Huntington’s Disease – New Perspectives Based on Neuroendocrine Changes in Rodent Models

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Key Words
Huntington’s disease · Neuroendocrine · Mouse · Rat · Hypothalamus · Model

Abstract
Huntington’s disease (HD) is a neurodegenerative disorder caused by an expanded CAG repeat in the huntingtin gene. Although it is characterized by progressive motor impairments, cognitive changes and psychiatric disturbances are major components of the disease. In addition, recent studies have shown that other non-motor symptoms such as alterations in sleep pattern, disruption of the circadian rhythm and increased energy metabolism are common and occur early. Emerging evidence suggests that the latter symptoms are likely results of disturbed functions of the hypothalamus and neuroendocrine circuits, which are known to be central in the regulation of emotion, sleep and metabolism. Whereas clinical data are essential to define key pathological features of HD, animal models that can recapitulate the neurobiological and behavioral features of the disorder are critical tools to elucidate the underlying pathogenic mechanisms. Recent studies employing different HD rodent models have been instrumental in identifying a number of neuroendocrine alterations as well as in highlighting novel potential disease pathways. This review summarizes the current state of knowledge derived from neuroendocrine studies in rodent models of HD in light of clinical relevance and points to future implications for this emerging field.

Introduction
Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat in the huntingtin gene [1]. The huntingtin protein is expressed ubiquitously throughout the central nervous system and peripheral tissues both during embryonic development and adult life [2–4]. The normal function of huntingtin is not fully known but is thought to involve regulation of transcription, intracellular trafficking, synaptic vesicle exocytosis as well as apoptosis [5, 6]. The classic triad of clinical symptoms comprises motor impairments, cognitive decline and psychiatric disturbances, and was first comprehensively described in the literature in 1872 by the clinician George Huntington, who gave the disease its name [7]. Depressed mood, anxiety, irritability and apathy are the most common psychiatric symptoms and have been reported to affect between 35 and 75% of HD cases in different patient series [8]. These symptoms usually precede motor abnormalities by many
Huntington’s Disease – Neuroendocrine Changes in Rodent Models

Long ago, George Huntington noticed that individuals with HD suffer from emaciation. Early studies investigating body weight changes in HD found that severe weight loss occurs despite adequate nutrition [16] and that the caloric intake was increased in HD patients compared to healthy individuals [17]. Moreover, it was noted that HD patients with a high body mass index have a slower disease progression than leaner patients [18]. It was suggested early on that weight loss could be due to altered hypothalamic function [19], as it was known that alterations occur in energy metabolism in animal models with experimental lesions of hypothalamic structures (recently reviewed in Abizaid and Horvath [20]). Pioneering quantitative postmortem studies of the hypothalamus in HD demonstrated atrophy of the lateral tuberal nucleus in the hypothalamus, including loss of up to 90% of cells in this particular area [21, 22]. However, this nucleus is without known function, and no corresponding region has been found in rodents. As dopaminergic antagonists exerted a beneficial effect on chorea, it was hypothesized that dopaminergic activity was increased in brains with HD and also in the hypothalamus. Initial observations of increased levels of growth hormone (GH), which is released upon dopaminergic stimulation from the hypothalamus, supported this theory [23–25]. Follow-up studies found increased basal levels or increased release of GH after stimulation by dopaminergic agonists in HD patients [26–30]. Since dopamine stimulation inhibits prolactin release, the notion of increased dopaminergic activity gained further support from reports of reduced prolactin levels, which would be expected if the dopaminergic tone was high in the hypothalamus [31]. However, a number of other studies could not replicate the results of reduced prolactin levels [26, 32–34] or increased GH levels [32, 34]. It is possible that these studies were limited by unreliable clinical diagnosis as the huntingtin gene was first identified in 1993. Since these early studies, it has become clear that hypothalamic and neuroendocrine circuits are not only involved in the control of body weight but are also central in the regulation of emotion and sleep. Recent studies have shown that weight loss in HD is likely due to increased energy metabolism and is correlated with CAG repeat length [35–37]. The presence of symptoms such as alterations in sleep pattern and disruption of the circadian rhythm further support that hypothalamic dysfunction occurs in HD [38–42]. With the development of transgenic animal models for HD (an overview of all HD rodent models was recently provided by Heng et al. [43]) as well as with the increasing knowledge of hypothalamic function, new possibilities have paved the way to the study of neuroendocrine and hypothalamic disturbances in HD. In fact, a number of neuroendocrine changes have now been identified in rodent models of HD. These have been important in inspiring new clinical studies in this area and have also opened new insights into the pathophysiology of HD. This review summarizes the current state of knowledge derived from neuroendocrine studies in rodent models of HD in light of clinical studies in this area, and points to future implications for this emerging field.

