The Role of Hypothalamic and Neuroendocrine Changes in the Pathogenesis of Huntington's Disease – Current Understanding and Implications for Future Treatments

Åsa Petersén

Associate Professor, Translational Neuroendocrine Research Unit, Department of Experimental Medical Sciences, Lund University

Abstract

Huntington's disease (HD) is a hereditary neurodegenerative disorder that leads to premature death. There is no satisfactory treatment or cure. The disease is caused by an expanded CAG repeat in the huntingtin gene. The clinical features are characterised by progressive motor symptoms, including chorea, which currently defines the clinical diagnosis of the disease. The motor aspect of HD is thought to be due to dysfunction and cell loss in the striatum of the basal ganglia. Cognitive impairment and psychiatric disturbances occur early and are major components of the disease. Recent studies have shown that other non-motor symptoms and signs, such as disruption of the circadian rhythm, sleep disturbances, autonomic dysfunction and metabolic changes, are also common and occur early. Several of these non-motor features are likely results of dysfunction of the hypothalamus and neuroendocrine circuits, which are known to be central in the regulation of emotion, sleep and metabolism. Increasing numbers of reports are now redefining HD as a disease with pathology spreading beyond the basal ganglia. This article provides an overview of current knowledge based on recent clinical studies demonstrating that hypothalamic and neuroendocrine changes are important features of HD.

Keywords

Huntingtin, Huntington's disease, hypothalamus, orexin, oxytocin

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Correspondence: Åsa Petersén, Translational Neuroendocrine Research Unit, BMC D11, 221 84 Lund, Sweden. E: Asa.Petersen@med.lu.se

Huntington's disease (HD) is a monogenetic disorder with a spectrum of clinical features. Besides the characteristic involuntary motor disturbances, such as chorea, individuals affected by the disease suffer from psychiatric symptoms and cognitive decline.[1–3] Despite this, focus on the movement disorder in clinical practice and the research of HD has been strong.

In recent years, studies of non-motor symptoms and signs in HD have revealed that sleep disturbances, disruption of the circadian rhythm, autonomic dysfunction and metabolic alterations are also common and occur early on in the disease process. Therefore the conventional notion that HD is solely a movement disorder caused by selective basal ganglia pathology had to be challenged.

The fact that the hypothalamus and its neuroendocrine circuitries are important regulators of emotion, sleep and bodyweight has stimulated research investigating to what extent this system is affected in HD. Although further studies are needed, the current literature now provides strong support for hypothalamic pathology and neuroendocrine alterations to be included as part of the clinical phenotype of HD.

This article reviews the current state of knowledge in terms of the clinical relevance of hypothalamic and neuroendocrine changes in HD.

The Genetics of Huntington's Disease

This hereditary and monogenetic neurodegenerative disease has a prevalence of around 1:10,000.[1] It is caused by an expanded CAG repeat in the huntingtin gene, which codes for an expanded polyglutamine in the huntingtin protein.[4] This protein is expressed in all tissues in the body. Although huntingtin protein's normal function is not fully known, it is thought to involve vesicle transport, transcriptional regulation and synaptic function.[5,6] CAG repeats of 40 or more cause the disease with full penetrance, with onset of motor symptoms in midlife. Huntingtin genes with between 37 and 39 CAG repeats have reduced penetrance. Intermediate repeats between 29 and 35 do not cause the disease but may expand to a pathogenic range in future generations. Juvenile onset (<20 years of age) occurs with more than 60 to 70 CAG repeats. Hence, longer CAG repeats are associated with a younger age of onset. The CAG repeat length accounts for around 60% of the variance in age of onset; genetic and/or environmental factors are thought to cause the rest.[7] Interestingly, the genetic modifiers that have so far been reported to influence the age of onset in HD include factors involved in the regulation of metabolism, such as huntingtin-associated protein 1 (HAP1) and PPARγ coactivator-1α (PGC-1α).[8,9]

Predictive and diagnostic genetic testing for HD is now available. Despite this, only around 15% of all individuals who develop the

