



## Huntington's disease and NMDA receptors; a new arena for therapeutic development

Mohamed Megahed<sup>a\*</sup>, Mona F El-Azab<sup>b</sup>, Moushira Ibrahim El Sayed<sup>c</sup>, Yasser M Moustafa<sup>b</sup>

<sup>a</sup> Department of pharmacology and Toxicology, faculty of pharmacy, university of Tabuk, Tabuk, Kingdom of Saudi Arabia.

<sup>b</sup> Department of Pharmacology and Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

<sup>c</sup> Department of Pharmacology and Toxicology, Faculty of Pharmacy, Sinai University, El-Arish, North Sinai, Egypt.

### Abstract

Huntington's disease (HD) is an inheritable autosomal dominant neurodegenerative disorder characterized by a clinical triad of progressive choreiform movements (dance-like movements), psychiatric symptoms, and a decline in the cognitive functions. It is caused by a CAG trinucleotide repeat expansion in the HD gene whereas principal pathology of this disease is the loss of striatal and cortical projection neurons. Different experimental animal models have been figured out to assist in understanding the mechanisms involved in the progress of the HD. Extensive researches had been done for testing a large array of neuroprotective agents using animal models which mimic such disorder and to examine the different mechanisms suggested to contribute in the progress of HD. Excitotoxicity in the central nervous system (CNS) results from glutamate exposure for prolonged periods or to excessive concentrations to glutamate. N-methyl-D-aspartic acid (NMDA) receptor is an ionotropic glutamate receptor responsible for the memory functions and exhibits several features of relevance to neuronal death. Neurotoxicity mediated by NMDA receptor with subsequent loss of striatal neurons contributes in the pathophysiology of HD. The current review focusing on using of NMDA receptor legends as a new strategy in treatment of HD.

### Keywords:

Excitotoxicity, Glutamate, Huntington, NMDA, Striatum

Received on: 24. 2. 2018

Revised on: 15. 4. 2018

Accepted on: 20.4. 2018

\*Correspondence Author:

Business Tel:

+966 580076707.

Fax number:

+966 14 456 1402.

Email:

mohamed.samir8592@yahoo.com

## 1. Introduction

Neurodegenerative diseases of the basal ganglia such as Parkinson's disease (PD) and Huntington's disease (HD) have received considerable concern, particularly in the past few years. In adult-onset HD, patients show a progressive deterioration of motor and cognitive functions that follows three well-defined stages spread over 15–20 years (Harper, 1991). At the initial stage and before the appearance of prominent motor alterations, HD patients are likely to show psychiatric symptoms that include apathy, irritability, depression, and other mood alterations (Reedeker, 2012; Thompson, 2012). Slight motor abnormalities, such as motor tics and jerky voluntary movements, also are likely (Beste et al., 2009). The second stage is characterized by a tragic increase in involuntary movements, which become generalized, abrupt, and uncontrolled. Deterioration of daily activities such as walking, eating, speaking, and swallowing occurs as choreic movements become more prominent. In some cases, bradykinesia may exist concomitantly with the choreic movements that become apparent in the third stage (Thompson et al., 1988). Cognitive abilities progressively decline and finally end with dementia. Another hallmark of the second stage is the loss of body weight (Marder et al., 2009). Overall health progressively worsens and by the third stage, nearly 10–15 years after diagnosis, the choreic movements are replaced by bradykinesia and rigidity. Death becomes abutting, and the most common causes are pneumonia and heart disease.

## 2. Genetic basis & Neuropathology

Huntingtin (HTT) was the first disease-associated gene to be molecularly mapped to a human chromosome (Gusella et al., 1983). Ten years later, the DNA sequence has been identified and the precise nature of the HD-associated mutation in HTT was determined (MacDonald et al., 1993). The HTT gene contains a region where the triplet nucleotide (CAG) is repeated several times. These CAG repeats generate a series of glutamine residues known as a polyglutamine tract (polyQ) and the number of CAG repeats present in the HTT gene determines whether an individual will have HD or not. Individuals less than 35 CAG repeats will be unaffected; if repeats increased up to 36–39 repeats, the individual will be at increased risk for HD; and individuals with 40 or more

repeats will definitely manifest disease phenotypes (Bates, 2005).

A rough inverse correlation between the number of CAGs and the age of HD onset occur (Langbehn et al., 2010). CAG repeats ranging from 50 to 200 (the highest number reported) may precipitate HD onset in childhood or teenage years that is characterized by psychiatric disturbances, accelerated mental and physical deterioration that culminates in death as soon as 5–10 years after onset (Quarrell et al., 2012).

Although the exact cause of neuronal death in HD remains unknown, it has been postulated that proteolysis of mutant huntingtin plays a role in disease pathogenesis resulting in an abnormal and toxic amino acid (N) terminal fragment that forms protein aggregates in neurons. Intra-cellular aggregates of mutant HTT are found in both the cytoplasm and nucleus (Vonsattel et al., 1985). In neurons, mutant HTT aggregates are also located in axon terminals, where the presence of aggregates has been correlated with decreased density of synaptic vesicles and decreased release of glutamate in striatum of HD mice (Gafni et al., 2004; Finkbeiner and Mitra, 2008). These aggregates sequester a variety of important cellular proteins leading to disruption of protein homeostasis and can be readily detected throughout the course of the disease. Some evidence has outlined that direct interactions between mutant huntingtin and transcription factors may be the proximal defect that leads to transcriptional dysfunction (Tunez et al., 2010). This then results in a cascade of compensatory and damaging events as mitochondrial dysfunction, energy depletion, oxidative stress, DNA damage and others that might play a role in neuronal death (Pringsheim et al., 2012).

The most prominent cell loss in HD occurs in cerebral cortex and striatum, the forebrain regions in which cortical pyramidal neurons (CPNs) and striatal medium spiny neurons (MSNs) are the most affected (Tunez et al., 2010).

## 3. Animal models of HD

### 3.1. Assessing the validity of animal models of human disease

The applicability of a given animal model of human disease is often judged based on three broad measures of validity: the animal model's *construct validity* (refers to how closely the animal model mimics the underlying pathogenic lesion that provokes the disease in humans), *face validity* (relates to the extent to which the animal model

develops the symptoms and phenotypes associated with the human disease) and *predictive validity* (indicates how closely improvements in response to treatment in the animal model parallel, or predict, improvements in patients). For diseases that lack an effective treatment, such as HD, assessment of the predictive validity of an animal model is currently impossible (Pouladi et al., 2013).

### 3.2. Models for HD:

A number of animal models of HD have been available for more than 30 years (Brouillet et al., 1999) in an effort to understand how the mutation causes the symptoms and pathology observed in patients in order to observe the process of cell death in a simpler, more controlled circumstances than the human disorder.

