bladder problems, and sexual problems [194]. Idiopathic Parkinson's disease was divided into two subgroups, which was identified by Zetusky *et al.* [202] as the "tremor predominant" and the "postural instability and gait disturbed (or PIGD).

Pathophysiology of Parkinson's Disease

Hypokinesia and Bradykinesia are cardinal features of akinesia in parkinson's disease. The early study indicated that dopamine depletion leads to a shift in the balance of basal ganglia activity towards the "indirect" circuit where the GPe-STN-GPi microcircuit plays an important rule. Hallett and Khoshbin [203] studied the physiological mechanisms of bradykinesia using surface EMGs in a ballistic elbow flexion movement. They found a fractionated pattern of agonist-antagonist muscle bursts which were repetitions of the normal triphasic (agonist-antagonist-agonist) muscle activation. Typical features in Parkinson's disease includes an alteration of automatic movements with reduced blinking rate, a positive Meyerson's sign, decreased aim swing and short stride length when walking. All of these are mediated by brainstem mechanisms which are functionally impaired by excessive basal ganglia inhibitory outputs. This is shown experimentally for the excitability of blink reflex [204]. As the striatonigral dopaminergic projection acts as inhibitory input to the indirect pathway (D_2 receptor) and as excitatory input to the direct pathway (D_1 receptor), its absence leads to the overactive indirect pathway and hypoactive direct pathway. The overall effect is excessive inhibitory influence upon the motor cortex which underlies bradykinesia or akinesia.

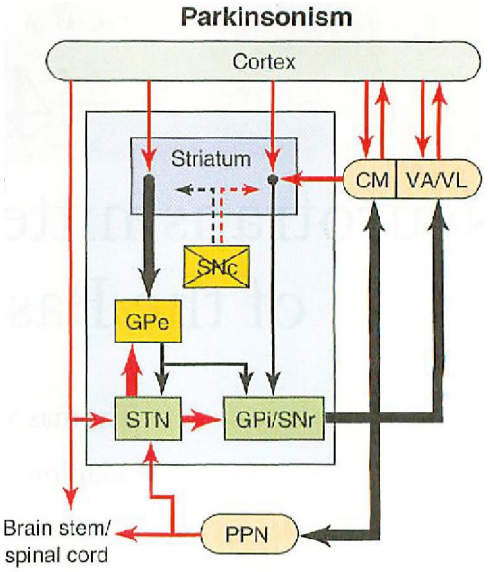


Fig.7.Diagram showing changes in the activity of basal ganglia nuclei associated with the development of parkinsonism. GPe,external pallidal segment; STN, subthalamic nucleus; GPi, internal pallidal segment; SNr, substantia nigra pars reticulata; PPN,pedunculopontine nucleus; CM, centromedian nucleus of the thalamus; VA, ventral anterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; Red arrows denote excitatory connections; black arrows denote inhibitory (GABAergic) connections. Changes in width of arrows indicate activity changes.

Pharmacological treatment of Parkinson's disease

During 1960s, antiparkinsonian medicines became available which had a tremendous impact on the management of Parkinson's disease. Prior to the levodopa, anticholinergics and stereotaxic surgery were used to treat PD patients. The disabling symptoms of akinesia and bradykinesia, which did not respond to anticholinergics, but responded to levodopa. The patients who became severely disabled became more mobile [205,206]. Levodopa has been the mainstay of pharmacological treatment of individuals with Parkinson's disease. Drugs were effective in treating some of the direct effects of the disease (including bradykinesia, rigidity, and tremor), but it is not clear till what extent drugs can affect postural instability and can impair motor planning [207].The unwanted side effects such as dyskinesia, hallucinations, and the "on-off" syndrome were also accounted with the positive results. Treatment consists of dopamine replacement, dopaminergic drugs (which act at the postsynaptic site), or anticholinergics. An additional level to drug therapy has been added in the last several years-neuroprotective therapy, with seligiline, retards the progression of the disease.

