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# Potential Drugs and Methods for Preventing or Delaying the Progression of Huntington's Disease

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## Abstract

Huntington's disease (HD) is an autosomal dominant inherited and progressive neurodegenerative disorder with motor dysfunction and cognitive deficits. Although, there are no treatments to delay the appearance and the progression of HD, there are potential drugs currently in preclinical and clinical trials that are focused on HD therapy. The signaling pathways involved in HD are not yet clearly elucidated; however, expression of mutant huntingtin protein is considered a key factor in the induction and/or progression of HD. The demonstration that the onset and progression of HD in models of transgenic mice, in particular, are delayed or improved by the application of neurotrophic factors has emphasized their importance in neuroprotection in HD. In addition, other compounds targeting the HD gene or mutant huntingtin protein are currently in preclinical and clinical testing and may show promising neuroprotective effects. There are current patented drugs that are currently being considered as potential therapeutics for HD. These patented drugs may provide promising therapy for HD.

### Keywords

Huntington's disease; neurodegenerative diseases; neuroprotection; oxidative stress

## 1. INTRODUCTION

Huntington's disease (HD) is an autosomal dominant inherited and progressive neurodegenerative disorder with symptoms that include motor dysfunction, cognitive deficits and psychiatric symptoms [1, 2]. Motor dysfunction is a major problem in HD. The CAG trinucleotide repeat expansion within exon 1 of the huntingtin gene on chromosome 4 is the key factor in HD (Huntington's Disease Collaborative Research Group, [3]). The huntingtin gene encoding polyglutamine extends in the N-terminal domain of the huntingtin protein. The degree of the pathology is impacted by the length of the polyglutamine. Individuals who carry CAG repeats from 6 to 35 do not develop HD; however, when the number of repeats exceeds 35, the gene encodes a version of huntingtin protein that can lead to HD [4, 5]. It is noteworthy that incomplete penetrance is around 36–39 CAG repeats [6]. The causality of HD is mainly the accumulation of the polyglutamine extended huntingtin protein fragments in the cytoplasm and nucleus. Although, the mechanism of action of neurodegeneration in HD is still not identified, a key factor in the induction of HD is the



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**CONFLICT OF INTEREST**
None.

mutant huntingtin protein. The formation of neuronal intranuclear inclusions containing mutant huntingtin protein may be the cause of neurodegeneration as demonstrated in animal models of HD [7]. The increases of intranuclear inclusions were found to be associated with HD symptoms [8].

HD is characterized by neuronal dysfunction and degeneration in the striatum and cortex [9, 10]. The neuropathology may involve atrophy and degeneration of GABAergic medium spiny neurons in the striatum that are connected to the cortical areas [11]. HD therapy has been a major problem, since there is currently no treatment for preventing or attenuating the progression of the HD. Patients suffering from HD are generally treated with neuroleptics or anticonvulsants to monitor only some of the symptoms. On the other hand, transplantation has been considered the only approach to replace degenerated neurons [12]. Transplantation of fetal neuroblasts into the striatum has been suggested to be safe and potentially therapeutic in HD patients [13, 14]. Furthermore, patients grafted with human fetal neuroblasts into the striatum show improvements in cognition and motor function [15]. Interestingly, a patent indicates the use of a method for treating HD using human teratocarcinoma cell line (hNT) [16]. The patent provides methods and compositions for the transplantation of differentiated hNT neurons for the treatment of HD. These methods are aimed to improve the motor skills of patients suffering from HD who might have been transplanted with hNT neurons. It has been demonstrated that transplantation of hNT neurons in lesion rat and monkey models improved motor dysfunction [17].

Moreover, neurotrophic factors have been considered as potential therapeutic proteins that play a key role in neuroprotection and neurogenesis. Findings demonstrate that there is an association between the mutant huntingtin protein and neurotrophic factors (for review see Ref. [18]). There are at least three types of neurotrophic factors that have been considered to be potentially used for treatment of the progression of HD. Among them are: brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2) and glial cell line-derived neurotrophic factor (GDNF). The deficits of endogenous neurotrophic factors are considered critical cause of the progression of HD and other neurodegenerative diseases [19–21].

Other non-trophic factor compounds and methods have been suggested as drug candidates for the treatment of HD. The identification of these drugs is based on the clear understanding of the signaling pathways involving mutant huntingtin protein, which is a major inducer for neuronal death in HD. Here, the discussion describes some of the drugs in pre-clinical and clinical trials for the treatment of the progression of HD and other patented drugs for potential treatments of the progression and/or prevention of HD.

