Sidharth Mehan*, Gurpreet Kaur, Rajesh Dudi, Manju Rajput and Sanjeev Kalra

Department of Pharamcology, Rajendra Institute of Technology & Sciences, Sirsa-125055, Haryana, India

*Corresponding author: Sidharth Mehan, Ph.D, M.Pharm, DNHE, CFN, CNCC, Associate Professor, Department of Pharmacology, Rajendra Institute of Technology & Sciences, Sirsa-125055, Haryana, India, Tel No: +91-8059889909, +91-9461322911; E-Mail: sidh.mehan@gmail.com

Review Article

Restoration of Mitochondrial Dysfunction in 6-Hydroxydopamine Induced Parkinson's disease: a Complete Review

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by neuronal cell death in the specific brain region like basal ganglia, cerebral cortex and hippocampus. Symptoms associated with PD patients are rigidity, akathesia, tremor, postural imbalance, cognitive and memory dysfunctions. Pathological hallmarks are dopaminergic neuronal degeneration, neuro-inflammation, oxidative stress, free radical generation. In the typical Parkinson's disease model, 6-Hydroxydopamine (6-OHDA) is delivered unilaterally by stereotactic injection into the SNc (substantia nigra pars-compacta) or the striatum mimics the PD symptoms. In addition, it has been shown that 6-OHDA is toxic to complex I & IV of the mitochondrial respiratory chain, leading to subsequent respiratory inhibition and further processed ATP depletion, oxidative stress and neuro-inflammation. Forskolin (FSK), a diterpene natural plant phytochemical obtained from (Coleus Forskohli), a potent direct activator of adenyl cyclase (AC) enzyme which further activates cAMP/PK$_A$/CREB pathway. FSK mediated activation of AC/cAMP/PK$_A$/CREB pathway is responsible for various neuroprotective mechanisms Based on important and versatile role of FSK, the present study has been designed to investigate the role of cAMP mediated CREB activation in 6-hydroxydopamine induced mitochondrial associated neurotoxicity in rats. Further the studies are extended to understand the disease pathogenesis and to investigate and discuss the various possible central mechanisms involved in the effect of such targets using behavioral paradigm and biochemical markers of neurodegeneration.

Introduction

Parkinson disease (PD) is a neurodegenerative disease characterized by manifestations of motor deficits such as tremors at rest, rigidity in muscles, akinesia and postural imbalance [1,2]. Brain pathology shows loss of neurons in the substantia nigra pars compacta (SNpc), with the presence of eosinophilic protein deposits (Lewy bodies) in the cytoplasm, and dopamine (DA) striatal depletion [3,4]. James Parkinson was first to describe the clinical pathological features of this disease as "shaking palsy" in his classic 1817 monograph as *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured"* [5]. India with one of the world's lowest incidence of PD (70 out of 100,000) [6]. Motor disabilities of PD associated with dopaminergic neuronal cell loss and resultant dysfunction of the basal ganglia (BG) where a cluster of deep nuclei that participate in the initiation and execution of movements [7]. Non-motor symptoms including impairments of memory and olfaction, disturbance sleep and neuropsychiatric manifestations like depression, hallucinations, and dementia become prominent, and these features are probably due to the spread of Parkinsonian pathology beyond the BG with the continued involvement of inflammation and oxidative stress [8-10]. Several genes that also involved in the progression of PD, are α-synuclein (SNCA), Parkin (PARK2), UCHL-1 (PARK5), DJ-1 (PARK7), PINK1 (PARK6), LRRK2 (PARK8), NR4A2 (NURR1), PARK3, PARK4, PARK9, PARK10 and PARK11 [11].

Neuropathological feature of PD includes degeneration of brain stem nuclei & loss of dopaminergic neurons, abnormalities in mitochondrial complexes I to V cellular protein transport, interaction between SNCA proteins & protein aggregation, excitotoxicity, oxidative stress and depletion of striatal DA levels, cholinergic deficit, presence of intra-neuronal proteinacious cytoplasmic inclusions, termed "lewy bodies", are the main cause of neuronal cell death in PD [12,13]. The output projections of the striatum have been divided into

a direct and an indirect pathway. The direct pathway projects from the striatum to the GPi (globus pallidus internal) and SNpr (substantia nigra pars reticulata) and from there to the thalamus. The indirect pathway projects from the striatum to the GPe (globus pallidus external), which in turn projects to the GPi and the SNpr, further terminates in the thalamus [14]. Decreased levels of DA results in increased activity along the indirect pathway and decreased activity along the direct pathway together result in increased excitation of GPi and SNPr neurons, then to increased inhibition of thalamic neurons, and finally to decreased excitation of the cortex [15-17]. The indirect pathway normally excites the output nuclei which is inhibited in PD [18,19].

In addition, mitochondrial free radical theory also explains the mechanistic basis of aging. Dysfunction of mitochondria is well known to generate reactive oxygen species (ROS), reduce adenosine-triphosphate (ATP) production, increased deoxyribonucleic acid (DNA) mutations as well as induces abnormal cristae structures and impairs intracellular calcium (Ca) levels ultimately affects neurons and accelerates neurodegenerative processes [20,21].

Furthermore, the link between oxidative stress and like dopaminergic neuronal degeneration, inhibition of mitochondrial complex I to V, lewy Bodies (LB) protein aggregation, neuro-inflammation and defect in mitochondrial morphology & membrane potential is further supported by modeling the motor aspects of PD in animals with toxins that cause oxidative stress including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, 1,1'- dimethyl-4,4'-bipyridinium dichloride (paraquat), and 6-hydroxydopamine (6-OHDA) [22-31]. The characterization of the hydroxylated analogue of DA i.e. 6-OHDA, a toxin inducing degeneration of dopaminergic neurons in the nigrostriatal region of brain [32]. The administration of 6-OHDA into the striatum of mice at a dose of 0.5 µl/min into the right striatum (*0.9 mm anterior and 1.8 mm lateral from bregma, 3.0 mm ventral from the dura*) and in rat 8µg/2µl in 0.1% ascorbic acid-saline (*anterior-posterior 0.5 mm, lateral 2.5 mm, 5mm dorso-ventral from dura*) mimics PD's like behavioral and biochemical alterations [33, 34]. 6-OHDA inside dopaminergic neuron destroys the dopaminergic nigrostriatal pathway by inducing oxidative stress, which can lead to the induction of inflammation, where neuro-inflammation lead to over activation of glial cell ultimately cause neuronal cell death [35-37]. The unilateral intra-striatal injection of 6-OHDA in rodents induces pronounced behavioral dysfunctions like aphagia, adipsia, paradoxical kinesia, tremulous jaw movement, epileptic seizures and biochemical damage of glutamatergic, cholinergic, tryptaminergic, GABAergic, noradrenergic and adrenergic alternation in various brain region i.e is similar to same as in PD [38-42].

cAMP (cyclic adenosine monophsphate) system is closely involved in the regulation of brain-derived neurotrophic factor (BDNF) plays an important role in the neuronal survival, neuronal proliferation and differentiation, synaptic plasticity, improvement in learning & memory, reduce excitotoxic damage and prevent amyloid-β (Aβ) toxicity, inhibit apoptotic and necrotic cell death [43-51]. Further elevation of cAMP levels is known to restore the energy levels, enhance biosynthesis & release of neurotransmitters in cholinergic, β-Adrenergic and dopaminergic neurons in specific brain regions like striatum, hypothalamus, nucleus basalis, substantia nigra (SN), locus ceruleus, dorsal raphe nucleus and dorsal vagal nucleus. Moreover, increase level of cAMP involved in the inhibition of apoptotic and necrotic cell death leads to improvement in cognitive functioning [52-61]. Elevation of cAMP is also responsible for both short and long-term enhancement in synaptic transmission and stimulates cholinergic cells to release acetylcholine in the proper initiation of memory formation [62-65].

Further, cAMP dependent CREB (cAMP responsive element binding protein) phosphorylation has too been reported to perform neuro-protective action such as long term memory potentiation (LTP), neuronal cell survival, proliferation, and differentiation in the developing brain, neuronal plasticity, regulate expression of neurotropic factors and anti-apoptotic genes, mitochondrial biogenesis, increase expression of BDNF, regulate levels of bcl-2, polysialylated neuronal cell adhesion molecule (PSA-NCAM), neuronal growth factor (NGF), cyclin D2 and controls the expression of both MeCP2 and miRNA participates in the neuronal morphogenesis, differentiation in response to neurotropic factor NGF, BDNF, FGF (fibroblast growth factor), IGF-1 (insulin like growth factor) and regulates cognitive deficits [66-78]. However, agents that enhance cAMP/PK$_A$/CREB pathways have potential for the prevention of stroke and various neurological disorders like Depression, Schizophrenia, Alzheimer's and Huntington disease (HD) [79-83]. Forskolin – FSK (*Coleus Forskohlii,* family Labiatae) used to treat heart and lung disease intestinal spasms, insomnia and convulsions [84-87]. FSK a labdane diterpenoid, is considered the active secondary metabolite because of its ability to directly activate the enzyme adenyl cyclase (AC) [88]. Recent research has shown that FSK has positive effects against a wide range of conditions such as asthma, glaucoma, hypertension, hair loss, cancer and obesity, cardiac remodeling and heart failure prevention, amelioration of mitochondrial dysfunction in cardiomyopathy, anti-platelet aggregation, hydrodynamic alterations in collecting tubule, anti-cystic fibrosis, diabetes, inflammation, glaucoma, smooth muscle relaxation [89-102].

