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EC NEUROLOGY
Review Article

Targeting Phytochemical Driver in AC/cAMP/PKA/CREB Activation: The Next Frontier for Alleviating Huntington's Type Neurodegenerative Disorders in 3-NP Animal Model: A Complete Review

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Received: March 13, 2017; **Published:** May 05, 2017

Abstract

Extracellular signals regulate various intracellular functions like neuron excitability, neurotransmitter biosynthesis and release, neuronal growth, differentiation, neurite growth, synaptic plasticity and cognition through secondary messengers (cAMP and cGMP). Secondary messengers subsequently activate target enzymes Protein kinase A (PKA) and Protein kinase G (PKG) that activate cyclic AMP responsive element binding protein (CREB) which plays an important role in learning and memory function especially long term memory following new protein synthesis. The second messenger concept of signalling was born with the discovery of cyclic AMP (cAMP) and its ability to influence metabolism, cell shape and gene transcription (via reversible protein phosphorylations). cAMP plays an important role as second messenger molecule controlling multiple cellular processes in the brain. cAMP is produced from ATP by the action of adenyl cyclase (AC) in response to a variety of extracellular signals such as hormones, growth factors and neurotransmitters. Elevated levels of cAMP in the cell lead to activation of different cAMP targets. cAMP function as an intracellular mediator for neurotransmitters and hormones regulate BDNF expression that regulate neuronal survival. cAMP also regulate synaptic plasticity, learning and memory, restore energy levels, reduce excitotoxicity damage, prevent Aβ toxicity, inhibit apoptotic and necrotic cell death and also increase synaptic strength. On the basis of these evidences it is clearly demonstrate that via activating of cAMP levels in brains with the help of synthetic and natural precursors should be a proper treatment criteria for neurodegenerative disorders like Alzheimer's and Huntington's diseases.

Keywords: *cAMP; cGMP; Adenyl cyclase; Neurodegeneration*

Introduction

Huntington's disease (HD) is an autosomal dominantly inherited, fully penetrant and fatal neurodegenerative disorder, characterized by progressively worsening chorea, psychiatric disturbances, cognitive impairment and weight loss involving the brain regions include basal ganglia, cerebral cortex and hippocampus [1]. HD was firstly described in 1872 by the American physician George Huntington. The onset of HD is typically in middle age approximately at 40 years [2]. The neurodegenerative process primarily involves medium spiny striatal neurons (MSN) and to a lesser extent cortical neurons. Importantly, γ-amino butyric acid (GABA)ergic projection neurons of the striatum, which make up roughly 90% of the striatal neurons are the most vulnerable in HD and their early dysfunction is responsible for the development of chorea [3]. To date, there is no cure or clinically proven therapeutic strategies that slow progression of this fatal neurodegenerative disease.

HD is caused by a mutation encoding an abnormal expansion of CAG encoded polyglutamine repeats in a protein called huntingtin (htt) [4]. The HD gene is localized on chromosome 4 more specifically, chromosome 4p16.3 and comprises 67 exons and 3144 amino acids. In transgenic mice expressing human huntingtin with an expanded CAG/polyglutamine, a progressive syndrome develops, which is charac-

teristic of human HD [5]. The protein huntingtin (htt) is widely expressed within the central nervous system and in extra neural tissues. Huntingtin is expressed more intensely in neurons than in glial cells [6]. Accumulation of proteolytic htt fragments and their aggregation trigger a cascade that leads to increasing neuronal dysfunction through oxidative injury and glutamate excitotoxicity [7-9], transcriptional dysregulation [10], apoptotic signals, mitochondrial dysfunction [11-13] and energy depletion [14]. These changes are accompanied by neuro-chemical alterations, which involve not only GABA receptors but also other receptors, such as the glutamate, dopamine (DA) and adenosine receptors involved in motor functions [15-17]. The age of onset and disease severity are dictated by the extent of the HD gene mutation and by the sex of the patient. However, environmental factors and genetic modifiers can modify the variability of clinical expression of Huntington's disease [18,19].

To investigate the mechanism of neurodegeneration in HD, experimental animal models of HD have been generated using various excitotoxins, neurotoxins and genetic manipulations. Injections of NMDA receptor agonists, such as quinolinic acid, into the striatum, induce HD-like pathology, with a loss of projecting MSN and sparing of cholinergic and NADPH diaphorase neurons [20,21]. Peripheral injections into rodents or primates of several mitochondrial toxins, including 3-nitroproprionic acid (3-NP), also reproduce the aspects of behavioral, biochemical and striatal pathological alterations found in HD [22,23]. 3-NP, a mycotoxin, is a suicidal irreversible inhibitor of succinate dehydrogenase (SDH), enzyme located in mitochondrial inner membrane [24-26], a member of both Kreb's cycle (oxidizing succinate to fumarate) and an entry point for electrons into the respiratory chain at the level of ubiquinol [27]. Inhibition of SDH interferes with the electron cascade and interrupts oxidative phosphorylation. This phenomenon leads to reduced ATP synthesis and responsible for the initiation of oxidative stress [28,29]. Growing body of evidences explore the involvement of impaired energy metabolism, excitotoxicity, microglial over activation and production of pro-inflammatory cytokines leading to neuronal cell death, by both necrosis and apoptosis [30-32]. These events of neurodegeneration are relevant to the striatal cell loss seen in HD and are gaining prominence for 3-NP lesions [33-35].

Elevation of cAMP causes both short and long-term increase in synaptic strength [36,37] and stimulates cholinergic cells to release acetylcholine [38,39]. However, the levels of cAMP are reported to be decreased in neuropathological conditions [40,41].

Further, cAMP dependent CREB phosphorylation has too been reported to induce long term memory (LTP) [42,43] and inhibit apoptotic and necrotic cell death [44]. CREB is a transcriptional factor responsible for synthesis of proteins which are important for the growth and development of synaptic connections and increase in synaptic strength [45,46]. Thus, agents that enhance cAMP/PK_A/CREB pathways have potential for the treatment of stroke and other neurological diseases [47].

Indeed, recent studies reported the beneficial effects of natural cAMP activator *Coleus Forskohlii* (Forskolin), against various neurodegenerative abnormalities through the modulation of CREB, and brain-derived neurotrophic factor [48-51]. cAMP, mediate signaling of several neurotransmitters including serotonin, acetylcholine, glutamate and dopamine [52,53] which play important role in cognitive functioning. The activation of the cAMP-dependent protein kinase (PK_A) significantly inhibits TNF [54,55] and iNOS (inducible nitric oxide synthase) in astrocytes and macrophages [56] which are implicated in neuro inflammation [57] and oxidative stress, respectively.

cAMP system is closely involved in the regulation of Brain-derived neurotrophic factor expression too [58,59] which plays an important role in neuronal survival, synaptic plasticity [60], learning and memory [61,62]. Further elevation of cAMP levels is known to restore the energy levels, reduce excitotoxic damage, prevent neurotoxicity [63,64], enhance biosynthesis and release of neurotransmitters [65,66], inhibit apoptotic and necrotic cell death [67] leading to improvement in cognitive functioning [68]. Central administration of cAMP has been reported to enhance neuronal survival and memory performance. In view of the above, the enhancement and prolongation of cAMP signaling can be helpful in dealing with neurodegenerative disorders. This can be accomplished by enhancing the cAMP level through activation of CREB protein.

Despite substantial research into neuro protection, treatment options for HD are still limited to supportive care and the management of complications. Currently available drugs provide symptomatic relief but do not stop progression of disease. Thus, the development of new therapeutic strategies remains an unmet medical need.

Failure of current drug therapy may be due to their action at only one of many neurotransmitters involved or their inability to upregulate signaling messengers reported to have important role in neuronal functioning, neurotransmitter biosynthesis and release neuronal growth and differentiation, synaptic plasticity and cognitive functioning. Therefore, as already mentioned above, one of the alternatives to enhance the levels of cAMP secondary messengers or to enhance CREB phosphorylation can be achieved directly through a specific phytochemical Forskolin (FSK) obtained from *Coleus Forskohlii* which activates these cyclic nucleotides and further performed extensive neuroprotective functions in HD related disorders.

Based on important and versatile role of cAMP/PKA/CREB signaling in regulation of neuronal functioning, the present study was designed to investigate the role of cAMP mediated CREB activation in 3-Nitropropionic acid induced experimental Huntington's disease in rats and to find out if cAMP mediated CREB pathway is equally implicated in the disease pathogenesis or progression. Further the studies were 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 paradigms and biochemical markers of neurodegeneration.

Huntington's Disease (HD)

HD is an autosomal, fully penetrant, progressive, and fatal neurodegenerative disease [69,70], characterized by the gradual development of involuntary muscle movements affecting the hands, feet, face, and trunk and progressive deterioration of cognitive processes and memory [71,72]. Neurological movement abnormalities may include uncontrolled, irregular, rapid, jerky movements (chorea) and athetosis, i.e. a condition characterized by relatively slow, writhing involuntary movements involving the basal ganglia and cerebral cortex region of the brain [73,74]. Cognitive dysfunction in HD usually progress at a similar rate to the motor disturbance and are generally classified as a progressive "sub-cortical dementia" [75]. Aphasia and agnosia are uncommon, with prominent loss of cognitive speed, flexibility, and concentration being the hallmark of cognitive changes in HD [76]. Onset of HD is typically in middle age approximately 40 years; however, the age span includes both young and old. The degenerative process primarily involves medium spiny striatal neurons and, to a lesser extent, cortical neurons [77,78]. γ-amino butyric acid (GABA) and enkephalin neurons of the basal ganglia are most vulnerable in HD, typically from diagnosis to death [79,80].

The neuropathological features of HD occur earlier and the specifically neuronal loss can be observed in the caudate and putamen (striatum). In HD, the medium spiny neurons (MSN) of the striatum are selectively vulnerable to the neurodegeneration [81]. These MSN's receive massive excitatory (glutaminergic) inputs from wide areas of neocortex and make efferent inhibitory projections (GABAnergic) to the globus pallidus and substantia nigra [82]. The other major cell type of the striatum the, aspiny interneurons are relatively resistant to degeneration in HD. Loss of projection neurons in the cerebral cortex and the hippocampus is also a feature of HD [83,84]. As the disease progress, degenerative changes become more generalized and include other brain regions such as the globus pallidus, sub thalamic nucleus, substantia nigra (SN), cerebellum and thalamus [85].

History

The first definite mention of HD was in a letter by Charles Oscar Waters, published in the first edition of Robley Dunglison's Practice of Medicine in 1842 (Figure 1). Waters described 'a form of chorea, vulgarly called magrums, including accurate descriptions of the chorea, its progression, and the strong heredity of the disease. In 1846 Charles Gorman observed how higher prevalence seemed to occur in localized regions. Johan Christian Lund also produced an early description in 1860 [86].

The first thorough description of this disease was described by American physician George Huntington (1850-1916) in 1872, examined the combined medical history of several generations of a family exhibiting similar symptoms, he realized their conditions must be linked; he presented his detailed and accurate definition of the disease as his first paper. Unknowingly, Huntington described the exact pattern of inheritance of autosomal dominant disease years before the rediscovery of Mendelian inheritance. During the rediscovery of Mendelian inheritance at the turn of the 20th century, HD was used tentatively as an example of autosomal dominant inheritance. In 1872 George Huntington described the disorder in his first paper "On Chorea" at the age of 22 [87].

