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Review article

Neuroendocrine and neurotrophic signaling in Huntington's disease: Implications for pathogenic mechanisms and treatment strategies

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ABSTRACT

Huntington's disease (HD) is a fatal neurodegenerative disease caused by an extended polyglutamine tract in the huntingtin protein. Circadian, sleep and hypothalamic-pituitary-adrenal (HPA) axis disturbances are observed in HD as early as 15 years before clinical disease onset. Disturbances in these key processes result in increased cortisol and altered melatonin release which may negatively impact on brain-derived neurotrophic factor (BDNF) expression and contribute to documented neuropathological and clinical disease features. This review describes the normal interactions between neurotrophic factors, the HPA-axis and circadian rhythm, as indicated by levels of BDNF, cortisol and melatonin, and the alterations in these intricately balanced networks in HD. We also discuss the implications of these alterations on the neurobiology of HD and the potential to result in hypothalamic, circadian, and sleep pathologies. Measurable alterations in these pathways provide targets that, if treated early, may reduce degeneration of brain structures. We therefore focus here on the means by which multidisciplinary therapy could be utilised as a non-pharmaceutical approach to restore the balance of these pathways.

Contents

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1. Introduction

Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disease caused by an expanded cytosine-adenine-guanine (CAG) repeat sequence in exon 1 of the Huntingtin gene (*HTT*) (The Huntington's Disease Collaborative Research Group, 1993). This expanded sequence encodes a mutant version of the protein, huntingtin (mHTT), which is associated with ubiquitous molecular and cellular anomalies, widespread neuronal dysfunction and cell loss (Kim et al., 2014) and the presentation of motor and non-motor features, including progressive impairments in motor control, cognitive function and mood (Tabrizi et al., 2013). Evidence also indicates that individuals suffer from sleep disturbances (Morton, 2013; Hansotia et al., 1985; Wiegand et al., 1991; Piano et al., 2015; Arnulf et al., 2008; Lazar et al., 2015a), autonomic abnormalities (e.g. hyperhidrosis, micturition disturbances, swallowing difficulties, sexual dysfunction, altered heart rate variability) (Andrich et al., 2002; Kobal et al., 2010) and metabolic irregularities (Browne et al., 1997; Mazziotta et al., 1987), with some non-motor features, such as cognitive and sleep abnormalities, emerging years before the onset of motor signs (Tabrizi et al., 2011; Lazar et al., 2015a).

Although the pathophysiology underlying the development and progression of these clinical features is complex, the accompanying alterations in neuroendocrine signalling, including cortisol (Aziz et al., 2009a; Hubers et al., 2015) and melatonin (Kalliolia et al., 2014; Aziz et al., 2009b) release, and changes in circadian rhythmicity (Morton et al., 2005; Aziz et al., 2010) suggest that the activity of the hypothalamic-pituitary-adrenal (HPA) axis and the suprachiasmatic nucleus (SCN) are impaired in HD (see Table 1 for summary of HD pathologies relevant to this review). Neuropathological changes including volume loss, the loss of orexin-releasing neurons and decreased protein levels of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP) in the hypothalamus support this supposition (Politis et al., 2008; Soneson et al., 2010; Petersén et al., 2005).

The HPA-axis is central to neuroendocrine signalling. Indeed, an intricate balance exists between neuroendocrine signalling and expression of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) (Issa et al., 2010; Smith et al., 1995a). In this review, we present for the first time the biological impact of HPA-axis dysfunction on circadian rhythm, neuroendocrine signalling, and neurotrophic factor support in HD (for a diagrammatic view, see Fig. 1). We also draw on existing evidence in animal models and patients with HD and other disorders to review non-pharmaceutical treatment strategies, particularly multidisciplinary therapy, exercise, cognitive therapy and social interaction, which may positively impact on HPA-axis dysfunction and potential downstream mechanisms and thereby delay disease onset in individuals with premanifest HD. Since candidate pharmaceutical treatment strategies for HD have been reviewed recently (Ross et al., 2014), here we detail non-pharmaceutical multidisciplinary approaches as they have been reported to exert beneficial effects on HPA-axis function, circadian rhythm and BDNF, are of minimal cost and can be implemented throughout life with few side effects.