L-dopa

The mainstay of treatment is dopamine replacement. Dopamine does not cross the blood-brain bamer, so the levo-isomer levodopa (L-dopa) is given, which enters the CNS and undergo enzymatic conversion to dopamine [208]. Almost 99% of the ingested L-dopa is metabolized peripherally before it can cross into the brain, which necessitates larger amounts of levodopa to achieve the effective CNS dosing. Such large doses causes nausea and vomiting, and orthostasis. The most commonly used form is combination of carbidopa and levodopa. The carbidopa is a peripheral decarboxylase inhibitor preventing peripheral conversion of the levodopa to dopamine, which allows more levodopa available to enter the CNS and smaller doses to be used[208,209].The combination of carbidopa ad levodopa is in a ratio of 1:10 or 1:4 ratio. The plasma half life of levodopa is about 1.3 hours which dictates multiple dosing throughout the day. The controlled-release preparation produced fewer fluctuations in the plasma concentration resulting in smoother therapeutic response [210]. Side effects of levodopa includes nausea and vomiting (reduced with carbidopa), orthostatic hypotension, and cardiac dysrhythmias. Central nervous system side effects include confusion, delirium, and behavioral changes[211]. This suggested that a metabolite of levodopa has deleterious effects on surviving dopaminergic neurons[212,213]. Later complications of levodopa includes dyskinesias, clinical fluctuations, and psychiatric disturbances as the disease progresses. Clinical fluctuations include the "wearing off" or the "on-off" syndrome.In "on-off" syndrome,there is abrupt loss of drug effectiveness, resulting in akinesia ("off "). The akinesia is followed by a sudden return of effectiveness which is dyskinesia ("on")[214]. The dyskinesia and clinical fluctuations are managed by lowering the dosage of levodopa and increasing the frequency of administration, along with the dopamine agonists.Levodopa therapy increases the survival among these patients about 5 years [215].

Dopamine Agonists

Dopamine agonists is used as an adjunctive or replacement therapy in patients with Parkinson's disease. Dopamine agonists are ergot alkaloids acting directly on the postsynaptic receptors which requires no endogenous enzymatic action[214]. Dopamine agonists affects rigidity and bradykinesia, but causes postural impairment to a lesser extent. When Bromocriptine and pergolide agonists were used as initial monotherapy, symptoms improved but recurred, necessitating addition of levodopa after 1 or 2 years. Early adjunctive therapy resulted in fewer clinical fluctuations, later in the course of the disease responded to the addition of a dopamine agonists[216]. Central nervous system side effects of agonists are insomnia, delusions and confusion. Other side effects include erythromelalgia, pulmonary and retroperitoneal fibrosis, postural hypotension, nausea, and vomiting [217].

Anticholinergics

Anticholinergic drugs alleviate the symptoms of Parkinson's disease by correcting the imbalance between dopamine and acetylcholine in the striatum. Anti cholinergic drugs were the first drugs used to improve tremor and treat patients with Parkinson's disease. There is little or no corrective effect on the disabling symptom of rigidity or bradykinesia, trihexyphenidyl and benztropine are used. Diphenhydramine is an antihistamine with anticholinergic properties that is helpful. Adverse side effects of anticholinergics involves memory impairment, hallucinations, dry mouth, constipation, urinary retention, and blurred vision.

Amantadine

Amantadine is used for influenza prophylaxis [218] and have both dopaminergic and anticholinergic properties but stimulates release of dopamine from surviving presynaptic terminals in the striatum[218]. The effects are short-lived, but can be used in suspected cases of Parkinson's disease. Side effects include livedo reticularis and ankle edema.

Seligiline

This drug is a recent addition in drug therapy for Parkinson's disease which only provides symptomatic relief, an inhibitor of monoamine oxidase, type B (MAO-B),which slows the progression of the disease([218,219]) . In 1960, this drug was designed as an antidepressant. During the mid-1980s, seligiline was found to prevent the development of parkinsonian symptoms induced by the neurotoxin MPTP (1 -methyl-4-phenyl-1,2,3,6-tetrahydropyridine) . MPTP is oxidized by MAO-B into a free radical (1-methyl-4-phenyl-pyridinium ion), the actual neural toxin that destroyed the dopamine-producing neurons. Seligiline selectively inhibits MAO-B, which inactivates dopamine in the brain [220]. Seligiline protected neurons by decreasing the generation of free radicals by reducing the oxidative metabolism of dopamine. This drug protected damaged neurons through activation of trophic mechanisms. Salo and Tatton [221] through their study suggested that when rats after axotomy were treated with selegiline,it was found to produce increase number of surviving rats motoneurons as seligiline compensated for the loss of target derived trophic support caused by the axotomy[221].

