

Neuroprotective strategies of solanesol in mitochondrial impairment in experimentally induced Huntington disease

Sidharth Mehan PhD¹, Manju Rajput PhD², Rajesh Dudi PhD², Krishna Ghimire PhD³

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ABSTRACT: HD is an autosomal dominant neurodegenerative disease characterized by functional incapacity, psychiatric impairment and memory dysfunction. Numerous pathological cascades are implicated in HD pathology, of which excitotoxicity and impaired cellular bio-energy are of major concern. Exploitation of these major pathological cascades shall prove to be efficient in slowing down the disease progression in HD. The existing treatment strategies include anti-psychotic drugs, NMDA receptor antagonists, caspase inhibitors, coenzyme Q10, transglutamine inhibitors, human single chain FV antibody, RNAi, stem cell therapy, ubiquitin and trophic factors. Despite

of various advancements in HD research, no treatment strategy was found to be effective to cure or to combat all the symptoms associated with the disease. Hence currently, Solanesol is a phytochemical that can influence different pathological pathways and facilitate the amelioration of all symptoms can be considered to be potent in the management of HD. Herein, an attempt was made to explore the neuroprotective protective strategies of Solanesol in mitochondrial impairment induced by 3-NP animal model of Huntington disease. This put forward the possibility of a novel neuroprotective therapy to ameliorate the major pathological features and to slow down the disease progression in HD.

Key Words: Huntington's disease; Neuroinflammation; 3-Nitropropionic acid; Solanesol

New developments in the study of brain are among the most exciting frontiers of contemporary neuro-scientific research for the clinical or surgical practitioner. Increasing knowledge of neurocomplications and of their discrete localization in the various regions of brain, the uppermost region of the central nervous system permits new modes of pharmacological management of some major neurological disorders like Huntington's disease and several others. Current concepts of the supplementary motor area, basal ganglia, hippocampus and cerebellum providing movements "Programs" serving volitional, goal-directed purposes to be turned on, monitored, and then switched off by sensory motor cortex – are more interesting and important. Knowledge of such basic physiological mechanisms may open the way for additional new uses of pharmacotherapeutic agents. During the past decades, negative influences on brain development were observed in laboratory animals and in humans. Such influences include malnutrition, infectious diseases, poisons and drugs and ionizing radiation. The extent of the disturbance can be judged as early as in the foetal phase of life, when data collected from the growth of damaged brains are compared with the normal values. The significance of knowledge pertaining to growth functions of the human brain and its various regions has achieved special recognition recently due to awareness of enhanced experimental vulnerability of the developing brain to injury such as toxins. Knowledge of normal development of different functional areas are required in order to determine whether all brain regions are equally susceptible and at which developing stage it is vulnerable to various modes of injury. This field of research seems promising but is still at its beginning.

HUNTINGTON'S DISEASE: AN OVERVIEW

Huntington's disease (HD) is a hereditary autosomal dominant disorder of central nervous system (1). The underlying genetic defect involves abnormal expansion of the CAG triple repeats (>40) in axon 1 of huntingtin gene (htt) (HDCRG, 1993). The htt gene located near the telomere of the short arm of chromosome 4 (locus 4p16.3) encodes for huntingtin (Htt) protein (2). Although, mutation in htt gene was discovered more than 17 years ago, the role of Htt in pathophysiology of HD is still under investigation (3). The most striking neuropathological hallmark of this disorder is the atrophy of the striatal region, that control movement, memory and emotions suggesting that striatal degeneration is an important aspect of HD pathophysiology (4). In patients with HD, selective loss of medium spiny neurons has not only been observed in the caudate and putamen of the striatum of basal ganglia, but also in pyramidal neurons of the cerebral cortex and to lesser extent

in hippocampal and sub-thalamus neurons (5). In patients with severe HD, neuronal loss to an extent of 80% has been observed (6). HD is characterized by chorea, seizures, involuntary movements, dystonia, cognitive decline, intellectual impairment and emotional disturbances (7). HD usually occurs in mid 40s with some exceptional cases of early onset (2 years of age) and of late onset (in the mid 80s) is reported (8,9).

