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Current Neuropharmacology, **2019**, *17*, **165-175**

REVIEW ARTICLE

Insight Into the Emerging Role of Striatal Neurotransmitters in the Pathophysiology of Parkinson's Disease and Huntington's Disease: A Review

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ARTICLE HISTORY

Received: June 07, 2017
Revised: November 06, 2017
Accepted: February 28, 2018

DOI:
10.2174/1570159X16666180302115032

Abstract: Alteration in neurotransmitters signaling in basal ganglia has been consistently shown to significantly contribute to the pathophysiological basis of Parkinson's disease and Huntington's disease. Dopamine is an important neurotransmitter which plays a critical role in coordinated body movements. Alteration in the level of brain dopamine and receptor radically contributes to irregular movements, glutamate mediated excitotoxic neuronal death and further leads to imbalance in the levels of other neurotransmitters *viz*. GABA, adenosine, acetylcholine and endocannabinoids. This review is based upon the data from clinical and preclinical studies to characterize the role of various striatal neurotransmitters in the pathogenesis of Parkinson's disease and Huntington's disease. Further, we have collected data of altered level of various neurotransmitters and their metabolites and receptor density in basal ganglia region. Although the exact mechanisms underlying neuropathology of movement disorders are not fully understood, but several mechanisms related to neurotransmitters alteration, excitotoxic neuronal death, oxidative stress, mitochondrial dysfunction, neuroinflammation are being put forward. Restoring neurotransmitters level and downstream signaling has been considered to be beneficial in the treatment of Parkinson's disease and Huntington's disease. Therefore, there is an urgent need to identify more specific drugs and drug targets that can restore the altered neurotransmitters level in brain and prevent/delay neurodegeneration.

Keywords: Movement disorders, neurotransmitters, striatum, dopamine, glutamate, GABA, adenosine, acetylcholine.

1. INTRODUCTION

Movement disorders like Parkinson disease (PD) and Huntington disease (HD) rank among the most common neurodegenerative disorders and are categorized as a complex group of neurological illness or diseases that manifest either increase or decrease in body movements [1]. Movement disorders mainly affect the momentum, smoothness, class, and easiness of movement. PD is a hypokinetic movement disorder and progressive neurodegenerative disorder, which results from the selective degeneration of dopaminergic neurons in substantia nigra pars compacta (SNpc) and is characterized by stable behavioral motor deficits [1]. The principal clinical features of PD include tremor, bradykinesia, akinesia and rigidity [1]. HD is a progressive neurodegenerative and hyperkinetic movement disorder which results from mutation in huntingtin gene, and characterized by progressive motor and non-motor symptoms [2]. The pathological hallmark that underlies HD is selective degeneration of GABAergic medium spiny neurons in striatum nuclei of basal ganglia. The cardinal clinical features of HD include both involuntary movement (chorea) and rigidity or dystonia and abnormal eye movements [2]. A considerable progress has been made in elucidating the pathophysiological basis of these disorders but exact mechanism is not known till date. Numerous strides have indicated the potential role of neurotransmitters alteration, excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation in the pathophysiology of PD and HD. Despite these several proposed mechanism, various clinical and preclinical studies have implicated altered level of neurotransmitters contributing to the striatal dysfunctioning as seen in movement disorders. It is believed that PD and HD progression is worsened by alteration in neurotransmitters level and their receptor density like dopamine, nor-epinephrine, serotonin, GABA, glutamate and adenosine in basal ganglia region of midbrain [3-5]. Behavioral symptoms in PD and HD have been reported to directly and indirectly correlate with neurotransmitters imbalance in brain [2]. Basal ganglia consist of numerous unified sub cortical nuclei with major projections extending to the cerebral cortex, thalamus, and brain stem nuclei which plays major role in controlling body movements. The principal neuropathological hallmarks of movement disorders like PD and HD are selective relapse of dopaminergic neurons in SNpc and GABAergic medium spiny neurons in striatum (GABAergic

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1570-159X/19 $58.00+.00

neurons), respectively [1, 2]. Loss of these neurons produces deficiency of dopamine in basal ganglia and further contributes to disrupted balance of all the neurotransmitters in the brain. This disrupted balance of neurotransmitters substantially contributes to progression of movement disorders like PD and HD. This review focuses on the role of individual brain neurotransmitters in the pathophysiology of movement disorders and will try to solve the question concerning the progressive neurodegeneration associated with movement disorders i.e. "What is the string of proceedings that leads to neuronal degeneration with respect to neurotransmitters imbalance?"