Surgery for Parkinson's Disease

The treatment of PD has changed over the last few decades. Stereotactic surgery was used before 1967 to treat the rest tremor[222]. With the discovery of L-dopa (L-dihydroxy phenylalanine, a precursor of dopamine), along with dopaminergic agonist and peripheral decarboxylator to minimise side effects outside CNS, which became the mainstay of therapy. Recently, transplant of dopamine-rich tissues into the striatum is most talked about therapy which has created excitement as well as interest. The results were found to be disappointing as post mortem studies done on some patients who died after the procedure revealed little living adrenal tissues [223]. This procedure is now not being used. Since the year 1980, Swedish group conducted experiment in which foetal cells was transplanted from the ventral mesecephalon, which develops into substantia nigra normally. They performed the experiments on rodents to determine amount of foetal tissue. Optimal site of injection as well as the protocol for handling the foetal cells. Histologically, biochemically and behaviourally improvement of animal was demonstrated using rodents and monkeys. Foetal cell transplants were carried out in two patients. Results were published in science reporting that one of the two patients, there was increased dopamine metabolism on transplanted side using Positron emission transmission scanner (PET). Neurotransplantation has become an exciting area,the foetal cells use posed an ethical dilemma and its use was discouraged in USA as it may encourage abortion. In the year 1940s and 1950s , when humans were used as experimental subjects without animal

studies, ethical committee review became necessary so that the newer therapeutic approaches go through a proper trial procedures. One such trial is going on in Birmingham, UK which involves more than 36 patients which has shown encouraging result. Foetal cell transplant mechanism is not definite but it may do so:-

a) by forming new connection with host neurons,
b) secreting neurotrophic factors which causes regeneration of degenerating fibres.
c) Secreting dopamine which replenish the depleted striatum.

There has been evidence where neurotrophic factors plays an important role in primate study where unilateral replacement caused regeneration bilaterally[224].This is possible by the use of genetically engineered cell lines secreting dopamine or neurotrophic factors which obviate the need of foetal cells.

Non pharmacological treatment of Parkinson's disease

Drug and surgical therapies do not shorten the duration of the disease. They reduce the direct effects of the disease and prolongs the time of onset of disability. Optimal management of Parkinson's disease includes physical, speech, and psychosocial intervention including the pharmacological treatment maximizes quality of life. These intervention depends on whether the treatment is preventive, corrective, or compensated for deficits, and whether treatment is directed at impaired performance. Early physical intervention is focused on preventing the general effects of deconditioning including losses of range of motion, aerobic capacity, and strength [225,226]. Physical therapy intervention improved aerobic capacity and general fitness through cardiovascular, strengthening, and flexibility exercises. Physical therapy treated musculoskeletal changes that occur as a result of rigidity, bradykinesia, loss of mobility, and inactivity. Speech therapy improved language problems associated with low volume, poor articulation, and faulty speed, as well as improved inspiratory muscle strength. Comella *et al.* [227] recently demonstrated repetitive exercises for range of motion, endurance, balance and gait, and fine motor dexterity in areas of rigidity and bradykinesia. In summary medictions have reduced rigidity and bradykinesia as well as tremor. The direct effect are alleviated by drugs, secondary effects by physical intervention. Urgent pharmacological and non pharmacological treatment provide optimal improvement for the patients with parkinson's disease.

New molecular therapeutic approaches to Parkinson's disease

The molecular therapies are searched for basal ganglia disorders which eventually leads to neurobiological information and renews the interest in neurosurgical approaches. The motor symptoms of basal ganglia disorders involve two extremes. In Parkinson's disease, patients find it difficult to initiate movements where as in Huntington's disease and related choreoathetotic disorders, patients make unwanted movements. The two main brain structures has been placed for research to study these disorders: the dopamine-synthesizing substantia nigra of midbrain degenerating in Parkinson's disease, and the striatum of the forebrain, which degenerates in Huntington's disease. The loss of dopaminergic innervations of the striatum found to produce the hypokinetic disorder of Parkinson's disease and also the loss of striatal cells themselves produces hyperkinetic disorders such as Huntington's disease. Recently, molecular approach was demonstrated by the recent cloning of the Huntington's disease gene [228]. This was a major steps towards the development of a gene-based therapy for Huntington's disease, but in case of Parkinson's disease, it is not associated with a clear genetic defect. The success of L-DOPA used in relieving symptoms of Parkinson's disease was a pioneering example of a successful molecular-replacement therapy in neurology; L-DOPA is the biosynthetic precursor of dopamine. L-DOPA-based therapies lose effectiveness with time, and itself can induce abnormal and debilitating motor side effects (dyskinesia). The new molecular approaches were used to manipulate the dopamine system even without a clear genetic basis for Parkinson's disease. 'Knockout' mice have been generated that lack single dopamine receptor subtypes[229-233], or the dopamine transporter [234] by targeting gene inactivation. These mutant mice led to the development of new pharmacological treatment of dopamine-based disorders. This was responsible for the molecular mechanism of addictive drugs such as amphetamine and cocaine. Zhou and Palmiter [235] demonstrated combined knockout/transgene strategy to generate mutant mice that lack dopamine in the substantia nigra. The first generated knockout mice lacks tyrosine hydroxylase, an enzyme involved in synthesis of catecholamines such as dopamine and noradrenaline. The knockout mice was rescued by a tyrosine hydroxylase transgene that conferred synthesis of noradrenaline, in neurons of the noradrenergic locus coeruleus but not dopamine. The rescued mice showed signs of dopamine deficiency dying at about two weeks of age. When L-DOPA therapy was given, the mice lived and showed greater improvement in the most complex motor tasks. Development in molecular biology for treating Parkinson's disease is the cloning of genes encoding neurotrophins and growth factors. For example, glial-derived neurotrophic factor (GDNF) reported to halt the progression of degeneration in the substantia nigra induced by the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)[236] or by axotomy [237]. The signalling molecule Sonic hedgehog, induced neurons of the developing midbrain to differentiate with a dopaminergic phenotype *invitro* [238]. These results suggested new therapeutic approaches in which molecules promote differentiation or survival of dopaminergic neurons and delivered to appropriate targets by infusion techniques or transplantation. The renewed interest in neurological treatment for Parkinson's disease was to use new neurobiological information which determine targets for brain lesion. The idea is to prompt the neurosurgical effort involving motor disability found in hyperkinetic and hypokinetic movement disorders which reflect imbalances between ' direct' pathway(from striatum to motor executive regions) and ' indirect' pathway that modulates direct one [239-241].

