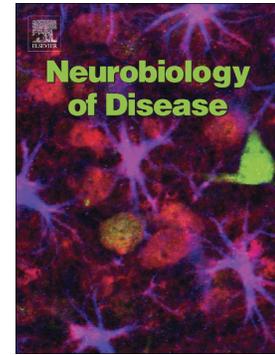


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Repeat Disorders

Why Woody got the blues: The neurobiology of depression in Huntington's disease

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Abstract

Huntington's disease (HD) is an extraordinary disorder that usually strikes when individuals are in the prime of their lives, as was the case for the influential 20th century musician Woody Guthrie. HD demonstrates the exceptionally fine line between life and death in such 'genetic diseases', as the only difference between those who suffer horribly and die slowly of this disease is often just a handful of extra tandem repeats (beyond the normal polymorphic range) in a genome that constitutes over 3 billion paired nucleotides of DNA. Furthermore, HD presents as a complex and heterogenous combination of psychiatric, cognitive and motor symptoms, so can appear as an unholy trinity of 'three disorders in one'. The autosomal dominant nature of the disorder is also extremely challenging for affected families, as a 'flip of a coin' dictates which children inherit the mutation from their affected parent, and the gene-negative family members bear the burden of caring for the other half of the family that is affected. In this review, we will focus on one of the earliest, and most devastating,

symptoms associated with HD, depression, which has been reported to affect approximately half of gene-positive HD family members. We will discuss the pathogenesis of HD, and depressive symptoms in particular, including molecular and cellular mechanisms, and potential genetic and environmental modifiers. This expanding understanding of HD pathogenesis may not only lead to novel therapeutic options for HD families, but may also provide insights into depression in the wider population, which has the greatest burden of disease of any disorder and an enormous unmet need for new therapies.

Keywords: Huntington's disease, affective disorders, depression, mood disorders, polyglutamine, psychiatric disorders, tandem repeats, tandem repeat disorder

1. Introduction

Huntington's disease (HD), which was first described by George Huntington (Huntington, 1872), involves a triad of cognitive, psychiatric and motor symptoms. HD is caused by a trinucleotide (CAG) repeat expansion ('genetic stutter') encoding an extended polyglutamine tract in the huntingtin protein. HD is one of the most common of an extensive group of tandem repeat disorders, many of which are also neurodegenerative diseases, including a large collection of ataxias (Hannan, 2018a).

The symptoms of HD are associated with neurodegeneration, most strikingly in the striatum and cerebral cortex, but also occurring in various other brain regions (Bates et al., 2015). Furthermore, the pathology of HD is not exclusively restricted to the brain and can also affect other parts of the body. The mechanisms mediating the selective vulnerability of particular cell populations in the brain and other tissues have not been fully elucidated. One challenge in understanding a complex disease such as HD, is to integrate information at molecular, cellular, circuit and systems levels. It has recently been proposed that HD is not

only a synaptopathy, but also a circuitopathy (Hannan, 2018b). A circuitopathy is defined as a disorder of neural circuits. We will discuss below some key neural circuits which have been shown to be dysfunctional in HD, and their potential relevance to the depressive symptoms in particular.

HD also exhibits temporal specificity, mediated by CAG repeat length as well as genetic and environmental modifiers (Mo et al., 2015). As for all neurodegenerative diseases, age is a major risk factor, and thus understanding how brain aging interacts with HD pathogenesis may provide novel therapeutic insights (Baskota et al., 2019).

In over a quarter of a century since HD was discovered to be a tandem repeat disorder, a wide variety of molecular and cellular processes have been implicated in the pathogenesis. In this review article, we will focus on a key aspect of HD pathogenesis, the increased susceptibility to depression, and associated therapeutic targets.

2. Overview of HD

One distinctive aspect of HD as a neurodegenerative disease is that it involves a complex combination of psychiatric, cognitive and motor symptoms. The most common psychiatric symptom is depression, which will be the focus of this article. However, in this section we will provide a brief overview of the cognitive and motor symptoms.

The cognitive symptoms in HD are complex and variable (Duff et al., 2010; Papoutsis et al., 2014). They include deficits of executive function that are thought to involve circuitry including the prefrontal cortex and striatum (Murphy et al., 2000). This executive dysfunction can impair judgement and decision making, negatively impacting quality of life. Broader cognitive symptoms observed in HD can involve problems in memory, although the presentation is generally distinct from the amnesia observed in Alzheimer's disease and other forms of dementia. The pathogenic mechanisms whereby the tandem repeat expansion

mutation leads to cognitive symptoms is unclear, but they are likely to include molecular pathways (including neurotransmitters, receptors and other synaptic signalling molecules) associated with synaptopathy and circuitopathy (Hannan, 2018b). The heterogeneity of cognitive symptoms in HD likely reflect the genomic background of each individual (and gene-gene interactions with the HD mutation) overlaid on their 'envirome', their total environmental exposures and lifestyle factors through development and into adulthood.

Motor symptoms of HD have been a major focus of researchers since George Huntington first described the disease in 1872. This is partly because the key symptoms, such as the involuntary and uncontrolled movements termed chorea, are overt and debilitating. In fact, clinical diagnosis of HD still relies on the presence of motor symptoms. However, chorea is not the only symptom observed in HD, and the movement disorder is complex and heterogeneous (Bates et al., 2013). Whilst the length of the CAG repeat expansion does inversely correlate with age of motor onset (with longer repeats leading to earlier onset and extremely long repeats beyond 70 or so producing juvenile-onset HD) the onset and presentation of movement disorder varies extensively between patients (Cronin et al., 2019). In fact, juvenile-onset HD exhibits different motor symptoms (compared to adult-onset disease), not typically showing chorea, but rather rigidity and dystonia. The variability in motor onset and presentation is also presumably due to a complex combination of genetic and environmental factors. Indeed, a genome-wide association study (GWAS) identified genetic modifiers that modulate the onset of motor symptoms (Lee et al., 2019, 2015). Other studies, following up the original preclinical discovery (van Dellen et al., 2000), have also found evidence for environmental modifiers of clinical (motor) onset (The U.S.-Venezuela Collaborative et al., 2004; Trembath et al., 2010).

2.1 Molecular aspects of HD pathogenesis

HD has been found to induce a wide range of molecular changes, across a diverse array of cell types (Rubinsztein and Carmichael, 2003). The molecular effects of the HD mutation can be considered on a spectrum from proximal to distal. The proximal molecular changes are more directly associated with the polyglutamine expansion in the mutant huntingtin protein (Daldin et al., 2017). Whilst potential toxicity of the trinucleotide expansion mediated directly at the RNA level cannot be excluded, the bulk of evidence supports polyglutamine-associated proteotoxicity as a key early step in HD pathogenesis (Nalavade et al., 2013; Riley, 2006).

However, even the conception of HD pathogenesis, triggered directly via expansion of the polyglutamine tract in the huntingtin protein may have hidden complexities. For example, HD pathogenesis may include a component of protein ‘change of function’ rather than simply ‘gain of function’ (Paine, 2015; Rubinsztein, 2002). Thus, the implication that the polyglutamine tract in the huntingtin protein serves a normal function leaves open the possibility that this function is distorted in HD by the extended polyglutamine tract. This ‘change of function’ of mutant huntingtin would be related to the normal function. In contrast, ‘gain of function’ effects of the polyglutamine expansion in HD would involve molecular pathways that are not actively engaged by the healthy wild-type huntingtin protein (Paine, 2015).

The molecular effects of the HD mutation are diverse. These include transcriptomic, proteomic, lipidomic, and metabolomic effects. Whilst many of these molecular changes may simply be correlations of the disease process, subsets have been shown to be causative components of pathogenesis (Labbadia and Morimoto, 2013). Below, we will focus on those molecular pathways where experimental data supports causation, and that are directly relevant to the pathogenesis of depression in HD.

