Huntington's disease : hypothalamic, endocrine and metabolic aspects

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GENERAL INTRODUCTION

&

AIMS OF THE THESIS

"…The hereditary chorea, as I shall call it, is confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire necessity, when it is mentioned as 'that disorder'. It is attended generally by all the symptoms of common chorea, only in aggravated degree hardly ever manifesting itself until adult or middle life, and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self… I know nothing of its pathology. I have drawn your attention to this form of chorea gentlemen, not that I consider it of any great practical importance to you, but merely as a medical curiosity, and as such it may have some interest."

George Huntington *On chorea. Medical and Surgical Reporter. 1872; Vol. XXVI., pp. 317-21.*

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1. INTRODUCTION

Huntington's disease (HD) is an autosomal dominant progressive, neurodegenerative disorder caused by an expanded trinucleotide (CAG) repeat in the HD (*HTT*) gene, located on the short arm of chromosome 4. Unwanted choreiform movements, psychiatric and behavioural problems and cognitive impairment characterize the disease.[74] Other less well-known, but debilitating manifestations of HD include weight loss, sleep disturbances and autonomic nervous system (ANS) dysfunction. Only little is known about the exact pathophysiological mechanisms underlying these symptoms. In recent years, novel insights have emerged from both animal and human studies indicating the existence of substantial hypothalamic pathology and dysfunction in HD, even in an early phase of the disease.[94] Considering the pivotal role of the hypothalamus in the regulation of systemic energy homeostasis, sleep-wake states and ANS functions,[92,207,208,232,236] hypothalamic dysfunction per se as well as secondary (neuro)endocrine and metabolic alterations could partly explain the pathogenesis of emaciation, sleep disturbances and autonomic failure in patients with HD; nonetheless, the anatomical and functional abnormalities of the hypothalamus in HD have not been systematically studied in conjunction with these and other clinical parameters. Therefore, after summarizing the precise characteristics of weight loss, sleep and ANS problems in HD, this review aims to: 1) describe the precise nature of hypothalamic dysfunction and neuroendocrine and metabolic alterations in HD, and 2) link these abnormalities to the aforementioned clinical manifestations, thereby providing rationale for future animal and clinical studies on the relation between hypothalamic dysfunction and symptomatology in HD. Assuming that hypothalamic dysfunction and consequent neuroendocrine and metabolic abnormalities could contribute to the weight loss and disturbances of sleep and autonomic functions in HD, some therapeutic strategies will be discussed as well.

2. CHARACTERISTICS OF WEIGHT LOSS, SLEEP DISTURBANCES AND AUTONOMIC DYSFUNCTION IN HD

2.1. Weight loss

Weight loss frequently complicates HD and is particularly marked in the later stages of the disease.[112,140]. Several studies, including clinical follow-up[187] and cross-sectional prevalence studies[52,181,215], anthropometric measurements with dietary evaluations[62,63,216] as well as one post-mortem study of 217 cases,[149] have all shown that many HD patients are either underweight or tend to lose weight in the course of their illness and eventually become cachectic. An exception is the recent study by Hamilton et al.[73] that assessed weight changes in 927 adults with HD who were followed prospectively for about 3 years. The authors found that most HD patients maintained their weight and that, on the whole, the patient group gained approximately 0.11 kg per year. However, on average their entire group of HD patients gained less weight than the United States national average, as per the third National Health and Nutrition Examination Survey,[73] and weighed almost 10 kg less than a community sample of comparably aged adults.[73] It is very likely that clinical information not available for that study—for example, the introduction of nutritional supplements, institutional placement, and types of drugs used (notably neuroleptics and antidepressants)—could account for the surprising pattern of weight change found by Hamilton et al.

In contrast to the weight loss associated with most other diseases, the emaciation in HD is not accompanied by anorexia but usually by an increased appetite.[62,63,146,187,216] An increased caloric intake could possibly also underlie the peculiar observation of an inverse relation between the age-at-onset of the disease and the daily milk consumption in Dutch HD patients[32] since the onset of HD could be marked by an increased demand for calories. Furthermore, in a longitudinal, prospective study of 30 patients with HD, Trejo et al.[215] found that although nutritional supplementation (i.e. 473 kcal added to the regular diet) over a 90-day-period could stabilize or slightly improve body weight, it could not induce a significant change in body mass index in 87% of the patients. These findings support the notion that HD patients have an increased energy requirement.[146]

Little is known about the pathophysiological mechanisms underlying weight loss in HD. Although dysphagia can complicate food intake.[91,124,216] and there are indications of a higher sedentary energy expenditure due to increased spontaneous physical activity (unwanted movements),[68,172,203] these findings do not explain the lower body mass index (BMI) found in certain groups of asymptomatic subjects at-risk for HD[62,63] nor do they account for the lower body weight of those HD patients who are at an early stage of the disease when both dysphagia and unwanted movements are still absent.[52] Moreover, it appears that HD patients tend to lose most weight in the final *hypokinetic* stages of the disease,[187] although weight gain may occur in some advanced-stage patients.[146] Weight loss frequently leads to progressive general weakening, resulting in an increasingly higher risk of developing co-morbidity, which causes a further decline in the patient's quality of life.[146] A survey of patients in Venezuela demonstrated that a substantial number of them were malnourished,[140] and in the United States nutritional deficiencies cause or contribute to death more frequently in HD patients than in controls.[118,119] Moreover, one study has demonstrated that a higher body weight in the early stages of the disease is associated with slower disease progression.[145] Therefore, the mechanisms which cause weight loss in HD may also underlie and/or aggravate the neurodegenerative process per se. In this regard dysfunction and pathology of various hypothalamic structures, notably the nucleus tuberalis lateralis (NTL) and the lateral hypothalamus, are likely to be involved (refer to the section 'Hypothalamic pathology in HD').

2.2. Sleep disturbances

From a postal self- or carer-completion questionnaire community survey Taylor et al.[212] estimated the prevalence of sleep problems to be almost 90 percent in HD patients. Nearly two-thirds of the respondents rated the sleep problems as either 'very' or 'moderately' important contributing factors to overall problems. Moreover, the majority of the principal carers also reported significant sleep disruption, primarily attributable to the patients' sleep problems, which adversely affected their relationship with the patient.[212] Polysomnography in patients with HD showed sleep fragmentation in moderately to severely affected cases, with progressive deterioration as the disease progresses.[231] Sleep efficiency (i.e. the ratio between time spent asleep and total amount of time spent in bed) has been reported as varying from 48% to 80%, with frequent nocturnal awakenings, an increase of stage I non-rapid eye movement (NREM) sleep and a reduced amount of slow wave sleep.[39,164,199,231] Also a shortening of rapid eye movement (REM) sleep latency, which is a cardinal characteristic of the sleeping pattern in narcolepsy patients, has been documented[86] as well as a significant increase in sleep spindle density during phase II NREM sleep.[58,199] Two recent studies applying wrist actigraphy demonstrated dysregulation of the

sleep-wake cycle and circadian timing in HD patients.[84,141] During sleep, patients not only showed significantly more activity and spent more time making high acceleration movements, but they also made significantly more movements than control subjects.[84] Although the presence of dyskinesia [66], medication effects and depression may contribute to sleep disturbances observed in HD,[39] the precise pathogenetic mechanisms responsible for sleep disturbances in HD patients remain largely unexplored. Particularly disease-specific neurodegenerative changes affecting (hypothalamic) structures regulating sleep-wakefulness have not been systematically investigated. However, changes in the suprachiasmatic nucleus (SCN) and (functional) alterations in the hypothalamic histaminergic and orexinergic systems in HD are probably among the mechanisms involved (for further details refer to the sections 'Hypothalamic pathology in HD' and 'Aminergic and neuropeptidergic alterations in HD brains suggestive of hypothalamic dysfunction'). Given the high prevalence of sleep disorders in HD and their devastating impact on the quality of life of both patients and carers,[212] it is of the utmost importance to elucidate the underlying pathogenic pathways in order to devise effective therapeutic strategies.