#### 3.2.1. Toxin Models of HD:

##### 3.2.1.1. Neurotoxin-mediated lesions in animals:

Early experimental models of HD relied on direct introduction of excitatory agonists into the central nervous system (Rothman, 1984). Kainic acid is an excitatory glutamate-type neurotoxin, which produces degeneration of striatal GABAergic projection neurons with preservation of striatal afferents (McGeer and McGeer, 1976). Kainic acid was also found to irreversibly reduce glutamic acid decarboxylase (GAD) but do not produce the entire constellation of histological changes observed in HD (Isacson et al., 1985; Hantraye et al., 1990).

Unlike kainic acid, quinolinic acid shows differential sparing of striatal neurons (Lehrmann et al., 2008). Quinolinic acid damages both GABAergic and substance P-containing neurons, with relative sparing of cholinergic neurons, that latter of which are known to be spared in HD (Ferrante et al., 1985; Ferrante et al., 1987).

The behavioural deficits in the excitotoxin rodent model of HD include locomotor hyperactivity and poor performance in mnemonic and cognitive tests (Koutouzis et al., 1994) but doesn't include dyskinesias or chorea like movements. Thus, the rodent excitotoxin model can't be used to study the progression of the disease or to replicate the widespread neuropathology observed in the human.

##### 3.2.1.2. Defective energy metabolism toxin models:

Impaired cellular energy maybe involved in the degenerative process in HD (Albin and Greenamyre, 1992) due to reduced ATP stores that results in membrane depolarization, removal of magnesium from the NMDA linked calcium channel and subsequent excitotoxic injury (Novelli et al., 1988).

3-Nitropropionic acid (3-NP) has been associated with neurological illness in animals and humans (Ludolph et al., 1991). 3-NP is an irreversible inhibitor of succinate dehydrogenase (SDH) that inhibits both the Krebs cycle and complex II activity of the electron transport chain. Moreover, striatal atrophy is apparent with systematic administration of low doses of 3-NP (Beal et al., 1993; Brouillet et al., 1993).

#### 3.2.2. Genetic models of HD:

In particular, genetic animal models of HD have been an accurate tool of elucidation of the progression of behavioral and physiological alterations, which had not been possible using classic neurotoxin models. Genetic models also provide an opportunity to test promising treatments and explore their potential ability to cure the disease (Ferrante et al., 2009).

##### 3.2.2.1. R6/2 transgenic mice:

The R6 line of transgenic mice (Mangiarini et al., 1996) remains one of the most widely used models because it offers many advantages. Particularly, R6/2 mice (expressing exon 1 with about 150 CAG repeats) manifest a very aggressive, rapidly progressing phenotype, similar to the juvenile form of HD in humans. They display overt behavioural symptoms as early as 5–6 weeks of age and die at about 15 weeks. Pathophysiological alterations include the formation of nuclear inclusions (Davies et al., 1997), which were later also shown to be present in human HD brains and can be observed in the presymptomatic stage, particularly in the striatum and CA1 region of the hippocampus (Morton et al., 2000). There are also changes in neurotransmitter receptor expression (Cha et al., 1998; Ariano et al., 2002) and altered signaling mechanisms (Bibb et al., 2000; Luthi-Carter et al., 2000; Menalled et al., 2000). Many of these alterations are correlated with motor (Carter et al., 1999) and learning impairments on a number of cognitive tasks (Lione et al., 1999), as well as deficits in synaptic plasticity in the hippocampus before an overt phenotype appears (Murphy et al.,

2000) and in the striatum of symptomatic animals (Kung et al., 2007).

### 3.2.2.2. *R6/1 transgenic mice:*

The R6/1 transgenic mice were developed at the same time as the R6/2 transgenic mice and express exon 1 of the human HD gene with approximately 116 CAG repeats. The R6/1 transgenic mice have not been as well studied as the R6/2 transgenic mice (Mangiarini et al., 1996). The R6/1 line has a later age of onset and a slower disease progression. They can live beyond 12 months (Naver et al., 2003).

### 3.2.2.3. *N171-82Q transgenic HD mice:*

N171-82Q mice have an N-terminal fragment of huntingtin incorporating both exon 1 and exon 2 of the huntingtin gene, with 82 polyglutamines (Schilling et al., 1999). The commercially available line has a life span range from 130-180 days (Yu et al., 2003).

### 3.2.2.4. *Murine huntingtin homologue knock-in mice:*

Knock-in models also contributed to understanding of HD. The major advantage of these models is that they express full-length mutant htt in its native genomic context. Several models have been generated and the difference is mainly in the number of CAG repeats (from 48 to 200) (Heng et al., 2007; Heng et al., 2009) (White et al., 1997; Levine et al., 1999; Wheeler et al., 2000; Lin et al., 2001). In the knock-in models early overt behavioural changes are often subtle, but sensitive and careful testing demonstrate abnormalities as early as 1–2 months of age (Menalled et al., 2002; Menalled et al., 2003).

A more severe phenotype develops as the mice age beyond one year (Hickey et al., 2008). A consistent feature of knock-in mice is the presence of nuclear staining and microaggregates very early in the course of the disease. By contrast, nuclear inclusions are observed only in older mice (10–18 months) (Menalled and Chesselet, 2002), and loss of MSNs occurs at about 2 years (Hickey et al., 2008).

A number of lines have been made:

Hdh/Q 72-80: with 72 to 80 CAG repeats (Alexi et al., 1998).

HdhQ111: with 109 to 111 CAG repeats (Brouillet et al., 1998).

CAG140: with 140 CAG repeats (Naver et al., 2003).

CAG150: with 150 CAG repeats ( Bizat et al., 2003).

### 3.2.2.5. *Full length human HD gene transgenic mouse models:*

A yeast artificial chromosome mouse model of HD with the entire human huntingtin gene containing 126 CAG repeats as well as flanking segments that might involve regulatory elements. Motor abnormalities develop consisting of initial hyperactivity followed by difficulty walking and then hypokinesia (Hodgson et al., 1999; Slow et al., 2003).

## 4. Mitochondria in HD

Mitochondrial function is impaired in HD and this occurs early in the disease process. The striatum might be particularly vulnerable to mitochondrial defects through multiple mechanisms involving molecular factors, as, dopamine and D<sub>2</sub> receptors and/or glutamate and NMDA receptors, which are selectively present in this brain in high concentrations and eventually play a role in the selective degeneration of striatal neurons expressing mutant Htt (Damiano et al., 2010).

