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Previews

Location, Location, Location: Contrasting Roles of Synaptic and Extrasynaptic NMDA Receptors in Huntington's Disease

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Abnormally enhanced N-methyl-D-aspartate (NMDA) receptor function is implicated in Huntington's disease (HD). In this issue of *Neuron* and a recent issue of *Nature Medicine*, an abnormal balance between the activity of NMDA receptors at synaptic (prosurvival) and extrasynaptic (proapoptotic) sites has been uncovered in a cellular and a mouse model of HD.

Huntington's disease (HD) is a progressive neurological disorder inherited in an autosomal, dominant fashion. The symptoms include abnormal dance-like movements, cognitive disturbances, and disorders of mood, many of which precede onset of the motor abnormalities. The HD gene is located on the short arm of chromosome 4 and contains an expansion in the normal number of CAG (glutamine) repeats (generally >40) (The Huntington's Disease Collaborative Research Group, 1993). Neuropathologically, HD is characterized primarily by neuronal loss in striatum and cortex, and specifically targets the medium-sized spiny striatal neurons (MSNs). The protein coded, huntingtin (htt), is highly conserved and ubiquitous. A number of roles for htt have been uncovered, but the precise mechanism(s) by which mutant (m)htt causes dysfunction and ultimate degeneration of neurons remains an area of intense study. Htt is a cytoplasmic protein closely associated with vesicle membranes, microtubules, and synaptic proteins, suggesting that it may have a role in vesicle trafficking, exocytosis, endocytosis, and synaptic function. It is probable that mhtt causes abnormal synaptic transmission involving a combination of pre- and postsynaptic mechanisms. Other possibilities exist for abnormal mtt function and among the more prominent are transcriptional dysregulation and altered autophagy.

Early models of HD, before identification of the gene, were based on treatments that produced degeneration of MSNs that replicated the human neuropathology. The most prominent was excitotoxicity in which quinolinic acid, a selective N-methyl-D-aspartate (NMDA) receptor agonist, was used to produce striatal degeneration (Coyle, 1979). Thus, abnormalities in glutamate transmission and especially postsynaptic NMDA receptors became important in the study of HD. Although these toxic models provided useful information, they did not allow mechanistic examination of the temporal course of the disease or of cause-effect relationships. The subsequent introduction of genetic mouse models of HD demonstrated that severe neuronal dysfunction precedes degeneration and is probably the major determinant of a number of symptoms.

Studies designed to test the excitotoxicity hypothesis in genetic mouse models of HD have generally provided evidence that NMDA receptor function is enhanced in MSNs (Fan and Raymond, 2007). However, human trials blocking NMDA receptor function have been disappointing, demonstrating little or no therapeutic value. The reasons for such differences are unclear but may relate to the fact that many human treatments occurred during later stages of the disorder when significant degeneration was already present or that NMDA receptors are differentially affected in different regions of the brain in HD or that blockade of all NMDA receptors is not the correct approach.

Recently, a dual role for NMDA receptors has been uncovered depending upon the location of the receptor to synaptic or extrasynaptic sites (Papadia and Hardingham, 2007). Synaptic NMDA receptors activate cellular survival pathways while extrasynaptic receptors activate pathways that lead to cell death (Figure 1). Thus, the balance of activity or the numbers of each of the types of NMDA receptors at each location can sway the outcome between cell survival and cell death. Using this idea, recent research has studied differential function of synaptic and extrasynaptic NMDA receptors in HD.

In this issue, Milnerwood et al. (2010) provide the first electrophysiological evidence that the balance between synaptic and extrasynaptic NMDA receptors is disrupted in MSNs in a mouse model of HD. Their experiments demonstrate increased extrasynaptic NMDA receptor-induced currents and signaling in the YAC128 mouse model of HD. This increased activity requires caspase-6 cleavage, a step necessary for formation of the toxic mhtt fragment, and involves NMDA receptors that contain the NR2B subunit. Furthermore, they provide tantalizing new evidence that treatment with memantine, an NMDA antagonist that at low dosages antagonizes extrasynaptic but not synaptic NMDA receptors, reverses the decrease in the nuclear cyclic AMP receptor element-binding protein (CREB) activity induced by activation of extrasynaptic NMDA receptors and improves performance of YAC128 mice on a rotarod motor learning task. These outcomes signify that the increased extrasynaptic NMDA activity is deleterious in this mouse model and, when blocked, its negative effects can be prevented.