2. ORIGIN OF MOVEMENT DISORDERS: BASAL GANGLIA AND STRIATAL ORGANIZATION

Basal ganglia consist of a number of nuclei of forebrain and midbrain which are functionally correlated and connected to each other as well as to different parts of cerebral cortex and thalamic nuclei. The four primary nuclei of the basal ganglia are striatum, Globus pallidus (GP), substantia nigra and subthalamic nucleus (STN). The striatum is further subdivided into the caudate nucleus, the putamen, and the ventral striatum. GABAergic MSNs make up 90–95% of striatal neuronal population and accept glutamatergic projections from the cortex and thalamic nuclei [2]. There are two different striatal pathways which expresses different dopamine receptors and neuropeptides [4, 6]. Direct pathway express dopaminergic D_1 receptors, substance P and dynorphin and projects into the SNpr and GP_i [4, 7] whereas the indirect pathway expresses dopaminergic D_2 receptors, adenosine A_{2A} receptors, and enkephalin, and projects to the GP_e [8-10]. The remaining 5–10% of striatal neuronal papulation are GABAergic interneurons (which provide feed forward inhibition to MSNs) and cholinergic inter neurons (which are responsible for maintaining acetylcholine levels in the striatum) [11-13].

3. ALTERATION IN NEUROTRANSMITTER LEVELS IN MOVEMENT DISORDERS

Equilibrium exists between the direct and indirect pathway and is responsible for coordinated body movements. An imbalance in the activity of these two pathways results in altered body movements i.e. hyperkinetic and hypokinetic movements in HD and PD, respectively [4, 14]. Neurotransmitters, like dopamine, acetylcholine, glutamate and GABA are mainly involved in motor coordination and alterations in the levels of these neurotransmitters results in motor deficits. The striatal level of various neurotransmitters in the PD and HD are summarized in Table **1**. Therefore, alteration in levels of these neurotransmitters is another hallmark of movement disorders.

4. DOPAMINE

Dopamine represents itself as the most ubiquitous catecholaminergic neurotransmitters in the midbrain and dopaminergic neurons are mainly found in SNpc, ventral tangmental area (VTA) and arcuate nuclei. Dopaminergic neurons comprise of four major dopaminergic systems i.e. nigro-striatal pathway, mesocortical and mesolimbic pathway and tubero-infundibular pathway, which help in regulating locomotor activity, cognition, emotion and positive reinforcement [15, 16]. A Dopaminergic system is involved in various physiological functions in brain and dysfunction of this systems leads to disorders like PD, HD and ADHD [17]. Dopamine has been reported to act as regulatory neurotransmitter in basal ganglia but dopamine or its metabolites might be neurotoxic at higher concentrations. Principally, dopamine exerts its neurotoxic effects by enzymatic and non-enzymatic mechanism which yield redox-active compound (ROS) and quinones/semiquinones. Monoamine oxidase is responsible for the enzymatic metabolism of dopamine into 3,4- dihydroxyphenylacetaldehyde (DOPAC) and hydrogen peroxide (H_2O_2). Further, DOPAC is enzymatically metabolized by the action of catecholamine- O- methyl transferase (COMT) to homovanillic acid (HVA) [18]. The toxic metabolite H_2O_2 further reacts with heavy metals such as iron (Fe^{2+}) to produce more toxic hydroxyl radicals [19]. In addition to this, dopamine undergoes non-enzymatic oxidation with molecular O_2 to form highly toxic semiubiquinones and superoxide free radicals [19].

5. DOPAMINE IN PD

It has been reported that optimal dopamine levels are required for efficient behavior and cognitive performance and shift in level of dopamine in dorsal striatum direct to altered motor behavior in PD. The level of metabolites of dopamine *i.e.* DOPAC and HVA has been found to be substantially increased in striatum of toxin (MPTP, Rotenone, 6-OHDA) induced animal models of PD [1, 20]. Numerous clinical as well as preclinical studies evidenced major loss of D_2 receptors as compared to D_1 receptors in SNpc and GPe nuclei's in the early stages of PD [21]. Various evidences have indicated vulnerability to both D_1 and D_2 receptors in late stages in PD patients. SNpc dopaminergic neuronal population is the most vulnerable neurons in PD due to multifaceted morphology, high ATP requirement, high calcium influx, and dopamine metabolism. Parkin knockout mice with a knockout of exon 3 have shown increased striatal dopamine whereas parkin knockout mice with a knockout of exon 2 demonstrate age associated decrease in striatal dopamine level and amplify D_1/D_2 receptor binding [22]. Elevation in striatal dopamine level and increased dopamine overflow has been reported in the striatum region of DJ-1 transgenic mouse [22]. Transgenic mice models have been developed to explore the function of PD-linked genes (e.g. alpha-synuclein, DJ-1, Parkin, and PINK1) in progression of PD. MitoPark mouse, is newly developed genetic model of PD, which has a specific dopaminergic neuron knock-out [22]. Numbers of studies from our lab have shown increased level of dopamine and its metabolites in MPTP, rotenone and 6-OHDA induced animal models of PD [20, 23]. Therefore, it can be concluded that dopamine levels get altered in animal models and restoration of dopamine level might prevent the development of PD symptoms.