2.3. Autonomic nervous system dysfunction

Vegetative symptoms indicative of autonomic nervous system (ANS) dysfunction have repeatedly been reported in patients with HD and include defects in postural vasoregulatory mechanisms,[2,3] hyperhydrosis of hands and feet, and disturbances of micturition,[28] and swallowing difficulties.[91,124] Although vegetative symptoms are most prominent in the advanced stages of the disease,[99,146] autonomic complaints such as dizziness following standing up, excessive perspiration and tachycardia can occur even in mildly disabled HD patients (i.e. Shoulson and Fahn stages I and II[196]) and even in otherwise asymptomatic gene carriers.[100]

Several studies have investigated ANS function in HD patients by means of a series of standardized tests, such as the blood pressure response to sustained handgrip,[50,100] the pupillary light reflex latency,[50] orthostatic blood pressure test,[6,50,100,192] heart rate variability at rest and during the Valsalva maneuver, and the sympathetic skin response.[6,50,192] Compared to controls, the blood pressure response to sustained handgrip, a test of sympathetic function, was diminished in the patient group with a relatively long duration of disease.[50,100] In contrast, the blood pressure response to sustained handgrip in a group of *mildly* disabled HD patients was elevated.[100] The pupillary light reflex latency[50] as well as the sympathetic skin response (SSR) latencies[6,192] were prolonged in HD patients, suggesting parasympathetic and sympathetic dysfunction, respectively. The SSR amplitudes were also diminished in the patient group.[6,192] Overall, patients showed lower heart rate variability (HRV) indices than controls.[6,192] Spectral analysis of HRV, which yields several frequency bands of interest, demonstrated sympathetic *hyper*activity in the *asymptomatic* gene carriers by a higher power of low frequency band (LFB; 0.04-0.15 Hz).[100] Similarly, a higher power of LFB and an increase in the ratio between LFB to high frequency band (HFB; 0.15-0.40 Hz) was demonstrated in *mildly disabled* HD patients.[100] LFB in the supine position reflects both the sympathetic and parasympathetic activities and HFB reflects mainly vagal activity. A higher LFB/HFB ratio, which can be considered as a marker of sympathovagal balance, indicates a relatively higher cardiac sympathetic activity in the group of *mildly* affected HD patients.[100] However, ANS *hypo*function, predominantly parasympathetic dysfunction, was found in more advanced HD patients,[100] although an earlier study of parasympathetic function in HD had not found any abnormalities.[34] Moreover, the prolonged SSR latencies, smaller amplitudes, and lower HRV detected in HD patients by some investigators seemed to closely

correlate with various components of the Unified Huntington Disease Rating Scale (UHDRS) scores.[6,192] The exact origin of impaired ANS function in individuals with HD remains to be elucidated.

3. HYPOTHALAMIC DYSFUNCTION IN HD

Emaciation, sleep disturbances and autonomic dysfunction are on the one hand important indicators of the rate of disease progression and on the other hand these symptoms can considerably diminish the quality of a patient's life. Therefore, it is important to elucidate the pathophysiology of these symptoms in order to strike novel and more effective therapeutic targets. As mentioned before, the precise aetiology of these symptoms in HD is largely unknown. Nevertheless, several lines of evidence derived from studies in both patients with HD and HD animal models indicate that HD is accompanied by considerable hypothalamic dysfunction, even in the very early stages of the disease. Since the hypothalamus is the main control centre in the brain involved in the regulation of body energy homeostasis, sleep-wake cycles and the coordination of autonomic functions,[89,92,207,208,232,236] we propose that hypothalamic dysfunction per se as well as subsequent (neuro)endocrine and metabolic abnormalities in patients with HD may be the primary underlying cause of the aforementioned symptoms or substantially contribute to their pathogenesis. In order to substantiate this hypothesis, we will give an overview of all the findings suggestive of hypothalamic dysfunction in HD and attempt to link them to the HD symptomatology with a special focus on weight loss, sleep and autonomic disturbances.

3.1. Hypothalamic pathology in HD

A comprehensive summary of hypothalamic changes in HD patients, found in post-mortem brain preparations, has been given by Swaab.[208] In short, qualitative changes are presumed in the supraoptic nucleus (SON) and the paraventricular nucleus (PVN), [188,227] the ventromedial nucleus (VMN) and the lateral hypothalamus.[29] Normally, the neurons of the PVN project not only to the neurohypophysis and the median eminence, but also to various brainstem nuclei as well as to the intermediolateral columns of the spinal cord, and in this way modulate and coordinate various autonomic functions,[92] including autonomic innervation and control of adipose tissue.[67,109,110] Moreover, the PVN, VMN and the lateral hypothalamus are tightly involved in the physiological regulation of body energy homeostasis. So, pathology of these structures in HD could cause symptoms such as weight loss and autonomic failure. However, the cited papers about hypothalamic changes in HD generally describe a single[188] or a few cases,[29,227] while systematic morphological studies, such as performed for the NTL (see further), have not been reported for the PVN, VMN or the lateral hypothalamus (H.P. Kremer, thesis). Quantitatively, no significant neuronal loss was found in the nucleus basalis of Meynert.[41] Kremer et al.[111,113,114] elaborated on the previous reports of a striking cell loss in the NTL of HD patients[228,229] and found that the NTL is indeed consistently affected in this disorder: up to 90% of the neurons in the NTL were lost in HD brains, while the remaining neurons showed features of degeneration.[113,114] Moreover, they found astrocytosis with an unchanged number of astrocytes, whereas the number of oligodendrocytes was reduced by 40%. The neurons of the tubero-mammillary nucleus (TMN) seemed to be largely well preserved.[113] The log-transformed neuronal counts in the NTL of HD patients correlated closely with age at death (n =16; $r = 0.66$; $p < 0.01$) and

age of onset (n = 16; $r = 0.78$; $p < 0.001$), but neither with the duration of the disease, nor with the severity of the neostriatal changes.[114] Patients who had died young or who first displayed motor disturbances at an early age had considerably fewer neurons left than HD patients who had died in old age.[114] The authors hypothesized that the NTL is entwined in a network of structures involved in the regulation of feeding and weight and that weight loss in the course of HD is the expression of NTL pathology[112] since the loss of NTL neurons is less marked in patients with an older age at onset of the disease and the fact that late-onset patients tend to have a higher BMI at initial examination which is associated with a slower rate of disease progression.[145] Recently, the neuropathological data obtained from the aforementioned studies were extended by an in vivo study which demonstrated, by using magnetic resonance imaging and the technique of voxel based morphometry, that even in the early stages of the disease considerable hypothalamic neuronal atrophy is present in HD patients,[94] which is in line with the view that hypothalamic changes are both consistent and early features of HD.

In HD mouse models considerable anatomical and/or functional hypothalamic alterations have also been identified recently [107,127,141,156,162]. For example, Morton et al. [141] found a profound disintegration of circadian behaviour in the R6/2 mouse strain which was accompanied by marked disruption of expression of the circadian clock genes *mPer2* and *mBmal1* in the suprachiasmatic nuclei and associated with reduced SCN expression of prokineticin 2, a transcriptional target of mBmal1 encoding a neuropeptide that normally suppresses daytime activity in nocturnal mammals [141]. These animal data are thus also in favour of the notion that pronounced hypothalamic changes may be a consistent feature of HD.

Exactly why the hypothalamus is involved in HD is not known. However, one intriguing possibility could be the abnormal interaction of mutant huntingtin with huntingtin-associated protein 1 (Hap1) which is more abundantly expressed in the hypothalamus than in other brain regions.[194] Inhibition of Hap1 expression in vitro decreases epidermal growth factor receptor signalling and cell viability whereas overexpression of Hap1 enhances this signalling activity and inhibits mutant huntingtin-mediated cytotoxicity.[127] Moreover, deletion of *Hap1* causes the selective degeneration of hypothalamic neurons.[127] Interestingly, recently it was demonstrated that Hap1 is involved in intracellular trafficking of the $GABA_A$ receptor, and that insulin exerts its feeding-inhibitory actions by downregulating Hap1 expression. Decreasing the expression of mouse hypothalamic Hap1 caused a decrease in food intake and body weight.[194] A link between mutant huntingtin expression, hypothalamic degeneration and weight loss may therefore be provided by Hap1.[161]

It is noteworthy that as yet intraneuronal aggregates of mutant huntingtin, the neuropathological hallmark of the disease, have not been studied systematically in the hypothalamus of patients with HD. Systematic assessments of polyglutamine aggregates in HD hypothalami could provide valuable insights into which hypothalamic loci are predominantly involved in HD, thereby providing precedent for more targeted evaluations of specific hypothalamic nuclei. Although it should be emphasized that the exact role of polyglutamine aggregates in cell death and dysfunction in HD is still much debated.[9,22,201] In the following section a recapitulation will be given of the aminergic and neuropeptidergic (post-mortem) findings in the brains of HD patients which appear to be of relevance for understanding the pathophysiology of, among other things, weight loss, sleep problems and vegetative symptoms in HD.

3.2. Aminergic and neuropeptidergic alterations in HD brains suggestive of hypothalamic dysfunction

3.2.1. Histamine

The distribution of histamine H2- and H3-receptors have been assessed in both control cases and patients with HD by means of autoradiographic techniques.[72,133] In healthy subjects, the highest levels of histamine H2-binding sites were found in the caudate, putamen, and accumbens nuclei,[133] and the highest levels of histamine H3-binding sites were detected within the external and internal segments of the globus pallidus, substantia nigra and the striatum (within the striatum, H3-binding was noticeably higher in both the nucleus accumbens and the acetylcholinesterase-deficient striosomes).[72] In HD patients the levels of histamine H2-receptor binding sites were found to be markedly decreased in virtually all brain regions investigated, particularly in the putamen and globus pallidus lateralis. Furthermore, the loss of H2-binding sites was found to be related to the grade of the disease.[133] Comparably, values for H3-binding were also significantly lower in the caudate nucleus, putamen and both the external and internal globus pallidus, although not the insular cortex, in HD cases.[72] Since the TMN, the only site in the brain where histamine-releasing neurons are located,[25] does not show a clear cell loss in this disorder,[113] a functional change of the histaminergic system may be expected in HD.[208] As the histaminergic system plays a major role in the maintenance of wakefulness,[25,198] its dysfunction could underlie some features of sleep complaints in HD patients such as, and in particular, daytime sleepiness.[212] Histaminergic neural circuits are also involved in the control of energy balance.[134,214] However, activation of H2 receptors inhibits food intake, and H3 receptor knock out mice are obese and insulin resistant,[130,214] suggesting that the diminution of these receptors in HD is a compensatory consequence rather than a cause of weight loss. It should be noted though that perturbations have also been described in other, extra-hypothalamic, aminergic systems which too are involved in the coordination of sleep-wake cycles and food intake,[198] such as the noradrenergic[14,38,235] and the serotoninergic pathways[135], which could likewise contribute to the pathogenesis of sleep disruptions and weight loss in HD subjects.

