Mol Neurobiol (2011) 43:1–11
DOI 10.1007/s12035-010-8153-1

Huntington's Disease and Group I Metabotropic Glutamate Receptors

Fabiola M. Ribeiro · Rita G. W. Pires · Stephen S. G. Ferguson

Received: 15 October 2010 / Accepted: 15 November 2010 / Published online: 9 December 2010

Abstract Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by involuntary body movement, cognitive impairment and psychiatric disturbance. A polyglutamine expansion in the amino-terminal region of the huntingtin (htt) protein is the genetic cause of HD. Htt protein interacts with a wide variety of proteins, and htt mutation causes cell signaling alterations in various neurotransmitter systems, including dopaminergic, glutamatergic, and cannabinoid systems, as well as trophic factor systems. This review will overview recent findings concerning htt-promoted alterations in cell signaling that involve different neurotransmitters and trophic factor systems, especially involving mGluR1/5, as glutamate plays a crucial role in neuronal cell death. The neuronal cell death that takes place in the striatum and cortex of HD patients is the most important factor underlying HD progression. Metabotropic glutamate receptors (mGluR1 and mGluR5) have a very controversial role in neuronal cell death and it is not clear whether mGluR1/5 activation either protects or exacerbates neuronal death. Thus, understanding how mutant htt protein affects glutamatergic receptor signaling will be essential to further establish a role for glutamate receptors in HD and develop therapeutic strategies to treat HD.

Keywords Huntington's disease · htt protein · Metabotropic glutamate receptor (mGluR)

Abbreviations

DHPG	(*S*)-3,5-dihydroxylphenylglycine
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CNS	Central nervous system
PLC	Phospholipase C
ERK	Extracellular signal-regulated kinase
MAPK	Mitogen-activated protein kinase
GPCR	G protein-coupled receptor
InsP	Inositol phosphate
AD	Alzheimer's disease
HD	Huntington's disease
htt	Huntingtin protein
IP3	Inositol-1,4,5-triphosphate
mGluR	Metabotropic glutamate receptor
NMDAR	*N*-methyl-D-aspartate receptor
PKC	Protein kinase C
PLCβ1	Phospholipase Cβ1
PLD	Phospholipase D
PLA_2	Phospholipase A_2
PI3K	Phosphoinositide 3-kinase
PDK1	Phosphoinositide-dependent kinase
PIKE	PI3K enhancer
MSNs	Medium-sized spiny neurons
PPE	Preproenkephalin
DARPP-32	Dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa

F. M. Ribeiro
Departamento de Bioquimica e Imunologia, ICB,
Universidade Federal de Minas Gerais,
Belo Horizonte, Brazil

R. G. W. Pires
Departamento de Ciencias Fisiologicas, CCS,
Universidade Federal do Espirito Santo,
Vitoria, Brazil

S. S. G. Ferguson (✉)
J. Allyn Taylor Centre for Cell Biology, Molecular Brain Research Group, Robarts Research Institute and Department of Physiology and Pharmacology, University of Western Ontario,
100 Perth Drive,
London, ON, Canada N6A 5K8
e-mail: ferguson@robarts.ca

GSK-3	Glycogen synthase kinase-3
EC	Endocannabinoid
BDNF	Brain-derived neurotrophic factor
AEA	Anandamide
2-AG	2- arachidonoyl glycerol
TRPV1	Transient receptor potential vanilloid 1

Huntington's Disease

Huntington's disease (HD) is a devastating autosomal dominant inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric symptoms, leading to death, inevitably [1, 2]. Cognitive and personality alterations are early symptoms, followed by chorea and loss of balance. Movement difficulties, which progressively worsen over time, are associated with both involuntary and voluntary movement. Among the psychiatric disturbances that take place in HD, affective disorders are the most commonly prevalent, with documented rates of major depression as high as 50% [3] and mania or hypomania as high as 12% [3, 4].

A polyglutamine expansion in the amino-terminal region of the huntingtin (htt) protein is the cause of HD [5]. The length of the polyglutamine repeat is inversely correlated with the age of disease onset and directly correlated with the severity of symptoms [6]. However, patient sex, environmental factors and genetic modifiers can alter the variability of clinical expression. Although the htt mutation is pointed to as the cause of HD, the mechanisms responsible for mutant htt pathogenicity are still largely unknown. There is no data explaining why the mutant protein, which is expressed throughout the body results in the selective death of medium sized spiny neurons (MSNs). In addition, it is still unclear whether HD pathology progresses due to either a lack of function of the htt protein or to a gain of toxic function of the mutant htt. Normal htt protein has been shown to be anti-apoptotic [7, 8] and essential for normal embryonic development [7, 9, 10]. On the other hand, mutant htt and htt aggregation triggers a cascade that leads to neuronal dysfunction through oxidative stress, transcriptional dysregulation, glutamate excitotoxicity, activation of apoptotic cascade, mitochondrial dysfunction and energy depletion [11–14].

Cleavage of polyglutamine expanded htt leads to the release of amino-terminal fragments containing the polyglutamine repeats, which can aggregate in neurites, cytoplasm, and nuclei. Importantly, htt aggregate formation and loss of striatal neurons strongly correlate with HD symptom severity [15]. MSNs in the striatum, containing GABA and enkephalin, are affected early in the disease and are the primary neurons targeted in HD. Over time, htt aggregates and inclusions spread to the remainder of the basal ganglia with subsequent dissemination through the cortex and substantia nigra. However, it is not known if the accumulation of htt aggregates results in cell death or if the soluble form of the protein is the toxic one [16–18].

Glutamate Receptors and Cell Signaling

Glutamate, the major excitatory neurotransmitter in the brain, is essential for a wide variety of physiological processes, such as integrative brain function and neuronal cell development. However, glutamate is also implicated in neuronal cell death and has been postulated to play an important role in the pathogenesis and excitotoxic neuronal cell loss that takes place in HD [19–22].

Glutamate exerts its actions by interacting with ionotropic glutamate receptors, which are ligand-gated ion channels that mediate fast excitatory neurotransmission, and metabotropic glutamate receptors (mGluRs), which are members of the family C of G protein-coupled receptor (GPCR) [23–27]. There are at least three different types of ionotropic glutamate receptor, *N*-methyl-D-aspartate receptor (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, and eight distinct mGluRs, which are divided into three subgroups based on sequence homology and G protein coupling specificity [22, 23, 28, 29]. Group I mGluRs (mGluR1 and mGluR5) are predominantly coupled to the activation of phospholipase C (PLC) via $G\alpha_{q/11}$, whereas Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluRs negatively regulate adenylyl cyclase via $G\alpha_i$.

mGluRs are differentially localized in presynaptic and postsynaptic neuronal regions [30, 31]. Group II and Group III mGluRs are mainly localized presynaptically and act as autoreceptors to inhibit glutamate release [32]. Group I mGluRs can be localized at both presynaptic and postsynaptic sites, although at synapses they are mainly located perisynaptically at the postsynaptic neuronal membrane, where they function to regulate neuronal excitability by modulating currents mediated by ionotropic glutamate receptors [33–36].