3. Psychiatric symptoms in HD

Psychiatric symptoms are a core feature of HD and have been associated with the disease since the first description of the illness where George Huntington in his original article highlighted a ‘tendency to insanity’ in the affected families (Huntington, 1872). Onset of HD symptoms usually strikes when individuals are in the prime of their lives. One famous example is the influential 20th century musician Woody Guthrie, who displayed behaviors described as erratic, with serious implications for his family and his stellar career. Woody received different psychiatric diagnoses before receiving the correct diagnosis, that he was suffering from HD, inherited via his mother’s mutated *JHT* allele. Another great singer-songwriter, Bob Dylan, who had been inspired by Woody’s folk music, visited his friend at a late stage of HD. Dylan was deeply moved by this first-hand experience of the devastating symptoms of HD and created ‘Song to Woody’, which includes the following timeless lyrics:

*Hey, hey Woody Guthrie, I wrote you a song,
'Bout a funny ol' world that's a-comin' along
Seems sick and it's hungry, it's tired and it's torn*

It looks like it's a-dyin' an' it's hardly been born (Bob Dylan, Columbia Records, 1962).

Indeed, it is estimated that the lifetime prevalence of psychiatric disorders among HD patients can vary between 33-76%, arising in different phases of its progression and worsening over time with disease severity (Epping et al., 2016; Paoli et al., 2017). Furthermore, it is estimated that an alarming 73-98% of motor symptomatic HD patients will be affected by a psychiatric disorder or symptom (Goh et al., 2018; Paulsen, 2001; van Duijn et al., 2014). Importantly, a greater prevalence of depression is observed in pre-symptomatic HD gene carriers, preceding motor symptoms up to one decade (Duff et al., 2007; Epping et al., 2016). Therefore, psychiatric symptoms can be considered to be part of the prodromal phase of HD (as clinical diagnosis does not officially occur until motor onset), characterizing

them as the earliest markers of the disease. Likewise, in juvenile HD, first signs of onset are also behavioral and psychiatric disturbances (Ribai et al., 2007), highlighting the main role of those symptoms in early stages of the disease.

Psychiatric symptoms impose a remarkable impact, not only to patients but also to relatives and caregivers, contributing substantially to the disease burden, lowering patients' autonomy and quality of life, impacting patients' social life and culminating in functional decline (Goh et al., 2018; Loi et al., 2018). Rather than the movement disorder having primacy, these psychiatric features are considered the most disabling to HD patients and often are the reason for hospitalization and/or are the most predictive of need for residential care (Eddy et al., 2016; Loi et al., 2018). This scenario is aggravated by the fact that many psychiatric symptoms worsen over time in both pre-symptomatic (Kirkwood et al., 2002) and diagnosed HD patients (Craufurd et al., 2001), reflecting a worsening of prognosis and constituting one of the most distressing aspects of the disease. Therefore, the scientific community has mobilized their efforts to investigate, and better treat, these important psychiatric features of HD.

The psychiatry of HD has been explored through independent small and large longitudinal observational and prospective registry studies in both presymptomatic and symptomatic patients. This effort includes The Neurobiological Predictors of Huntington's Disease study (PREDICT-HD) that has aimed to detect and track the earliest signs of HD, enrolling over 1,400 participants at risk for HD around the world (Epping et al., 2016; Kim et al., 2015) and the multinational TRACK-HD study (Tabrizi et al., 2013). Also, the COHORT study (Dorsey, 2013) and the Observational Study of the European Huntington's Disease Network (REGISTRY) (Callaghan et al., 2015; Cubo et al., 2016), who merged to create the multinational Prospective Registry Study in a Global Huntington's Disease Cohort (Enroll-HD) (Landwehrmeyer et al., 2017), further enhanced our understanding of the

psychiatry of HD. Collectively, clinical studies have identified the most common behavioral and psychiatric symptoms that occur in HD patients, which include depression, mania, anxiety, obsessive-compulsive symptoms, irritability/aggression, apathy, psychosis and suicide (**Box 1**) (recently reviewed by (Eddy et al., 2016; Goh et al., 2018; Paoli et al., 2017)).

4. Depression in HD

There is a consensus in the literature that the most frequent psychiatric symptom occurring in HD is depression. However, it is important to highlight how difficult it is to make psychiatric diagnoses in HD. Firstly, this is due to the rigid psychiatric diagnostic criteria and the presence of confounding factors like cognitive impairment, as well as the fact that patient medical history is usually based on self-reporting or from caregiver interviews (Reedeker et al., 2012). Secondly, physical symptoms of depression also occur as part of HD pathology *per se* (e.g. weight loss), making it difficult to determine a specific diagnosis (Paoli et al., 2017; Roos, 2010). And finally, some other behavioral symptoms that occur in HD overlap with depression, including apathy, irritability, sleep disturbances and suicidal ideation (Paulsen et al., 2017). Taken together, all of these potential cofounders could help explain the large range of prevalence of depression that has been estimated for HD, and how other overlapping symptoms may arise during the disease course, as demonstrated in **Box 1**. From a research perspective, different methodologies for assessment of depression may also lead to underestimation of the impact of depression in HD.

Nevertheless, even with the occurrence of depression varying across the different stages of the disease, leading to the large range of prevalence estimates and the confounders in diagnosis as mentioned above, it has been estimated that approximately half of the people affected with HD are diagnosed with depression (Bates et al., 2015; Goh et al., 2018). Since

depression is often one of the earliest symptom in HD, this positions depression as a core feature of HD patients, rather than merely a response to diagnosis, as already previously suggested (Paoli et al., 2017; Paulsen et al., 2017). In addition, depression has already been shown to be associated with cognitive deficits in HD, following the demonstration that the severity of depression is correlated with poorer cognitive performance (Ramos and Garrett, 2017; Smith et al., 2012; Unschuld et al., 2012). Some previous studies have suggested that depression in HD does not correlate with the duration of illness (Craufurd et al., 2001), however there is a correlation between the severity and prevalence of depression with the HD disease progression (Duff et al., 2007). Altogether, these studies indicate that depression should receive special attention in clinical approaches to the management of HD, since it is a treatable feature of the disease (although not all patients respond to current treatments) and it has serious implications not only for HD patients, but also relatives and caregivers.

It is also important to highlight that depression in HD, although clinically managed similarly to major depression in general population, presents atypically in some respects, indicating a potential differential neurobiology of depression in HD. One important characteristic involves the age of onset, since in individuals with HD, depressive symptoms appear approximately 14 years later than in major depression in the general (non-HD) population (Eddy et al., 2016; Jennifer Charlotte de Souza, 2015). One of the most robust phenomena described in psychiatry is a gender difference in depression within the general population, where it is far more prevalent in females than in males (with an approximately 2:1 ratio). However, curiously, the majority of studies haven't reported such a gender disparity for depression in HD (Dale et al., 2016; Eddy et al., 2016; Paoli et al., 2017), with the exception of one study (Epping et al., 2013).

The collective evidence indicates that depression is endogenous to HD, and that the tandem repeat expansion mutation adds to the genetic predisposition to depression, which

then interacts with environmental risk factors. Identifying the neurobiology of depression in HD would not only help to better understand the physiopathology of the disease, but may also improve early diagnosis, consequent treatment and potentially modify the trajectory of disease progression.

5. The neurobiology of depression in HD

Despite the high prevalence, importance and impact of depression in HD, there is a dearth of knowledge of the neurobiology of depression in HD. Due to the small number of studies that specifically address this scientific question, researchers have been empirically comparing depression in HD and depression in the general population in order to understand the peculiarities associated with the disease (for a comprehensive review, see (Du et al., 2013)). In fact, only a limited number of clinical studies have focused on this problem, most probably due to the intrinsic limitations associated with clinical psychiatric studies, and especially in HD. In the meantime, preclinical models of HD have been investigated and have proven highly informative in enlightening the neurobiology of depression in HD.

Preclinical animal models have many advantages for the investigation of pathogenic mechanisms, and therapeutic approaches, in neurological and psychiatric disorders. In contrast to clinical studies of central nervous system (CNS) disorders, preclinical studies permit access to the neural tissues of greatest relevance, leading to advancements in the understanding of neurobiological mechanisms of disease and identification of therapeutic targets for the development of new treatments. Unlike many many diseases, HD is a monogenic autosomal dominant disorder, with transgenic mice accurately modelling the disease pathogenesis, providing face validity and constituting an ideal platform for molecular, cellular and systems analyses (Chesselet and Carmichael, 2012). Most transgenic mouse models of HD not only mimic the motor symptoms of the disease, but also the complete

extent of presentation of the disease in humans, with the presence of cognitive impairment and psychiatric endophenotypes, thus providing models with excellent construct and face validity. Assorted rodent models have been used, including transgenic models expressing truncated HTT (e.g. R6/1 and R6/2 mice) or full-length HTT (e.g. Yeast Artificial Chromosome (YAC) and Bacterial Artificial Chromosome (BAC) transgenic lines), as well as knock-in (KI) models involving a trinucleotide repeat expansion in the endogenous mouse *huntingtin* gene (Pla et al., 2014).