3.2.2. Somatostatin and neuropeptide Y

Somatostatin (SST) 1-12 immunoreactivity is normally abundantly present in the neurites and perikarya of the NTL, while SST immunoreactivity is greatly reduced in the NTL of HD patients.[213] In general, higher staining intensity is present in HD patients who have more NTL neurons left than in those who have fewer NTL neurons left. The data obtained so far suggest that NTL neurons cease to express SST-like peptides quite some time before their actual disappearance.[208,213] Since the SST neurons in the periventricular nucleus are thought to be primarily involved in the neurohumoral regulation of growth hormone (GH) secretion,[71] it is unclear to what extent elevated plasma GH levels observed in HD patients (see 'Endocrine abnormalities in HD') can be attributed to diminished SST availability in the NTL of HD subjects. In contrast to the diminished levels of NTL SST, the concentrations of both SST and neuropeptide Y (NPY) are markedly increased in the basal ganglia of patients with HD[7,11-13,48,136] which is consistent with selective preservation of a population of aspiny neurons in which both SST and NPY are colocalized[48]. Beal et al.[13] examined both SST-like immunoreactivity

and NPY-like immunoreactivity in 24 pathologically graded HD cases and 12 controls. Both SST and NPY immunoreactivity were significantly increased (about threefold) in the caudate, putamen, and the nucleus accumbens. Increases of SST and NPY immunoreactivity in mild and severe grades were similar indicating a relative but not absolute sparing of striatal aspiny neurons in which SST and NPY are colocalized.[13] Moreover, because neuropeptide changes were seen in the nucleus accumbens in early grade cases, when there is relatively little tissue atrophy, it is probable that not atrophy alone but also some other process, such as increased terminal sprouting, could contribute to the increased levels seen in these cases.[13] Among the other subcortical regions examined, SST immunoreactivity was significantly increased in the external pallidum, red nucleus, and locus ceruleus, whereas significant increases of NPY immunoreactivity were found in the external pallidum, subthalamic nucleus, substantia nigra compacta, claustrum, anterior and dorsomedial thalamus, bed nucleus of stria terminalis and locus ceruleus.[13] Interestingly, the locus ceruleus is known to contain NPY neurons, indicating that this nucleus could provide increased NPY innervation to other regions.[13] Except for the subthalamic nucleus, the NPY concentrations have not yet been determined in other structures of the hypothalamus of HD patients. NPY is a naturally occurring appetite transducer, and under normal conditions NPY-ergic transmissions represent an essential component of the common final pathway in the hypothalamic integration of energy homeostasis.[92] Although NPY-producing neurons are normally located in several sites in the brain, two subpopulations, one representing the extra-hypothalamic cluster in the brainstem including the locus ceruleus, and the other located in the hypothalamus along the length of the infundibular (or arcuate) nucleus and in the dorsomedial nucleus, apparently participate in a disparate manner in the daily management of food intake [92]. Regarding the disturbed systemic energy balance in HD, it would be very interesting to know whether perturbations also exist in the *hypothalamic* NPY-ergic system of these patients, especially the NPY neurons located in the infundibular nucleus, since animal studies suggest that huntingtin, the protein product of the *HTT* gene, may fulfil a physiological role in the homologue of this structure (i.e. the arcuate nucleus) in rodents.[77]

3.2.3. Neurotensin and thyrotropin-releasing hormone

Nemeroff et al.[147] measured the concentrations of neurotensin (NT) and thyrotropin-releasing hormone (TRH) by means of radioimmunoassay in post-mortem brain samples from patients with HD. Compared to patients without psychiatric or neurological disease, the patients with HD showed significantly elevated concentrations of these two neuropeptides in the nucleus caudatus, while in the amygdala only TRH levels were elevated.[147] However, it is unclear to what extent the elevated NT and TRH levels might reflect increased hypothalamic production of these neuropeptides. Apart from its many other physiological functions, hypothalamic NT seems to be implicated in the regulation of energy homeostasis, particularly in the anorexigenic networks of the hypothalamus.[92] Moreover, recently Cui et al.[44] demonstrated that all the anorexigenic hormones leptin, insulin, and α-melanocyte-stimulating hormone directly induce NT gene expression in immortalized hypothalamic cell lines, which is in support of the notion that NT may have a direct role in the neuroendocrine control of feeding and energy homeostasis.[44] Increased hypothalamic NT levels may thus underlie the disturbed energy regulation in HD subjects as well as some endocrine (particularly hypercortisolism) and metabolic derangements in these patients (for further details refer to the sections 'Endocrine abnormalities in HD' and 'Metabolic abnormalities in HD') as NT dose-dependently increases adrenocorticotropic hormone (ACTH) secretion and causes an increase in blood corticosterone and glucose concentration.[217] In addition, NT exerts other potent central nervous

system effects including hypothermia, antinociception, and modulation of dopamine neurotransmission. Peripherally, it acts as a paracrine and endocrine peptide of both the digestive and cardiovascular systems.[217] TRH is a tripeptide hormone which induces the secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary and, at least in humans, can also act as a prolactin-releasing factor.[148] Thus elevated levels of TRH in the caudate nucleus of HD patients could possibly be secondary to increased hypothalamic production of this peptide, which in turn may partly explain the deviant response to the TRH-stimulation test and the elevated basal plasma prolactin levels in HD subjects found by some investigators.[75] In addition, TRH is directly involved in the complex hypothalamic networks that establish energy balance by modulation of food intake, satiety, thermogenesis, and other autonomic responses.[1,93] Elevated hypothalamic levels of both NT and TRH could therefore partly account for the negative energy balance observed in HD[52,172] as well as some of the autonomic dysfunctions, especially disturbed vasomotion and thermoregulation, which can give rise to symptoms such as orthostatic hypotension and dyshydrosis in some of these patients.[3,6,28]

3.2.4. Gonadorelin

Gonadorelin or Gonadotropin-Releasing Hormone (GnRH) is a decapeptide hormone released by the hypothalamus that stimulates the synthesis and secretion of both luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the adenohypophysis. GnRH concentrations have been reported to be increased fourfold in the median eminence of *female* choreic patients as compared with controls.[18] However, there was no difference in the median eminence levels of GnRH of the *male* choreic patients when compared with controls. Although the authors and others,[178] including George Huntington himself in his seminal paper, present some anecdotal descriptions of increased libido among HD patients,[18,83] a retarded menarche[151] but increased fertility among the female choreic as compared to her nonchoreic sibling,[178] later studies mainly suggest a high incidence of hypoactive sexual disorder in HD, notwithstanding the fact that certain HD patients may exhibit increased sexual interest and paraphilias.[64] It is questionable, though, whether the behavioural alterations have anything to do with changes in GnRH levels in HD, as they could also be accounted for by other mechanisms such as pathology of the prefrontal cortex in this disorder.[191]

Lavin et al.[120] performed a GnRH stimulation test in 8 HD patients and 10 controls, but found no clear differences or obvious abnormalities indicating intact pituitary responsiveness and gonadotropin release, although because of small subgroups (i.e. males, premenopausal and postmenopausal females) the data from the GnRH test were difficult to analyze. The findings of Bird et al.[18] seem to be at odds with those of others who found normal 24-hour curves of LH-secretion[54] and those of Markianos et al.[132] who found normal plasma levels of FSH but decreased plasma levels of both LH and testosterone in male HD patients. However, sex differences cannot be ruled out as the findings of Bird et al.[18] pertained only to the female patients. Moreover, the testosterone plasma concentrations correlated negatively with the severity of the disease and low testosterone levels were associated with dementia but not with depression or psychotic features.[132] The expected positive correlations of LH and FSH to age and the negative correlation of testosterone to age were, however, present in the patient samples studies by Markianos et al.[132] and the authors proposed that, in addition to blunted LH secretion, the direct neural hypothalamic–testicular pathway that interferes with synthesis and secretion of testosterone in the Leydig cells, independent of the pituitary, could be involved, especially for explaining the great reductions in

testosterone in patients with severe symptomatology in whom LH levels were found to be normal. A possible explanation for the increased immunoreactive GnRH concentrations in HD hypothalami[18] could thus be a decreased release of this neuropeptide from the hypothalamus. Nonetheless, recently a progressive reduction in the numbers of GnRH-immunoreactive neurons in the medial septum, diagonal band of Broca and medial preoptic area of the hypothalamus of the R6⁄2 mouse model of HD has been found starting at 5 weeks of age, prior to the onset of overt motor symptoms at 7-8 weeks of age, and becoming statistically significant with only 10% of the neurons remaining by 9 weeks of age.[156] Therefore, both the neuropathological data and the clinical findings concerning the hypothalamo-gonadal axis function in HD patients need further clarification.