Group I mGluR stimulation can lead to activation of a wide variety of cell signaling pathways, generating very complex responses [27] (Fig. 1). Activation of PLC by mGluR1/5 leads to diacylglycerol and inositol-1,4,5-triphosphate (InsP3) formation [37]. InsP3 binding to its receptor leads to release of calcium from intracellular stores. Both calcium and diacylglycerol lead to the activation of protein kinase C (PKC), which has been proposed to activate phospholipase D (PLD), phospholipase A_2 (PLA_2) and mitogen-activated protein kinase (MAPK), as well as to modulate a variety of ion channels

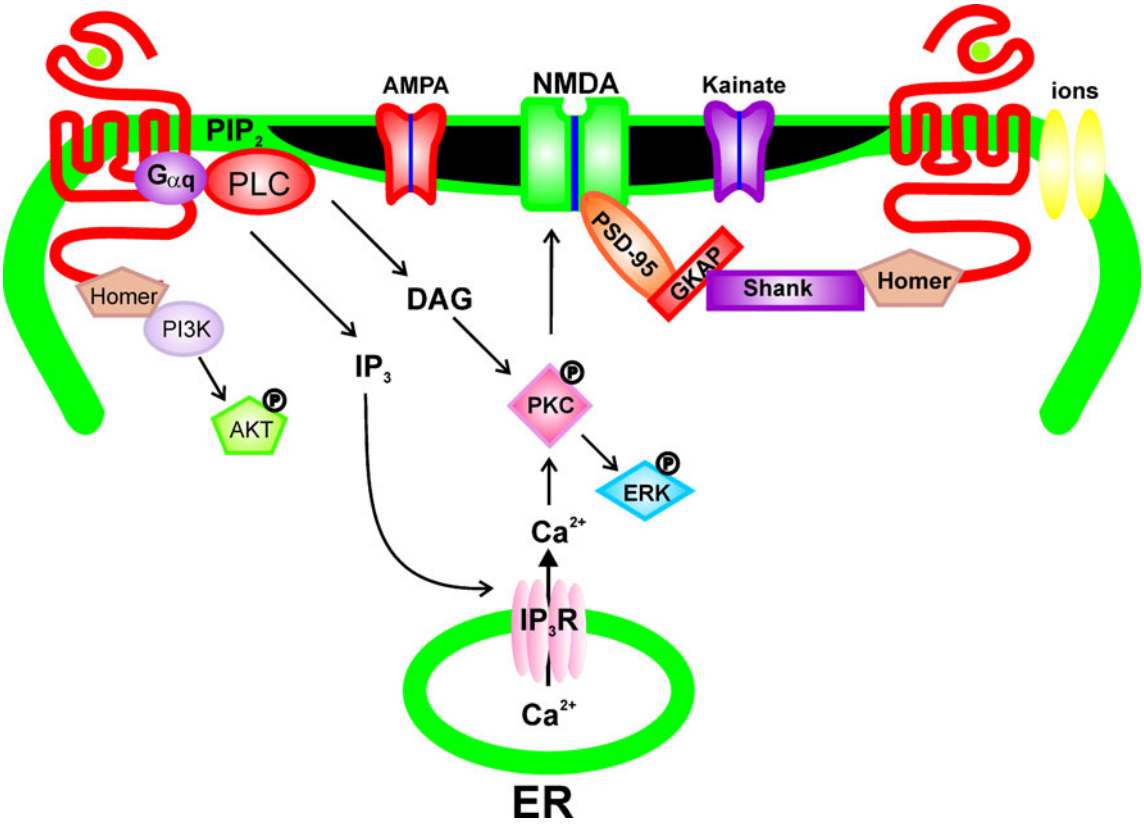

Fig. 1 Cell signalling pathways activation by Group I mGluRs. Group I mGluRs activate the hydrolysis of PIP_2 by phospholipase C (PLC) following the activation of the heterotrimeric G protein Gαq resulting in increases in intracellular DAG and InsP3 (IP_3) levels. InsP3 activates the InsP3 receptor (IP_3R) resulting in increased intracellular Ca^{2+} concentrations which in conjunction with DAG activate protein kinase C (PKC) PKC activation can lead to the activation of ERK1/2 phosphorylation and the phosphorylation of the NMDA receptor. Homer interacts with the C-tails of Group I mGluRs and can either contribute to the activation of Akt via PI3 kinase (PI3K) or can directly regulate NMDA receptor activity via its association with Shank

[38]. mGluR1/5 can also modulate calcium channels in a PLC/PKC-independent and G protein-dependent manner [39, 40]. Moreover, Group I mGluRs can also modulate potassium channels employing different cell signaling strategies [41, 42]. Ionotropic glutamate receptors can also be regulated by mGluRs, as stimulation of mGluR5 leads to PKC activation, which can activate NMDAR by increasing its open probability, leading to calcium influx [43]. Interestingly, it has been shown that mGluR5 and NMDAR can be cross-linked through the interaction with Homer and Shank proteins [44, 45]. Group I mGluR stimulation also leads to activation of other signaling pathways important for cell survival and proliferation, such as extracellular signal-regulated kinase (ERK) and AKT [46–48]. mGluR1/5 signaling complexity may underlie different responses, depending on activation context (agonist type and concentration, disease state, neuronal cell type, etc.). Group I mGluRs signaling can be modified in various disease states [27, 49] and understanding mGluRs regulation will be essential for developing efficient pharmacological strategies to treat such disorders.

Cell Signaling Alterations Caused by Mutant htt

Mutant htt protein has been implicated in a wide variety of cell signaling alterations that are appearing as important features underlying the progression of HD pathology. Mutant htt protein promotes cellular alterations mainly by modifying htt-protein interaction patterns [50] and/or by altering transcription of key cellular components [51]. Htt interaction with other proteins can be modified by htt polyglutamine expansion resulting in altered htt-mediated cellular processes. In particular, alteration in mutant htt protein interaction can modify htt functions involved in clathrin-mediated endocytosis, neuronal transport processes, postsynaptic signaling, apoptosis and cell survival [52–56].

Numerous studies in both HD patients and mouse models have demonstrated that mutant htt protein can alter neuronal function and cell signaling by disrupting transcriptional pathways and altering striatal gene expression profiles [57]. The down-regulation of several specific transcripts, such as preproenkephalin (PPE) [58, 59],

dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa (DARPP-32) [60], D1 and D2 dopamine receptors [61], adenosine A2A receptor [62], and the CB1 cannabinoid receptor [63, 64], has been particularly well studied and quantified. Thus, the htt polyglutamine expansion can affect its interactions with other proteins and transcriptional regulation of multiple genes, causing a wide variety of cell signaling alterations that are crucial for disease progression.

Htt-Mediated Cell Signaling Alterations Involving the Glutamatergic System

An important cell signaling alteration promoted by the htt polyglutamine expansion is an increase in intracellular Ca^{2+} levels, which may contribute to the neuronal cell death that takes place in HD. Mutant htt leads to NMDAR sensitization, increasing Ca^{2+} influx into the cell [65, 66], as discussed further in "Role of Glutamate Receptors in Neuronal Survival in HD". Moreover, mutant htt protein can also cause an increase in intracellular Ca^{2+} levels by destabilizing mitochondrial Ca^{2+} regulation [67, 68] and sensitizing InsP3 receptor-mediated release of Ca^{2+} from intracellular stores [69, 70]. As a consequence of InsP3 receptor sensitization, the stimulation of $G\alpha_{q/11}$ coupled receptors (e.g., mGluR1/5) leads to an increase in Ca^{2+} release from intracellular stores [49, 70].