Moreover, FSK can potentiate the absolute inhibition of striatal AC mediated by D-2 dopamine receptors and found that a little change in the percent D-2 inhibition in the presence of FSK, suggesting that its effects on inhibitory guanine nucleotide-binding (cGMP) subunit were minimal [103]. As FSK, a direct activator of AC is responsible for the activation of cAMP-dependent protein kinase (PK$_A$) mediated CREB performed neuro-protective functioning associate with mitochondrial dysfunctioning [104-106]. FSK, cAMP analogs, or neuropeptides effectively alleviated the mitochondrial neuronal impairment through PK$_A$ mediated CREB activation [107]. FSK at the dose of 10-20µM *in-vitro* induces phosphorylation of CREB results in increase in level of CREB, involved in the amelioration of mitochondrial dysfunctioning [108,109]. Indeed, recent studies reported the beneficial effects

of natural AC activator *Coleus Forskohlii* (FSK), against various neurodegenerative abnormalities through the modulation of cAMP CREB, BDNF, Phosphoinositide 3-kinase (PI3K)/Akt and Mitogen-Activated Protein Kinase (ERK1/2) [90,110-113].

FSK has been shown to activate AC in various brain regions like striatum, concentrated in the hippocampus, cerebellum, neocortical areas and peripheral tissues [114-116]. Although the activation of FSK is commonly stated to be mediated primarily by a direct action on the catalytic subunit. A few reports suggest that its effects at the catalytic subunit may potentiate interactions of the catalytic subunit with the cAMP [88,117-118]. In brain, FSK has been reported to elicit the most marked stimulation (~15-fold) of AC activity in the striatum, frontal cortex, hippocampus and in some cases in the middle temporal gyrus, and also localized in pituitary and spinal cord [119,120]. FSK at submaximal doses increases the potency, efficacy, or both of the stimulatory hormones for AC in intact cells [121,122]. However, despite the significantly greater stimulation by FSK in this brain region, little is known concerning the effects of FSK on the stimulation of striatal enzyme activity mediated by cAMP or D-1 3,4 dihydroxyphenylethylamine (DA) receptors[103]. cAMP, mediated signaling of several neurotransmitters including serotonin, acetylcholine, glutamate & DA, plays an important role in the memory & cognitive functioning [123-126]. The activation of the cAMP/PK_A/CREB pathway significantly inhibits inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukins (IL-1β, IL-6, and IL-8), i-NOS (inducible nitric oxide synthase), plasminogen activating factor (PAF), human basophils, mast cell degranulation and oxidative stress [127-131]. Mitochondrial dysfunctioning is associated with loss of ATP in the cell further leads to decrease in the level of cAMP which are implicated in various abnormalities [132]. This decrease in the level of cAMP could be overcome by the FSK administration [104]. Therefore, on the basis of above relative information the present review was designed to investigate the neuro-protective role of direct AC activator FSK through activation of cAMP/PK_A mediated CREB pathway in 6-OHDA induced PD's like symptoms in rats.

Parkinson disease (PD)

PD, the most common movement disorder is characterized by a progressive loss of DA releasing neurons in the SNpc, resulting in slowness of movement, rigidity, and tremor as well as the death of neurons in catecholaminergic and cholinergic nucleus [133-135]. PD is typically considered to be a motor disorder ,through the clinical manifestations are highly variable.The etiology behind PD include excessive levels of SNCA, environmental toxicants and genetic factors leading to an atypically low number of dopaminergic neurons at birth and increased susceptibility to PD development [136,137]. The pathophysiology however is characterized by the degeneration of DA neuron in the SN, a region of the degeneration of the midbrain, and axon loss in the striatum, a region of the forebrain. The resulting DA deficiency leads to dysfunction in the BG network [138]. Moreover, serotonergic, noradrenergic, and cholinergic cells are lost [139].

Prevalence of PD

Parkinson's disease is the second most prevalent neurodegenerative disorder after Alzheimer's disease and is anticipated to impose an increasing social and economic burden on society as populations continue to age [142-145]. A report by the National Parkinson Foundation (NPF) in the United States (US) suggested that PD affects an estimated four to six million worldwide [146]. In the UK, PD is estimated to affect 100–180 people per 100,000 of the population and has an annual incidence of 4-20 per 100,000 [147]. The incidence of the disease rises with increasing age .One in seven are diagnosed before 50 years of age, with a fivefold increase in diagnosis in those aged over 65 [148,149]. India with one of the world's lowest incidence of PD (70 out of 100,000) [6].

Genetics in PD

Over 20 loci and 15 disease-causing genes for Parkinsonism have been identified [150]. Mutations in seven genes are robustly associated with autosomal dominant (SNCA, LRRK2, EIF4G1, VPS35) or recessive (parkin/ PARK2, PINK1, DJ1/ PARK7) PD.

SNCA

SNCA encodes a 140 amino acid synaptic vesicle-associated protein that regulates synaptic vesicle exocytosis [151]. SNCA was identified as the main component of lewy bodies and lewy neurites in PD patients [152]. SNCA is a natively unfolded soluble protein that can aggregate to form oligomers or protofibrils, and eventually insoluble polymers or fibrils [153]. Oligomeric SNCA may mediate neurodegeneration by disrupting synaptic vesicles [154]. Mitochondrial dysfunction, axonal transport deficits, and SNCA aggregation may participate in a self-perpetuating cycle of neuron damage in PD [155].

Leucine-rich repeat kinase 2 (LRRK2)

 LRRK2 is a 2527 amino acid protein that contains functional kinase and guanosine triphosphate (GTP) as domains, and leucine-rich repeat and WD40 protein-interaction domains [156,157]. It is expressed throughout various brain regions, including SN, BG, cortex, hippocampus, and cerebellum [158,159]. Mutations in LRRK2 are the most common cause of familial PD and are linked to both autosomal dominant and sporadic forms [160].

Parkin (PARK2)

PARK2 acts as a regulator of protein breakdown [161]. Mutations in the parkin gene, which encodes for an E3 ubiquitin ligase, are the leading cause of early-onset, autosomal recessive Parkinsonism [162-163]. Parkin levels in neurons are associated with protection from cellular stress and cell-cycle regulation [164]. PARK2 pathological effects on mitochondria were Decrease electron transport chain (ETC) enzyme activities, decreaseprotein levels of several subunits of complexes I and IVdecrease mitochondrial integrity, ubiquitin proteasome system (UPS) & autophagy lysosomal pathway (ALP) dysfunction [165-167].

PTEN-induced putative kinase 1 (PINK1)

PINK1 gene mutations represent the second most common cause of autosomal recessive PD. The gene encodes a 581-amino acid protein with a predicted N-terminal mitochondrial targeting sequence and a conserved serine/threonine kinase domain [168]. More than 40 PINK1 mutations have been identified in PD patients [169].

DJ-1

Point mutations (L166P, D149A) in DJ-1 cause rare autosomal recessive PD with early onset. DJ-1 is a redox-sensitive cytosolic chaperone protein that associates with mitochondria and the nucleus upon oxidation. Mutations cause a loss of function of DJ-1 by inducing instability of the dimeric, functional form of the protein, or lack of expression. Mutations also affect the serine protease activity of DJ-1, another crucial function of this protein [170]. DJ-1 seems to be an important redox-reactive signaling intermediate controlling oxidative stress associated with ischemia, neuroinflammation, and age-related neurodegeneration [171].

Neuropsychological & neuropsychiatric aspects of PD

Psychiatric syndromes as well as cognitive impairment frequently complicate PD, a neurodegenerative disorder defined by its movement abnormalities.Development of psychopathology in PD is attributed to a number of factors, including underlying disease processes related to PD, medication effects, and psychological reactions to the illness [5].

Motor features

The hallmark clinical signs of PD are its motor triad: a pill-rolling rest tremor, rigidity, bradykinesia/akinesia, internal tremor associated with anxiety, cramps, aches, pains, gait and postural disturbances with a loss of righting reflexes, unsteadiness, imbalance and falls, sialorrhea, dysarthria, visual and genitourinary dysfunction, sleep disturbances, sweating, seborrhea, edema, constipation, paresthesias, fatigue, and a decreased sense of smell [172-175].