This review will concentrate on studies that have investigated the neurobiology of depression in HD, briefly summarizing clinical evidence and dedicating more attention to scrutinizing preclinical findings (see **Table 1**), considering their potential to uncover mechanisms, identify new therapeutic targets and future intervention approaches. We will discuss the main domains of research that have specifically evaluated the neurobiology of depression in HD, as schematized in **Figure 1**, including neuroimaging studies, and particular molecular and cellular aspects of pathogenesis, as described below.

5.1. Neuroimaging approaches to illuminate the pathogenesis of depression in HD

Findings from clinical functional neuroimaging studies have been a critical source to interrogate the central relationship between HD and depression, providing novel insights into the circuitopathy of this key psychiatric feature of HD. It was demonstrated in early stages of HD that functional brain changes specific to depressive HD patients, when compared to non-depressed patients and controls, included selective dysfunction of the paralimbic regions of the frontal lobes, suggesting an orbital frontal-inferior prefrontal cortex (OFC) hypometabolism (Mayberg et al., 1992). These authors proposed that a disruption in the pathway between frontal lobe regions and the striatum could explain symptoms of depression in HD patients.

In the prodromal stage of HD, a correlation was found between depressive symptoms, evaluated on the Center for Epidemiologic Studies-Depression (CES-D) scale, and functional connectivity in the ventromedial prefrontal cortex (vmPFC), which is a node of the default-mode network (DMN) (Unschuld et al., 2012). Furthermore, this same study showed that this correlation was even stronger in patients with longer CAG repeat lengths. Likewise, during the pre-symptomatic phase of HD, a specific connection was shown between the DMN and basal ganglia network (BGN) associated with depression symptoms (McColgan et al., 2017), indicating that the DMN is a key promising target for different stages of the disease.

Interestingly, pre-symptomatic and early-stage HD patients with the highest cumulative probability to onset (CPO) showed a different structural integrity in the white matter associated with depression, evaluated by the PBA-s interview (the Track-HD investigators et al., 2015). Similarly, another study divided pre-symptomatic HD patients into 'far from' and 'close to' clinical onset (i.e. motor symptoms) and observed that pre-symptomatic HD patients close to onset have increased symptoms of depression (assessed by the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory Version II (BDI-II)) associated with activity in the right dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) during a working memory performance, corroborating the relation between depression and cognitive impairment in HD (Poudel et al., 2015).

Verifying neural responses during all stages of HD, including pre-symptomatic, prodromal and symptomatic stages of HD, improves our understanding of HD neurobiology and brain reorganization not only for depression but also to the neurodegeneration process by itself. Hence, more clinical neuroimaging studies are required to validate previous literature and to expand our knowledge of HD circuitopathy.

5.2. The role of the huntingtin (HTT) gene in depression in HD

5.2.1. What do we know from clinical findings?

A few studies demonstrate no correlation between the CAG repeat size of HTT and psychiatric manifestation, nor with specific depressive symptoms (Berrios et al., 2001; Weigell-Weber et al., 1996; Zappacosta et al., 1996; Craufurd et al., 2001). Conversely, it was demonstrated in one study that there is a correlation between the length of CAG repeat with the progression of clinical symptoms, including psychiatric symptoms (Illarioshkin et al., 1994). While it is clear that the trinucleotide repeat expansion mutation contributes to the pathological process of psychiatric manifestation, such symptoms are not as amenable to demonstrations of disease progression. Furthermore, it is possible that motor symptoms relate to a progressive neurodegenerative process, such as death of medium spiny neurons in the striatum, whereas psychiatric symptoms such as depression, may relate to aspects of synaptopathy and circuitopathy that do not progress in a linear fashion. This question requires further investigation.

Indeed, more recently, one study has analysed two well-characterised cohorts, including 2165 individuals with depression, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria using the Composite Interview Diagnostic Instrument, and 1058 controls and has demonstrated a non-linear association between CAG repeat size and the risk of lifetime depression (Gardiner et al., 2017). Importantly, this study has shown that the risk of depression increased with both relatively short and relatively large alleles when compared to alleles with CAG repeat sizes close to the centre of the distribution. Furthermore, individuals with HTT alleles containing CAG repeats ranging between 27 – 35, considered upper normal range, also showed more depressive symptoms when compared to controls (Hogarth, 2013; Killoran et al., 2013). In

fact, a very recent post-mortem case study of an 80-year-old individual with a clinical history of chorea and 28 CAG repeat expansion in a HTT allele, identified neuronal atrophy in the caudate and putamen with gliosis and huntingtin aggregation associated, suggesting a role of intermediate CAG repeat lengths in late-onset HD (Jevtic et al., 2020).

These studies indicate that CAG repeat polymorphisms could potentially not only act on the known motor pathology, but also on the symptoms of depression in HD patients. The promising relationship between CAG repeat length, including in the accepted normal range, and relative depression occurrence should be better explored, not only due its potential to clarify depression aetiology in HD, but also ultimately to uncover a potential relation with depression in general population.

5.2.2. What do we know from preclinical findings?

As transgenic mice for the HD gene exhibit depression-like behavior, it appears that CAG repeat size variations in HTT modulate regulation and predisposition to clinical depression. Indeed, Pouladi and colleagues demonstrated in both males and females an increase in immobility time at the forced swim test (FST) and a decrease in sucrose intake at the sucrose preference test (SPF) in YAC128 mice when compared with WT and YAC transgenic animals who expresses a variant of mutant HTT that is resistant to cleavage at residue 586 (C6R). They also showed no difference between C6R and WT mice in any of the depression tests, indicating that as a single intervention, preventing the cleavage of mutant HTT at residue 586 is able to modulate depressive phenotype observed in YAC128 (Pouladi et al., 2009).

Furthermore, other investigators have used recombinant adeno-associated viral vectors of serotype 5 expressing cre (rAAV-cre) injection into the hypothalamus of female BACHD mice in order to inactivate mutant HTT. It was demonstrated that decreased

immobility time in inactivated BACHD compared to BACHD mice while no difference was found between inactivated BACHD when compared to WT mice, suggesting that HTT expression specifically in hypothalamus contributes to the development of depression in HD (Hult Lundh et al., 2013). On the other hand, when investigators inactivated mutant HTT in a specific neuronal population of the ventromedial hypothalamus (VMH) expressing the transcription factor steroidogenic factor 1 (SF1) in female and male BACHD mice (using cross-breeding based on a Cre-loxP system) they observed that was not enough to prevent depressive-like behavior in female BACHD mice. That outcome indicates that the development of the psychiatric phenotype in BACHD mice does not involve the mutant HTT expression in SF1 neurons specific to the ventromedial hypothalamus (Baldo et al., 2014).

Furthermore, targeting the polyQ-HTT-mediated toxicity, female and male knock-in mice were generated to isolate the codons for serines at positions 1181 and 1201 of the gene encoding mouse HTT (Hdh); these were replaced by codons for alanine (Hdh^{S1181A/S1201A}) or aspartic acid (Hdh^{S1181D/S1201D}), mimicking the absence of phosphorylation and constitutive phosphorylation of HTT by cyclin-dependent kinase 5 (Cdk5) on these sites. It was demonstrated that abolition of mutant HTT phosphorylation at S1181/S1201 reduced depression-related behavior in mice assessed by the splash test (ST). An increase of grooming time was observed after 10% sucrose was sprayed on the mouse coat in Hdh^{S1181A/S1201A} in comparison with WT and Hdh^{S1181D/S1201D} mice, which in turn was not different from their WT controls (Ben M'Barek et al., 2013). Something to be considered is the specificity of ST for depressive-like behavior, since it is also considered an apathy-like test (Willner, 2005). Interestingly the constitutive phosphorylation of HTT didn't result in motor impairment, and the abolition of mutant HTT phosphorylation lead to other outcomes including a decrease in anxiety-related behavior, and an increase in BDNF expression and hippocampal neurogenesis. Thus, further studies are needed to expand on these findings and

better understand the specificity of response to the HTT phosphorylation and the potential roles of neurotrophic signalling and neurogenesis.