MITOCHONDRIAL DYSFUNCTION & HD

Mitochondrial dysfunctions are suggested to be involved in HD pathogenesis (3). The nature and cause of mitochondrial deficits in HD is multifactorial, involving direct interaction of mutant Htt (mHtt) with mitochondria and indirect effects via transcriptional dysregulation accompanied by impaired trafficking, which compromise mitochondrial bioenergetics and dynamics (10). An aberrant association between mHtt and elements of the cellular metabolic machinery has been reported, demonstrating interaction between mHtt and mitochondria through the expanded CAG repeats (11). The mHtt is reported to affect mitochondrial calcium buffering that, leads to mitochondrial dysfunctions and increase in free radical generation (12). Whether excessive free radical generation results in mitochondrial dysfunction or mitochondrial alterations cause an increase in reactive oxygen species (ROS) is not yet clear. It is certain, however, that these pathologic processes are intertwined and each likely exacerbates the other (13). Evidence suggests that HD may be associated with impaired energy metabolism. Inhibition of enzymes present in the respiratory chain can lead to an increase in electron leakage from the mitochondria, resulting in ROS production (14). Activity of mitochondrial complexes I, II, III, and IV including aconitase enzyme were found to be reduced in the caudate and putamen of HD brains (Figure 1) (15). In patients with HD, a reduction in striatal glucose use precedes tissue loss (16). Lactate has also been shown to be elevated in the basal ganglion of patients with HD, indicating that neuronal death in HD may arise from the defect in energy metabolism (17).

EXPERIMENTAL ANIMAL MODEL FOR HD

The hypothesis that mitochondrial dysfunctions contribute to the pathogenesis of HD was first tested pharmacologically by using 3-nitropropionic acid (3-NP), an irreversible inhibitor of succinate dehydrogenase (18). (3-NP induced HD model replicates most of the clinical and pathophysiological hallmarks of HD, such as spontaneous choreiform and dystonic movements, cognitive deficits, including progressive degeneration of striatal tissue (19). One of the mechanisms following 3-NP administration is the development

¹Department of Pharmacology, ISF College of Pharmacy, Punjab, India, ²Department of Pharmacology, Rajendra Institute of Technology & Sciences, Haryana, India, ³Faculty of Medical Sciences, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, India.

Correspondence: Sidharth Mehan, Department of Pharmacology, ISF College of Pharmacy, Punjab, India. Telephone +91-9461322911, email sidh.mehan@gmail.com

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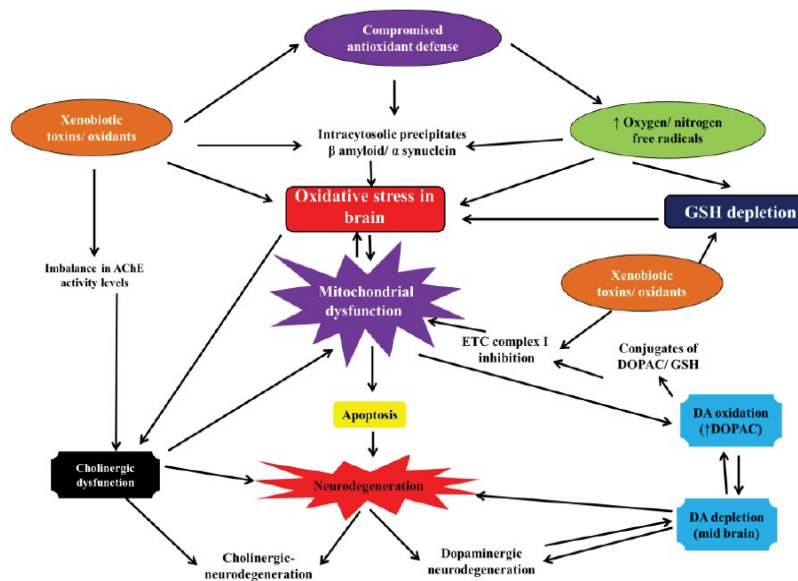