## 2. THERAPEUTIC EFFECTS OF NEUROTROPHIC FACTORS IN HD

Neurotrophic factors are identified based on their activity in preventing neuronal death. These proteins have been shown to promote survival or prevent oxidative stress that induces cell death. Neurotrophic factors may increase the neuronal metabolism, cell growth and processes that can lead to the growth of new axons and the reestablishment of synaptic connections. These may result in neuroprotection, cell restoration and improvement of cellular function. The first neurotrophic factor identified is nerve growth factor (NGF). NGF is a member of a family of trophic factors termed neurotrophins, which include BDNF. GDNF and FGF-2 are also identified as growth factors that have a key role in neuroprotection. On the other hand, the use of derived peptides from activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP) have been considered as trophic peptides for the attenuation of neurodegeneration in Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS). Both ADNF and ADNP are synthesized and released from astroglia [22, 23]. The release of these trophic factors is

regulated by vasoactive intestinal peptide (VIP) [24] as shown in Fig. (1). We have recently demonstrated that the neuroprotective effects of these derived peptides ADNF-9 (SALLRSIPA) and NAP (NAPVSIPQ) from ADNF and ADNP, respectively, in oxidative stress models [25, 26]. Thus, these derived peptides, ADNF-9 and NAP, have been shown to protect neuronal degeneration against the insults of oxidative stress and other related neurodegenerative models *in vitro* and *in vivo* (for review see Ref. [26, 27]).

The pharmacological actions of neurotrophic factors are considered promising new therapeutic agents for the treatment of HD. There are at least three neurotrophic factors that have been tested in pre-clinical and clinical settings for the treatment of the progression of HD. The outcomes of these neurotrophic factors are discussed in this review. There are also other neurotrophic factors tested in other neurodegenerative diseases that might be considered potential drugs for the treatment of HD.

### 2.1. BDNF

BDNF is found to be an important trophic factor for the treatment of HD. It is noteworthy that the level of BDNF is found to be downregulated in HD patients [28–30]. In accordance, downregulation of BDNF was found to be associated with CAG repeats [31]. Deficit in BDNF levels is associated with alteration of BDNF transport by mutant huntingtin protein [32, 33]. In general, normal huntingtin protein is found to enhance vesicular transport of BDNF along microtubules, but mutant huntingtin can alter this mechanism. Regulating the levels of BDNF in the corticostriatal pathway might promote cell survival and consequently delay the progression of HD. BDNF was found to be produced in cortex and transported in the corticostriatal pathway in the medium spiny neurons [34, 35], which are the neurons most affected by HD. This suggests that therapeutic approaches targeting the increase of BDNF levels might be a potential strategy to slow the progression of HD (for review see Reference [18]).

BDNF has been shown to be linked mechanistically with the underlying genetic defect in HD (for review see Ref. [36]). BDNF is considered as a potent factor to prevent cell death, as shown *in vitro,* and to delay the progression of HD, as demonstrated in animal models [31, 37–41]. Studies have assessed the effects of upregulation of BDNF using chemically induced disease. Thus, delivery of BDNF by protein infusion, intrastriatal injection of adenovirus expressing BDNF, or implantation of cells expressing BDNF induced neuroprotection in striatum that was exposed to toxins [41–43]. Moreover, studies using HD mouse models showed that BDNF is neuroprotective [7]. Thus, BDNF administration reversed the increased of GABAergic function found in HD mouse models [44]. The delivery of BDNF using osmotic minipump into the striatum in mice overexpressing exon 1 of human mutant huntingtin protein was associated with elevated expression of encephalin, which is affected mostly in HD [31]. This study also demonstrated delayed motor impairment and extended survival time in these animal models. Another study using a combination of BDNF-adenovirus vector delivery and noggin molecule showed promoting neurogenesis, striatal neuronal regeneration, and delayed motor impairment and extended the survival time in HD mouse models [45].

Similar to HD, BDNF is also a potential neurotrophic factor for treatment of AD. Deficits of cholinergic neurons are possibly the cause of cognitive deterioration, which is one of the major symptoms of AD [21]. The use of BDNF in AD is more effective for ameliorating the cholinergic functions [46]. In addition, BDNF mediates synaptic plasticity and cognitive function [47]. In humans suffering from AD, BDNF mRNA and protein were found to be decreased in cholinergic neurons in the cortex and hippocampus. A deficit in pro-BDNF protein also was found in the parietal cortex in AD [48]. It is clear that the reduction of BDNF levels in AD, particularly in cholinergic neurons, indicates that this neurotrophic

factor is considered a key factor in AD. The acetylcholinesterase inhibitors, antioxidants, and glutamate antagonists have been used mostly in clinical settings for the treatment of AD [49–51]. A patent relates to novel analogs of choline and methods of use for treatment of AD, HD and other neurodegenerative diseases [52]. Together, these findings provide ample information about the uses of BDNF in several neurodegenerative diseases including HD.

Although, the mechanism of action of BDNF in the prevention of the effects of mutant huntingtin protein is unclear, studies have shown that there is cross-talk between adenosine 2A receptors and BDNF (for review see Ref. [53]). The adenosine 2A receptors play a role in the mechanism of action involving the transactivation of BDNF receptor TrkB and also regulate the effect of BDNF on the synaptic neurotransmission as shown in Fig. (2). On the other hand, the molecular mechanisms underlying downer-gulation of BDNF level by mutant huntingtin protein might be associated with dysregulation of BDNF exon IV and VI transcription [32].