Cognitive Deficits

The cognitive features of PD are present to varying degrees early in the course of the disease and are multifactorial in origin, involving subcortical–frontal dopaminergic systems as well as extra striatal systems [174,175]. The various forms of executive dysfunction, visuospatial impairment, memory impairment, and attention deficits that occur in PD .The presence of a mood disorder, which can precede, accompany, or follow cognitive changes, may also confound assessment of cognitive impairment, intensify deficits ,aphasia , apraxia, and memory deficits [176-179] (Table 1).

Psychiatric complications

Common psychiatric disturbances observed in PD subjects

Table 1: Symptom associated with dysfunctions in PD [177,178]

S.No.	Sites	Symptoms
01	Motor and sensory	Resting tremor, lead pipe rigidity,Slowness of movement,Expressionless face Soft monotonous voice ,Festinant gait Loss of arm swing on walking,Restless legs syndrome
02	Cardiovascular system	Orthostatic hypotension
03	Respiratory system	Restrictive ventilatory defect, Aspiration, Sleep apnoea, Respiratory dyskinesia
04	Gastro-intestinal	Sialorrhoea and drooling ,Constipation ,Nausea (due to anti parkinsonian medication), Neurological dysphagia
05	Genito- urinary	Bladder disturbance, Sexual dysfunction
06	Musculoskeletal	Muscle aches and cramps ,Flexion deformity of neck
07	Neuropsychiatric	Depression ,Anxiety,Dementia ,Sleep disturbance
08	Dermatological	Disordered sweating and oily skin ,Pressure sores

include: depression, apathy (i.e., lack of motivation), anxiety, sleep disturbances, psychosis, cognitive impairment, and impulse control disorders, with at least one neuropsychiatric symptom being reported in over 60% of patients [180-182]. Furthermore, several clinical features of PD and depression overlap, altered appetite or sleep, weight change, loss of libido, memory impairment, low energy, lack of facial expression and psychomotor retardation. Sleep disorders, such as insomnia, hypersomnia (excessive daytime sleepiness), restless leg syndrome and rapid eye movement sleep behaviour disorder (RBD), affect the majority of PD patients. Psychosis manifests as hallucinations (visual, auditory or tactile), paranoid delusions or delirium [181,183-186].

Mood disturbances

Up to 90% of PD patients with idiopathic PD experience psychiatric complications, including major mood disorders (major depression, dysthymia, or bipolar disorder); adjustment disorders; disabling anxiety syndromes; drug-induced mood changes; pathological tearfulness; dementia; apathetic states; psychosis; or delirium [187].

Non-motor symptoms of PD

Recent reports in PD patients have confirmed the existence of a variety of non-motor symptoms .These includes hyposmia (reported in 80% of the patients at the time of diagnosis), pain, cognitive deficits (about 50%; deficits in memory, attention, executive function and dementia are reported), sleep disturbances, rapid eye movement (REM) behavior change, constipation and urinary problems, depression (10 – 40 %), changes in aversion, fear and anxiety, compulsive behavior and lack of impulse control [33,188-191].

Pre-motor stages of PD

According to the Hoehn and Yahr scale for PD stages [192], PD patients go through five stages:

Stage I: Very subtle, unilateral existence of one or more of the primary symptoms.

Stage II: Bilateral primary symptoms and additional secondary symptoms.

Stage III: Symptoms from stage two increases in severity, and problems with balance become prominent. At this stage, the person with Parkinson's is still independent.

Stage IV: Motor symptoms result in disability, leading to the patient needing assistance in most daily activities.

Stage V: Patient is bed or wheelchair bound and needs complete assistance.

Neuropathology of PD

The pathology in PD is known to affect the central, peripheral, and the entric nervous systems [140]. It has been shown to cause substantial cytoskeletal alterations in various brain regions in a slow but persistent manner [42]. In addition to being a disorder of the DA projection system, glutamatergic, cholinergic, tryptaminergic, GABAergic, noradrenergic, and adrenergic damage has also been reported in PD [42,193]. Presence of lewy bodies, lewy neuritis, and dopaminergic degeneration are hallmarks of PD pathology, as was first demonstrated by F. Lewy in 1912 [194]. Lewy bodies are protein aggregates that, among other proteins contain ubiquitin and SNCA. These can proteins be found in cell bodies and neurites of certain neuronal populations including hypothalamus, nucleus basalis, substantia nigra, locus ceruleus, dorsal raphe nucleus and dorsal vagal nucleus [195-199].

Structural alteration in PD

Basal ganglia: Parkinsonism is considered to result primarily from abnormalities of BG function.The BG include the neostriatum (caudate nucleus and putamen), the GPe, GPi, subthalamic nucleus (STN), and the SN with its SNpr and SNpc. They participate in anatomically and functionally segregated loops that involve specific thalamic and cortical areas. These parallel circuits are divided into 'motor', 'associative' and 'limbic' loops, depending on the function of the cortical area involved [200-203]. Patterns of neuronal discharge within the basal ganglia are disturbed in PD [204]. The loss of DA in the SNpc increases the overall excitatory drive in the BG, disrupting voluntary motor control and causing the characteristic features of PD [205].

Striatum: The striatum, a part of the BG, which receives dopaminergic projections from the SN, is also significantly impacted in PD [206,207]. The striatal damage is more severe in the putamen than in the caudate nucleus. The ventral tegmental area is affected to a lesser extent as compared to the SN [208]. The loss of DA in the nucleus accumbens is to a much lesser extent, and the dopaminergic neurons in the hypothalamus appear to be spared in PD [209]. The association of *SNCA* and mitochondria was especially significant in PD-vulnerable brain regions that are SNpc and striatum [210].

Cerebral cortex: Decreased dopaminergic input to the striatum from the SNpc in PD results in a complex alteration in activity between input and output stations of the BG. Decreased levels of DA result in increased activity along the indirect pathway and decreased activity along the direct pathway, which together result in increased excitation of GPi and SNpr neurons, then to increased inhibition of thalamic neurons, and finally to decreased excitation of the cortex. [16-17].

Mechanism of PD pathogenesis

The first link between mitochondria and PD came with the identification of the deficiency of mitochondrial ETC (electron transport chain) protein complex I activity in SN from patients with PD [211-213]. The role of mitochondria in the pathogenesis of PD has been enhanced by the subsequent identification of mutations in genes encoding mitochondrial proteins like PINK1, DJ1, and parkin, environmental agents, increased intracellular Ca^{2+}, free radical–mediated damage to proteins, lipids, and DNA in SN of PD patients [214-217]. A defect of mitochondrial respiratory chain activity results in impaired oxidative phosphorylation and an increase in free radical generation and thus will affect UPS function by both limiting activity and increasing the substrate load of oxidized protein. (Figure 1) [218].

Oxidative stress & PD

The extensive production of ROS in the brain may provide an explanation for the magnitude of the role that these reactive molecules play in PD. The brain consumes about 20% of the oxygen supply of the body, and a significant portion of that oxygen is converted to ROS [219]. ROS can be generated in the brain from several sources, both in neurons and glia, with the ETC being the major contributor at the mitochondrial level, monoamine oxidase (MAO), NADPH oxidase (NOX) and other flavo-enzymes along with nitric oxide (NO) [219-221]. Oxidative stress have been found not only in brain tissues but also in peripheral tissues of individuals affected by PD, mild cognitive impairment (MCI) and other degenerative diseases, including HD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and others [222].
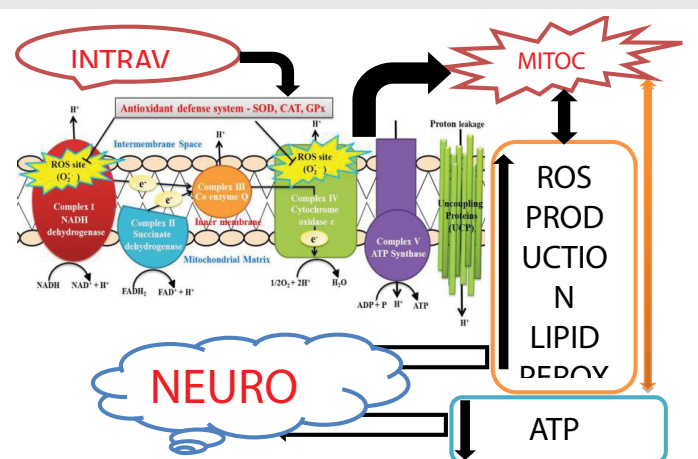
Mitochondrial dysfunction & PD

Figure 1: Intraventricular injection of 6-OHDA inducing neurotoxic effect in mitochondrial respiratory chain (ETC).