6. DOPAMINE IN HD

Abnormal dopamine function contributes significantly to the motor and cognitive symptoms in HD. Numerous strides have indicated that elevated dopamine level in HD stimulates chorea while decline in dopamine guide akinesia [24, 25], thus producing biphasic movement in early and late phase of

Table 1. Striatal level of various neurotransmitters in the Parkinson's disease and Huntington's disease.

Sr. No.	Striatal Neurotransmitter	Parkinson's Disease	Huntington's Disease
1.	***Dopamine***	Decreased	Increased (Early stages) Decreased (Late stages)
2.	***GABA***	Decreased	Decreased
3.	***Glutamate***	Increased	Increased
4.	***Adenosine***	Decreased	Decreased
5.	***Acetylcholine***	Increased	Increased

HD. Earlier studies have showed that elevated dopamine levels in brains of HD patients and it was thought that dopamine-reducing agents and dopamine receptor agonists could be of therapeutic value in HD. Later on, clinical studies have revealed that dopamine level increases in the early stages of the disease [26] whereas decreases in late-stage HD patients [27, 28]. Therefore, it has been concluded that HD disease progression shows biphasic and time- dependent changes with respect to dopamine level. Using PET and autoradiography techniques, it has been demonstrated that dopamine signaling is disrupted very early in HD as indicated by reduction in striatal D_1 and D_2 receptor density, even in asymptomatic HD patients [29-31]. Major loss of the D_2 receptor has been reported in the HD brain. D_1 receptors accommodates moderate decrease in their density in SNpc and GPe in early phases of HD. Using transgenic mouse models, it has been revealed that dopamine release decreases during late stages of the HD and these reports were found to be consistent with human HD. It has been reported that striatal dopamine and its metabolites level are decreased in both R6/2 and YAC 128 mice [32-34]. Significant reductions were seen in mRNA levels of striatal D_1 and D_2 receptors in late stage YAC 128 mice, but not in BACHD mice [35]. The tgHD rat model displays an increase in striatal dopamine levels in the SNpr and VTA [36]. Using 3-NP and QA induced animal models of HD, our lab has demonstrated decreased levels of dopamine and its metabolites in Wistar rats [2, 37]. Since the results from animal models are not entirely consistent, future studies on dopamine release dynamics in HD will be needed to parse out changes in dopamine levels that occur in the early and late disease stages.

7. GLUTAMATE

Glutamate is the most abundant and excitatory type of neurotransmitter present in the central nervous system and mediates its action by acting upon ionotropic (N-methyl-D-aspartate (NMDA), α-amino-3-hyroxy-5-methylisoxazole proprionic acid (AMPA) and Kainate or metabotropic (mGlu1-mGlu8) receptors [38]. Glutamate plays central role in mediating excitatory neurotransmission, as alterations in its homeostasis results in the creation of neurotoxic or excitotoxic events [39]. These events are principally initiated after the activation of the NMDA, AMPA receptors, and voltage gated calcium channels followed by massive influx of extracellular calcium. Numerous clinical and pre-clinical studies have clearly pointed out glutamate induced excitotoxic neuronal death in neurodegenerative diseases like PD and HD [40, 41]. An alteration in membrane permeability and polarity, due to defect in mitochondrial respiration results in the removal of voltage dependent extracellular magnesium (Mg^{2+}) block, which normally blocks the calcium (Ca^{2+}) influx. Glutamate is also the principal excitatory neurotransmitter in the basal ganglia region of midbrain, and is the major culprit for the various motor deficits as seen in movement disorders like PD and HD [37].

8. GLUTAMATE IN PD

NMDA receptors are primarily composed of NR1, NR2A and NR2B subtypes in the striatum nuclei [42]. Enhancement in glutamatergic signaling is associated with hyperphosphorylation of these subunits and is responsible for development of levodopa induced dyskinesia (LID) in both the 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced animal models of PD [43, 44]. Normal glutamate concentration is required for the physiological brain functioning, but, increase in its concentration beyond normal limit leads to excitotoxic neuronal death [45, 46]. The extreme release of glutamate into the SNpc from both the cerebral cortex and the STN, is one of the pathophysiological hallmark in PD. In the brain, glutamatergic transmission plays a pivotal role in the normal physiology of those systems which modulate motor activity (especially in the basal ganglia). In pathological conditions such as PD, glutamatergic transmission is considerably affected, thereby contributing to the alterations involved in this disorder. Neurotransmitter alterations in direct and indirect nigro-striatal pathways occurring in PD are known to involve glutamatergic hyperactivity. It has been recommended that this hyperactive pattern of glutamate plays a dual role: on one hand, it promotes excitotoxic events that contribute to the neurodegenerative process; while on the other hand, it contributes to the pathophysiology of dyskinesias and motor fluctuations that have been associated with the chronic use of levodopa (L-DOPA). The activation of ionotropic glutamate receptors (NMDA, kainate and AMPA) initiates the influx of Ca^{2+} ions, which further triggers a variety of impending destructive cascades. Studies from our lab have clearly shown increased level of glutamate and hyperactive glutamatergic signaling in striatum nuclei using HPLC-ECD [37]. Therefore, it can be concluded that agents who restore normal glutamatergic signaling might prove to be of therapeutic interventions and bypass the severe motor side effects associated with current dopamine replacement therapy.