There are compounds that regulate the levels of BDNF in the brain. Cystamine, an inhibitor of transglutaminase, is a neuroprotective drug that inhibits caspase-3 activation [54] and increases the levels of antioxidants, glutathione and L-cysteine [54, 55]. The neuroprotective effect of cystamine is mediated through upregulation of chaperone, HSJ1B, and the inhibition of transglutaminase. These proteins are key players in the secretion of clathrin-coated vesicles containing BDNF [56]. Moreover, this latter study showed also that an FDA-approved drug, cysteamine, was effective in increasing BDNF levels and consequently inducing neuroprotective effects in HD mouse models. In addition, cysteamine up-regulates serum BDNF levels in mouse and primate models of HD [56]. Together, these findings suggest that cysteamine is considered a potential compound for the treatment of HD and BDNF levels in serum might be used as biomarker to determine the efficacy of the treatment of HD.

Moreover, a patent provides novel methods to improve or prevent cognitive dysfunction in pre-symptomatic or asymptomatic patients carrying mutations in the huntingtin gene [57]. These novel methods involve the increase of the expression or activity of the BDNF protein in the brains of HD patients using several compounds (e.g. ampakines, desipramine, afobazole, and others). In certain embodiments, this patent indicates that increasing the BDNF level or activity in humans comprises administering glutamate AMPA receptor modulators (e.g. ampakines) to upregulate the expression or activity of BDNF. This patent provides the use of compounds that increase the level or activity of BDNF in a mammal for the treatment or prevention of cognitive dysfunction in a pre- or asymptomatic mammal having one or more mutations in the huntingtin gene [57].

BDNF can also be regulated by activation of the serotonergic system as discussed in our previous review (for review, see Ref. [58]). Studies have shown that administration of selective serotonin re-uptake inhibitors (SSRIs) increased the levels of BDNF in hippocampus [59–62]. This suggests that SSRIs might be used to modulate the level of BDNF in HD.

### 2.2. FGF-2

Fibroblast growth factor-2 (FGF-2) has been shown to be neuroprotective against exposure to toxins or excitatory amino acids [63]. FGF-2 upregulates the level of normal huntingtin protein in a dose-dependent manner, which indicates its involvement in the expression of normal huntingtin levels [63]. FGF-2 has been found to be protective in striatal neurons [64–66]. FGF-2 increases neurogenesis and induces neuroprotection, which has a positive effect on the survival of R6/2 transgenic mice [67]. This suggests that an increase of neurogenesis in striatum with administration of FGF-2 may have an effect on the migration of nascent

neurons, which become medium spiny neurons; these neurons are replaced in HD. A patent involves the identification of FGF-2 that stimulates neurogenesis, and induction of migration of newborn cells in the striatum and cortex; this patent indicates FGF-2 as a neuroprotective factor that may extend the lifespan of patients suffering from HD and other neurodegenerative diseases [68]. In certain embodiments, this patent suggests methods of promoting neurogenesis and neuroprotection by upregulating the expression or availability of endogenous FGF-2 or by administering FGF-2 in a sufficient amount to induce neuroprotection. The methods consist of administration of FGF-2 by systemic route or directly into the brain. Increased FGF-2 expression can be monitored by radiation treatment, anti-depressant or 2-adrenergic receptor agonist administrations [68].

### 2.3. GDNF

A third trophic factor is GDNF, which has been considered a potential neurotrophic factor for the treatment of neurodegenerative diseases, including HD [69–73]. GDNF is a glycosylated disulfide-bonded homodimer which has closest structural homology to the transforming growth factor-β (TGF-β) family of neurotrophic proteins [74, 75]. The delivery of GDNF using viral vector technology has been shown to be effective in N171-82Q transgenic HD mice [71]. The administration of GDNF induced neuroprotection and overcome the behavioral deficits found in this HD mouse model. However, GDNF viral delivery fails to improve the behavioral deficits in the R6/2 mouse model [76]. This might be due to the fact that R6/2 mice have a larger number of repeats as compared to N171-82Q transgenic mice. Together, these findings suggest that GDNF has limited therapeutic effects that may depend on the CAG repeats. On the other hand, a patent provides a method for preventing or reducing cell death mediated by NMDA receptor agonist by administering GDNF [77]. This new developed method relates, in particular, to the treatment of HD and other neurodegenerative diseases. Similar to its neuroprotective role in HD, GDNF has been found to attenuate the loss of nigrostriatal dopaminergic neurons in animal models of PD and in clinics [74, 78–86], and prevents neurodegeneration of motoneurons in mutant SOD1, ALS mouse models [87–89]. The pool of target thera-pies contains several trophic factors that may protect and maintain the functionality of the motoneurons [90, 91]. Together, these findings suggest that GDNF plays an important role in neurodegenerative diseases, including HD.