Within the mitochondria, ROS is produced at several sites along the ETC, coupled with a process called oxidative phosphorylation via complex V i.e. ATP synthase. Direct and imprecise interactions of reduced nicotinamide adenosine dineucleotide phosphate (NADH) /reduced flaiv adenosine dineucleotide phosphate (FADH) derived electrons with molecular oxygen or any other electron acceptors lead to generation of ROS [22,223]. Major complexes of ETC indulged in generation of ROS include complex I and complex-III [224]. Figure 1 shows a schematic diagram of the flow of electrons across the ETC and the major sites involved in ROS production. Interestingly, uncoupling proteins (UCP) present in mitochondrial membranes have been found to minimize the generation of excessive ROS by leaking the protons inside mitochondria from the cytoplasm, thereby reducing the overall membrane potential [225]. Though mitochondria have been found to be the major contributors target site of cellular ROS, oxidative stress, inflammatory mediators and Ca^{2+} overload is the pathological hallmark for mitochondrial dysfunctioning [226]. The amount of ROS present inside a cell has phenomenal physiological significance. Increased levels of ROS lead to cellular damage and reduced levels result in impairment of various signaling pathways essential for cellular proliferation and operation of host defense mechanisms [227-228]. Therefore, a delicate balance between the levels of oxidants and antioxidants is essential to maintain the optimum levels of ROS [229]. An efficient antioxidant defense system which includes enzymes such as superoxide dismutase (SOD), catalase (CAT), total glutathione (GPx) and glutathione reductase (GRd) ensures the optimal level of cellular ROS and any imbalance or impairment in this system results in oxidative stress and its subsequent consequences (Figure 2) [230].

Excitotoxicity and PD

The concept of excitotoxicity has also been applied to PD. various studies have demonstrated that Parkin regulates the function and stability of excitatory glutamatergic synapses [231,232]. Postsynaptic expression of Parkin dampens excitatory synaptic transmission and causes a marked loss of excitatory synapses in hippocampal neurons [233]. Conversely, knockdown of endogenous Parkin or expression of PD-linked Parkin mutants profoundly enhances synaptic efficacy and triggers a proliferation of glutamatergic synapses. This proliferation is associated with increased vulnerability to synaptic excitotoxicity [234]. The resulting excessive glutamatergic drive could be a source of excitotoxicity in the nigra and activation of NMDA receptor increases intracellular Ca^{2+} levels [12]. A role for elevated intracellular Ca^{2+} in the events leading to cell death in PD is supported by the observation that dopaminergic neurons expressing the Ca^{2+}-binding protein calbindin may be selectively preserved in PD [235].

Neuro-inflammation and PD

In PD One of the first features of the inflammatory-associated modifications was the unregulated expression of major histocompatibility complex (MHC) molecules [236]. Whether a microglia T-cell dialogue exists and is important for local amplification of the proinflammatory immune response in PD remains to be determined [237]. Another main feature of inflammatory-related processes in PD is a marked increase in cytokine levels in the striatum and cerebrospinal fluid (CSF) of Parkinsonian patients compared with control subjects [238]. These include proinflammatory cytokines (TNF-α, IL-1β, IL-6), T-cell activation−associated cytokine (IL-2), anti-inflammatory cytokine (IL-4), and several growth factors like endothelial growth factor (EGF), transforming growth
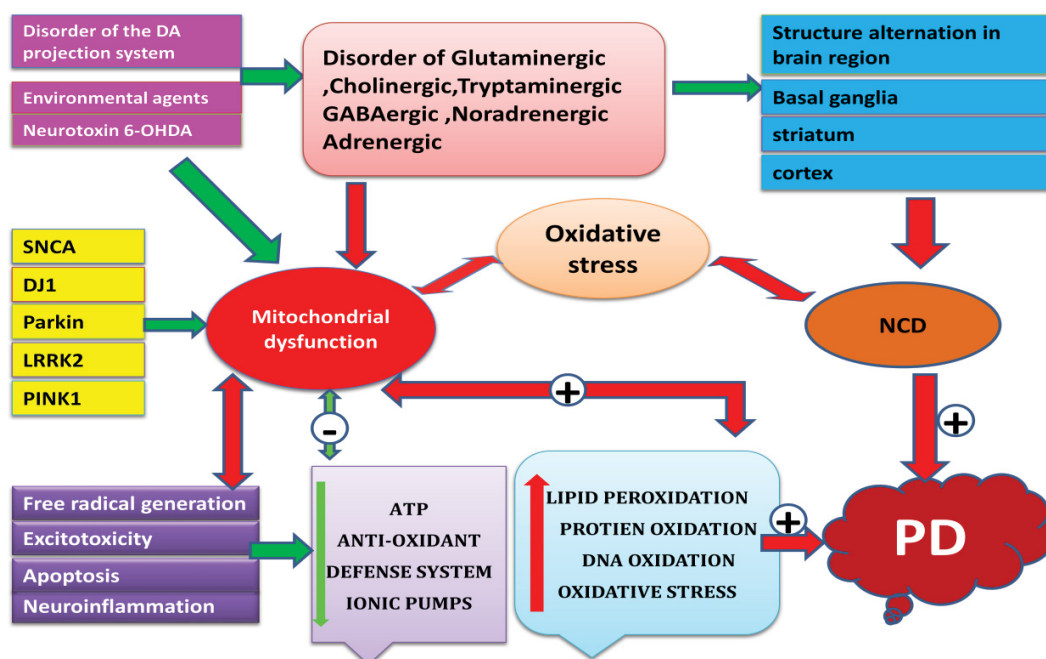

Figure 2: Mechanisms of selective neuronal vulnerability in PD.

factor alpha (TGF-α), β-FGF, transforming growth factor beta1 (TGF-β1) [239,240]. Because an increase in the level of cytokines was specific to the nigrostriatal pathway and is not observed in cortical regions, it has been suggested that cytokine production may be strictly confined to the sites of injury [241,242]. Cytokine-induced dopaminergic cell death may involve more direct cytotoxic mechanisms through direct activation of cytokine receptors localized on dopaminergic neurons and coupled to intracellular death–related signaling pathways [240].

Apoptosis/caspases & PD

A pathogenic role for apoptosis in PD is supported by findings of activated caspase-3, 8 and 9 and higher activities of caspases-1 and 3 in dopaminergic SN neurons in PD brain [241,242].

An oxidative mechanism for neuronal apoptosis has been suggested to involve ROS generation, inhibition of mitochondrial complex I activity, and caspase-3 activation, overexpression of mutant SNCA in association with elevated 8-hydroxyguanine, protein carbonyls, lipid peroxidation and 3-nitrotyrosine, consistent with oxidative stress [243-247] (Figure 2).

Neurochemistry of PD

DA in PD

There are two distinct populations of DA receptors, which differentially regulate second messenger pathways in the striatum. D1 receptor activation leads to stimulation of AC, the enzyme responsible for the synthesis of cAMP. D2 receptor activation inhibits AC, which results in decreased synthesis of cAMP. Levels of cAMP regulate the activity of cAMP/PKA, which plays an important role in cell phosphorylation events such as ion channel modulation and regulation of gene expression (Figure 3) [248,249]. DA differentially regulates the direct and indirect pathways. The direct and indirect pathways work together to balance the motor control wielded by the BG. While the direct pathway facilitates movement by means of decreases in tonic inhibition of BG output and disinhibition of thalamocortical and brainstem pathways, the indirect pathway suppresses movement by increasing the inhibitory BG output to the thalamus [58,59]. DA fibers have therefore an inhibitory action on the striatal GABAergic/enkephalinergic cells projecting to the GPe, but an excitatory action on the GABAergic/substance-P (SP) containing neurons projecting directly to the GPi (and the SNPr) [250-252].

GABA in PD

Gamma-aminobutyric acid (GABA), a putative inhibitory neurotransmitter, is distributed throughout the brain and spinal cord [253]. GABA is the main inhibitory neurotransmitter within the central, peripheral and enterinal nervous systems [254,255]. Recent studies indicate a possible diagnostic value of plasma glial cell derived neurotropic factor (GDNF) levels in depression, but whether GDNF and related Ca^{2+}/GABA mechanisms may play prominent role in the development and
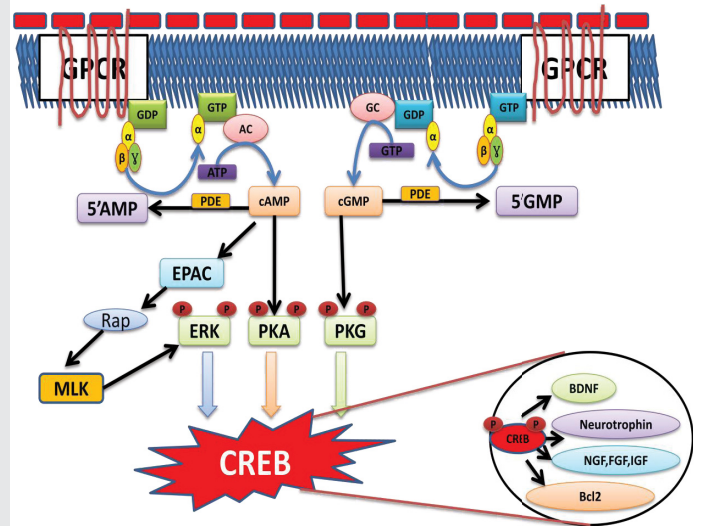

Figure 3: CREB molecular pathway.

progression of PD-related depression is unclear at the moment [256]. SNpc DAergic efferents project to GABAergic cells in the striatum these conections can be excitatory & inbihitory mediated by D1 & D2 DA receptors respectively. DAergic neuron loss in the SNpc cause the net inhibition thalmic output to the cortex through both the direct and indirect pathway of the BG, are parrallel pathway from the striatum to the BG output nuclei-GPi & SNpr that mediate thalmocortical activity. The direct pathway normaly provides inhibition to the output nuclei which is disinhibited in PD as well as indirect pathway normally excits the output nuclei also disturbed in PD [18,19].

