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# Of mice, rats and men: Revisiting the quinolinic acid hypothesis of Huntington's disease

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We dedicate this article to the loving memory of our friend Paolo Guidetti, who passed away prematurely on December 28, 2007.

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ABSTRACT

The neurodegenerative disease Huntington's disease (HD) is caused by an expanded polyglutamine (polyQ) tract in the protein huntingtin (htt). Although the gene encoding htt was identified and cloned more than 15 years ago, and in spite of impressive efforts to unravel the mechanism(s) by which mutant htt induces nerve cell death, these studies have so far not led to a good understanding of pathophysiology or an effective therapy. Set against a historical background, we review data supporting the idea that metabolites of the kynurenine pathway (KP) of tryptophan degradation provide a critical link between mutant htt and the pathophysiology of HD. New studies in HD brain and genetic model organisms suggest that the disease may in fact be *causally* related to early abnormalities in KP metabolism, favoring the formation of two neurotoxic metabolites, 3-hydroxykynurenine and quinolinic acid, over the related neuroprotective agent kynurenic acid. These findings not only link the excitotoxic hypothesis of HD pathology to an impairment of the KP but also define new drug targets and therefore have direct therapeutic implications. Thus, pharmacological normalization of the imbalance in brain KP metabolism may provide clinical benefits, which could be especially effective in early stages of the disease.



**Contents**



*Abbreviations:* 3-HK, 3-hydroxykynurenine; 3-HAD, 3-hydroxyanthranilic acid dioxygenase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP5, D-amino-phosphonopentanoic acid; AP7, D-amino-phosphonoheptanoic acid; CNS, central nervous system; HD, Huntington's disease; htt, huntingtin; IDO, indoleamine-2,3-dioxygenase; KMO, kynurenine-3-monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; NMDA, N-methyl-D-aspartic acid; QUIN, quinolinic acid; QPRT, quinolinic acid phosphoribosyltransferase; ROS, reactive oxygen species.

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## 1. Excitotoxins and Huntington's disease: the beginning

Huntington's disease (HD), originally termed Huntington's chorea because of the characteristic involuntary movements shown by affected individuals, is a chronic neurodegenerative disorder, which is inherited in an autosomal dominant fashion. Overt motor symptoms usually develop in mid-life, and patients succumb to the disease after another 15–20 years on average. Long believed to be an exclusive basal ganglia disease because of the substantial and progressive neostriatal shrinkage and the massive dilation of the adjacent lateral ventricles, the neuropathology of HD is now known to involve a large number of brain regions and neuronal populations (Jackson et al., 1995; Rosas et al., 2008; Vonsattel et al., 1985).

For a century following the first description of the disease by Huntington (1872), speculations about the cause of neuronal loss in HD were sporadic and mostly based on clinical observations, occasionally supported by insights from microscopic studies of HD brains (Barbeau et al., 1973). Several of these hypotheses, which focused, for example, on the excessive glucose consumption of patients and on abnormal iron deposits in the basal ganglia, remain attractive to this day and may eventually turn out to be useful for a comprehensive understanding of HD pathophysiology. It was not until the 1970s, however, that a new concept provided a plausible mechanism for the characteristic nerve cell death seen in the disease.

As is often the case in the biomedical sciences, this breakthrough in HD research was made possible by disparate and seemingly unrelated findings. The first clue came from neurochemical post-mortem studies of the HD striatum, which revealed a peculiar sparing of dopaminergic afferent fibers even in the final stages of the disease, when intrinsic striatal neurons, identified by measuring GABA and its biosynthetic enzyme glutamate decarboxylase, were dramatically depleted (Bernheimer et al., 1973; Bird and Iversen, 1974; McGeer et al., 1973). This at the time unprecedented neuropathological feature was reminiscent of the "axon-sparing" lesions caused by glutamate and other excitatory amino acids, which John Olney had described in a series of publications in the late 1960s and early 1970s (Olney et al., 1971; Olney and Sharpe, 1969). In the course of these studies, which were mainly concerned with neuronal damage in the hypothalamus and the retina, Olney made two seminal observations: (a) axons of extrinsic origin do not degenerate at the lesion site and (b) the neurotoxic potency of acidic amino acids parallels their neuroexcitatory efficacy. Subsequently, he introduced the operational term "excitotoxicity" to describe neuronal lesions that were characterized by the survival of myelinated axons "en passage" and afferent axon terminals (Olney, 1974). The corresponding excitotoxins ranged from endogenous metabolites such as glutamic, aspartic and cysteine sulfinic acid to more potent exogenous compounds, including the seaweed-derived kainic acid, which was found to be approximately 500 times more effective than glutamate both as a toxin and as an excitant (Olney et al., 1971, 1974). Notably, however, the excitotoxic concept remained merely correlative in nature. No attempts to study the mechanism underlying the characteristic features of excitotoxic lesions were made in those early years when excitatory amino acid receptors were still beyond the reach of neurochemists and molecular biologists.

Interest in excitotoxicity increased substantially in the mid-1970s following the demonstration by Coyle and Schwarcz (1976), and shortly thereafter by McGeer and McGeer (1976), that stereotaxic microinjections of kainic acid cause selective, axon-sparing lesions in the rat striatum. These studies not only introduced kainate as a distinct lesioning tool that was easy to use and applicable to a wide variety of experimental situations (McGeer et al., 1978) but also, based on the duplication of the earlier post-mortem findings, provided a novel animal model of HD (Fig. 1). In relatively quick succession, a number of laboratories described further morphological and neurochemical features of the kainate-lesioned striatum and also described motor and other behavioral abnormalities in these animals (Divac et al., 1978; Mason et al., 1978; Sanberg et al., 1979). Jointly, these studies resulted in a remarkably consistent catalog of data, which not only confirmed the similarities between HD and the new animal model (Coyle et al., 1983) but also prompted investigators to study additional human neurodegenerative diseases based on excitotoxic lesions of other brain structures (Bergman et al., 1990; Flicker et al., 1983; Wenk et al., 1984).

## 2. The Swedish connection: rotational behavior and ibotenic acid

### 2.1. A dopaminergic component of excitotoxicity

The postdoctoral tenure of one of us (R.S.) at the Karolinska Institute in the late 1970s coincided with two significant advances in the excitotoxic model of HD. The first innovation was the development of a rapid, behavioral *in vivo* test for assessing

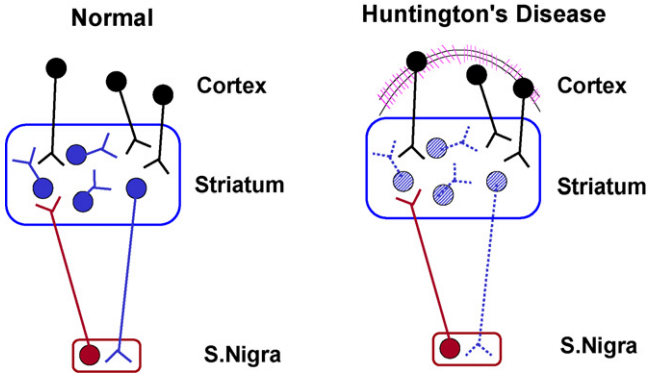


**Fig. 1.** Schematic representation of the "axon-sparing", excitotoxic nerve cell loss in the HD neostriatum. Degenerated neurons in this simplistic model are indicated by dotted lines. Cortical damage in HD is indicated in the right cartoon.