**Hypothalamus and Neuroendocrine Circuits**

The neuroendocrine system comprises a network of specialized neurons and endocrine cells that regulate energy metabolism, reproduction, blood pressure, mood, stress, thermoregulation, sleep, and body fluid homeostasis. These cells are localized in areas such as the hypothalamus, the pituitary, the adrenal gland, the thyroid gland, the gonads, and white adipose tissue. The hypothalamus is the major regulatory area in the neuroendocrine system. It consists of several small interconnected nuclei that together play important roles in regulating metabolism, sleep as well as emotions [44–47]. The hypothalamic nuclei receive input from the periphery and send outgoing signals to other areas of the brain as well as back to the periphery. The endocrine axes originate from neurons in the hypothalamus which express factors which in turn stimulate the release of other factors in the pituitary and are released into the blood, and then act on peripheral organs such as the adrenal gland, the thyroid gland and the gonads. The hormones released from the peripheral glands exert a negative feedback on the hypothalamic neurons to regulate the endocrine circuitry.
Other peripheral signals that act on the hypothalamus include ghrelin (an appetite-promoting factor derived from adipocytes), leptin (a satiety factor released from adipocytes) and insulin (secreted from the pancreas) [20]. These factors enter the brain through the median eminence, which lacks a blood brain barrier and thereby regulate the activity of the arcuate nucleus, which is the most ventral part of the hypothalamus. Leptin inhibits neurons that co-express neuropeptide Y/agouti-related protein and activate neurons that co-express proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus, whereas ghrelin has the opposite effect [20]. These neurons project to orexin and melanin-concentrating hormone expressing neurons in the lateral hypothalamus where the signals are further processed and then sent to other areas of the brain as well as the periphery to regulate feeding and emotion. Thus, these peripheral hormones not only affect energy metabolism but also emotional regulation by exerting antidepressant functions [48, 49]. In fact, many other neuropeptides released from the hypothalamus are involved not only in regulation of metabolism but also emotion and sleep [45, 46].

Hence, the neuroendocrine circuitry is complex and interregulated. Besides important input from endocrine signals, the hypothalamus is also regulated by different neurotransmitter systems. Glutamate is the primary excitatory neurotransmitter in the hypothalamus, and all hypothalamic neuroendocrine populations receive glutamatergic input, and express both ionotropic and metabotropic glutamate receptors [50]. Recent studies indicate that these neurons c-release glutamate together with their hormone [51]. Furthermore, endocrine changes have been found to regulate the expression of vesicular glutamate transporters in hypothalamic neurons, and thereby regulate glutamate release from these cells [51]. Hypothalamic neurons also express D1 and D2 receptors, and dopaminergic input is known to modulate many hypothalamic functions, including metabolic control, and release of GH and prolactin [52, 53]. Interestingly, altered glutamatergic and dopaminergic signaling has been proposed as a contributing factor to selective striatal cell death observed in HD [5, 54–56]. Considering that not only the striatum but also the hypothalamus receives glutamatergic and dopaminergic input, this hypothesis could potentially be valid also for the vulnerability of specific hypothalamic neurons in HD. Hence, alterations in dopaminergic and/or glutamatergic signaling in the hypothalamus could lead to dysfunction and/or death of specific neuroendocrine populations, which would then affect the neuroendocrine circuitry. In fact, the lateral tuberal nucleus that is severely affected in HD expresses a high density of glutamate receptors [57] and downregulation of hypothalamic D2 receptors has recently been found in a positron emission tomography study of presymptomatic HD patients [58]. Taken together, when a change is observed in one component in the neuroendocrine system, it may be secondary to alterations in other parts of the system.