Glutamate in PD

Glutamate is also the predominant excitatory neurotransmitter in the BG, is the seat of the motor deficits seen in PD [257]. In addition to sending glutamatergic projections to the striatum, the cortex also sends projections to the STN, thalamus, and SNpc, in addition to other nuclei in the brainstem and spinal cord. The SNpc receives further glutamatergic innervation from the STN in the indirect basal ganglia pathway. Evidence has supported that the dopaminergic projection from the SNpc to various nuclei in the BG circuit exerts an important regulatory function on the firing pattern of certain glutamatergic pathways (Figure 4) [258]. Glutamate release can be regulated by GABA receptors located on corticostriatal terminals activation of these receptors exerts a significant inhibitory effect [259]. Glutamate systems are extensively distributed throughout the brain and have been implicated in the central control of many physiological functions. As a consequence, disturbance in glutamatergic activity may underlie many psychological and neurodegenerative disorders including AD, HD, ALS, AIDS dementia complex, and PD [260]. Excessive stimulation of glutamate receptors can have numerous detrimental effects such as Ca^{2+} homeostasis dysfunction, increased NO production, activation of proteases, an increase in cytotoxic transcription factors, and increased free radicals [261]. Glutamate receptor over-stimulation leads to excessive influx of Ca^{2+} (and Na^+) through glutamate receptor-gated ion channels, followed passively by movements
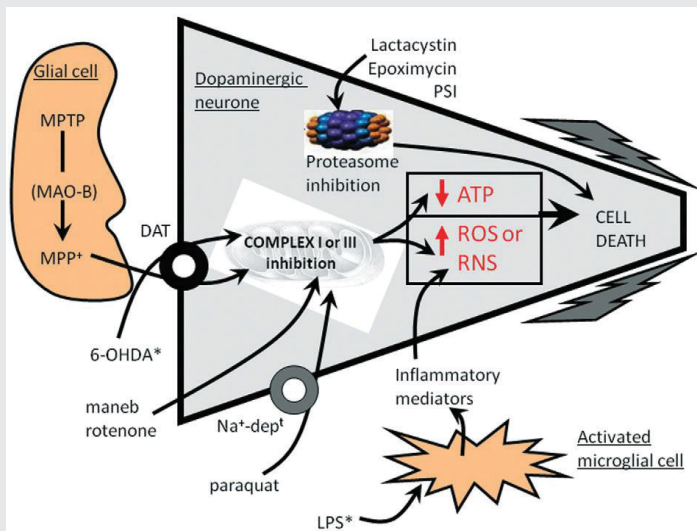
Figure 4: Dopaminergic SNpc neuron showing the molecular targets for the various agents used to induce animal models of PD.

of chloride (Cl−) and water. It causes postsynaptic neurons to be overloaded by extracellular Ca^{2+} and Na^+ as well as intracellular Ca^{2+} via release from mitochondria. The resulting combination of increased intracellular volume and Ca^{2+} overload induces various lethal metabolic derangements, internal organelle swelling, and plasma membrane failure leads to necrosis [262].

Acetylcholine in PD

Ach is a prominent neurotransmitter of the peripheral and the central nervous system (CNS). In the CNS, Ach is involved in attention, learning, memory, consciousness, sleep, and control of voluntary movements [263]. In the brain, ACh mediates distant signaling through projection neurons and local signaling via interneurons; the type of message conveyed by Ach depends on a variety of factors, including site of release, the localization of the target neurons, the target receptor subtypes, and the status of the target cells at the time of release [264]. Furthermore, Ach signaling may be circumscribed to the synapse or result from the delocalized diffusion of the neurotransmitter in the extracellular milieu and binding to nonsynaptic sites [265,266]. Among brain structures, the striatum contains some of the highest levels of Ach and DA. The two neurotransmitter systems interact extensively in a bidirectional manner, both at the presynaptic and postsynaptic levels, mediating cognitive mechanisms, the selection of motor responses, and reward [267,268]. In a recent study in 137 PD patients, cholinergic denervation could be related to REM behavior disorder, fall history, gait disorders, and cognitive dysfunction [269].

Adenosine receptors in PD

Adenosine receptors have a unique cellular and regional distribution in the BG and are particularly concentrated in caudate, putamen and the GP areas, which are richly innervated by DA [270]. In the BG, A2A receptors are prevalently and selectively localised in dendrites, dendritic spines and axons of GABAergic neurons of the indirect pathway projecting from the caudate putamen to the GPe [271,272]. Adenosine

influences striatal output pathways known to be involved in motor symptoms and the onset of dyskinesia in PD. Therefore, inhibition of A2A receptors seems to be a potential target for neuroprotection in PD [273,274]. Indeed, in rodent models of PD, A2A antagonism exerts Anti-parkinsonian actions [272,275,276]. The highest expression of adenosine A2A receptors is found in the BG, particularly in the corpus striatum, which is involved in controlling complex motor activities by specific motivational stimuli as well as in habit formation [277]. Evidence for presynaptic localization of A1 receptors on DA axons is indirect, with confirmed absence of A2A receptors [271,278-281]. Nevertheless, both regulate striatal DA release, likely indirectly, with inhibition by A1-receptor activation and enhancement by A2A receptors activation [282-284].

Cannabinoid receptors in PD

Cannabinoids mainly act through two types of receptors, CB1 (present in CNS and to a lesser extent in the peripheral nervous system) and CB2 (present outside the CNS, preferentially in the immune system). The hypokinetic effect associated with the activation of CB1 receptors located in different neuronal subpopulations within the BG [285]. It is reasonable to expect that the cannabinoid signaling system, and particularly this receptor type, would experience an up regulatory response in PD or other hypokinetic disorders [286]. A therapy with cannabinoids in PD would imply the use of CB1 receptor antagonists for the alleviation of motor inhibition but also the use of different types of cannabinoids, preferably antioxidant cannabinoids, for the control of disease progression [285,287-289].

Neuropeptides in PD

Neuropeptides are found in many mammalian CNS neurons where they play key roles in modulating neuronal activity [290]. Other peptides such as neuropeptide Y (NPY) are synthesized throughout the brain, and neurons that synthesize the peptide in one region have no anatomical or functional connection with NPY neurons in other brain regions [291]. Neuropeptides are thought to modulate the excitability of dopaminergic neurons in the extrapyramidal system [206,292]. NPY-medulla; neuronal loss was found in PD patient. Damage to multiple neuronal systems causing complex biochemical changes and pathophysiological disturbances may represent the basis for the variable clinical picture of PD including motor, vegetative, behavioral, and cognitive dysfunctions, depression, pharmacotoxic psychoses, and other symptoms that usually increase with progressive stages of the disease [293,294].

SP and Enkephalin (Enk) in PD

SP that is highly concentrated in SN and the inner pallidum and neurons of the ponto mesencephalic tegmentum have an excitatory effect on dopaminergic neurons [58]. The PD brains shows a 30-40% decrease in SP in SN and pallidum without essential changes in cortex, hippocampus, striatum, and hypothalamus [295]. There is reduction of SP-immonoreactivity in SN or pallidum was observed in PD, AD, and Guam-PDC but significant reduction of SP was observed

immunoreactivity in GPi, in SNpr and SNpc, and in the NBM in PD [206,290,296,297].

Animal models for PD

Mitochondrial complex I and IV toxin PD models (6-OHDA)

The characterization of the hydroxylated analogue of DA, 6-OHDA, as a toxin-inducing degeneration of dopaminergic neurons in the nigro-striatal tract has led to it being a widely used tool to induce Parkinsonism in rodents [32,34, 35, 298]. 6-OHDA is injected into the nigro-striatal tract at one of three locations: into the SNpc where the A9 dopaminergic cell bodies are located; into the median forebrain bundle (mfb), through which the dopaminergic nigro-striatal tract ascends; or into the terminal region, the striatum [299-301]. Current understanding behind 6-OHDA mechanism is that, once inside dopaminergic neurons, 6-OHDA initiates degeneration through a combination of oxidative stress and mitochondrial respiratory dysfunction [32,302]. Certainly, 6-OHDA readily oxidizes to form ROS, to reduce striatal levels of antioxidant enzymes, elevate levels of iron in the SN and to interact directly with complexes I and IV of the mitochondrial respiratory chain, leading to subsequent respiratory inhibition [35,303-306] (Figure 5). The 6-OHDA model also mimics many of the biochemical features of PD, including reduced levels of striatal DA and tyrosine hydroxylase (TH; rate-limiting step of DA biosynthesis), increased firing of the STN parallely increase in glutamate levels and firing within the BG output regions (entopeduncular nucleus and SNpr) , elevated striatal Enk levels or depressed striatal SP and dynorphin levels , increased firing in the GPi in PD patients and Parkin-containing aggregate formation in 6-OHDA-lesioned rat (Figure 6). [307-316].