3.2.5. Hypocretin (orexin)

Recently it was demonstrated that there is a significant loss and atrophy of hypocretin-immunostained neurons in the lateral hypothalamus of post-mortem HD brain preparations,[162] extending an earlier report of qualitative changes in this hypothalamic structure.[29] Hypocretin, a novel neuropeptide discovered in 1998, can be synthesized in the brain exclusively by neurons in the lateral hypothalamus.[186] This neuropeptide appears to play a crucial role in the regulation of sleep-wake cycles, body energy metabolism and autonomic functions,[92,232] partly by modification of the endocrine system including influences on the corticotropic, somatotropic and thyrotropic axes.[103,104,155] Hypocretin loss might therefore partly account for sleep, ANS and body weight abnormalities in patients with HD. However, four recent papers reported normal hypocretin-1 concentrations in the cerebrospinal fluid (CSF) of HD patients.[10,21,69,137] The apparent discrepancy between these latter findings and those of Petersen et al.[162], who found a 27 % loss of hypocretin neurons in HD brains, could be accounted for by the fact that in human brain tissue the reduction in hypocretin-positive cell number was not as striking as in the concurrently studied R6/2 mouse model (27% vs. 72%).[162] This comparatively modest reduction in cell number appears not to be reflected in the CSF of HD patients, possibly due to compensatory mechanisms whereby the remaining hypocretin neurons in HD are still able to release a sufficient amount of hypocretin to prevent narcoleptic-like symptoms,[10,69,137] which is in accordance with rat studies indicating a need for a 73% decline in neuronal number to decrease CSF hypocretin levels by half.[70] Nevertheless, apart from one study in seven HD patients that found normal CSF hypocretin-1 levels independent of the presence of sleep disorders and nutritional status,[10] CSF hypocretin levels have not yet been investigated more accurately in conjunction with neuroendocrine and clinical parameters, particularly those concerned with sleep, ANS function and body weight and its composition. Thus, at present, any (sub)clinical consequences of a relative hypocretin deficiency in HD cannot be excluded with certainty. It would be interesting to assess another neuronal population in HD brains that is localized in the lateral hypothalamus, namely the melanin-concentrating hormone (MCH)-producing neurons. Like hypocretin, MCH plays a pivotal role in the orchestration of hypothalamic functions, in particular systemic energy homeostasis[195,220] and, therefore, MCH neuronal loss or dysfunction might also partly explain the relentless weight loss in HD patients.

3.2.6. Corticotropin-releasing hormone

Kurlan et al. found elevated corticotropin-releasing hormone (CRH) concentrations in the CSF of 56 (30 male and 26 female) nonmedicated patients with early (stages I and II) HD in comparison with a control group of

21 subjects without neurological illness.[116] Patients with HD who had depressive disorders (major depression or dysthymia) did not differ from those without depression with respect to CRH concentration. However, a positive correlation was observed between the severity of *major depression* (but not dysthymia) and CRH concentrations in HD patients. Even though it is assumed that CSF concentrations of CRH generally originate from extra-hypothalamic sources rather than the PVN[207], three observations nonetheless suggest a hypothalamic origin of the elevated CRH found in the CSF of HD patients.[116] First, the CSF concentration of CRH was positively correlated with the severity of major depression, which could indicate the PVN as the origin of the CRH, since an increase of CRH neuron number, CRH-mRNA, and vasopressin colocalization in CRH neurons in the PVN of depressed patients have been demonstrated.[176,177] Second, various studies have found increased plasma levels of both ACTH and cortisol, indicating HPA axis hyperactivity in HD (see below under 'Endocrine abnormalities in HD'). And third, De Souza et al.[49] measured CRH-like immunoreactivity in control and HD brain tissues obtained post-mortem and found that the concentration of CRH-like immunoreactivity was markedly *decreased* in the caudate/putamen, while no significant differences were observed in the concentrations of CRH-like immunoreactivity between controls and HD patients in frontal, parietal, temporal, occipital and cingulate cortex and in globus pallidus, which also argues against an extra-hypothalamic source of the increased CRH concentration in the CSF of HD subjects [116]; although it should be noted that there are also other sources of extra-hypothalamic CRH such as the thalamus.[8] Assuming a hypothalamic origin of the elevated liquor CRH in HD, two questions remain to be sorted out: first, what is the cause of this elevation, and second, what are exactly the functional consequences of increased CRH production in the hypothalami of HD patients? Regarding the first question, Heuser et al.[79] suggested that the endogenous CRH overdrive in HD subjects might be due to a loss of GABA-containing medium-spiny neurons in the striatum of patients with HD. Interestingly, experimental data in the rat shows that loss of GABA-ergic innervation per se can independently add to the the anorexigenic actions of excess CRH as discussed below.[92] However, administration of muscimol, a potent GABA-agonist, seemed to have no effects on plasma cortisol levels in 4 HD patients,[209] rendering the explanation offered by Heuser et al.[79] somewhat questionable. With regard to the second question, CRH is the primary hypothalamic hormone stimulating the release of pituitary ACTH, which stimulates cortisol secretion from the adrenal glands. CRH-producing cells involved in regulation of the pituitary-adrenal axis are localized mainly in the parvocellular subdivision of the PVN.[92] Central injection of CRH produces behavioral effects suggestive of major depression as well as anorexia, as evidenced by attenuation of nocturnal and fasting-induced feeding, and diminishes feeding in a number of pharmacological and behavioral paradigms designed to evaluate ingestive behavior in rodents.[92,208] Microinjection studies imply that the site of anorectic action of CRH lies within the PVN, and that CRH, if released locally in the PVN, may tonically restrain the action of endogenous orexigenic signals such as NPY.[92] Heinrichs et al.[78] reported that increased availability of CRH/urocortin in the hypothalamus by the chronic central infusion of rat/human CRH(6 –33), a high affinity CRH binding protein inhibitor, significantly decreased body weight in Zucker obese rats that normally have reduced CRH stores in the hypothalamus. However, hyperphagia was unabated in these animals, and the investigators suggested that the loss in body weight was due to CRH/urocortin-induced increase in energy expenditure and sympathetic tone produced by thermogenesis and lipolysis[78,92] since CRH neurons from the PVN project extensively to several autonomic centres in the brain stem. Thus likewise, a chronic CRH overdrive in the PVN of HD subjects may substantially contribute to the emaciation seen in these patients, who nevertheless, frequently report an insatiable appetite. Although it should be noted that, apart from the physiological stimulus caused by a protracted state of negative energy balance, increased appetite in HD patients may, at the very least, also originate from direct pathology and/or dysfunction of the nucleus accumbens[11,24,65,182] and alterations

of its enkephalinergic input from the more dorsal domains of the striatum.[193] This is because the hedonic experience of the feeding consummatory act, particularly with regard to palatable foods, is largely mediated by opioid transmission throughout both the ventral (i.e. nucleus accumbens) and dorsal striatum[96] and the opioid-peptide containing medium-sized spiny neurons of the (particularly dorsal) striatum are among the neuronal groups preferentially affected in HD.[138,193] Altered dopaminergic transmission through the nucleus accumbens could also play a role.[96]

3.2.7. α-Melanocyte-stimulating hormone

Konagaya and Konagaya[105] measured α-melanocyte-stimulating hormone (α-MSH)-like-immunoreactivity in the CSF of, among others, 2 patients with HD. As compared to the values measured in control subjects, the α-MSH immunoreactivity in HD patients was not deviant. α-MSH is, along with ACTH, a peptide cleavage product of the proopiomelanocortin (POMC) molecule and the main endogenous ligand of the melanocortin-3 and melanocortin-4 receptors which when stimulated suppress food intake. Levels of POMC mRNA are normally markedly reduced in fasted animals and increased by exogenous administration of leptin.[236] Leptin increases melanocortin signalling, both by increasing α-MSH release from POMC neurons and by decreasing production of the melanocortin receptor antagonist agouti-related protein (AGRP).[233] As HD patients are often underweight[52] and as plasma leptin concentrations appear to be decreased in HD patients,[171] α-MSH values within the control range[105] seem to be paradoxically normal in this group. In addition, melanocortin signalling in the hypothalamus appears to be involved in the pathogenesis of the anorexia and weight loss associated with inflammatory and neoplastic disease processes.[234] Although the precise mechanism whereby peripheral inflammatory/neoplastic factors activate the melanocortin system remains unknown, the proinflammatory cytokines (interleukin-1, interleukin-6, and tumour necrosis factor-alpha) that are produced in the hypothalamus during both inflammatory and neoplastic disease processes are likely to play a role.[233] Interestingly, activation of various immune system compartments in HD have been reported as well.[123] Thus, alterations in the hypothalamic melanocortin system may also bear a part in the pathogenesis of wasting in HD.

4. ENDOCRINE ABNORMALITIES IN HD

For a discussion of alterations in hypothalamic-releasing/-inhibiting factors in HD patients please refer to the previous section. In the following section the functional integrity of the hypothalamo-pituitary-target organ axes will be dealt with.