9. GLUTAMATE IN HD

Excitotoxicity is one of the key hypotheses that endeavor to explain the severe vulnerability of the GABAergic MSN of the striatum resulting in neurodegeneration in HD. In the context of HD, this hypothesis lay downs that unnecessary activation of glutamate signaling, decrease in glutamate uptake by glial cells and hypersensitivity of post- synaptic glutamate receptors on striatal neurons, results in altered Ca^{2+} homeostasis, mitochondrial dysfunction, and death of striatal MSNs [47, 48]. Further, excitotoxic hypothesis is supported by radio-ligand binding studies in post-mortem HD brain tissues. These studies revealed that lopsided loss of NMDARs in the striatum nuclei of HD patients occurs very early in symptomatic HD and, in very few cases of pre-symptomatic stages. In view of the fact that NMDA receptors and excitoxicity are well correlated to each other, they emerge as first glutamate receptors studied in mouse models of HD. Normally, glutamate and dopamine systems works in conjunction with each other and provide an excellent balance in which glutamate-induced excitation is well modulated by dopamine in the basal ganglia and cortex.

Selective loss of NMDA and AMPA receptors have been reported in both striatum and cortex of HD patients [49, 50] whereas some studies have reported non-significant loss in the caudate nuclei of striatum and rejected any change in the cortex [51]. Reduced glutamate uptake has been reported in the prefrontal cortex of HD patients, proposing that altered glutamate uptake might be responsible for motor dysfunction and neurodegeneration in HD [52]. It has been revealed that striatal NMDA mRNA decreases at 8-12 week in R6/2 mice and AMPA receptors population decreases at 12 week in R6/2 mice [53, 54]. Moreover, reduction in basal striatal glutamate levels in R6/1 mice by 43% at 16 weeks of age [55]. It has been found that AMPA and NMDA currents were augmented in R6/2, YAC128 and HD100 mice models of HD [56-58]. In contrast to this, NMDA and AMPA receptor-induced currents in striatum and cortex were found to be reduced in pre-symptomatic R6/2 mice and were found to be unchanged in symptomatic R6/2 mice when compared to control [53, 59]. Using toxin based animal models of HD (3-NP and QA), it has been documented that glutamate levels were significantly increased in striatum [37].

10. GABA

GABA is the principal inhibitory neurotransmitter present in the CNS and was first discovered by Flory and Bazemore in 1957. The principal neurons in the striatum i.e. about 77-97% of medium spiny projection neurons are GABAergic neurons [60]. GABA principally acts *via* two types of receptors viz. ionotropic ($GABA_A$ and $GABA_C$) and metabotropic $GABA_B$ receptors. GABAergic ionotropic receptors belong to the family of ligand gated ion channels and primarily involved in synaptic transmission whereas metabotropic $GABA_B$ receptors belong to family of GPCR and are involved in mediating neuromodulatory effects of GABA. Generally, neurons are activated by glutamate, and depressed by GABA whereas alteration in activation of these two systems is responsible for pathophysiological basis of neurological disorders like PD and HD.

11. GABA IN PD

Significant alteration has been suggested in GABAergic neurotransmission within basal ganglia circuit in PD. Increased mRNA levels of glutamate decarboxylase (GAD) viz. (GAD67 and GAD65), a GABA-synthesizing enzyme has been reported in GP_e, GP_i and SNpr nuclei of basal ganglia. Using *in-vivo* microdialysis technique, it has been revealed that mRNA levels of GAD67 were increased but not GAD65 [61, 62] whereas GABA levels were also found to be increased in GP_e [62]. It has been documented that the expression levels of $GABA_A$ and $GABA_B$ receptors were found to be changed whereas $GABA_A$ receptor binding and mRNA levels were found to be decreased in the GPi/SNr of PD subjects. Furthermore, using clinical and pre-clinical evidences, mRNA as well as protein levels of $GABA_B$ receptors were found to be decreased in GPe, and increased in GPi [63-65]. The specific pattern of changes in $GABA_A$ and $GABA_B$ receptor as observed in the GPe and GPi/SNr appear to be compensating for the over-activated striatal-GPe indirect pathway and under-active striatal-GPi direct pathway [2]. Numerous strides of pieces from our lab have clearly shown decreased level of GABA in striatum in MPTP, rotenone and 6-OHDA induced animal models of PD [23].