Intrastriatal injection of malonate (a reversible inhibitor of succinate dehydrogenase) supported the hypothesis that impairment of mitochondrial function plays an important role in the pathogenesis of HD (Beal et al., 1994). Also, mitochondrial dysfunction is evident in two well-established HD mice models; the 150/150Q mutant huntingtin knock-in mice (Lin et al., 2001), and the R6/2 mice (Mangiarini et al., 1996).

The formation of reactive oxygen species (ROS) and the imbalance between oxidant and antioxidant systems due to mitochondrial dysfunction usually associated with cellular damage and neuronal death that plays a crucial role in the neurodegenerative process of HD (Beal, 1995; Banoei et al., 2007; Browne, 2008; Gil and Rego, 2008; Lim et al., 2008, Kalonia, 2009; Kumar et al., 2009; Tasset et al., 2009; Tunez and Santamaria, 2009; Kumar and Kumar, 2010).

## 5. Glutamate induced excitotoxicity

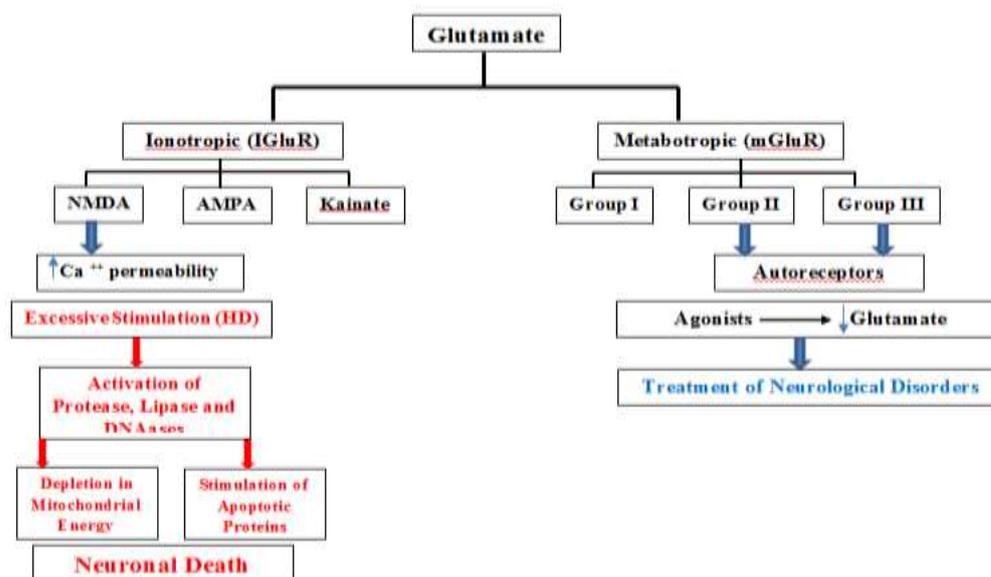
Glutamate is the main excitatory neurotransmitter in the vertebrate central nervous system, it's essential for a wide variety of physiological processes, such as integrative brain function and neuronal cell development and it's also implicated in neuronal cell death and has been postulated to play an important role in the pathogenesis of different degenerative disorders (Meldrum, 2000; Koller and Cersosimo, 2004;

Rego and de Almeida, 2005; Yi and Hazell, 2006; Corona et al., 2007; Hazell, 2007; Mamelak, 2007; Farooqui, 2008).

The uncontrolled release of glutamate is known to induce a pathological process named excitotoxicity (Olney, 1994). Excitotoxicity is one of the most extensively studied processes of neuronal cell death, and it plays an important role in many CNS diseases, including ischemia, trauma, and neurodegenerative disorders (Dong et al., 2009).

Many electrophysiological data support the view that abnormal glutamatergic transmission in the corticostriatal pathway is a prominent aspect of striatal degeneration in HD (Cepeda et al., 2007). Also, decortication which removes the central striatal glutamate, protects against striatal degeneration in R6/2 mice model of HD (Stack et al., 2007).

As shown in (Figure 1), there are at least three different types of ionotropic glutamate receptor, N-methyl-D-aspartate (NMDA) receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, and eight distinct metabotropic glutamate receptors (mGluRs), which are divided into three subgroups based on sequence homology and G protein coupling specificity (Pin and Duvoisin 1995, Conn and Pin 1997, Dhimi and Ferguson 2006). Group II and Group III of mGluRs are mainly localized presynaptically (autoreceptors) and have become a target of potential therapeutics for various neurological diseases and conditions, because of the ability of agonists to suppress glutamate release (Kew et al., 2001; Schoepp, 2001).



**Fig.1. Types of glutamate receptors and their involvement in excitotoxicity and treatment of neurological disorders.**

## 6. Role of NMDA receptors in HD

NMDA receptors are tetrameric complexes of two subunit 1 (GluN1) (NR1) with two GluN2 (NR2) and/or GluN3 (NR3) subunits. The differences in receptor channel properties, pharmacology, and temporal and spatial brain distribution are determined by these subunits (Cull-Candy and Leszkiewicz, 2004).

Considerable literature suggests that activation of extrasynaptic NMDA receptors promotes neuronal death, while activation of intrasynaptic NMDA receptors promoting neuronal survival (Hardingham et al., 2002, Leveille et al., 2008). Other literature suggests that NR2B containing NMDA receptors are excitotoxic mediators, while NR2A containing NMDA receptors promote

neuronal survival (Hansson et al., 2001). Striatal neurons express both NR2A and NR2B containing NMDA receptors and it is likely that medium spiny extrasynaptic NMDA receptors preferentially contain NR2B subunits (Stack and Ferrante, 2007).

NMDA receptors activation requires presynaptic glutamate release coupled with postsynaptic depolarization to allow ion flux through the channel. Also, overstimulation of NMDA receptors results in activation of proteases, DNAses, mitochondrial failure, and/or signalling to a variety of apoptotic proteins, leading to neuronal death (Lipton and Rosenberg, 1994; Arundine and Tymianski, 2003). Thus, NMDA receptors are ideal candidates for contributing to early neuronal dysfunction, learning deficits and later neuronal degeneration in HD.

Several lines of evidence suggest that abnormal activation of NMDA receptors and subsequent excitotoxicity aggravates striatal neuronal loss and plays important role in HD pathogenesis (Wojda et al., 2008). Previous studies have shown that intrastriatal injection of NMDA receptor agonists, including NMDA and quinolinic acid in laboratory animals produces neurochemical, neuropathological, and behavioural changes characteristic to HD (Laforet et al., 2001). Also, increased NMDA receptor mediated currents and enhanced susceptibility to exogenous NMDA agonists are described in murine genetic models of HD (Fan and Raymond, 2007).