4.1. Hypothalamo-neurohypophysial system

In order to assess the functionality of the hypothalamo-neurohypophysial system Lavin et al.[120] performed a water deprivation test in a group of eight HD patients: the patients seemed to have retained their ability to concentrate urine which suggests intact osmoreceptor function and sufficient vasopressin release from the posterior lobe of the pituitary in HD. However, hypothalamic/neurohypophysial vasopressin and oxytocin

contents have never been evaluated in HD brains. Apart from their neuroendocrine functions, both vasopressin and oxytocin appear to have central neuromodulatory roles as well, with effects on, among others, blood pressure, thermoregulation, food intake, cognition, mood and hypothalamo-pituitary-adrenal axis,[207] all of which are domains that may be affected to some degree in patients with HD. Post-mortem amounts of vasopressin immunoreactivity in the locus ceruleus and substantia nigra of 10 cases of HD were comparable to those of normal controls.[183] As in the human brain the vasopressin immunoreactivity in these areas is confined to fibers originating in the hypothalamus, in all probability the PVN,[219,225] the latter findings would argue for an intact hypothalamic vasopressinergic innervation. It is not known, however, to what extent disturbed central vasopressin synthesis and/or release could account for orthostatic hypotension in some HD patients. No data are available with respect to oxytocin in HD patients. Although parturition and lactation difficulties are not noticeably common in the past history of female HD subjects, this does not exclude abnormalities in oxytocin production and/or release during the illness since the disease often commences after the usual age of childbirth.

As described before, cell degeneration and gliosis have been reported in HD subjects in both the SON and PVN,[188,227] which are the production sites of pituitary vasopressin and oxytocin, and in a recent study in a mouse model of HD the hypothalamic expression of the mRNAs of both vasopressin and oxytocin were shown to be significantly down-regulated.[107] This creates precedent for further exploration of this area in HD patients.

4.2. Hypothalamo-pituitary-adrenal (HPA) axis

Originally, Bruyn et al. [31] reported decreased plasma levels of cortisol in some patients with HD, but later studies by others consistently indicate hyperfunction, instead of hypofunction, of the HPA axis in HD. CSF levels of CRH in HD individuals have been reported to be increased (see above under the subheading 'CRH' for a discussion of this finding). Basal levels of both ACTH[79] and cortisol[79,122] seem to be increased as well. However, after an intravenous CRH challenge test, ACTH responses tended to be blunted in concert with normal cortisol levels, indicating that the negative feedback regulation of glucocorticoid secretion is probably intact at the pituitary-adrenal level.[79] Following an overnight dexamethason suppression test, the mean cortisol levels did not differ significantly between the HD and the control group, whereas mean plasma dexamethason concentration was 57 % lower in patients than in controls,[79] although the precise cause and significance of this latter finding remains unclear. Moreover, the cortisol (and GH) rise during hypoglycaemia, induced by intravenous insulin administration, occured earlier in HD patients, though peak responses were the same in each group.[120] Durso et al.[56] found no significant differences in mean plasma cortisol concentrations between their patient and control samples, though it should be noted that their samples consisted exclusively of female subjects and that three of the nine participating HD patients had the rigid-akinetic variant of the disease whose response may be diametrically opposed to that of choreic patients.[75] On the other hand, Leblhuber et al. found significantly higher basal plasma levels of cortisol in 11 drug-free male HD patients compared with age- and sex-matched normals.[122] In addition, in a recent study Björkqvist et al. reported progressive alterations in the HPA axis in the R6/2 mouse reminiscent of a Cushing-like syndrome.[20] The R6/2 mice showed enlargement of the intermediate lobe of the pituitary, hypertrophy of the adrenal cortex, increased ACTH plasma concentrations as well as a progressive increase in serum and urine corticosterone levels. However, the hypothalamic CRH levels were reduced by 62 % in the R6/2 mice suggesting that CRH released from the hypothalamus is not driving

the pituitary ACTH production in these mice, which appears to be at odds with the available data on CRH in humans with HD.[116] Normally dopamine represses ACTH expression, but in the R6/2 mice the expression of pituitary dopamine D2 receptors was reduced by half which therefore could explain the increase in ACTH levels in these mice.[20] Björkqvist et al. corroborated some of their findings in the human disease by measuring cortisol contents in urinary samples from 82 HD patients and 68 controls: the cortisol levels were significantly elevated in moderate (stage III) and moderate-advanced stage (stage IV) patients, whereas pre-symptomatic and early disease stage (stage I/II) patients exhibited levels that were not significantly different from age- and sex-matched controls. It is important to note that the R6/2 mice also exhibited muscular atrophy, reduced bone mineral density, abdominal fat accumulation and insulin resistance, all of which could be consequences of increased glucocorticoid levels. Therefore, elevated levels of cortisol may also contribute to the clinical symptoms like muscular wasting, mood changes and some of the cognitive deficits that occur in patients with HD [20].

Although Bruyn et al.[30] could not detect any changes in serum levels of dehydroepiandrosterone sulphate (DHEAS), the major androgen secreted by the adrenals, Leblhuber et al.[122] found, apart from higher basal levels of cortisol, significantly lower serum levels of DHEAS; consequently, there was also a significant difference between the DHEAS/cortisol ratio in their index and reference group which is in line with some previous findings.[150] Because DHEAS is known to reduce the levels of glucocorticoids as well as antagonize their functions, DHEAS suppletion could be a strategy to counteract the noxious effects of prolonged hypercortisolaemia on e.g. cognition, mood and metabolism in HD subjects.[121,122,150]

4.3. Somatotropic axis

Alterations in GH secretion in HD have frequently been reported and often entail an increase in *mean* basal plasma GH levels and exaggerated or paradoxical responses of GH secretion during stimulatory and/ or inhibitory functional tests.[98] In contrast, most authors have found non-deviant GH concentrations during *single* baseline measurements.[17] However, exaggerated GH responses followed administration of L-dopa[167], apomorphine[55], bromocriptine[35], arginine[125,168], insulin[97,120,165] and muscimol[55]. Paradoxical GH responses have been observed to occur after administration of glucose[51,115,166,167], L-dopa[51] or bromocriptine.[36,51] It should be noted though that exaggerated and paradoxical GH responses were not always uniformly present, i.e. while some HD patients exhibited an exaggerated response during a particular functional test, others exhibited a normal or even paradoxical response,[51] and not all authors have been able to detect significant abnormalities in GH secretion,[47,115,190] either suggesting the existence of considerable heterogeneity among individual HD patients in this respect and/or reflecting different methods in performing and interpreting the endocrine tests or, alternatively, differences in the severity of the disease.[115] Interestingly, Hayden et al. found that a dose of 25 mg of chlorpromazine suppressed GH release in adults with HD, but not in controls, perhaps indicating dopamine receptor hypersensitivity in the HD group.[75] Although Durso et al.[56] and Murri et al.[144] have evaluated, respectively, basal 24-hour and nocturnal plasma levels of GH in HD, their long blood sampling interval (i.e. 30-minutes or more) does not allow for definite judgments regarding the precise secretory pattern of GH release in HD, and any possible alteration therein, because of the fairly short half-life of this hormone in plasma.[226] Kremer et al.[115] measured plasma levels of insulin-like growth factror-1 (IGF-1), an important

peripheral mediator of GH activity with a comparatively long half-life, in 10 HD patients at baseline and in 8 of them also after a 2.5-year follow-up, but found no significant differences, either between the two intra-individual measurement points or in comparison to values in matched controls; yet the authors stated that the assay applied probably has not been sufficiently accurate in detecting small differences.[115] Non-deviant basal IGF-1 levels were also reported by other authors.[171] Since the nature of impaired GH regulation in (some) patients with HD does not imply hypophysiotropic pathology, deviant GH release in HD might be attributed to impaired input from structures elsewhere (H.P. Kremer, thesis). GH has long been known to have profound effects on systemic substrate metabolism. Prolonged elevated levels of GH can induce glucose-intolerance and insulin-insensitivity as is the case in acromegalics. On the other hand GH is a potent physiological stimulator of lipolysis and e.g. GH suppletion can result in considerable loss of body fat and weight in (adult) patients with Prader-Willi, the most common syndromal cause of morbid obesity.[81] Therefore, the abnormalities in carbohydrate metabolism in HD (see below under the section 'Metabolic abnormalities in HD') and wasting in this disorder could both be attributed, at least in part, to hypersomatotropism in some of these patients.

4.4. Lactotropic axis

Many studies have targeted lactotropic axis function in HD patients. In general, prolactin dynamics are considered to be normal or slightly increased.[98] Most studies report normal plasma prolactin concentrations during single daytime[35,36,120,126,142], nocturnal[144] or 24-hour determinations.[56] Although a few authors have described lower[76,158] or increased basal levels[33,35], in these studies an insufficient wash-out period of previous neuroleptic medication may have confounded the results.[98] Normal suppression of plasma prolactin followed dopaminergic stimulation[35,36,55,126,143] and the prolactin response to muscimol (a GABA-agonist) as well as arecoline (a muscarinic agonist) were found to be similar in the HD and the control group.[55] Initially, blunted prolactin responses were reported after chlorpromazine or TRH stimulation,[33,76] but subsequent studies could not confirm these findings.[35,120,126] Considering the methodological shortcomings or strengths of the various studies, the evidence from these early findings favours a slight increase in plasma prolactin levels.[98] Interestingly, Kremer et al.[115] reported a decrease in the mean basal prolactin levels over 2.5 years of follow-up in 7 patients with HD (though it should be noted that at baseline the prolactin levels of their patients and controls did not differ and that the control subjects could not be reinvestigated after the follow-up period), which clearly contradicts earlier findings.[98] It remains to be sorted out to what extent this should be attributed to seasonal fluctuations,[115] a statistical type I error[115] or be considered as evidence for a 'hyperdopaminergic state' in HD as proposed in the earliest report by Hayden et al.[76] Interestingly, more recent experimentation indeed hints at an important role for altered dopaminergic signaling in the striatal vulnerability associated with HD,[37,87] although the implications for the hypothalamic tubero-infundibular dopaminergic system and its regulation of prolactin release are still obscure.

