ELSEVIER

Progress in Neurobiology 81 (2007) 272–293

progress in Neurobiology

www.elsevier.com/locate/pneurobio

# *N*-Methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease

Mannie M.Y. Fan, Lynn A. Raymond *

*Department of Psychiatry/Kinsmen Laboratories of Neurological Research, Brain Research Centre, University of British Columbia, Vancouver, BC, Canada*

Received 1 September 2006; received in revised form 30 October 2006; accepted 15 November 2006

**Abstract**

Many lines of evidence support a role for neuronal damage arising as a result of excessive activation of glutamate receptors by excitatory amino acids in the pathogenesis of Huntington disease. The *N*-methyl-D-aspartate subclass of ionotropic glutamate receptors (NMDARs) is more selective and effective than the other subclasses in mediating this damage. As well, neurons expressing high levels of NMDARs are lost early from the striatum of individuals affected with Huntington's disease (HD), and injection of NMDAR agonists into the striatum of rodents or non-human primates recapitulates the pattern of neuronal damage observed in HD. Altered NMDAR function has been reported in corticostriatal synapses in one mouse model of HD, and NMDAR-mediated current and/or toxicity have been found to be potentiated in striatal neurons from several HD mouse models as well as heterologous cells expressing the mutant huntingtin protein. Changes in NMDAR activity have been correlated with altered calcium homeostasis, mitochondrial membrane depolarization and caspase activation. NMDAR stimulation is also closely linked to mitochondrial activity, as treatment with mitochondrial toxins has been demonstrated to produce striatal damage that can be reversed by the addition of NMDAR antagonists. Recent efforts have focused on the elucidation of molecular pathways linking huntingtin to NMDARs, as well as the mechanisms which underlie the enhancement of NMDAR activity by mutant huntingtin. Here, we review the literature to date and recent findings concerning the role of NMDARs in HD pathogenesis.


*Keywords:* Huntington's disease; Huntingtin; *N*-Methyl-D-aspartate receptors; Excitotoxicity

**Contents**

1. Introduction . . . 273
2. Excitotoxicity hypothesis . . . 274
   2.1. What is excitotoxicity? . . . 274
   2.2. Structure and functional characteristics of NMDARs . . . 275
   2.3. Striatal expression of NMDARs in HD-affected individuals and mouse models . . . 275
   2.4. Chemical models of HD . . . 276

*Abbreviations:* 3-NP, 3-nitropropionic acid; ADP, adenosine 5′-diphosphate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; AMPAR, AMPA receptor; AP-2, adaptor protein-2; ATP, adenosine 5′-triphosphate; cAMP, cyclic adenosine 5′-monophosphate; CNS, central nervous system; CSF, cerebrospinal fluid; DARPP-32, dopamine- and cAMP-regulated phosphoprotein 32 kDa; EPSC, excitatory post-synaptic current; EPSP, excitatory post-synaptic potential; ER, endoplasmic reticulum; ethyl-EPA, ethyl-eicosapentanoic acid; GABA, γ-aminobutyric acid; GST, glutathione-*S*-transferase; GTP, guanosine 5′-triphosphate; HD, Huntington's disease; HEK, human embryonic kidney; HFS, high-frequency stimulation; htt, huntingtin; iGluR, ionotropic glutamate receptor; IP3, inositol 1,4,5-trisphosphate; IP3R, IP3 receptor; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; mGluR, metabotropic glutamate receptor; mhtt, mutant htt; mPT, mitochondrial permeability transition; mRNA, messenger RNA; MSN, medium-sized spiny neuron; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; PDZ, PSD-95/Discs large/Zona occludens-1; PKA, protein kinase A; PKC, protein kinase C; polyQ, polyglutamine; PSD-95, post-synaptic density protein 95 kDa; QA, quinolinic acid; RNA, ribonucleic acid; SAP-102, synapse-associated protein 102 kDa; SNARE, soluble NSF (*N*-ethylmaleimide-sensitive fusion protein) attachment protein receptor; wt, wild-type; YAC, yeast artificial chromosome

* Corresponding author. Tel.: +1 604 822 0723.
*E-mail address:* lynnr@interchange.ubc.ca (L.A. Raymond).