Similarly, chronic treatment of female and male BACHD mice with ED11, a peptide that reduces mutant Huntingtin proteolysis by caspase-6, aimed at protecting vulnerable cells from mutant HTT toxicity. It was observed that treatment at both at presymptomatic and symptomatic stages had positive results in BACHD mice, being able to, respectively, prevent and reverse the immobility time assessed by FST (Aharony et al., 2015). Curiously, when inactivating mutant HTT expression in *Sim1*-expressing cells mainly in paraventricular nucleus of hypothalamus (PVN) and sparsely in other areas of the hypothalamus and in the amygdala in BACHD mice, the metabolic and depressive-like phenotype was affected in a sex-specific manner. This selective inactivation does not prevent the depressive-like behavior in female BACHD mice, as was hypothesised, and was only observed in males at 8 months of age, associated with a possible alteration in the HPG axis in these BACHD male mice (Soylu-Kucharz et al., 2016). These results indicate that sex significantly affects the behavioral manifestation in BACHD mice.

Intriguingly, due to clinical observation of depression progression in HD patients, a study aimed to investigate the progression of depression-like phenotype in a preclinical model, to establish whether that feature is also modelled in HD transgenic mice. Female and male R6/2 mice expressing 120, 250, or 350 CAG repeats, and knock-in *Hdh* mice expressing 50, 150, or 250 CAG repeats, were used in this study. It was demonstrated that by an early stage, both strains have an increase in floating behavior in the FST, and then, as the mice aged, the floating behavior decreased, while the active behaviors of swimming and climbing increased, with an interaction between CAG repeats length and age (Ciamei et al., 2015). That pattern indicates that an increase in FST floating behavior or immobility time (depressive-like behavior) in HD mice indeed does not progress linearly with time, exactly as

it was hypothesized and as seen in HD patients (Craufurd et al., 2001). Furthermore, based on previous studies, it was suggested that an increase in serotonergic and noradrenergic activity led to inhibition of floating by promoting horizontal swimming, and inhibition of floating by enhancing climbing behavior (Cryan et al., 2005). It was concluded that at the late stages of the disease, an increase in serotonergic and noradrenergic activity might contribute to a decrease in the depression phenotype in HD mice. This hypothesis should be further investigated, since it could facilitate additional treatment options, including personalised pharmacotherapy approaches.

Altogether, these studies indicate that the HTT tandem repeat mutation contributes as a primary basis of depression in HD, with a potential pro-agonism of the hypothalamus in this response. Different technologies and ways of targeting mutant HTT have been applied, from direct genetic manipulation to external interventions, to reach the same conclusion, that protecting cells from mutant HTT toxicity leads to the prevention of depression-related endophenotype, also indicating the direct role of the HTT gene mutation in the development of depression in HD. In the sections below we will discuss other aspects of the neurobiology of depression in HD.

5.3. The role of neurotransmitters and associated signalling pathways in depression in HD

5.3.1. What do we know from clinical findings?

Using transcranial sonography, a relationship was demonstrated between depression (assessed by Hamilton Rating Scale for Depression (HAM-D) and BDI) and mesencephalic raphe echogenicity in patients genetically confirmed with HD, indicating an alteration of the serotonergic brain stem raphe in HD patients with depression (Krogias, 2011). On the other

hand, an analysis in cerebrospinal fluid of the main metabolite of serotonin, the 5-hydroxyindoleacetic acid (5-HIAA) levels in depressed versus nondepressed HD patients (determined by Schedule for Affective Disorders and diagnosis by DSM-III) didn't show any difference between groups (Kurlan et al., 1988). In fact, serotonin reuptake inhibitors (SSRIs) already are the first drug of choice as treatment for depression in HD (Holl et al., 2010; Petersén and Weydt, 2019), including at the prodromal phase (Rowe et al., 2012). However, it is important to point out that this antidepressant treatment reflects the general practice for major depressive disorders, not an evidence-based treatment choice specific to HD, since there is a lack in clinical studies testing the efficacy of such drugs on psychiatric symptoms in HD, despite their frequent use (Moulton et al., 2014).

Moreover, in 15 pre-manifest HD patients, a strong inverse correlation was recently described between prefrontal cerebral type 1 cannabinoid receptor (CB₁R) levels and scores of depression (evaluated by BDI), when compared to 32 gene-negative controls. CB₁R binding was evaluated with [18F]-MK-9470 (N-[(2S,3S)-3-(3-cyanophenyl)-4-(4-ethoxyphenyl)butan-2-yl]-2-methyl-2-(5-methylpyridin-2-yl)oxypropanamide) PET imaging. This study ultimately suggests the cannabinoid system as a new avenue of investigation for HD pathophysiology and its relation with depression (Ceccarini et al., 2019). Due to the promising correlation, this study should be replicated with increased sample sizes.

5.3.2. What do we know from preclinical findings?

Using R6/1 transgenic mice, Pang and colleagues (2009) showed that the SSRI, sertraline, and not the tricyclic antidepressant (TCA) desipramine, is able to decrease FST immobility time observed in female, but not in male, HD mice, indicating that modulated serotonergic signalling can specifically ameliorate the depressive phenotype observed in these female HD mice. They also demonstrated genotype differences of hippocampal

expression of serotonergic receptors *htr1A*, *htr1B* and *htr2A* (Pang et al., 2009). Furthermore, environmental enrichment (EE) rescued the depressive phenotype in female HD mice and increased *htr1A* and *htr1B* expression in hippocampus and cortical *htr2C*, suggesting a serotonergic action. Interestingly, the same study found sex-specific depressive-like behaviors in female R6/1 HD mice and demonstrated a significant decrease in gene expression of serotonin transporter in female cortex (Pang et al., 2009). In addition, a later study demonstrated a global reduction of serotonergic transmission in female HD mice, as suggested by the decreased tissue levels of serotonin (5-HT) and its metabolite (5-HIAA) in cortex, hippocampus and striatum. Acute sertraline was able to prevent depressive-like behavior (Renoir et al., 2011). Together, these studies indicate that disrupted serotonin signalling mediates the sexually dimorphic depression-like phenotype in R6/1 HD mice.

Likewise, chronic sertraline treatment was able to prevent the increase in immobility time in FST and the decrease in saccharin preference demonstrated by female R6/1 HD mice, while the use of running wheels prevented the FST outcome. Both interventions prevented the exaggerated 5-HT_{1A} autoreceptor function exhibited by HD mice, demonstrating an ability to correct the serotonergic dysfunction while preventing the behavioral outcome, indicating that this autoreceptor is associated with the depressive-like phenotype in HD (Renoir et al., 2012b). Despite this abnormal hypothermic response to the serotonin 5-HT_{1A} receptor agonist, a reduction in 5-HT_{1A} receptor mediated stimulation of [³⁵S]GTP- γ -S binding in the dorsal raphe nucleus and the hippocampus of female HD mice was also demonstrated (Renoir et al., 2013). Furthermore, the exposure to 4 weeks of early EE wasn't able to modulate this response, neither to prevent the despair- and anhedonia-like behaviors displayed by these HD mice, and only had an impact on anxiety-like behavior (Renoir et al., 2013). Regardless, dysfunction in serotonergic signalling has been robustly demonstrated

and, in light of the promising specific regulatory role of the 5-HT_{1A} autoreceptor in mediating depressive-like behavior in HD, further investigations are warranted.

Dysfunction in dopaminergic signalling has also been verified. In female R6/1 HD mice, acute treatment with bupropion, a dopamine-norepinephrine reuptake inhibitor, was able to prevent the depressive-like behavior, assessed with FST. Interestingly, pre-treatment with haloperidol blocked this effect, suggesting a dopamine D2/D3 receptor mechanism of action for bupropion (Renoir et al., 2012a). Furthermore, it was shown in female and male YAC128 HD mice that clorgyline treatment inhibits MAO-A activity, rescuing striatal dopamine, serotonin and norepinephrine deficits, reflecting an improvement of anxiety and depressive-like phenotype (Garcia-Miralles et al., 2013). Taken together, these studies indicate that monoaminergic dysfunction in HD has a role in not only depressive-like behaviors, but also the anxiety-related phenotype observed in some preclinical HD models.