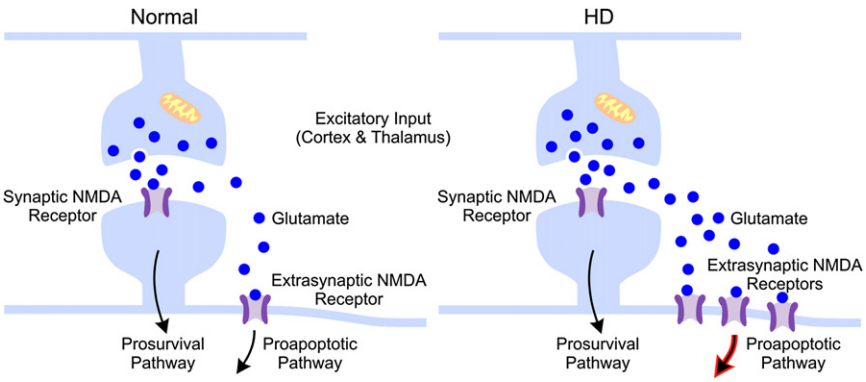

Figure 1. Synaptic and Extrasynaptic Receptors in HD
The left side shows synaptic and extrasynaptic NMDA receptors functioning in a balanced manner in the normal condition. On the right in HD there is an increase in extrasynaptic NMDA receptor function due to increase in either the number of receptors and/or an increase in extracellular glutamate that shifts the functional balance toward the extrasynaptic receptors enhancing the proapoptotic pathway.

Another recently published report (Okamoto et al., 2009) provides strikingly similar outcomes demonstrating a relationship between synaptic and extrasynaptic NMDA receptor activity and inclusion formation in cultured rat cortical cells expressing mhtt and in the YAC128 mouse model of HD. Activation of synaptic NMDA receptors made cultured mhtt-expressing cortical cells more resistant to cell death by inducing mhtt inclusions via a mechanism involving the T complex-1 (TCP-1) ring complex (TRiC). In contrast, activation of extrasynaptic NMDA receptors reduced inclusions and increased the vulnerability of mhtt-expressing cortical neurons by impairing the neuroprotective CREB-peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) cascade and increasing the level of the small binding protein Rhes, which has been shown to sumoylate and disaggregate mhtt (Subramaniam et al., 2009). Of clinical importance, Okamoto et al. (2009) also showed that treatment of YAC128 mice with low but not high dosages of memantine ameliorated adverse neuropathological and behavioral effects.

There are a number of important points and questions relevant to HD and potentially other neurodegenerative disorders emanating from these reports. First and primary is that, in HD, therapeutic treatments aimed at blocking NMDA receptors should be designed to target extrasynaptic receptors. Memantine, at low dosages, more selectively targets these receptors, and a recent, but small, open label human clinical trial showed promising results (Ondo et al., 2007). In addition, in that trial virtually all patients were also being treated with tetrabenazine, a drug that affects catecholamine systems in the brain and was recently approved for use in HD by the FDA. Clearly, there is now strong support for larger and more controlled trials with memantine in HD. Second, although there is clear evidence for altered selectivity of activation of synaptic and extrasynaptic NMDA receptors, where does this activation and the "extra" glutamate come from, and why is there more of it in HD? Normally, excitatory glutamatergic synapses in the striatum are derived from neurons in the cortex and thalamus. Since extrasynaptic NMDA receptors require glutamate spillover and higher activity for their activation compared to synaptic receptors, especially in HD as demonstrated by Milnerwood et al. (2010), what is the source of this greater activity in HD? Electrophysiological studies in genetic HD mouse models demonstrated early and progressive biphasic changes in synaptic transmission in the corticostriatal pathway, as shown by increases followed by decreases in excitatory synaptic events (Cepeda et al., 2007; Joshi et al., 2009). There also appears to be a progressive disconnection between cortex and striatum that might predict a redistribution of glutamate receptors to extrasynaptic sites (Cepeda et al., 2007). There is significant evidence for pathological changes in the cortex as well, and many of these appear to precede gross pathology in the striatum in humans (Rosas et al., 2005). We do not yet know if the balance of synaptic and extrasynaptic NMDA receptor function is altered in the cortex in HD. However, unlike the striatum, NMDA receptor activity does not appear to be enhanced in the cortex (André et al., 2006). Synaptic changes in the cortex in HD also are complex, involving both excitation and inhibition (Cummings et al., 2009). But unlike the striatum, there is a progressive increase in excitatory synaptic inputs to pyramidal neurons that appears to be associated with a progressive decrease in inhibition. Thus, in contrast to the striatum, increased excitation in the cortex may not be a consequence of alterations in NMDA receptor activity. Other possibilities for the sources of the increased extrasynaptic glutamate or NMDA receptors in the striatum are leakage of glutamate via reverse transport or some other mechanism adversely affected by mhtt (Re et al., 2006) or possibly abnormal insertion and migration of receptors between synaptic and extrasynaptic sites in HD (Tovar and Westbrook, 2002).