12. GABA IN HD

GABA, a principal inhibitory neurotransmitter in CNS has been assumed to be responsible for spontaneous involuntary movements in HD [66]. The GABAergic-MSNs are most abundant neuronal population in striatum (> 90%) and most vulnerable to neurodegeneration in HD [20]. It has been documented that decreased level of GAD and GABA were found in the post- mortem HD brains [67, 68]. Further, it has been revealed that larger aspiny inter-neurons remain unaffected whereas spiny neurons get brutally lost in the early stages of HD [69]. The early loss of GABA receptors in striatum probably represents the striatal neurodegeneration. However, increased GABA receptors density in the GPe, might represents denervation super-sensitivity in basal ganglia in HD [3]. Alteration in GABA signaling are not confined to the striatum area but decreased GAD and GABA levels were also reported in cerebral cortex [70]. It has been reported that glutamate release is also regulated by GABA receptors located on cortico-striatal terminals [71, 72] and activation of these receptors wields a significant inhibitory effect on glutamate [73, 74]. It is well established that imbalance between inhibitory neurotransmitters and excitatory neurotransmitters of indirect and direct pathway significantly contribute to the pathophysiology of HD. In particular, excessive inhibition of enkephalin- positive GABA-ergic neurons reduces striatal output through the indirect pathway. This leads to reduced inhibition of the GP_e and could explain the fact why lesions ameliorate HD symptoms in this area [73, 75]. Studies from our lab have shown reduced level of GABA in 3-NP and QA induced animal models of HD [37].

13. ADENOSINE

Adenosine is metabolic product obtained from the degradation ATP/AMP and serve as a important signaling molecule in the nervous system. Adenosine is well established to

perform the function as neuromodulator and a homeostatic adjuster in the CNS. The neuromodulatory role of adenosine is based on the controlled activation of inhibitory A_1 receptors (A_1R) and facilitatory A_{2A} receptors ($A_{2A}R$), regulating post-synaptic glutamatergic actions. A_1R inhibits glutamate mediated excitatory transmission, whereas A_{2A} are involved in enhancing synaptic plasticity. This neuromodulatory role of adenosine makes it valuable and effective therapeutic target in different neurodegenerative conditions such as ischemia, epilepsy, PD, HD or AD and also seem to afford benefits in some psychiatric conditions.

14. ADENOSINE IN PD

Adenosine A_{2A} receptors are selectively located in the indirect output pathway of basal ganglia. Due to its location, it can be targeted to modulate the output from the striatum and to control motor components of PD [76, 77]. To be sure, the efficacy of A_{2A} antagonist in modulating basal ganglia neurotransmission has shown promising results by improving motor dysfunction in experimental models of PD. Studies have documented that increased density of adenosine A_{2A} receptors in striato-pallidal pathway is correlated with the development of LID in PD [77, 78]. These results suggest that use of A_{2A} antagonists will produce effective improvement in humans without aggravating noticeable dyskinesia. In support of this, treatment with A_{2A} antagonist istradefylline lessens off time in moderate- to late-stage patients with LID. Adenosine and its receptors modulators exert appropriate actions to improve pathophysiological mechanisms in PD, lifting the opportunity of their utilization as neuroprotective agents. Both, clinical and preclinical data strongly stand in support for the use of A_{2A} antagonists in defending dopaminergic neurons and modulating the onset and progression of PD [76-78]. In addition to this, recent studies from our lab showed decreased level of adenosine in response to MPTP, rotenone and 6-OHDA treatment [23].

15. ADENOSINE IN HD

As stated above, uppermost expression of adenosine A_{2A} receptors is limited to basal ganglia, circuit particularly in the corpus striatum region, which is believed to be involved in controlling complex motor functions [76]. A_{2A} receptors are located pre as well as post-synaptically, but interesting fact is A_{2A} receptors are post-synaptically present on the GABAergic striato-pallidal neurons. These neurons projects to the GP nuclei, which enclose the enkephalin and are supplement with dopamine D_2 receptors [77, 78]. This location of A_{2A} receptors makes them promising target for therapeutic use in HD subjects. In excitotoxic-animal models [Quinolinic acid (QA)-induced striatal lesions, cerebral ischemia], inhibition of A_{2A} receptor have been reported to produce neuroprotective effects *via* inhibiting glutamate release [79-84]. Adenosine receptors have unique distribution in the basal ganglia circuit, particularly in caudate, putamen and the GP areas, which are highly innervated by dopamine [85]. Altered A_{2A} receptor expression and signaling has been well documented in various experimental models of HD. Increased A_{2A} adenosine receptor density has been reported in striatal-derived cells which are wangled to express mhtt [86], thus, unlocked the possibility that aberrant expression of A_{2A} receptor represent itself as potential novel biomarker in HD subjects [86]. This has been proved to be useful in monitoring disease progression and assessing the efficacy of novel neuroprotective strategies in HD [87]. In addition, increased A_{2A} receptor density has been reported in a 3- nitropropionic acid (3-NP) induced animal model of HD [88]. Further, recent studies from our lab showed decreased level of adenosine in 3-NP and QA induced animal model of HD [37]. Furthermore, it has been proposed that modulation of striatal damage by using A_2A receptors modulators may lead to opposite outcomes depending on their anatomical distribution. Therefore, the use of A_{2A} receptor antagonists in the treatment of HD should be considered with caution.