Also, NMDA receptor-mediated excitotoxicity and cell death were enhanced in many non-neuronal cell lines expressing mutant Htt and in striatal neurons from transgenic mice models of HD, for example; data obtained from experiments using YAC72 mouse model (Fan and Raymond, 2007) showed overexpression of the synaptic NMDA receptor subunits of the striatal neurons, which would aid to understand the increased current and toxicity, and another example where mutant Htt increases the sensitivity of neurons to excitotoxicity induced by stimulation of NMDA receptors bearing NR2B subunits (Zeron et al., 2001; Zeron et al., 2002). The specificity of these effects for the NR2B-subtype of NMDA receptors may explain partly the selective degeneration of certain neurons in HD.

The extent of sensitivity to excitotoxic insult is not correlated to NMDA receptor current. The R6/2 transgenic mouse model of HD exhibits an increased NMDA receptor-mediated current and a decreased sensitivity to quinolinic acid

excitotoxic insults (Zeron et al., 2002; Zeron et al., 2004; Li et al., 2003; Li et al., 2003).

Also, studies showing that MSNs are more vulnerable to NMDA receptors mediated toxicity compared to other striatal neuronal types led to the hypothesis that enhanced NMDA receptors activation could contribute to selective striatal degeneration in HD. For example YAC72 and YAC128 mice showed increased striatal lesion size after quinolinic acid injection compared to controls (Graham et al., 2009). Remarkably, R6/1 and R6/2 mice exhibit wide spread brain atrophy, without selective striatal neuronal degeneration, whereas YAC transgenic HD mice show mild but significant striatal neuronal loss with lesser losses of cortical neurons and no significant atrophy in other brain regions (Slow et al., 2003). These data suggest that protein context is important for accurately modelling selective neuronal degeneration, and that the YAC and other full-length mutant Htt models may be better suited for study of the earliest molecular mechanisms underlying striatal neuronal susceptibility.

To be mentioned, striatal NMDA receptor-mediated responses are enhanced in HD transgenic mice prior to onset of motor deficits and neuronal loss (Li et al., 2004; Andre et al., 2006; Milnerwood and Raymond, 2007), and this consistent with studies showed that intrastriatal injection of quinolinic acid produces a significantly larger lesion in YAC128 and R6/1 models prior to symptoms onset (Graham et al., 2009).

## **7. Effect of NMDA receptor antagonists on treatment of HD**

NMDA receptor antagonists describe a category of compounds that functionally inhibit or deactivate NMDA receptor activity. They can act broadly or specifically at various sites on the NMDA receptor including the agonist binding domains, allosteric sites, and the ion channel pore. This category of compounds has a potential use in any disease that results from glutamate-induced excitotoxicity ranging from epilepsy to neurodegenerative disorders like HD (Leveille et al., 2008).

Depending on the excitotoxic nature of NR2B containing NMDA receptors especially those present in striatal medium-sized spiny neurons, blockage of this type of receptors with selective antagonist (subunit specific compounds) is a rational approach to neuroprotection in HD. NR2B-selective antagonist (remacemide)

ameliorates the phenotype of the R6/2 transgenic model of HD with improved therapeutic efficacy and minimum side effects (Stack et al., 2007). Also, clinically available antagonists such as memantine or amantadine may be candidates for large clinical trials of HD, but some trials demonstrated little therapeutic value due to the adverse effects of synaptic NMDA receptor blockade (Fan and Raymond, 2007).

The balance between synaptic and extrasynaptic NMDA receptor activation appears to determine whether receptor activation is beneficial or detrimental (Hardingham et al., 2002). It has been shown that treatment of YAC128 mice with low dose of memantine, which preferentially blocks extrasynaptic NMDA receptors, was ameliorative and therapeutically effective. While at higher doses, memantine treatment exacerbated striatal degeneration in YAC128 mice, most probably, due to loss of selectivity and the blockade of both synaptic and extrasynaptic NMDA receptors, obviating the benefits of inhibiting extrasynaptic NMDA receptors and possibly exacerbating mutant huntingtin toxicity by inhibiting the neuroprotective effects of synaptic NMDA receptor activation (Okamoto et al., 2009).

Another study (Tallaksen-Greene et al., 2010) demonstrated lack of efficacy of selective NR2B-antagonists such as; ifenprodil, RO25,6981 and CP101,606 in the R6/2 model of HD due to use of them in high doses in an effort to obtain maximal effects. It is plausible that this approach resulted in blockade of pro-survival signaling effects of synaptic NMDA receptors, counteracting any beneficial effects of reducing the excitotoxic effects of extrasynaptic NMDA receptors.

Therefore, targeting extrasynaptic NMDA receptors specifically is a very difficult issue and determination of appropriate dose of any selective NR2B antagonist for neuroprotective trials in HD subjects will be crucial. Dose selection may require some type of human pharmacodynamic biomarker of neuroprotective NMDA receptor blockade which consider a formidable obstacle.

## 8. Conclusion

HD is an autosomal dominant neurological disorder. Clinical course of the disease involves motor, cognitive and behavioural symptoms. Several animal models have been used to describe

the underlying mechanisms of disease progression. One of these mechanisms is the NMDA receptors mediated excitotoxicity. NMDA receptor is an ionotropic glutamate receptor that regulates  $Ca^{+2}$  efflux and contributes to the progress of HD. Thus, the use of NMDA receptor antagonists especially those which are selective to extrasynaptic NR2B containing NMDA receptors may be of therapeutic interest to treat HD, but selection of appropriate dose is a must.

## Conflict of Interest

The authors report no declaration of conflict of interest.

## References

- Albin, R. L. and J. T. Greenamyre, 1992. Alternative excitotoxic hypotheses. *Neurology*, 42(4), 733-738.
- Alexi, T., P. E. Hughes, B. Knusel and A. J. Tobin, 1998. Metabolic compromise with systemic 3-nitropropionic acid produces striatal apoptosis in Sprague-Dawley rats but not in BALB/c ByJ mice. *Exp Neurol*, 153(1), 74-93.
- Andre, V. M., C. Cepeda, A. Venegas, Y. Gomez and M. S. Levine, 2006. Altered cortical glutamate receptor function in the R6/2 model of Huntington's disease. *J Neurophysiol*, 95(4), 2108-2119.
- Ariano, M. A., N. Aronin, M. Difiglia, D. A. Tagle, D. R. Sibley, B. R. Leavitt, M. R. Hayden and M. S. Levine, 2002. Striatal neurochemical changes in transgenic models of Huntington's disease. *J Neurosci Res*, 68(6), 716-729.
- Arundine, M. and M. Tymianski, 2003. Molecular mechanisms of calcium-dependent neurodegeneration in excitotoxicity. *Cell Calcium*, 34(4-5), 325-337.
- Banoei, M. M., M. Houshmand, M. S. Panahi, P. Shariati, M. Rostami, M. D. Manshadi and T. Majidzadeh, 2007. Huntington's disease and mitochondrial DNA deletions: event or regular mechanism for mutant huntingtin protein and CAG repeats expansion?. *Cell Mol Neurobiol*, 27(7), 867-875.