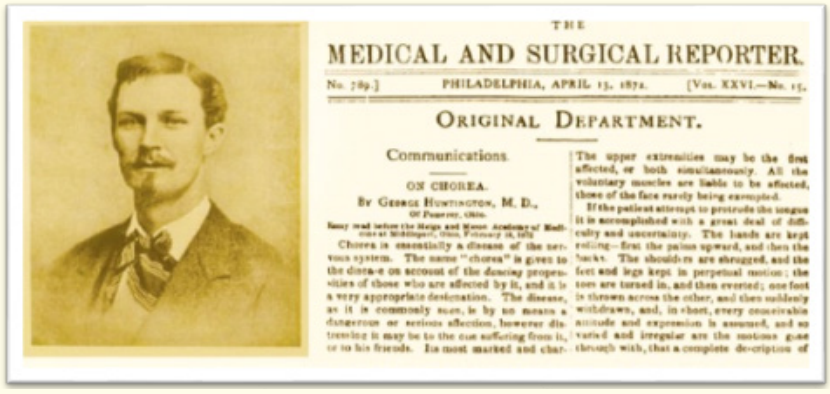
THE
MEDICAL AND SURGICAL REPORTER.
No. 769.] PHILADELPHIA, APRIL 15, 1871. [VOL. XXVI.—No. 15.
ORIGINAL DEPARTMENT.
Communications.
ON CHOREA.
By George Huntington, M. D.,
Of Pomeroy, Ohio.
Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic features are the involuntary muscles are liable to be affected, those of the face rarely being exempted.
If the patient attempts to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

Figure 1: *George Huntington (1850–1916), From Harper PS (ed), HD, 2nd edition (1996), London: WB Saunders [88].*

Prevalence of HD

The gene for the HD appears to occur frequently among those who are white in origin, and is believed to have spread worldwide with emigration from northern Europe [89]. HD is considered to be relatively rare: approximately four to eight cases per 100,000 populations [90]. In the United States alone about 30,000 people are believed to have HD; in addition, 35,000 people will exhibit some symptoms and 75,000 people are gene carriers in whom the disease will appear during a normal life span (National Human Genome Research Institute, 2011). In isolated regions, such as Lake Maracaibo in Venezuelan, prevalence is higher [91]; in fact, the Venezuelan Kindred's comprise the world's largest genetically related community of HD [72].

Although HD is relatively rare in native Africans compared with whites, a survey conducted in the 1980s in Maryland found prevalence among African Americans to equal that of whites. Mean age onset of motor symptoms was younger in African Americans at 36.2 years compared with 41.8 years in whites. Clinical features were similar to those seen in juvenile-onset HD: African Americans had more severe bradykinesia and abnormalities of eye movement and less frequent psychiatric disorder, particularly depression. In the United States, it is estimated that 25000 individuals have HD with another 125,000 individuals at risk (Table 1) [92].

Population	Frequency of HD (cases per million people)
India	1.7
South Africa (blacks)	0.6
Japan	1 - 4
Hong Kong	3.7
Finland	6.0
Europe and countries of European descent	40 - 100
Northern Ireland	64
South Wales	76.1
Scotland (Grampian Region)	99.4
United State	100

Table 1: *Worldwide prevalence of HD [93].*

In India

A recent study on the distribution of C-A-G repeats in the normal population suggests a higher prevalence of HD in India closer to that seen in Western Europe. Based on the results, haplotype analysis suggested the presence of a founder mutation in a subset of families and

provide evidences for multiple and geographically distinct origins for HD mutation in India. One of the studies conducted on 124 (94 male and 30 female) elderly patients (aged more than 60 years) in a teaching hospital in India reported that there were 2.4% cases of HD and Parkinson's disease (PD) in India [94]. In a study of genetically confirmed HD patients from India, adult onset HD was found to be more common than Juvenile HD (below 20 years). HD commonly presents as chorea (88.5%) or with psychiatric symptoms (11.5%) (Table 2).

Ability	Huntington's Disease	Parkinson's Disease
Disease type	Terminal genetic neurodegenerative	Terminal late onset neurodegenerative disease
History	In 1872 by American physician George Huntington	In 1817 by Doctor James Parkinson
Symptoms	Uncontrollable jerking movement (chorea), Dementia, Hallucination, Facial movement, Speech impairment	Muscle rigidity, Bradykinesia, Resting tremor, Postural instability
Brain part affect	Striatum (Caudate and putamen)	Substantianigra (SN)
Neurons affected	GABA ergic neurons (Both projection neurons and interneurons)	Dopamine neurons (Projection neurons with dopamine and inter-neurons without dopamine)
Movement type	Hyperkinetic movement	Hypokinetic movement
Gene involved	Huntingtin gene (Htt)	Alpha synucline, Parkin, UCH-L1
Backbone of therapy	Tetrabenazine	Levodopa
Animal models	3-Nitropropionic acid Model, Quinolinic acid model, Malonate model	MPTP model, Reserpine antagonism model, Tremorine and oxotremorine antagonism model

***Table 2**: Comparison between Huntington's and Parkinson's disease.*

Genetics in HD

HD is caused by the expansion of a polymorphic CAG tri-nucleotide repeat encoding a poly-glutamine tract within the huntingtin (htt) protein (Figure 2) [4]. The mechanisms responsible for mutant htt pathogenicity are still largely unknown, as is the reason why striatal medium spiny neurons are most vulnerable in HD despite ubiquitous expression of mutant and normal htt (Table 3). Normal htt has been shown to be anti-apoptotic and essential for normal embryonic development [95,96].

Number of CAG repeats	Outcome
≤ 28	Normal range; individual will not develop HD
29 to 35	Individual will not develop HD, but the next generation is at risk
36 to 39	Some, but not all, individuals in this range have, or will develop HD; the next generation is also at risk
≥ 40	Individual in this range has, or will develop, HD

***Table 3:** Number of CAG repeats and outcomes.*

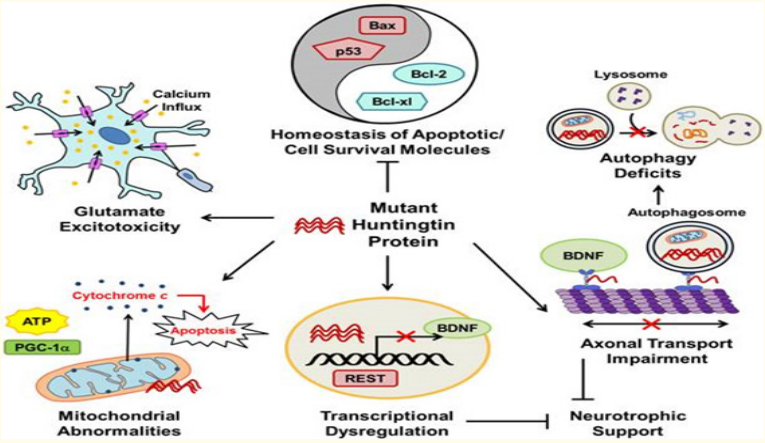

Figure 2: *The major pathophysiological pathway in Huntington's disease (HD).*

In 1983, Gusella localized the HD gene to the short arm of chromosome 4; more specifically, chromosome 4p16.3 [97]. Human htt is a large protein comprising 3144 amino acids. The polyQ domain, which begins at the 18th amino acid position, usually contains 11 - 34 glutamine residues (CAG repeats) in unaffected individuals and expands to > 37 CAG repeats in HD patients. Two proline-rich domains (polyP, which contain 11 and 10 prolines) immediately follow the polyQ domain [98,99].

Mutant huntingtin (mHtt) protein disrupts many normal physiological processes and leads to unbalanced homeostasis of apoptotic molecule, deficit in autophagy, axonal transport impairment, transcriptional dysregulation, reduced cellular neurotropic support, mitochondrial abnormalities, and glutamate excitotoxicity. mHtt disturbs the balance between pro- apoptotic (such as Bax and p53) and cell survival (such as Bcl-2 and Bcl-xl) molecules. Transcription regulation is disrupted in HD; as described in the text, mHtt allow s REST translocation to the nucleus resulting in repression of genes including BDNF. As a result of decrease BDNF axonal transport and repression of gene transcription by REST, neurotropic support of cells is diminished in HD. Impaired axonal transport of autophagosomes also increase autophagy deficit observed in HD. Mitochondrial abnormalities in HD include decreased ATP production and PGC1-a expression, as well as increase cytochrome c release which leads to cell apoptosis. Glutamate excitotoxicity, caused by hyperactivation of excitatory amino acid receptors that increase cell ion permeability and leads to intracellular calcium overload and ultimately cell death, is strongly implicated in HD. The pointed arrow indicates that mHtt increases the described physiological pathway; arrows with blocked ends indicate prevention of physiological events [100].

Neuropsychological and neuropsychiatric aspects of HD

HD is an inherited neurodegenerative disease, damages specific areas of the brain resulting in movement difficulties as well as cognitive and behavioural disturbances. People with HD have specific and characteristic cognitive difficulties, with other aspects of cognitive function remaining well preserved. Behavioural alterations are the characteristic feature of HD and are often most distressing aspect of the condition for individuals and families dealing with HD [101].

Motor symptom's

The most typical presentations of HD are symptoms that are visible or apparent, with motor symptoms such as "restlessness" being the most visible [102]. Chorea is classically identified but initially may be subtle, mild, or limited to distal extremities. Later motor findings may become more proximal and also result in akinetic or rigid features, fixed dystonic postures, or increasing gait and balance disorder. With disease progression chorea often becomes less apparent. Motor symptoms evolve over time in degree and disability; 70% of patients with HD are believed to have chorea at some time in their illness [103]. Cognitive difficulties are characteristic as well and are likely more

disabling than chorea, while chorea is more visible to the casual observer. Oculomotor abnormalities are well recognized in HD. Some patients may exhibit "parakinesia," or purposeful appearing [104].

Chorea

Chorea is an abnormal involuntary movement derived from the Greek word "dance". It is characterized by brief, abrupt, irregular, unpredictable, non-stereotyped movements [105]. In milder cases, they may appear purposeful; the patient often appears fidgety and clumsy. They can affect various body parts, and interfere with speech, swallowing, posture and gait. Chorea may worsen with anxiety and voluntary movements, and subsides during sleep [106]. They may occur with athetosis, a more distal, slower, writhing, abnormal movement, and is known as choreoathetosis. In more severe choreiform movements, they appear wild, violent, and may involve flinging of a body part and induce injuries, and is known as ballism. Chorea may also occur with other abnormal movements such as dystonia [107]. There is a wide range of seemingly unrelated causes, from pregnancy (chorea gravidarum) to inherited forms such as HD and benign hereditary chorea, infection/immune-related such as Sydenham's chorea and systemic Lupus erythematosus. Its pathophysiology involves a functional dysregulation motor circuit of the basal ganglia, where the final thalamo-cortical output is increased, resulting in increased movement and chorea [108].

Dystonia

Dystonia is a syndrome of abnormal, involuntary muscle movements due to sustained muscle contractions resulting in twisting and/or repetitive, patterned movements. The neural mechanism underlying all dystonia probably involves a common final pathway of reduced inhibition of thalamo cortical output resulting in simultaneous contraction of agonist and antagonists muscles [109]. Dystonia can affect either a single body part, termed focal dystonia; contiguous body parts called segmental dystonia; or can be generalized. Focal dystonias include blepharospasm, resulting in repetitive forceful eyelid closure; spasmodic dysphonia affecting speech; tongue, jaw opening and jaw closing called oromandibular dystonia; cervical dystonia or torticollis involving the neck region [110].

In dystonia, primary dystonia may be either idiopathic (the commonest group in adults) or genetic and several DYT genes have been described [111]. Secondary dystonia may be due to drugs, particularly dopamine antagonists called tardive dystonia. Dystonia can also be associated with perinatal cerebral palsy, Wilson's disease, or acquired brain injury/lesions or associated with a number of neurodegenerative disorders such as HD, PD, and progressive supra-nuclear Palsy [110].

Tics

A "tic" is an involuntary movement or vocalization that is usually sudden onset, brief, repetitive, stereotyped but non-rhythmical in character, frequently imitating normal behaviour, often occurring out of a background of normal activity. Tics are usually associated with a premonitory sensation or "build up" sensation to perform the specific movement, and usually are associated with the sensation of relief once performed [112]. Tics are associated with insults to the basal ganglia, pervasive developmental disorder, genetic and chromosomal disorder, other movement disorder, psychogenicity and other non-movement related neurological disorder [113]. The diagnosis of tics in HD patient may be difficult because of overlapping phenomenology of tics and chorea (abrupt, brief, jerk-like and multifocal movements); particularly in early stage share common feature such as involuntary vocalizations, disinhibited and impulsive behaviour, affective disorder, poor attention, obsessive compulsive feature and family history [114].