16. CANNABINOIDS

Cannabinoids primarily act *via* two types of receptors viz. CB_1 (present in CNS) and CB_2 (present in immune system). CB_1 receptors and their endogenous ligands (AEA and 2-AG) are mainly expressed and found in MSNs of striatum. These receptors are concentrated on both pre-synaptic and post-synaptic neurons, innervating GPe, GPi, SNpc and SNpr. CB_1 receptors are present pre-synaptically in excitatory projection from STN to GPi/SNpr as well as excitatory terminals from cortex to striatum. Due to high levels of cannabinoid receptors and endocannabinoids in the basal ganglia, it is well established that endocannabinoids signaling system has potential role in the controlling motor dysfunctions as well as in the basal ganglia related movement disorders like PD, HD and TD. CB_1 receptors are expressed along with D_1 and D_2 receptors on GABAergic striatonigral and striatopallidal neurons, respectively. Cannabinoids by acting on CB_1 receptors modulate the activity of inhibitory GABAergic efferent MSNs and excitatory afferent glutamate neurons. Simultaneous activation of D_2 and CB_1 receptor has been reported to decrease motor response and same is reported to occur with simultaneous activation of D_1 and CB_1 receptors.

17. CANNABINOIDS IN PD

Several studies have reported an alteration in cannabinoid signalling in PD, which initially compensate the loss of dopamine levels in basal ganglia. Using animal models of PD (6-OHDA and Reserpine treated animals), it has been revealed that CB_1 receptor expression increases and degradation of Cannabinoids by FAAH decreases, resulting in overactivation of CB_1 receptor mediated endocannabinoid signaling [89, 90]. In addition to this, CB_1 receptors population and CB_1 receptor-G-protein coupling were found to be increased in MPTP-lesioned rats and in basal ganglia of PD patients, resulting in CB_1 mediated increased cannabinoid signalling. In contrast to this, some studies have shown decrease in CB1 receptor expression in basal ganglia in PD [89, 90]. Several studies have shown preclinical potential of CB1 receptor agonist as well as antagonist in treatment of PD but despite of their high therapeutic potential, their use in PD is still controversial and is a matter of further research.

18. CANNABINOIDS IN HD

Generally, cannabinoids act together in conjunction with three other major neurotransmitters of the basal ganglia cir-

cuit: GABA, glutamate and dopamine [89]. Dopamine is the chief neurotransmitter released by SN neurons and these neurons further project their fibers into corpus striatum. Continuous loss of dopaminergic neurons of SN results in lessens dopamine concentrations in the striatum region of basal ganglia. This decline in dopamine level is accountable for the regular manifestation and progression of slowness, rigidly, and tremor, the signs and symptoms of PD. It is well established that CB_1 receptors are co-localized with dopaminergic receptors i.e. D_1 and D_2 receptor [89, 90]. In addition to this, activation of CB_1 receptor by endogenous ligands or cannabinoid agonist results in the inhibition of dopaminergic D_1 and D_2 receptors in the striatum. This inhibition of dopaminergic system by cannabinoids can be well correlated with reduced motor functions and sedation. In addition to this, activation of the CB_1 receptor alter the release pattern of other neurotransmitter and modulate a variety of processes, such as regulation of motor behavior, synaptic plasticity, memory formation and pain parception [90]. Several studies have revealed complete loss of CB_1 receptor binding in the various nuclei of basal ganglia like SN, GP and up to some extent in the putamen nuclei in HD. Using autoradiography technique, it has been documented that human brain showed a complete loss of the CB_1 receptor in HD patients in striatum nuclei [90].

19. ACETYLCHOLINE

The cholinergic system in the CNS is divided into inter neuronal system and projection neuronal system. The former system contains cholinergic inter-neurons with acetylcholine as neurotransmitter whereas in the latter system, acetylcholine is provided all the way through axons of cholinergic neurons whose somata are localized in other nuclei. The major brain areas including, cerebral cortex, fall in the latter category, whereas the former system constitute the striatum, the nucleus accumbens and olfactory tubercle. In addition to this, these nuclei are highly innervated by dopamine. This notable profusion of acetylcholine and dopamine in the striatum nuclei sturdily suggests that both of them play critical role in the physiological functioning of the basal ganglia. Thus, any alteration or imbalance between cholinergic signaling and dopaminergic signaling in the striatum nuclei give rise to variety of neurological disorders, such as PD, AD and HD. Since long time, it is well established that nicotinic acetylcholine receptors (nAChR) are highly articulated on nerve terminals of dopamine neurons. Furthermore, nicotinic agonists and endogenous cholinergic ligands powerfully regulate dopamine release through nAChR in the striatum nuclei [3, 20].