(Complex I: NADH dehydrogenase; Complex III: Cytochrome bc1 or cytochrome c reductase; Complex IV: Cytochrome c oxidase; Complex V: ATP synthase)

6-OHDA activates inflammatory features including NF-κB-mediated responses accompanied by inhibition of antioxidant systems regulated by Nrf2, TNF-α, complement component 1q subcomponent- binding protein, increases the expression levels of neuroinflammation markers such as TNF-α, IL-

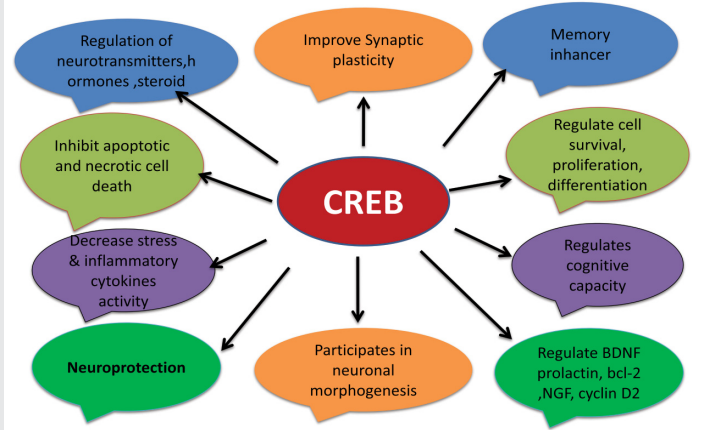**Figure 5:** Coleus forskohlii whole plant and powder.

Figure 6: Role of CREB in neuronal functioning.

1b, and IL-6 and in astrocytes increases pro-inflammatory cytokine TNF-α, nitric oxide synthease (iNOS) and NO, cyclo-oxygenase-2 (COX-2), and PGE2 [244,317-319].

(That exhibit nigro-striatal tract degeneration. *Indicates those agents that are administered directly into the brain; all other agents are delivered systemically. Maneb is believed to inhibit complex III of the mitochondrial respiratory chain, whilst the other mitochondrial toxins mainly inhibit complex I. This activity leads to the generation of ROS or reduced ATP production, which lead to apoptosis and the cells demise. 6-OHDA and MPP+ may also induce the production of ROS directly within the cytoplasm. LPS-activates microglial cells to stimulate the release of inflammatory mediators, which in turn produce reactive nitrogen species (RNS). Inhibition of proteasome activity allows a build up damaged proteins that through DNA damage (not shown for clarity), and other processes can lead to cell death. Cell death is most likely apoptotic in nature, though this remains controversial for some agents)

Cyclic Nucleotides

The cyclic nucleotides 3-5-cAMP and 3-5-cyclic GMP are diffusible intracellular second messengers that act as critical modulators of neuronal function [320]. cAMP is generated in response to binding of a number of neurotransmitters to G-protein coupled receptors (GPCRs) and subsequent activation of AC [321]. Serotonin, adrenergic, dopaminergic, adenosine, vasoactive intestinal peptide, muscarinic, GABA, and opioid receptors, among others, signal through the cAMP cascade via specific heterotrimeric G proteins [322]. Through these effectors cAMP controls a bewildering number of neuronal functions, ranging from regulation of ion channel activity and, consequently, neuronal excitability, to cell volume control and axon guidance; from metabolism and transcription to neurotransmitter release and learning and memory formation [323].

Cyclic adenosine monophosphate (cAMP)

cAMP is synthesized from ATP by AC located on the inner side of the plasma membrane and anchored at various locations in the interior of the cell [324]. The brain contains a large number of different GPCRs. Each individual neuron can express at its

plasma membrane a number of these receptors, each of which will generate a cAMP signal upon binding to its ligand [322]. In addition, glutamatergic stimulation can generate both cAMP and cGMP signals in response to Ca2+ influx [325]. The second messenger concept of signaling was developed with the finding of cAMP and its ability to influence metabolism, cell shape and gene transcription (via reversible protein phosphorylations) [326]. cAMP exerts an important role as second messenger molecule controlling multiple cellular processes in the brain [327]. Elevation of cAMP causes both short and long-term increase in synaptic strength and stimulates cholinergic cells to release Ach [63-65,328]. However, the levels of cAMP are reported to be decreased in neuropath logical conditions [50,329]. Further, cAMP dependent CREB phosphorylation has too been reported to induce LTP by the action of an enzyme AC in response to a variety of extracellular signals such as hormones, growth factors and neurotransmitters [66,67, 330]. cAMP controls a bewildering number of neuronal functions ranging from regulation of ion channel activity , neuronal excitability, control cell volume and axon guidance ; from metabolism and transcription to neurotransmitter release, regulate BDNF , improve learning and memory, restore energy levels, reduce excitotoxic damage, prevent Aβ toxicity ,inhibit apoptotic and necrotic cell death, regulate synaptic efficacy [43,48-51,63,328,331-334]. Furthermore, cAMP/PKA signaling pathway seems to play a role in the final phases of memory consolidation, which requires protein synthesis [66,335].

cAMP response element binding protein (CREB)

CREB activation

CREB is one of the most well-characterized transcription factors in learning and memory [66]. It was originally described due to its association with the cAMP response element (CRE) DNA sequence, and widely expressed throughout the brain, playing a critical role in plasticity in many brain regions, including hippocampus [336,337]. CREB increases the synaptic availability of DA and induces many DA dependent adaptive responses culminating in the transcription of striatal CRE-1 dependent genes, such as the immediate early gene c-and the neuropeptides dynorphin, SP, and Enk's. CREB phosphorylation, initially thought to be mediated exclusively by the cAMP/PK$_A$ pathway, is also induced by Ca^{2+} –dependent signal transduction pathways [338]. Two members of the Ca^{2+}/calmodulin-dependent kinase family (CaMK), CaMKII and CaMKIV, are activated by Ca^{2+} entry through an L-type voltage-sensitive Ca^{2+} channel or glutamate N-methyl-D-aspartic acid (NMDA) receptors and induce CREB phosphorylation [339-342]. There are a number of signaling cascades upstream of CREB phosphorylation, such as the cAMP/PK$_A$, CaMKII and IV) [68,336].

Cyclic nucleotide mediated CREB activation. GDP: Guanosine diphosphate, GTP : Guanosine Triphosphate, AC : Adenylyl Cyclase, GC: Guanylyl cyclase, ATP : Adenosine Triphosphate, cAMP : Cyclic Adenosine monophosphate, 5 AMP :5 Adenosine monophosphate, PDE : Phosphodiesterase, cGMP : Cyclic Guanosine monophosphate, 5 GMP : 5 Guanosine monophosphate, EPAC: Exchange protein activated cAMP, ERK : Extracellular signal- regulated Kinase, PKA :

Protein Kinase A, PKG : Protein Kinase G, CREB : Cyclic AMP Response element binding Protein, BDNF : Brain Derived Neurotrophic Factor, NGF : Nerve Growth Factor.

These cascades are activated by stress, inflammatory cytokine MAPK or PI3)/Akt pathways, growth factor/receptor tyrosine kinase activity (Ras/Erk/RSK2 pathway), and phospholipase C (PLC)–PKC signaling [68,343]. All these cascades have been shown to induce CREB phosphorylation [331,344] (Figure 3). CREB phosphorylation is facilitated by membrane-bound NMDA receptors, the non-receptor tyrosine protein kinase c-Src, fibroblast growth factor receptor1 (FGFR1), and estrogen receptors, all of which are part of distinct intracellular cascades [345-348]. The molecules involved in the modulation of CREB phosphorylation include several neurotransmitters DA, glutamate, serotonin, GABA, growth factors like IGF-1; vascular endothelial growth factor, VEGF), and neurotrophins BDNF [68]. However, CREB also regulated by multiple signaling cascades downstream of neuronal activity, including cAMP and Ca^{2+} (Figure 3) [349].