- Bates, G. P., 2005. History of genetic disease: the molecular genetics of Huntington disease - a history. *Nat Rev Genet*, 6(10), 766-773.
- Beal, M. F., 1994. Huntington's disease, energy, and excitotoxicity. *Neurobiol Aging*, 15(2), 275-276.
- Beal, M. F., 1995. Aging, energy, and oxidative stress in neurodegenerative diseases. *Ann Neurol*, 38(3), 357-366.
- Beal, M. F., E. Brouillet, B. G. Jenkins, R. J. Ferrante, N. W. Kowall, J. M. Miller, E. Storey, R. Srivastava, B. R. Rosen and B. T. Hyman, 1993. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. *J Neurosci*, 13(10), 4181-4192.
- Beste, C., C. Konrad, C. Saft, T. Ukas, J. Andrich, B. Pfliegerer, M. Hausmann and M. Falkenstein, 2009. Alterations in voluntary movement execution in Huntington's disease are related to the dominant motor system: evidence from event-related potentials. *Exp Neurol*, 216(1), 148-157.
- Bibb, J. A., Z. Yan, P. Svenningsson, G. L. Snyder, V. A. Pieribone, A. Horiuchi, A. C. Nairn, A. Messer and P. Greengard, 2000. Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. *Proc Natl Acad Sci U S A*, 97(12), 6809-6814.
- Bizat, N., J. M. Hermel, S. Humbert, C. Jacquard, C. Creminon, C. Escartin, F. Saudou, S. Krajewski, P. Hantraye and E. Brouillet, 2003. In vivo calpain/caspase cross-talk during 3-nitropropionic acid-induced striatal degeneration: implication of a calpain-mediated cleavage of active caspase-3. *J Biol Chem*, 278(44), 43245-43253.
- Brouillet, E., F. Conde, M. F. Beal and P. Hantraye, 1999. Replicating Huntington's disease phenotype in experimental animals. *Prog Neurobiol*, 59(5), 427-468.
- Brouillet, E., M. C. Guyot, V. Mittoux, S. Altairac, F. Conde, S. Palfi and P. Hantraye, 1998. Partial inhibition of brain succinate dehydrogenase by 3-nitropropionic acid is sufficient to initiate striatal degeneration in rat. *J Neurochem*, 70(2), 794-805.
- Brouillet, E., B. G. Jenkins, B. T. Hyman, R. J. Ferrante, N. W. Kowall, R. Srivastava, D. S. Roy, B. R. Rosen and M. F. Beal, 1993. Age-dependent vulnerability of the striatum to the mitochondrial toxin 3-nitropropionic acid. *J Neurochem*, 60(1), 356-359.
- Browne, S. E., 2008. Mitochondria and Huntington's disease pathogenesis: insight from genetic and chemical models. *Ann N Y Acad Sci*, 1147, 358-382.
- Carter, R. J., L. A. Lione, T. Humby, L. Mangiarini, A. Mahal, G. P. Bates, S. B. Dunnett and A. J. Morton, 1999. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J Neurosci*, 19(8), 3248-3257.
- Cepeda, C., N. Wu, V. M. Andre, D. M. Cummings and M. S. Levine, 2007. The corticostriatal pathway in Huntington's disease. *Prog Neurobiol*, 81(5-6), 253-271.
- Cha, J. H., C. M. Kosinski, J. A. Kerner, S. A. Alsdorf, L. Mangiarini, S. W. Davies, J. B. Penney, G. P. Bates and A. B. Young, 1998. Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. *Proc Natl Acad Sci U S A*, 95(11), 6480-6485.
- Conn, P. J. and J. P. Pin, 1997. Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol*, 37, 205-237.
- Corona, J. C., L. B. Tovar-y-Romo and R. Tapia, 2007. Glutamate excitotoxicity and therapeutic targets for amyotrophic lateral sclerosis. *Expert Opin Ther Targets*, 11(11), 1415-1428.
- Cull-Candy, S. G. and D. N. Leszkiewicz, 2004. Role of distinct NMDA receptor subtypes at central synapses. *Sci STKE*, 2004(255), re16.
- Damiano, M., L. Galvan, N. Deglon and E. Brouillet, 2010. Mitochondria in Huntington's disease. *Biochim Biophys Acta*, 1802(1), 52-61.
- Davies, S. W., M. Turmaine, B. A. Cozens, M. DiFiglia, A. H. Sharp, C. A. Ross, E. Scherzinger, E. E. Wanker, L. Mangiarini and G. P. Bates, 1997. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction

in mice transgenic for the HD mutation. *Cell*, 90(3), 537-548.

Dhami, G. K. and S. S. Ferguson, 2006. Regulation of metabotropic glutamate receptor signaling, desensitization and endocytosis. *Pharmacol Ther*, 111(1), 260-271.

Dong, X. X., Y. Wang and Z. H. Qin, 2009. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. *Acta Pharmacol Sin*, 30(4), 379-387.

Fan, M. M. and L. A. Raymond, 2007. N-methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. *Prog Neurobiol*, 81(5-6), 272-293.

Farooqui, A. A., Ong, W., Horrocks, L., 2008. Glutamate receptors and neurological disorders. *Neurochemical Aspects of Excitotoxicity*. New York, Springer: 161-204.

Ferrante, R. J., M. F. Beal, N. W. Kowall, E. P. Richardson, Jr. and J. B. Martin, 1987. Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease. *Brain Res* 411(1), 162-166.

Ferrante, R. J., N. W. Kowall, M. F. Beal, E. P. Richardson, Jr., E. D. Bird and J. B. Martin, 1985. Selective sparing of a class of striatal neurons in Huntington's disease. *Science* 230(4725), 561-563.

Ferrante, R.J., 2009. Mouse models of Huntington's disease and methodological considerations for therapeutic trials. *Biochim. Biophys. Acta.*, 1792(6), 506-520.

Finkbeiner, S. and S. Mitra, 2008. The ubiquitin-proteasome pathway in Huntington's disease. *ScientificWorldJournal*, 8, 421-433.

Gafni, J., E. Hermel, J. E. Young, C. L. Wellington, M. R. Hayden and L. M. Ellerby, 2004. Inhibition of calpain cleavage of huntingtin reduces toxicity: accumulation of calpain/caspase fragments in the nucleus. *J Biol Chem*, 279(19), 20211-20220.