Neurosurgical lesions are made first in MPTP treated parkinsonian monkeys [242] and in patients with Parkinson's disease to increase mobility by decreasing tonic direct pathway inhibition of the thalamus. The targets for the lesions are the subthalamic nucleus, the thalamus and the internal segment of the globus pallidus. Immediate and dramatic symptomatic relief can occur with a posteroventral pallidal lesion,as documented by Leksell [243] and Laitinen [244] and coworkers. Most striking key feature of the pallidotomy procedure is to confine the lesion to the most strictly 'motor' (posteroventral) part of the pallidum and/or associated fiber bundles. PET (positron emission tomography) scans [245,246] demonstrated normalization of metabolic activity in premotor/supplementary motor cortex following posteroventral pallidotomy. This result suggests that pallidal lesion decreases inhibition of thalamo-cortical circuits. The posteroventral pallidotomy procedure is effective in reducing L-DOPA-induced dyskinesias but it has not been clear that how it fits with enabling movement in parkinson's patients. Molecular therapies based on direct and indirect pathways were developed. Glutamate receptors are targeted to control the interaction between direct and indirect pathways [247]. Studies of knockout mice showed that dopamine D1 and D2 receptors selectively controls the expression of direct and indirect pathway neuropeptides. D1 receptor mutants have diminished basal ganglia expression of dynorphin [229] and substance P [229,230], the neuropeptides coexpressed with GABA in the direct pathway, whereas D2 receptor mutants showed loss of basal ganglia expression of enkephalin, the neuropeptide coexpressing with GABA in the indirect pathway [233]. These contrasting effects suggested that dopamine, acting at D1 and D2 receptors can affect the functioning of the direct and indirect pathways. The gene- and growth-factor-based therapies were devised to prevent neurodegeneration, strategies which were aimed at symptomatic relief of Parkinson's disease and other basal ganglia disorders which can be benefited from innovative combinations of molecular biology and neurosurgery.

DISCUSSION

Though the role of basal ganglia has been studied, but still the function of basal ganglia in health and disease remains controversial. Basal ganglia are closely related structure and have specific afferent and efferent connections with cerebral cortex and thalamus. Basal ganglia should not be studied as a nuclei or individual structure in fact it has a role dependent on other neighbouring structures. In this summary, the anatomical-pharmacological perspective has been analysed, it has been clear from the evidence based studies that basal ganglia is a collective group of structure and part of circuit, integral to not only voluntary motor function but also oculomotor, prefrontal, associative and limbic area. Thus, understanding of these anatomical intrinsic connections within basal ganglia has led to a breakthrough in determining the disorder of basal ganglia and further extended study is required in order to evaluate and provide better therapeutic implications for the diagnosis, treatment and cure of basal ganglia disease. Although, the progress has been made in order to provide symptomatic treatment for the movement disorder, but still therapies targeting pathogenesis are still lacking. Thus, in order to develop such therapeutic strategies, better understanding of pathophysiological mechanisms are required which should be purely based on anatomical, physiological and pharmacological knowledge of basal ganglia.

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