European Journal of Pharmacology 769 (2015) 33–42

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Antidepressants for neuroprotection in Huntington's disease: A review

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ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form
7 October 2015
Accepted 19 October 2015
Available online 25 October 2015

Keywords:
Huntington's disease
Antidepressants
Huntingtin protein
Brain derived neurotrophic factor
Wnt-GSK-3β Signalling
MAPK–ERK signalling

ABSTRACT

Huntington Disease (HD), which is characterized by abnormal dance-like movements, is a neurodegenerative disorder caused by a genetic mutation that results in an expanded polyglutamine stretch in the NH_2 terminus of huntingtin protein (HTT). The principal neuropathological hallmarks of disease include loss of striatal and cortical projection neurons. HTT is ubiquitously expressed and is implicated in several cellular functions including neurogenesis, cell trafficking and brain-derived neurotrophic factor (BDNF) production. Major depression is the most common symptom among pre-symptomatic HD carriers and numerous pieces of preclinical evidence have suggested the use of antidepressants in HD not only elevates mood but also slows down the disease progression by activating different neuroprotective mechanism like BDNF/TrkB pathway, MAPK/ERK signalling, neurogenesis and Wnt signalling. HTT plays major role in neurogenesis, a physiological phenomenon that is implicated in some of the behavioral effects of antidepressants. Currently, there is no clinically available treatment that can halt or slow down the progression of HD except tetrabenazine (the only FDA approved drug); however, this drug also induces depression and sedation in patients. In this review, a brief discussion has been made about the mutant HTT that induced various cellular and molecular mechanisms underlying behavioral disorders in HD. Further, an attempt has been made to understand the various cellular mechanisms involved in mediating the neuroprotective effects of antidepressants in HD.

Contents

Abbreviations: Akt, Protein Kinase B; AD, Alzheimer's disease; APC, the tumor suppressor adenomatous polyposis coli gene product; BDNF, brain derived neurotrophic factor; Bcl-2, B-cell lymphoma-2; BrdU, bromodeoxyuridine; CK1, casein kinase-1; CREB, cAMP response element binding protein; CNS, central nervous system; CAG, cytosine-adenine-guanine; Dvl, Dishevelled; ERK, extracellular signal-related kinase; Fzd, frizzled; GSK-3β, glycogen synthase kinase3βeta; GLT-1, glial glutamate transporter; HD, Huntington's disease; HTT, huntingtin protein; mHTT, mutant huntingtin protein; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindole acetic acid; IKK, I Kappa B Kinase; Lrp, lipoprotein receptor-related protein; MAPK, mitogen activated protein kinase; MSNs, medium spiny neurons; MMTV, mouse mammary tumor virus; MEK, mitogen-activated protein kinase kinase; MAOI, monoamine oxidase inhibitors; 3-NP, 3-nitropropionic acid; NGF, nerve growth factor; NF < kappa > B, (nuclear factor kappa-light-chain-enhancer of activated B cells); NRSE, neuron restrictive silencer element; NRSF, neuron restrictive silencer factor; NMDAe, n- methyl–D-aspartat; NASSA, noradrenaline and specific serotoninergic antidepressants antagonizing alpha 2 receptors and selected serotonin receptors; 3-NPd, 3-nitropropionic aci; PDe, Parkinson's diseas; PTPe, permeability transition por; PKCC, Protein Kinase; Pi3K, phosphoinositide 3-kinase; QAd, quinolinic aci; ROS, reactive oxygen species; RESTr, RE1-Silencing Transcription facto; RSK, 40S ribosomal protein S6 kinase; SDHe, succinate dehydrogenas; SNPca, substantia nigra pars compact; SSRIr, selective serotonin reuptake inhibito; SNRIr, selective serotonin and noradrenaline reuptake inhibito; TCF/LEFr, T-cell factor/lymphoid enhancer facto; TrkBB, tyrosine kinase receptor type; Wnte, winglesstype MMTV integration sit; YAC, yeast artificial chromosome

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http://dx.doi.org/10.1016/j.ejphar.2015.10.033
0014-2999/

1. Introduction

Huntington's disease (HD) is an hyperkinetic movement disorder and progressive neurodegenerative disorder, which gives rise to motor (chorea, gait abnormalities, resting tremor) and non-motor symptoms (cognitive deficit, depression, anxiety) (Kumar et al., 2011a; Chen et al., 2013; Pla et al., 2014). HD has a worldwide prevelance of 5–8 per 1,00,000 people (Pringsheim et al., 2012). HD results from expanded polyglutamine cytosine-adenine-guanine (CAG) nucleotide repeat sequence (exceeding 40 repeats) in the NH_2-terminus of a 350 kDa protein called huntingtin protein (HTT) in huntingtin gene (4p16.3) (Pla et al., 2014). Physiological HTT is ubiquitously expressed and implicated in several cellular functions including control of transcription, neurogenesis, axonal transport and brain derived neurotrophic factor (BDNF) production (Zuccato and Cattaneo, 2009; Pla et al., 2014). During the past few decades substantial progress has been made in understanding the pathophysiology of HD and numbers of theories have been put forward like mutant huntingtin protein (mHTT) protein accumulation, transcriptional dysregulation, proteosomal and mitochondrial dysfunctions, oxidative stress, apoptosis, neuro-inflammation, and consequent neuro-degeneration. Besides the motor symptoms of HD, psychiatric symptoms like psychosis, bipolar, depressive, and anxiety are other principal features of HD (Reedeker et al., 2012: Pla et al., 2014).