Non-motor symptoms

Frustration, Irritability, Aggression and Anxiety

People suffering from HD may remain even-tempered; others may lose the ability to control their emotions. The highest frequencies of HD are emotional volatility may evident in increased irritability or episodes of explosiveness [115]. These individuals may become irritable, frustrated or aggressive if demands are not met. Anxiety, a behavioural symptom of HD, is characterized by nervousness, restlessness, fidgeting, shallow breathing, sweating, fear, and panic rapid heart rate [116]. For individuals with HD, continual life changes as HD progresses can be a source of anxiety. Depression is often dismissed as an understandable reaction being diagnosed with HD [117].

Altered Sexuality

A very common behavioural symptom of HD is altered sexuality. Possible cause is that the delicate balance of hormones in the brain is disrupted by the progression of HD causing changes in behaviours regulated by hormone levels [118]. Most commonly, people with HD suffer from a decreased sex drive. Increased sex drive and inappropriate sexual behaviour are less common alterations of sexuality resulting from HD [119].

Cognitive dysfunctions

The term "cognitive" refers to tasks of the brain that involve knowing, thinking, remembering, organizing and judging. Cognitive changes in the HD may be due to the disruption of striatal–frontal circuits [120,121]. Cognitive dysfunctioning is also being seen in other neurodegenerative diseases like Alzheimer's disease (AD), characterized by cognitive and memory dysfunctions [122-124].

Memory and visual spatial ability

An individual suffering from the cognitive symptoms of HD may have memory difficulties. Investigators have shown that memory recall is generally affected more than memory storage in HD [125]. It is important to note that the memory problems that can occur in people with HD are different from the memory difficulties that can occur in people with AD [126]. Most commonly, the individual suffering from cognitive symptoms of HD is aware of his/her visual spatial impairment. Reading difficulties may also be the result of visual spatial impairment; however, the inability to maintain attention may be a contributing factor in the progression of HD [127].

Neuropathology of HD

Neuropathologically, HD is mainly characterized by neuronal loss in the striatum and cortex region of the brain [128]. However, many other nuclei including the globus pallidus (GP), thalamus, hypothalamus, subthalamic nucleus, substantia nigra (SN), and cerebellum also are affected [129]. In addition, diffusion tensor imaging has demonstrated pathology of the white matter in pre- and early symptomatic patients of HD [130].

The brain abnormalities in HD develop well before evident symptoms, are progressive, and eventually involve the entire brain to a greater or lesser extent, resulting in about 25% brain weight loss in advanced HD. Nonetheless, the most prominent neuropathology in HD occurs within the striatal part of the basal ganglia, in which gross atrophy is accompanied by extensive neuronal loss and astrogliosis, both of which become more severe as the disease progresses [131,132]. The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region.

Striatum

In striatum, neurons constitute about 90 - 95% of medium spiny neurons and they utilize GABA as the main neurotransmitter, as well as co-localizing specific neuropeptides [133]. The several thalamic nuclei and the cortical areas refuse the parallel set of dispersed glutaminergic inputs to the dorsal striatum [134]. These inputs primarily synapse onto spines of MSNs. The striatum also contains a number of modulatory components including dopamine (DA) projections from the SN parscompacta (SNc) and cholinergic or GABAnergic inputs from striatal interneurons (Figure 3) [135].

The basal ganglia that clinical include clinically includes subthalamic nucleus and substantia nigra whose component structures are highly interconnected. The striatum is associated with input signal and output associated with the globus pallidus and substantia nigra [136].

These elements constitute the basic striatal microcircuit, a circuit that is severely disrupted in HD [137]. In the striatum, GABAergic MSNs are most affected and degeneration of these neurons occurs progressively. The large aspiny cholinergic inter neurons and the numerous other inter neuronal GABAergic populations are relatively spared from degeneration [138].

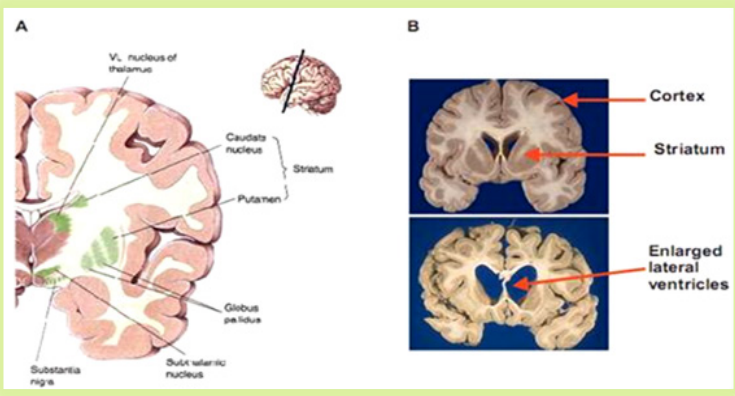

Figure 3: *Structural changes of basal ganglia in HD.*

Striatal output is largely segregated into two populations of MSNs (the direct and indirect pathways) with distinct projections, as well as DA receptor and neuropeptide expression, although some overlap exists [139]. The direct pathway consists of MSNs that predominantly express D1 receptors as well as substance P (SP) and dynorphin and project to the SN and the internal segment of the GP (GPi). The indirect pathway is comprised of MSNs that express predominantly D2 receptors, met-enkephalinor neurotensin and project to the external segment of the GP (GPe) [140-143]. This segregation is important in the context of HD, as there is evidence during disease progression for a time- dependent, differential loss of the two populations of striatal projection neurons. MSNs of the indirect pathway appear to be particularly vulnerable in HD and markers for these neurons and their projections, such as enkephalin, are lost in postmortem brains of fully symptomatic patients as well as, in early symptomatic and pre-symptomatic brains and also in genetic mouse models [144]. In contrast, MSNs of the direct pathway are relatively spared in the early stages, although the SP- containing projections to the SN pars reticulata (SNr) are more severely affected than the SP-containing projections to the GPi and SNc [145]. These results are consistent with the hypothesis that chorea results from preferential dysfunction and ultimate loss of indirect pathway MSNs and possibly that akinesia and dystonia, which occur later in HD, are a consequence of the additional dysfunction and loss of direct pathway MSNs [146].

Cerebral cortex

In the cortex, pyramidal neurons of layers III, V, and VI ultimately degenerate. Whereas striatal neuronal death may underlie many symptoms in late stage of HD [147,148]. Early deficits, which are apparent years before the overt movement disorder, are more likely associated with cellular and synaptic dysfunction in the cortex [149,150]. Advances in neuro imaging techniques have contributed greatly to a better understanding of HD pathology, providing correlations between morphological brain changes and the development of cognitive deficits in attention, working memory, and executive functions [151,152]. Magnetic resonance imaging (MRI)-based morphometric analyses have shown that subjects carrying the HD mutation have significant volume reductions in the cortex and such changes occur before the onset of motor symptoms [153,154].

In manifest HD, differential involvement of specific cortical areas might help explain much of the clinical heterogeneity and complexity of the disease, as specific regional cortical pathology correlates well with the nature of symptoms [155]. For example, motor dysfunction correlates with the extent of cell loss in the primary motor cortex whereas mood changes are associated with cell loss in the cingulate cortex [156]. Among the earliest prodromal changes in HD are alterations in cognitive function and sensory integration [157]. In sensory tests that do not involve motor components, sensory-evoked brain activation is reduced in cortical (somatosensory and frontal) and subcortical (basal ganglia) areas [158]. Cognitive deficits have been shown in HD mutation carriers, decades before motor diagnosis [159]. These cognitive changes affect functional skills and work performance [160], and include deficits in attentional set shifting and semantic

verbal fluency [161]. Performance on the self-timed finger-tapping task, reflecting skilled motor learning, begins to decline more than 20 years prior to predicted age of HD onset. Moreover, the decline in a variety of other cognitive and motor tasks begins approximately 10 - 15 years prior to HD onset and correlates well with a sharply progressive reduction in tissue volume in the striatum and cortical white matter as assessed by MRI [162].

Mechanism of HD pathogenesis

The exact mechanism by which neurons die in HD remains unknown. The discovery of the HD gene and, more recently, the development of transgenic mouse, fly, and worm models have led to an explosion of discovery of the pathogenic mechanisms caused by mutant huntingtin. Far from arriving at a unifying mechanism, there is instead robust evidence that multiple pathologic mechanisms occur in HD.

Oxidative stress and HD

Compounds such as superoxide and hydroxyl free radicals, are endogenously formed, highly reactive molecules that can oxidize lipids, proteins and DNA, thereby altering neuronal structure and function [163]. Several findings suggest that reactive oxygen species (ROS) might be important mediators of cell death in HD [164,165]. For example, levels of the markers of oxidative stress, which include oxidized glutathione and the nucleotide 8-hydroxydeoxy guanosine, are significantly increased in the striatum in individuals with HD [166]. Moreover, mitochondrial aconitase activity, the inactivation of which is an indirect indicator of ROS production [167], is decreased by more than 90% in caudate and by more than 2.60% in putamen of individuals with HD, whereas enzyme activity in cerebellum and fibroblasts, tissues that are not affected pathologically in HD, is increased [168]. Oxidative stress have been found not only in brain tissues but also in peripheral tissues of individuals affected by AD, mild cognitive impairment (MCI) and other degenerative diseases, including HD, PD, amyotrophic lateral sclerosis (ALS), and others [169].

In human tissues, a condition of oxidative stress can be revealed through searching for specific biomarkers of oxidative damage to lipids, proteins and nucleic acids [170]. ROS attack to cellular membrane lipids generates highly reactive aldehydes, such as 4-hydroxynonenal (HNE), malondialdehyde (MDA), lipid hydro-peroxides and isoprostanes, and thiobarbituric acid-reactive substances (TBARS). Oxidative attack on proteins results in the formation of protein carbonyls, often with loss of functionality of the parent molecule. Protein carbonyls and protein nitration (resulting from peroxynitrite attack) are common markers of oxidative damage to proteins [171].

Mitochondrial dysfunction and HD

Mitochondrial dysfunction has been proposed to underlie a number of neurodegenerative disorders, including HD [172,173]. Defects in energy metabolism is further associated with decreased glucose metabolism and increased lactate and the cerebrospinal fluid lactate/pyruvate ratio in the brain of HD patients as compared with age-matched controls [174]. In addition, metabolic defects in skeletal muscle have been reported, a finding consistent with observations that HD patients suffer progressive weight loss despite increased caloric intake [175]. Thus, defects in energy metabolism appear to be widespread in HD, affecting both the brain and peripheral tissues. Changes in the activity of enzymes involved in oxidative phosphorylation lend further support to the mitochondrial dysfunction hypothesis in HD. Reduced activity of the complex II enzyme succinate dehydrogenase (SDH) has been found in post-mortem HD brain tissue. In addition, a decrease in complex II-III SDH activity in HD basal ganglia has been observed (Figure 4) [176].

Systemic administration of the mitochondrial toxin 3-nitropropionic acid (3-NP), an irreversible inhibitor of SDH, to nonhuman primates like rodents produces a movement disorder and cognitive deficits similar to HD [177,178]. 3-NP treated animal's shows series of neuronal loss similar to HD with degeneration in medium spiny neurons and sparing of the NADPH diaphorase inter neurons and nucleus accumbens [179]. Malonate, is also being an another complex II inhibitor, used to produce "chemical lesion", a models of HD [180].

The technique by which neuronal death leads through mitochondrial dysfunction has been proposed to be linked with excitotoxicity because effect of mitochondrial inhibits or scan reverse by NMDA receptor antagonists [181]. Recent data show that 3-NP treatment induces long-term NMDA-mediated excitation in medium spiny neurons [182]. HD mitochondria are relatively depolarized. Since the

mitochondrial membrane potential is directly related to ATP production, reduced membrane potential likely contributes to energy failure [183]. Derangements in energy metabolism are well documented in HD; it is still unclear whether these defects are a cause of the disease or a consequence. Some studies have shown that disorders in metabolism are found in both pre-symptomatic and symptomatic HD individuals (glucose, lactate, and muscle). However, other studies have shown no evidence of perturbations in mitochondrial transport in the brains of postmortem HD patients and in transgenic mice expressing full-length mutant huntingtin. Therefore, mitochondrial dysfunction plays a key role in the pathogenesis of HD [184].