4.4. Hypothalamo-pituitary-thyroid (HPT) axis

Relatively few studies in HD patients have evaluated HPT axis activity. Basal levels of total thyroxine, triiodothyronine, triiodothyronine resin uptake and TSH have been reported to be comparable to values in normal controls.[76,120] Lavin et al.[120] found that the TRH test revealed no differences in basal levels of TSH,

or in peak response to TRH or in the increment at 20 minutes, although one of the 8 patients, but none of the 10 controls, had a delayed response typical of a hypothalamic disorder.[120] However, Hayden et al.[75] reported impaired TSH response to TRH stimulation in 7 adults with HD as compared to 11 normal controls. Since depression is very common in HD and TRH stimulation test reveals a lower or blunted TSH response to TRH in a substantial proportion of depressed patients as well,[59] it remains unclear to what extent the findings by Hayden et al.[75] in fact might have reflected a concomitant depressive disorder in the patient group. Importantly, neither Lavin et al.[120] nor Hayden et al.[75,76] reported the mean body weight and the overall nutritional status of their subjects. Since it is well known that levels of thyroid hormones drop during fasting or negative energy balance[90] and as many HD patients are underweight, values of T3, T4, fT4 and TSH within the 'normal' range in this group could, nonetheless, be indicative of HPT axis dysfunction. It is in this regard of interest to note that in a retrospective chart review study of 97 HD patients residing in long-term care facilities, the most commonly prescribed drug (6%) for problems 'unrelated' to HD was found to be levothyroxine.[146] Moreover, both leptin and glucocorticoids appear to exert substantial modulatory effects on the thyroid axis[90,170] and as there are indications that both hypoleptinaemia and hypercortisolaemia may be features of at least some patients with HD (see above under the headings 'Ghrelin and leptin' and 'Hypothalamo-pituitary-adrenal (HPA) axis'), it can be argued that closer examination of the HPT axis function in this disorder may demonstrate abnormalities, which would be of particular relevance for elucidating the pathogenesis of wasting and mood changes in this disease.

4.6. Hypothalamo-pituitary-gonadal (HPG) axis

For a review of HPG axis function in HD refer to the subheading 'Gonadorelin' in the section 'Hypothalamic dysfunction in HD'.

4.7. Ghrelin and leptin

Ghrelin, an orexigenic factor of gastric origin, and leptin, a peptide hormone secreted by adipose tissue, are two peripherally produced hormones that exert opposite effects on the neuronal populations within the arcuate nucleus, VMN and lateral hypothalamus that play a key role in the regulation of body energy homeostasis.[236] Popovic et al.[171] measured both circulating and CSF levels of ghrelin and leptin in 15 patients with HD and 20 normal-weight subjects undergoing orthopaedic surgery. Blood samples were obtained by venipuncture and in-parallel CSF samples for ghrelin and leptin determination were obtained by lumbar puncture. Patients with HD had increased concentrations of ghrelin in plasma compared with healthy subjects (4523.7 ± 563.9 vs. 2781.1 ± 306.2 pg/ml, P<0.01). On the other hand, patients with HD had decreased concentrations of leptin in plasma compared with healthy subjects (4.8 ± 1.6 vs. 10.9 ± 2.4 ng/ml, P<0.01). Comparably, in the CSF, the concentrations of ghrelin tended to be higher and the levels of leptin tended to be lower, but these differences failed to reach statistical significance, possibly due to the relatively small sample size.[171] It should be noted though that the index and the reference group were not matched for BMI (20.2 ± 0.6 vs. 24.8 ± 0.8 respectively, p = 0.001) and that the total fat mass was not calculated and as a result the circulating leptin levels were not corrected for total fat mass. Nevertheless, *only* in the control group did plasma leptin concentration correlate with BMI. Two other studies reported equivalent plasma leptin levels in HD patients and controls matched for

BMI, fat mass and fat-free mass.[68,172] However, the patients in these studies were, by selection, asymptomatic or were at a mild to moderate stage of the disease (stages I and II). Other confounders which could account for the discrepancy between the findings in these studies are: a) the circadian rhythm of plasma leptin levels, which are (like ghrelin levels) high in the morning and low at night;[236] b) plasma levels of cortisol and insulin,[45] both of which could be deranged in HD patients (refer to the subheadings 'Hypothalamo-pituitary-adrenal (HPA) axis' and 'Carbohydrate metabolism' for further details) and c) differences in sympathetic tone,[102] which as mentioned before, may vary in the course of HD. Furthermore, it is not known to what extent increased levels of circulating ghrelin, which is the native substrate for the GH-releasing peptide (GHRP) receptor, could underlie the hypersomatotropism in some HD patients (see under the subheading 'Somatotropic axis' below), as high GH responses are induced by ghrelin infusions which act synergistically to growth-hormone releasing hormone (GHRH) stimuli.[101,163]

5. SYSTEMIC METABOLIC ABNORMALITIES IN HD

In the following section we will give an overview of alterations in carbohydrate, lipid and protein metabolism in HD as well as their relation to the afore discussed hypothalamic and endocrine alterations and clinical symptomatology.

5.1. Carbohydrate metabolism

The studies on carbohydrate metabolism in HD subjects have yielded quite ambiguous and conflicting results.[115] Considerably large groups of HD patients have been identified with impaired glucose tolerance on oral glucose loading,[51,168,169,190] although none of the participants displayed clinical signs or symptoms of diabetes mellitus. These studies compared the findings in individual patients with a pre-chosen standard, which was lower than currently used[168,169] or ill-defined.[51] Remarkably, other investigators identified appreciably fewer HD patients with impaired glucose tolerance.[47,115] Though it should be emphasized that generally, in the earlier studies, information about the precise clinical condition (especially body weight and composition, stage of the disease, medication and immobility status) of the participants is lacking and the results of individual patients are not shown and therefore cannot be reinterpreted according to the current WHO-criteria.[115] Several authors have also performed an analysis of their pooled data on the oral glucose tolerance tests by comparing the mean values of HD patients with those of control subjects: only Podolsky et al.[168,169] were able to detect significant differences, while others could not replicate their findings.[47,97,115,166] In addition, Kremer et al. reported glycosylated haemoglobin (HbA1c) levels in their HD patients to be comparable to those of controls, excluding marked blood glucose fluctuations over the preceding three to four weeks in their sample.[115] Elevated levels of circulating insulin were noted in all patients with impaired glucose tolerance,[168,169] whereas other studies reported mean insulin levels during glucose tolerance testing to be normal and fasting glucose,[68,172,216] insulin and C-peptide levels to be unchanged.[47,97,115,115] Despite the increased insulin levels found by some authors, insulin tolerance tests in HD patients did not demonstrate any abnormalities.[97,120,166] Of note is that during the insulin tolerance tests all patients, although awake, lost their involuntary movements;[97,120] in Lavin's group the disappearance of the movements coincided with the onset of hypoglycaemia: a possible explanation could be

that the basal ganglia in HD are especially susceptible to neuroglycopenia.[120] Only one follow-up study has been performed in which glucose tolerance, HbA1c and insulin values were assessed in HD patients; none of the investigated parameters showed any significant change after 2.5 years, although the drop-out rate was substantial (4 of the original 10 HD patients could not be reinvestigated for the evaluation of glucose tolerance and in 2 of them HbA1c and insulin could not be assessed either).[115]

In a retrospective study by Farrer et al.[61] information about the incidence and control of diabetes mellitus in 620 probands (278 living, 332 deceased) with HD and in their first and second degree relatives was obtained by a questionnaire method. Among the probands, 65 individuals (10.5%) were identified by the informant or verified by examination of the family records as diabetic. The age adjusted prevalence rate for the year 1975 of diabetes in HD was calculated to be 4 times as high as in the general population. Incidence rates were not calculated because of ascertainment and other biases in their data. Interestingly, results from the analysis of family data indicated that HD affected relatives of an HD proband with diabetes were 7 times as likely to have diabetes over the proband's non-HD relatives, while a non-diabetic HD proband was equally likely to have an HD or non-HD relative with diabetes, suggesting genetic clustering of diabetes and HD. It should be noted that unambiguous interpretation of Farrer's findings is hampered by incomplete data on their criteria for diabetes, body composition, the use of drugs, intercurrent illness, and the level of activities, as well as by the intrinsic difficulties associated with a retrospective survey.[115]

More recently, Underwood et al.[218] applied metabolic profiling to serum samples from HD patients (10 asymptomatic gene carriers and 20 patients in the early to moderate stages of their disease) in a non-hypothesis driven systems biology search for disease biomarkers and found, among others, significant changes in various monosaccharide levels (including glucose) between asymptomatic gene carriers/patients on the one hand and 20 controls of similar age and sex distribution on the other hand. However, the authors did not indicate the direction of the changes and whether the blood samples were taken in a fasting state.