In regards to the mechanism of actions of GDNF in neuroprotection, it has been demonstrated that GDNF binds to GFRα1/Ret receptor complex and in turn activates the inositol triphosphate and the mitogen-activated protein kinase intracellular cascades [92]. This leads to activation of Akt which in turn inactivates caspases 9 and 3, consequently inhibiting cell death as shown in Fig. (3). Importantly, huntingtin and mutant huntingtin proteins are phosphorylated proteins. For example, huntingtin can be phosphorylated by Akt [93–97], which is considered a survival kinase that can lead to neuroprotection Fig. (3). Note that the expression of mutant huntingtin protein can lead to the reduction of phosphorylation of huntingtin protein at Ser421 [95, 97]. This is one of the mechanisms involved in neurodegene-ration in HD.

### 2.4. Other Potential Neurotrophic Factors for the Treatment of the Progression of HD

There are other neurotrophic factors that are potentially useful for the treatment of the progression or delay of HD. For example, Insulin-like growth factor (IGF) is another factor that has been suggested to play a role in neuroprotection in HD. The neuroprotection is mediated through the prosurvival kinase Akt that has an effect in the phosphorylation of huntingtin protein at Ser421 [94]. The signaling pathways involving IGF-1 and Akt are affected in HD animal models [93]. Akt has an inhibitory effect on mutant huntingtin protein, thus preventing cell death [98]. Akt may induce phosphorylation of ADP-

ribosylation factor-interacting protein 2 (arfaptin 2), which is a key factor in cell survival. Arfaptin 2 phosphorylation inhibits the blockade of proteasome caused by the mutant huntingtin protein [98]. IGF-1 has also been considered as a potent neurotrophic factor for the treatment of ALS [99, 100]. Together, these findings suggest that IGF-1 might be a potential neurotrophic factor for the treatment of HD.

VEGF is also another trophic factor that might be suggested for the treatment of HD. VEGF has been considered as a promising factor for the treatment of ALS. In animal models, the role of VEGF in ALS has been investigated through the establishment of a new line of transgenic mice with the deletion of the hypoxia-inducible response element in the VEGF promoter. In this case, there was reduction in the expression of VEGF, progressive muscle weakness, and degeneration of motoneurons that are characteristic of ALS [101]. In addition, the levels of endogenous VEGF were found low in the cerebrospinal fluid, which is identified early in ALS patients [102]. Based on these findings, it is warranted to investigate the role of VEGF in HD.

A synthetic hybrid peptide, Colivelin, composed of ANDF-9 and AGA-(C8R)HNG17, is a potent derivative of humanin (bioactive peptide with anti-AD activity) and has been shown to improve motor performance and prolong the survival of mutant SOD1 mice models of ALS [103]. The addition of humanin to the synthetic peptide ADNF-9 prevents the degradation of this peptide and consequently increases its efficiency for neuroprotection. Colivelin is considered a new trophic factor to improve motor performance and prolong survival of ALS mouse models. The advantage of using the complex ADNF-9-Humanin is based on its stability and its ability to cross the blood-brain barrier [104]. Colivelin has also been found to have a neuroprotective effect in fetal alcohol exposure model, as demonstrated recently by our laboratory [105]. A patent filed from our laboratory indicates the neuroprotective role of Colivelin against oxidative stress [106]. Since Colivelin has been found to have neuroprotective effects in ALS and AD models, investigating its role in HD is warranted. Importantly, a patent indicates the use of Colivelin for the treatment and prevention of HD and other neurodegenerative diseases [107]. It has been demonstrated that in mice treated intracerebroventricularly with β-amyloid, Colivelin has a potent neuroprotective effect on β-amyloid-induced memory dysfunction [108]. In regard to humanin alone, studies have shown that the rescue activity of humanin is mediated by formyl peptide receptor-like 1, a G-protein coupled receptor (GPCR humanin receptor) [109]. A patent has been disclosed for methods of examining whether a potential drug is considered a modulator of the GPCR humanin receptor [110]. Moreover, there are other humanin receptors besides the formyl peptide receptor-like 1 that can play a role in neuroprotection [111].

Moreover, another derived peptide from ADNP, NAP, was found to inhibit β-amyloid aggregation by binding to its 25–35-fragment at high affinity and consequently preventing its toxic effect [112]. NAP also was found to interact with tubulin (principle unit for axonal transport) or stimulate neuronal target receptor for neuronal protection processes [112]. Regarding the second derived peptide, ADNF-9 has been tested in a model of apolipoprotein E (ApoE)-deficient mouse; apolipoprotein deficiency is considered one of the risk factors of AD. Daily injections of ADNF-9 to newborn ApoE-deficient mice were found to improve the acquisition of developmental reflexes and prevent short-term memory deficits [22]. ADNF-9 has been suggested also to aggregate with β-amyloid and consequently block its toxic effect [108]. There is a patent that relates to the use of ADNF-9 peptide for treatment of neurotoxicity induced by chemicals or by disease process [113]. In addition, another patent relates to the treatment of oxidative stress in a patient for reducing a condition associated with fetal alcohol syndrome in a subject and methods of enhancing learning and memory [114]. Moreover, another patent relates to ADNF-9 peptide for its neuroprotective

action and its uses thereof for the treatment of neurological deficiencies and for the prevention of cell death [115].