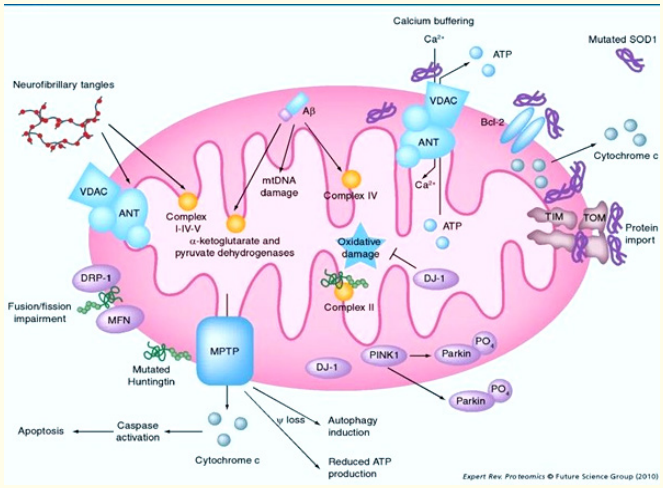

Figure 4: *Mitochondrial alterations in HD.*

Excitotoxicity and HD

Excitotoxicity is being defined as a term in which the death of neurons occurs as a result of glutamate over activity [185]. Over the last few decades, the theory of excitotoxicity as a pathogenic mechanism in HD has come into view, starting with the observation that neuronal depletion and a neurologic phenotype caused by injections of excitatory amino acids into the striatum of rodents and primates shows symptoms similar to HD (Figure 5) [186]. As the striatum receives large glutaminergic input from corticostriatal afferents, it is a structure at risk of glutamate-mediated excitotoxic injury. Intrastriatal injections of glutamate agonists, particularly those acting at NMDA receptors, have been used to create animal models of HD. The NMDA agonists, quinolinic acid, an endogenous metabolite of tryptophan, has been shown to most closely mimic the neuropathology and neurologic phenotype of HD, producing selective degeneration of medium spiny neurons with sparing of interneuron populations.

Mitochondrial dysfunction induced by mutated or misfolded-aggregated proteins involved in neurodegeneration. Misfolded/aggregated and mutated proteins involved in neurodegenerative diseases localize at the mitochondrial level and induce dysfunction of Ca^{2+} buffering, protein import, mitochondrial membrane potential, mitochondrial respiration and ATP production, fusion/fission impairment, mtDNA damage. The final result is the loss of the mitochondrial membrane potential, causing the induction of mitophagy and/or the release of pro-apoptotic factors from the organelle [187].

In addition, glutamate receptors have been shown to be reduced in human HD brains [188,189]. In more recent studies, subsets of glutamate receptors, specifically the metabotropic glutamate receptor mGluR2, appear to be significantly decreased in a transgenic mouse model of HD [190].

Mutant huntingtin perturbs $Ca2^{+}$ signalling by enhancing NMDAR function, possibly through decrease interaction with PSD95-NR1A/NR2B complex. Moreover, mutant huntingtin binds strongly to InsP3 R1, causing $Ca2^{+}$ release through the InsP3 R1. Dopamine release

from midbrain dopaminergic neurons stimulates D1 and D2 receptor (D1R, D2R). D1R are coupled to activation of AC, increase in cAMP level, and activation of PKA. PKA potentiates glutamate induced Ca2+ signals by facilitating the activity of NMDAR and InsP3 R1. D2R are coupled directly to InsP3 production and activation of InsP3 R1. Supra normal $Ca2^{+}$ signals activate calpain, which cleave huntingtin and other substrates. Excessive cytostolic $Ca2^{+}$ signals result also in mitochondrial $Ca2^{+}$ uptake, which eventually triggers mtPTP opening and apoptosis. The mitochondrial $Ca2^{+}$ handling is further destabilized by direct association of mutant huntingtin with mitochondria. muHtt, mutant huntingtin; MCU, mitochondrial calcium uniporter, mtPTP, mitochondrial permeability transition pore; VGCC, L- type voltage gated calcium channel [191].

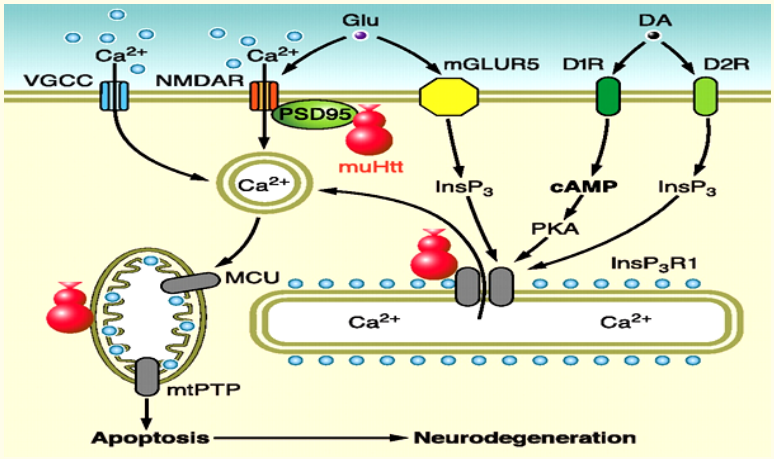

Figure 5: *Dysfunction of $Ca2^{+}$ signalling in HD. Mutant huntingtin causes cytosolic and mitochondrial $Ca2^{+}$ overload and apoptosis of HD.*

mGluR2 receptors down-regulate glutamate release at corticostriatal pre-synaptic terminals, and depletion of these receptors could lead to overstimulation of postsynaptic striatal neurons. Further data supporting the sensitivity of excitotoxic model to NMDA receptor activation and enhanced excitotoxicity in HD transgenic mice [192]. Finally, perturbations in glutamate handling in the brain may also contribute to excitotoxicity in HD as there appears to be down-regulation of the glial glutamate transporter (GLT-1) in a transgenic mouse model of HD [193]. Data suggest that regional expression of the NR2B receptor subunit of the NMDA receptor accounts for the severity of neuronal death in HD [194,195].

Mutant huntingtin also selectively increases current flow through NMDA receptors comprised of NR1/NR2B subunits [196,197]. Although the excitotoxic hypothesis is a persuasive one, there are still some features of HD that remain unexplained. For example, in addition to the striatum, the hippocampus, cortex, and cerebellum contain similar or higher levels of glutamate receptors, yet there is a strikingly selective loss of striatal neurons in HD. Thus, the high-level glutamate receptors cannot explain the regional specificity of HD pathology. One possibility is that the selective loss of striatal neurons is due to differences in glutamate receptor subtypes in these brain regions. The cell selectivity within the striatum remains similarly unexplained.

Neuro-inflammation and HD

The inflammatory process is a defence process that protects our body from damage and disease, by releasing cell mediators that combat foreign substance and help to prevent infection. However, the same inflammatory mediators can also be harmful to the body, when "switched on" for too long, a condition known as chronic inflammation. Neuroinflammation is mediated by soluble pro-inflammatory molecules such as cytokines, prostaglandins, and nitric oxide (NO) (Figure 6).

In a recent report observed that post-mortem human HD tissue has a distinct profile of inflammatory mediators [198]. Some inflammatory mediators such as IL-1β and TNF-α were increased only in the striatum; IL-6, IL-8 and MMP-9 were also upregulated in cortex and,

surprisingly, the cerebellum, a CNS region commonly thought to be spared in HD [199]. This is considerably different from the more generalized neuro-inflammatory profile of other neurodegenerative disease such as AD or PD, which show up regulation of a wide range of inflammatory mediators [200,201]. Believe that the inflammatory mediators detected in the striatum are a sign of the ongoing pathology, whereas the widely dysregulated factors IL-6, IL-8 and MMP-9 reflect a more generalized effect of htt. Neuroinflammation in HD seems solely sustained by the interactions of microglia, neurons, and macroglia [202].

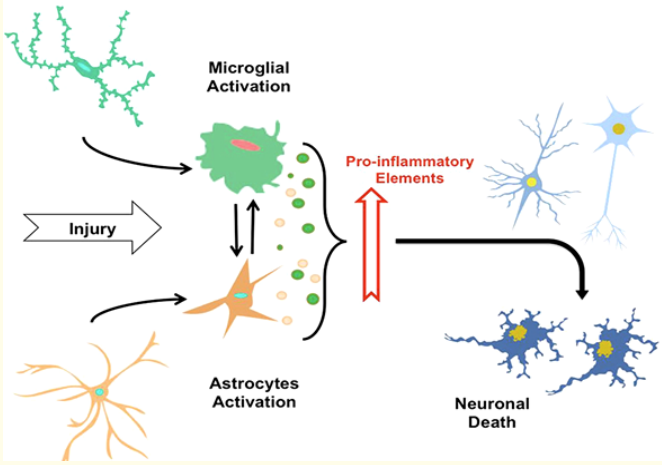

Figure 6: *Neuro-inflammatory process.*

Apoptosis/Caspases and HD

The neuronal death may occurs by inappropriately activating the apoptosis cell death program (Figure 7) [203]. From the previous studies, it has been found that the role of apoptosis and caspases, the apoptosis-related cysteine proteases, has been proposed in the pathogenesis of HD [204,205]. Apoptosis is also called as programmed cell death, is a characteristic feature of a number of chronic neurodegenerative diseases (HD, AD, ALS, dementia), Caspases plays an important role in starting and further implementing the cell death program. Evidence revealed that there is increased activation of caspase-1 in pre-symptomatic and early symptomatic HD transgenic mice.

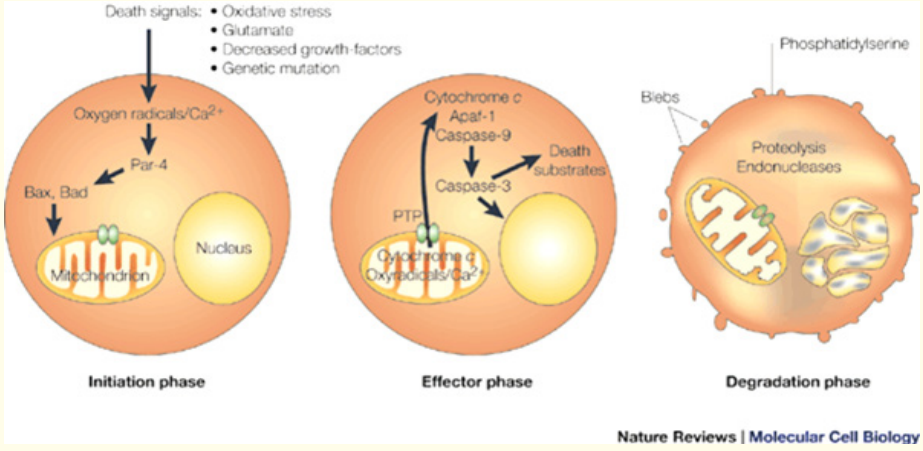

Figure 7: *Morphological and biochemical features of apoptosis.*

By sensing signals of damage or injury, astrocytes and microglia suffer a gradual activation process, leading to morphological changes and secretion of pro- inflammatory elements (i.e. cytokinins, cytotoxic elements, ROS). Thus, the constant exposure of astrocytes and microglia to factor causing injuries and secretion of these elements include mutual activation of microglial cells and astrocytes, along with neuro-inflammatory process that eventually trigger neuronal death [206].

In cellular model systems, apoptosis can be induced by expression of mutant huntingtin [207,208]. The normal and mutant huntingtin proteins are substrates for caspase-1 and caspase-3, and both are cleaved, generating N-terminal fragments [209,210]. The mutant huntingtin N-terminal fragments, which contain the expanded polyglutamine moiety, are translocated to the nucleus, where they accumulate into aggregates. The presence of these mutant N-terminal fragments in the nucleus is a stimulus for caspase-1 up-regulation [211]. As the disease progresses, caspase-3, 8, and 9 are activated, and there is release of cytochrome c, which serves as an apoptotic trigger. Inhibition of caspase-1 appears to slow disease progression in HD transgenic mice; transgenic HD mice also expressing a dominant-negative caspase-1 gene survived longer and had delayed appearance of symptoms, neuronal inclusions, and neurotransmitter receptor changes. The activation of caspases has also been shown in human HD striatal tissue [212].