Gil, J. M. and A. C. Rego, 2008. Mechanisms of neurodegeneration in Huntington's disease. *Eur J Neurosci*, 27(11), 2803-2820.

Graham, R. K., M. A. Pouladi, P. Joshi, G. Lu, Y. Deng, N. P. Wu, B. E. Figueroa, M. Metzler, V. M. Andre, E. J. Slow, L. Raymond, R. Friedlander, M. S. Levine, B. R. Leavitt and M. R. Hayden, 2009. Differential susceptibility to excitotoxic stress in YAC128 mouse models of Huntington disease between initiation and progression of disease. *J Neurosci* 29(7), 2193-2204.

Gusella, J. F., N. S. Wexler, P. M. Conneally, S. L. Naylor, M. A. Anderson, R. E. Tanzi, P. C. Watkins, K. Ottina, M. R. Wallace, A. Y. Sakaguchi and et al., 1983. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature*, 306(5940), 234-238.

Hansson, O., E. Guatteo, N. B. Mercuri, G. Bernardi, X. J. Li, R. F. Castilho and P. Brundin, 2001. Resistance to NMDA toxicity correlates with appearance of nuclear inclusions, behavioural deficits and changes in calcium homeostasis in mice transgenic for exon 1 of the huntington gene. *Eur J Neurosci*, 14(9), 1492-1504.

Hantraye, P., D. Riche, M. Maziere and O. Isacson, 1990. A primate model of Huntington's disease: behavioral and anatomical studies of unilateral excitotoxic lesions of the caudate-putamen in the baboon. *Exp Neurol*, 108(2), 91-104.

Hardingham, G. E., Y. Fukunaga and H. Bading, 2002. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat Neurosci* 5(5), 405-414.

Harper, P. S., 1991. *Huntington's Disease*. Philadelphia, PA, W. B. Saunders.

Hazell, A. S., 2007. Excitotoxic mechanisms in stroke: an update of concepts and treatment strategies. *Neurochem Int*, 50(7-8), 941-953.

Heng, M. Y., P. J. Detloff, P. L. Wang, J. Z. Tsien and R. L. Albin, 2009. In vivo evidence for NMDA receptor-mediated excitotoxicity in a murine genetic model of Huntington disease. *J Neurosci*, 29(10), 3200-3205.

Heng, M. Y., S. J. Tallaksen-Greene, P. J. Detloff and R. L. Albin, 2007. Longitudinal evaluation of the Hdh(CAG)150 knock-in murine model of Huntington's disease. *J Neurosci*, 27(34), 8989-8998.

- Hickey, M. A., A. Kosmalska, J. Enayati, R. Cohen, S. Zeitlin, M. S. Levine and M. F. Chesselet, 2008. Extensive early motor and non-motor behavioral deficits are followed by striatal neuronal loss in knock-in Huntington's disease mice. *Neuroscience*, 157(1), 280-295.
- Hodgson, J. G., N. Agopyan, C. A. Gutekunst, B. R. Leavitt, F. LePiane, R. Singaraja, D. J. Smith, N. Bissada, K. McCutcheon, J. Nasir, L. Jamot, X. J. Li, M. E. Stevens, E. Rosemond, J. C. Roder, A. G. Phillips, E. M. Rubin, S. M. Hersch and M. R. Hayden, 1999. A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron*, 23(1), 181-192.
- Isacson, O., P. Brundin, F. H. Gage and A. Bjorklund, 1985. Neural grafting in a rat model of Huntington's disease: progressive neurochemical changes after neostriatal ibotenate lesions and striatal tissue grafting. *Neuroscience*, 16(4), 799-817.
- Kalonia H, K. P., Kumar A, Nehru B., 2009. Effects of caffeic acid, rofecoxib, and their combination against quinolinic acid-induced behavioral alterations and disruption in glutathione redox status. *Neurosci Bull*, 25(6), 343-352.
- Kew, J. N., J. M. Ducarre, M. C. Pflimlin, V. Mutel and J. A. Kemp, 2001. Activity-dependent presynaptic autoinhibition by group II metabotropic glutamate receptors at the perforant path inputs to the dentate gyrus and CA1. *Neuropharmacology*, 40(1), 20-27.
- Koller, W. C. and M. G. Cersosimo, 2004. Neuroprotection in Parkinson's disease: an elusive goal. *Curr Neurol Neurosci Rep*, 4(4), 277-283.
- Koutouzis, T. K., D. F. Emerich, C. V. Borlongan, T. B. Freeman, D. W. Cahill and P. R. Sanberg, 1994. Cell transplantation for central nervous system disorders. *Crit Rev Neurobiol*, 8(3), 125-162.
- Kumar, P., H. Kalonia and A. Kumar, 2009. Lycopene modulates nitric oxide pathways against 3-nitropropionic acid-induced neurotoxicity. *Life Sci*, 85(19-20), 711-718.
- Kumar, P. and A. Kumar, 2010. Protective effect of hesperidin and naringin against 3-nitropropionic acid induced Huntington's like symptoms in rats: possible role of nitric oxide. *Behav Brain Res*, 206(1), 38-46.
- Kung, V. W., R. Hassam, A. J. Morton and S. Jones, 2007. Dopamine-dependent long term potentiation in the dorsal striatum is reduced in the R6/2 mouse model of Huntington's disease. *Neuroscience*, 146(4), 1571-1580.
- Laforet, G. A., E. Sapp, K. Chase, C. McIntyre, F. M. Boyce, M. Campbell, B. A. Cadigan, L. Warzecki, D. A. Tagle, P. H. Reddy, C. Cepeda, C. R. Calvert, E. S. Jokel, G. J. Klapstein, M. A. Ariano, M. S. Levine, M. DiFiglia and N. Aronin, 2001. Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. *J Neurosci*, 21(23), 9112-9123.
- Langbehn, D. R., M. R. Hayden and J. S. Paulsen, 2010. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. *Am J Med Genet B Neuropsychiatr Genet*, 153B(2), 397-408.
- Lehrmann, E., P. Guidetti, A. Love, J. Williamson, E. H. Bertram and R. Schwarcz, 2008. Glial activation precedes seizures and hippocampal neurodegeneration in measles virus-infected mice. *Epilepsia*, 49 Suppl 2, 13-23.
- Leveille, F., F. El Gaamouch, E. Gouix, M. Lecocq, D. Lobner, O. Nicole and A. Buisson, 2008. Neuronal viability is controlled by a functional relation between synaptic and extrasynaptic NMDA receptors. *FASEB J*, 22(12), 4258-4271.
- Levine, M. S., G. J. Klapstein, A. Koppel, E. Gruen, C. Cepeda, M. E. Vargas, E. S. Jokel, E. M. Carpenter, H. Zanjani, R. S. Hurst, A. Efstratiadis, S. Zeitlin and M. F. Chesselet, 1999. Enhanced sensitivity to N-methyl-D-aspartate receptor activation in transgenic and knockin mouse models of Huntington's disease. *J Neurosci Res*, 58(4), 515-532.
- Li, H., T. Wyman, Z. X. Yu, S. H. Li and X. J. Li, 2003. Abnormal association of mutant huntingtin with synaptic vesicles inhibits glutamate release. *Hum Mol Genet*, 12(16), 2021-2030.