In sum, due to principal and/or methodological inadequacies of most of the studies on carbohydrate metabolism in HD patients and the very small sample sizes often examined, which in all probability both could account for the contradictory results, it still remains to be ascertained whether impaired carbohydrate metabolism is an inherent feature of HD and whether it has any special clinical relevance in this disorder (especially with regard to weight loss). If this is the case, the precise underlying mechanisms (i.e. pancreatic ß-cell dysfunction,[4,19,82,85] possibly due to transcriptional dysregulation,[4] and/or peripheral insulin insensitivity[20] secondary to neuroendocrine and ANS dysbalance due to hypothalamic dysfunction (see previous sections)) should be elucidated in order to devise effective therapeutic strategies. As recent experimentations in animal models of HD demonstrate that the prevalence of impaired glucose tolerance is consistently higher in the affected animals compared to controls[4,19,20,82,85,88,129,218] and that dietary manipulations that affect glucose metabolism may lead to amelioration of symptoms and/or increase overall life-span in these animals[53] combined with strong indications that lately have emerged for a saccharide-polyglutamine interaction both in vitro and in vivo,[95,210,211] corroboration of these data in humans, in both principally and methodologically sound and rigorous experimental settings, seems to be necessary.

5.2. Lipid metabolism

Notwithstanding the progressive weight loss in HD patients, which is accompanied by substantial loss of body fat stores, as indicated by decreased abdominal circumference and subscapular skinfold (both measures of central/visceral adiposity) as well as triceps skinfold thickness (a measure of peripheral adiposity),[62,63,216] *systemic* lipid metabolism has hardly received any direct study in individuals with this disorder. Schubotz et al.[190] measured serum lipids and the plasma fatty acid composition of the cholesterylesters, triglycerides and phospholipids in 25 subjects with or at risk for HD (9 at-risk asymptomatics, 5 with light and 11 with severe symptoms) and found minor deviations in the fatty acid patterns in various lipid classes. Other authors have reported high fasting concentrations of non-esterified fatty acids (NEFAs) in choreic patients when compared with control subjects.[166] This difference was maintained under hypoglycaemic conditions, while during hyperglycaemia the differences in NEFAs concentrations between the groups was abolished.[166] In addition, plasma and CSF leptin concentrations have been measured (refer to the subheading 'Ghrelin and leptin' in the section 'Endocrine abnormalities in HD' for a discussion of these measurements). Recently, Underwood et al.[218] applied metabolic profiling to serum samples from HD patients (10 asymptomatic gene carriers and 20 patients in the early to moderate stages of the disease) in a non-hypothesis driven systems biology search for disease biomarkers. Among other things, they found significant changes in various markers of fatty acid breakdown (including glycerol and malonate) between asymptomatic gene carriers/patients and controls of similar age and sex. This could indicate a pro-catabolic phenotype early on in the disease progression,[218] although the precise significance of these and previous findings still remains to be clarified. In addition, the possible contribution of hypothalamic dysfunction in HD, and subsequent endocrine abnormalities (especially GH and cortisol) and autonomic dysregulations (in particular a possible dysbalance between sympathetic and parasympathetic innervation of adipose tissue,[108,109] to the genesis of systemic alterations of fat metabolism in HD is far from clear and needs further exploration.

Circumstantial evidence initially obtained from a small series of publications in the 1970s that all claimed to have discovered membrane abnormalities in cells of peripheral tissues (especially fibroblasts and erythrocytes) from HD patients, led to the belief that a 'generalised cell membrane defect' may be involved in HD.[15] This prompted intensive efforts by many investigators over a considerable time span to reproduce these initial findings, but most of the later studies failed to substantiate the existence of a 'generalised membrane defect' in HD.[15,131,189] In particular, since biochemical findings regarding phospholipid concentration, fatty acid analysis, lipid-bound sialic acid, neutral glycolipids, and total cholesterol were reported to be normal in erythrocyte lipid fractions from HD patients[23,80,230] and as membrane fluidity of HD fibroblast, erythrocyte and lymphocyte membranes did not appear to be significantly different from that of controls,[16,117,205,206] Beverstock[15] concluded that in any event lipid fractions of *peripheral* cell membranes and blood plasma are not involved in HD. However, in a recent study, Valenza et al.[222] extracted RNA from primary fibroblasts taken from control and HD patients and analyzed the expression of three key genes of the cholesterol biosynthetic pathway, viz. HMG-CoA reductase, cytochrome P450 lanosterol 14 α-demethylase and 7-dehydroxy-cholesterol reductase, and found that HD fibroblasts show a 35-40% decrease in the mRNA levels of these three genes. Although they observed no differences in cholesterol biosynthesis between normal cultured fibroblasts and HD fibroblasts in standard medium, exposure of the cells to lipoprotein-deficient serum (LPDS) demonstrated that HD fibroblasts were less capable of upregulating the mevalonate pathway, and thus de novo cholesterol synthesis, in response to low levels of cholesterol;[222] this latter finding is in line with that of Menkes et al. who showed that control fibroblasts were not affected unduly by LPDS over a four day period, whereas three-quarters of the

HD lines failed to grow in LPDS.[139] The discrepancy between the recent findings of Valenza et al.[222] and the conclusion drawn by Beverstock,[15] which was based on a review of earlier studies on lipid metabolism in HD, could be accounted for by the possibility that some degree of stressing of cells might be necessary to unveil a phenotypic difference in HD cells. However, in a later study Sakai et al.[185] did find that the mean level of docosahexanoic acid in the erythrocyte membrane in six HD patients was significantly lower than in that of 14 matched controls. Therefore, considerable controversy remains about any putative defects of peripheral tissue lipid metabolism in HD.

Contrary to *peripheral* lipid metabolism, the indications of a defect in *neuronal* lipid metabolism in HD are more consistent. Ellison et al.[57] reported the concentrations of phosphoethanolamine and ethanolamine to be significantly reduced in the caudate, putamen and nucleus accumbens of brain samples from HD subjects. More recently, by applying the niacin skin flush response (i.e. measuring the cutaneous erythematous vasodilatation response to a topical aqueous methyl nicotinate solution) Puri[173] demonstrated that the response in 6 patients with advanced HD (stage III) was significantly lower than the mean response in a group of 14 age- and sex-matched controls, suggesting an abnormality of neuronal membrane fatty acid metabolism, particularly an impaired phospholipid-related signal transduction, in advanced HD.[173] Still more recently it was shown that the transcription of key genes of the cholesterol biosynthesis pathway is severely affected in both human post-mortem HD striatal and cortical tissue [222] as well as in HD animal derived brain tissues.[200,222]

Based on the hypothesis that a membrane defect might be fundamental in HD pathogenesis and that this might be partly corrected by the provision of essential fatty acids,[46] a few open label studies with γ-linolenic acid and eicosapentaenoic acid (EPA) were conducted in patients with HD that showed significant clinical improvement in both motor and cognitive performances.[221] Subsequent small-scale studies showed that treatment with ethyl-EPA in HD is associated with decreased abnormal movements and changes on brain magnetic resonance imaging when compared to a placebo-treated group.[174,221] In a recent large-scale (n = 135) clinical trial on the efficacy of 2 g/d ethyl-EPA versus placebo for the treatment of HD patients,[175] intention-to-treat analysis after 12 months of treatment did not reveal a significant difference between ethyl-EPA and placebo on the primary end point of the study, viz. Total Motor Score 4 subscale (TMS-4) of the UHDRS. However, restriction of the analysis to those patients who had completed the study without protocol violations (n = 83), did indicate ethyl-EPA to be better than placebo as judged by the TMS-4 scores. It should be noted though that intention-to-treat analysis showed a significant worsening of the behavioural score in the EPA-treated group compared with the placebo-treated group.

In conclusion, the studies on lipid metabolism in HD patients hitherto have yielded equivocal results and clearly do not suffice to pass a well-considered judgment on any possible systemic defects in lipid metabolism in these subjects. As recent findings in animal models of HD[5,42,60,223,224] do support the notion of systemic anomalies of lipid metabolism in HD and as supplementation of certain lipid groups could be efficacious in patients with HD,[175,221] further systematic exploration of this field, e.g. by measuring lipid synthesis and/or lipolyis in vivo, could yield interesting results.

5.3. Protein metabolism
Using the anthropometric data on upper arm and calf circumferences and triceps and calf skinfold thicknesses

from the studies by Farrer et al.[62,63] in combination with the following formulae: upper arm muscle circumference = upper arm circumference $-\pi$. (triceps skinfold thickness) and calf muscle circumference = calf circumference $-\pi$. (calf skinfold thickness), it can be calculated that individuals affected with HD have a significantly smaller upper arm as well as calf muscle circumferences compared to controls, despite a comparable protein and fat intake and even a higher carbohydrate intake and less strenuous physical activity.[62] These findings were recently confirmed in a study by Trejo et al. in 25 HD patients and an equally large group of age- and sex-matched controls.[216] Thus apart from fat loss, muscle wasting probably also contributes to the emaciation in HD. In fact, three more recent studies have indeed found abnormal in vivo skeletal muscle energy generation in both symptomatic HD subjects and presymptomatic mutation carriers.[106,128,184] These findings indicate that systemic mitochondrial dysfunction is an early and persistent component of the pathophysiology of HD[184] and it is therefore likely that impaired mitochondrial function will partly underlie muscle wasting in subjects with HD. In addition, microarray profiling of gene expression in skeletal muscle biopsies from HD patients and controls demonstrated distinct expression profiles;[204] none of the biopsy donors had frank diabetes or was emaciated, so it is unlikely that HD muscle gene expression changes would be caused by diabetes or weight loss. Corroboration of these data in a HD mouse model indicated that although both the diabetic phenotype and weight loss in these mice partly contributed to the observed changes in muscle gene expression, neither could explain the complete set of alterations.[204] These data suggest a primary, local biochemical defect in HD muscles (see also[180]), although other factors, such as endocrine abnormalities and aberrant signalling from the central nervous system, are likely to be involved as well.