### Hypothalamic Changes in HD

Different rodent models for HD have been used to study hypothalamic and neuroendocrine changes in HD (table 1; recently reviewed in Heng et al. [43]). The most extensively studied transgenic HD model is the R6/2 mouse [59]. The R6/2 mouse constitutes the most rapidly progressing HD mouse model as it expresses the N-terminal fragment of human huntingtin encoded by exon 1 carrying around 150 CAG repeats [59]. The mice have a short life span and exhibit a number of important clinical features such as cognitive and motor disturbances, as well as neuronal intranuclear inclusions and transcriptional dysregulation [59–65]. Also, a number of hypothalamic changes have been found in this model. The hypothalamic area is atrophied as determined by postmortem analysis as well as using voxel-based morphometry of magnetic resonance images [82, 83]. However, stereological assessment of cresyl-violet-stained cells have not revealed major cell loss in this region [82]. Several distinct neuronal populations in the hypothalamus are small, however. Therefore, changes in their numbers may not be easily detected when total cell counts in the whole region are assessed. Indeed, loss of NeuN-positive neurons has been found in the lateral hypothalamic area of R6/2 mice [84]. Similarly, degenerative changes at the electron microscopic level have been detected in the hypothalamus of another transgenic mouse model of HD expressing the first 171 amino acids of the N-terminal huntingtin protein with 82 CAG repeats (the N171-82Q mouse) [60, 68, 69]. Furthermore, we have demonstrated progressive reduction in the number of orexin-expressing neurons in R6/2 mice [84]. Orexin is a neuropeptide selectively expressed in the hypothalamus, and is involved in the regulation of the sleep-wake cycle, energy metabolism as well as emotion [85]. The YAC128 mouse model expresses the full length the human huntingtin gene with 128 CAG repeats and recapitulates a number of clinical features such as motor disturbances, cognitive impairment, depressive-like behav-
ior as well as striatal neuronal loss [71–74]. Loss of orexin, although to a smaller extent, has also been found in the YAC128 mouse, which is likely to represent an earlier stage than the R6/2 mice [75]. Other specific neuronal populations expressing CART, proopiomelanocortin, vasopressin and melanin-concentrating hormone have been found to decline with time in R6/2 mice [82, 86]. Whether these changes are due to loss of neurons or reduced expression of the specific neuropeptides remains to be established. Decreased expression of mRNAs for CART and vasopressin as well as oxytocin, neuropeptide Y, thyroid-stimulating-hormone-releasing hormone and prepro-matostatin have been demonstrated in a transgenic mouse model expressing a mutant truncated N-terminal fragment of huntingtin with 190 CAG repeats as well as in R6/2 mice [87]. Reduced expression of the clock genes mPer2, mBmal1 as well as the vasoactive intestinal polypeptide in the suprachiasmatic nucleus, an important regulator of the diurnal rhythm, have also been found in R6/2 mice [38, 88]. Taken together, these results suggest broad transcriptional changes in the hypothalamus of at least two rodent models of HD.

Neuropathological analyses of the human HD hypothalamus are sparse. The finding of reduced numbers of orexin neurons in the rodent models (10–70%) have now been established in human HD where there is a decrease of around 30% of orexin-positive neurons in the hypothalamus [84, 89]. Hypothalamic atrophy, similar to that detected in R6/2 mice, has been reported in two clinical studies using voxel-based morphometry of magnetic resonance images from early HD patients [90, 91], but detailed neuropathological studies examining the survival of distinct neuronal subtypes in the whole hypothalamic region in human HD have yet to be performed.

### Alterations in the Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis begins with corticotropin-releasing factor (CRF) and vasopressin produced by the parvocellular neurons in the paraventricular nucleus of the hypothalamus. These neurons integrate information relevant to stress and receive input from limbic regions implicated in emotion regulation such as the prefrontal cortex, hippocampus and the amygdala (reviewed in Herman et al. [92]). CRF and vasopressin activate the secretion of adrenocorticotropic hormone from the pituitary, which in turn stimulates the release of glucocorticoids (corticosterone in rodents; cortisol in humans) produced in the adrenal gland. Glucocorticoids then act on glucocorticoid receptors and mineralocorticoid receptors present in the hypothalamus, the pituitary as well as the hippocampus. Glucocorticoids

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**Table 1. Overview on rodent models for HD used in studies of the neuroendocrine system**