Mutant htt protein can alter Group I mGluR cell signaling by a mechanism involving its interaction with optineurin, a protein that has been demonstrated to contributed to the attenuation of mGluR1/5 signaling [56]. Although wild-type htt protein does not enhance optineurin mediated mGluRs desensitization, mutant htt functions to synergistically increase optineurin-mediated mGluR desensitization in HEK 293 cells [56]. New data from our group confirmed that InsP3 formation stimulated by endogenous mGluR5 is selectively attenuated in the striatum of a knock-in mouse model of HD ($Hdh^{Q111/Q111}$ mice), as compared to control mice ($Hdh^{Q20/Q20}$ mice) [49]. However, InsP formation in response to activation of muscarinic acetylcholine receptors remains unaltered in the $Hdh^{Q111/Q111}$ mice. Interestingly, the attenuation of mGluR5 signaling observed in $Hdh^{Q111/Q111}$ mice is PKC dependent and is only present in young asymptomatic mice, and is lost in mice that are older than 11 months [49]. PKC-dependent mGluR1/5 attenuation might be protective, as activation of mGluRs in striatal neurons and inhibition of PKC lead to increased death of neurons derived from $Hdh^{Q111/Q111}$ mice without affecting survival of $Hdh^{Q20/Q20}$ neurons [49]. Despite decreased InsP formation, DHPG-mediated Ca^{2+} release is higher in $Hdh^{Q111/Q111}$ than in $Hdh^{Q20/Q20}$ neurons. Thus, it is possible that the PKC-mediated mGluR1/5 desensitization is protective as it avoids further increases in calcium release that could result in increased cell death.

In addition to the attenuation of mGluR1/5-mediated InsP3 formation, other Group I mGluRs signaling pathways that may be protective against cell death are increased in HD [49]. mGluR5 activation leads to higher levels of ERK1/2 phosphorylation in $Hdh^{Q111/Q111}$ striatal neurons than in $Hdh^{Q20/Q20}$ neurons. Moreover, basal levels of Akt are increased in $Hdh^{Q111/Q111}$ neurons, and inhibition of either NMDA receptors or mGluR5 decreases phospho-Akt levels in $Hdh^{Q111/Q111}$ neurons as compared to $Hdh^{Q20/Q20}$ neurons [49, 71]. Phosphorylation of Akt by glutamate receptors is particularly important because it has been shown that Akt activation can protect against neuronal death [72, 73]. The activation of Akt by mGluR5 involves phosphoinositide 3-kinase (PI3K) and phosphoinositide-dependent kinase (PDK1) [47, 48]. A PI3K enhancer (PIKE) couples group I mGluRs to PI3K via Homer proteins [47]. mGluR activation leads to formation of the functional complex mGluR-Homer-PIKE, allowing PI3 kinase activation by PIKE, which results in reduced apoptosis [47]. Thus, mGluR-mediated Akt activation is independent of InsP3/PLC pathway.

Akt is emerging as a key component to protect against neuronal cell death in a growing number of neurodegenerative disorders. In HD, Akt can promote phosphorylation of mutant Htt protein, which leads to reduced Htt aggregate formation and neuronal cell death, providing a protective pathway in HD [74, 75]. It has also been demonstrated that a myristoylated form of Akt, which is constitutively active, has a potent in vivo anti-apoptotic effect on dopaminergic neurons of the substantia nigra in a mouse model of Parkinson's disease [76]. In addition, Akt also has an important protective role in Alzheimer's disease (AD), as Akt activation leads to inhibition of glycogen synthase kinase-3 (GSK-3) and GSK-3 promotes phosphorylation of tau leading to neurofibrilary tangle formation and neuronal cell death [77]. Interestingly, amyloid-beta can activate GSK-3 by inhibiting PI3K/Akt pathway and Akt activation can reverse amyloid-beta toxic effects [78]. Thus, Akt occupies a pivotal role in Alzheimer's disease pathology, modulating both amyloid-beta and tau pathologies, constituting a potential therapeutic target to treat AD patients. It is possible that the observed increase in Akt activation in $Hdh^{Q111/Q111}$ striatal neurons plays a similar role in HD by protecting neurons against cell death during the asymptomatic stages of the disease.

Htt-Mediated Cell Signaling Alterations Involving the Dopaminergic System

The dopaminergic system appears to play a role in HD, as a dopamine transporter knock-out mice display both spontaneous striatal death and behavioural alterations that

resemble HD [79]. Moreover, exacerbation of HD symptoms and augmentation of aggregate formation occur when these mice are mated to a knock-in HD mice [80]. In vitro data demonstrate that dopamine stimulation can lead to the formation of reactive oxygen species and the activation of pro-apoptotic pathways, as well as aggregate formation and mitochondria dysfunction via D2 dopamine receptor activation [81, 82]. Furthermore, D2 antagonist treatment protects against aggregate formation and striatal dysfunctions induced by mutant htt [81, 83]. D2-mediated activation of aggregate formation involves a Rho/ROCK signaling pathway, as inhibition of ROCK activity reverses D2-promoted aggregate formation, neuritic retraction and neuronal death induced by mutant htt [84]. Glutamate and dopamine signaling pathways can also act synergistically to induce apoptosis of MSNs via elevated Ca^{2+} signaling [85, 86]. Moreover, it has been shown that, in cells expressing mutant htt, NMDAR activation potentiates D1-induced Cdk5 phosphorylation, which can lead to neurotoxicity and apoptosis [86].

Htt-Mediated Cell Signaling Alterations Involving the Cannabinoid System

Cannabis sativa, popularly known as marijuana, has been used as recreational drug for the past 4,000 years by numerous cultures. In 1964, Gaoni and Mechoulam [87] identified Δ^9-tetrahidrocanabinol (Δ^9-THC) as the major psychoactive constituent of the plant. The effects of Δ^9-THC are mediated mainly by two cannabinoid receptors named CB1 and CB2 which were cloned and characterized in the early 1990s [88, 89] and one of the most surprising findings was that these receptors could bind endogenous ligands recently known as endocannabinoids (ECs). Five ECs have been identified thus far, including anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), which are the two most studied ECs [90, 91]. The ECs are released by post-synaptic neurons and act predominantly at pre-synaptic neurons [92]. This retrograde signaling pathway has emerged as being important in synaptic plasticity and, recently, neurobiologists have increasingly turned their attention to EC system as it has been implicated in numerous neurophysiologic functions such as pain, appetite, learning and memory, and motor functions [93–96]. It has been shown that AEA can also act as a full agonist of transient receptor potential vanilloid 1 (TRPV1) and, since these receptors are expressed both in the periphery and in the CNS, this AEA endovanilloid activity may influence many physiological brain functions [97]. A role for ECs in a variety of CNS disorders, especially neurodegenerative diseases, is suggested by the high levels of expression of CB1 receptors in brain regions involved in cognition and motor activity [98].

The activation of EC signaling by direct receptor agonists and/or inhibition of EC metabolism has powerful effects on the control of movement, mostly inhibitory [99, 100]. The motor effects of the EC system are related to the capacity of this system to modulate the activity of glutamate, GABA and dopamine which participate in the control of basal ganglia function [101, 102]. The presence of CB1 receptors at GABAergic and glutamatergic synapses within the basal ganglia, as well as the presence of TRPV1 receptors in nigrostriatal dopaminergic neurons, enables ECs to directly control the function of these key neurotransmitters [102]. Thus, the main function of cannabinoid system within the basal ganglia is to modulate GABAergic and glutamatergic synapses through a retrograde signaling mechanism [101].

The first evidence linking EC signaling with HD was provided by Glass et al. [103]. They demonstrated a loss of approximately 97% of CB1 receptors in the subtantia nigra of human HD brains [103]. This loss of CB1 receptors preceded the loss of D1 and D2 dopamine receptors and occurred even before the onset of major HD symptoms [104]. Thus, CB1 receptors may play a central role in either the pathogenesis and/or progression of the neurodegeneration in HD patients. These findings are consistent with the observation that medium spiny-GABAergic neurons, which specifically express CB1 receptors, are the predominant neuronal population lost in the basal ganglia in HD [98].