## 3. POTENTIAL THERAPEUTIC COMPOUNDS AND METHODS FOR THE TREATMENTS OF HD

Research projects are testing other compounds and methods for the treatment of HD. The discovery of these new drugs and methods has been possible due to the identification of the signaling pathways involving the gene and/or mutant huntingtin protein and the implications of glutamatergic system in HD.

### 3.1. Potential Compounds Targeting Glutamatergic System for the Treatment of HD

HD is one of the diseases that show dysregulation of glutamate [2, 116–118]. Importantly, a decline in glutamate uptake has been observed in HD transgenic mouse models [119–121] as well as HD patients post-mortem [122]. Dysregulation in glutamate uptake might be associated with a deficit in glutamate transporter 1 (GLT1 or EAAT2), which plays a critical role in HD and other neurodegenerative diseases [119, 123]. GLT1 was found dysfunctional in HD mouse models [119, 120, 124]. We recently demonstrated that a deficit in glutamate uptake in the R6/2 mouse model can be reversed with the ceftriaxone [121], which is a β-lactam antibiotic that upregulates more specifically the level of GLT1 [125]. It is noteworthy that a phase III clinical trial of ceftriaxone for treatment of ALS is already underway (for review see Ref. [126]).

Glutamate receptors have been important targets for the treatment of HD. For example, guanidine derivatives, which show high binding affinity to phencyclidine (PCP) receptors and low affinity to sigma receptors, inhibit NMDA receptors. These compounds are suggested to be neuroprotective and might be useful in the treatment of HD and other neurodegenerative diseases [127]. Moreover, another patent provides a method for producing a therapeutic vaccine, which consists of NMDA-NR1 subunit expressed in insect cells, to produce recombinant proteins which are encapsulated in poly-lactide-co-glycolic acid microparticles and used for oral immunization for the treatment of HD and other neurodegenerative diseases [128].

A patent provides a pharmacological composition and a method for treating HD using Naaladase (N-acetylated-a-linked acidic dipeptidase) inhibitors [129]. N-acetylaspartylglutamate (NAAG) has been suggested to play a role as a potential storage form of glutamate. NAALADase can induce hydrolysis of NAAG into N-acetylaspartate (NAA) and glutamate. The inhibition of NAALADase might be neuroprotective in diseases involving excess glutamatergic transmission, and this may include HD and other neurodegenerative diseases [130]. Moreover, NAAG can also be considered as an agonist to metabotropic glutamate receptors and as a mixed agonist/antagonist to NMDA receptors. These suggest that inhibition of NAALADase may increase NAAG levels that can lead to neuroprotection associated with NAAG actions toward these glutamatergic receptors.

Another patent provides a method for the treatment of HD by slowing the onset and/or the progression of HD or preventing the development of HD using hydrogenated pyrido[4,3-b] indoles, including Dimebon [131]. Dimebon was characterized as a low-affinity NMDA receptor antagonist (for review see Ref. [132]). Although Dimebon is considered to have weak action, it is suggested that the drug has a mechanism of action involving mitochondria [132]. On the other hand, studies have shown that Dimebon has clinical relevance that might result from the inhibition of alpha-adrenergic receptors (alpha1A, alpha1B, alpha1D, and alpha2A), histamine H1 and H2 receptors and serotonin 5-HT2c, 5-HT5A, 5-HT6 receptors [133].

In regard to mitochondrial dysfunction in HD, there is a patent that indicates a method of ameliorating HD by administration of a formulation that includes mitochondrial coenzyme Q10 [134]. This formulation contains Hydro-Q Sorb®, which is composed of coenzyme Q10 and cyclo-dextrin. In addition, another patent indicates the uses of compositions and methods for the treatment of mitochondrial dysfunction in neurodegenerative diseases, including HD [135]. The methods consists of administering pyrimidine nucleotide precursors, which regulate mitochondrial biosynthesis.

Moreover, there are compounds that are suggested to be effective in alleviating and/or reversing neurodegeneration in HD and other neurodegenerative diseases [52, 136–138]. The patented compounds are substituted pyrrolines that are used as kinase inhibitors for the treatment of disorders involving kinase. In addition, another patent provides the use of Efaroxan or therapeutically-acceptable salts, in their racemic forms or in the forms of optically-active isomers, for the treatment of HD [128]. Efaroxan is a 2-[2-(2-ethyl-2,3-dihydrobenzofuranyl)]-2-imidazoline that has antagonistic properties on the α 2-adrenergic receptors. The patent indicates the advantages of Efaroxan in reducing the excitotoxic effects of quinolinic acid in the striatum, as well as its advantage in the prevention of disorders involving glutamate receptors in neurotoxicity.