During the initiation phase of apoptosis, the death signal activates an intracellular cascade. The effector phase of apoptosis involves increased mitochondrial $Ca2^{+}$, production of Par-4 and translocation of pro-apoptotic Bcl-2 family members (Bax and Bad) to the mitochondrial membrane. Certain caspases (caspase-8, for example) can also act early in the cell death process before, or independently of, mitochondrial changes. The effector phase of apoptosis involves increased mitochondrial $Ca2^{+}$, and oxyradical levels, the formation of permeability transition pore (PTP) in the mitochondrial membrane, and the release of cytochrome c into the cystosol. Cytochrome-c forms a complex with apoptotic protease- activating factor-1 (Apaf-1) and caspase-9. Activated caspase-9, in turn, activates caspase-3, which begin the degradation phase of apoptosis in which various caspase and other enzyme substrates are cleaved, resulting in characteristic changes in the plasma membrane (blebbing and exposure of phosphatidyl serine on the cell surface, which is a signal that stimulates cell phagocytosis by macrophages/microglia). Finally, the nuclear chromatin becomes condensed and fragmented [205].

Neurochemistry of HD

The voluntary movement is mediated by the balance between the direct pathway (excitatory) and indirect pathway (inhibitory). Direct pathway involved GABA and SP and indirect pathway involved GABA and enkephalin, GABA is the main neurotransmitter in both pathways. The imbalance between these two pathways and the resulting alteration in the output nuclei are thought to account for the hypo- and hyperkinetic feature of basal ganglia disorder like HD [213]. It is an imbalance in the relative contribution of these two regulatory pathways which triggers and dictates the nature of the motor dysfunction in HD. Alteration in neurotransmitter levels, especially those of glutamate, GABA and DA receptors, is another hallmark of HD (Figure 8) [214]. Altered expression of neurotransmitter receptors precedes clinical symptoms in transgenic mice and contributes to subsequent pathology relevant to HD [215].

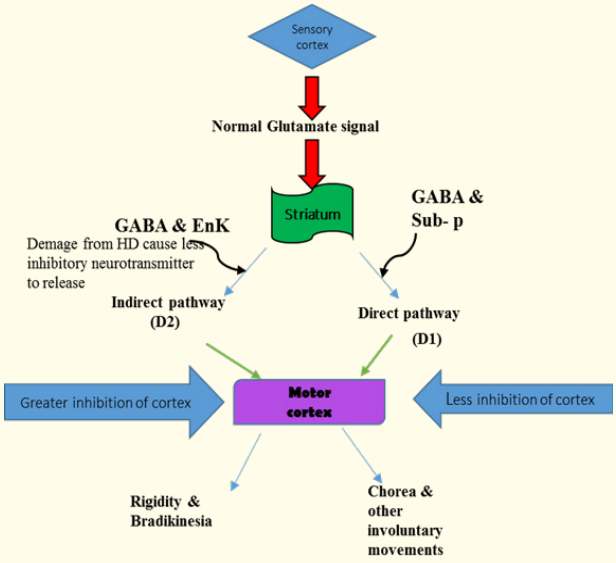

Figure 8: *Schematic diagram of circuitry and neurotransmitters of the basal ganglia.*

GABA in HD

GABA is an inhibitory neurotransmitter with a postulated link to the inhibition of spontaneous involuntary movements [216]. In the striatum, 90% of neurons are medium spiny neurons, GABA-containing projection neurons that are preferentially lost in HD [217]. Early evidence suggests a decreased level of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD) in the postmortem HD brains [218,219]. Whereas, larger a spiny inter neurons are unaffected in the early stages of HD, spiny neurons are severely diminished [220]. The loss of striatal GABA receptors probably represents the loss of striatal neurons. However, the increase in GABA receptors in the GP external (GPe), an area that normally receives synaptic input from striatal projections, probably represents a measure of denervation super sensitivity [221]. Disruptions in GABA systems are not limited to the striatum. It has also shown that decreased GABA levels in the hippocampus and cerebral cortex as well as reduced levels of the synaptic enzyme GAD throughout the brain [222]. Glutamate release can be regulated by GABA receptors located on corticostriatal terminals [223,224] activation of these receptors exerts a significant inhibitory effect [225].

Although a specific link between a particular biochemical abnormality and HD pathogenesis has yet to be found, neuropathological studies have underscored the role of small-to-medium-sized striatal spiny neurons that contain GABA [226]. In particular, increased inhibition of enkephalin- positive GABAergic neurons would reduce striatal output along the indirect pathway, similar to a functional ablation. This may lead to disinhibition of the GPe and could explain why lesions ameliorate HD symptoms in this area [227,228]. As shown in Figure 8, indirect pathways involved in the pathophysiology and expression of HD symptoms (such as chorea and other involuntary movements) are due to an imbalance between inhibitory neurotransmitters and excitatory neurotransmitters.

Glutamate in HD

Excitotoxicity can be defined as cell death ensuing from the toxic actions of excitatory amino acids [229]. Glutamate is a major excitatory neurotransmitter in the mammalian CNS. Neuronal excitotoxicity usually refers as neuronal death arising from prolonged exposure to glutamate and the associated excessive influx of calcium ions and water into the cell [230]. The resulting calcium overload is particularly neurotoxic, leading to the activation of enzymes that degrade proteins, membranes and nucleic acids [231]. One hypothesis that attempts to explain the exquisite vulnerability of the medium spiny projection neurons of the striatum to degeneration in HD is the excitotoxicity

hypothesis. In the context of HD, this hypothesis stipulates that excessive activation of glutamate receptors, increased glutamate release from cortical afferent, reduced uptake of glutamate by glia or hypersensitivity of post- synaptic glutamate receptors on striatal projection neurons, and causes an alteration in intracellular calcium homeostasis and mitochondrial dysfunction, resulting in neuronal dysfunction and death of striatal medium spiny neuron's [232,233]. Support for the excitotoxic hypothesis came in part from radio ligand binding studies in post-mortem HD brain tissue, which showed a disproportionate loss of NMDARs from the striatum of patients in early symptomatic and, in a few cases, pre-symptomatic stages of the disease. These studies suggest that striatal neurons with high NMDAR expression are the most vulnerable and are lost early during disease progression [234,235]. Since NMDA receptors are intimately associated with excitoxicity, they were one of the first glutamate receptors studied in mouse models of HD [236].

Acetylcholine in HD

Acetylcholine is a prominent neurotransmitter of the peripheral and the central nervous system. In the central nervous system, acetylcholine is involved in attention, learning, memory, consciousness, sleep, and control of voluntary movements [237]. Loss of acetylcholine and its synthesizing enzyme choline acetyltransferase (ChAT) has been observed in HD patients. Further imbalance in DA and acetylcholine levels may contribute to HD symptoms [238]. The acetylcholine synthetic enzyme ChAT decreases in the nucleus accumbens, septal nuclei, and hippocampus [239]. Muscarinic M2 acetylcholine receptors also decrease in the striatum and GPe but are unchanged in the substantia nigra pars reticulate and cortex [240]. Decreased choline levels have been observed in cerebrospinal fluid samples of HD patients [241]. Choline is the physiologic precursor of acetylcholine, the discovery that choline administration produces sequential elevations in blood choline, brain choline, and brain acetylcholine levels in rats led to its use in treating human diseases in which there may be deficient central cholinergic tone. Choline administration provided an opportunity to test the long-term effects of chronic cholinergic stimulation in patients with HD [242].

Dopamine in HD

The neostriatum is densely innervated by dopaminergic fibres that originate in the substantia nigra. Despite the high concentrations of DA in the striatum, there is increasing evidence that DA or one of its metabolites might be neurotoxic [243]. Dopaminergic and glutaminergic systems interact closely at the level of medium spiny neurons. Dopaminergic nigro-striatal neurons synapse mainly onto the necks of dendritic spines of medium spiny projection neurons, whereas glutaminergic cortical afferents synapse specifically on the heads of the same dendritic spines [244]. In addition, recent studies suggest that DA may also modulate striatal interneuron activity. Since the activity of medium spiny neurons is also finely regulated by inter neurons, by modulating the activity of these inter neurons, DA exerts indirect but potent control over striatal output neurons [245,246]. There are compelling data suggesting that DA or its metabolites (or both) can generate ROS.

In rodents, DA is metabolized via monoamine oxidase to 3,4-dihydroxyphenylacetaldehyde (DOPAC) and hydrogen peroxide (H_2O_2) [247]. Although not lethal, H_2O_2 can react with transition metals such as iron to generate highly toxic hydroxyl radicals via 'Fenton-type' chemistry [248,249]. Dopamine can also undergo non-enzymatic auto-oxidation with molecular O2 to form radical semi-ubiquinone and superoxide free radicals [250]. A number of investigators have assessed DA levels in the HD brain. Major loss of the D2 receptor was observed in the HD brain. D1 receptors are moderately decreased in the substantia nigra as well as in the GPe in early stages of HD [251]. As the disease progresses, vulnerability of both D1 and D2 receptors increase in the HD brain. These receptors (especially D2) are markedly reduced in asymptomatic HD mutation carriers, suggesting that the loss of DA innervations contributes to HD pathophysiology [252].

Adenosine receptors in HD

Adenosine is a purinergic messenger that can be released to the extracellular medium by membrane transporters, can result from the cytoplasmic leakage of dying cells and represents the final product of extracellular nucleotide hydrolysis by enzymes known as ecto nucleotidases, known to reduce neuronal activity through the activation of high affinity receptors [253,254]. Adenosine activities are mediated by binding to four distinct G-protein-coupled receptors such as A1, A2A, A2B, and A3 adenosine receptor subtypes [255]. Adenosine

receptors have a unique cellular and regional distribution in the basal ganglia and are particularly concentrated in caudate, putamen and the GP areas, which are richly innervated by DA [256]. Changes in A2A receptor expression and signalling have been observed in various experimental HD models. In 2001, Varani., *et al*. reported an aberrant amplification of A2A adenosine receptor-stimulated AC in striatal-derived cells engineered to express mutant htt [257], opened the possibility that an aberrant A2A receptor phenotype may represent a novel potential biomarker of HD. This is useful for monitoring disease progression and assessing the efficacy of novel neuroprotective strategies [258]. An increase in A2A receptor density has been found in a 3-nitropropionic acid (3-NP) model of HD [259,260].

A2A receptors are found both pre- and post-synaptically, they found post-synaptically on the GABAnergic striato-pallidal neurons projecting to the GP, which contain the peptide enkephalin and are enriched with DA D2 receptors [261,262]. The highest expression of adenosine A2A receptors is found in the basal ganglia, particularly in the corpus striatum, which is involved in controlling complex motor activities by specific motivational stimuli as well as in habit formation [263].

Cannabinoid receptors in HD

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). Activation of the CB1 receptor may influence neurotransmitter release and influence a variety of processes, such as regulation of motor behaviour, learning and memory and anti-nociception [264,265]. Several studies have clearly demonstrated that there is an almost complete disappearance of CB1 receptor binding in the substantia nigra, in the lateral part of GP and, to a lesser extent, in the putamen in HD. An autoradiography study regarding the human brain showed a complete loss of the CB1 receptor in HD patients [266]. Cannabinoids at the doses of 4.63 mg/kg, i.p. [267] and 700 mg/kg, p.o. effective in Huntington's disease [268]. From the previous data, we came to know that cannabinoid administration was performed to induce neuroprotective effect against neurodegenerative disease like Huntington's disease (HD) [269-271].

Neuropeptides in HD

Neuropeptides are found in many mammalian CNS neurons where they play key roles in modulating neuronal activity. In contrast to amino acid transmitter release at the synapse, neuropeptide release is not restricted to the synaptic specialization, and after release, a neuropeptide may diffuse some distance to exert its action through a G protein-coupled receptor. Some neuropeptides such as hypocretin/orexin are synthesized only in single regions of the brain, and the neurons releasing these peptides probably have similar functional roles. 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 [272]. According to previous studies it has been reported that, the concentration of NPY- immunoreactive neurons are significantly decrease in case of Huntington disease and although infusion of NPY in this model did not rescue this deficit [273,274].