- Li, J. Y., M. Plomann and P. Brundin, 2003. Huntington's disease: a synaptopathy?. *Trends Mol Med*, 9(10), 414-420.
- Li, L., M. Fan, C. D. Icton, N. Chen, B. R. Leavitt, M. R. Hayden, T. H. Murphy and L. A. Raymond, 2003. Role of NR2B-type NMDA receptors in selective neurodegeneration in Huntington disease. *Neurobiol Aging*, 24(8), 1113-1121.
- Li, L., T. H. Murphy, M. R. Hayden and L. A. Raymond, 2004. Enhanced striatal NR2B-containing N-methyl-D-aspartate receptor-mediated synaptic currents in a mouse model of Huntington disease. *J Neurophysiol*, 92(5), 2738-2746.
- Lim, D., L. Fedrizzi, M. Tartari, C. Zuccato, E. Cattaneo, M. Brini and E. Carafoli, 2008. Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease. *J Biol Chem*, 283(9), 5780-5789.
- Lin, C. H., S. Tallaksen-Greene, W. M. Chien, J. A. Cearley, W. S. Jackson, A. B. Crouse, S. Ren, X. J. Li, R. L. Albin and P. J. Detloff, 2001. Neurological abnormalities in a knock-in mouse model of Huntington's disease. *Hum Mol Genet*, 10(2), 137-144.
- Lione, L. A., R. J. Carter, M. J. Hunt, G. P. Bates, A. J. Morton and S. B. Dunnett, 1999. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. *J Neurosci*, 19(23), 10428-10437.
- Lipton, S. A. and P. A. Rosenberg, 1994. Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med*, 330(9), 613-622.
- Ludolph, A. C., F. He, P. S. Spencer, J. Hammerstad and M. Sabri, 1991. 3-Nitropropionic acid-exogenous animal neurotoxin and possible human striatal toxin. *Can J Neurol Sci*, 18(4): 492-498.
- Luthi-Carter, R., A. Strand, N. L. Peters, S. M. Solano, Z. R. Hollingsworth, A. S. Menon, A. S. Frey, B. S. Spektor, E. B. Penney, G. Schilling, C. A. Ross, D. R. Borchelt, S. J. Tapscott, A. B. Young, J. H. Cha and J. M. Olson, 2000. Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. *Hum Mol Genet*, 9(9), 1259-1271.
- Mamelak, M., 2007. Alzheimer's disease, oxidative stress and gamma-hydroxybutyrate. *Neurobiol Aging*, 28(9), 1340-1360.
- Mangiarini, L., K. Sathasivam, M. Seller, B. Cozens, A. Harper, C. Hetherington, M. Lawton, Y. Trotter, H. Lehrach, S. W. Davies and G. P. Bates, 1996. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell*, 87(3), 493-506.
- Marcy E. MacDonald, C. M. A., Mabel P. Duyao, Richard H. Myers, Carol Lin, Lakshmi Srinidhi, Glenn Barnes, Sherryl A. Taylor, Marianne James, Nicolet Groot, Heather MacFarlane, Barbara Jenkins, Mary Anne Anderson, Nancy S. Wexler and James F. Gusella, 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*, 72, 971-983.
- Marder, K., H. Zhao, S. Eberly, C. M. Tanner, D. Oakes and I. Shoulson, 2009. Dietary intake in adults at risk for Huntington disease: analysis of PHAROS research participants. *Neurology*, 73(5), 385-392.
- McGeer, E. G. and P. L. McGeer, 1976. Duplication of biochemical changes of Huntington's chorea by intra-striatal injections of glutamic and kainic acids. *Nature*, 263(5577), 517-519.
- Meldrum, B. S., 2000. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J Nutr*, 130(4S Suppl), 1007S-1015S.
- Menalled, L., H. Zanjani, L. MacKenzie, A. Koppel, E. Carpenter, S. Zeitlin and M. F. Chesselet, 2000. Decrease in striatal enkephalin mRNA in mouse models of Huntington's disease. *Exp Neurol*, 162(2), 328-342.
- Menalled, L. B. and M. F. Chesselet, 2002. Mouse models of Huntington's disease. *Trends Pharmacol Sci*, 23(1), 32-39.
- Menalled, L. B., J. D. Sison, I. Dragatsis, S. Zeitlin and M. F. Chesselet, 2003. Time course of early

motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. *J Comp Neurol*, 465(1), 11-26.

Menalled, L. B., J. D. Sison, Y. Wu, M. Olivieri, X. J. Li, H. Li, S. Zeitlin and M. F. Chesselet, 2002. Early motor dysfunction and striosomal distribution of huntingtin microaggregates in Huntington's disease knock-in mice. *J Neurosci*, 22(18), 8266-8276.

Milnerwood, A. J. and L. A. Raymond, 2007. Corticostriatal synaptic function in mouse models of Huntington's disease: early effects of huntingtin repeat length and protein load. *J Physiol*, 585(Pt 3), 817-831.

Morton, A. J., M. A. Lagan, J. N. Skepper and S. B. Dunnett, 2000. Progressive formation of inclusions in the striatum and hippocampus of mice transgenic for the human Huntington's disease mutation. *J Neurocytol*, 29(9), 679-702.

Murphy, K. P., R. J. Carter, L. A. Lione, L. Mangiarini, A. Mahal, G. P. Bates, S. B. Dunnett and A. J. Morton, 2000. Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. *J Neurosci*, 20(13), 5115-5123.

Naver, B., C. Stub, M. Moller, K. Fenger, A. K. Hansen, L. Hasholt and S. A. Sorensen, 2003. Molecular and behavioral analysis of the R6/1 Huntington's disease transgenic mouse. *Neuroscience*, 122(4), 1049-1057.

Novelli, A., J. A. Reilly, P. G. Lysko and R. C. Henneberry, 1988. Glutamate becomes neurotoxic via the N-methyl-D-aspartate receptor when intracellular energy levels are reduced. *Brain Res*, 451(1-2), 205-212.