The EC system has also been studied in a variety of animal models of HD [105–108]. These mouse models develop many HD features such as striatal atrophy, intraneuronal aggregates and progressive dystonia and also exhibit decreased CB1 mRNA levels and activity in basal ganglia. This reduction CB1 mRNA expression occurs prior to the development of motor symptoms and neuronal degeneration. TRPV1 also seems to be involved in HD as the stimulation of this receptor subtype, located at nigrostriatal dopaminergic neurons of basal ganglia, reduces hyperkinesia in HD animal models [109, 110].

Htt-Mediated Cell Signaling Alterations Involving Trophic Factors

Trophic factors, such as brain-derived neurotrophic factor (BDNF), largely influence neuronal survival and function [111]. Wild-type, but not mutant, huntingtin promotes the transcription and vesicular transport of BDNF [112–114]. Polyglutamine expansion of the htt protein results in the reduction of BDNF transcription and axonal transport, which may affect the survival of both striatal and cortical neurons [112, 113]. It has also been shown that BDNF is able to prevent the death of striatal projection neurons in a quinolinic acid model of HD and in a 3-NP-induced toxicity mouse model, which causes abnormal movement,

cognitive deficits and neuronal degeneration similar to that seen in HD patients [115–117]. Most of BDNF neuroprotective effects are mediated by TrkB receptor-induced activation of pro-survival signaling pathways, including: PLC-γ, Ras/MEK/MAPK and PI3K/Akt pathways [118]. BDNF also protects cortical neurons from 3-NP toxicity through the activation of PI3K and ERK1/2 intracellular signaling pathways resulting in decreased mitochondrial abnormalities and apoptosis [119]. These data highlight the importance of altered BDNF signaling in HD pathology.

Research on BDNF and HD has focused on drugs that could boost BDNF production, as this trophic factor does not cross the blood–brain barrier. Recent data have demonstrated that ampakine, a positive modulator of AMPA glutamate receptors, can up-regulate endogenous BDNF levels, rescuing plasticity and reducing learning problems in a HD mouse model [120]. However, ampakine treatment has no measurable effect on decreased locomotor activity. Nevertheless, as ampakines are well tolerated by patients, they may represent a novel strategy for treatment of the cognitive difficulties that occur in HD, as well as for preventing neuronal cell death [120].

Role of Glutamate Receptors in Neuronal Survival in HD

Glutamate receptors are appearing as important pharmacological targets in HD. It is well known that glutamate plays an important role in neuronal excitotoxicity through the activation of ionotropic receptors [11, 19, 121]. Excitotoxicity is one of the most extensively studied processes of neuronal cell death, and plays an important role in many CNS disorders, including ischemia, trauma, and neurodegenerative disorders, such as AD, HD, Parkinson's disease, and amyotrophic lateral sclerosis [122–128]. Excitotoxicity is characterized by an excessive synaptic release of glutamate, leading to glutamate receptor over-stimulation and Ca^{2+} overload, compromising mitochondria function and leading to cell death [129, 130]. Elevation of intracellular Ca^{2+} by glutamate is mainly achieved by activation of the ionotropic NMDAR via calcium influx and, to a lesser degree, Group I mGluRs (mGluR1 and mGluR5), which are coupled to Ca^{2+} release from intracellular stores [25, 29].

Several studies have implicated NMDAR signaling in excitotoxic neuronal loss in HD [11, 19, 121]. Radioligand binding studies, using post-mortem brain tissue from HD patients in the early symptomatic phase, showed a loss of striatal NMDARs suggesting that striatal neurons with high NMDAR expression are more vulnerable and are lost early during disease progression [131, 132]. Moreover, a mouse model of HD was created by injecting the NMDAR agonist quinolinic acid into the striatum [133, 134]. This HD mouse model exhibits many of the HD-like lesions and symptoms [133, 134]. Furthermore, NMDAR-mediated excitotoxicity may explain why MSNs are more vulnerable in HD. NMDARs that are comprised of the NR1A/NR2B, but not NR1A/NR2A subunit combination, can be sensitized by mutant htt [65, 135]. Interestingly, MSNs mainly express the NR1A and NR2B subunits [136], whereas other brain regions express combinations of both NR2A and NR2B with a variety of NR1 splice variants [137, 138]. Thus, NMDAR-specific subunit expression might underlie the preferential death of MSNs in the striatum. Group I mGluRs may also play a role in the selective loss of MSNs in the striatum as DHPG stimulation strongly enhances membrane depolarization and intracellular calcium accumulation induced by NMDAR in MSNs, but not in cholinergic striatal interneurons, which are spared in HD [20].

The prominent role of NMDARs in neuronal excitotoxicity and cell death has led to a concerted effort to design and assess NMDAR antagonists such as ketamine, phencyclidine, and MK-801 for the treatment of neurological disorders involving cell death. However, although ionotropic glutamate receptors are likely to be essential for the neuronal cell loss that occurs in HD, pharmacological approaches targeting these receptors is not an ideal strategy. This is because the blockage of ionotropic receptors leads to many toxic effects, including psychosis, nausea, memory impairment, and neurotoxicity, which have led to their failure in clinical trials and a search for alternative therapeutic targets [139, 140]. Group I mGluRs have a modulatory rather than excitatory role in neurotransmission, making these receptors exciting targets for new therapeutic strategies for a number of neurological disorders, including HD.

It is not clear yet whether Group I mGluRs have a role in HD. However, a direct link between htt and Group I mGluRs has been established by our group, as we have shown that mGluR1/5 interact with both Htt and optineurin, which is also a Htt-interacting protein [50, 56]. Nevertheless, the role of mGluR5 in HD and neuronal cell death is very controversial. Treatment of an HD transgenic mouse model with a mGluR5 antagonist increases survival, indicating that mGluR5 activation can accelerate HD progression [141]. In addition, disturbed calcium signaling and apoptosis observed in primary cultured MSNs of an HD mouse model has been attributed to activation of mGluR1/5 and NMDA receptors containing the NR2B subunit [69, 70]. Treatment with mGluR1 antagonists results in a decrease in the tissue infarct size and cell death in an in vivo animal models of ischemic stroke [142–146]. On the other hand, it has been reported that mGluR1 knockout mice do not show any difference in infarct size when

compared to control mice [147]. Moreover, other studies have provided evidence that Group I mGluRs activation may be protective. For example, when cortical neuronal cultures are consecutively incubated two times with DHPG (3,5-dihydroxyphenylglycine), an agonist for group I mGluRs, NMDA excitotoxicity is attenuated [148]. In rat hippocampal organotypic slices, DHPG stimulation protects CA1 hippocampal cells and this effect is lost when mGluR1 antagonists are applied [149]. As outlined in "Glutamate Receptors and Cell Signaling", data from our group suggest that mGluR1/5 signaling is modified in a mouse model of HD during the presymptomatic phase of the disease and we suggest that these alterations have a protective role [49, 56]. Thus, depending on the context of activation, group I mGluR stimulation is found to be either neurotoxic or neuroprotective and this may be related to the precise molecular mechanism by which mGluR signaling is achieved.