20. ACETYLCHOLINE IN PD

The elevated levels of ACh in PD were believed to involve the effect of dopamine D_2 receptors on cholinergic neurons. On the other hand, cholinergic neurons also have D_5 receptors, which perform opposite actions to D_2 receptors. In contrast, studies have revealed that auto inhibition of ACh release was predominantly mediated by M_4 receptors in the striatum using brain slices obtained from M_2 and M_4 receptor single knockout mice. Further, this auto inhibitory activity by M_4 receptors was disturbed by upregulation of RGS4 (regulators of G protein signaling 4) proteins. In addition to this, the expression of RGS4 is negatively modulated by protein kinase A (PKA), which is normally up-regulated by the activation of D_5 receptors on cholinergic neurons. Consequently, the cholinergic neurons continuously releases ACh without having a feedback inhibition by M_4 receptors in PD and seems that elevated ACh levels in striatum severely and selectively affects the indirect-pathway neurons and contribute to motor and non-motor symptoms in PD [20, 91].

21. ACETYLCHOLINE IN HD

Clinical studies have documented a severe loss of Ach synthesizing enzyme choline acetyltransferase (ChAT) and Ach in HD patients. Further, it has been reported that alteration in the levels of dopamine and Ach may contribute to motor dysfunction in HD [3]. The activity of ChAT has been reported to decrease in the nucleus accumbens, septal nuclei, and hippocampus [20]. The density of muscarinic M_2 receptors decreases in the striatum and GPe but remain unaffected in the SNpr and cortex [91]. Decreased level of choline, a precursor required for Ach synthesis have been observed in cerebrospinal fluid samples of HD patients.

22. NEUROPEPTIDES

The direct and indirect pathways of basal ganglia circuit differ in the presence of peptidergic co-neurotransmitter, in addition to GABA as common neurotransmitter. The striatolateral-pallidal neuron contains enkephalin as co-transmitters whereas striatomedial pallidal and striatonigral neurons contain Substance P and dynorphin as co-transmitters [92]. Substance P is member of small peptide family called tachykinins. The tachykinins family of peptides has wide distribution in both central as well as peripheral tissues, and serves the function of neurotransmitter, neuromodulator, or neurotropic-like factors *via* acting on NK-1, NK-2 and NK-3 receptors. NK-1, NK-2, and NK-3 receptors are indulged in regulating various biological activities, such as pain perception, inflammation, smooth muscle contraction, and vasodilation.

23. SUBSTANCE P AND ENKEPHALIN IN PD

[93] have documented that direct delivery of substance P (SP) or selective neurokinin-1 receptor agonist into nigral region results in enhanced striatal dopamine metabolism in PD. Striatum has high level of SP where it binds to NK1 receptors expressed on dopaminergic nerve terminals, followed by internalization of the SP/NK1 complex and ultimately results in excitation as well as dopamine release into the striatum [94]. However, dopamine enhances the SP release within the nigral region by binding to D_1 receptor located on striatal SP-GABAergic neurons. Studies have shown that SP antagonist treatment result in neuroprotection in mouse model of PD. In addition, it has been revealed that over expression of phosphorylated Enk (pEnk) in the striatum region of MPTP mice results in increased levels of the ENK in the striatum, increased density of Enk-positive fibers in GP and SN and striatal tyrosine hydroxylase-positive fibers in the striatum. Furthermore, striatal over-expression of pEnk in MPTP treated mice contributes to higher level of dopamine as well as dopamine turnover [95].

24. SUBSTANCE P AND ENKEPHALIN IN HD

The gradual loss of GABAergic MSN has preferential impact in HD, but decreased concentrations of co-neurotransmitter peptides have been reported in striatal areas. SP has been reported to be significantly decreased in the SN and GPi, but with slighter reductions reported in the striatum, SNpc, and GPe. Studies have documented reduction of SP levels in the spinal cord of HD patients. The co-transmitters of indirect pathway Enk, restricted only to GABAergic MSN that project to the GPe, has been reported to be decreased levels in HD patients [68]. Decrease in mRNAs levels of SP and Enk have been detected in early-stage HD patients, demonstrating that GABAergic MSN dysfunction is an early happening in HD pathogenesis. The degeneration of indirect pathway striato-external pallidal neurons is forecasted to result in involuntary movements, whereas degeneration of direct pathway striatonigral and striato-internal pallidal neurons results in bradykinesia [96, 97].