1.1. Normal function of the HPA-axis and the SCN

The structures of the HPA-axis, including the hypothalamus, pituitary and adrenal glands, function in a tightly regulated manner to control responses to physiological and psychological stress, autonomic and immune functions and sleep-wake behaviour through the release of hormones, such as cortisol, in a circadian manner (Webster Marketon and Glaser, 2008; Ulrich-Lai and Herman, 2009; Steiger, 2002).

The paraventricular nucleus (PVN) releases corticotrophin releasing factor (CRF) into the hypophyseal portal system, where it stimulates the release of adrenocorticotrophic hormone (ACTH) from the corticotropes of the anterior pituitary (Rivier and Vale, 1983). ACTH is released into the systemic circulation and stimulates the adrenal cortex to release glucocorticoids, such as corticosterone in mice and cortisol in humans, which regulate responses to stress in central and peripheral systems. These glucocorticoids then provide negative feedback, inhibiting further release of CRF and ACTH by binding to glucocorticoid receptors (GRs) at the PVN and pituitary level, inhibiting further HPA-axis activation via glucocorticoid response elements (GREs) (Keller-Wood and Dallman, 1984).

Glucocorticoid release is subject to inputs from other brain regions, particularly the amygdala, stria terminalis and hippocampus, which are all regions fundamentally involved in emotional regulation and memory (Hauger and Dautzenberg, 2000). However the basal circadian release of glucocorticoids is facilitated by the connection between the PVN and SCN.

The SCN is located in the anterior hypothalamus and functions as the central circadian clock that is the principle site of circadian rhythm coordination in mammals (Nishino et al., 1976). The SCN receives information from the retina and other brain regions and synchronises the circadian rhythms of the organism emerging at cellular, physiological and behavioural levels to various zeitgebers, the most important of which is ambient light. Synchronization is mediated through neural and humoral signals. On a molecular level the circadian rhythm in mammals is based on an autoregulatory transcriptional-translational feedback mechanism involving *CLOCK* and *BMAL1* transcription factors and *PERIOD* (*PER1*, *2* and *3*) and *CRYPTOCHROME* (*CRY 1* and *2*) core clock genes (Gekakis et al., 1998). This molecular clock regulates a considerable proportion of the human genome. Importantly, through its connections with the PVN and mediation of the HPA-axis, the SCN controls daily variations in melatonin and cortisol release which are involved, amongst other things, in sleep-wake behaviour and autonomic arousal regulation.

More specifically, activity of the SCN is synchronised to the environmental light-dark cycle directly through the retinal-hypothalamic tract and indirectly through the retinogeniculate pathways and conveys this information to other hypothalamic nuclei, the reticular formation and the pineal gland, coordinating the diurnal activities of these brain regions (Brzezinski, 1997). Melatonin coordinates circadian rhythms in response to the day-night cycle and initiates the thermoregulatory cascade, decreasing core body temperature to induce sleepiness (Brzezinski, 1997; Krauchi et al., 2000). The circadian variation of core body temperature is also associated with the internal structure of sleep, particularly with the circadian rhythm of REM (Dijk and Czeisler, 1995).

1.2. Stress and the role of cortisol

Cortisol secretion follows a circadian rhythm in individuals with normal sleep-wake cycles. Within the first 30 min of awakening, cortisol levels increase by up to 75% (Pruessner et al., 1997). Cortisol levels then tend to plateau and around midnight reach their nadir. There is large variation in circadian cortisol levels between individuals, however morning cortisol levels are relatively stable intra-individually, allowing for measurement of the cortisol awakening response (CAR), which serves as an indication of HPA-axis function and circadian rhythmicity (Stone et al., 2001).

In addition to its natural circadian rhythm, cortisol is released in response to physiological and psychological stress (Staufenbiel et al., 2013). Stress has many contributing factors and occurs when environmental demands surpass the individual's coping abilities (Fink, 2010). The response to stress, particularly adaptation, varies