Another issue raised is the relationship between extrasynaptic NMDA receptor activation and abnormal protein folding, which generates the cellular inclusions in HD. Okamoto et al. (2009) provide strong evidence that activation of the cell survival pathway increases mhtt aggregation, indicating that the formation of aggregates may be a positive response of the cell. In contrast, activation of extrasynaptic NMDA receptors does the opposite. Misfolded proteins are associated with a number of neurodegenerative diseases, like Alzheimer's and Parkinson's diseases as well as HD. It becomes important to know if there is a common neurophysiological mechanism modifying and possibly controlling protein misfolding in these disorders.

These exciting findings have provided new targets for the therapeutic treatment of HD. Together the two studies link abnormal neuronal electrophysiology with the deleterious activity of extrasynaptic NMDA receptors. They provide insight into the signaling pathways involved and demonstrate that treatment with a compound that selectively blocks

extrasynaptic NMDA receptors has beneficial outcomes. Although these studies represent an important contribution to the understanding of the pathophysiology of HD, this disease involves multiple organs, multiple brain regions and changes in numerous neurotransmitter and receptor systems. It is probable that combination drug therapies, accounting for the multiple brain areas affected, the different ways they are affected, and the progression of the symptoms of HD, will provide the most efficacious approach to treatments.

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Excitatory Neuromodulator Reduces Dopamine Release, Enhancing Prolactin Secretion

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Hypothalamic dopamine neurons inhibit pituitary prolactin secretion. In this issue of *Neuron*, Lyons et al. provide evidence for a novel model, whereby the excitatory neuropeptide TRH depolarizes gap-junction-coupled dopamine neurons, leading to a shift in the population pattern of action potentials from phasic burst firing to regular tonic firing, hypothetically reducing dopamine release while increasing total spike number.

Prolactin is a fascinating pituitary hormone that promotes milk synthesis during lactation; its chemical structure is similar to that of growth hormone. Prolactin also enhances maternal behavior, and paternal behavior in some species, modulates immune responses, and is luteotrophic. Prolactin has also been associated with reduced fertility during lactation, thereby enhancing the direction of maternal energy stores toward a new infant rather than toward pregnancy (Freeman et al., 2000). Most of the functions of prolactin, including lactation, are carried out in concert with other hormones that collaborate to achieve a functional response.

Hypothalamic peptides released by axons in the median eminence regulate hormones synthesized and released by the anterior pituitary, or adenohypophysis. In contrast to other pituitary hormones that are controlled by releasing factors, secretion of prolactin is controlled by an inhibiting factor, dopamine. Dopamine is synthesized by a subset of neurons in the hypothalamic arcuate nucleus, sometimes called tuberoinfundibular dopamine (TIDA) neurons, that release the monoamine from axon terminals in the median eminence. Dopamine is then carried by the portal blood system to the pituitary where it activates dopamine G protein coupled D2 receptors that reduce cAMP and attenuate prolactin release, synthesis, and division of prolactin cells. The current model of CNS control of prolactin secretion is based on the view that when dopamine neurons in the arcuate nucleus stop firing, this leads to a loss of dopamine-mediated inhibition of the prolactin-secreting cells, thereby increasing prolactin release.

In a new paper in *Neuron*, Lyons, Horjales-Araujo, and Broberger (Lyons et al., 2010) from the Karolinska Institute in Sweden record from hypothalamic slices, and demonstrate for the first time that arcuate dopamine neurons show phasic bursts of spikes (20 spikes over 4–5 s)