<table>
<thead>
<tr>
<th>Model</th>
<th>CAG expansion</th>
<th>Characteristics</th>
<th>Survival</th>
<th>Selected ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R6/2 mouse</td>
<td>150 CAG repeats in exon 1 of the human huntingtin gene</td>
<td>reduced motor function, cognitive deficits, reduced anxiety-like behavior, progressive weight loss, NII, widespread central and peripheral pathology, transcriptional dysregulation</td>
<td>12–15 weeks</td>
<td>[59–65]</td>
</tr>
<tr>
<td>R6/1 mouse</td>
<td>120 CAG repeats in exon 1 of the human huntingtin gene</td>
<td>reduced motor function, cognitive deficits, depressive-like behavior, NII, transcriptional dysregulation</td>
<td>normal life span</td>
<td>[59, 66, 67]</td>
</tr>
<tr>
<td>N171-82Q mouse</td>
<td>82 CAG repeats in first 171 amino acids of human huntingtin gene</td>
<td>reduced motor function, progressive weight loss, NII; neuropathology in the cortex, striatum and hypothalamus, altered thermogenesis</td>
<td>20–24 weeks</td>
<td>[68–70]</td>
</tr>
<tr>
<td>YAC128 mouse</td>
<td>120 CAG repeats in the full-length huntingtin gene</td>
<td>hyperactivity followed by hypoactivity, cognitive deficits, depressive-like behavior, increased body weight, NII, striatal neuropathology</td>
<td>normal life span</td>
<td>[71–75]</td>
</tr>
<tr>
<td>CAG140 mouse</td>
<td>knock-in of chimeric mouse/human exon 1 containing 140 CAG repeats in the mouse huntingtin gene</td>
<td>hyperactivity followed by hypoactivity, altered anxiety-like behavior, striatal neuropathology, NII</td>
<td>normal life span</td>
<td>[76, 77]</td>
</tr>
<tr>
<td>tgHD rat</td>
<td>51 CAG repeats in the first 22% of the rat huntingtin gene</td>
<td>hyperactivity, cognitive deficits, reduced anxiety-like behavior, weight loss, NII, striatal neuropathology</td>
<td>98 weeks</td>
<td>[78–81]</td>
</tr>
</tbody>
</table>

NII = Neuronal intranuclear inclusions.
exert a negative feedback on the HPA axis both in the hypothalamus and the pituitary. The activated HPA axis exerts effects on both energy metabolism and immunity as well as on the regulation of cognitive and emotional functions [93, 94]. Increased activity of the HPA axis has been one of the most consistent findings in depression, and is thought to be a result of decreased responsiveness to glucocorticoids due to decreased function of glucocorticoid receptors. This phenomenon is known as glucocorticoid resistance and contributes to excessive inflammation as well as hyperactivity of CRF [94, 95].

We have previously reported that the HPA axis is upregulated in R6/2 mice [96]. These mice exhibit a progressive increase in corticosterone levels in serum and urine, and display typical consequences of an up-regulated HPA axis such as reduced bone mineral density, insulin resistance, muscle atrophy and reduced neurogenesis [96–100]. The R6/1 mouse, which expresses the same N-terminal fragment of the human HD gene as the R6/2 mouse but with only 120 CAG repeats, has normal corticosterone levels [59, 66]. The R6/1 displays a slower progressive phenotype than R6/2 mice with behavioral symptoms including depressive-like behavior as well as transcriptional dysregulation [66, 67]. Whether increased activity of the HPA axis is present in other transgenic models of HD is not yet known. The underlying mechanism responsible for the upregulated HPA axis in R6/2 mice has not been established. The recently described early immune activation with increased levels of IL-6 in R6/2 and YAC128 mice as well as in premanifest HD patients [101] could play a role as increased levels of cytokines can activate the HPA axis [93, 94]. Interestingly, inflammatory cytokines and their signaling pathways, including nuclear factor-κB, have been found to inhibit glucocorticoid receptor function and thereby to induce glucocorticoid resistance, and increased levels of cytokines such as IL-6 have repeatedly been found in depression [93, 95]. Hence, up-regulation of both the HPA axis and the immune system in HD may have relevance for the psychiatric disturbances as well as for wider hypothalamic disturbances as microglia activation was recently found to be present in the hypothalamus of premanifest HD subjects [58, 93, 94].