Substance P and enkephalin in HD

Reflecting the preferential impact of striatal medium spiny neurons in HD, decreased concentrations of co-neurotransmitter peptides have been reported in synaptic target areas [275]. SP is decreased in the substantianigra and GPi, with lesser reductions being reported in the striatum, substantianigra pars compacta, and GPe. Reduction of SP has also been reported in the HD spinal cord [276]. Enkephalin (Enk), contained in GABAergic medium spiny neurons that project to the GPe, has decreased levels in HD patients [277]. Decreases in mRNAs of SP and Enk have been detected in early-grade HD, indicating that medium spiny neuron dysfunction is an early event in HD pathogenesis. The loss of indirect pathway striato-external pallidal neurons is predicted to result in a relative excess of involuntary movements, whereas the loss of direct pathway striato-nigral and striato-internal pallidal neurons tend to produce bradykinesia [278,279].

Animal models of HD

Animal models of HD may aid in the understanding of dysfunctions underlying behavioural phenotypes, neuronal abnormalities and neurodegeneration. A great advantage of these classic models of HD is that they can be used to understand the evolution of the disease and the cause-effect relationships involved [280-282]. The nature of the disease phenotype expressed depends on the context in which

the mutant gene is expressed. In general terms, mice expressing N-terminal fragments of HD exon-1 develop a rapidly progressing disease phenotype that recapitulates aspects of motor defects and weight loss seen in HD, whereas mice expressing full-length human mutant huntingtin (mhtt) or have mutations knocked into the full-length endogenous murine Hdh gene have a more protracted disease course with fewer prominent motor defects but develop selective neuronal degeneration. The majority of reports of oxidative damage in HD mice are from "fragment" mouse models of HD that express an N- terminal fragment of human mhtt [283-285].

Toxin models of HD

The activity of mitochondrial complex II (succinate ubiquinoloxidoreductase) of the respiratory chain is severely reduced in affected brain regions (caudate and putamen) of symptomatic HD patients. Consequently, pharmacologic inhibitors of mitochondrial complex II have been found to induce striatal damage and motor phenotypes in animals, which closely resemble the symptoms seen in HD patients. Here, various studies show mitochondrial complex II toxins (3-NP and malonate) and excitotoxins (quinolinic acid), suggesting that oxidative damage associated with HD-like lesions is linked with mitochondrial energy dysfunction and excitotoxicity [286-288].

Mitochondrial Complex II toxin HD models

Nitropropionic acid (3-NP) and HD

The mitochondrial toxin 3-NP irreversibly inhibits the activity of the mitochondrial metabolic enzyme succinate dehydrogenase, which participates in both the TCA cycle and complex II–III of the electron transport chain (Figure 9) [289,290]. Systemic administration of 3-NP to humans, nonhuman primates, and rodents, results in CNS lesions that selectively target medium spiny neurons within the striatum, recapitulating the regional and neuronal specificity of pathologic events in HD [291-293]. In humans, ingestion of 3-NP induces cognitive impairment and motor abnormalities, including dystonia, involuntary jerky movements, torsion spasms, and facial grimaces [294,295]. 3-NP has become a widely used experimental tool to study neuronal susceptibility and motor phenotypes that are characteristic of HD (Table 4) [296].

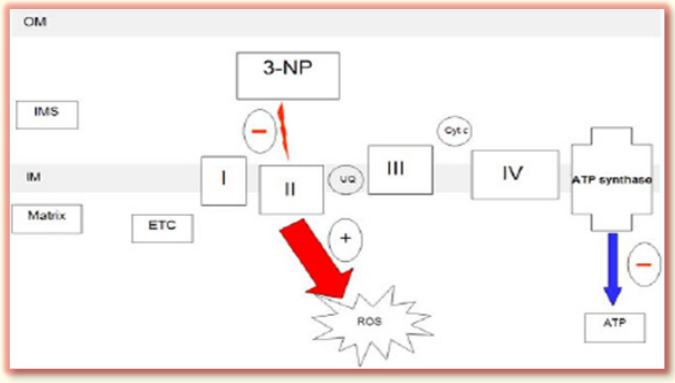

Figure 9: *3-NP irreversibly inhibits succinate dehydrogenase (SDH; complex II) of electron transport chain (ETC) and tri-carboxylic acid cycle.*

Schematic representation of the effect of 3-NP on ETC. IM: inner membrane; IMS: Inter membrane space; OM: outer membrane. Complex I: NADH dehydrogenase; Complex III: Cytochrome bc1 or cytochrome c reductase; Complex IV: Cytochrome c oxidase; Complex V: ATP synthase.

In rats, 3-NP- induced lesions in the basal ganglia that are associated with elevated lactate levels resulted in increased NMDA-receptor binding [297]. This effect can be ameliorated by reducing glutaminergic innervations of the striatum, through either application of NMDA-receptor antagonists or decortications. These observations are consistent with the 3-NP toxicity arising from secondary excitotoxic mechanisms, whereby energy depletion within vulnerable neurons facilitates abnormal activation of NMDA receptors and subsequent

$Ca2^{+}$ influx [298]. Stimulating energy generation by administering creatine markedly attenuates 3-NP toxicity and ameliorates lesion volume, lactate production and ATP depletion in the striatum of 3-NP-treated rats [299]. Numerous reports assert that 3-NP toxicity is associated with increased oxidative damage within the CNS. Administration of 3-NP to rodents results in elevations of striatal hydroxyl (OH^{-}) and superoxide ($O_2\bullet-$) free radical generation and a number of oxidative damage markers [300]. Susceptibility to 3-NP induced oxidative stress also worsens with age, demonstrated by increased DNA fragmentation and reduced expressions of the DNA repair enzyme apurinic/apyrimidinic endonuclease in older mice. The involvement of impairments in intrinsic anti-oxidant protection pathways after 3-NP administration is further supported by observations of reduced striatal glutathione (GSH) levels [301,302].

Adenosine release	Increased
ATP production	Decreased
Intracellular calcium levels	Increased
Caspase-3 activity	Increased
Caspase-9 activity	Increased
Choline acetyltransferase	Decreased
Cytochrome c release	Increased
Dopamine	Increased
Dopamine 3,4-dihydroxyphenylacetic acid (DOPAC)	Increased
Endocannabinoids	Decreased
Enkephalin	Decreased
GABA	Decreased
Homovanillic acid (HVA)	Increased
LDH	Increased
Neuropeptide Y	Increased
Neurotensin	Increased
NMDA-R	Increased sensibility to basal levels of glutamate
NO	Increased
ROS production	Increased
RNS production	Increased
SDH activity	Decreased
Somatostatin	Increased
Substantia P	Decreased

Table 4: *Molecular changes induced by 3-NP in rats.*

Malonate and HD

Malonate is another selective inhibitor of succinate dehydrogenase that causes motor impairments and neuronal pathology resembling HD after intra-striatal administration in rodents [303]. Similar to 3-NP, malonate produces age-dependent striatal lesions that can be significantly attenuated by NMDA-receptor antagonists [304]. Malonate induced an increase in the conversion of salicylate to 2,3- and 2,5- dihydroxybenzoic acid, an index of hydroxyl radical generation, which is exacerbated in mice lacking the free radical scavenger glutathione peroxidise [305]. A mouse lacking a neuronal iso- form of the NOS gene, with impaired nitric oxide generation, shows reductions in the sizes of malonate induced striatal lesions [306].

Further, 3-NP concentrations are elevated after intra-striatal malonate injection; whereas lesion size is attenuated by free radical spin traps and NOS inhibitors [307].

Substantial evidence suggests that NO-mediated oxidative damage is involved in cell death processes after energetic disruption induced by both 3-NP and malonate. These mitochondrial toxins induce a pattern of cell damage mimicking that seen in HD by a mechanism that involves interference with the activity of an oxidative phosphorylation enzyme complex known to be impaired in the HD brain [308,309]. It is therefore tempting to extrapolate a key role for oxidative damage as an execution step in the cell-death pathway initiated by mhtt in HD patients.

Excitotoxic model of HD

Quinolinic acid (QA)

Intra-striatal injections of the endogenous NMDA-receptor agonist QA results in behavioural and neuropathological changes, which is the hallmark of HD [310], which further induces preferential loss of medium spiny neurons but spares NADPH-d and parvalbumin-positive neurons, while injection of non-NMDA-receptor agonists (kainate or quisqualate) results in a loss of both spiny and NADPH-d-positive aspiny neurons [311,312]. NMDA receptor-mediated lesions in primates are associated with an apomorphine-inducible movement disorder that resembles the choreic movements seen in HD [313]. Some but not all genetic models of HD also show age-dependent declines in glutamate-receptor densities in the striatum and cerebral cortex, altered striatal neuron responses to glutamate agonists, increased vulnerability to NMDA and QA-induced excitotoxic damage [314]. Toxicity induced by the kynurenine pathway metabolite QA involves an increase in ROS, DNA damage, reduced glutathione levels and peroxidative damage that can be rescued by Fe-porphyrin compounds. The energy substrate pyruvate is also protective against quinolinic acid toxicity [315]. Interestingly, intra-striatal administration of QA in rodents has been shown to increase htt immune reactivity, leading to the suggestion that htt may be induced as a cyto-protective agent after activation of the kynurenine pathway, again emphasizing the close links between this pathway and HD pathogenesis [316].

Cyclic Nucleotides

Extracellular signals regulate various intracellular functions in brain like neuron excitability, biosynthesis and release of neurotransmitter, neuronal growth and differentiation, neurite growth, synaptic plasticity and cognition through secondary messengers cyclic adenosine monophosphate (cAMP) [317,318]. Secondary messengers subsequently activate target enzymes Protein kinase A (PK_A) that activate cyclic AMP responsive element binding protein (CREB) which plays an important role in learning and memory function especially long term memory following new protein synthesis and nourishment of nervous system [319].

Cyclic AMP (cAMP)

The second messenger concept of signaling was developed with the finding of cyclic AMP (cAMP) and its ability to influence metabolism, cell shape and gene transcription (via reversible protein phosphorylations) [320]. cAMP exerts an important role as second messenger molecule controlling multiple cellular processes in the brain. cAMP is produced from ATP [319] by the action of an enzyme adenyl cyclase (AC) in response to a variety of extracellular signals such as hormones, growth factors and neurotransmitters [321]. Elevated levels of cAMP in the cell lead to activation of different cAMP targets [322]. cAMP function as an intracellular mediator for neurotransmitters and hormones [323], regulate BDNF expression [324] that regulate neuronal survival [325,326]. cAMP also regulate synaptic plasticity [327], improve learning and memory [328], restore energy levels [329], reduce excitotoxic damage [330], prevent Amyloid-β (Aβ) toxicity [40,331] inhibit apoptotic and necrotic cell death [67] and also increase synaptic strength [332].

cAMP response element binding protein (CREB)

On the basis of collectively research database, it shows involvement of cyclic nucleotides, also known as intracellular second messenger i.e. cAMP in cognitive functioning and neuronal survival [40]. This cyclic nucleotide is known to activate cAMP/PKA/CREB signaling pathway. Activation (phosphorylation) of CREB seems to be a crucial event in the neuronal growth and development and in cognitive

functioning. Inhibition of the component of the cAMP/PKA/CREB pathway is known to suppress CREB phosphorylation [326]. Infact, proper CREB function is essential for neuronal survival not only during development, but also during neuronal response to harmful or toxic stimuli. Moreover, the inability of a cell to activate proper adaptive CREB-mediated survival responses would have devastating effects (Figure 10) [42,333].