Figure 1) Mitochondrial dysfunction and impaired cellular energy metabolism in HD pathology

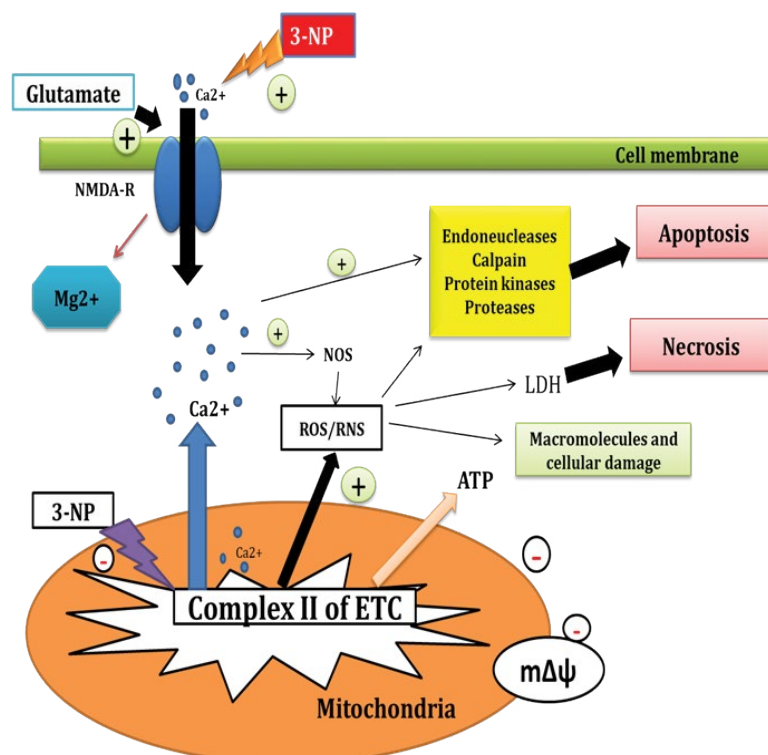


Figure 2) 3-NP induced neurotoxicity

Neurotoxicity by 3-NP: 3-NP prompts complex II inhibition and increased sensibility of NMDA-R (excitotoxicity). 3-NP toxicity affects microglia, astrocytes and neurons, and causes secondary excitotoxicity by making neurons more vulnerable to endogenous basal levels of glutamate, while prompting a reduction of ATP availability. This scenario causes relief of voltage-dependent Mg^{2+} blockade at the NMDA-R pore. In turn, the activation of these receptors leads to massive entry of Ca^{2+} to cytoplasm and further activation of a number of calcium dependent enzymes, including calpains and NOS. All together, these events lead to cell death by different pathways: necrosis and/or apoptosis, depending of intensity of insult and cell type. ETC: Electron transport chain; LDH: Lactatedehydrogenase; $m\Delta\psi$: Membrane Potential; NMDA-R: N-methyl D-aspartate (NMDA) receptor; 3-NP: 3-Nitropropionic acid; RNS: Reactive nitrogen species; ROS: Reactive Oxygen Species

of mitochondrial dysfunctions in HD animals. This bio-energetic defect involves three interacting processes such as: energy impairment, oxidative stress and excitotoxicity (20). 3-NP administration results in ATP depletion, which impairs intracellular calcium buffering thereby leading to production of damaging ROS (21). The most precise simulation of HD by 3-NP is produced when 3-NP is systemically and chronically injected in the animals (22). Specific motor abnormalities and cognitive deficits, including working memory deficits can also be easily replicated in animals treated with 3-NP (23). Other behavioral abnormalities in the 3-NP treated animals