Role of CREB in neuronal functioning

CREB regulates a wide range of neuroprotective processes, including the expression of trophic factors, antiapoptotic genes, detoxifying enzymes, mitochondrial biogenesis, as a regulator of cell survival, proliferation, and differentiation in the developing brain, whereas its roles in the adult brain include learning, memory, neuronal plasticity [68-70,350,351]. Among the molecules related to adult neurogenesis that are also affected by CREB signaling, BDNF expression, prolactin release, bcl-2 activation, PSA-NCAM, NGF, cyclin D2, MeCP2 and miRNA-132, participates in neuronal morphogenesis, and regulates cognitive capacity [71-78,319,352]. A number of more recent studies have demonstrated that CREB is the main element underlying the conversion of short term memory (STM) to long term memory (LTM) [353-355]. In addition, some neuropsychiatric or neurodegenerative diseases such as depression, schizophrenia, HD and AD are associated with memory loss. In this regard, CREB has been postulated to change the sensitivity of the nucleus accumbens to rewarding and aversive drugs [80-83,356,357]. Moreover CREB modulates adult neurogenesis through the control of other adult neurogenesis regulators such as neurotransmitters, steroid hormones, or cytokines (Figure 6) [358].

Forskolin

Biological source

FSK, a labdane diterpene, is a major active compound isolated from tuberous roots of *Coleus forskohlii* Briq. (Labiatae) (Figure 5) [359]. *C. forskohlii* has been used as an important folk medicine in India. Futher, FSK has been found to be a potent activator of AC, leading to an increase in levels of c-AMP dependent PK$_A$ mediated CREB activation [360]. The presence of yellowish to reddish brown cytoplasmic vesicles in cork cells of *C. forskohlii* tubers is unique character of this plant and these vesicles store contains secondary metabolites i.e. FSK [361]. It grows wild in arid and semi-arid regions of India, Nepal and

Thailand and the plant is found mostly on the dry and barren hills [362].

Ethnopharmacological profile of FSK

The genus Coleus of the family Lamiaceae (Labiatae) comprises a number of herbaceous medicinal plants which are particularly employed in home remedies for various ailments. Three species are most popular and commonly cultivated. They are Coleus aromaticus, C. vettiveroides and C. forkoshlii.long slender raceme [363]. Fruits are orbicular or ovoid nutlets. The leaves are useful cephalgia, otalgia, anorexia, dyspepsia, flatulence, colic, diarrhoea and cholera especially in children, halitosis, convulsions, epilepsy, cough, chronic asthma,high cough, bochitis, renal and vesical calculi, strangury, hepatopathy, malarial fever, antispasmodic and cathartic [87,364,365]. The whole plant is useful in hyperpiesia, vitiated conditions of pitta, burning sensation, strangury, leprosy, skin diseases, leucoderma, fever, vomiting, diarrhoea, and ulcers and as hair tonic [302,366,367]. FSK is also used as a condiment in India and the tubers are prepared as pickle and eaten [368]. The roots are used in treatment of worms, festering boils, and eczema and skin infections [369,370,371]. The leaves are bitter, acrid, thermogenic, aromatic, anodyne, appetizing, digestive, carminative, stomachic, anthelmintic, constipating, deodorant, expectorant, lithontriptic, diuretic and liver tonic [363,372,373]. *Coleus forskohlii* has been used to treat hypertension, congestive heart failure, eczema, colic, respiratory disorders, painful urination, insomnia, and convulsions. Clinical studies of the plant and the FSK constituent support these traditional uses, but also indicate that it may have therapeutic benefit in asthma, angina, psoriasis, and prevention of cancer metastases [87,302,363]. In traditional Indian systems of medicine, the roots of *Coleus forskohlii* are used as a tonic as well as used for veterinary purposes [374]. FSK is also used in the preparation of medicines preventing hair greying and restoring grey hair to its normal colour [375] Forskolin is also a potent vasodilatory, hypotensive and inotropic agent [117].

Pharmacokinetic profile

FSK ability to inhibit platelet aggregation is of additional benefit in cardiovascular disease [376,377]. FSK also demonstrates a direct effect on cerebrovascular vasodilatation via cAMP activation [378]. Asthma and other allergic conditions are characterized by decreased cAMP levels in bronchial smooth muscle, as well as high levels of plasminogen activating factor. In response to allergenic stimuli, mast cells degranulate, histamine is released, and bronchial smooth muscle contracts. FSK activation of cAMP inhibits human basophil and mast cell degranulation, resulting in subsequent bronchodilation [131]. Research has demonstrated aerosolized dry FSK powder results in significant relaxation of bronchial muscles and relief of asthma symptoms [379,380]. In one randomized, double-blind, placebo-controlled trial, 16 asthma patients were given a single inhaled (aerosolized) 10-mg dose of dry FSK powder, an asthma medication (0.4 mg fenoterol), or placebo [380]. The ability of FSK to regulate cAMP levels in skin cells has been shown to have therapeutic benefit for sufferers of psoriasis [87]. A significant decrease in intraocular pressure (IOP) in

rabbits, monkeys, and humans administered a topical FSK suspension (1% FSK). This effect was present at one hour post application and remained significant for at least five hours [381]. In vitro and animal studies demonstrate lipolysis in fat cells is stimulated by FSK via activation of AC and increased levels of cAMP antioxidant status of different parts of *Coleus forskohlii* including roots, stem, leaves and tubers shows the activities of SOD, peroxidase, polyphenol oxidase and CAT were significantly higher ($P < 0.05$) in tubers than in the leaves, roots and stem [369,382]

Pharmacological action of FSK (Table 2)

FSK and Brain

FSK Binding sites

There is increasing evidence of neurotropic effects of FSK. Specific binding sites for FSK have been shown in rat brain membranes and visualized by quantitative *in vitro* autoradiography in rat CNS [397,398]. FSK exhibits marked stimulatory effects on striatal AC activity [88]. Direct binding studies with a suitable, labelled derivative of FSK may be useful in determining the site of its action. Accordingly [3H] 14,15-dihydroforskolin as a ligand of binding sites in membranes of rat liver and rat brain [399]. 14,15-Dihydroforskolin has been reported to activate AC, FSK binds in frontal cortex as well as in hippocampus and in some cases in the middle temporal gyrus, striatum and also localized in pituitary and spinal cord [400]. High densities of binding sites were observed, particularly in the limbic system and the basal ganglia [119,120]. The highest density of binding was in the corpus striatum, in which AC is particularly sensitive to stimulation by FSK [103].

Role of FSK in brain

Several co-activators that influenced the DAergic differentiation have been reported. These co-activators are DA, cAMP, phorbol 12-myristate 13-acetate (TPA), isobutylmethylxanthine (IBMX) and FSK [401,402]. The percentage of DAergic neurons in the present conditions indeed needs to be modulated to further increase the DAergic neuron population, however FSK plays the co-activator role on growth factors and these extrinsic cues may be crucially effective in promoting the differentiation of a DAergic phenotype in human-derived NPCs [403].

GPCR and FSK

DA signaling is mediated by two major classes of DA receptors. D1 type receptors activate AC through coupling to Gs/Golf G-proteins whereas D2 type receptors inhibit AC through Gi/Go G-proteins [404-406]. AC, the mutual target of both D1 and D2 like receptor signaling pathways, is a membrane bound protein which catalyzes the conversion of ATP to cAMP. The patterns of alteration of AC and the regional selectivity are both of particular interest. In the midbrain plus brainstem, nicotine initially enhanced basal AC activity; inferences about the underlying mechanism for this alteration can be drawn from the fact that FSK stimulation of AC was also increased. FSK also suggests that neuroprotective effects through the activation of