Varenicline, a partial agonist of the alpha4/beta2 subtype of the nicotinic acetylcholine receptor, was administered to male and female YAC128 HD mice for 28 days in their late-stage symptomatic phase and was found to ameliorate the abnormal immobility time in the FST (McGregor et al., 2017). However, varenicline has multi-target directed effects, including the demonstrated action in hippocampal neuroprotection, proliferation and survival, and these results suggest that dysfunctional cholinergic neurotransmission may contribute to the depressive-like behavior in late-stage symptomatic HD. More studies are needed, including other stages of the disease, in order to clarify the role of cholinergic modulation in the development of the depression phenotype in HD.

In light of the glutamatergic hypothesis of depression (reviewed by (Sanacora et al., 2012)) in combination with the suggested role of glutamatergic signalling as one of the major sources of cell dysfunction and death in HD (Milnerwood et al., 2010), N-acetylcysteine (NAC) was used to supplement cysteine, ultimately aiming to ameliorate glutamatergic

dysfunction. Indeed, it was demonstrated that female HD mice have lower basal levels of cystine, and the administration of NAC prevented the depression-like phenotype in the FST test, with glutamate transporter activity being required for the antidepressant effects of NAC (Wright et al., 2015, 2016). NAC was also able to specifically increase glutamate in mice, in a glutamate transporter-dependent manner and rescue changes in key glutamate receptor proteins related to excitotoxicity in HD, including NMDAR2B. Reductions in cysteine/cystine may contribute to glutamate imbalance and thus depressive-like behavior in HD, indicating an important role of glutamatergic dysfunction contributing to the depression-associated endophenotype in HD.

It is not surprising that these neurotransmitters and their signalling pathways would be related to depression in HD, in light of their known involvement in psychiatric disorders and their roles in HD pathogenesis. These studies confirm that relationship and suggest specific pathways and therapeutic targets to guide future investigations.

5.4. The role of brain-derived neurotrophic factor (BDNF) in depression in HD

5.4.1. What do we know from clinical findings?

BDNF has important pro-survival and pro-neurogenic properties in neurons and the evidence supporting a role for BDNF dysregulation in the pathogenesis of HD is compelling (for review (Bartlett et al., 2016; Illarioshkin et al., 2018; Smith-Dijk et al., 2019)). Furthermore, the relationship between BDNF and major depression is quite robust; clinical studies demonstrate that serum BDNF is significantly decreased in antidepressant-naïve depressed patients when compared with controls and with antidepressant-treated patients,

showing a significant negative correlation between BDNF levels and the score of the Hamilton Rating Scale for Depression (Shimizu et al., 2003).

The potential role of BDNF as a biomarker in HD patients was recently verified in 21 manifest HD patients, 30 pre-manifest gene-positive subjects and 33 controls (Gutierrez et al., 2020). Indeed, this study suggested that salivary BDNF measures could potentially be an early marker of disease onset for HD, since lower levels of salivary BDNF was observed in premanifest and manifest HD patients when compared to controls, being even lower in premanifest patients within 10 years of prediction to disease onset. Interestingly, the same study also showed that DNA methylation at the *BDNF* promoter IV inversely correlated with scores of anxiety and depression (assessed by HADS), suggesting this as a biomarker for psychiatric symptoms in HD patients. These are interesting findings, nonetheless they need to be replicated and expanded in future studies including the differentiation of depression and anxiety symptomatology.

5.4.2. What do we know from preclinical findings?

There is extensive evidence that BDNF plays a major role in the pathogenesis of HD. One direct piece of evidence is that HTT is able to regulate the intracellular transcription and trafficking of BDNF (Gentner et al., 2004; Pla et al., 2014; Zuccato, 2001). Consistent with clinical findings, in rodent models of HD it has been demonstrated that lower levels of BDNF occur, at both protein (Pang et al., 2006; Spires, 2004; Strand et al., 2007; Xie et al., 2010) and mRNA (Pang et al., 2006; Zajac et al., 2009) levels. Additionally, mutant HTT also has a negative impact on BDNF signalling, leading to the impairment of both ligand and receptor in the BDNF/TrkB pathway (for a comprehensive review, see (Pla et al., 2014)). Together with the evidence that BDNF also participates in the pathophysiology of mood disorders (Autry and Monteggia, 2012), and is a key mediator of the antidepressant response

(Monteggia et al., 2004; Saarelainen et al., 2003), this evidence is consistent with the proposal that BDNF may provide a molecular link between HD and depression.

Recently, in order to address this question, a study using female and male YAC128 mice performed an intranasal administration of BDNF for 15 consecutive days during the early-symptomatic phase (da Fonsêca et al., 2018). They demonstrated that BDNF treatment is able to prevent the development of anhedonia and apathy-like behaviors in early-symptomatic YAC128 mice. BDNF treatment prevented the decrease in sucrose consumption, increased grooming time in ST and prevented the increase in immobility time in TST observed in YAC128 mice. On the other hand, the intranasal BDNF administration did not have an effect on the increase in immobility time in FST observed in YAC128 mice. Together with this overall positive behavioral outcome, this neurotrophin had no effect on adult hippocampal neurogenesis in YAC128 mice, therefore it is unclear as to how BDNF can prevent depressive-like behavior in these HD mice.

5.5. The role of hypothalamic axis dysfunctions on depression in HD

5.5.1. The hypothalamic-pituitary-adrenal (HPA) axis

5.5.1.1. What do we know from clinical findings?

The hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine signalling system involved in physiological homeostasis and stress response, with cortisol secretion being controlled by the hypothalamic corticotrophin releasing hormone (CRH) and pituitary adrenocorticotrophic hormone (ACTH). Stress leads to the hyper-secretion of corticosteroids by the adrenal glands and this neuroendocrine dysfunction has been robustly related to major depression (Nandam et al., 2019; Pariante and Lightman, 2008). This has also been evaluated

in HD patients, where HPA-axis dysfunction was identified (reviewed by (Bartlett et al., 2016)), with notable higher basal cortisol levels in different timepoints, in early and late stages of the disease (Heuser et al., 1991; Leblhuber et al., 1995; van Duijn et al., 2010). Not surprisingly, the question regarding the relationship between dysregulation of the HPA axis as a mediator of depression in HD has also been raised (for a comprehensive review, see Du and Pang, 2015), however, very few studies have addressed this question.

HPA-axis function was assessed by salivary cortisol measurement in 20 pre-diagnosed and 17 early-stage HD patients, together with 20 controls (Shirbin et al., 2013). Depression symptoms were assessed using the Inventory of Depressive Symptomatology – Self Report and revealed an association between depression and morning cortisol levels in early stage HD, since non-depressed early stage HD patients showed significantly lower cortisol levels during the morning period when compared to non-depressed pre-symptomatic HD patients and control groups. Additionally, another study enrolled 49 pre-motor and 102 symptomatic patients and 55 controls and evaluated HPA-axis function through cortisol quantification in saliva samples. They found an association between a higher area under the curve (AUC_i) with depressive symptoms (determined by the Problem Behaviors Assessment (PBA)) in mutation carriers from both pre-motor symptomatic and early disease stages (Hubers et al., 2015). More research is required to clarify the role of HPA-axis dysfunction in depressed HD patients, in terms of its regulation, response to stress and potential involvement in progression of the disease.

5.5.1.2. What do we know from preclinical findings?

HPA-axis dysfunction has been demonstrated in various animal models of HD. In R6/2 transgenic mice, an aggressive model of HD with early onset, hypertrophy of the adrenal cortex, a progressive increase in both serum and urines corticosterone levels and

increased circulating adreno-corticotrophic hormone (ACTH) levels were found (Björkqvist et al., 2006). In R6/1 transgenic mice, which provide a better model of adult-onset HD than R6/2 mice, HPA-axis dysfunction was demonstrated specifically in females prior to onset of motor deficits, with no difference in baseline but an increased corticosterone release after acute physiological or pharmacological stress, such as in the dexamethasone (DEX)-ACTH challenge (Du et al., 2012). In addition, there was evidence of an *in vitro* exaggerated response of adrenal cortical cells when stimulated by ACTH. Interestingly, no differences in GR or CRF gene expression levels were found in the R6/1 hypothalamus (Du et al., 2012). This study indicates a sex-specific dysfunction of the adrenal's, that leads to elevated post-stress corticosterone levels in female HD mice prior to onset of motor deficits (Du et al., 2012). This pattern of response may help to explain the tendency of HD female mice to present more severe depressive-like behaviors than HD male mice in various models, first reported by Pang and colleagues (2009).

