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Archives of Medical Research 39 (2008) 265–276

Archives of Medical Research

REVIEW ARTICLE

Excitotoxic Neuronal Death and the Pathogenesis of Huntington's Disease

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Received for publication July 2, 2007; accepted November 15, 2007 (ARCMED-D-07-00296).

Huntington's disease (HD) is a neurodegenerative hereditary illness originated by the mutation of the gene encoding the huntingtin-protein (htt). Mutated htt (mhtt) is characterized by an increased number of glutamine repeats in the N-terminal end; when 40 or more glutamine residues are present, the disease is manifested. Expression of mhtt leads to the selective death of the medium spiny neurons (MSN) in the neostriatum, resulting in the appearance of generalized involuntary movements, the main phenotypic alteration of HD. The relationship between the expression of mhtt and the death of the MSN is not fully understood. Nonetheless, according to experimental evidence indicating that MSN are selectively vulnerable to the toxicity of glutamate (excitotoxicity) or its analogues, excitotoxic neuronal death is suggested to be involved in neurodegeneration associated with HD. Support for this hypothesis comes from studies in HD postmortem tissue and transgenic mice models, suggesting a correlation between mhtt expression and altered glutamatergic neurotransmission, mainly altered conductance of the *N*-methyl-D-aspartate (NMDA) glutamate receptor subtype and decreased levels of glutamate transporters. On the other hand, alterations in energy metabolism are well documented in HD patients, which might facilitate excitotoxicity. Throughout this review we will discuss relevant evidence suggesting that altered glutamatergic neurotransmission plays a role in neurodegeneration associated with HD, as well as the possible contribution of deficient energy metabolism to the development of an excitotoxic cell death cascade in MSN. We show data supporting protection by energy substrates against neuronal damage in a rat model combining energy deficit and glutamate toxicity.

Key Words: Glutamatergic neurotransmission, Energy deficit, Excitotoxicity, Huntingtin, Energy substrates.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that equally affects men and women. HD occurs when the gene of huntingtin protein (htt), located in the 4p16.3 region of the short arm of chromosome 4, shows an increased number of CAG nucleotides (1,2). Mutant htt (mhtt) contains an elongated N-terminal site characterized by numerous glutamine repeats; when it shows ≥40 glutamine residues the illness is expressed during adulthood. A juvenile form of the disease is observed when the number of glutamine repeats exceeds 60. This is present in 15- to 20-year-old individuals and is characterized by the rapid progression of the illness, the presence of rigidity, seizures, and the accentuated loss of cognitive functions; the death of the patients occurs 7–10 years later (3). HD in adults is characterized by psychiatric disturbances such as irritability, aggressiveness and depression, which precede involuntary motor alterations, the main feature of HD. Progression of motor alterations, also known as choreic movements because of its resemblance to dancing postures, follows three stages. Initially, voluntary movements are accompanied by tremor; progressively, during the

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0188-4409/08 $–see front matter.
doi: 10.1016/j.arcmed.2007.11.011

second or hyperkinetic phase patients lose their body coordination due to the presence of involuntary abrupt movements (choreic) including the muscles of the limbs, head and trunk, limiting the patient's capacities for daily tasks. A progressive decline in cognitive functions and loss of body weight are also present in this phase. At the final stage, approximately 20 years after its onset, choreic movements are substituted by rigidity and bradykinesia. Death of the patient generally takes place at this stage (4).