Only a few studies have so far examined the HPA axis in HD patients. Increased CRF levels have been found in the cerebrospinal fluid from patients with early HD [102]. Increased cortisol and vasopressin levels have been found in plasma and urine in clinical HD [86, 96,103, 104]. Ongoing studies in different laboratories are now examining these changes in further detail.

### Alterations in the Hypothalamic-Pituitary-Gonad Axis

The hypothalamic-pituitary-gonad axis consists of gonadotropin-releasing hormone (GnRH) expressed in the hypothalamus, luteinizing hormone and follicle-stimulating hormone released from the pituitary, and testosterone or estrogen produced in the gonads. Recent studies indicate that this axis is disturbed in obesity [105]. While there is a progressive reduction in the number of GnRH-expressing neurons in the R6/2 mouse, no changes have been found in the YAC128 mouse model [106, 107]. It is not known whether the GnRH-producing population in the human HD hypothalamus is affected. Both R6/2 and YAC128 mice display the testicular atrophy which has been found in HD patients, but only the R6/2 mouse recapitulates the clinically reduced testosterone levels in male HD patients [106–108]. A recent study investigated peripheral sex hormones in a rat model for HD expressing 51 CAG repeats in the first 22% of the huntingtin gene (tgHD rat) [78, 79]. This model recapitulates several important clinical aspects of HD such as hyperactivity, cognitive deficits, weight loss as well as striatal neuropathology [78–81]. Reduced testosterone levels and increased levels of dehydroepiandrosterone sulfate (DHEA; the major androgen secreted by the adrenals) were found in female tgHD rats [79]. However, female HD patients do not show alterations in testosterone or DHEA [109] and studies in male HD patients revealed reduced DHEA levels [104]. Interestingly, male tgHD rats displayed biphasic alterations in 17β-estradiol with increased levels in 4-month-old rats and decreased levels in 14-month-old rats compared to wild-type littermates [79]. This hormone has not yet been examined in clinical HD.

### Alterations in Peripheral Hunger and Satiety Signals Including Peripheral Neuroendocrine Pathology in HD

White adipose tissue has emerged as an important neuroendocrine regulator of energy metabolism through its secretion of factors such as leptin and adiponectin that act on the hypothalamus [110–112]. Abnormalities in adipocytes including a disturbed lipolysis were first found in R6/2 mice [76]. A recent study investigated adipocyte function in both R6/2 mice and a knock-in mouse model for HD, the CAG140 mouse, and found impaired expression of fat storage genes [77]. The CAG140 mouse model...
expresses a chimeric mouse/human exon 1 containing 140 CAG repeats inserted into the mouse huntingtin gene and displays a slow progression of motor and cognitive disturbances as well as striatal neuropathology [113, 114]. Adipocyte function has not yet been studied in clinical HD. Decreased levels of leptin have been found in N171-82Q mice, R6/2 mice, CAG140 mice [77, 115] and in clinical HD [116]. Interestingly, increased levels of leptin were found in younger stages of the CAG140 mice, which represent earlier disease stages than the other mouse models [77]. This finding indicates a biphasic pattern of leptin changes. As changes in adipokines were found prior to weight loss and behavioral symptoms in the R6/2 and CAG140 mice, these may be important for disease progression, and measurements of adipokines in symptomatic HD gene carriers would therefore be very interesting. Reports of reductions in ghrelin both in plasma and in the stomach mucosa in R6/2 mice and N171-82Q mice [82, 115] are however opposite to the increased plasma levels found in HD patients [116]. The findings of reduced levels of leptin and increased levels of ghrelin in clinical HD support a state of negative energy balance, as leptin levels are usually reduced to preserve energy whereas increased ghrelin levels serve to increase the energy stores. A negative energy balance caused by an increased metabolic rate has recently been demonstrated in N171-82Q mice, R6/2 mice and HD patients [35, 37, 70, 82, 117], although the link to hypothalamic dysfunction remains to be fully established. Importantly, peripheral changes in mitochondria due to transcriptional interference of PPARγ coactivator 1α (PGC1α), a key regulator of metabolism, may also lead to weight loss in HD [70]. Interestingly, it has been shown that cold challenge of the N171-82Q mouse leads to hypothalamic-driven sympathetic upregulation of PGC1α in brown adipose tissue, which suggested normal hypothalamic regulation of temperature [70]. In this study, the altered temperature control and weight loss were found to arise from interference on the level of PGC1α transcription of the uncoupling protein 1, the main effector of adaptive thermogenesis in mitochondria. This result indicated an interesting link between altered PGC1α function, transcriptional dysregulation and mitochondrial dysfunction in HD.