Despite evidence that targeting HPA-axis dysfunction could be a valuable next step for preclinical studies of depression in HD, little work has been done in this area. Pharmacological studies are needed in order to specifically target the overactive HPA axis in HD, and assess the effect on the depression phenotype as well as its relationship with the neurobiology of depression in HD.

5.5.2. The role of hypothalamic-pituitary-gonadal (HPG) axis in depression in HD

5.5.2.1. What do we know from clinical findings?

The hypothalamus also regulates the hypothalamic-pituitary-gonadal (HPG) axis, which is central for human reproduction. Neuroendocrine networks that integrate wide-

ranging internal and external inputs in order to coordinate reproductive competence constitute the HPG axis (for comprehensive review, see (Dwyer and Quinton, 2019)).

Dysfunction of the HPG axis has been related to HD pathology. Lower testosterone and luteinizing hormone (LH) levels in HD male patients have been demonstrated. The severity of illness was negatively correlated with plasma testosterone levels and low testosterone levels in turn were associated with dementia, but not with depression or psychotic symptoms (evaluated by the Unified HD Rating Scale (UHDRS) – analysing mood in the behavior assessment) (Markianos et al., 2005). Intriguingly, several features of testosterone deficiency, such as reduced muscle mass, depressive mood, and cognitive impairment, are already often reported in HD patients, suggesting an urgent need for studies addressing these aspects of pathogenesis and their potential as therapeutic targets.

On the other hand, when female data were analysed, a significant negative correlation with age was found for testosterone and dehydroepiandrosterone sulfate (DHEAS) in both controls and HD patient groups. However, there were no significant differences in hormone levels among patients, subjects at risk and controls, either when dichotomized between premenopausal or in postmenopausal state. Interestingly, the subgroup of patients with depression in their symptomatology had significantly lower testosterone and DHEAS levels compared to patients without depression, or to controls, suggesting a role for the HPG axis in the pathogenesis of depression (Markianos et al., 2007).

5.5.1.2. What do we know from preclinical findings?

Similarly, in different rodent models of HD, the HPG axis dysfunction has also been related to the phenotype of the disease (Novati et al., 2018; Papalexi et al., 2005). In the R6/1 transgenic mouse model of HD, at the pre-motor symptomatic age of 12 weeks, male R6/1 mice were found to have significantly reduced serum testosterone levels when compared to

WT littermate controls (Hannan and Ransome, 2012). Female R6/1 HD mice, also at the pre-motor symptomatic stage of 12 weeks of age, were found to have ovarian atrophy, decreased serum testosterone levels and hypothalamic gonadotropin-releasing hormone (GnRH) gene expression in HD, as well as increased ER α expression in the adrenal gland (Du et al., 2015). Curiously, ovariectomized mice didn't show any difference in the FST test, although decreased corticosterone levels were found for both WT and HD littermates, demonstrated by the DEX-ACTH challenge. However, promisingly, a single injection of diarylpropionitrile (DPN), an estrogen receptor- β (ER β) agonist, was able to decrease immobility time in HD at the FST test, indicating that alterations to sex-hormone regulation in early stages in females may contribute to depression aetiology in HD (Du et al., 2015).

In light of these exciting findings, further studies should be performed in both the preclinical and clinical spheres. Targeting the HPG axis may not only facilitate understanding of the neurobiology of depression, it may also increase treatment options and identify potential peripheral biomarkers.

The sex-specific phenotypic presentation of R6/1 mice, only showing depressive-like behavior in females, was linked to sexually dimorphic HPA-axis dysfunction and serotonergic signalling. This pattern of sexual dimorphism was also demonstrated in BACHD mice (Soylu-Kucharz et al., 2016). Additionally, HdhQ111 HD mice show an increase in anxiety-like behavior, specifically in males (Orvoen et al., 2012). Thus, sex could be another factor that determines the manifestation and extent of psychiatric phenotypes in HD. This should be further investigated, both to more deeply illuminate pathogenesis and also facilitate novel approaches to precision medicine in HD.

5.6. Other directions

A drug currently under clinical development for HD, pridopidine, was administered to female and male YAC128 mice in order to characterize its potential therapeutic benefit and mode of action. Surprisingly, the most robust finding described by the authors was the antidepressant effect that pridopidine had at both doses and in both early and late stages of HD (Garcia-Miralles et al., 2017). Considering that pridopidine has higher affinity for the sigma-1 receptor (S1R), in comparison with D2 dopamine receptor (D2R), the previous known target of action (Sahlholm et al., 2015), these findings indicate that S1R potentially plays a promising role in the neurobiology of depression in HD. More studies are needed to test this promising hypothesis.

Additionally, another study showed beneficial results of chronic treatment with probucol, a phenolic lipid-lowering compound that presents antioxidant properties, on the depression-like phenotype of female and male YAC128 mice (de Paula Nascimento-Castro et al., 2018). This pointed to a promising oxidative dysfunction focus for the neurobiology of depression in HD. Chronic treatment (3 and 5 months) with probucol was able to prevent the occurrence of depressive-like behavior in YAC128 at both 4 and 6 months of age, curiously with no effect in motor impairment and not related to an increase in hippocampal progenitor cell proliferation and neuronal differentiation. This promising finding specific to the depression phenotype in HD should be further explored, in order to understand the specific pathways and brain regions where the drug is acting.

One of the more fascinating, and therapeutically relevant, aspects of HD pathogenesis is that it affects not only the brain, but also various peripheral organs and systems. This ranges from retina, the above mentioned HPA and HPG peripheral participation to heart and gut. Most recently, evidence has emerged that the gut microbiome is altered in HD transgenic mice (Kong et al., 2018). This gut dysbiosis precedes the onset of overt motor

deficits and may be causatively involved in pathogenesis, although this possibility needs to be experimentally tested.

6. Conclusions and future directions

The collective evidence indicates that depression is in fact endogenous to HD and defining its neurobiology would not only help to better understand the physiopathology of the disease, but also to improve early diagnosis, consequent treatment and potentially modify the trajectory of disease progression. In this regard, we have integrated preclinical and clinical studies that have illuminated the neurobiology of depression in HD. We have identified key domains that may be central to understanding the neurobiology of depression, both preclinically and clinically, as schematized in **Figure 1**. However, we have also identified major gaps in knowledge in important areas that should be pursued in future research.

More clinical neuroimaging studies are required to validate previous literature and to expand the overall knowledge of HD circuitopathy, verifying neural responses during all stages of HD (including pre-symptomatic, prodromal and symptomatic stages) to improve our understanding of the neurobiology of depression in HD. The promising relationship between the CAG repeat polymorphism in the HTT gene, including in the normal range, and depression occurrence should be better explored, not only because of its potential to clarify depression aetiology in HD, but also ultimately to uncover a potential role in depression in the general population. Importantly, mutant HTT seemed to be robustly related to the pathogenesis of depression in HD, and more studies are necessary in order to understand this causative relationship and associated molecular and cellular mechanisms.

Enlightening the role that aberrant neurotransmission has in the pathogenesis of depression in HD has the potential to eventually personalize depression therapeutics for HD patients. Serotonergic signalling has been most intensively investigated and provides an

important focus, together with the glutamatergic signalling abnormalities that represent a promising new avenue of therapeutic targeting for depression in HD. Some other areas such as neurotrophin (particularly BDNF) signalling and HPA-axis dysfunction, also need to be more extensively explored, including clarification of the sexual dimorphism observed in different animal models of HD.

We conclude that, although we have reported a few promising pathways to focus on in both preclinical and clinical spheres, the scientific community is still at the beginning of this journey to fully understand the neurobiology of depression in HD. This understanding of the pathogenesis of depression may lead to novel therapeutic approaches, not only for HD families, but also for the millions in the general population who suffer from this devastating disorder.