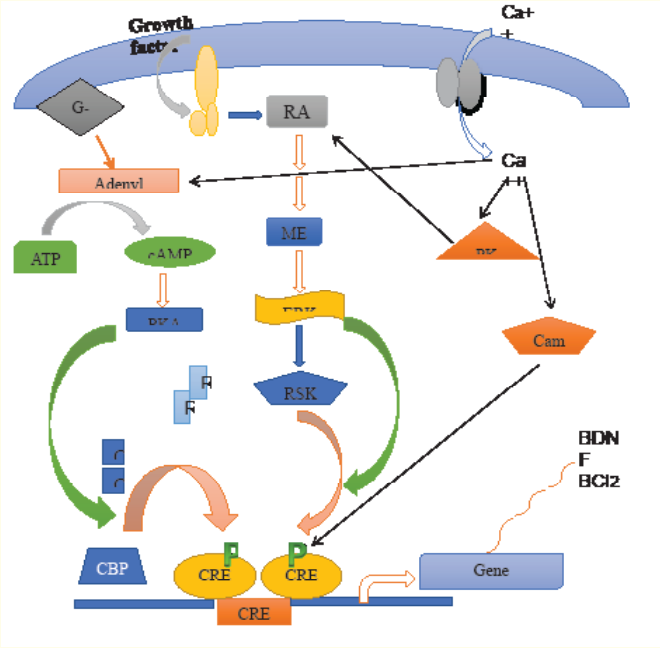

Figure 10: *CREB activation pathways.*

cAMP response element binding protein (CREB) belongs to a family of transcription factors that have been implicated in many crucial neuronal functions [334] such as learning and memory in different species ranging from invertebrates to mammals [335,336]. Activation of this system has been shown to be potentially beneficial in conditions such as Rubinstein Taybi-syndrome [337], a condition characterized by mental retardation [338], stroke [339] and in age related memory loss [340]. CREB-dependent gene expression has been shown to underlie long-term memory formation, probably through the formation of new synaptic connections [341], cell survival, neuronal plasticity, growth and development, nerve cell excitation, CNS development and circadian rhythms [342]. CREB also plays a key role in regulating neuronal survival and differentiation in response to neurotrophic factors NGF, BDNF, FGF and IGF-1 [343]. Furthermore, CREB appears to be a primary transcriptional activator of the anti-apoptotic gene, bcl-2 [344].

CREB activation

CREB can be activated (phosphorylated) by a variety of signaling pathways. The most common and best elucidated is the cAMP-PKA pathway. Extracellular signals (ex: Hormones and neurotransmitters) activate heterotrimeric G-proteins, that directly stimulate AC, which can then catalyze the production of cAMP. cAMP then leads to the activation of PKA, which dissociates into active catalytic subunits which can diffuse into the nucleus and phosphorylated CREB [345,346]. Additionally, growth factors can stimulate their respective receptors, which can lead to stimulation of Raf and the downstream kinases RAS, MEK and ERK. Activated ERK can them stimulate RSK to translocate to the nucleus to phosphorylate CREB. Furthermore, intracellular Ca^{++} can stimulate the PK_A pathway (through calmodulin) or activate members of the Calmodulin-dependent kinase family (CcamK) which can phosphorylate CREB directly. Once activated, CREB controls the transcription of various important genes [347].

Interestingly taken together, all these scientific reports confirm that CREB, together with its upstream cyclic nucleotides and downstream gene products, play an important role in the regulation of neuronal survival throughout the life of a neuron. Activation during development, as well as during times of stress is critical for determining neuronal fate, opening up the possibility that disruption of this important signaling pathway would have detrimental consequences [326].

Role of CREB in neuronal functioning

The cyclic nucleotides play a significant role in neuronal growth and development and improve cognitive functioning partly by activating CREB and by increasing synaptic availability of neurotransmitters and their cross talk. One of the way to enhance cAMP levels to improve neuronal functioning can be achieved through selective activation of an enzyme AC which activates these cyclic nucleotides into their respective nucleotides. Elevation of cAMP causes both short and long-term increase in synaptic strength [348,349] and stimulates cholinergic amacrine cells to release acetylcholine [350,351]. However, Aβ is found to inhibit cAMP/PKA/CREB signaling and impairs memory, especially long-term memory [49], while stimulation enhances cognitive functioning (Figure 11) [68].

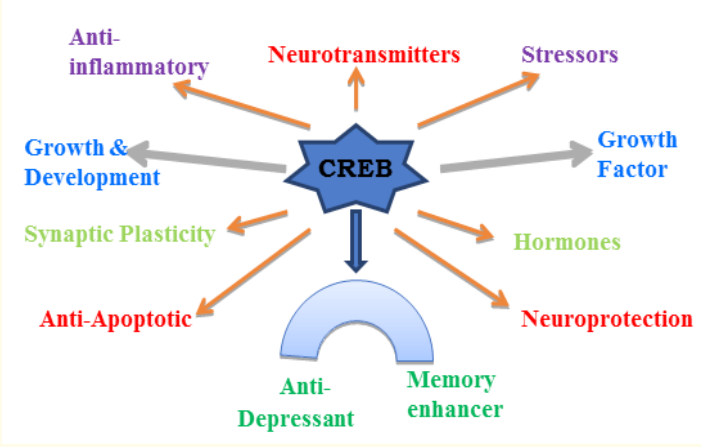

Figure 11: *Role of CREB in neuronal functioning.*

Summarizing the whole information given above cAMP stand well implicated in cognitive functioning and the levels of this cyclic nucleotide can be raised through selective activation on enzyme AC [352]. There is least availability of selective activation of AC and among these; so far only limited reports suggest beneficial effects of FSK in various *in-vitro* and *in-vivo* preclinical studies.

Forskolin (FSK)

Biological source

Plants are the first medicines for mankind and are harvested for their medicinal properties all over the world. Despite of modern development of pharmaceutical chemicals, medicinal plants remain an important tool for treating illness. According to World Health Organization, 80% of the world's population depends on traditional medicine for their health needs. India is one of the 12 mega diversity regions of the world and 1/5th of all plants found in India are used for medicinal purpose.

FSK (Coleonol) is the only source of the diterpenoid Forskolin that is produced by the Indian Coleus plant (*Coleus forskohlii*) (Figure 12). *Coleus forskoli*i is an important indigenous medicinal plant in India; it has been used traditionally for curing various disorders. 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 [353]. 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 [354].

Figure 12: *Coleus Forskohlii (Plant Leaves and roots).*

Medicinal properties

FSK is also used as a condiment in India and the tubers are prepared as pickle and eaten. The roots are used in treatment of worms, festering boils, and eczema and skin infections [355]. In traditional Indian systems of medicine, the roots of *Coleus forskohlii* are used as a tonic as well as used for veterinary purposes [356]. FSK is also used in the preparation of medicines preventing hair greying and restoring grey hair to its normal colour. Essential oil in tubers of this plant has potential uses in food flavouring industry and can be used as an antimicrobial agent and has very attractive and delicate odour with spicy note [357].

FSK is commonly used to raise levels of cyclic AMP (cAMP) in the study and research of cell physiology. FSK activates the enzyme AC and increases intracellular levels of cAMP. cAMP is an important second messenger necessary for the proper biological response of cells to hormones and other extracellular signals. It is required for cell communication in the hypothalamus/pituitary gland axis and for the feedback control of hormones [358,359].

Clinical pharmacokinetic profile

FSK ($C_{22}H_{34}O_{7,}$ MW- 410.5) is an off-white crystalline solid with a melting point of 228 - 230°C and UV-absorption maxima at 210 – 305 nm. FSK is minimally soluble in water and bioavailability is poor after oral administration. FSK has been shown to stimulate digestive secretions, including hydrochloric acid, pepsin, amylase, and pancreatic enzymes, suggesting clinical benefit in digestive disorders and mal-absorption [360]. Absorption was studied in cats, and intra-duodenal administration produced hypotension of about the same degree as observed after intravenous administration except for a latency interval of 3 - 6 minutes [361]. *Coleus Forskohlii* is well absorbed in the gastrointestinal tract of cat after oral administration and can be absorbed in all areas of the intestines and colon (in rats) although the duodenum seems to have highest uptake [362]. FSK appears to be subject to P-Glycoprotein efflux in the intestines, and co-ingestion of a P-glycoprotein inhibitor may increase oral bioavailability. FSK clinically used in various of the disease – 10 -15 mg/day orally (capsules) in case of glaucoma and effective in preventing asthma attacks in patients with mild persistent or moderate persistent asthma [363,364]. *Coleus forskohlii* supplementation can cause an increase in stomach acid levels, and may be a bad idea for those currently suffering from stomach ulcers [365].

Various clinical studies used a concentrated extract of FSK in a non-oral delivery form (injectable, aerosolized, topical ophthalmic) – for cardiovascular, respiratory, or ocular conditions. Whether oral FSK provides clinical benefit in these conditions has not been established. Oral *Coleus forskohlii* extracts are typically standardized to 10 %FSK, with recommended dosages ranging from 100 - 250 mg twice daily in case of cardiovascular disease. In a small study of seven patients with dilated cardiomyopathy, intravenous FSK administered

at 3 µg/kg/minute significantly reduced diastolic blood pressure without increasing myocardial oxygen consumption; left ventricular function also improved. Moreover, in a similar study, 4 µg/kg/ minute of intravenous FSK given to dilated cardiomyopathy patients resulted in decreased vascular resistance and improvement in left ventricle contractility [366]. FSK is having various side effects which are lowering of blood pressure, headache and increased heart rate [367]. FSK may cause cyst enlargement in patients with polycystic kidney disease. When inhaled, FSK can cause throat irritation. It can also cause tremors and restlessness. It is recommended that these patients avoid all compounds containing FSK [368].

Pharmacological action of FSK

S.No	P'cological Activity	Mechanism of action	Dose and route	Reference No.
1.	Cardiac remodeling and Heart Failure prevention	FSK stimulates Sarco endoplasmic reticulum Ca^{2+} ATPase (SERCA) activity via an AC/protein kinase A–dependent pathway	10 µM/L, *in-vitro* (Cardiomyocytes)	[369]
	Amelioration of Mitochondrial dysfunction in cardiomyopa-thy	Reduction of I_{Na} (cardiac Na+ current) and over production of mitochondrial ROS in deoxycorticosterone acetate (DOCA) mouse myocytes by activating PKA and PKC	5 µM, *in-vitro* (mice ventricular myocytes)	[370]
2.	Anti-platelet Aggregation	Reduction in the extent of platelet aggregation	2.5µM-100µM, *in-vitro* (human blood platelet)	[371]
		Induced a partial deaggregation of ADP- or collagen-aggregated human platelets	0.1mM/I, *in-vitro* (human blood platelet)	[372]
3.	Inhibition of human neutrophil degranulation Anti-Histaminic activity	cAMP mediated phosphodiesterase inhibition. Reduction in the histamine release from human basophiles and mast cells by modulating the release of mediators of the immediate hypersensitivity reaction, through activation of AC	50-75µM, *in-vitro* (Human neutrophil) 10^{-5} M, *in-vitro* (Human basophiles and mast cell)	[373] [374]
4.	Hydrodynamic alterations in collecting tubule Anti-cystic fibrosis	FSK resulted in increase in osmotic water flux and hydraulic conductivity of the rabbit cortical collecting tubule	50µM, *in-vitro* (rabbit cortical collecting tubules)	[375]
		FSK leads to cyst formation in culture media	10µM, *in-vitro*	[376]

5.	Anti-Diabetic activity	FSK predominantly decreased basal glucose in healthy rats and attenuated the severity of hyperglycemia in diabetic rats FSK increase intracellular cAMP, which, together with the increase in ATP, enhance the priming of insulin granules	6mg/kg, *p.o.* 10µM, *in-vitro*	[377] [378]
6.	Anti- inflammatory	Reduction in the level of Interleukin-1β, 6 and 8 Over-expression of Tank binding kinase1 (TBK1) reduced phosphorylation of Hormone sensitive lipase (HSL) in response to FSK Inhibit mast cell degranulation	0.5µg/kg/min (*Intra-operative*) 50µM, *in-vitro* (3T3-L1 fibroblasts cell culture) 10µM, *in-vitro* (human mast cell culture media)	[379] [380] [381]
7.	In Glaucoma	Reduction of intra ocular pressure Decrease IOP by reducing aqueous humor production in animals and humans	0.15%w/v, *Ophthalmic* 10–100 µM, *Intra-vitreal*	[382] [383]
8.	Smooth muscle relaxant	Increase both the cytosolic Ca^{2+} concentration and the cytosolic NO concentration ([NO]c) in the endothelial cells leads to cause vasodilatation Increases uterine smooth muscle AC	1µM, *in-vitro* (Rat aorta) 20µM, *in-vitro* (uterus smooth muscle)	[384] [385]
9.	Anti-Asthmatic	Decrease lipid per-oxidation Bronchiodilatation	0.2 mg/kg 1 or 5 mg, *intra-nasal*	[386] [387]
10.	Hepatoprote-ctive activity	Regeneration of hepatocytes, normalization of inflammatory hepatic and necrosis Elevations of cAMP level	500mg/kg, *Intra-gastrically (i.g.)* 10^{-7} mol/L *in–vitro* (cell culture of bile duct)	[388] [389]
11.	Anti–cancer	Decreases proliferation in Prostate cancer cells (PCa) by PP2A activation Enhances Protein phosphatase-2A (PP2A) activity in leukemia cells	40µM, *in-vitro* (human PCa cell lines) 40µM, *in-vitro*	[390] [391]