CONCLUSION

Neurotransmitters imbalance in the basal ganglia has been considered major culprit which substantially contributes to the pathophysiology of movement disorders. Considerable evidences from clinical and preclinical studies described in this review stand in support of the notion that altered neurotransmitters imbalance in basal ganglia region specifically dopamine, glutamate, GABA and glutamate are solely responsible for the behavioral and motor deficits as observed in PD and HD. Various toxins as well as transgenic animal models have been developed to know the mechanism underlying neurotransmitters alteration but the exact reason underlying this alteration is not known yet. Although, drugs have been developed that prevent alteration in brain neurotransmitters but the exact understanding of the mechanism by which these drugs work has not yet been fully explained. A better understanding of these mechanisms could serve as a guide for scientists to develop more efficient drugs for movement disorders associated with neurotransmitter imbalance. Thus, it can be concluded that restoring the neurotransmitters balance in the brain may prevent or delay the symptoms of movement disorders.

FUTURE DIRECTIONS

On the basis of data reviewed and discussed above, it is quite clear that neurodegeneration in the basal ganglia circuit produces neurotransmitters alteration, further giving rise to various motor and non motor symptoms. It is well established that dopamine in conjunction with other neurotransmitters like glutamate, GABA, endocannabinoids, adenosine plays major role in coordinating balanced body movements. Alteration in dopamine levels mimics glutamate induced excitotoxic neuronal death which further leads to caspase activation, calcium overload, neuroinflammation and accompanied by alteration in all other neurotransmitters signalling. A number of preclinical studies have revealed that dopamine and its metabolites i.e. DOPAC and HVA decrease in the late stages of PD and HD. Similar results have been obtained from post-mortem studies. But still it is a matter of debate whether metabolites are decreased or not; as a number of studies have reported an increase in metabolites level. The key findings from the research done so far are; alteration in dopaminergic system in basal ganglia is central player in the pathophysiology of movement disorders specifically PD and HD. There are a lot of weak points in the research done so far as none of the animal models reflect same pathophysiology as seen clinically. Thousands of drugs have been tested against various animal models and shown to exhibit neuroprotection but as we move from bench to bed side, the efficacy of those drugs diminished. The exact reason for their failure is not known; either some of them produce severe adverse effects or some of them fail to provide optimal neuroprotection. There is extreme need to improve the quality of research in the field of neuroscience so that better results can be yielded both pre-clinically as well as clinically. Movement disorders are challenge among the neuroscientist as no therapy is available. Current therapy for movement disorders is only palliative; temporarily ameliorate the symptoms but do not slow progressive loss of neurons in basal ganglia. Accordingly, new approaches are urgently needed to combat neurodegeneration in basal ganglia. A complete or better understanding of the complex neurodegenerative mechanism will be beneficial and will provide strong basis to design efficacious drug therapy. Recently, a number of natural potent antioxidants like curcumin, lycopene, Epigallocatechin, Epigallocatechin-3-gallate, tocopherols, resveratrol, polyamines, antidepressants and statins have been successfully tested in various animal models of movement disorders. These compounds have been shown to exhibit potent antioxidant, anti-inflammatory and antiapoptotic properties but none of the research has shown their effect on neurotransmitters level. These compounds still lack neurotransmitters data, in this regard long term studies should be carried out beyond proof of concept studies. Also, some more preclinical studies should be carried out to get more reliable data on each and every aspect of neurodegeneration so that these natural compounds can be taken to clinics. It is our strong belief that in future, there is a need for exhaustive studies to delineate the relationship between movement disorders and the neurotransmitters levels. We expect more confirmative studies supporting the notion that restoring the dysregulated neurotransmitters level in striatum may be beneficial in the treatment of movement disorders. Importantly, more studies in future are warranted that will generate mechanistic data to clearly explain the role of neurotransmitters in pathophysiology of movement disorders so that better and efficacious drug therapy can be developed for these lethal brain disorders. We suggest an interdisciplinary approach and greater role of clinical and molecular pharmacology in unraveling the mystery of role of various neurotransmitters in pathophysiology of movement disorders.

ABBREVIATIONS

3-NP	=	3-nitropropionic acid
3-NP	=	3-nitropropionic acid
CNS	=	Central nervous system
COMT	=	Catechol-o-methyl transferase
CREB	=	cAMP response element binding protein
DOPAC	=	Dihydroxyphenylacetaldehyde

GP = Globus pallidus

GPe = Globus pallidus externa

GPi = Globus pallidus interna

HD = Huntington's disease

HTT = Huntingtin protein

HVA = Homovanillic acid

mHTT = Mutant huntingtin protein

MSNs = Medium spiny neurons

NGF = Nerve growth factor

NMDA = n- methyl-d-aspartate

PD = Parkinson's disease

QA = Quinolinic acid

ROS = Reactive oxygen species

SNpc = Substantia nigra pars compacta

SNpr = Substantia nigra pars reticulate

STN = Subthalamic nuclei

VTA = Ventral tagmental area

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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