Concluding Remarks

Polyglutamine expansion of the htt protein results in altered htt protein interactions and gene transcript that results in perturbations in cell signaling that affect neuronal homeostasis. It is possible that several of these alterations in htt function occur in the pre-symptomatic phase of the disease and might be crucial to determine the rate of HD progression. Understanding these early changes in cell signaling caused by mutant htt will be essential for the development of pharmacological therapies to prevent neuronal cell death in HD and slow disease progression. Mutant htt can induce alterations of the dopaminergic and cannabinoid system and these alterations can also influence the glutamatergic system. Moreover, mutant htt-induced decrease in BDNF function may also contribute to neuronal cell loss and motor alterations. In addition, Htt mutation promotes several alterations in the glutamatergic system, involving both ionotropic and metabotropic glutamate receptors. NMDARs are sensitized by mutant htt and Group I mGluRs signaling is significantly altered in mouse models of HD. The glutamatergic system is closely linked to the regulation of neuronal cell death. However, glutamate receptor activation may be either excitotoxic or protective depending upon the context of activation. In particular, it is possible that pharmaceutical agents may be developed that selectively activate mGluR-stimulated pro-survival pathways as opposed to activating mGluR signaling that leads to neuronal cell death.

Acknowledgements S.S.G.F. holds a Tier I Canada Research Chair in Molecular Neurobiology and is a career investigator of the Heart and Stroke Foundation of Ontario. This work was supported by CIHR grant MA-15506 to S.S.G.F.

References

1. Li SH, Li XJ (2004) Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends Genet 20:146–154
2. Young AB (2003) Huntingtin in health and disease. J Clin Invest 111:299–302
3. Heathfield KW (1967) Huntington's chorea. Investigation into the prevalence of this disease in the area covered by the North East Metropolitan Regional Hospital Board. Brain 90:203–232
4. Perez-De La Cruz V, Santamaria A (2007) Integrative hypothesis for Huntington's disease: a brief review of experimental evidence. Physiol Res 56:513–526
5. Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983
6. Kremer B, Goldberg P, Andrew SE, Theilmann J, Telenius H, Zeisler J, Squitieri F, Lin B, Bassett A, Almqvist E (1994) A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measuring CAG repeats. N Engl J Med 330:1401–1406
7. Dragatsis I, Dietrich P, Zeitlin S (2000) Expression of the Huntingtin-associated protein 1 gene in the developing and adult mouse. Neurosci Lett 282:37–40
8. Rigamonti D, Bauer JH, De-Fraja C, Conti L, Sipione S, Sciorati C, Clementi E, Hackam A, Hayden MR, Li Y, Cooper JK, Ross CA, Govoni S, Vincenz C, Cattaneo E (2000) Wild-type huntingtin protects from apoptosis upstream of caspase-3. J Neurosci 20:3705–3713
9. Nasir J, Floresco SB, O'Kusky JR, Diewert VM, Richman JM, Zeisler J, Borowski A, Marth JD, Phillips AG, Hayden MR (1995) Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell 81:811–823
10. Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A (1995) Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nat Genet 11:155–163
11. Beal MF, Ferrante RJ, Swartz KJ, Kowall NW (1991) Chronic quinolinic acid lesions in rats closely resemble Huntington's disease. J Neurosci 11:1649–1659
12. Jarabek BR, Yasuda RP, Wolfe BB (2004) Regulation of proteins affecting NMDA receptor-induced excitotoxicity in a Huntington's mouse model. Brain 127:505–516
13. Li JY, Plomann M, Brundin P (2003) Huntington's disease: a synaptopathy? Trends Mol Med 9:414–420
14. Lim D, Fedrizzi L, Tartari M, Zuccato C, Cattaneo E, Brini M, Carafoli E (2008) Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease. J Biol Chem 283:5780–5789
15. Myers RH, Vonsattel JP, Stevens TJ, Cupples LA, Richardson EP, Martin JB, Bird ED (1988) Clinical and neuropathologic assessment of severity in Huntington's disease. Neurology 38:341–347
16. Bates G (2003) Huntingtin aggregation and toxicity in Huntington's disease. Lancet 361:1642–1644
17. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 431:805–810
18. Miller J, Arrasate M, Shaby BA, Mitra S, Masliah E, Finkbeiner S (2010) Quantitative relationships between huntingtin levels, polyglutamine length, inclusion body formation, and neuronal death provide novel insight into huntington's disease molecular pathogenesis. J Neurosci 30:10541–10550

19. DiFiglia M (1990) Excitotoxic injury of the neostriatum: a model for Huntington's disease. Trends Neurosci 13:286–289
20. Calabresi P, Centonze D, Pisani A, Bernardi G (1999) Metabotropic glutamate receptors and cell-type-specific vulnerability in the striatum: implication for ischemia and Huntington's disease. Exp Neurol 158:97–108
21. Ferraguti F, Crepaldi L, Nicoletti F (2008) Metabotropic glutamate 1 receptor: current concepts and perspectives. Pharmacol Rev 60:536–581
22. Nakanishi S, Masu M (1994) Molecular diversity and functions of glutamate receptors. Annu Rev Biophys Biomol Struct 23:319–348
23. Dhami GK, Ferguson SS (2006) Regulation of metabotropic glutamate receptor signaling, desensitization and endocytosis. Pharmacol Ther 111:260–271
24. Olney JW (1994) New mechanisms of excitatory transmitter neurotoxicity. J Neural Transm Suppl 43:47–51
25. Dingledine R, Borges K, Bowie D, Traynelis SF (1999) The glutamate receptor ion channels. Pharmacol Rev 51:7–61
26. Pin JP, Galvez T, Prezeau L (2003) Evolution, structure, and activation mechanism of family 3/C G-protein-coupled receptors. Pharmacol Ther 98:325–354
27. Ribeiro FM, Paquet M, Cregan SP, Ferguson SS (2010) Group I metabotropic glutamate receptor signalling and its implication in neurological disease. CNS Neurol Disord Drug Targets
28. Pin JP, Duvoisin R (1995) The metabotropic glutamate receptors: structure and functions. Neuropharmacology 34:1–26
29. Conn PJ, Pin JP (1997) Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 37:205–237
30. Ferraguti F, Shigemoto R (2006) Metabotropic glutamate receptors. Cell Tissue Res 326:483–504
31. Wieronska JM, Pilc A (2009) Metabotropic glutamate receptors in the tripartite synapse as a target for new psychotropic drugs. Neurochem Int 55:85–97
32. Schoepp DD (2001) Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. J Pharmacol Exp Ther 299:12–20
33. Shigemoto R, Nomura S, Ohishi H, Sugihara H, Nakanishi S, Mizuno N (1993) Immunohistochemical localization of a metabotropic glutamate receptor, mGluR5, in the rat brain. Neurosci Lett 163:53–57
34. Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, Flor PJ, Neki A, Abe T, Nakanishi S, Mizuno N (1997) Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. J Neurosci 17:7503–7522
35. Baude A, Nusser Z, Roberts JD, Mulvihill E, McIlhinney RA, Somogyi P (1993) The metabotropic glutamate receptor (mGluR1 alpha) is concentrated at perisynaptic membrane of neuronal subpopulations as detected by immunogold reaction. Neuron 11:771–787
36. Park YK, Galik J, Ryu PD, Randic M (2004) Activation of presynaptic group I metabotropic glutamate receptors enhances glutamate release in the rat spinal cord substantia gelatinosa. Neurosci Lett 361:220–224
37. Abdul-Ghani MA, Valiante TA, Carlen PL, Pennefather PS (1996) Metabotropic glutamate receptors coupled to IP3 production mediate inhibition of IAHP in rat dentate granule neurons. J Neurophysiol 76:2691–2700
38. Hermans E, Challiss RA (2001) Structural, signalling and regulatory properties of the group I metabotropic glutamate receptors: prototypic family C G-protein-coupled receptors. Biochem J 359:465–484
39. Chavis P, Fagni L, Lansman JB, Bockaert J (1996) Functional coupling between ryanodine receptors and L-type calcium channels in neurons. Nature 382:719–722
40. Fagni L, Chavis P, Ango F, Bockaert J (2000) Complex interactions between mGluRs, intracellular Ca2+ stores and ion channels in neurons. Trends Neurosci 23:80–88
41. Fagni L, Bossu JL, Bockaert J (1991) Activation of a large-conductance Ca^{2+}-dependent K^{+} channel by stimulation of glutamate phosphoinositide-coupled receptors in cultured cerebellar granule cells. Eur J Neurosci 3:778–789
42. Sharon D, Vorobiov D, Dascal N (1997) Positive and negative coupling of the metabotropic glutamate receptors to a G protein-activated K^{+} channel, GIRK, in Xenopus oocytes. J Gen Physiol 109:477–490
43. Lu WY, Xiong ZG, Lei S, Orser BA, Dudek E, Browning MD, Macdonald JF (1999) G-protein-coupled receptors act via protein kinase C and Src to regulate NMDA receptors. Nat Neurosci 2:331–338
44. Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M, Worley PF (1999) Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. Neuron 23:583–592
45. Husi H, Ward MA, Choudhary JS, Blackstock WP, Grant SG (2000) Proteomic analysis of NMDA receptor–adhesion protein signaling complexes. Nat Neurosci 3:661–669
46. Mao L, Yang L, Tang Q, Samdani S, Zhang G, Wang JQ (2005) The scaffold protein Homer1b/c links metabotropic glutamate receptor 5 to extracellular signal-regulated protein kinase cascades in neurons. J Neurosci 25:2741–2752
47. Rong R, Ahn JY, Huang H, Nagata E, Kalman D, Kapp JA, Tu J, Worley PF, Snyder SH, Ye K (2003) PI3 kinase enhancer-Homer complex couples mGluRI to PI3 kinase, preventing neuronal apoptosis. Nat Neurosci 6:1153–1161
48. Hou L, Klann E (2004) Activation of the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway is required for metabotropic glutamate receptor-dependent long-term depression. J Neurosci 24:6352–6361
49. Ribeiro FM, Paquet M, Ferreira LT, Cregan T, Swan P, Cregan SP, Ferguson SS (2010) Metabotropic glutamate receptor-mediated cell signaling pathways are altered in a mouse model of Huntington's disease. J Neurosci 30:316–324
50. Harjes P, Wanker EE (2003) The hunt for huntingtin function: interaction partners tell many different stories. Trends Biochem Sci 28:425–433
51. Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, Penney JB, Bates GP, Young AB (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 95:6480–6485
52. Wanker EE, Rovira C, Scherzinger E, Hasenbank R, Walter S, Tait D, Colicelli J, Lehrach H (1997) HIP-I: a huntingtin interacting protein isolated by the yeast two-hybrid system. Hum Mol Genet 6:487–495
53. Kalchman MA, Koide HB, McCutcheon K, Graham RK, Nichol K, Nishiyama K, Kazemi-Esfarjani P, Lynn FC, Wellington C, Metzler M, Goldberg YP, Kanazawa I, Gietz RD, Hayden MR (1997) HIP1, a human homologue of S. cerevisiae Sla2p, interacts with membrane-associated huntingtin in the brain. Nat Genet 16:44–53
54. Singaraja RR, Hadano S, Metzler M, Givan S, Wellington CL, Warby S, Yanai A, Gutekunst CA, Leavitt BR, Yi H, Fichter K, Gan L, McCutcheon K, Chopra V, Michel J, Hersch SM, Ikeda JE, Hayden MR (2002) HIP14, a novel ankyrin domain-containing protein, links huntingtin to intracellular trafficking and endocytosis. Hum Mol Genet 11:2815–2828
55. Cattaneo E, Rigamonti D, Goffredo D, Zuccato C, Squitieri F, Sipione S (2001) Loss of normal huntingtin function: new developments in Huntington's disease research. Trends Neurosci 24:182–188

56. Anborgh PH, Godin C, Pampillo M, Dhami GK, Dale LB, Cregan SP, Truant R, Ferguson SS (2005) Inhibition of metabotropic glutamate receptor signaling by the huntingtin-binding protein optineurin. J Biol Chem 280:34840–34848
57. Cha JH (2007) Transcriptional signatures in Huntington's disease. Prog Neurobiol 83:228–248
58. Augood SJ, Faull RL, Love DR, Emson PC (1996) Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: a detailed cellular in situ hybridization study. Neuroscience 72:1023–1036
59. Menalled L, Zanjani H, MacKenzie L, Koppel A, Carpenter E, Zeitlin S, Chesselet MF (2000) Decrease in striatal enkephalin mRNA in mouse models of Huntington's disease. Exp Neurol 162:328–342
60. Bibb JA, Yan Z, Svenningsson P, Snyder GL, Pieribone VA, Horiuchi A, Nairn AC, Messer A, Greengard P (2000) Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. Proc Natl Acad Sci U S A 97:6809–6814
61. Augood SJ, Faull RL, Emson PC (1997) Dopamine D1 and D2 receptor gene expression in the striatum in Huntington's disease. Ann Neurol 42:215–221
62. Tarditi A, Camurri A, Varani K, Borea PA, Woodman B, Bates G, Cattaneo E, Abbracchio MP (2006) Early and transient alteration of adenosine A2A receptor signaling in a mouse model of Huntington disease. Neurobiol Dis 23:44–53
63. Denovan-Wright EM, Robertson HA (2000) Cannabinoid receptor messenger RNA levels decrease in a subset of neurons of the lateral striatum, cortex and hippocampus of transgenic Huntington's disease mice. Neuroscience 98:705–713
64. McCaw EA, Hu H, Gomez GT, Hebb AL, Kelly ME, Denovan-Wright EM (2004) Structure, expression and regulation of the cannabinoid receptor gene (CB1) in Huntington's disease transgenic mice. Eur J Biochem 271:4909–4920
65. Chen N, Luo T, Wellington C, Metzler M, McCutcheon K, Hayden MR, Raymond LA (1999) Subtype-specific enhancement of NMDA receptor currents by mutant huntingtin. J Neurochem 72:1890–1898
66. Sun Y, Savanenin A, Reddy PH, Liu YF (2001) Polyglutamine-expanded huntingtin promotes sensitization of *N*-methyl-D-aspartate receptors via post-synaptic density 95. J Biol Chem 276:24713–24718
67. Panov AV, Gutekunst CA, Leavitt BR, Hayden MR, Burke JR, Strittmatter WJ, Greenamyre JT (2002) Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5:731–736
68. Choo YS, Johnson GV, MacDonald M, Detloff PJ, Lesort M (2004) Mutant huntingtin directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome *c* release. Hum Mol Genet 13:1407–1420
69. Tang TS, Slow E, Lupu V, Stavrovskaya IG, Sugimori M, Llinas R, Kristal BS, Hayden MR, Bezprozvanny I (2005) Disturbed Ca^{2+} signaling and apoptosis of medium spiny neurons in Huntington's disease. Proc Natl Acad Sci U S A 102:2602–2607
70. Tang TS, Tu H, Chan EY, Maximov A, Wang Z, Wellington CL, Hayden MR, Bezprozvanny I (2003) Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1, 4, 5) triphosphate receptor type 1. Neuron 39:227–239
71. Gines S, Ivanova E, Seong IS, Saura CA, MacDonald ME (2003) Enhanced Akt signaling is an early pro-survival response that reflects *N*-methyl-D-aspartate receptor activation in Huntington's disease knock-in striatal cells. J Biol Chem 278:50514–50522
72. Datta SR, Brunet A, Greenberg ME (1999) Cellular survival: a play in three Akts. Genes Dev 13:2905–2927
73. Kandel ES, Hay N (1999) The regulation and activities of the multifunctional serine/threonine kinase Akt/PKB. Exp Cell Res 253:210–229
74. Humbert S, Bryson EA, Cordelieres FP, Connors NC, Datta SR, Finkbeiner S, Greenberg ME, Saudou F (2002) The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves Huntingtin phosphorylation by Akt. Dev Cell 2:831–837
75. Warby SC, Doty CN, Graham RK, Shively J, Singaraja RR, Hayden MR (2009) Phosphorylation of huntingtin reduces the accumulation of its nuclear fragments. Mol Cell Neurosci 40:121–127
76. Ries V, Henchcliffe C, Kareva T, Rzhetskaya M, Bland R, During MJ, Kholodilov N, Burke RE (2006) Oncoprotein Akt/PKB induces trophic effects in murine models of Parkinson's disease. Proc Natl Acad Sci U S A 103:18757–18762
77. Hanger DP, Hughes K, Woodgett JR, Brion JP, Anderton BH (1992) Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: generation of paired helical filament epitopes and neuronal localisation of the kinase. Neurosci Lett 147:58–62
78. Magrane J, Rosen KM, Smith RC, Walsh K, Gouras GK, Querfurth HW (2005) Intraneuronal beta-amyloid expression downregulates the Akt survival pathway and blunts the stress response. J Neurosci 25:10960–10969
79. Cyr M, Beaulieu JM, Laakso A, Sotnikova TD, Yao WD, Bohn LM, Gainetdinov RR, Caron MG (2003) Sustained elevation of extracellular dopamine causes motor dysfunction and selective degeneration of striatal GABAergic neurons. Proc Natl Acad Sci U S A 100:11035–11040
80. Cyr M, Sotnikova TD, Gainetdinov RR, Caron MG (2006) Dopamine enhances motor and neuropathological consequences of polyglutamine expanded huntingtin. FASEB J 20:2541–2543
81. Charvin D, Vanhoutte P, Pages C, Borrelli E, Caboche J (2005) Unraveling a role for dopamine in Huntington's disease: the dual role of reactive oxygen species and D2 receptor stimulation. Proc Natl Acad Sci U S A 102:12218–12223
82. Benchoua A, Trioulier Y, Diguet E, Malgorn C, Gaillard MC, Dufour N, Elalouf JM, Krajewski S, Hantraye P, Deglon N, Brouillet E (2008) Dopamine determines the vulnerability of striatal neurons to the N-terminal fragment of mutant huntingtin through the regulation of mitochondrial complex II. Hum Mol Genet 17:1446–1456
83. Charvin D, Roze E, Perrin V, Deyts C, Betuing S, Pages C, Regulier E, Luthi-Carter R, Brouillet E, Deglon N, Caboche J (2008) Haloperidol protects striatal neurons from dysfunction induced by mutated huntingtin in vivo. Neurobiol Dis 29:22–29
84. Deyts C, Galan-Rodriguez B, Martin E, Bouveyron N, Roze E, Charvin D, Caboche J, Betuing S (2009) Dopamine D2 receptor stimulation potentiates PolyQ-Huntingtin-induced mouse striatal neuron dysfunctions via Rho/ROCK-II activation. PLoS One 4: e8287
85. Tang TS, Chen X, Liu J, Bezprozvanny I (2007) Dopaminergic signaling and striatal neurodegeneration in Huntington's disease. J Neurosci 27:7899–7910
86. Paoletti P, Vila I, Rife M, Lizcano JM, Alberch J, Gines S (2008) Dopaminergic and glutamatergic signaling crosstalk in Huntington's disease neurodegeneration: the role of p25/cyclin-dependent kinase 5. J Neurosci 28:10090–10101
87. Gaoni Y, Mechoulam R (1964) Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 86:1646–1647
88. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346:561–564

89. Munro S, Thomas KL, bu-Shaar M (1993) Molecular characterization of a peripheral receptor for cannabinoids. Nature 365:61–65
90. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946–1949
91. Stella N, Schweitzer P, Piomelli D (1997) A second endogenous cannabinoid that modulates long-term potentiation. Nature 388:773–778
92. Wilson RI, Nicoll RA (2001) Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 410:588–592
93. Ameri A (1999) The effects of cannabinoids on the brain. Prog Neurobiol 58:315–348
94. Iversen L (2003) Cannabis and the brain. Brain 126:1252–1270
95. De Oliveira AL, Genro BP, Diehl F, Quillfeldt JA (2008) Differential role of the hippocampal endocannabinoid system in the memory consolidation and retrieval mechanisms. Neurobiol Learn Mem 90:1–9
96. Kinsey SG, Long JZ, Cravatt BF, Lichtman AH (2010) Fatty acid amide hydrolase and monoacylglycerol lipase inhibitors produce anti-allodynic effects in mice through distinct cannabinoid receptor mechanisms. J Pain 11(12):1420–8
97. Starowicz K, Nigam S, Di Marzo V (2007) Biochemistry and pharmacology of endovanilloids. Pharmacol Ther 114:13–33
98. Micale V, Mazzola C, Drago F (2007) Endocannabinoids and neurodegenerative diseases. Pharmacol Res 56:382–392
99. Fride E, Mechoulam R (1993) Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. Eur J Pharmacol 231:313–314
100. Beltramo M, de Fonseca FR, Navarro M, Calignano A, Gorriti MA, Grammatikopoulos G, Sadile AG, Giuffrida A, Piomelli D (2000) Reversal of dopamine D(2) receptor responses by an anandamide transport inhibitor. J Neurosci 20:3401–3407
101. Fernandez-Ruiz J (2009) The endocannabinoid system as a target for the treatment of motor dysfunction. Br J Pharmacol 156:1029–1040
102. Fernandez-Ruiz J, Hernandez M, Ramos JA (2010) Cannabinoid–dopamine interaction in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther 16:e72–e91
103. Glass M, Faull RL, Dragunow M (1993) Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. Neuroscience 56:523–527
104. Glass M, Dragunow M, Faull RL (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97:505–519
105. Page KJ, Besret L, Jain M, Monaghan EM, Dunnett SB, Everitt BJ (2000) Effects of systemic 3-nitropropionic acid-induced lesions of the dorsal striatum on cannabinoid and mu-opioid receptor binding in the basal ganglia. Exp Brain Res 130:142–150
106. Lastres-Becker I, Gomez M, De MR, Ramos JA, Fernandez-Ruiz J (2002) Loss of cannabinoid CB(1) receptors in the basal ganglia in the late akinetic phase of rats with experimental Huntington's disease. Neurotox Res 4:601–608
107. Naver B, Stub C, Moller M, Fenger K, Hansen AK, Hasholt L, Sorensen SA (2003) Molecular and behavioral analysis of the R6/1 Huntington's disease transgenic mouse. Neuroscience 122:1049–1057
108. Dowie MJ, Bradshaw HB, Howard ML, Nicholson LF, Faull RL, Hannan AJ, Glass M (2009) Altered CB1 receptor and endocannabinoid levels precede motor symptom onset in a transgenic mouse model of Huntington's disease. Neuroscience 163:456–465
109. Lastres-Becker I, Fezza F, Cebeira M, Bisogno T, Ramos JA, Milone A, Fernandez-Ruiz J, Di Marzo V (2001) Changes in endocannabinoid transmission in the basal ganglia in a rat model of Huntington's disease. NeuroReport 12:2125–2129
110. Lastres-Becker I, De MR, De PL, Makriyannis A, Di Marzo V, Fernandez-Ruiz J (2003) Compounds acting at the endocannabinoid and/or endovanilloid systems reduce hyperkinesia in a rat model of Huntington's disease. J Neurochem 84:1097–1109
111. Connor B, Dragunow M (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res Brain Res Rev 27:1–39
112. Gauthier LR, Charrin BC, Borrell-Pages M, Dompierre JP, Rangone H, Cordelieres FP, De MJ, MacDonald ME, Lessmann V, Humbert S, Saudou F (2004) Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 118:127–138
113. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293:493–498
114. Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmusk T, Rigamonti D, Cattaneo E (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nat Genet 35:76–83
115. Perez-Navarro E, Canudas AM, Akerund P, Alberch J, Arenas E (2000) Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 prevent the death of striatal projection neurons in a rodent model of Huntington's disease. J Neurochem 75:2190–2199
116. Kells AP, Fong DM, Dragunow M, During MJ, Young D, Connor B (2004) AAV-mediated gene delivery of BDNF or GDNF is neuroprotective in a model of Huntington disease. Mol Ther 9:682–688
117. Ryu JK, Kim J, Cho SJ, Hatori K, Nagai A, Choi HB, Lee MC, McLarnon JG, Kim SU (2004) Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. Neurobiol Dis 16:68–77
118. Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736
119. Almeida S, Laco M, Cunha-Oliveira T, Oliveira CR, Rego AC (2009) BDNF regulates BIM expression levels in 3-nitropropionic acid-treated cortical neurons. Neurobiol Dis 35:448–456
120. Simmons DA, Rex CS, Palmer L, Pandyarajan V, Fedulov V, Gall CM, Lynch G (2009) Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. Proc Natl Acad Sci U S A 106:4906–4911
121. Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, Hayden MR, Raymond LA (2002) Increased sensitivity to *N*-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. Neuron 33:849–860
122. Dong XX, Wang Y, Qin ZH (2009) Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin 30:379–387
123. Koller WC, Cersosimo MG (2004) Neuroprotection in Parkinson's disease: an elusive goal. Curr Neurol Neurosci Rep 4:277–283
124. Rego AC, de Almeida LP (2005) Molecular targets and therapeutic strategies in Huntington's disease. Curr Drug Targets CNS Neurol Disord 4:361–381
125. Yi JH, Hazell AS (2006) Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. Neurochem Int 48:394–403