12.	Anti-Alzheimer's	FSK induced abipolar neuron-like cell morphology and it enables neurogenin-2 (Ngn2) to convert human fibroblasts into cholinergic neurons Neuronal differentiation of adult rat neural progenitor cells (NCP's) was achieved	10μM, *in-vitro* (Normal and Alzheimer's Disease Human Fibroblasts cells) 5μM, *in-vitro* (human pluripotent stem cells)	[392] [393]
13.	Anti-Depressant	FSK stimulated AC activity in rat brain and leads to enhancement of the coupling between stimulatory GTP-binding protein (G protein) and AC catalytic molecules FSK stimulates AC and regulates brain-derived neurotrophic factor (BDNF) and TrkB expression in the rat brain	0.01-0.1 mg/kg, *p.o.* 1.0 mg/kg, *i.p.*	[394] [395]

Table 5: *Various pharmacological action of FSK.*

FSK and Brain

FSK Binding sites

The binding sites for a radio-labeled form of the potent activator of AC, FSK, have been localized in the rat brain, pituitary and spinal cord [396]. Using the quantitative technique of *in-vitro* autoradiography, a high density of [3H] FSK binding was detected in brain structures such as the caudate-putamen, nucleus accumbens, olfactory tubercle, giobus pallidus, substantia nigra and the hilus of the area dentata [397]. A comparison of the distribution of [3H] FSK binding sites with those reported for several neurotransmitter receptor types indicated that FSK identified AC was probably not linked to any single type of neurotransmitter receptor. These results also presented several new brain areas in which to investigate the neuronal role of AC [398,399].

Role of FSK in brain

FSK a universal activator of AC in both membranes and intact cells [400,401]. This unique molecule activates AC rapidly and reversibly and potentiates the response of cyclic AMP-generating systems to a number of putative neurotransmitters [402]. FSK stimulates the conversation of tyrosine to dopamine in brain slices and synaptosomes from rat striatum, in synaptosomes from rat hypothalamus. Cyclic AMP is thought to play a modulatory role in synaptic transmission in vertebrate sympathetic ganglia. FSK appears to provide a new clue for elucidating the physiological role of cAMP in the synaptic transmission in the sympathetic ganglia. FSK exerts two opposite pharmacological actions at the synapse, i.e. a facilitation of transmitter release at the pre-synaptic site and a depressant action on nicotinic acetylcholine receptor at the post synaptic site. The former is probably due to an increase in intracellular cAMP level whereas the latter is probably unrelated to the cAMP formation. FSK could increase transmitter release pre-synaptically in hippocampal CA1 neurons. However, this effect is reversible, which is in contrast to that seen at mossy fiber–CA3 synapses, where activation of AC and adenosine-3*,5*-cyclic monophosphate (cAMP)-dependent protein kinase (PKA) results in a long-lasting facilitation of transmitter release, a phenomenon known as a pre-synaptic form of long-term potentiation (LTP) [403].

Furthermore, FSK activates AChE promoter and up-regulate its expression [404]. Researchers observed that the second messenger cAMP along with FSK enhanced the neuronal differentiation process of mesenchymal stem cells (MSCs) [405]. FSK has also been found to generate neuron-like morphology when cultured in serum-free conditions. Adipose derived mesenchymal stem cells (ADMSCs) ex-

pressed sodium current on treatment with basic fibroblast growth factor (BFGF) and FSK by increasing the intracellular cAMP levels, which was found to be useful in neural induction [406].

Stem cells from human exfoliated deciduous teeth (SHED), transplanted post-neural induction with FSK, differentiated into dopaminergic neurons, which elevated the dopamine content [407]. Induction by BDNF/DA was found to be greatly amplified by adding FSK 10 μM to the rat and human cerebral cortex cultures. Moreover, FSK-induced expression of tyrosine hydroxylase in human foetal brain cortex [408].

Neuroprotective action of FSK

FSK against mitochondrial dysfunctioning

Mitochondria are crucial regulators of energy metabolism and apoptotic pathways and have been closely linked to the pathogenesis of various neurodegenerative disorders such as Parkinson's disease (PD) [409], Alzheimer's disease (AD) [410], Huntington's disease (HD) [411], Amyotrophic lateral sclerosis (ALS) [412]. Oxidative stress, inflammatory mediators and calcium overload are the pathological hallmark for mitochondrial dysfunctioning [163,413]. Mitochondria are known to produce the majority of ATP in cells and also function to maintain Ca^{+2} homeostasis.

Mitochondrial dysfunctioning is associated with loss of ATP in the cells, which further leads to decrease in the level of cAMP. This decrease in the level of cAMP could be overcome by FSK induction. As FSK is a direct activator of AC is responsible for activation of cAMP lead to PK_A activation further leads to CREB activation and perform neuroprotective functioning associate with mitochondrial dysfunctioning [414]. Stimulation of protein kinase A (PK_A) by FSK, cAMP analogs, or neuropeptides effectively alleviated the mitochondrial neuronal impairment [415]. FSK at the dose of 10 μM, *in-vitro* [416] and 10 - 20 μM, *in-vitro* [417] induces phosphorylation of CREB results in increase in level of CREB which further involve in the amelioration of mitochondrial dysfunctioning.

FSK against Neuro-inflammation

Neurogenic inflammation is inflammation arising from the local release from afferent neurons of inflammatory mediators such as Substance P, Calcitonin Gene-Related Peptide (CGRP), neurokinin A (NKA), and endothelin-3 (ET-3) [418,419]. It is now well-known that immune responses or inflammation in the central nervous system (CNS) play important roles in both chronic and acute neurological disorders. Brain inflammation might be an essential cofactor in progression of Alzheimer's disease (AD) [420] and other neurodegenerative disorders such as Parkinson's disease [421], dementia with Lewy bodies [422], Huntington's disease [423] and Prion's diseases. In these complications, inflammation is atypical and occurs in the absence of overt leucocyte infiltration [424,425].

Microglia, the macrophages of brain parenchyma, are central to the inflammatory response, may drive a self-propagating toxic cycle in which several factors like protein aggregates, abnormal cellular components, injured neurons and abnormal synapses – activate microglia to release neuro-inflammatory mediators. Among the pro-inflammatory molecules found in association with plaques, cytokines are thought to play a central role in the self-propagation of neuro-inflammation, with a prominent function for IL-1a and IL-1b, IL-6, tumor necrosis factor (TNF) and nitric oxide (NO) are associated with a higher risk for developing these neurodegenerative disorders. FSK is also being natural phytochemical having potential to treat neuro-inflammation via cAMP/CREB activation. cAMP is being a secondary messenger is known to play a regulatory role in leukocyte adhesion to endothelium and transendothelial migration during inflammation [426]. Actions of cAMP are mediated by a variety of cAMP effectors proteins such as PK_A, Epac, PDZ-GEF and cyclic nucleotide-gated channels. Among these, PK_A and Epac are two major targets of cAMP, which have been implicated in the regulation of leukocyte trans-endothelial migration and endothelial barrier function [427]. FSK at the dose of 10 and 20 mM is being used to produce the anti-inflammatory action via cAMP activation and thus reduced the released of inflammatory mediators like IL-1, IL-6, TNF-α [428,429].

FSK against Neuro-oxidation

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides, oxygen and nitrogen free radical that damage all components of the cell, including proteins, lipids, and DNA [170,430]. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA caused by reactive oxygen species (ROS) and nitrogen species (NO) generated, e.g. O^{2-} (superoxide radical), OH (hydroxyl radical) and H_2O_2 (hydrogen peroxide) [431].

Oxidative stress is suspected to be important in neurodegenerative diseases including Lou Gehrig's disease (aka MND or ALS) [432], Parkinson's disease [433], Alzheimer's disease [434,435], Huntington's disease [436], and Multiple sclerosis [437]. FSK which is responsible for activation of cAMP mediated CREB, is when pretreated at a dose of 5 μM, *in-vitro* is able to inhibit expression of inducible nitric oxide synthase via inhibiting the mitogen activated protein kinase (MAPK) in C6 cells [438]. FSK at the dose of 10 μM, *in-vitro* is able to increase the cellular level of glutathione (GSH), and provide protection against H_2O_2 mediated oxidative stress.

FSK is reported to suppress the cell death caused by either serum deprivation or the withdrawal of neurotrophic factors by transcription and translation independent mechanism in PC12 cells [439].

FSK in Cognitive dysfunctioning

Cognitive disorders are a category of mental health disorders that primarily affect learning, memory, perception, and problem solving, and include amnesia, dementia, and delirium [440]. 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 [441].

The various diseases which are being associated with cognitive dysfunctioning are obsessive-compulsive disorder [442], post-traumatic stress disorder [443], Rubinstein-Taybi syndrome [337], Huntington's disease [444], Parkinson's disease [445], Alzheimer's disease [446,447]. FSK 5 mg/kg, i.p. is able to activating cAMP/CREB in the hippocampal region causes memory improvement [448]. FSK 50 μM direct potentiates synaptic response and induced LTP [449].

Possible involvement of FSK in 3-NP induced Huntington's disease

Summarizing the whole information given above, cAMP stands well implicated to play significant role in Huntington's disease (HD) and the level of this cyclic nucleotide can be raised through selective AC enzyme cAMP/CREB activator Forskolin (Figure 13). There is least availability of selective AC activation and so far only limited reports suggest beneficial effect of FSK in neurodegeneration animal model.

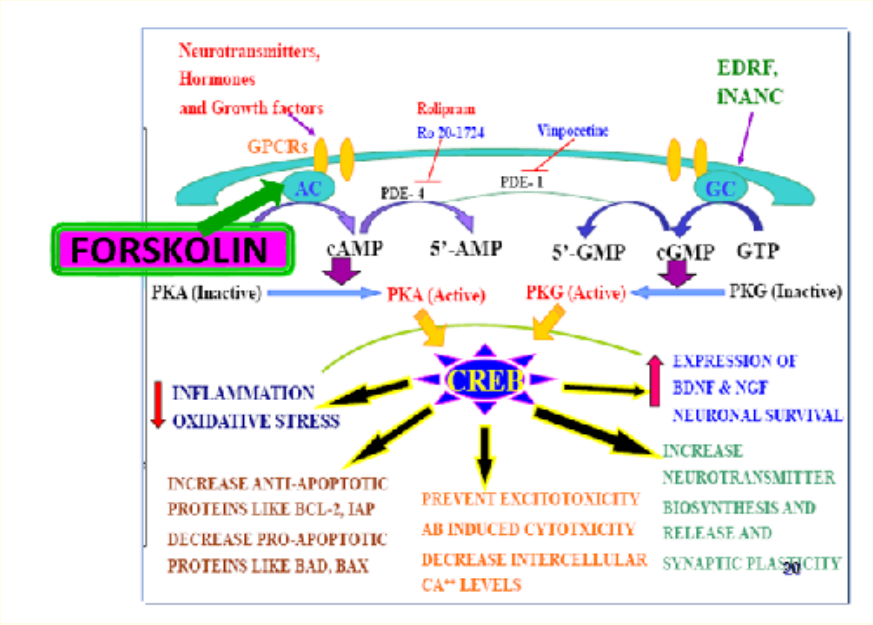

Figure 13: *Neuroprotective strategies and therapeutic implication of FSK through AC/cAMP/PKA/CREB pathway activation.*

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