The main phenotypic alterations of HD are the consequence of the selective loss of the medium spiny neurons (MSN) in the neostriatum, which include the putamen and the globus pallidus (5,6). The MSN constitute 95% of the total neuronal population and receive cortical inputs releasing glutamate, the main excitatory neurotransmitter in the mammalian brain. In addition to its role as a neurotransmitter, glutamate can cause the death of neurons through a mechanism known as excitotoxicity (see below). Early studies show that intrastriatal injection of glutamate or some of its analogs such as quinolinic acid and kainic acid induces a similar pattern of neuronal death as described in HD (7–9). Based on this experimental evidence, excitotoxic neuronal death has been suggested to be involved in the pathogenesis of HD. Supporting this hypothesis, modifications in some of the components of glutamatergic neurotransmission have been reported in postmortem studies of HD patients and transgenic models, suggesting that altered glutamatergic transmission might culminate in the development of an excitotoxic mechanism (see below). However, the relationship between excitotoxicity and expression of mhtt is far from being understood. Diverse experimental paradigms from pharmacological approaches to transgenic models have been used in an attempt to understand the mechanisms leading to MSN degeneration in HD. Throughout this review we will discuss the most relevant evidence supporting the role of excitotoxicity in neurodegeneration associated with HD.

Huntingtin Protein and Transgenic Mouse Models

The htt gene is constituted by 67 exons, and a polymorphic unstable repeated sequence of CAG nucleotides is located in the first exon (10). The product of this gene is a 348 kDa protein ubiquitously expressed throughout the body. The physiological role of htt remains unknown, although it has been related to vesicular transport and to cell transcription (11). The mechanisms underlying the expression of mhtt and the development of the disease are not completely understood. Transgenic mouse models have been useful tools for the study of the biochemical, morphological and functional neuronal changes associated with the expression of mhtt. These are created by the insertion of the full-length gene or the first exon of mhtt. The yeast artificial chromosome (YAC) mouse model expresses the full-length human mhtt gene carrying 46 or 72 CAG repeats (YAC46 and YAC72, respectively) (12). These mice show several phenotypical alterations resembling those observed in HD patients. The R6 transgenic mice express the first exon of the human mhtt gene carrying ~113 and ~156 CAG repeats, the R6/1 and the R6/2 mice, respectively (13). Like the YAC model, the R6 transgenic mice show some phenotypic features of HD such as motor alterations, cognitive impairment and loss of body weight. Knock-in mice are generated by the insertion of CAG repeats in the endogenous htt gene. Several knock-in mice have been developed and both the onset and severity of the phenotypic manifestations differ depending on the number of CAG repeats inserted (14). In spite of the genetic variations in each one of the transgenic models, all develop motor and neurochemical alterations similar to those distinctive in patients.

Glutamatergic Neurotransmission and Excitotoxic Neuronal Death

After its release from synaptic terminals, glutamate activates three different receptor subtypes in postsynaptic neurons: *N*-methyl-D-aspartate (NMDA) receptors; non-NMDA receptors, sensitive to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid; and metabotropic receptors. Activation of non-NMDA receptors induces the influx of sodium ions and the subsequent depolarization of the plasma membrane, promoting the extrusion of the magnesium ion normally blocking the NMDA receptor channel. Once the magnesium ion is extruded, binding of glutamate and its co-agonist, glycine, to their respective sites fully activates NMDA receptors, allowing the influx of sodium and Ca^{2+} ions into the cell. Metabotropic receptors are coupled to G-proteins and induce the activation of second messenger systems such as inositol-3-phosphate (IP-3), triggering the release of Ca^{2+} from the endoplasmic reticulum. Some metabotropic receptors are negatively coupled to adenylate cyclase.

The extracellular concentration of glutamate is highly regulated through specific Na^{+}-dependent high affinity transporters located both in neurons and glial cells. Five glutamate transporter subtypes have been described: 1) the neuronal excitatory amino acid carrier 1 (EAAC1); 2) the glutamate-aspartate transporter (GLAST) located mainly in glial cells; 3) the glutamate transporter 1 (GLT-1) located both in neurons and glia; 4) the excitatory amino acid transporter 4 (EAAT4) present in the Purkinje cells in the cerebellum; and the excitatory amino acid transporter 5 (EAAT5) located in the retina (15). Glutamate transport activity depends on the presence of the transmembrane sodium gradient generated by Na^{+}/K^{+} ATPases. Transporters bind one glutamate molecule and two sodium ions externally and translocate them into the cytoplasm, while one potassium ion is extruded to the extracellular medium. Glutamate taken up by glial cells is metabolized to glutamine, which in turn is