Neuropharmacology 60 (2011) 1187–1192

Contents lists available at ScienceDirect

Neuropharmacology

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

Review

Huntington's Disease is a disorder of the corpus striatum: Focus on Rhes (Ras homologue enriched in the striatum)☆

Srinivasa Subramaniam [a], Solomon H. Snyder [a,b,c,*]

[a] Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA
[b] Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA
[c] Department of Psychiatry, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA

ARTICLE INFO

Article history:
Received 31 July 2010
Received in revised form
20 October 2010
Accepted 26 October 2010

Keywords:
Huntington Disease
mutant Huntingtin
HIP
HAP
Rhes
mTOR
Striatum
Atrophy

ABSTRACT

Despite identification of the gene for huntingtin (Htt) as causal in Huntington's Disease (HD), explication of HD symptoms and selective damage to the corpus striatum has been elusive. The small G protein Rhes Ras homolog enriched in striatum, highly localized to the striatum, binds selectively to mutant Htt (mHtt) and enhances sumoylation of mHtt. Sumoylation disaggregates mHtt and augments its cytotoxicity. Thus, it appears likely that Rhes–mHtt interaction accounts in substantial part for the selective striatal neurotoxicity of HD with associated extrapyramidal symptomatology. Rhes also binds and activates mTOR, enhancing its influence on protein synthesis, and may be the principal determinant of striatal mTOR activation. In HD, sequestration of Rhes by mHtt may decrease its access to mTOR. The attendant loss of protein translational stimulation may explain the pronounced striatal atrophy of HD.

This article is part of a Special Issue entitled 'Trends in Neuropharmacology: In Memory of Erminio Costa'.

Huntington's Disease (HD) has long been one of the most important models of genetically determined neurologic disability. It is a Mendelian dominant condition so that if one parent is affected, each progeny has a 50% chance of developing the disease. Because HD doesn't develop till middle age, children of patients live in fear of a mortal condition for which they have a high probability of succumbing. The identification in 1993 of the offending gene which codes for the protein huntingtin (Htt) offered the possibility of genetic diagnosis (Anon, 1993). In normal individuals the protein contains 11–34 glutamines in a repeat sequence at the N-terminus of the protein (commencing at the 18th amino acid position). Expansion to more than 37 glutamines leads to HD, with a larger number of glutamines leading to an earlier onset of disease. Early symptoms of HD include psychiatric disturbances, but the predominant symptomatology is motoric and led to the earlier designation of the disease as Huntington's chorea. The motor disabilities stem from massive damage to the corpus striatum which can shrink to as little as 10% of its normal volume in advanced disease. The subsequent dementia presumably reflects somewhat lesser damage to the cerebral cortex. Surprisingly, the cerebellum is completely protected. Within the striatum the medium spiny neurons are destroyed but small interneurons enriched in neuronal nitric oxide synthase (nNOS) can remain completely normal even in advanced disease (Ferrante et al., 1985).

With the discovery of the genetic abnormality in HD, it was assumed that the bases for principal features of the disease would be immediately apparent. One would have expected Htt to be a protein uniquely expressed in the striatum with moderate amounts in the cerebral cortex and none in the cerebellum. Surprisingly, Htt is a ubiquitously expressed protein occurring with equal density in neurons and glia and with no differences in various parts of the brain. Moreover, Htt is expressed at similar levels in all organs of the body. Hence discovery of the HD mutation raised more questions than it answered. Despite the major disruption of brain function in patients, their livers, kidneys and other peripheral organs appear to be reasonably normal.

For a variety of reasons it is generally thought that HD is a gain-of-function condition so that mHtt presumably elicits some cytotoxic action. Indeed, overexpression in various types of cells is

Abbreviations: mHtt, mutant Huntingtin; HIP, Huntingtin interacting proteins; HAP, Huntingtin associated protein; mTOR, mammalian target of Rapamycin; Rhes, Ras homologue enriched in striatum.

☆ Supported by USPHS Grant MH18501 to SHS.

* Corresponding author at: Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA.
E-mail address: ssnyder@jhmi.edu (S.H. Snyder).

0028-3908/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.neuropharm.2010.10.025

cytotoxic (Liang et al., 2009; Lievens et al., 2008; Sarkar et al., 2007; Weiss et al., 2009). mHtt forms aggregates in tissues which were first thought to be toxic but more recently have been appreciated to sequester mHtt with soluble, non-aggregated mHtt being the toxic culprit (Arrasate et al., 2004; Kitamura et al., 2006; Poirier et al., 2005; Ratovitski et al., 2009; Saudou et al., 1998). Elucidating exact molecular mechanisms for mHtt cytotoxicity has been challenging. Substances that kill cells generally elicit a myriad of effects so that it is difficult to sort out which are primary, secondary or tertiary. However, regardless of the exact mechanism of mHtt-elicited cytotoxicity, finding the way in which mHtt damages cells does not address the unique essence of the clinical disorder of HD. Why does HD involve such a selective damage to the corpus striatum? Why are regions such as the cerebellum completely resistant to damage?

Since studies of mHtt in isolation failed to address adequately these fundamental issues, numerous investigators have sought proteins that might interact uniquely with mHtt to cause damage. Many huntingtin protein interactors and a number of mechanisms linking these interactors to HD pathogenesis have been described (Kaltenbach et al., 2007; Landles and Bates, 2004; Li and Li, 2004; Ross, 2004), some of which we will review here. One of these, Rhes (Ras Homologue Enriched in the Striatum) will be the principal focus of this essay, as Rhes appears to account for the selective damage to the striatum.