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Figure legend

Figure 1. The neurobiology of depression in Huntington's disease. *What do we know from clinical studies?* From neuroimaging studies, some brain areas and pathways of connections have been related to depression in Huntington's disease (HD) patients, such as between the default-mode network (DMN) and basal ganglia network (BGN) and between the right dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Also, hypometabolism of orbital frontal cortex (OFC) was demonstrated, which is an important link of the frontal lobe and striatum communication. In addition, structural integrity of white matter, functional connectivity in ventromedial prefrontal cortex (vmPFC), a node of the DMN, and serotonergic signalling via the raphe nuclei, have been described. Furthermore, cannabinoid receptor 1 (CB1R) has also been implicated in the pathogenesis of depression in HD. Hypothalamus-pituitary-gonadal (HPG) axis and hypothalamus-pituitary-adrenal (HPA) axis dysfunction has also been implicated in the pathogenesis of depression in HD. Importantly, the CAG/glutamine repeat length of mutant huntingtin (HTT) was also associated with depression in HD and salivary brain-derived neurotrophic factor (BDNF) was suggested as a potential biomarker. *What do we know from preclinical studies?* Various neurotransmitter pathways have been implicated, including glutamatergic, cholinergic and dopaminergic, and the well-established the serotonergic signalling, with the 5-HT1A receptor proposed to be a main mediator. This neurotransmitter system, together with dysfunction at the HPG-axis, has also been associated with the observed sexual dimorphism observed in some animal models of HD, with depression being specific to females. Oxidative dysfunction and a role for sigma 1 receptor (SR1) have been also implicated in the pathogenesis of depression in HD.

Abbreviations: Huntington's disease (HD); default mode network (DMN); basal ganglia network (BGN); orbital frontal cortex (OFC); ventromedial prefrontal cortex (vmPFC); cannabinoid receptor 1 (CB1R); hypothalamus-pituitary-gonadal (HPG); hypothalamus-pituitary-adrenal (HPA); huntingtin (HTT); brain-derived neurotrophic factor (BDNF); sigma 1 receptor (SR1).

Journal Pre-proof

Table 1. Preclinical findings of the neurobiology of depression in Huntington's disease

| Animal Model | Sex | Intervention | Depression task | Behavioral outcome | Main outcome | Major conclusion | Reference |
|--|-------------------|---|------------------|---|---|--|--------------------------|
| HTT | | | | | | | |
| YAC128 FVB/N strain background | females and males | YAC transgenic animals expressing a variant of mutant huntingtin that is resistant to cleavage at residue 586 (C6R) | FST SPT | ↑ immobility time and ↓ sucrose intake in YAC128 mice compared to WT and C6R mice φ between C6R and WT mice regarding both immobility time and SCT | Preventing cleavage of mutant HTT at residue 586 ameliorates depressive phenotype observed in YAC128 | HTT contributes as a primary basis of depression in HD | Poulac et al., 2014 |
| BACHD FVB/N strain background | females | rAAV-cre injection into the hypothalamus in order to inactivate mutant HTT | FST | ↓ immobility time in inactivated BACHD compared to BACHD mice φ immobility time between inactivated BACHD compared to WT mice | Inactivation of mutant HTT specifically in subset of the hypothalamic neurons prevented the development of the depressive phenotype | Hypothalamic HTT expression contributes to the development of depression in HD | Hult et al., 2014 |
| BACHD Tg(Nr5a1-Cre)7Lowl/J mice expressing Cre under the SF1 promoter (SF1) FVB/N and C57BL6/J strain background | females and males | Inactivation of mutant HTT in a specific neuronal population of the VMH expressing SF1 in the BACHD mouse using crossbreeding based on a Cre ^{loxP} system | FST | ↑ immobility time in BACHD females' mice when compared to WT and SF1 control littermates φ between BACHD-SF1 and BACHD mice φ in males | Inactivation of mutant HTT in SF1 neurons was not enough to prevent depressive-like behavior in female BACHD mice | Mutant HTT expression in VMH SF1 neurons is not responsible for the development of the psychiatric phenotype in BACHD mice | Baldo 2014 |
| Hdh ^{S1181A/S1201A} and Hdh ^{S1181D/S1201D} mutant mouse lines | females and males | Generation of knock-in mice in which the codons for serines at positions 1181 and 1201 of the gene encoding mouse HTT (Hdh) were replaced by codons for alanine (Hdh ^{S1181A/S1201A}) or aspartic acid (Hdh ^{S1181D/S1201D}), | Splash test (ST) | ↑ grooming time after 10% of sucrose was sprayed on the mouse coat in Hdh ^{S1181A/S1201A} in comparison with WT and Hdh ^{S1181D/S1201D} mice φ grooming between WT and | Abolition of mutant HTT phosphorylation at S1181/S1201 reduced depression-related behavior in mice | Unphosphorylated HTT is related to depression-related behavior | Ben M'Barak et al., 2014 |

| | | | | | | | |
|--|-------------------|---|-----|---|--|--|-------------------------|
| | | mimicking the absence of phosphorylation and constitutive phosphorylation of HTT by Cdk5 on these sites in order to decrease polyQ-HTT-mediated toxicity | | Hdh ^{S1181D/S1201D} mice | | | |
| BACHD FVB/N strain background | females and males | ED11 for 28 days, at a dose of 4 mg/kg/day – peptide that reduces mutant HTT proteolysis by caspase-6, protecting cells from mutant HTT toxicity | FST | Pre-symptomatic treatment prevented the ↑ in immobility time observed in BACHD mice Symptomatic treatment reversal the ↑ in immobility time observed in BACHD mice | ED11 protects against the depression-related phenotype | Protecting cells from mutant HTT toxicity lead to the protection of depression-related phenotype | Aharon et al., 20 |
| BACHD B6.FVB(129 × 1)-Tg(Sim1-Cre)1Lowl/J (Sim1-Cre) FVB/N strain background | females and males | Sim1-Cre mice express Cre under the Sim1 promoter thereby inactivating mutant HTT expression in Sim1 expressing cells mainly in PVN and sparsely in other areas of the hypothalamus and in the amygdala | FST | ↑ in immobility time between BACHD/Sim1-Cre and WT females at 2mo and 8mo of age ↑ in immobility time in BACHD males at 8mo of age, prevented in BACHD/Sim1-Cre | Inactivating the expression of mutant HTT in Sim1 neurons does not prevent the depressive-like behavior in female BACHD mice, only in males at 8mo of age together with a possible alteration in the HPG axis in BACHD male mice | Inactivation of mutant HTT in Sim1 neurons of the hypothalamus and amygdala in BACHD mice affected the metabolic and depressive-like phenotype in a sex-specific manner | Soylu-Kuchal et al., 20 |
| R6/2 Hdh knock-in CBB6 and C57BL6/J strain background | females and males | R6/2 mice carrying 120, 250, or 350 CAG repeats Hdh mice carrying 50, 150, or 250 CAG repeats | FST | R6/2 - floating 110CAG ↑6w, =8w, ↓12w 250CAG ↑6w, ↑↑8w, =12/16w 350CAG ↑6w, ↑8w, ↑↑12w, ↑16, =24 Hdh knock-in - floating φQ50 φQ150 Q250 ↑3mo, =6mo, =12mo | By an early stage increase in floating, and then, as the mice aged, floating decreased, whereas active behaviors of swimming and climbing increased | Floating in HD mice does not progress linearly, similarly to humans, suggesting that, at the late stages of the disease, an increase in serotonergic and noradrenergic activity might contribute to lower floating levels in HD mice | Ciamer et al., 20 |

Neurotransmitters

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|------|-------------|---------------------------|------------|------------------------|--|----------------------|-----------|
| R6/1 | females and | EE from 8-12 weeks of age | FST TST | Only females displayed | Altered serotonin receptor expression is | Altered serotonergic | Pang 2009 |
|------|-------------|---------------------------|------------|------------------------|--|----------------------|-----------|