Table 2: Various pharmacological action of FSK

S. No	P'cological Activity	Mechanism of action	Dose & route	Ref. No.
01.	Cardiovascular system	Cardiac remodelling and Heart Failure prevention Amelioration of Mitochondrial dysfunction in cardiomyopa-thy Antihypertensive	10 μm/l, *in-vitro* (Cardiomyocytes) 5 μM, *in-vitro* (mice ventricular myocytes) 0.1,0.3,1mg/kg *p.o.* in dogs, cats, rabbits, and rats	[94] [95] [91]
02.	Haematopoietic system	Reduction in the extent of platelet aggregation Induced a partial deaggregation of ADP- or collagen-aggregated human platelets Inhibition of human neutrophil degranulation Anti-Histaminic activit	2.5μM-100μm, *in-vitro*(human blood platelet) 0.1mM/l, *in-vitro* (human blood platelet) 50-75μM, *in-vitro*(Human neutrophil	[96] [383] [384]
03.	Central nervous system	Huntington's disease Alzheimer's disease Antidepressant Antistress activity	10, 20, 30mg/kg, *p.o.* in rat (3-nitroproponic acid) *in-vitro* (Normal and Alzheimer's Disease Human Fibroblasts cells) 5μM, *in-vitro* (human pluripotent stem cells) 0.01-0.1mg/kg, *p.o.*in rat(forced swimming method) 25,50,100mg/kg *p.o*(*in-vivo*) in mice (Elevated plus maze test,Forced swim)	[87] [384,385] [386] [387] [388]
04.	Gastro-intestinal system	Inflammatory bowel disease (IBD)	10 μm mucosal and serosal *in vitro*	[92]
05.	Cancer Metastases	block platelet aggregation via its Stimulation of platelet adenylate cyclase and increase of intracellular cAMP. Enhances Protein phosphatase-2A (PP2A) activity in leukemia cells	82/μg forskolin to mice 30-60 minutes prior to injection with a highly metastatic melanoma 40μM, *in-vitro* (human PCa cell lines)	[92] [95]
06.	Eye	Intraocular pressure and open angle glaucoma, and was branded as Ocufors® Retinal ischemic injury via upregulation of phosphoinositide 3-kinase (PI3K)/Akt pathway	*0.15% w/v intravitreal administration* 0.6–6 nmol/eye *intravitreal administration*	[101] [389]
07.	Endocrine system	Downregulation of the renal parathyroid hormone (PTH)'-via cAMP increase intracellular cAMP, which, together with the increase in ATP, enhance the priming of insulin granules	0.1,1,10μm in chicken kidney slices 10μM, *in-vitro in rat*	[390] [391]
08.	Renal system	Hydrodynamic alterations in collecting tubule	50μM, *in-vitro* (rabbit cortical collecting tubules)	[97]
09.	Urinary system	Uterine smooth muscle relaxant	20μM, *in-vitro* (uterus smooth muscle)	[392]
10.	Hepatic system	Hepatoprotective activity through Regeneration of hepatocytes, normalization of inflammatory hepatic and necrosis	500mg/kg, *Intra-gastrically (i.g.)* 10^{-7} mol/L *in−vitro* (cell culture of bile duct)	[393] [394]
11.	Anti-inflammatory activity	Reduction in the level of Interleukin-1β, 6 and 8 Inhibit mast cell degranulation	0.5μg/kg/min (*Intra-operative*) 10μm, *in-vitro* (human mast cell culture media)	[100] [395]
12.	Respiratory system	Asthma	(dose range 7-10μ M.)in *vitro & in vivo*(ovalbuminsensitized guinea pigs, intravenously and intraduodenally administered forskolin significantly reduced the bronchospasm due to aerosol administration of ovalbumin	[396]

AC mediated cAMP activation are obtained in the presence of Gs [407].

Acetylcholine and FSK

The increase in the level of acetylcholinesterase (AChE) in FSK treated cells could be also an indirect effect of cAMP. cAMP is a second messenger and modulates a plethora of other factors within the cell [20,408–410]. The release of Ach from the presynaptic nerve terminal of nicotinic synapses and subsequent binding to recognition sites located on the subunits of the Ach receptor–ion channel complex (AchR) results in conformational changes of the AchR which yield

channel opening [411]. A widely accepted hypothesis is that subunit phosphorylation, in particular that induced by cAMP-dependent PKA, desensitizes nicotinic acetylcholinesterase (nAChR) [412-414]. The direct action of FSK on nAChRs was demonstrated by exposing patch-membrane nAChRs to FSK, which inhibits channel activity possibly through non-competitive mechanisms [415]. The indirect action of FSK on nAChR was proven by applying FSK to the non-patch membrane, after the gigaseal were formed, and by observing a decrease in the activity of nAChR-channels. This indirect action was most likely mediated by cytosolic mechanisms, namely the cAMP/PK$_A$ pathway and can be attributed to nAChR phosphorylation [88,414].

Neuroprotective action of FSK

FSK against mitochondrial dysfunctioning

Mitochondrial dysfunctioning is associated with loss of ATP in the cell, further leads to decrease in the level of cAMP. This decrease in the level of cAMP could be overcome by FSK induction [232]. As FSK is a direct activator of AC is responsible for activation of cAMP leads to PKA activation further leads to CREB activation and performs neuroprotective functioning associate with mitochondrial dysfunctioning [104,416].

FSK against Neuro-inflammation

FSK has other properties as well, including inhibition of the pro-inflammatory substance known as platelet-activating factor (PAF) [417]. Inflammatory related processes in PD are a marked increase in cytokine levels in the striatum and CSF of parkinsonian patients [238]. Because an increase in the level of cytokines was specific to the nigrostriatal pathway and is not observed in cortical regions, it has been suggested that cytokine production may be strictly confined to the sites of injury. In support of this idea, the density of glial cells expressing proinflammatory cytokines, including TNF-α, IL-1β and IFN-λ, also was elevated in the SNpc of PD patients [241,242]. Administered a water soluble derivative of FSK (colforsin; 0.5µg/kg/min), they showed a reduced inflammatory response [100]. Recent studies have shown that FSK had an antagonistic effect on TNF-α, and it reduced the levels of IL-1β, 6, and 8 [418].

FSK against Neuro-oxidation

ROS can be generated in the brain from several sources, both in neurons and glial cell with in the ETC, major contributor at the mitochondrial level [220,221]. Other ROS sources include MAO, NOX and other flavo-enzymes along with NO, is abundant in the brain due to the presence of NOS [219]. FSK which is responsible for activation of cAMP mediated CREB, is when pretreated at a dose of 5µM, *in-vitro* and is able to inhibit expression of inducible nitric oxide synthase via inhibiting the mitogen activated protein kinase (MAPK) in C6 cells [419]. Chronic administration of FSK may induce a change in the balance of cAMP in response to glucose, which could enhance insulin release. This may be another mechanism for reducing glucotoxicity, in addition to the reduction of oxidative stress [420].

FSK and Cognitive dysfunctions

The various forms of executive dysfunction, visuospatial impairment, memory impairment, and attention deficits that occur in PD can render patients less able to accomplish familiar tasks or make them feel overwhelmed in situations that were not previously challenging [421,422]. The presence of a mood disorder which can precede, accompany or follow cognitive changes may also confound assessment of cognitive impairment and intensify deficits [142,177]. Like most mental disorders, cognitive disorders are caused by a variety of factors. Some are due to hormonal imbalances in the womb, others to genetic predisposition and still others to environmental factors [423]. FSK 5 mg/kg, *i.p.* is able to activating cAMP/CREB in the hippocampal region responsible for memory improvement [424]. Moreover FSK 50 µM direct potentiates synaptic response and induced LTP [425,426].

Possible involvement of FSK in 6-OHDA induced PD

Summarizing the whole information given above, FSK confirmed a versatile role in PD where it activates the AC/cAMP mediated PK$_A$/CREB activation (Figure 7) Moreover, on other side FSK act as a coactivator in brain that follows the G$_s$ pathway through the activation of D1 receptor. There is least availability of selective AC activation and so far only limited reports suggest beneficial effect of FSK in neurodegeneration animal model.

Thus, combined with all information given above on the basis of review and research papers, it was first effort by us to explore the restorative and symptomatic profile of FSK through the activation of cAMP/PKA/CREB pathway in 6-OHDA induced neurotoxic PD's like behavioral and biochemical parameters in rats.

Conclusion

Thus in conclusion neuroprotective and neurorestoration effects of FSK may be due to favorable modulation of CREB
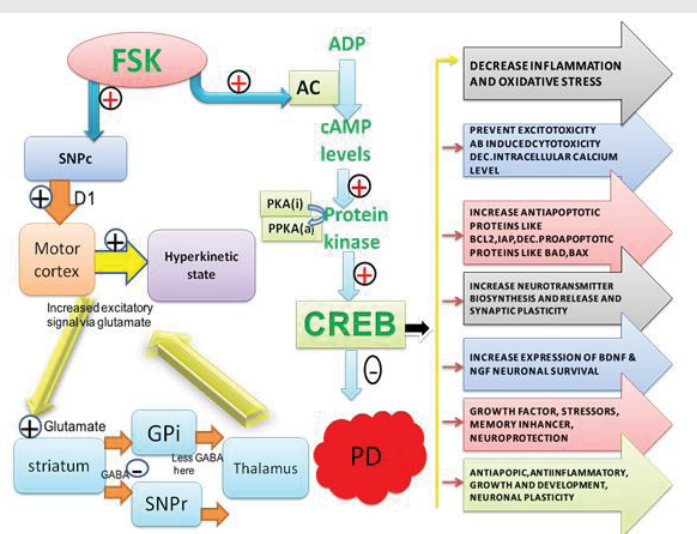

Figure 7: Neuroprotective strategies & therapeutic implication of FSK through AC/cAMP/PKA/CREB pathway activation.

mediated signaling and direct D1 activation in the striatum. The involvement of cAMP/PK$_A$/CREB pathway, anti-oxidant, anti-inflammatory and neuro-modulatory effect of test drug FSK may be the possible mechanisms at least in part underlying the observed effects.

Based on important and versatile role of cAMP/PK$_A$/CREB signaling in regulation of neuronal functioning, essential to investigate the role of cAMP mediated CREB activation in 6-OHDA induced experimental PD in rats and to find out if cAMP mediated CREB pathway is equally implicated in the disease pathogenesis or progression. It may perhaps be safe to further conclude that the beneficial effects of the investigated test drug FSK may be due to its combined improved motor functions, pro-cognitive and to restore the energy levels as well as antioxidant and anti-inflammatory defense system in 6-OHDA model.

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