Antidepressants are widely used to treat depression for last 50 years. The different types of antidepressants are mainly classified under following five main types viz. SSRIs (selective serotonin reuptake inhibitors), SNRIs (serotonin and noradrenaline reuptake inhibitors), NASSAs (noradrenaline and specific serotoninergic antidepressants antagonizing alpha 2 receptors and selected serotonin receptors), tricyclics, MAOIs (monoamine oxidase inhibitors). Earlier, it was thought that antidepressants work by increasing levels of noradrenaline (NA) and serotonin in synaptic cleft but this process is not fully understood. But nowadays numerous pieces of evidence suggest cellular and molecular adaptations at several levels of brain neurons in response to antidepressant treatment (Lauterbach, 2013). Antidepressants have been reported to produce their neuroprotective effects by activating the mitogen-activated protein kinase (MAPK), extracellular signal-related kinase (ERK), phosphatidyl inositol 3-kinase (PI3K) and wingless-type MMTV integration site (Wnt)- glycogen synthase kinase (GSK-3β) signalling pathways. Also, antidepressants upregulate the expression of neurotrophic/neuroprotective factors such as brain derived neurotrophic factor (BDNF) protein and mRNA, nerve growth factor (NGF), B-cell lymphoma-2 (Bcl-2) associated athanogene 1 and inactivate proapoptotic molecules such as GSK-3β (Hunsberger et al., 2009; Lauterbach, 2013; Pla et al., 2014). In addition, they promote neurogenesis and are found to be neuroprotective in the animal models of neurodegenerative diseases Kumar et al., 2009c,d). Taken together, it can be suggested that antidepressants have wide therapeutic potential not only in mood disorders, but also in neurodegenerative diseases like HD and other movement disorders.

There is no available clinical therapy that can limit or halt the progression of HD. The only FDA approved drug tetrabenazine [dopamine-depleting agent that inhibits the vesicular dopamine transporter] for dyskinesia, and is only palliative, leading to temporarily limited improvement of clinical symptoms and produces side effects like depression and sedation. Consequently, new approaches are required to develop disease modifying agents that may delay or stop the neurodegeneration. Suppression of huntingtin gene, dissolving the aggregates of mHTT in the neurons are other approaches that might prove to be beneficial in the treatment of HD. In this review, we have collected and discussed the data of commonly used antidepressant drugs on gene expression, pathogenic protein metabolism, mitochondrial dysfunction, BDNF level, apoptosis, neuroinflammation and various other neurodegenerative processes in HD.

2. Physiological and pathological role of Huntingtin protein

Physiological HTT is ubiquitously expressed cytoplasmic protein, and contains a polyglutamine chain at the NH_2-terminus. HTT is found in all mammalian cells with the highest expression in the brain and is implicated in neurogenesis and neuronal functions, transcription, cell trafficking axonal transport and upregulates the expression of neurotrophic factors, such as BDNF and NGF (Zuccato and Cattaneo, 2009; Pla et al., 2014). In the brain, HTT is normally found in high concentrations and lack of this important protein may explain some of the clinical features of HD, as BDNF deficiency is characterized by memory loss and motor dysfunction, which are alterations also observed in HD. HTT has been reported to play substantial role in the development of embryonic brain, as severe impairment of neurogenesis has been observed in HTT knockout mice (Zeitlin et al., 1995).

mHTT has enlarged polyglutamine chain (polyQ) with more than 40 CAG repetitions. The pathogenesis of HD is mediated by mHTT, since misfolding of this protein leads to neurotoxicity. mHTT is not degraded by ubiquitin-proteosomal and lysosomal system but its toxic protofibrils and fibrils are neutralized in aggregates and inclusions. These aggregates get accumulated in the cytoplasm and nucleus of neurons (Borrell-Pages et al., 2006; Gill and Rego, 2008). The expression of pathological HTT has been reported to be the highest in the striatum nuclei of brain (Saudou et al., 1998). The mechanism by which mHTT causes neuronal dysfunction and degeneration is not fully understood. Nevertheless, impaired ubiquitin-proteosome activity, defective autophagy-lysosomal function, transcriptional dysregulation, oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, neuroinflammation and abnormal protein-protein interaction are