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|-----------------------------|-------------------|---|--|---|---|---|---------------------|
| CBB6 strain background | males | Acute anti-depressant sertraline (20mg/kg) or desipramine administration | | depression-like phenotype Sertraline ↓ FST but not TST immobility time of female HD ϕ desipramine treatment in HD EE rescued depressive phenotype of female HD | associated with depressive-like behavior in females R6/1 HD. EE rescue depressive phenotype acting on same receptors and an SSRI is able to prevent depressive phenotype | signalling in hippocampus and cortex participates in the basis for the development of depression during the preclinical stages of HD | |
| R6/1 CBB6 strain background | females and males | Acute sertraline (20mg/kg) 5-HT _{2A/C} receptor agonist, 1-(2, 5-dimethoxy-4-(2-aminopropyl)-2-aminopropane ((6)DOI) and the 5-HT _{1A} receptor agonist, 8-hydroxy-di-n-propylaminotetralin ((6)-8-OH-DPAT) | FST TST SPT | Only females displayed depression-like phenotype Sertraline ↓ FST immobility time of female HD | The female-specific depression-like behavior was associated with an increased response to 8-OH-DPAT and a global reduction of serotonergic transmission | Disrupted serotonin signalling mediates the sexually dimorphic depression-like phenotype in HD mice | Renoir et al., 2010 |
| R6/1 CBB6 strain background | females | Chronic sertraline (10 and 20mg/kg) Exercise (running wheels) Both interventions from 8-12 weeks of age | FST TST SPT | Sertraline prevents ↑ immobility time in FST and ↓ saccharin preference Exercise prevents ↑ immobility time in FST | Chronic sertraline treatment and exercise corrected the serotonergic dysfunction and prevented the depressive-like behavior | Dysfunction of the 5-HT _{1A} autoreceptor is associated with depressive-like behavior exhibited by pre-motor symptomatic female HD mice | Renoir et al., 2010 |
| R6/1 CBB6 strain background | females | EE from 4-8 weeks of age [35S]GTP- γ -S for quantitative autoradiography of 5-HT _{1A} -mediated (\pm)-8-OH-DPAT | FST TST (stress-induced hyperthermia response) SPT | ϕ EE on prevention the despair- and anhedonia-like behaviors displayed by HD EE corrected the altered stress response observed in HD mice in TST at the stress-induced hyperthermia response | Antidepressant/anxiolytic-like effect of EE, regardless of genotype Reduction in 5-HT _{1A} receptor mediated stimulation of [35S]GTP- γ -S binding in the dorsal raphe nucleus and the hippocampus of HD animal | There is a specific regulatory role of the 5-HT _{1A} autoreceptor in mediating depressive-like behavior in HD but still remains to be elucidated | Renoir et al., 2010 |
| R6/1 | females | Acute bupropion (10 mg/kg) - | FST | Bupropion prevented ↑ | Bupropion was able to correct the depressive- | Dopaminergic signalling plays a | Renoir et al., 2010 |

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|---------------------------------------|-------------------|--|--|---|--|---|--------------------------|
| CBB6 strain background | | dopamine-norepinephrine reuptake inhibitor Acute haloperidol (0.3 mg/kg) - D2/3 receptor antagonist | | immobility time in FST observed in HD Pre-treatment with haloperidol blocked this effect | like behavior of HD mice possibly through dopamine D2/D3 receptor mechanisms. | role in the depressive-like pre-motor phase in HD | |
| YAC128 FVB/N strain background | females and males | Clorgyline (1.5, or 3 mg/kg) for 21-28d - irreversible MAO-A inhibitor | FST TST | φ on FST immobility time Clorgyline 3mg/kg ↓ immobility time in TST in HD | Clorgyline treatment inhibits MAO-A activity and rescues striatal neurotransmitter deficits in YAC128 HD mice reflecting in improvement of anxiety and depressive-like behaviors | Monoaminergic impairments in striatum has a role in the affective phenotypes observed in HD mice | Garcia Mirall et al., 20 |
| YAC128 FVB/N strain background | females and males | Varenicline (5mg/kg/day) for 28d - partial agonist of the alpha4/beta2 subtype of the nicotinic acetylcholine receptor | FST | Varenicline prevented ↑ immobility time in FST observed in late-stage symptomatic YAC128 ↑ swimming behavior in WT ↑ climbing behavior in YAC128 | varenicline decreased depressive-like behavior in late-stage symptomatic YAC128 | Dysfunctional cholinergic neurotransmission may contribute to depressive-like behavior in late-stage symptomatic HD | McGre et al., |
| R6/1 CBB6 strain background | females | Acute and chronic (4w) N-acetylcysteine (NAC) (500 mg/kg) DHK (20 mg/kg) - GLT-1 inhibitor CPG (200 mg/kg) - system xc- inhibitor Both 1.5h prior FST | FST | NAC rescues a depression-like endophenotype in HD mice | NAC shows antidepressant effects dependent on system xc- and GLT-1 and glutamate transporters in HD | Reductions in cysteine/cystine cause glutamate unbalance leading to depressive-like behavior in HD | Wright et al., 20 |
| BDNF | | | | | | | |
| YAC128 FVB/N strain background | females and males | Human recombinant BDNF (1.66 μg/kg) was injected intranasally once a day for 15d | SPT ST Tail suspension test (TST) FST | Prevented the ↓ in sucrose consumption in YAC128 ↑ grooming time in YAC128 Prevent the ↑ immobility time in TST observed in YAC128 φ immobility time in FST on | BDNF treatment is able to prevent the development of anhedonic- and apathetic-like behaviors in early-symptomatic YAC128 mice | BDNF treatment prevents depressive-like behavior in HD not through hippocampal neurogenesis | da F et al., |

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|---------------------------------------|-------------------|--|------------|--|---|---|-----------------------|
| | | | | the ↑ observed in YAC128 | | | |
| Hypothalamic axis dysfunctions | | | | | | | |
| R6/1 CBB6 strain background | females | Acute diarylpropionitrile (DPN, 0.1mg/kg) administration - ERβ agonist Acute dexamethasone (DEX, 0.1 mg/kg) and after 6h ACTH (500 μg/kg) – DEX-ACTH challenge Ovariectomy (OVX) | FST | φ OVX in HD mice, still ↑ immobility time compared to WT DPN ↓ immobility time in HD | Females HD have abnormalities of the HPG-axis in early stages and boosting the ERβ signalling via DPN injection, is able to reduce depression-like behavior | Alterations to sex-hormone regulation in early stages in females may contribute to depression aetiology in HD | Du e 2015 |
| Other directions | | | | | | | |
| YAC128 FVB/N strain background | females and males | Pridopidine 10 or 30 mg/kg - a phenylpiperidine, high affinity for the S1R Early treatment - for 10.5mo Late treatment - 8w | FST | Both doses in both early and late stage ↓ immobility time in YAC128 | Pridopidine leads to anxiolytic and antidepressant effects in YAC129 mice | Potentially sigma-1 receptor is involved in the neurobiology of depression phenotype in HD | Garcia Mirall al., 20 |
| YAC128 FVB/N strain background | female and male | Probucol (30mg/kg/day) for 5mo - phenolic lipid-lowering compound with antioxidant properties | TST FST | ↓ immobility time in YAC128 at TST at 4 and 6 mo ↓ immobility time in YAC128 at FST at 6 mo | Chronic treatment (3 and 5 months) with probucol was able to prevent the occurrence of depressive-like behaviors in YAC128 at both 4 and 6 months of age | Potentially oxidative dysfunction is related to the neurobiology of depression phenotype in HD | de Nascir Castro 2018 |

Huntingtin (HTT); YAC transgenic animals expressing a variant of mutant huntingtin that is resistant to cleavage at residue 586 (C6R); wild type (WT); forced swim test (FST); sucrose preference test (SPT); Huntington's disease (HD); transcription factor steroidogenic factor 1 (SF1); ventromedial nucleus of the hypothalamus (VMH); cyclin-dependent kinase 5 (Cdk5); splash test (ST); brain derived neurotrophin factor (BDNF), paraventricular nucleus of hypothalamus (PVN); hypothalamic gonadotropin-releasing hormone (GnRH); hypothalamus pituitary gonadal (HPG) axis; environmental enrichment (EE); tail suspension test (TST); 5-hydroxytryptamine/serotonin (5-HT); CBA6C57/B6 (CBB6); hydroxylase-2 (TPH2); monoamine oxidase A (MAO-A); dihydrokainic acid (DHK); (S)-4-carboxyphenylglycine (CPG); N-acetyl cysteine (NAC); glutamate transporter 1 (GLT1); dexamethasone (DEX); ovariectomy (OVX); sigma-1 receptor (S1R)