include bradykinesia, hypo activity followed by hyperactivity. Such specific behavioral changes arise from the selective striatal lesions produced by 3-NP administration (Figure 2) (24). The therapies currently available to HD patients are aimed at symptomatic management rather than disease cure. These include SSRIs and atypical antipsychotics for psychiatric disturbances and Tetrabenazine for chorea [the first drug to be approved by the FDA specifically for the treatment of HD] (25). However, different laboratory reports suggest the possible involvement of excitotoxic, neuroinflammatory, oxidative damage, neurochemical disturbance, mitochondrial dysfunction in

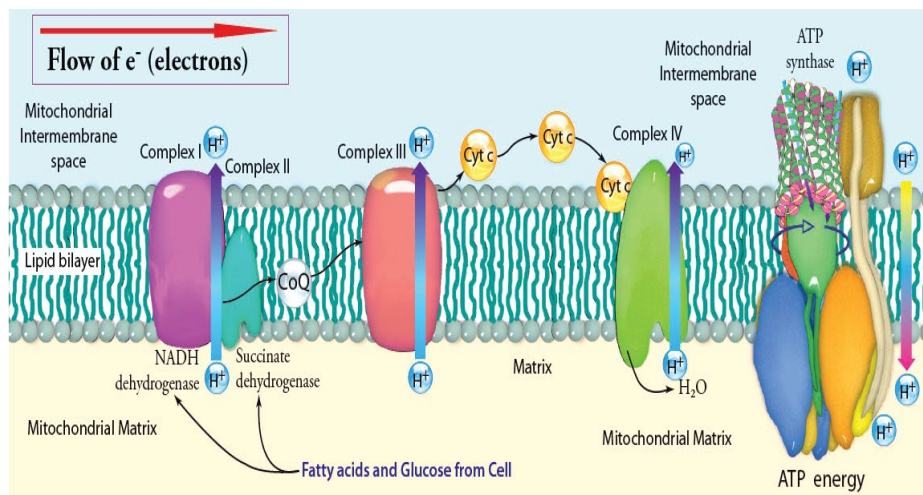


Figure 3) Involvement of solanesol produced CoQ10 during mitochondrial electron transport chain

its pathogenesis (26-29). At present, N-methyl-D-aspartate (NMDA) receptor antagonist (30), gamma amino butyric acid (GABA) modulators, dopamine blockers (31), cannabinoid agonists (32), energy production boosters, creatine (33) are being tried with a hope to treat and manage this disease symptomatically. Though HD has a single genetic cause, it has a very complex pathology with detrimental effects on a wide variety of cellular processes. As a result, a wide variety of therapies has been aimed at downstream events in both preclinical and clinical trials (34,35).