### 3.2. Blockade of Mutant HD Gene for Symptomatic Treatment

A patent provides methods for suppressing the mutant huntingtin gene by using a double-stranded RNA (dsRNA) [139]. This patent provides a method for targeting a specific sequence of mRNA immediately upstream of CAG repeats in the HD gene; the mutant huntingtin gene expression is suppressed by using a dsRNA homologous to the sequence. The patent indicates also that a short siRNA (short double-stranded RNA) having bp as short as around 21–23 bp may be as effective as dsRNA homologous to a specific RNA sequence in a region immediately upstream of CAG repeats. The dsRNA is suggested to be used as an inhibitor of mutant huntingtin gene to delay the progression or prevent neurodegeneration in HD [139]. Moreover, a patent indicates the identification of a new nucleotide sequence as an anti-sense strand that complements at least part of the HD gene [140]. The patent also relates to pharmaceutical composition comprising the dsRNA together with a pharmaceutically acceptable carrier that has an effect on inhibiting the expression of the mutant huntingtin gene. There is also another patent that relates to methods and assays for identifying compounds that modulate the aberrant conformation, aggregation or expression of mutant huntingtin protein [141]. This patent provides polypeptide, nucleic acid targets and siRNA sequences to modulate the expression of mutant huntingtin protein [141]. In addition, a patent provides the use of small interfering RNA and methods of treating HD and other neurodegenerative diseases [142]. Another patent provides the use of these siRNA and methods to treat HD [143]. The methods consist of surgically implanted catheters that discharge siRNA vectors targeting huntingtin gene. Furthermore, another patent indicates the use of isolated nucleic acid duplex sequences for reducing huntingtin gene [144]. These sequences, molecules and methods provide treatment for HD by reducing the mRNA without causing death, locomotor impairment or cellular dysfunction, as demonstrated in primates [144].

In addition, a patent provides apoptosis modulators that interact with the HD gene [145]. This patent indicates the identification of proteins designated as huntingtin-interacting proteins (HIP-1) that interact differentially with the gene product of a normal (16 CAG repeat) and an expanded (>44 CAG repeat) HD gene. The HIP-1 protein isolated from a yeast two-hybrid screen is encoded by a 1.2 kb cDNA devoid of stop codons expressing ~400 amino acid poly-peptide. The present patent provides a new class of apoptotic modulators which are referred to as HIP-apoptosis modulating proteins.

### 3.3. Targeting Mutant Huntingtin Protein Using Selective Antibodies

In the focus of mutant huntingtin protein, a patent relates to the generation and characterization of anti-huntingtin antibodies binding on the mutant huntingtin protein [146]. This patent indicates the generation of antibodies, particularly monoclonal antibodies including antibody fragments such as single-chain variant fragments that bind to the mutant huntingtin protein. The antibodies may have a neuroprotective effect that is mediated through the prevention of mutant huntingtin protein aggregation and the regulation of its toxic effects. In one embodiment of this patent, the antibodies are suggested to bind to an epitope within a polyproline region of the mutant huntingtin protein having a more than 5 consecutive proline residues, which may inhibit its aggregation [146]. The idea of the uses of antibodies against proteins or peptides involved in neurodegenerative diseases is in accordance with a patent providing the uses of anti-amyloid antibodies for the treatment of AD [147].

### 3.4. Uses of Selective Compound Aggregating Mutant Huntingtin Protein

Geldanamycin is a compound that has been shown to inhibit mutant huntingtin protein aggregation [148]. Geldanamycin is a benzoquinone ansamycin antibiotic that binds to Hsp90 (Heat Shock Protein 90) and alters its function. Hsp 90 is associated with another protein called HSF-1 (Heat Shock Factor 1). Geldanamycin binds to Hsp 90 and consequently makes this protein unable to associate with HSF-1 [148]. Free HSF-1 induces expression of Hsp70 and Hsp40, which consequently unfold and promote the degradation of misfolded mutant huntingtin protein through the proteasome [148, 149]. On the other hand, a patent indicates the use of a method to modulate the aggregation of polyglutamine protein in HD and proteins in other neurodegenerative diseases [150]. For example, the Y-27632, an inhibitor of the Rho-associated kinase p160ROCk, reduces polyglutamaine protein aggregation at micromolar concentrations and reduces neurodegeneration in a Drosophila model of polyglutamaine disease [150].

### 3.5. Utilization of Electrical Stimulation for the Treatment of HD Symptoms

A patent relates to introducing one or more stimulating drugs to the brain and/or applying electrical stimulation to the brain for the treatment of HD [151]. An implantable system control unit may induce electrical pulses delivered via electrodes implanted in the brain and/or drug infusion pulses delivered via a catheter implanted in the brain of HD patients. The goal of this method is to adjust the activity of a specific brain region with stimulation.