Despite initial and exciting reports on severe pancreatic pathology in R6/2 mice including reduced beta cell mass, reduced exocytosis and altered pancreatic gene expression [118–120], histological and gene expression analyses of human HD pancreas have not revealed any pathological changes [121]. R6/1 and R6/2 mice have repeatedly been found to have increased glucose levels and impaired glucose tolerance indicative of a diabetic phenotype [61, 96, 115, 118–120, 122]. Several of these studies have also reported that both R6/2 and N171-82Q mice develop insulin resistance [96, 115]. Interestingly, traditional treatments targeting the diabetic-like phenotype with insulin and metformin have had no effects on these mice [123, 124]. Importantly, a recent study using a glucagon-like peptide 1 receptor agonist, exendin 1, reported beneficial effects on changes in insulin, glucose and leptin as well as on motor performance and life span in N171-82Q mice [115]. In this article, it was suggested that insulin resistance develops from defective insulin/phosphoinositide 3-kinase signaling in the hypothalamus, which is accompanied with the observed reduced leptin levels [115]. Further studies are, however, needed to establish this causative link. Insulin resistance may be a clinical feature of HD as it was recently found that HD patients with a normoglycemic state exhibit impaired insulin secretion and develop insulin resistance [125]. Altered glucose metabolism per se is less likely to be a clinical HD feature. Although earlier studies have indicated that 10–25% of HD patients exhibit altered glucose metabolism [126], more recent studies have reported normal blood glucose levels [115, 125].

**Summary and Perspectives**

Animal models of neurodegenerative disorders are useful tools to discover novel pathological features as well as to elucidate underlying pathogenic mechanisms. Recent studies employing different HD rodent models have been instrumental in identifying a number of neuroendocrine changes as well as in highlighting novel potential disease pathways (table 2). The R6/2 mouse with its severe pathology has played a particularly important role in the emergence of novel candidate mechanisms for neuroendocrine changes in HD. On one hand, several neuroendocrine changes that are present in clinical HD were first detected, while the importance of others was re-discovered using this model. These changes include hypothalamic pathology with loss of orexin neurons, upregulation of the HPA axis, reduced leptin levels and insulin resistance (table 3).

On the other hand, as for every other model system, the R6/2 model has its limitations. First, the expression of an artificially short fragment of the huntingtin gene with a very long CAG repeat causes a widespread pathology and a representation of late to end-stage HD in this mouse. Thus a number of changes that have been detect-
ed in this model might simply not be present in the majority of the clinical HD populations. Secondly, the large range of both central and peripheral changes in the R6/2 model may render mechanistic studies difficult. Models representing an earlier stage of HD or new model systems where the expression of the transgene can be controlled spatially and temporally may therefore serve as more useful tools to dissect the underlying mechanism of the neuroendocrine changes. To date, however, relatively few studies are published examining neuroendocrine aspects in other rodent models of HD. Preclinical studies utilizing a variety of models with complementary but distinct disease-related relevance will enable more rapid testing of hypotheses as well as establishment of causative