While the earliest studies of amino acid metabolism in subjects with HD could not detect any appreciable abnormalities,[27,43,152] subsequent investigations have found significant differences in plasma concentrations of certain amino acids.[153,154,159,160,166,179,218,237] The most consistent finding appears to be a decrease in the plasma concentrations of neutral amino acids (especially alanine, valine, leucine and isoleucine) compared to healthy controls. Interestingly, in a recent non-hypothesis driven experimental approach, Underwood et al.[218] found decreased levels of valine in asymptomatic HD-gene carriers as well as symptomatic patients, while the levels of alanine and leucine were elevated in the group of asymptomatic gene-carriers and tended to be lower in more symptomatic patients, suggesting a negative correlation between these metabolites and disease progression.[218] Also considerable systemic alterations in the kinetics of the kynurenine pathway (a major route accounting for the metabolism of over 90% of the non-protein tryptophan in most tissues) have been reported in patients with advanced HD,[202] extending the earlier findings of abnormal tryptophan metabolism in the central nervous system of HD subjects (see[202] and the references therein). However, baseline blood levels of melatonin, also a product of tryptophan metabolism, as well as the rise in melatonin levels after tryptophan loading were recently reported not to be different between HD patients and healthy controls.[40] Notably, a case report has described the stabilization of a HD patient by a low tryptophan diet.[157]

Concluding, as yet it is poorly understood to what extent the aforecited alterations in protein metabolism are due to local changes (especially peripheral mitochondrial dysfunction (see below under 'Basal metabolism and energy expenditure')), and to what extent endocrine alterations (including impaired insulin secretion) or ANS dysregulation could account for these abnormalities.

5.4. Basal metabolism and energy expenditure

The first study on basal metabolic rate (BMR) in HD subjects found that the BMR was markedly increased in a number of patients.[17] However, a subsequent study reported that the BMR, as measured by oxygen consumption in a resting state, was not greater in HD subjects (n = 41; stages I and II) compared with the spouses (n = 22) who did not differ from the patients in regard to age, height or lean body mass (LBM); although unexplained weight loss exceeding 3 kg in the past years was reported by 43% of the HD patients but only by 9% of the spouses.[197] More recently, the BMR and energy expenditure have been investigated more thoroughly in HD patients.[68,172] Prately et al. measured sleeping metabolic rate (SMR) and 24-hour sedentary energy expenditure (24-h EE) in a human respiratory chamber in 17 patients with mild to moderate HD (3 of whom were asymptomatic) and 17 control subjects matched for age, sex, BMI and fat mass.[172] They did not find any differences in SMR between the two groups, but the 24-h EE was approximately 14% higher in patients than in controls and the patients seemed to be in a state of negative energy balance. The increase in 24-h EE appeared to be the result of increased spontaneous physical activity (as measured by radar in the chamber and as reflected in the ratio of 24-h EE to SMR) that was proportional to the severity of the patients' chorea score. However, the increase in 24-h EE did not translate into an increase in total energy expenditure (TEE) measured during 7 days in free-living conditions by using the doubly labelled water technique, apparently because patients with HD engage in less voluntary physical activity.[172] Unfortunately, because not all food records were completed, the authors could not assess dietary intake in most of the subjects during free-living conditions, and therefore, energy balance during this period cannot be judged. Gaba et al. assessed SMR, waking metabolic rate (WMR) and 24-h EE (via indirect calorimetry in a human respiratory chamber) in 13 subjects with HD (stages I and II) and 9 controls matched for age, sex, BMI and body fat percentage.[68] They found a tendency for higher SMR and 24-h EE in HD patients compared to controls, although the differences nearly failed to reach statistical significance, probably owing to the small group sizes. The WMR was, nevertheless, significantly higher in patients and was related to a significantly greater displacement of the centre of mass by HD subjects on a force platform (a measure of physical activity), in all probability as a result of the involuntary movements in the choreic subjects.[68]

Although the findings of a similar resting metabolic rate and SMR in patients and matched controls[172,197] argue against an intrinsic metabolic defect in whole body energy metabolism in subjects with HD, other reports of significant and nearly significant increases in BMR[17,17,68] in HD are more consistent with the possibility of an overall defect in mitochondrial oxidative phosphorilation, as suggested by studies in which the phosphocreatine to inorganic phosphate ratios were measured and shown to be decreased in both presymptomatic and symptomatic subjects with HD.[106,128,184] An extensive review of the evidence in favour of peripheral defects in mitochondrial energy generation in both animals and humans with HD is given by Browne and Beal.[26] While the findings of significantly elevated 24-h EE and WMR in HD subjects, which both correlated with the chorea score, do indicate that *involuntary* movements can contribute to a considerable extent to the energy loss in these patients,[68,172] the fact that the total free-living energy expenditure is the same for patients and matched controls, as a consequence of less *voluntary* physical activity by the patients,[172] does not explain the lower body weight of HD patients despite their normal or even increased appetites. Moreover, the greatest rate of body weight loss appears to be in the final hypokinetic stages of the disease when involuntary movements are far less prominent.[187] However, as pointed out by Gaba et al., it might be that the variability in food intake increases as the total functional capacity (TFC) decreases and as a consequence the higher intakes reported on some

days may not be enough to offset the lower energy intakes reported on other days.[68] All together, the precise contribution of altered BMR and TEE to weight loss in patients with HD still remains elusive. In addition, endocrine parameters and ANS function have not yet been assessed in conjunction with measures of energy intake and/or expenditure in individuals with HD and consequently their precise roles in the emaciation in this group of patients also await further elucidation.

6. CONCLUSIONS

Since the hypothalamus is a major control centre in the brain for the regulation of body energy homeostasis, sleep-wake cycles and the coordination of autonomic functions [89,92,232,236], we postulated that hypothalamic dysfunction per se as well as subsequent (neuro)endocrine and metabolic abnormalities in patients with HD may substantially contribute to the pathogenesis of weight loss, sleep disturbances and ANS dysfunction in HD. Moreover, some mood and cognitive disturbances associated with HD may also partially originate from hypothalamic involvement in this disorder. As reviewed, many studies in both animal models and human patients with HD indeed strongly indicate that hypothalamic dysfunction, (neuro)endocrine and metabolic abnormalities may be consistent as well as important features of HD, which could at least partly account for the pathogenesis of the aforementioned signs and symptoms. However, as noted before, the dyskinesia per se as well as peripheral tissue anomalies are in all likelihood also implicated in the pathogenesis of symptoms such as unintended loss of body weight in this disorder.

Emaciation, sleep disturbances and autonomic dysfunction are important indicators of the rate of disease progression and can considerably impair the already diminished quality of a patient's life. It is therefore of crucial and practical importance to elucidate the pathophysiology of these signs and symptoms in order to find novel and more effective therapeutic targets. On the basis of this review, it can be inferred that therapies aimed at affecting hypothalamic, (neuro)endocrine and metabolic parameters may indeed be promising potential candidate treatments for the control of these signs and symptoms that should be put to the test in future animal studies and subsequently in human clinical trials as well.

7. AIMS OF THE THESIS

Part I: Secondary signs in Huntington's disease

In the first part of the thesis, we aim to delineate of the characteristics of the less well-known symptoms and signs of HD, and assess their association with other aspects of the disease, including mutation size and motor, cognitive and behavioural indices. The course of weight loss and its determinants is assessed in **Chapter 2**. Guided by findings from the previous chapter, in **Chapter 3** the effects the interaction between mutant and normal *HTT* on clinical phenotype, including body weight, are described. Subsequently, the prevalence, nature and correlates of sleep disturbances (**Chapter 4**) and autonomic complaints (**Chapter 5**) in HD patients are

Chapter 1

presented.

Part II: Hypothalamic pathology in Huntington's disease

The subject of this part of the thesis (**Chapter 6**) is the neuropathological evaluation of hypocretin-1 (also known as orexin-A) and melanin-concentrating hormone neurotransmission in HD patients, as well as the assessment of various hypothalamic regions for the presence of neuronal intranuclear and cytoplasmic inclusions of mutant huntingtin.

Part III: Endocrine studies in Huntington's disease

This part of the thesis contains a compilation of a number of endocrine studies in early stage HD patients. The objective is to investigate whether the corticotropic (**Chapter 7**), somatotropic (**Chapter 8**), thyrotropic and lactotropic axes (**Chapter 9**) function, and adipokine (**Chapter 10**) and melatonin (**Chapter 11**) secretion are altered in HD patients compared with matched control subjects.

Part IV: Metabolic studies in Huntington's disease

The studies detailed in this section (**Chapter 12**) are aimed at the evaluation of the systemic metabolism in a group of early stage HD patients, focusing on basal energy expenditure, and glucose and fat metabolism.

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