Okamoto, S., M. A. Pouladi, M. Talantova, D. Yao, P. Xia, D. E. Ehrnhoefer, R. Zaidi, A. Clemente, M. Kaul, R. K. Graham, D. Zhang, H. S. Vincent Chen, G. Tong, M. R. Hayden and S. A. Lipton, 2009. Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. *Nat Med*, 15(12), 1407-1413.

Olney, J. W., 1994. New mechanisms of excitatory transmitter neurotoxicity. *J Neural Transm Suppl*, 43, 47-51.

Pin, J. P. and R. Duvoisin, 1995. The metabotropic glutamate receptors: structure and functions. *Neuropharmacology*, 34(1), 1-26.

Pouladi, M. A., A. J. Morton and M. R. Hayden, 2013. Choosing an animal model for the study of Huntington's disease. *Nat Rev Neurosci*, 14(10), 708-721.

Quarrell, O., K. L. O'Donovan, O. Bandmann and M. Strong, 2012. The Prevalence of Juvenile Huntington's Disease: A Review of the Literature and Meta-Analysis. *PLoS Curr* 4: e4f8606b8742ef8603.

Reedeker W., v. d. M. R. C., Giltay E.J., Kooistra T.A., Roos R.A., van Duijn E., 2012. Psychiatric disorders in Huntington's disease: a 2-year follow-up study. *Psychosomatics* 53(3), 220-229.

Rego, A. C. and L. P. de Almeida, 2005. Molecular targets and therapeutic strategies in Huntington's disease. *Curr Drug Targets CNS Neurol Disord*, 4(4), 361-381.

Rothman, S., 1984. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J Neurosci*, 4(7), 1884-1891.

Schilling, G., M. W. Becher, A. H. Sharp, H. A. Jinnah, K. Duan, J. A. Kotzuk, H. H. Slunt, T. Ratovitski, J. K. Cooper, N. A. Jenkins, N. G. Copeland, D. L. Price, C. A. Ross and D. R. Borchelt, 1999. Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. *Hum Mol Genet*, 8(3), 397-407.

Schoepp, D. D., 2001. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther*, 299(1), 12-20.

Slow, E. J., J. van Raamsdonk, D. Rogers, S. H. Coleman, R. K. Graham, Y. Deng, R. Oh, N. Bissada, S. M. Hossain, Y. Z. Yang, X. J. Li, E. M. Simpson, C. A. Gutekunst, B. R. Leavitt and M. R. Hayden, 2003. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. *Hum Mol Genet*, 12(13), 1555-1567.

Stack, E. C., A. Dedeoglu, K. M. Smith, K. Cormier, J. K. Kubilus, M. Bogdanov, W. R. Matson, L. Yang, B. G. Jenkins, R. Luthi-Carter, N. W. Kowall, S. M. Hersch, M. F. Beal and R. J.

- Ferrante, 2007. Neuroprotective effects of synaptic modulation in Huntington's disease R6/2 mice. *J Neurosci*, 27(47), 12908-12915.
- Stack, E. C. and R. J. Ferrante, 2007. Huntington's disease: progress and potential in the field. *Expert Opin Investig Drugs*, 16(12), 1933-1953.
- Tallaksen-Greene, S. J., Janiszewska, A., Benton, K., Ruprecht, L., & Albin, R. L., 2010. Lack of efficacy of NMDA receptor-NR2B selective antagonists in the R6/2 model of Huntington disease. *Experimental neurology*, 225(2), 402-407.
- Tasset, I., F. Sanchez and I. Tunez, 2009. The molecular bases of Huntington's disease: the role played by oxidative stress. *Rev Neurol* 49(8), 424-429.
- Thompson J.C., H. J., Sollom A.C., Stopford C.L., Howard E., Snowden J.S., Craufurd D., 2012. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin. Neurosci.*, 24(1), 53-60.
- Thompson, P. D., A. Berardelli, J. C. Rothwell, B. L. Day, J. P. Dick, R. Benecke and C. D. Marsden, 1988. The coexistence of bradykinesia and chorea in Huntington's disease and its implications for theories of basal ganglia control of movement. *Brain*, 111 ( Pt 2), 223-244.
- Tunez, I. and A. Santamaria, 2009. Model of Huntington's disease induced with 3-nitropropionic acid. *Rev Neurol*, 48(8), 430-434.
- Tunez, I., I. Tasset, V. Perez-De La Cruz and A. Santamaria, 2010. 3-Nitropropionic acid as a tool to study the mechanisms involved in Huntington's disease: past, present and future. *Molecules*, 15(2), 878-916.
- Vonsattel, J. P., R. H. Myers, T. J. Stevens, R. J. Ferrante, E. D. Bird and E. P. Richardson, Jr., 1985. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol*, 44(6), 559-577.
- Wheeler, V. C., J. K. White, C. A. Gutekunst, V. Vrbancac, M. Weaver, X. J. Li, S. H. Li, H. Yi, J. P. Vonsattel, J. F. Gusella, S. Hersch, W. Auerbach, A. L. Joyner and M. E. MacDonald, 2000. Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in HdhQ92 and HdhQ111 knock-in mice. *Hum Mol Genet*, 9(4), 503-513.
- White, J. K., W. Auerbach, M. P. Duyao, J. P. Vonsattel, J. F. Gusella, A. L. Joyner and M. E. MacDonald, 1997. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. *Nat Genet*, 17(4), 404-410.
- Wojda, U., E. Salinska and J. Kuznicki, 2008. Calcium ions in neuronal degeneration. *IUBMB Life*, 60(9), 575-590.
- Yi, J. H. and A. S. Hazell, 2006. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. *Neurochem Int*, 48(5), 394-403.
- Yu, Z. X., S. H. Li, J. Evans, A. Pillarisetti, H. Li and X. J. Li, 2003. Mutant huntingtin causes context-dependent neurodegeneration in mice with Huntington's disease. *J Neurosci*, 23(6), 2193-2202.
- Zeron, M. M., N. Chen, A. Moshaver, A. T. Lee, C. L. Wellington, M. R. Hayden and L. A. Raymond, 2001. Mutant huntingtin enhances excitotoxic cell death. *Mol Cell Neurosci*, 17(1), 41-53.
- Zeron, M. M., H. B. Fernandes, C. Krebs, J. Shehadeh, C. L. Wellington, B. R. Leavitt, K. G. Baimbridge, M. R. Hayden and L. A. Raymond, 2004. Potentiation of NMDA receptor-mediated excitotoxicity linked with intrinsic apoptotic pathway in YAC transgenic mouse model of Huntington's disease. *Mol Cell Neurosci*, 25(3), 469-479.
- Zeron, M. M., O. Hansson, N. Chen, C. L. Wellington, B. R. Leavitt, P. Brundin, M. R. Hayden and L. A. Raymond, 2002. Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntingtin