Chapter 3

Pathogenesis of Huntington's Disease: How to Fight Excitotoxicity and Transcriptional Dysregulation

Marta Anglada-Huguet, Laura Vidal-Sancho, Nuria Cabezas-Llobet, Jordi Alberch and Xavier Xifró

Additional information is available at the end of the chapter

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Abstract

Huntington's disease (HD) is a neurodegenerative disorder caused by an expanded CAG repeat in the exon-1 of the *huntingtin* (htt) gene. The presence of mutant htt (mhtt) results in multiple physiopathological changes, including protein aggregation, transcriptional deregulation, decreased trophic support, alteration in signaling pathways and excitotoxicity. Indeed, the presence of mhtt induces changes in the activities/levels of different kinases, phosphatases and transcription factors that can impact on cell survival. Many studies have provided evidence that transcription may be a major target of mhtt, as gene dysregulation occurs before the onset of symptoms. The greatest number of downregulated genes in HD has led to test the ability of a large number of compounds to restore gene transcription in mouse models of HD. On the other hand, mhtt engenders multiple cellular dysfunctions including an increase of pathological glutamate-mediated excitotoxicity. For that reason, targeting the excess of glutamate has been the goal for many promising drugs leading to clinical trials. Although advances in developing effective therapies are evident, currently, there is no known cure for HD and existing symptomatic treatments are limited.

Keywords: CREB, glutamate, HDAC inhibitors, excitotoxicity, transcriptional dysregulation

1. Introduction

Huntington's disease (HD) is a progressive, fatal, dominantly inherited neurodegenerative disorder [1] characterized by motor and cognitive dysfunction. Neuropathologically, HD is primarily characterized by neuronal loss in the striatum and cortex [2] together with hip-

pocampal dysfunction [3]. The disease is caused by an unstable expansion of CAG repeats in the huntingtin (htt) protein [4]. Htt is ubiquitously expressed [5, 6] and interacts with proteins that cover diverse cellular roles including apoptosis, vesicle transport, cell signaling and transcriptional regulation [7].

Although it is well established that the disease occurs as a consequence of an expanded polyglutamine repeats above 35 [4], the pathological mechanisms are not fully understood yet. Increasing evidence suggests that in addition to the gain of toxic properties, reduced htt physiological activity may render, in part, striatal neurons particularly vulnerable [8, 9]. The presence of mutant htt (mhtt) results in multiple pathophysiological changes, including protein aggregation, transcriptional dysregulation and chromatin remodeling, decreased trophic support, alteration in signaling pathways and disruption of calcium homeostasis and excitotoxicity.

Htt functions in transcription are well established. Htt has been shown to interact with a large number of transcription factors [10, 11], indicating a role of the protein in the control of gene transcription [12]. Htt is also believed to have a prosurvival role. Several *in vitro* and *in vivo* studies have demonstrated that expression of the full-length protein protected from a variety of apoptotic stimuli [13–17]. Currently, there is no known cure for HD and existing symptomatic treatments are limited. However, recent advances have identified multiple pathological mechanisms involved in the disease, some of which have now become the focus of therapeutic intervention; progressing toward developing safe and effective therapies which eventually may be successfully translated into clinical trials. These new prospects offer hope for delaying and possibly halting this disease. The aim of this chapter is to describe molecular pathways involved in HD, which offer new targets for the development of therapeutics focusing on the control of excitotoxicity and transcriptional alterations. Indeed, the presence of mhtt induces changes in the activity/levels of different kinases and transcription factors that can impact on cell survival and the selective vulnerability of medium spiny neurons in the striatum.

2. Transcriptional dysregulation in HD and potential therapies

Many studies have provided evidence that transcription may be a major target of mhtt [11, 18–20], as gene dysregulation occurs before the onset of symptoms [21]. Subsequently, a large number of studies showed transcriptional abnormalities in HD [21–23].

Initially, it was shown that mhtt establishes abnormal protein-protein interactions with several nuclear proteins and transcription factors, recruiting them into aggregates and inhibiting their activity [11, 24] (**Figure 1**), as occurs with CREB (cyclic-adenosine monophosphate (cAMP) response element (CRE) binding protein)-binding protein (CBP) [11, 24]. On the other hand, mhtt can also fail to interact with other transcription factors (**Figure 1**), altering their activity which could induce the repression of a large cohort of neuronal-specific genes [25, 26]. Mhtt fails to interact with repressor element-1 transcription/NRSE, so then the complex can translocate from the cytoplasm to the nucleus and bind NRSE repressing a large cohort of neuronal-specific genes, including the brain-derived neurotrophic factor (*bdnf)* [26].

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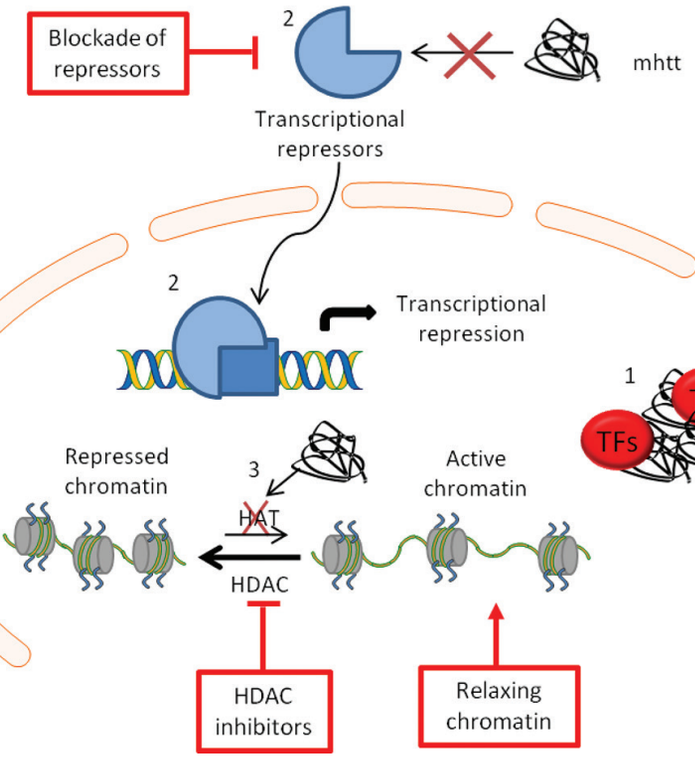

Figure 1. Mechanisms of transcriptional dysregulation in Huntington's disease. Different mechanisms by which mhtt disrupts normal transcriptional activity and possible therapeutic interventions. (1) Mhtt can bind transcription factors (TFs) and sequesters them into mhtt inclusions. (2) Mhtt loses the capacity to bind to transcriptional repressors allowing them to get into the nucleus and represses transcription. (3) Transcription depends on the acetylation status of histones, regulated by activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Mhtt interaction with HATs inhibits proper histone acetylation and causes repression of the transcription. Inhibition of HDAC, compounds promoting the detachment of histones from DNA and molecules targeting transcriptional repressors could represent promising therapeutic targets in HD.

Moreover, htt can also interfere in chromatin structure. Histone acetyltransferases (HATs) favors gene transcription through the opening of chromatin, whereas histone deacetyltransferases (HDACs) repress gene transcription through chromatin condensation. Mhtt binds to the acetyltransferase domain of some factors, such as CBP and p300/CBP-associated factor, blocking their activity [27, 28] (**Figure 1**).

The greatest number of downregulated genes in HD [21] has led to the initiation of new lines of research aimed at testing the ability of a number of compounds to restore gene transcription in mouse models of HD. However, the development of therapies targeting altered transcription faces serious challenges, as no single transcriptional regulator has emerged as a main factor of the disease. Nevertheless, potential therapeutic advances have emerged recently. Some of them include inhibition of HDAC [29, 30], compounds that directly interact with DNA [31], as well as drug-targeting proteins involved in the modulation of transcription [32, 33] (**Figure 1**).

Increasing evidence indicates that CREB is essential for activity-induced gene expression and memory formation [34]. CBP is a CREB-transcriptional coactivator that enhances

CREB-mediated transcription of specific genes [35] and can also act as a HAT allowing gene transcription [36]. Decreased levels of CBP due to sequestration into mhtt aggregates or increased degradation have been associated with striatal neurodegeneration in HD [20, 37]. Moreover, hippocampal-dependent cognitive deficits have been related to a reduced expression of CBP and reduced levels of histone acetylation [38]. Consistent with deficits in striatal and hippocampal CBP function, either CBP overexpression or HDAC inhibition could represent therapeutic strategies to improve transcriptional dysregulation. HDAC inhibitors have been under study for several years (**Figure 1**). Indeed, McCampbell et al. [20, 39] demonstrated that overexpression of CBP reduced polyglutamine-mediated toxicity in neuronal cell culture. CBP overexpression reversed the hypoacetylation phenomenon observed in polyglutamine-expressing cell which reduced cell loss. A similar effect was observed when cells were treated with HDAC inhibitors demonstrating that altered protein acetylation in neurons could play an important role in polyglutamine diseases [39]. Pharmacological treatments using the HDAC inhibitors, sodium butyrate and suberoylanilide hydroxamic acid (SAHA), significantly improve survival, motor performance, modulate transcription and delay neuropathology in the R6/2 transgenic mouse model of HD [29, 40]. In this line, benzamide-type HDAC inhibitor 4b, ameliorated motor and behavioral symptoms and corrected transcriptional abnormalities in R6/2 and N171-82Q transgenic mice [30, 41]. Moreover, 4b treatment induced DNA methylation changes that were inherited to the next generation. First filial generation offspring from drug-treated male HD transgenic mice shows significantly improved HD disease phenotypes compared with the offspring from vehicle-treated male HD transgenic mice [42]. Likewise, administration of the HDAC inhibitor trichostatin A (TSA) rescues hippocampal-dependent recognition memory deficits and increases the transcription of selective CREB/CBP target genes in HdhQ7/Q111 mice [38]. Moreover, more physiological approximations to increase CBP levels and reduce HDAC activity have been recently suggested. Moreno et al. observed that dietary restriction not only induces the expression of *Cbp* in WT and YAC128 mouse model of HD, but also reduces the expression of HDAC. These changes were accompanied by changes in the expression of different neuroprotective genes [43]. **Table 1** lists the different HDAC inhibitors, their specificity and the reported beneficial effects in HD models.

Inhibition of HDAC by 4b was shown not only to affect transcription but also posttranslational modification processes which can influence aggregate formation [41]. On the other hand, inhibition of HDAC4 resulted in a delay in cytoplasmic aggregate formation, together with restored Bdnf transcript levels, rescued neuronal function and improved phenotype in HD mouse models, pointing HDAC4 as a novel strategy for targeting htt aggregation [44]. This potential role of acetylation in mhtt degradation adds importance to HDAC inhibitors as a therapeutic target in HD pathology. These promising results have led to the enrollment of HD patients in clinical trials as HDAC inhibitors are safe and well tolerated [45]. However, these compounds can cause some side effects [46]. It is therefore important to improve our knowledge, to be able to generate effective and specific HDAC inhibitors. Sirtuins belong to the class III of HDAC enzymes and have been a recent focus of therapeutic development for neurodegenerative disease [47]. Interestingly, activation, instead of inhibition of sirtuins, with their ligand resveratrol, was found to be neuroprotective in HD worms [48, 49]. Resveratrol and other potent activators of sirtuins have been used in preclinical trials, but further experiments need to be performed to assess the therapeutic potential of these enzyme targets in HD [50].

HDAC	Compound	Model	Effect	Reference
1,2,3,4,5,7,8 and 9	Valproic acid	N171-82Q mouse and YAC128	↑ Survival Improve motor performance ↑ BDNF and Hsp70 levels	[189]
1,2,3,4,5,7,8 and 9	Sodium butyrate	R6/2 mice	↑ Survival Improve motor performance ↑ Body weight	[40]
1,2,3,4,5,7,8 and 9	Phenyl butyrate	N171-82Q mouse	↑ Survival ↓ Brain atrophy ↑ Proteasome pathway ↓ Caspase activation	[190]
All HDAC	TSA	HdhQ7/Q111	↑ CREB target genes Rescue memory deficits	[38]
All HDAC	SAHA or vorinostat	R6/2 mice	Improve motor performance ↑ BDNF levels ↓ mhtt cortical aggregates	[29, 191]
3	RGFP966 (benzamide)	N171-82Q mouse	Improve motor performance ↓ Striatal degeneration ↓ GFAP	[192]
1 and 3	HDACi 4b	N171-82Q mouse and R6/2 mice	Improve phenotype ↓ mhtt aggregates	[41, 42, 30]
Sirtuin	Nicotinamide	R6/1 mice	↑ BDNF and PGC-1α levels Improve motor performance	[193]
Sirtuin (activation)	Resveratrol	*C. elegans*	Rescue mhtt toxicity	[49]

Table 1. HDAC inhibitors and effects of HDAC inhibition in different models of HD.

Apart from HDAC, other drugs like anthracyclines could produce a beneficial effect in promoting transcription in HD. Anthracyclines are DNA topoisomerase II inhibitors and are broadly used in cancer chemotherapeutics [51]. A novel function of these molecules has recently been identified. Anthracyclines can induce histone eviction from the DNA [31] making it more accessible to the transcriptional machinery and maybe being able to counteract the transcriptional inhibition that occurs in HD. Nevertheless, side effects promoted by these treatments should be taken in high consideration.

When thinking about potential genes downregulated in HD, Bdnf is considered to be one of the principal focuses of attention. BDNF has emerged as the major regulator of neuronal development, synaptic plasticity and neuronal survival and also a key molecular target for drug development in HD [9, 52]. When targeting BDNF deficits in HD, different approximations

have been developed. Several evidence suggest that HDAC inhibitors induce the expression of multiple downstream targets that might work collectively to elicit neuroprotective effects, like neurotrophins. For instance, it was observed that BDNF was induced by treatment with valproic acid, sodium butyrate, or TSA [53, 54]; thus, it is conceivable that restoring BDNF to their normal levels is part of the molecular mechanism underlying the beneficial effects elicited by HDAC inhibition in various HD models. Moreover, inhibition of HDAC6 increases vesicular transport of BDNF in a similar way to the cystamines, compensating for the transport deficit in HD [48, 55]. Focusing on BDNF deficits, identification of compounds or small molecules capable of antagonizing the repressive action of REST/NRSF in gene transcription has begun and represents a rational and promising target to break down with transcriptional repression present in HD [33, 56]. To this aim, Cattaneo's laboratory has developed a cell-based reporter assay to monitor re1 activity in brain cells and identify compounds that specifically upregulate BDNF expression in HD [57]. It has also been identified a benzoimidazole-5-carboxamide derivative that inhibited REST silencing in an RE1-dependent manner, the X5050 compound. X5050 targets REST degradation and produces an upregulation of neuronal genes targeted by REST. This activity was confirmed in human-induced pluripotent stem cells derived from an HD patient and in mice with quinolinate-induced striatal lesions [32].

3. Breaking signaling pathways

Protein kinases/phosphatases regulate most aspects of normal cellular function. Inhibitory or stimulatory actions at these signaling pathways strongly affect neuronal function by altering the phosphorylation state of target molecules and by modulating gene expression [58]. In fact, several kinases and phosphatases have been reported to be altered in HD patients and animal models. Some of these kinases altered in HD are closely related to synaptic plasticity, cell survival and transcriptional regulation such as cAMP-dependent protein kinase (PKA) [59], the kinase Akt [60, 61], the mitogen-activated protein kinases (MAPKs) [62–64] and kinases downstream MAPK pathway [65–67]. Furthermore, also several phosphatases are altered in HD mouse models. Some examples are the phosphatase calcineurin [68, 69], the PH domain and leucine-rich repeat protein phosphatases (PHLPP) [61] and the striatal-enriched protein tyrosine phosphatase (STEP) [61]. Therefore, therapies with potential to modulate cell signaling pathways could provide protection against neurodegeneration [70, 71].

3.1. Kinases and downstream targets

Numerous kinase signaling pathways are thought to contribute to HD pathophysiology. They are known to counter toxic metabolic changes induced by mhtt and help to maintain neuronal survival [72, 73].

3.1.1. Extracellular signal-regulated kinase (ERK)

Transcription of target genes is controlled by a series of transcription factors, which are, in turn, regulated by a number of kinases. Among the kinases implicated in HD, those involving ERK signaling cascades are of particular interest [74]). ERK 1/2 is a strong antiapoptotic and

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prosurvival mediator. Moreover, ERK 1/2 downregulation is linked to neurodegenerative conditions [75, 76]. Recent studies using HD mouse and cellular models provide strong evidence that activation of ERK has the neuroprotective effect, while the specific inhibition of ERK activation enhances cell death [62, 64, 71]. Supporting the neuroprotective role of ERK activation, we have previously reported that enhanced activity of the ERK pathway may participate in the reduced neuronal loss observed after quinolinic acid (QUIN) injection in R6/1 mice (**Figure 2**) [64]. When injected with QUIN, both WT and R6/1 mice display an increase in the phosphorylation of ERK levels, but activation of ERK was more prolonged in resistant R6/1 mice than in susceptible controls [64]. Moreover, inhibition of ERK has been found to block the induction of BDNF-regulated genes [77], thus implicating this pathway as an important regulator of BDNF-induced transcription. For that reason, the ERK pathway has been investigated as a potential neuroprotective modulator of HD pathology [62, 64]. In this context, it has been suggested that reduced levels of ERK in the cortex of HD models can lead to increased cell dead and reduction in the expression of BDNF. Then, less BDNF is available to striatal neurons, which activates, in response, compensatory mechanisms increasing the expression of ERK (**Figure 2**) [62].

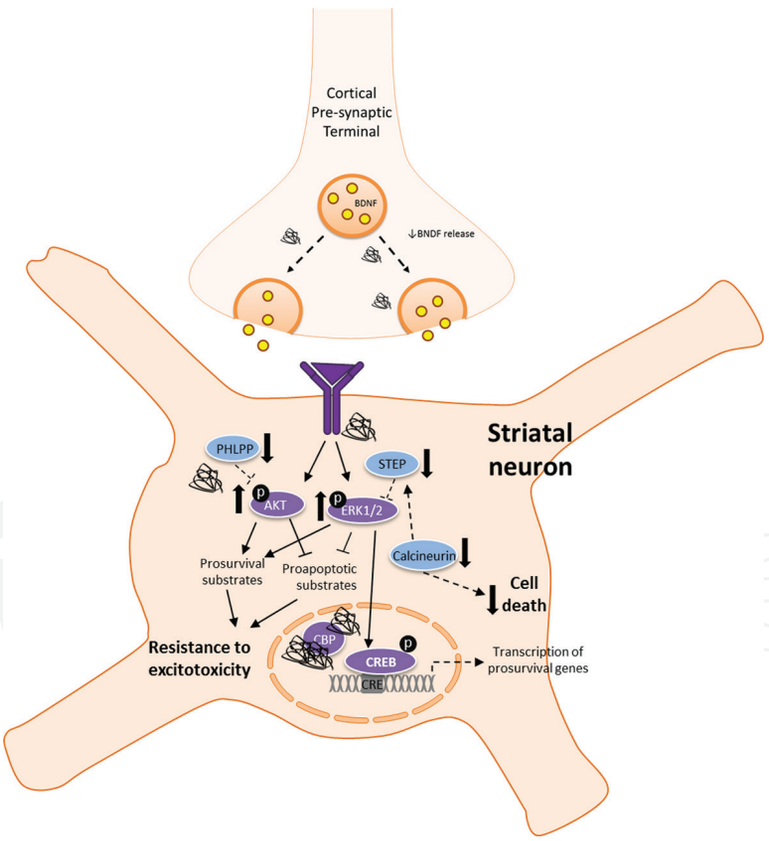

Figure 2. Proposed compensatory mechanism activated in the presence of mhtt in response to reduced cell death and increased resistance to excitotoxicity in HD mouse models. Decreased BDNF delivery from cortical neurons activates compensatory mechanism in striatal neurons by increasing ERK phosphorylation. Reduced STEP and calcineurin activity contribute to the maintenance of ERK activity. PHLPP levels are downregulated which contribute to the increased activation of Akt. Both ERK and Akt are proposed as a possible mechanisms related to the increase resistance to excitotoxicity observed in mouse models of HD, by activating prosurvival pathways (like CREB) and by the inactivation of proapoptotic factors.

Drugs, targeting the ERK pathway, may provide a basis for developing disease modifying therapeutic interventions for HD. Neuroprotective compounds identified using a neuronal cell culture model of HD in combination with a library of 1040 biologically active compounds were shown to prevent cell death by activation of ERK and Akt signaling, with the ERK pathway playing the major role [78]. More recently, results from another screening showed that pizotifen caused transient ERK activation in an immortalized striatal cell line expressing mhtt (STHdhQ111/Q111) and inhibition of ERK activation increases cell death in this *in vitro* model. In addition, R6/2 mouse treated with pizotifen showed increased activation of ERK in the striatum, reduced neurodegeneration and significantly enhanced motor performance [79]. To further test the hypothesis that pharmacological activation of ERK might be protective in HD, a polyphenol (fisetin), which was previously shown to activate the Ras-ERK cascade [80], was tested in three different models of HD: PC12 cells, *Drosophila* expressing mhtt and the R6/2 mouse model of HD [71]. Fisetin was able to reduce the impact of mhtt expression in each model. Likewise, the previously discussed resveratrol, a related polyphenol, could also activate ERK and was also protective in HD models [71]. Also activation of cannabinoid receptor type 1 protects PC12 and STHdhQ111/111 cells from mhtt-induced cell death in an ERK-dependent manner [81, 82]. Additionally, different antipsychotic drugs, such as clozapine and olanzapine, also promote and cause an increase in ERK phosphorylation [83].

3.1.2. p90 ribosomal s6 kinase (Rsk)

These aforementioned studies suggest that pharmacological intervention at the level of ERK activation or downstream ERK may be an appropriate approach in HD therapy. Most common kinases phosphorylated by ERK1/2 include Rsk and the mitogen- and stress-activated protein kinases (MSK) [84, 85]. In this context, we have reported changes in the expression of Rsk related to the presence of motor symptoms in HD. Meanwhile, an increase in Rsk protein levels was observed in the striatum of HdhQ111/Q111 and R6/1 mice at presymptomatic stages of the disease [67], they were downregulated in the same models when motor symptoms were present [65], indicating that Rsk downregulation is associated with the presence of motor impairment, the main clinical feature in HD [2]. Similarly, Rsk levels were increased in STHdhQ111/Q111 cells [67], but strongly decreased in postmortem caudal and putamen samples from HD patients [65]. Knockdown experiments indicated that Rsk activity exerted a protective effect against mhtt-induced cell death in STHdhQ7/Q7 cells transfected with mhtt and overexpression of Rsk in R6/1 mice at the onset of motor sympt oms rescues motor impairment, enhanced expression of synaptic markers and increased expression of genes related to synaptic plasticity, such as cfos and egr1 [65, 67]. We also observed that downregulation of Rsk was due, at least in part, to the depletion of BDNF in HD striatum suggesting that Rsk could be a downstream effector of BDNF function. These results place Rsk as a new element regulating striatal alteration that leads to motor phenotype in HD, making it a good target for neuroprotective therapies in HD.

Different drugs could be used to increase Rsk activation. As a downstream target of ERK [84], activation of ERK pathway could result in an activation of Rsk as an effector. In this line,

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previously proposed drugs could be also useful in promoting Rsk activation. As for ERK activation, clozapine treatment also increases levels Rsk phosphorylation in the cortex and striatum in an ERK-dependent manner, meanwhile Rsk activation by olanzapine and haloperidol is not concomitant with ERK signaling [83]. Although the Rsk pathway can be activated by increased ERK activity, more research focusing on specific drugs targeting Rsk should be carried out.

3.1.3. Activation of transcription factors: CREB and Elk-1

ERK 1/2 cannot only phosphorylate different kinases, but also some transcription factors such as CREB (**Figure 2**) [86, 87]. But CREB can also be phosphorylated by other kinases as Rsk [88–90] and PKA [91]. Once activated, CREB interacts with CBP and CREB-mediated gene expression is induced [92]. CREB is a widely expressed transcription factor known to mediate stimulus-dependent expression of genes critical for plasticity, growth and survival of neurons [93]. Activation of CREB is necessary for synaptic transmission [94] and CREB-mediated gene expression is sufficient for the survival of multiple neuronal subtypes [95, 96]. CREB may exert this prosurvival effect by regulating the transcription of prosurvival factors, such as *Bcl-2* and *Bdnf* [97].

Different studies observed that CREB signaling is compromised in different mouse and cellular models of HD and in human HD samples, where the expression of mhtt induces aggregation of its coactivator CBP (**Figure 2**) [11, 28, 98], reduces the levels of cAMP [72] and downregulates CRE-mediated transcription of numerous genes [19]. This decrease in CREB-induced transcriptional activity is believed to contribute to HD pathogenesis [97]. One of the genes regulated by CREB is *Bdnf* [97]. Reduced CREB-dependent transcription of *Bdnf* is a robust feature of HD pathology. In human samples, BDNF protein and mRNA levels are decreased in the frontoparietal cortex [99]. Reduced levels of cortical and striatal BDNF have also been reported in multiple mouse models of HD, including R6, N171-82Q, Hdh and YAC-72 lines [17, 19].

The beneficial effect of restoring CREB phosphorylation has been observed by us and others in both excitotoxic and genetic mouse models of HD [100, 101]; thus pathways targeting CREB activation can also lead to an increase in BDNF together with cognitive improvements in HD models [102]. Furthermore, regulation of possible downstream effectors of BDNF function also shows clearly motor improvements together with a restoration of CREB-mediated gene transcription and expression of synaptic markers in R6/1 mouse model of HD [102, 103].

ERK1/2 can also phosphorylate the transcription factor Elk-1, which, together with CREB, is considered to be one of the most important transcription factors in neurons [104, 105]. In the cortex, Elk-1 is activated after QUIN-induced lesion and has the capacity to prevent excitotoxic cell death [106]. Increased phosphorylation of ERK-activated transcription factors, such as Elk1, has been correlated with increased ERK phosphorylation in R6 striatum [107, 108]. However, the expression of *c-fos* and *egr-2*, two genes regulated by Elk-1 [109], was downregulated in these mice and in STHdhQ111/111 [108]. This downregulation was

correlated to a strong decrease in the expression and the phosphorylation of MSK-1 in R6/2 mice [107], a kinase that phosphorylates the histone H3 and promotes the expression of c-Fos [110]. Both MSK-1 and Elk-1 inhibition induced mhtt-specific cell death, with no effect on wild-type cells. Moreover, overexpression of MSK-1 restores c-fos expression and protects striatal cells against neurodegeneration induced by mhtt expression, showing a neuroprotective role of this protein in HD [107]. Reinforcing this hypothesis, the inhibition of Elk-1 in STHdhQ111/Q111, but not in STHdhQ7/Q7 cells, resulted in a decrease of *c-Fos* and *Egr-2* mRNA levels [108].

3.2. Regulating cAMP

To increase activation of CREB, it is also important to take into account the levels of cAMP. The major kinase that is in charge of CREB activation is PKA, which in turn needs cAMP to be activated [91]. The cAMP signaling pathway has a key role in the neurobiology of learning and memory and therefore could serve as a target for cognitive enhancers and to reduce memory deficits in HD. In support to this idea: (1) reduced levels of cAMP were reported in the cerebral spinal fluid of symptomatic HD patients [111] and (2) forskolin, which stimulates adenylyl cyclases to produce cAMP from ATP, was able to ameliorate mhtt-induced phenotypes in PC12 cells [112]. Reduced levels of cAMP were also observed in STHdhQ111/Q111 striatal cells together with a decreased nuclear localization of CBP [72]. Activation of cAMP/PKA signaling by forskolin restored a nuclear CBP expression in the mutant striatal cells [72] and could partially rescue the loss of neurite outgrowth and cell death due to reduced CRE-mediated transcriptional activity [112].

3.2.1. Role of phosphodiesterases

Different studies [113] suggest that phosphodiesterase (PDE) inhibitors might be good candidates for enhancing CREB activation. PDE inhibitors prevent the breakdown of cAMP to 5′-AMP, prolonging the activation of protein kinases that promote phosphorylation of CREB [114]. It has been shown that the expression of different PDEs is altered in the striatum [115, 116] and hippocampus [38] of HD mouse models. The use of drugs that maintains CREB phosphorylated, like the specific PDE4 and 10 inhibitors rolipram and T10, decreases striatal cell loss after the injection of QUIN in an excitotoxic model of HD [100, 117]. Following this research, the same group reported that administration of rolipram in R6/2 mice enhanced the expression of both phosphorylated CREB and BDNF in striatal neurons and ameliorated neurodegeneration, decreased mhtt inclusions preventing the sequestration of CBP, reduced microglia activation and rescue motor function [118, 119]. Likewise, beneficial effects of PDE inhibition on cognitive function were also observed in the hippocampus of HD mouse model [101]. We recently observed that papaverine, which is considerably selective for PDE10A, could improve spatial and object recognition memories in R6/1 mice and significantly increase phosphorylation of CREB and cAMP levels in the hippocampus [101].

Although PDE10A has been proposed as a therapeutic target for HD based on the observation that pharmacologic inhibition of PDE10A in transgenic HD mice significantly

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improved behavioral and neuropathologic abnormalities [101, 119], some conflicts appear when focusing on HD patients. Earlier work had shown that striatal PDE10A levels in HD mice already decline to minimal levels before onset of motor symptoms [115, 116]. In humans, decreased PDE10A levels were found in postmortem striatal tissue [115] and in PET studies from Huntington's disease patients with significant striatal atrophy [120] and premanifest Huntington's disease gene carriers [121, 122]. It is unclear how the alteration of PDE10A expression is related to the neuropathological out-standing networks. Depletion of PDE10A in HD striatum would at first sight seem hard to reconcile with a beneficial effect of PDE10A inhibitors in HD. However, a recent study reported a dramatic increase in PDE10A levels in the perikarya of striatal medium spiny neurons [123] and moreover, we did not observe changes in the expression of this protein in the hippocampus of R6/1 mice compared to controls [101]. Taking together all these results, it is important to determine whether PDE10A levels are affected in HD patients and in *in vivo* models of HD in the different brain areas and if these alterations are functionally significant in order to choose PDE10A inhibitors for use in clinical trials in HD.

3.2.2. Role of G protein couple receptors

G protein-coupled receptors (GPCRs) constituted a large family of receptors coupled to G proteins that activated two main signaling pathways: cAMP and phosphatidylinositol pathways [124]. GPCRs are involved in many diseases and are also the target of approximately 40% of all modern medicinal drugs [125].

In order to increase the levels of cAMP, molecules targeting GPCRs could be useful. Depending on the subunit of G protein that the receptors are coupled, they can activate ($G\alpha_s$) or inactivate ($G\alpha_{i/o}$) adenylate cyclases [125]. Therefore, drugs targeting the activation of $G\alpha_s$-coupled receptors or the inhibition of $G\alpha_{i/o}$-coupled receptors would result in an increase in the levels of cAMP and probably in turn an increase in the activation of CREB. In line with this idea, we have recently demonstrated that fingolimod (FTY720) treatment improves synaptic plasticity and memory in the R6/1 mouse model of HD, through regulation of BDNF signaling [103]. FTY720 targets GPCRs $G\alpha_{i/o}$ SP1 receptor and inhibits it [126]. Between the different effects of SP1 receptor activation there is a reduction on cAMP as $G\alpha_{i/o}$ inhibits adenylate cyclases [127]. Therefore, inhibition of SP1 receptor could result in increased levels of cAMP. Indeed, FTY720 treatment increased cAMP levels and promoted phosphorylation of CREB in the hippocampus of R6/1 mice [103].

Another approximation to increase cAMP levels is inducing the activation of $G\alpha_s$-coupled receptor. Prostaglandin (PG) receptors are well-known GPCRs [128]. EP2 prostaglandin receptor is known to stimulate cAMP and activation of the transcription factor CREB [129]. EP2 receptor activation is associated with neuroprotection and hippocampal-dependent synaptic plasticity [130] and can lead to the induction of BDNF [102, 131]. In terms of HD, we have recently shown that chronic treatment of R6/1 mice with misoprostol, an EP2 receptor agonist, ameliorated hippocampal-dependent long-term memory deficits in these animals [102]. Importantly, misoprostol treatment promoted the expression of hippocampal BDNF and increased cAMP levels, together with a recovery in the expression of different synaptic

markers. All these data suggest that mhtt leads to alterations of CRE-mediated gene transcription and reinforce the idea of a beneficial effect of increasing gene expression mediated by CREB could be a good therapeutic approach in HD.

4. Cycle of neurotoxicity

Ultimately, excitotoxicity contributes to neuronal degeneration in many acute as well as chronic central nervous system diseases [132]. Polyglutamine expansion produces a hyperactivation of N-methyl-D-aspartate receptor (NMDAR and kainite receptors) [133]; stabilizes NMDA receptors in the postsynaptic membrane [134]; inhibits the uptake and release of glutamate at the synapses [135]; and can also sensitize the inositol (1,4,5)-triphosphate receptor type 1 located in the membrane of the endoplasmatic reticulum [136]. In addition, mhtt can contribute to excitotoxicity by decreasing the expression of the major astroglial glutamate transporter (GLT-1) [137], which reduces the glutamate uptake (**Figure 3**) [138]. All these alterations promote glutamate-mediated excitotoxicity by a massive increase of intracellular Ca^{2+}, which affect the calcium homeostatic mechanism [139] and lead to deleterious consequences. Imbalance in the calcium homeostasis has been previously reported in different HD mice [140–142] that it is in agreement with consistent changes in the expression levels of many Ca^{2+} signaling proteins [143]. Moreover, different proteins involved in neuronal Ca^{2+} signaling have been proposed as attractive targets for developing therapies for HD [144]. Excitotoxicity and mhtt expression also promote the activation/inhibition of several pathways regulated by different kinases and phosphatases [74, 145]. In the following lines, we will review some of the mechanism implicated in this excitotoxic process that occurs in HD, together with the prosurvival mechanism activated in HD brains to fight against this process. Moreover, we will discuss about potential and new state-of-the-art therapies to fight neurodegeneration and reduce excitotoxicity.

4.1. Fighting glutamate

4.1.1. NMDA receptors

Alterations in proteins involved in glutamatergic signaling have been reported in mouse models of HD [146, 147]. Since the main hypothesis underlying striatal neurodegeneration in HD has been excitotoxicity, due in part to increase in glutamate release, NMDA receptors were the first glutamate receptors studied. At early stages of the disease, when cognitive and plasticity alterations are detected, no changes in the protein levels of any NMDAR subunit are observed in the striatum and hippocampus of HD mouse models [148–150]. Conversely, HD mouse models do not respond to intrastriatal NMDAR agonists (**Figure 2**) [141, 149, 151]; which support the idea that signaling downstream the receptor is affected in HD [152] and contributes to synaptic plasticity impairment. Not only the expression of these receptors is important, but also their location. Stimulation of synaptic NMDAR conveys the synaptic activity-driven activation of the survival-signaling protein ERK and triggers an increase in nuclear calcium, leading to the activation of the transcription factor CREB and the production of the survival-promoting protein BDNF [153]. In contrast, global or extrasynaptic NMDAR

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stimulation decreases ERK and CREB activation and BDNF production, promoting cell death (**Figure 3**) [153].

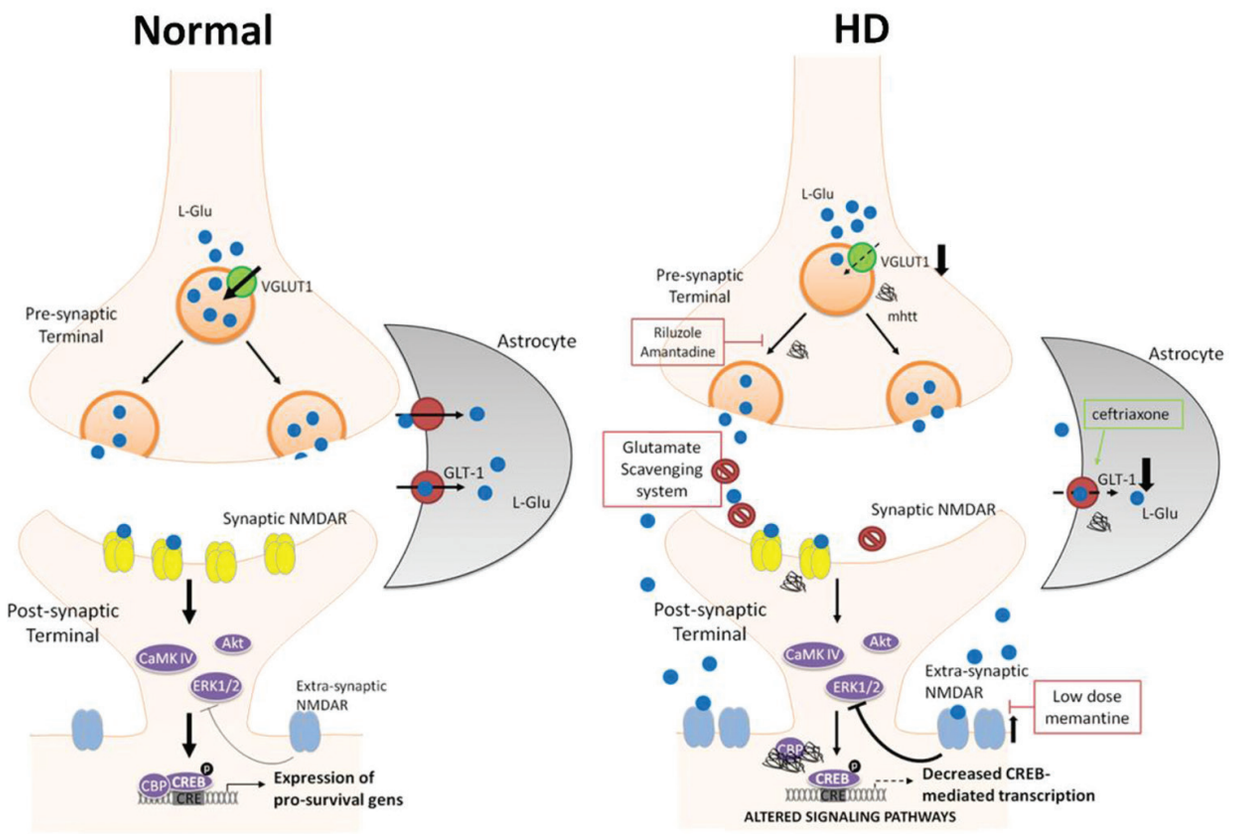

Figure 3. Changes in glutamate regulatory system in the presence of mutant huntingtin. In the presence of mhtt, there is an increase in the levels of glutamate together with an imbalance in the levels of synaptic and extrasynaptic NMDAR. Increased activation of extrasynaptic NMDAR leads to neuronal death by inhibition of ERK and the activation of the transcription factor CREB. Moreover, there is a downregulation/dysfunction of the glial glutamate transporter (GLT-1), which leads to an increase in glutamate at the synaptic cleft. Reduced VgluT1 transporter also affects glutamate recruitment into the synaptic vesicles contributing to deficits in synaptic transmission. Different drugs to modulate these mechanisms are shown.

4.1.2. Glutamate transporters

On the other hand, not only glutamate receptors but also glutamate transporters are altered in HD, such as the vesicular glutamate transporter 1 (VGluT1) [154] that contributes to the imbalance of glutamate in neurons could play a role in cell dysfunction in HD. Presynaptic expression of VGluT1 contributes to the proper expression of other synaptic proteins and reduced levels of this glutamate transporter, as occurs in the striatum of R6 mice [154, 155], can disrupt cortico-striatal synaptic transmission [154, 156]. The expression of glutamate transporters is also altered in glial cells. GLT-1 is the major molecule responsible for the clearing of glutamate from synaptic cleft [157], making it an attractive therapeutic target. Reduced mRNA levels of GLT-1 and decreased glutamate uptake have been described in HD postmortem brains [22] as well as in R6/2 mice [137], suggesting decreased glutamate removal at synapses in HD.

Moreover, alterations in the palmitoylation of this transporter were detected, which can alter its function [158]. In addition, strategies aiming at the upregulation of GLT-1, like ceftriaxone treatment [159], attenuate some behavioral alterations in the R6/2 mice model (**Figure 3**) [160].

4.1.3. Strategies to decrease glutamate excitotoxicity

Drugs inhibiting glutamate neurotransmission [161, 162], glutamate antagonists [163] and blockade of NMDAR [164, 165] have been used for the first time to attempt for blocking the excess of glutamate at the synapse. Riluzole and amantadine are two antiglutamatergic therapies that have been investigated in rigorous trials in HD [162]. Moreover, riluzole is already marketed for the treatment of amyotrophic lateral sclerosis. Riluzole is a drug that inhibits glutamate release and the current evoked by the stimulation of excitatory amino acid receptors [166]. Treatment of R6/2 mice with riluzole showed positive effects in reducing the progression of neurological abnormalities in this mice model of HD [161]. Specific blockade of NMDAR has been also extensively studied, but accuracy has to be taken into account. Drugs like memantine are shown to inhibit NMDAR [164, 165, 167], but their beneficial effects depend on the right dose. At high concentrations, memantine blocks synaptic and extrasynaptic NMDAR, inducing neuronal death, as NMDAR once at the synapse can activate prosurvival pathways [167]. When used in a lower dose, memantine can specifically block extrasynaptic NMDAR producing a potential therapeutic effect in mouse models of HD [164, 165]. A new technique to combat the glutamate exposure developed recently is the blood glutamate scavenging system (Braintact) [168, 169]. Braintact is developing a platform solution that overcomes the excess glutamate level in blood by using a new approach developing drugs that remain in the blood circulation and boost a natural mechanism that reduces glutamate levels in the bloodstream and leads to lowering of glutamate concentrations in the brain (**Figure 3**).

Although common strategy is to treat with NMDA glutamate antagonist for reducing excitotoxicity, their clinical viability has not been proven [162]. Some agents showed efficacy in terms of motor dysfunction, but no treatment has been identified as appropriated. Moreover, many present treatments considerable side effects or effects in cognitive improvement were not even considered. Therefore, there is a need to continue the research on antiglutamatergic drugs in HD for the treatment of excitotoxicity. Also cellular pathways and drugs trying to enhance or inhibit these cellular pathways related to survival will be discussed further in this section.

4.2. Role of kinases

Increasing our understanding on the pathways behind the excitotoxic events and neuronal dead occurring in HD is necessary in order to identify targets downstream glutamate receptors cascade that may represent useful therapeutic strategies do reduce or halt neuronal dysfunction. Alterations in numerous signal transduction pathways and aberrant activity of specific kinases have been identified in multiple cell and mouse models of HD, as well as in human HD brain. Unbalanced activities within these pathways provide a potential mechanism for many of the pathological events associated with HD. Aberrant kinase signaling

regulation in HD has a wide range of effects on multiple pro and antiapoptotic kinases, resulting in the activation of compensatory mechanisms to fight excitotoxicity or prodeath mechanisms triggered by excitotoxicity [74].

4.2.1. ERK

The ERK pathway is a strong mediator of antiapoptotic and prosurvival signaling. Although both protective and deleterious roles have been proposed for ERK activation in neuronal cells [170], recent studies using mhtt-expressing cells provide strong evidence that activation of ERK is neuroprotective, while specific inhibition of ERK enhances cell death [62]. The phosphorylation of ERK activates neuroprotective factors [62, 107] and inactivates proapoptotic mediators by phosphorylation [171]. Data derived from cell culture experiments showed that ERK is activated in response to mhtt and increases cell survival [62]. The ERK pathway is also upregulated in several transgenic animal models of HD. Significant ERK activation was observed in the striatum of R6/1 and R6/2 mouse (**Figure 2**) [64, 107]. The timing of ERK activation in HD mice supports the hypothesis that the ERK pathway might not be involved in a primary pathological process, but rather that it is a compensatory mechanism activated in response to mhtt and could participate in delaying striatal cell death because R6 mice show no significant cell loss [172]. Accordingly and as previously mentioned, ERK pathway activation in response to mhtt may participate in the reduced neuronal loss observed after QUIN injection in R6/1 mice (**Figure 2**) [64]. Moreover, changes in ERK levels and activation can modulate transcription in HD what triggers, in part, the neuroprotective role of ERK mediated by its downstream effectors.

Checking on the ERK mechanism along the different sections, we can conclude that ERK has a prosurvival role in the presence of mhtt, which can be achieved by the activation/inactivation of different proteins promoting survival and transcriptional regulation of protective genes. Therefore, ERK activation might provide a novel therapeutic approach to prevent neuronal dysfunction in HD.

4.2.2. AKT

The AKT signaling pathway has been extensively characterize in models of HD and its activation is considered to be antiapoptotic and neuroprotective in different models of acute and chronic neurodegeneration [72, 173]. A primary mechanism of AKT-mediated neuroprotection is by its phosphorylation and inactivation of proapoptotic machinery [61, 72, 174].

In HD, the AKT pathway has been proposed as a crucial neuroprotective pathway, because it is one of the serine/threonine kinases that phosphorylate Ser421 of mhtt, attenuating its toxicity [174]. Activation of the AKT pathway has been determined in several cells and mouse models of HD. Increased levels of phosphorylated AKT were observed in the striatum of full-length and exon-1 mouse models and also in striatal cells expression mhtt [61, 72]. We observed that enhanced AKT signaling correlates with decreased expression of PH domain leucine-rich repeat protein phosphatase (PHLPP), a phosphatase that dephosphorylates AKT (**Figure 2**) [61]. PHLPP1 protein levels were reduced in the striatum of HdhQ111/Q111,

R6 and Tet/HD94 mouse models of HD as well as in the putamen of HD patients. In addition, we showed that intrastriatal QUIN injection in R6/1, but not in control, mice upregulates the phosphorylated AKT protein levels, which can contribute to the absence of striatal cell death observed in these animals after an excitotoxic injury [61, 151]. This increase in the phosphorylated AKT is still detected at later stages of the neurodegenerative process, offering together with phospho-ERK, a mechanistic explanation to the small amount of neuronal death observed in these HD models (**Figure 2**). In accordance with our results, AKT prevents neuronal death induced by mhtt [174] and increasing AKT expression has beneficial effects on Drosophila models of HD [175]. Thus, on the basis of these results, it is not too daring to suggest that use of therapeutic approaches focusing on AKT prosurvival pathway could delay neuronal death in HD.

4.3. Role of phosphatases

Concomitantly to kinases, several Ser/Thr protein phosphatases activate to counteract the effect of kinases. They are of particular interest in this respect as several phosphatases are altered in HD mouse models [145] and, most importantly, in the caudate/putamen of HD patients [176]. Many of these altered phosphatases in HD play a role in memory and plasticity phenomena and then this imbalance likely contributes to synaptic alterations and cognitive impairment in HD.

4.3.1. Striatal-enriched protein tyrosine phosphatase (STEP)

Striatal-enriched protein tyrosine phosphatase (STEP) is a brain-specific phosphatase involved in neuronal signal transduction. STEP is enriched in the striatum and plays an important role in synaptic plasticity through the opposition to synaptic strengthening [177]. We and others recently reported reduced STEP protein levels in the striatum and increased inactivity in different HD mouse models [64]. Reduced STEP activity in HD can lead to an increase in the activity of the NMDAR [178]. Additionally, STEP has been implicated in susceptibility to cell death through the modulation of ERK1/2 signaling pathway, as we have previously reviewed [64]. The STEP pathway is severely downregulated in the presence of mhtt and participates in compensatory mechanisms activated by striatal neurons that lead to resistance to excitotoxicity (**Figure 2**) [64]. When injected with QA, R6/2 mice displayed a greater increase in STEP inactivation compared to WT together with decreased neuronal death, but overexpression of STEP in R6/2 animals increased QUIN-induced cell death [64]. Moreover, it has been suggested that an increase in STEP activation at the synapse in YAC128 mice together with calpain activation contributes to altered NMDAR localization (increased extrasynaptic localization of GluN2B receptors) and increases excitotoxicity [179].

In order to select STEP as a potential therapeutic target in HD different aspects have to be taken in consideration. In HD, STEP downregulation is initially neuroprotective to mhtt-induced glutamate excitotoxicity [64], but a decrease in synaptic plasticity and cognitive impairment still occurs. On the other hand, increased STEP activation produces alterations

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in the trafficking of NMDA and AMPA receptors, dephosphorylating them and producing an excessive internalization of these receptors which decreases synaptic plasticity [177]. On the basis of this evidence, a suitable expression of STEP might be a good therapeutic strategy in different neurodegenerative diseases. Pharmacological inhibition of STEP by a recently discovered inhibitor, TC-2153, reversed cognitive deficits in a mouse model of Alzheimer's disease, where STEP levels are increased [180]. But the effect of STEP activation is still not clear in a model like R6/1 mice, where STEP levels are reduced.

4.3.2. Calcineurin

The role of protein phosphatases in the cascade of events triggered during excitotoxic cell death has not been extensively studied, but some protein phosphatases, such as Ca^{2+}-dependent calcineurin, were found to contribute to excitotoxicity (because its inhibition is neuroprotective [181]). Calcineurin is a ser/thr protein phosphatase activated physiologically by calcium/calmodulin and it is highly expressed in the brain [182]. Calcineurin plays an important role in synaptic plasticity and learning and memory [183]. Interestingly, it is enriched in MSNs [182] and thus variations in its expression levels/activity can seriously alter their function. Some studies have shown that activation of calcineurin promotes apoptosis and pharmacological inhibition of calcineurin reduces the activation of excitotoxic molecules and decreases cell death after different toxic insults [184, 185].

Calcineurin levels are reduced in R6 and Tet-HD94 mice striatum [19, 69] and lower calcineurin activity has been shown in the striatum of YAC128 mice at 12 months of age (**Figure 2**) [186]. Inhibition of calcineurin with FK-506 drastically reduced cell death in an excitotoxic model of HD [69]. Moreover, calcineurin levels were downregulated during the progression of the disease in R6/1 mice and the induction of calcineurin after QUIN injection in these excitotoxicity-resistant mice [151] was lower than that in control animals [69]. These finding suggested that altered calcineurin activity contributes to the excitotoxic resistance observed in R6/1 mouse models (**Figure 2**). On the contrary, in HdhQ111/Q111 mice calcineurin activity was shown to be increased in the cortex [187] and higher expression and activity of calcineurin was also observed in STHdhQ111/111 cells [68]. These cells presented increased vulnerability to NMDAR stimulation, which was associated with higher calcineurin protein levels and activity [68] (**Table 2**).

However, controversial data have been reported about the role of calcineurin in HD. Although decreased calcineurin activity increases resistance to excitotoxicity [69] and high levels of calcineurin increase mhtt toxicity [68, 186, 187], it has been shown that inhibitors of calcineurin accelerates the neurological phenotype in R6/2 mice [188], which are resistant to excitotoxicity [151]. Moreover, decreased calcineurin activity appears when pathological symptoms are present in these animals and not in presymptomatic stages [69], suggesting a dual role of calcineurin during the progression of the disease and a possible involvement of this protein in the striatal neuronal dysfunction. Therefore, like it is occurring with STEP, it is reasonable to suggest that a therapy targeted to maintain normal levels of calcineurin could represent a good approach to delay neuronal dysfunction in HD.

Model		Calcineurin change	Age	Susceptibility to excitotoxicity	Age	Reference
Cellular models	STHdhQ7/Q111	Increased		Increased		[68]
	YAC128 primary cortical neurons	Not reported		Increased		[186]
	YAC72 primary striatal neurons	Not reported		Increased		[194]
Exon-1 mouse models	R6/1	Decreased	16 weeks	Decreased	8 weeks	[69, 141]
	R6/1: BDNF$^{-/+}$	Decreased	12 weeks	Decreased	12 weeks	[69, 150]
	R6/2	Decreased	10 weeks and earlier	Decreased	3 weeks	[141, 195]
	Tet/HD94	Decreased	22 months	Not reported		[69]
	N171-82Q	Not reported		Decreased	15 weeks	[149]
Full-length models	YAC72	Not reported		Increased	6 and 10 months	[194]
	YAC128	No change	3 months	Increased	1.3–6 months	[186, 196]
		Reduced	12 months	Decreased	10–18 months	[186, 21]
Knock-in models	HdhQ111/Q111	Increased	12 months	Not reported		[187]
	HdhQ7/Q111	Increased	12 months	Not reported		
	FVB/CAG140$^{-/+}$	Not reported		Decreased	12 months	[197]
	FVB/CAG140$^{+/+}$	Not reported		Decreased	4 months	
	C57Bl/6/ CAG140$^{-/+}$	Not reported		Decreased	4 months	
	C57Bl/6/ CAG140$^{+/+}$	Not reported		Decreased	4 months	
Human samples		Decreased				[69]

Table 2. Changes in calcineurin levels and resistance to excitotoxicity in different HD mouse and cellular models.

5. Discussion

As we have seen in this chapter, many pathways are interconnected and related between them, even making a "cycle." This "cycle" could be used for developing therapies that maybe targeting one or several proteins which can modify different pathogenic events. As an example, when increasing activation of some kinases, excitotoxicity can be counteracted and at the same time promote the activation of transcription factors that can burst transcription. Then, different expressed genes can contribute to further fight against excitotoxicity completing the "cycle." But, the development of therapies targeting altered transcription or modulation of cell signaling pathways face difficult challenges as, nowadays, no single transcriptional regulator has been identified as a main player of the disease. Nevertheless, potential therapeutic advances have recently emerged. Some of them include the inhibition of HDAC, compounds

that directly interact with DNA and drugs targeting proteins involved in the modulation of transcription, representing promising therapies to protect against neurodegeneration. Also drugs inhibiting glutamate/NMDAR neurotransmission or glutamate scavenging systems have been used as a first attempt to block the excess of glutamate at the synapse. Altogether, these findings show us that although HD is a disease cause by a single gene mutation, multi-factorial drug treatments could be applied in order to reduce or delay the symptoms and open a wide spectrum of research fields to reach the final cure to this de

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Author details

Marta Anglada-Huguet[1,2,3,†], Laura Vidal-Sancho[1,2,3,4], Nuria Cabezas-Llobet[4], Jordi Alberch[1,2,3] and Xavier Xifró[1,2,3,4]*

*Address all correspondence to: xavier.xifro@udg.edu

1 Department of Cellular Biology, Immunology and Neuroscience, Faculty of Medicine, University of Barcelona, Barcelona, Spain

2 Institut of Biomedical Research August Pi i Sunyer (IDIBAPS), Barcelona, Spain

3 Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Spain

4 TargetsLab, Department of Medical Science, Faculty of Medicine University of Girona, Spain

† Present address: German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

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