## CURRENT & FUTURE DEVELOPMENTS

HD is characterized by neuronal dysfunction and degeneration that are suggested to be caused by the expression of mutant huntingtin protein. Although, there are no treatments to slow or prevent the progression of HD, neurotrophic factors, selective compounds, and methods are considered therapeutic tools for the treatment of HD to overcome neuronal dysfunction and behavioral abnormalities. In HD therapy, BDNF, GDNF, and FGF-2 have been well studied and showed promising effects on neuroprotection in HD. On the other hand, since the key factor in HD is the mutant huntingtin protein, new compounds and methods have been identified and are considered to be potentially effective in targeting the HD gene or mutant huntingtin protein. Moreover, targeting glutamatergic system has been a key player in the treatment of HD. There are current patents that are in preclinical and clinical testing and may show promising therapeutic effects. It is important to note that there are patented compounds or methods to monitor the regulatory effects of neurotrophic factors and glutamatergic system in HD. Importantly, these treatments might be combined with new patented drugs targeting the mutant huntingtin protein involved in the progression of HD. A

combination of several methods might be a key role in the prevention or delay of the progression of HD.

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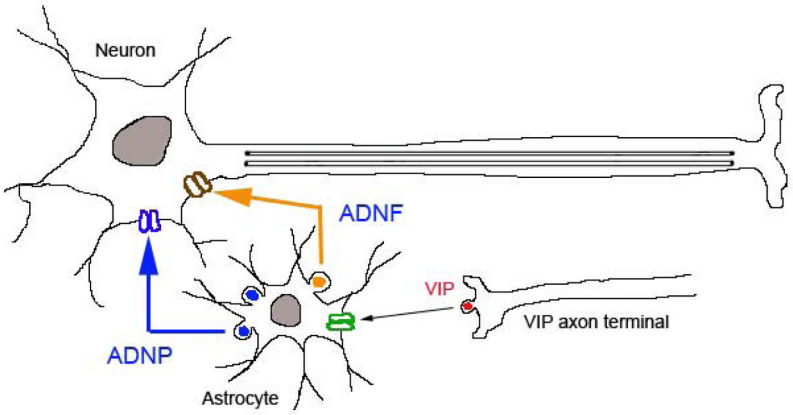


**Fig. 1.**

Model shows the mechanism of release of activity dependent neurotrophic factor (ADNF) and activity dependent neuroprotective protein (ADNP). The release of vasoactive intestinal peptide (VIP) stimulates glial target receptor and induce vesicular excytosis contained ADNF and ADNP. ADNF and ADNP maintain neuronal survival in neurodegenerative diseases through unknown mechanism.