TARGET DRUG: SOLANESOL

Several metabolic modifiers have been tried to ameliorate mitochondrial dysfunctions and oxidative stress in HD, but have been found to be beneficial to a limited extent (36,37). Therefore, improving mitochondrial functions has now become a prime focus to combat neurodegeneration in HD. Mitochondrial cofactors, particularly Co-enzyme Q10, also known as ubiquinone (is a vitamin-like substance used by the human body to help produce ATP in the electron transport chain and is found throughout the body) (38-40) isolated from Solanesol obtained from Solanaceous plants, especially tobacco (*Nicotiana tabacum* L.) in combination have been shown to effectively ameliorate mitochondrial dysfunctions, reduce oxidative damage to neurons and improve behavioral functions in animals and increase ATP production, thus helps to maintain efficient mitochondrial functions (Figure 3). Solanesol is commonly found in plant leaves and is one of the ingredients present in tobacco, potato leaf and mulberry leaves (41). Tobacco especially has up to 0.85-3.75% of Solanesol. It is also found widely distributed in higher plants of Solanaceae family like *Solanum melongena*, *Solanum lycopersicum*, and *Capsicum annum*. These contain Solanesol to an extent of 0.30 to 0.40%, while *Datura stramonium*, *Solanum nigrum*, *Nicandra physaloides*, *Cestrum nocturnum* and *Solanum xantho carpum* contain Solanesol to an extent of 0.05 to 0.25%. Solanesol ($C_{45}H_{94}O$) is a tri-sesquiterpenoid alcohol which was first isolated from tobacco. Solanesol is widely distributed in plants of Solanaceae family. *Nicotiana* genus (*tabacum*) is the richest source of Solanesol, other members of the family containing Solanesol include pepper plants, potato plants, tomato plants and egg plants. Some of the chemical compounds related to Solanesol are Solanesyl acetone, Solanesyl bromide, Phytol, Solanofuran, Solanesol Acetate, Solanesol 3, 5-Dinitrobenzoate, Solanesol 3-Nitrophthalate, Solanesol p-Phenylbenzoate, etc. Solanesol is considered to be a good source of a large number of bioactive substances and is the starting material for many high value bio-chemicals, including Co-enzyme Q10 and vitamin-K analogues. Solanesol is also a potentiating agent in many medicines (42). Solanesol is medically important noncyclic terpene alcohol that is synthesized by the condensation of nine isoprene units. The molecule is a precursor of ubiquinone, also known as coenzyme Q10, vitamin K2, and anticancer drugs, including N-solanesyl-N,N'-is (3,4-dimethoxybenzyl) ethylenediamine (SDB) (43-45). Coenzyme Q10 possesses both antioxidant and anti-aging properties and is reported to strengthen the body's immune system and cardiovascular function, to improve brain health, and to moderate blood lipids. As a result, coenzyme Q10 has potential usefulness in the treatment of migraines, neurodegenerative diseases, hypertension, and cardiovascular diseases (46,47), and it is also being used as a dietary supplement by patients with type-2 diabetes (48). Meanwhile, vitamin K2

promotes bone formation and mineralization, inhibits bone resorption, prevents and mitigates osteoporosis, promotes blood coagulation, and improves arterial stiffness (49); and SDB, mediated by P-proteins, is used in the treatment of several types of drug resistance in tumors and plays a synergistic role with certain antitumor drugs (50,51). Recently, Yao et al. (52) reported that Solanesol can protect human hepatic L02 cells from ethanol-induced oxidative injury via up regulation of HO-1 and Hsp70 expression. Thus, the medical benefits of Solanesol and its derivatives are well established. The molecule was first isolated from tobacco (*Nicotiana tabacum* L.) in 1956 and has subsequently been reported to occur in other solanaceous plants, including tomatoes, potatoes, eggplants, and peppers (53,54), in which it occurs in both free and ester-bound states (55,56). Additionally, Solanesol participates in cellular energy production and in repair of damaged neurons (57-61). On the basis of previous studies, supplementation with Solanesol can be effective in cognitive and motor performance tests and this supplementation could ameliorate age-associated mitochondrial functional changes and mitochondria associated structural damage and oxidative stress in animals (62-65).

CONCLUSION AND FUTURE PERSPECTIVES

In recent years, many studies have focused on the fate and potential of neural progenitors in vertebrates while much progress has been made, many questions remain about the mechanism which lead to neural diversity, in terms of both the regionalization of the nervous system and specification of cell fates within those regions. There is no cure or effective treatment for HD till date. It is currently being treated symptomatically and drugs are used to reduce the severity of its symptoms. For many of these treatments, comprehensive clinical trials to confirm their effectiveness in treating HD symptoms is in various phase of clinical trial so far. As the disease progresses and a person's ability to tend to their own needs reduce, carefully managed multidisciplinary care giving becomes increasingly necessary. The research work to be reported by our research team to study the role of neuroinflammation and excitotoxicity in the pathogenesis of Huntington's disease and further to explore the potential targets for the development of newer therapeutics for the management of HD and related problems.

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