0301-0082/$ – see front matter 
doi:10.1016/j.pneurobio.2006.11.003

2.5. Mitochondrial dysfunction in HD . . . 276
3. Aberrant NMDAR activity in HD . . . 277
3.1. Synaptic abnormalities in the corticostriatal pathway in the R6/2 mouse model . . . 277
3.2. Alterations in NMDA-LTP and NMDA-LTD in HD models . . . 277
3.3. Enhanced sensitivity to NMDA in HD mouse models . . . 278
3.3.1. Involvement of NR1/NR2B-type NMDARs . . . 279
3.4. Effect of NR2 gene variations on age of onset of HD . . . 280
4. Signaling downstream of altered NMDAR activity . . . 280
4.1. Calcium homeostasis . . . 280
4.2. Mitochondrial membrane depolarization . . . 281
4.3. Caspase activation . . . 282
4.4. Cellular toxicity . . . 282
4.4.1. Sensitivity and resistance to NMDA toxicity *in vivo* in HD mouse models . . . 283
5. Mechanisms underlying mhtt-induced alterations in NMDAR signaling . . . 284
5.1. Interaction via PSD-95 . . . 284
5.2. Phosphorylation of NMDARs . . . 285
6. Clinical trials of NMDAR antagonists . . . 286
7. Summary . . . 287
Acknowledgements . . . 287
References . . . 288

## 1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder affecting cognition, motor function and mood (Harper, 1991). Neuropsychiatric changes are caused by dysfunction and/or death of specific neuronal types and brain regions; GABAergic projection medium-sized spiny neurons (MSNs) of the neostriatum (caudate and putamen nuclei) are most severely affected (Vonsattel et al., 1985; Vonsattel and DiFiglia, 1998). In recent years, a plethora of research has been directed towards understanding the pathogenic mechanisms underlying development of HD. Specifically, since the identification of the *HD* gene and its protein product huntingtin (htt) over a decade ago (Huntington's Disease Collaborative Research Group, 1993), much research has focused on elucidating the function of both normal and mutant htt.

The causative mutation in the *HD* gene is the expansion of a polymorphic CAG repeat >36, with a longer repeat length being associated with an earlier age of onset (Brinkman et al., 1997; Gusella and MacDonald, 2000). Many actions harmful to the cell have been ascribed to the resulting polyglutamine (polyQ)-expanded mutant htt (mhtt). Among these are roles for the aberrant protein in promoting oxidative stress, impaired energy metabolism, compromised ubiquitination and proteasomal function, impaired axonal transport and endocytosis, as well as abnormal interactions with other proteins, some of which lead to dysregulation of the transcriptional machinery and hence altered gene expression (reviewed in Tobin and Signer, 2000; Davies and Ramsden, 2001; Menalled and Chesselet, 2002; Ross, 2002; Rubinsztein, 2002; Harjes and Wanker, 2003; Sugars and Rubinsztein, 2003; Li and Li, 2004).

The investigation of mechanisms underlying neuronal dysfunction and degeneration in HD has been greatly facilitated by development of a variety of mouse models of the disease. Some of the salient features of these models are summarized in Table 1. Mouse models expressing a severely truncated form of human mhtt, such as the R6/1, R6/2 and N171, exhibit an early phenotype with some motor features typical of HD and death by 4–5 months of age. These mice show a widespread distribution of neuronal htt aggregates and little evidence for selective neuronal loss. The accelerated phenotype facilitates therapeutic trials targeted toward the proximate causes of neuronal dysfunction in the symptomatic stages of disease. Transgenic mice expressing full-length polyQ-expanded human htt, such as the YAC46, YAC72 and YAC128 mice, develop motor signs consistent with HD at older ages (3–6 months or later, depending on polyQ length and expression levels of human htt), and death is accelerated only in a subgroup of the most extreme model, the YAC128 (Van Raamsdonk et al., 2005). However, these mice exhibit selective neuronal degeneration, which makes this a good model for studying mechanisms that target certain neuronal populations in HD. Knock-in mouse models, such as the CAG80 and 94 as well as the *Hdh*Q92 and Q111, express a CAG-expanded version of the endogenous mouse *HD* gene, thus representing the most accurate genetic model of HD. The phenotype is very mild and the mice generally lack neuronal degeneration, but they do exhibit some of the typical early neuropathological changes found in human HD brains, such as neuritic aggregates in the most vulnerable subpopulation of striatal MSNs (Albin et al., 1990, 1992; Li et al., 2001). These mice may be useful for understanding mechanisms of neuronal dysfunction that precede apparent motor onset and neuronal degeneration.

Although many effects of the htt mutation, including both gain and loss of functions of the mutant and wild-type (wt) forms of the protein, respectively, have been identified as potential contributors to neuronal dysfunction or death in HD, the reasons for selective neuronal degeneration are poorly understood. Expression of the protein is widespread in both the central nervous system (CNS) and peripheral tissues (Aronin et al., 1995; Trottier et al., 1995) and therefore does not explain the selectivity with which mhtt targets striatal MSNs for