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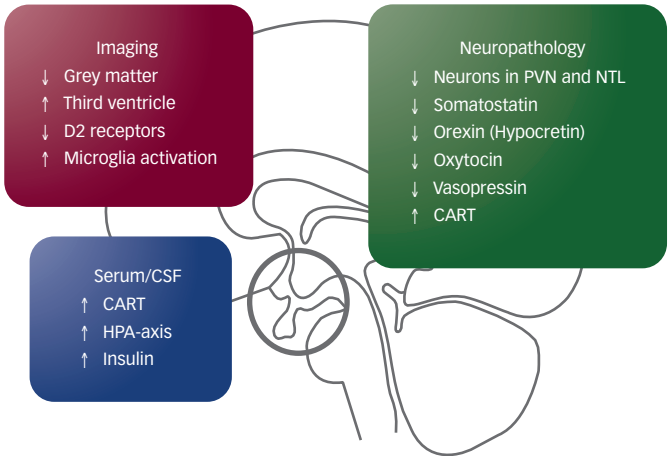
Figure 1: An Overview of the Main Hypothalamic and Neuroendocrine Changes in Clinical Huntington's Disease



CART = cocaine and amphetamine-regulated transcript; CSF = cerebrospinal fluid; D2 = dopamine D2; HPA = hypothalamic pituitary adrenal axis; NTL = nucleus tuberalis lateralis; PVN = paraventricular nucleus.
Source: Figure adapted from several articles.[48–51,56,66,67,69,70,72,76–78,82,93]

disease choose to undergo predictive testing, i.e. genetic testing, before they manifest any symptoms.[10]

Clinical Features

Clinical diagnosis currently requires unequivocal signs of motor disturbances, such as chorea, and death usually occurs 15 to 25 years after the onset of motor symptoms.[1,2] Psychiatric symptoms are common and include depression, anxiety and irritability.[11–13] There is an increased prevalence of suicidal ideation and suicide attempts in HD, particularly after receiving the formal diagnosis and at a later stage when independence diminishes.[14] Early cognitive changes include a 'frontal behaviour' characterised by apathy, disinhibition and executive dysfunction.[15] Other cognitive changes involve reduced processing speed and attention, and often progress to dementia.[16] Psychiatric and cognitive changes are now thought to precede the motor symptoms by many years.[17] Other non-motor features are also common and occur early. Sleep disturbances have a prevalence of around 90% and are characterised by an increased latency of sleep onset, reduced sleep efficiency, frequent nocturnal awakenings and delayed and shorted rapid eye movements.[18–21] HD patients also have an altered circadian rhythm and autonomic dysfunction.[22–25] Metabolic changes in HD include increased appetite, increased metabolism and weight loss in advanced stages of the disease.[26–28] In summary, the clinical presentation of HD is characterised by a relatively wide range of non-motor features that often precede the progressive motor symptoms. Therefore, unraveling the pathogenic mechanisms and the neurobiological origin of these early non-motor features is therefore likely to be crucial in understanding the full disease process and in identifying novel targets for disease-modifying intervention.

Pathology in the Basal Ganglia and Beyond

Cell loss and gliosis in the striatum of the basal ganglia are hallmarks of HD.[29] Medium spiny-aminobutyric acid (GABA)-ergic neurons in the striatum are selectively affected; whereas NADPH-diaphorase-expressing interneurons are spared.[29] The staging of neuropathological changes in HD is based on the extent of these changes in the striatum.[30] Loss of neurons and general atrophy also occur in the cerebral cortex and have recently been studied using imaging techniques.[31–33] Neuronal intranuclear inclusions (NIIs) of aggregated mutant huntingtin are present in these regions in HD patients.[34]

Interestingly, a study of a transgenic HD mouse model revealed that NIIs were present in many tissues in the body.[35] These results drew attention to the possibility that mutant huntingtin may exert pathological effects beyond the basal ganglia and the cerebral cortex. Indeed, peripheral tissues in HD patients display several pathological alterations. These include skeletal muscle wasting with mitochondrial dysfunction, atrophy of the testis with reduced testosterone production and hyperactive monocytes with peripheral immune activation (recently reviewed in van der Burg et al.).[36] The notion of HD being a selective basal ganglia disorder has hence been profoundly challenged.

Neuropathological Changes in the Hypothalamus in Huntington's Disease

The hypothalamus consists of a number of interconnected nuclei that express a variety of hormones and neuropeptides involved in control of the endocrine system as well as in the regulation of emotion, metabolism and sleep.[37–42] Studies investigating alterations of the hypothalamus and the neuroendocrine system in HD began over 60 years ago. The findings so far in both clinical HD and in animal models of the disease have been discussed in detail in a few reviews published in recent years.[43–46] The major positive results from studies investigating alterations in the hypothalamic and neuroendocrine system in clinical HD are illustrated in *Figure 1*.

Few studies have focused on neuropathology in the hypothalamus in HD. The first systematic analysis of a hypothalamic nucleus in HD was performed by Kremer et al., who described loss of somatostatin neurons in and atrophy of the nucleus tuberalis lateralis.[47–49] The function of this specific nucleus is still unclear. Loss of the neuropeptide orexin (also called hypocretin) – implicated in the sleep disorder narcolepsy as well as in the control of emotion and glucose metabolism – was demonstrated in the lateral hypothalamus of HD patients.[50,51] Although the loss of around 30% of orexin-expressing neurons in HD was not sufficient to be reflected in the cerebrospinal fluid (CSF), this finding inspired further studies focusing on sleep in HD as well as on the full extent of neuropathological changes in the hypothalamus in HD.[52–55]

Progress of the investigations into hypothalamic changes in HD has been limited by the scarcity of tissue from this region in brain banks and due to lack of a clear morphological definition of the borders of this region and its nuclei. A method has recently been established to accurately and in a reproducible fashion delineate this region using robust anatomical landmarks in brain sections stained with the cell marker cresyl violet and the myelin-staining luxol fast blue.[56] This technique has been used to perform a systematic stereological analysis of the hypothalamic region in HD. A trend towards atrophy of the whole hypothalamic volume was found in a relatively small cohort of nine HD cases compared with eight controls.[56]

Analysis of specific nuclei, such as the paraventricular nucleus, revealed that there was significant loss of neurons in this area in HD cases compared with controls.[56] Interestingly, reductions were also detected in the number of oxytocin- and vasopressin-expressing neurons in the HD hypothalamus. These neuropeptides have both been implicated in social behaviour.[38] In particular, oxytocin has been

found to increase trust, empathy and facial memory.[38,57,58] Therefore, it is possible that loss of oxytocin could be involved in the reduced recognition of facial expression of emotions that has been reported in HD patients.[59–65] Neuronal populations expressing neuropeptide Y and melanin-concentrating hormone were not found to be altered in the HD hypothalamus.[50,56] Hence, not all neuropeptide-expressing populations in the hypothalamus are affected in HD. Taken together, the neuropathological studies to date show that there is neuronal loss in specific nuclei of the human HD hypothalamus as well as alterations in emotion- and metabolism-controlling neuropeptides.

Imaging of the Hypothalamus in Huntington's Disease

The hypothalamic region has no clear anatomical borders and therefore provides a challenge for delineation in magnetic resonance images (MRIs). Using voxel-based morphometry (VBM), significant differences have been found in the grey-matter contents in the hypothalamic region between HD patients with motor symptoms and age- and sex-matched controls.[66,67]

A recent study continued to investigate the extent of changes in the hypothalamic region using MRI scans from the PREDICT-HD study. The PREDICT-HD study is a multicentre observational study that has enrolled a large number of individuals who have tested positive for the disease-causing huntingtin gene but who do not yet have motor symptoms, i.e. prodromal HD.[68] A significant reduction in gray matter signal was found in the hypothalamic region in prodromal HD that paralleled alterations in the striatum and insula over a decade before the expected onset of motor symptoms using VBM.[69]

A different approach based on mathematical modelling revealed that the gray matter content alone in the hypothalamic region in these MRIs was powerful enough to distinguish prodromal HD from controls. It was also possible to distinguish different groups of prodromal HD divided on expected time to motor onset using this approach. Another study using positron emission tomography has found reductions in dopamine D2 receptors as well as microglia activation in the hypothalamic region of prodromal HD.[70] Taken together, these results show that the hypothalamic region is affected early on in the pathogenesis of HD.

Alterations of Neuroendocrine Factors in the Cerebrospinal Fluid, Blood and Urine

It is well-known that some factors secreted from neurons in the central nervous system can be measured in the CSF. In other neurodegenerative disorders, such as Alzheimer's disease, alterations in CSF levels of tau, phosphorylated tau and the 42 amino acid form of amyloid-beta proteins are considered to reflect the disease process.[71] Measurements of these factors today guide the diagnosis of Alzheimer's disease and are used as biomarkers.

Biomarkers are usually divided into trait biomarkers – indicating a specific disease – and state biomarkers—reflecting the state in the disease process. In HD, the trait marker consisting of the mutant huntingtin gene is well established. State markers, which reflect disease process before the onset of motor symptoms in HD, are urgently needed for the evaluation of new, potential treatments. As factors in the neuroendocrine system can be measured in CSF and serum, and given the fact that this system is affected in HD, the hope of finding an altered neuroendocrine factor as a state biomarker for the disease has emerged. However, the search for a neuroendrocrine factor suitable as a biomarker is complicated. Such factors are part of interconnected and complex circuitries where the overall system strives to maintain homeostasis. Therefore, each factor is closely regulated. This is not the only challenge – a change in the level of one factor may be primary, due to the effects of the mutant HD gene, or secondary, due to changes in another part of the circuitry. Neuroendocrine factors may also be affected by the diurnal rhythm, satiety level, gender, age, medication and so forth. Variation in the available assays used to measure neuroendocrine factors is another major consideration. The reports published so far investigating the neuroendocrine system using CSF and blood measurements in HD have suffered from a large variation between and within studies.[43–46]

A few clinical studies investigating neuroendocrine factors in HD have revealed promising results. Increased levels of cocaine and amphetamine-regulated transcript (CART) have been found in the CSF. These levels may reflect the increased numbers of CART-immunopositive neurons detected in the human HD hypothalamus using immunohistochemistry.[56,72] CART is a neuropeptide known to increase anxiety-like behaviour in animal models and has been implicated in mood disorders.[73–75]

Analyses of the hypothalamic–pituitary–adrenal (HPA) axis in blood and urine have collectively pointed to an upregulation of this endocrine axis in HD.[76–78] An activated HPA axis has been one of the most consitant findings in clinical depression and may have negative effects on cognitive function and energy homeostasis.[79] Moreover, a delayed onset in the diurnal rise of melatonin has been found in HD patients, suggesting dysfunction in the hypothalamic suprachiasmatic nucleus.[80] This nucleus functions as a circadian clock, being the principal rhythm-generating system in humans.

Changes in hypothalamic function can also be reflected in alterations in afferent signals from the periphery. These afferent signals to the hypothalamus include:[81]

- leptin, a satiety signal from adipose tissue;
- ghrelin, an appetite signal from the gastric mucosa; and
- insulin, an anabolic peptide secreted from the pancreas.

Indeed, insulin resistance has been found in the early stages of HD.[82] Reduced leptin and increased ghrelin levels have been reported in later stages of HD, possibly reflecting the catabolic stage commonly occuring in advanced HD.[83] Despite these results, other studies have failed to detect a significant difference in leptin and ghrelin levels between HD patients and controls.[84,85] Further studies of different stages of HD, including prodromal HD, are therefore clearly required to elucidate how and to what extent the neuroendocrine system is affected in HD.

Current and Future Medical Treatment

There is no cure or disease-modifying treatment available for HD.[86] However, a variety of symptomatic treatments exist that can have significant beneficial effects on the psychiatric and motor symptoms of the disease.[1–3,87] Irritability, depression and anxiety are usually treated with selective serotonin-reuptake inhibitors. Motor symptoms are treated with the monoamine-depleting agent tetrabenazine or neuroleptic agents. The common combination of psychiatric symptoms with depression and/or anxiety, motor symptoms and

sleep disturbances often leads to an atypical neuroleptic agent, such as olanzapine, being chosen.[2]

A larger number of preclinical therapeutic studies and some emerging clinical trials are ongoing for HD.[3] Many of the clinical trials are based on promising effects of therapies in animal models of the disease. The possibility to reduce or inactivate the expression of the mutant huntingtin gene with different gene silencing approaches has recently gained significant attention.[88–90] Technical concerns remain, as does the choice of which region to target given that not all cells are likely to be reached using this technique. Naturally the striatum, with its severe pathology in human HD, has been the first site of choice for intracranial delivery in animal models. To what extent silencing the mutant huntingtin gene in the hypothalamus and/or the neuroendocrine system will have beneficial effects remains to be tested.

Importantly, hypothalamic dysfunction is implicated in mood disorders, obesity and type 2 diabetes. Intense research and drug development for these conditions is ongoing, with the aim of targeting distinct pathways in the hypothalamus.[91,92] The potential of there being common molecular changes between HD and other diseases affecting the hypothalamus opens up exciting possibilities for individuals with HD to benefit from the progress made for these much more common disorders. Likewise, HD with its monogenetic nature may provide a useful system model for similar disorders. Therefore, pre-clinical and clinical studies in HD may possibly facilitate advances that will be beneficial for a larger group of individuals affected by related disorders with hypothalamic dysfunction.

Huntington's Disease – A Hypothalamic Disorder?

Huntington's disease has traditionally been viewed as a movement disorder caused by selective striatal pathology. Today, HD is increasingly being recognised as a disorder at the crossroads of neurology, psychiatry, cognitive medicine and genetics. It has distinct but widespread pathology in both the brain and the periphery. It is now clear that one aspect of the disease constitutes hypothalamic dysfunction and pathology. Given the spectrum of non-motor symptoms and signs arising from disturbed functions that are normally, at least in part, regulated by the hypothalamus, it is tempting to speculate that hypothalamic dysfunction plays a role in causing them. Experiments using specific animal models are ongoing to better establish such structure-to-function relationships. Animal studies have been instrumental in getting clinicians to appreciate the non-motor signs in HD and to closer investigate hypothalamic and neuroendocrine changes.[46] Translational research will continue to be pivotal for determination of the full extent and clinical significance of hypothalamic and neuroendocrine changes in HD. ■

Åsa Petersén is an Associate Professor in Neuroscience at Lund University in Sweden. She is funded by a senior research fellowship from the Swedish Research Council allowing her to combine her research time with a residency in psychiatry. She directs the Translational Neuroendocrine Research Unit focusing on the neurobiological mechanisms underlying the psychiatric and metabolic aspects of Huntington's Disease (HD). Dr Petersén is a Member of the Scientific and Bioethics Advisory Committee of the European HD Network.

1. Novak MJ, Tabrizi SJ, Huntington's disease, *BMJ*, 2010;340:c3109.
2. Phillips W, Shannon KM, Barker RA, The current clinical management of Huntington's disease, *Mov Disord*, 2008;23(11):1491–504.
3. Sturrock A, Leavitt BR, The clinical and genetic features of Huntington disease, *J Geriatr Psychiatry Neurol*, 2010;23(4):243–59.
4. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes, The Huntington's Disease Collaborative Research Group, *Cell*, 1993;72(6):971-983.
5. Imarisio S, Carmichael J, Korolchuk V, et al., Huntington's disease: from pathology and genetics to potential therapies, *Biochem J*, 2008;412(2):191–209.
6. Zuccato C, Valenza M, Cattaneo E, Molecular mechanisms and potential therapeutical targets in Huntington's disease, *Physiol Rev*, 2010;90(3):905–81.
7. Gusella JF, MacDonald ME, Huntington's disease: the case for genetic modifiers, *Genome Med*, 2009;1(8):80.
8. Weydt P, Soyal SM, Gellera C, et al., The gene coding for PGC-1alpha modifies age at onset in Huntington's Disease, *Mol Neurodegener*, 2009;4:3.
9. Metzger S, Rong J, Nguyen HP, et al., Huntingtin-associated protein-1 is a modifier of the age-at-onset of Huntington's disease, *Hum Mol Genet*, 2008;17(8):1137–46.
10. Morrison P, Harding-Lester S, Bradley A, Uptake of Huntington disease predictive testing in a complete population, *Clin Genet*, Sept 6 2010; [Epub ahead of print].
11. Paulsen JS, Nehl C, Hoth KF, et al., Depression and stages of Huntington's disease, *J Neuropsychiatry Clin Neurosci*, 2005;17(4):496–502.
12. van Duijn E, Kingma EM, van der Mast RC, Psychopathology in verified Huntington's disease gene carriers, *J Neuropsychiatry Clin Neurosci*, 2007;19(4):441–8.
13. Kloppel S, Stonnington CM, Petrovic P, et al., Irritability in pre-clinical Huntington's disease, *Neuropsychologia*, 2010;48(2):549–57.
14. Paulsen JS, Hoth KF, Nehl C, et al., Critical periods of suicide risk in Huntington's disease, *Am J Psychiatry*, 2005;162(4):725–31.
15. Duff K, Paulsen JS, Beglinger LJ, et al., 'Frontal' behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: evidence of early lack of awareness, *J Neuropsychiatry Clin Neurosci*, 2010;22(2):196–207.
16. Peavy GM, Jacobson MW, Goldstein JL, et al., Cognitive and functional decline in Huntington's disease: dementia criteria revisited, *Mov Disord*, 2010;25(9):1163–9.
17. Duff K, Paulsen JS, Beglinger LJ, et al., Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study, *Biol Psychiatry*, 2007;62(12):1341–6.
18. Arnulf I, Nielsen J, Lohmann E, et al., Rapid eye movement sleep disturbances in Huntington disease, *Arch Neurol*, 2008;65(4):482–8.
19. Emser W, Brenner M, Stober T, et al., Changes in nocturnal sleep in Huntington's and Parkinson's disease, *J Neurol*, 1988;235(3):177–9.
20. Videnovic A, Leurgans S, Fan W, et al., Daytime somnolence and nocturnal sleep disturbances in Huntington disease, *Parkinsonism Relat Disord*, 2009;15(6):471–4.
21. Wiegand M, Moller AA, Lauer CJ, et al., Nocturnal sleep in Huntington's disease, *J Neurol*, 1991;238(4):203–8.
22. Aziz NA, Anguelova GV, Marinus J, et al., Sleep and circadian rhythm alterations correlate with depression and cognitive impairment in Huntington's disease, *Parkinsonism Relat Disord*, 2010;16(5):345–50.
23. Aziz NA, Anguelova GV, Marinus J, et al., Autonomic symptoms in patients and pre-manifest mutation carriers of Huntington's disease, *Eur J Neurol*, 2010;17(8):1068–74.
24. Hurelbrink CB, Lewis SJ, Barker RA, The use of the Actiwatch-Neurologica system to objectively assess the involuntary movements and sleep-wake activity in patients with mild-moderate Huntington's disease, *J Neurol*, 2005;252(6):642–7.
25. Morton AJ, Wood NI, Hastings MH, et al., Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease, *J Neurosci*, 2005;25(1):157–63.
26. Goodman AO, Murgatroyd PR, Medina-Gomez G, et al., The metabolic profile of early Huntington's disease – a combined human and transgenic mouse study, *Exp Neurol*, 2008;210(2):691–8.
27. Trejo A, Tarrats RM, Alonso ME, et al., Assessment of the nutrition status of patients with Huntington's disease, *Nutrition*, 2004;20(2):192–6.
28. Marder K, Zhao H, Eberly S, et al., Dietary intake in adults at risk for Huntington disease: analysis of PHAROS research participants, *Neurology*, 2009;73(5):385–92.
29. Vonsattel JP, DiFiglia M, Huntington disease, *J Neuropathol Exp Neurol*, 1998;57(5):369–84.
30. Vonsattel JP, Myers RH, Stevens TJ, et al., Neuropathological classification of Huntington's disease, *J Neuropathol Exp Neurol*, 1985;44(6):559–77.
31. Rosas HD, Lee SY, Bender AC, et al., Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection", *Neuroimage*, 2010;49(4): 2995–3004.
32. Rosas HD, Liu AK, Hersch S, et al., Regional and progressive thinning of the cortical ribbon in Huntington's disease, *Neurology*, 2002;58(5):695–701.
33. Rosas HD, Salat DH, Lee SY, et al., Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity, *Brain*, 2008;131(Pt 4): 1057–68.
34. DiFiglia M, Sapp E, Chase KO, et al., Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, *Science*, 1997;277(5334):1990–3.
35. Sathasivam K, Hobbs C, Turmaine M, et al., Formation of polyglutamine inclusions in non-CNS tissue, *Hum Mol Genet*, 1999;8(5):813–22.
36. van der Burg JM, Björkqvist M, Brundin P, Beyond the brain: widespread pathology in Huntington's disease, *Lancet Neurol*, 2009;8(8):765–74.
37. Hill JW, Elmquist JK, Elias CF, Hypothalamic pathways

linking energy balance and reproduction, *Am J Physiol Endocrinol Metab*, 2008;294(5):E827–32.
38. Insel TR, The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior, *Neuron*, 2010;65(6):768–79.
39. Kishi T, Elmquist JK, Body weight is regulated by the brain: a link between feeding and emotion, *Mol Psychiatry*, 2005;10(2):132–46.
40. Kleinridders A, Konner AC, Bruning JC, CNS-targets in control of energy and glucose homeostasis, *Curr Opin Pharmacol*, 2009;9(6):794–804.
41. Morton GJ, Cummings DE, Baskin DG, et al., Central nervous system control of food intake and body weight, *Nature*, 2006;443(7109):289–95.
42. Swaab DF, Neuropeptides in hypothalamic neuronal disorders, *Int Rev Cytol*, 2004;240:305–75.
43. Aziz NA, Swaab DF, Pijl H, et al., Hypothalamic dysfunction and neuroendocrine and metabolic alterations in Huntington's disease: clinical consequences and therapeutic implications, *Rev Neurosci*, 2007;18(3-4):223–51.
44. Hult S, Schultz K, Soylu R, et al., Hypothalamic and Neuroendocrine Changes in Huntington's Disease, *Curr Drug Targets*, 2010;11(10):1237–49.
45. Petersén A, Björkqvist M, Hypothalamic-endocrine aspects in Huntington's disease, *Eur J Neurosci*, 2006;24(4):961–7.
46. Petersén A, Hult S, Kirik D, Huntington's disease – new perspectives based on neuroendocrine changes in rodent models, *Neurodegener Dis*, 2009;6(4):154–64.
47. Kremer HP, The hypothalamic lateral tuberal nucleus: normal anatomy and changes in neurological diseases, *Prog Brain Res*, 1992;93:249–61.
48. Kremer HP, Roos RA, Dingjan G, et al., Atrophy of the hypothalamic lateral tuberal nucleus in Huntington's disease, *J Neuropathol Exp Neurol*, 1990;49(4):371–82.
49. Timmers HJ, Swaab DF, van de Nes JA, et al., Somatostatin 1-12 immunoreactivity is decreased in the hypothalamic lateral tuberal nucleus of Huntington's disease patients, *Brain Res*, 1996;728(2):141–8.
50. Aziz A, Fronczek R, Maat-Schieman M, et al., Hypocretin and melanin-concentrating hormone in patients with Huntington disease, *Brain Pathol*, 2008;18(4):474–83.
51. Petersén A, Gil J, Maat-Schieman ML, et al., Orexin loss in Huntington's disease, *Hum Mol Genet*, 2005;14(1):39–47.
52. Baumann CR, Hersberger M, Bassetti CL, Hypocretin-1 (orexin A) levels are normal in Huntington's disease, *J Neurol*, 2006;253(9):1232–3.
53. Björkqvist M, Petersén A, Nielsen J, et al., Cerebrospinal fluid levels of orexin-A are not a clinically useful biomarker for Huntington disease, *Clin Genet*, 2006;70(1):78–9.
54. Gaus SE, Lin L, Mignot E, CSF hypocretin levels are normal in Huntington's disease patients, *Sleep*, 2005;28(12):1607–8.
55. Meier A, Mollenhauer B, Cohrs S, et al., Normal hypocretin-1 (orexin-A) levels in the cerebrospinal fluid of patients with Huntington's disease, *Brain Res*, 2005;1063(2):201–3.
56. Gabery S, Murphy K, Schultz K, et al., Changes in key hypothalamic neuropeptide populations in Huntington disease revealed by neuropathological analyses, *Acta Neuropathol*, 2010;20(6):777–880.
57. Kosfeld M, Heinrichs M, Zak PJ, et al., Oxytocin increases trust in humans, *Nature*, 2005;435(7042):673–6.
58. Savaskan E, Ehrhardt R, Schulz A, et al., Post-learning intranasal oxytocin modulates human memory for facial identity, *Psychoneuroendocrinology*, 2008;33(3):368–74.
59. Calder AJ, Keane J, Young AW, et al., The relation between anger and different forms of disgust: implications for emotion recognition impairments in Huntington's disease, *Neuropsychologia*, 2010;48(9):2719–29.
60. Gray JM, Young AW, Barker WA, et al., Impaired recognition of disgust in Huntington's disease gene carriers, *Brain*, 1997;120(Pt 11):2029–38.
61. Hennenlotter A, Schroeder U, Erhard P, et al., Neural correlates associated with impaired disgust processing in pre-symptomatic Huntington's disease, *Brain*, 2004;127(Pt 6):1446–53.
62. Johnson SA, Stout JC, Solomon AC, et al., Beyond disgust: impaired recognition of negative emotions prior to diagnosis in Huntington's disease, *Brain*, 2007;130(Pt 7):1732–44.
63. Montagne B, Kessels RP, Kammers MP, et al., Perception of emotional facial expressions at different intensities in early-symptomatic Huntington's disease, *Eur Neurol*, 2006;55(3):151–4.
64. Sprengelmeyer R, Schroeder U, Young AW, et al., Disgust in pre-clinical Huntington's disease: a longitudinal study, *Neuropsychologia*, 2006;44(4):518–33.
65. Sprengelmeyer R, Young AW, Calder AJ, et al., Loss of disgust. Perception of faces and emotions in Huntington's disease, *Brain*, 1996;119(Pt 5):1647–65.
66. Douaud G, Gaura V, Ribeiro MJ, et al., Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study, *Neuroimage*, 2006;32(4):1562–75.
67. Kassubek J, Juengling FD, Kioschies T, et al., Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study, *J Neurol Neurosurg Psychiatry*, 2004;75(2):213–20.
68. Paulsen JS, Hayden M, Stout JC, et al., Preparing for preventive clinical trials: the Predict-HD study, *Arch Neurol*, 2006;63(6):883–90.
69. Soneson C, Fontes M, Zhou Y, et al., Early changes in the hypothalamic region in prodromal Huntington disease revealed by MRI analysis, *Neurobiol Dis*, 2010;40(3):531–43.
70. Politis M, Pavese N, Tai YF, et al., Hypothalamic involvement in Huntington's disease: an in vivo PET study, *Brain*, 2008;131(Pt 11):2860–9.
71. Blennow K, Hampel H, Weiner M, et al., Cerebrospinal fluid and plasma biomarkers in Alzheimer disease, *Nat Rev Neurol*, 2010;6(3):131–44.
72. Björkqvist M, Leavitt BR, Nielsen JE, et al., Cocaine- and amphetamine-regulated transcript is increased in Huntington disease, *Mov Disord*, 2007;22(13):1952–4.
73. Pae CU, Lee C, Paik IH, Therapeutic implication of cocaine- and amphetamine-regulated transcript (CART) in the treatment of depression, *Med Hypotheses*, 2007;69(1):132–5.
74. Stanek LM, Cocaine- and amphetamine related transcript (CART) and anxiety, *Peptides*, 2006;27(8):2005–11.
75. Wiehager S, Beiderbeck DI, Gruber SH, et al., Increased levels of cocaine and amphetamine regulated transcript in two animal models of depression and anxiety, *Neurobiol Dis*, 2009;34(2):375–80.
76. Aziz NA, Pijl H, Frölich M, et al., Increased hypothalamic-pituitary-adrenal axis activity in Huntington's disease, *J Clin Endocrinol Metab*, 2009;94(4):1223–8.
77. Björkqvist M, Petersén A, Bacos K, et al., Progressive alterations in the hypothalamic-pituitary-adrenal axis in the R6/2 transgenic mouse model of Huntington's disease, *Hum Mol Genet*, 2006;15(10):1713–21.
78. Saleh N, Moutereau S, Durr A, et al., Neuroendocrine disturbances in Huntington's disease, *PLoS One*, 2009;4(3):e4962.
79. Gallagher P, Reid KS, Ferrier IN, Neuropsychological functioning in health and mood disorder: Modulation by glucocorticoids and their receptors, *Psychoneuroendocrinology*, 2009;34(Suppl. 1):S196–207.
80. Aziz NA, Pijl H, Frolich M, et al., Delayed onset of the diurnal melatonin rise in patients with Huntington's disease, *J Neurol*, Jun 9 2009; [Epub ahead of print].
81. Jordan SD, Könner AC, Brüning JC, Sensing the fuels: glucose and lipid signaling in the CNS controlling energy homeostasis, *Cell Mol Life Sci*, 2010;67(19):3255–73.
82. Lalic NM, Maric J, Svetel M, et al., Glucose homeostasis in Huntington disease: abnormalities in insulin sensitivity and early-phase insulin secretion, *Arch Neurol*, 2008;65(4):476–80.
83. Popovic V, Svetel M, Djurovic M, et al., Circulating and cerebrospinal fluid ghrelin and leptin: potential role in altered body weight in Huntington's disease, *Eur J Endocrinol*, 2004;151(4):451–5.
84. Aziz NA, Pijl H, Frölich M, et al., Growth hormone and ghrelin secretion are associated with clinical severity in Huntington's disease, *Eur J Neurol*, 2010;17(2):280–8.
85. Aziz NA, Pijl H, Frölich M, et al., Leptin secretion rate increases with higher CAG repeat number in Huntington's disease patients, *Clin Endocrinol (Oxf)*, 2010;73(2):206–11.
86. Mestre T, Ferreira J, Coelho MM, et al., Therapeutic interventions for disease progression in Huntington's disease, *Cochrane Database Syst Rev*, 2009(3):CD006455.
87. Mestre T, Ferreira J, Coelho MM, et al., Therapeutic interventions for symptomatic treatment in Huntington's disease, *Cochrane Database Syst Rev*, 2009(3):CD006456.
88. Boudreau RL, McBride JL, Martins I, et al., Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice, *Mol Ther*, 2009;17(6):1053–63.
89. Drouet V, Perrin V, Hassig R, et al., Sustained effects of nonallele-specific Huntingtin silencing, *Ann Neurol*, 2009;65(3):276–85.
90. DiFiglia M, Sena-Esteves M, Chase K, et al., Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits, *Proc Natl Acad Sci U S A*, 2007;104(43):17204–9.
91. Krishnan V, Nestler EJ, Linking molecules to mood: new insight into the biology of depression, *Am J Psychiatry*, Sept 15 2010; [Epub ahead of print].
92. Sargent BJ, Moore NA, New central targets for the treatment of obesity, *Br J Clin Pharmacol*, 2009;68(6):852–60.
93. Kremer HP, Roos RA, Dingjan GM, et al., The hypothalamic lateral tuberal nucleus and the characteristics of neuronal loss in Huntington's disease, *Neurosci Lett*, 1991;132(1):101–4.