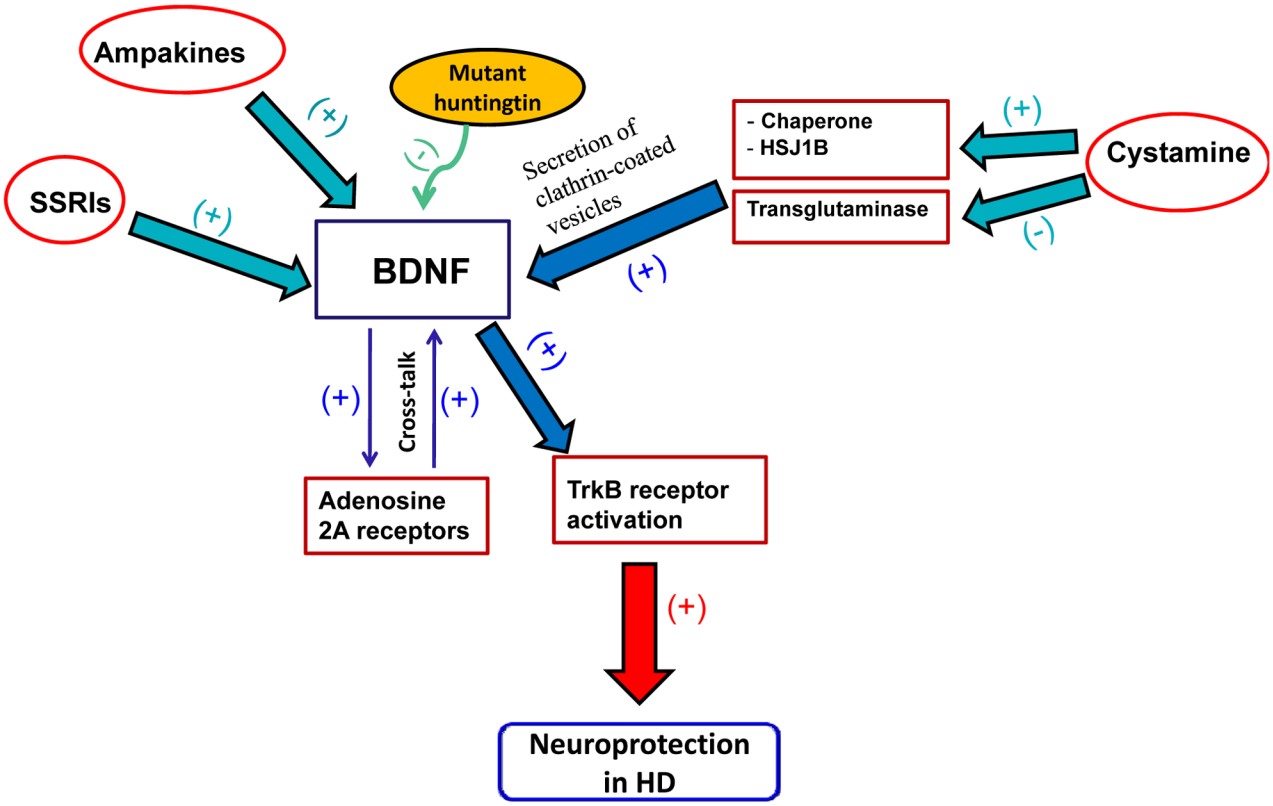


**Fig. 2.**

Molecular and pharmacological mechanism of actions of BDNF in the prevention against the effects of mutant huntingtin protein. First, adenosine 2A receptors play a role in the mechanism of action involving the transactivation of BDNF receptor TrkB. Second, cystamine has a neuroprotective effect that is mediated through the upregulation of chaperone, HSJ1B, and the inhibition of transglutaminase. These proteins are key players in the secretion of clathrin-coated vesicles containing BDNF. Third, ampakines and SSRIs are also suggested to increase the expression or activity of BDNF. Together, these compounds may induce BDNF expression, which leads to neuroprotection. (+) Stimulatory effect; (−) Inhibitory effect.

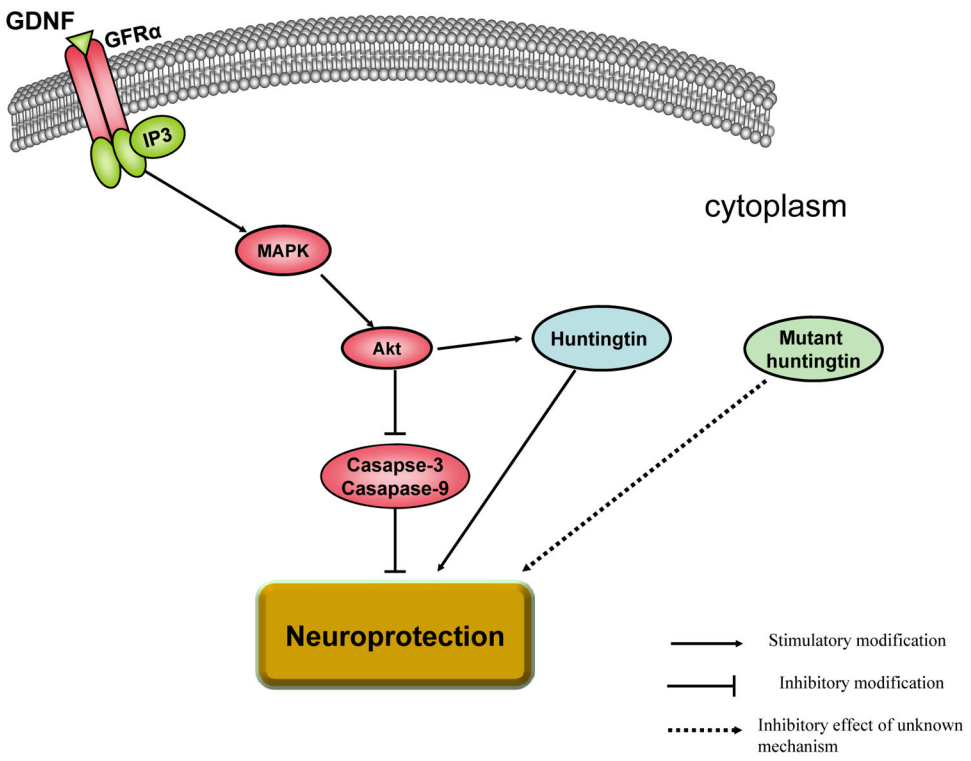


**Fig. 3.**

Molecular mechanism of actions of GDNF in neuroprotection. GDNF binds to GFRα1/Ret receptor complex and in turn activates the inositol triphosphate (IP3) and the mitogen-activated protein kinase (MAPK) intracellular cascades. MAPK activates Akt, which consequently inactivates caspases 3 and 9 and thus inhibits cell death. Moreover, Akt activates normal huntingtin protein, which in turn maintains cell survival. However, when mutant huntingtin protein is expressed, it may induce downregulation of phosphorylated normal huntingtin protein leading to cell death.