1. HAP1 and HIP1

Soon after the cloning of Htt, application of the then young yeast two-hybrid technology to seek Htt interacters (Li et al., 1995) identified Htt associated protein-1 (HAP1), the first reported Htt interacting protein. Whereas Htt itself occurs to a similar extent in neurons and glia, HAP1 is neuron-specific. HAP1 binds with greater avidity to mHtt than to wild-type Htt. HAP1 knockout mice display substantial abnormalities including marked decreases in feeding behavior so that they fail to gain weight and often die within a few days of birth (Chan et al., 2002a). Electronmicroscopy reveals neurodegeneration in their hypothalami (Li et al., 2003). A conceivable link to HD is suggested by these findings, because HD patients also display hypothalamic degeneration and body weight loss.

HAP1 is a cytosolic protein without conserved transmembrane domains nor nuclear localization signals (Li et al., 1995). It is thought to function as a scaffold, which may be associated with its coiled-coiled domain. One protein whose interactions with HAP1 have been well characterized is dynactin, a component of the dynein motor complex (Engelender et al., 1997; Li et al., 1998). HAP1 binds to the p150 (glued) subunit of dynactin. HAP1 also interacts with kinesin light chain 2, a subunit of the kinesin motor, which, like dynactin, participates in transport within axons (McGuire et al., 2006). HAP1 also is involved in endocytic trafficking of various types of membrane receptors including the epidermal growth factor receptor (EGFR), the nerve growth factor receptor TrkA and the GABA-A receptor (Rong et al., 2006). HAP1 has been detected in a complex with IP3 receptors and Htt (McGuire et al., 2006). Introduction of mHtt into this complex enhances intracellular release of calcium, suggesting that excess calcium might be a source of cytotoxicity elicited by mHtt.

Studies by Saudou and associates have established an elegant mechanism involving mHtt and HAP1 that might influence transport of brain derived neurotrophic factor (BDNF) (Gauthier et al., 2004). They showed that wild-type Htt enhances intracellular transport of BDNF-containing vesicles, while transport is diminished with mHtt. Defects in vesicular BDNF transport were observed in murine models of HD (Spires et al., 2004). Htt-mediated vesicular transport requires HAP1, as truncated versions of mHtt that don't interact with it failed to stimulate transport. Also, these workers noted that the complex of HAP1, Htt and the dynactin complex is disrupted in HD (Gauthier et al., 2004). Thus, it appears that a normal function of the Htt protein is to act together with HAP1 to facilitate BDNF transport, a function that is markedly disrupted in HD.

Htt interacting protein 1 (HIP1) is related to the yeast protein Sla2p, which participates in cytoskeletal assembly and endocytosis in yeast (Kalchman et al., 1997). While HIP1 binds mHtt reproducibly, its affinity for mHtt is substantially less than that of HAP1. HIP1 also binds components of the endocytic machinery such as clathrin and the α-adaptin subunit AP-2 (Waelter et al., 2001). Thus, HIP1 plays some role in clathrin-mediated endocytosis. HIP1 knockout mice display a variety of neurologic defects (Hyun et al., 2004; Metzler et al., 2003). Neurons cultured from the mutant mice display defects in clathrin-mediated internalization of the glutamate-AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic) receptor. Overexpressed HIP1 interferes with clathrin-mediated receptor trafficking (Legendre-Guillemin et al., 2005).

While both HAP1 and HIP1 occur selectively within neurons in the brain, they do not display a regional distribution consistent with the damage of HD, as their levels in the striatum are not greater than in other brain regions. Both of these proteins interact physiologically with wild-type Htt, while mHtt interactions with the proteins lead to disordered function. Accordingly, it seems possible that HAP1 and HIP1 participate in the cytotoxic actions of mHtt even if they fail to explain the clinical syptomatology of the disease.

Strategies employed in identifying HAP1 and HIP1 would likely select for proteins that are either highly abundant or which bind with notably high affinity to Htt. To seek Htt-interacting proteins in an unbiased fashion, Kaltenbach and associates (Legendre-Guillemin et al., 2005) conducted an extensive high-throughput yeast-two hybrid screen technique as well as affinity pull down followed by mass spectrometry. With these procedures they identified 234 Htt-associated proteins. They were interested in finding interacting proteins that act as genetic modifiers of HD neurodegeneration. Accordingly, they arbitrarily selected 60 of the 234 and examined these for their ability to behave as genetic modifiers of neurodegeneration in a Drosophila model of HD. They found that 27 of the 60 were likely genetic modifiers, a hit rate at least 10 times greater than one typically observes in unbiased genetic screens. Whether any of these proteins is of physiologic importance in regulating functions of wild-type Htt or influences the disease's pathophysiology is unclear.

2. Our interest in HD

Our interest in HD goes back to the mid-1970s, when one of us (SHS) had been identifying receptors for opiates and various neurotransmitters (Snyder, 2009). At that time there was evidence of disorders in GABA neurotransmission in the disease and speculations that GABA agonists might be therapeutic (Shoulson et al., 1977). We wondered whether the extensive neurodegeneration of HD would lead to loss of GABA receptors precluding therapeutic efforts with GABA agonists. In a screen of numerous neurotransmitter receptors, none were notably altered in HD and none were highly selectively expressed in the striatum (Enna et al., 1976). The normal levels of GABA receptors provided justification for therapeutic attempts with GABA agonists, though we did find abnormalies in GABA-associated benzodiazepine receptors (Trifiletti et al., 1984). We observed highly selective concentrations of angiotensin converting enzyme in the corpus striatum which was fairly selectively depleted in HD (Arregui et al., 1977). Besides