**Table 2. Overview on neuroendocrine changes in rodent models for HD**

<table>
<thead>
<tr>
<th>Neuropeptide or hormone</th>
<th>Model</th>
<th>Change</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamic expression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orexin</td>
<td>R6/2</td>
<td>70% loss</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>YAC128</td>
<td>10% loss</td>
<td>[86]</td>
</tr>
<tr>
<td>CART, POMC, MCH</td>
<td>R6/2</td>
<td>reduced</td>
<td>[82]</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>R6/2</td>
<td>reduced</td>
<td>[86]</td>
</tr>
<tr>
<td>CRF</td>
<td>R6/2</td>
<td>reduced</td>
<td>[96]</td>
</tr>
<tr>
<td><strong>Serum levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>R6/2</td>
<td>increased</td>
<td>[96]</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>R6/2</td>
<td>increased</td>
<td>[96]</td>
</tr>
<tr>
<td>Leptin</td>
<td>R6/2</td>
<td>reduced</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td>NI71-82Q</td>
<td>reduced</td>
<td>[115]</td>
</tr>
<tr>
<td></td>
<td>CAG140</td>
<td>biphasic</td>
<td>[115]</td>
</tr>
<tr>
<td>Gherlin</td>
<td>R6/2</td>
<td>reduced</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>NI71-82Q</td>
<td>reduced</td>
<td>[115]</td>
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<tr>
<td></td>
<td>NI71-82Q</td>
<td>reduced</td>
<td>[115]</td>
</tr>
<tr>
<td></td>
<td>CAG140</td>
<td>reduced</td>
<td>[77]</td>
</tr>
<tr>
<td>Testosterone</td>
<td>R6/2</td>
<td>reduced</td>
<td>[106]</td>
</tr>
<tr>
<td></td>
<td>tgHD rat</td>
<td>increased</td>
<td>[79]</td>
</tr>
<tr>
<td>DHEA</td>
<td>tgHD rat</td>
<td>increased</td>
<td>[78]</td>
</tr>
<tr>
<td>Estradiol</td>
<td>tgHD rat</td>
<td>biphasic</td>
<td>[79]</td>
</tr>
<tr>
<td>Insulin</td>
<td>R6/2</td>
<td>biphase</td>
<td>[96, 120]</td>
</tr>
<tr>
<td></td>
<td>NI71-82Q</td>
<td>reduced</td>
<td>[115]</td>
</tr>
<tr>
<td>Glucose</td>
<td>R6/2</td>
<td>increased</td>
<td>[61, 118–120]</td>
</tr>
<tr>
<td></td>
<td>R6/1</td>
<td>increased</td>
<td>[122]</td>
</tr>
<tr>
<td></td>
<td>NI71-82Q</td>
<td>increased</td>
<td>[115]</td>
</tr>
</tbody>
</table>

CART = Cocaine- and amphetamine-regulated transcript; POMC = proopiomelanocortin; MCH = melanin-concentrating hormone; ACTH = adrenocorticotropic hormone.

**Table 3. Neuroendocrine changes in rodent HD models that have been confirmed in clinical HD**

<table>
<thead>
<tr>
<th>Areas</th>
<th>Animal model</th>
<th>Clinical HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>atrophy: R6/2 [82, 83]</td>
<td>atrophy [90, 91]</td>
</tr>
<tr>
<td>Orexin</td>
<td>loss of orexin: R6/2, YAC128 [84, 86]</td>
<td>loss of orexin [84, 89]</td>
</tr>
<tr>
<td>HPA axis</td>
<td>upregulation: R6/2 [96]</td>
<td>upregulation [96, 102, 104]</td>
</tr>
<tr>
<td>Testosterone</td>
<td>increased plasma levels: R6/2 [106]</td>
<td>increased plasma levels [108]</td>
</tr>
<tr>
<td>Insulin</td>
<td>insulin resistance: R6/2, N171-82Q [96, 115]</td>
<td>insulin resistance [125]</td>
</tr>
<tr>
<td>Leptin</td>
<td>decreased plasma levels: R6/2, N171-82Q, CAG140 [77, 115]</td>
<td>decreased plasma levels [116]</td>
</tr>
</tbody>
</table>

relationships between biological changes and behavior. While performing such studies in model systems, it will be essential to retain a parallel effort to validate the findings in HD patients in order to ascertain the clinical relevance of the discoveries. It is also likely that important lessons can be learnt from studies in the fields of depression and obesity where similar, if not identical, changes occur in the neuroendocrine and immune systems [46–48, 84, 85]. The identification of neuroendocrine and hypothalamic changes in HD, the definition of their precise relationship to alterations in immune and neurotransmitter systems and how they cause behavioral abnormalities in patients will lead us to better understand underlying mechanisms of nonmotor symptoms. In our view, such precise mechanistic information will be critical in the development of novel therapeutic strategies, especially those aiming at intervention at early stages and modification of the natural progression of HD.

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