126. Corona JC, Romo LB, Tapia R (2007) Glutamate excitotoxicity and therapeutic targets for amyotrophic lateral sclerosis. Expert Opin Ther Targets 11:1415–1428
127. Hazell AS (2007) Excitotoxic mechanisms in stroke: an update of concepts and treatment strategies. Neurochem Int 50:941–953
128. Mamelak M (2007) Alzheimer' s disease, oxidative stress and gammahydroxybutyrate. Neurobiol Aging 28:1340–1360
129. Turley KR, Toledo-Pereyra LH, Kothari RU (2005) Molecular mechanisms in the pathogenesis and treatment of acute ischemic stroke. J Invest Surg 18:207–218
130. Sims NR, Muyderman H (2010) Mitochondria, oxidative metabolism and cell death in stroke. Biochim Biophys Acta 1802(1):80–91
131. Albin RL, Young AB, Penney JB, Handelin B, Balfour R, Anderson KD, Markel DS, Tourtellotte WW, Reiner A (1990) Abnormalities of striatal projection neurons and *N*-methyl-D-aspartate receptors in presymptomatic Huntington's disease. N Engl J Med 322:1293–1298
132. Young AB, Greenamyre JT, Hollingsworth Z, Albin R, D'Amato C, Shoulson I, Penney JB (1988) NMDA receptor losses in putamen from patients with Huntington's disease. Science 241:981–983
133. Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB (1986) Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 321:168–171
134. Hantraye P, Riche D, Maziere M, Isacson O (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 108:91–104
135. Zeron MM, Chen N, Moshaver A, Lee AT, Wellington CL, Hayden MR, Raymond LA (2001) Mutant huntingtin enhances excitotoxic cell death. Mol Cell Neurosci 17:41–53
136. Landwehrmeyer GB, Standaert DG, Testa CM, Penney JB Jr, Young AB (1995) NMDA receptor subunit mRNA expression by projection neurons and interneurons in rat striatum. J Neurosci 15:5297–5307
137. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH (1994) Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron 12:529–540
138. Thompson CL, Drewery DL, Atkins HD, Stephenson FA, Chazot PL (2000) Immunohistochemical localization of *N*-methyl-D-aspartate receptor NR1, NR2A, NR2B and NR2C/D subunits in the adult mammalian cerebellum. Neurosci Lett 283:85–88
139. Gerber AM, Vallano ML (2006) Structural properties of the NMDA receptor and the design of neuroprotective therapies. Mini Rev Med Chem 6:805–815
140. Ikonomidou C, Turski L (2002) Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol 1:383–386
141. Schiefer J, Sprunken A, Puls C, Luesse HG, Milkereit A, Milkereit E, Johann V, Kosinski CM (2004) The metabotropic glutamate receptor 5 antagonist MPEP and the mGluR2 agonist LY379268 modify disease progression in a transgenic mouse model of Huntington's disease. Brain Res 1019:246–254
142. Pellegrini-Giampietro DE, Peruginelli F, Meli E, Cozzi A, Albani-Torregrossa S, Pellicciari R, Moroni F (1999) Protection with metabotropic glutamate 1 receptor antagonists in models of ischemic neuronal death: time-course and mechanisms. Neuropharmacology 38:1607–1619
143. De VJ, Horvath E, Schreiber R (2001) Neuroprotective and behavioral effects of the selective metabotropic glutamate mGlu (1) receptor antagonist BAY 36-7620. Eur J Pharmacol 428:203–214
144. Cozzi A, Meli E, Carla V, Pellicciari R, Moroni F, Pellegrini-Giampietro DE (2002) Metabotropic glutamate 1 (mGlu1) receptor antagonists enhance GABAergic neurotransmission: a mechanism for the attenuation of post-ischemic injury and epileptiform activity? Neuropharmacology 43:119–130
145. Meli E, Picca R, Attucci S, Cozzi A, Peruginelli F, Moroni F, Pellegrini-Giampietro DE (2002) Activation of mGlu1 but not mGlu5 metabotropic glutamate receptors contributes to postischemic neuronal injury in vitro and in vivo. Pharmacol Biochem Behav 73:439–446
146. Murotomi K, Takagi N, Takayanagi G, Ono M, Takeo S, Tanonaka K (2008) mGluR1 antagonist decreases tyrosine phosphorylation of NMDA receptor and attenuates infarct size after transient focal cerebral ischemia. J Neurochem 105:1625–1634
147. Ferraguti F, Pietra C, Valerio E, Corti C, Chiamulera C, Conquet F (1997) Evidence against a permissive role of the metabotropic glutamate receptor 1 in acute excitotoxicity. Neuroscience 79:1–5
148. Bruno V, Battaglia G, Copani A, Cespedes VM, Galindo MF, Cena V, Sanchez-Prieto J, Gasparini F, Kuhn R, Flor PJ, Nicoletti F (2001) An activity-dependent switch from facilitation to inhibition in the control of excitotoxicity by group I metabotropic glutamate receptors. Eur J Neurosci 13:1469–1478
149. Werner CG, Scartabelli T, Pancani T, Landucci E, Moroni F, Pellegrini-Giampietro DE (2007) Differential role of mGlu1 and mGlu5 receptors in rat hippocampal slice models of ischemic tolerance. Eur J Neurosci 25:3597–3604