Alertness and feeding behaviors in ADHD: Does the hypocretin/orexin system play a role?

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Summary Increasing evidence has suggested that patients with attention-deficit/hyperactivity disorder (ADHD) may present with a deficit of alertness and sleep disturbances. Recent studies have also pointed out a previously underestimated association between ADHD and abnormal eating behaviors, including binge eating. Since sleep/alertness disturbances and eating disorders may significantly increase the functional impairment of ADHD, gaining insight into their pathophysiology as well as into their treatment is of relevance to provide a better clinical management of patients suffering from ADHD. The hypocretin/orexin system comprises two distinct peptides, located in the hypothalamus, which are involved in several homeostatic functions. In particular, it has been suggested that hypocretin/orexin neurons located in perifornical and dorsomedial hypothalamic nuclei increase arousal, whereas those located in the lateral hypothalamus are primarily implicated in reward processing, stimulating feeding and other reward seeking behaviors. Given the involvement of the hypocretin/orexin system in the control of alertness and reward seeking (including feeding), we hypothesize that hypocretin/orexin neurons located in perifornical and dorsomedial hypothalamic areas are hypoactivated, while those located in the lateral hypothalamus are overactivated in patients with ADHD. If confirmed by further neurophysiological, imaging, and genetics studies, our hypothesis may help us progress in the understanding of the complex pathophysiology of ADHD. This might set the basis for the study of novel molecules, acting on the hypocretin/orexin system, aimed at increasing wakefulness and reducing binge eating and other abnormal reward seeking behaviors in patients with ADHD. We also suggest future studies on the potential therapeutic role of other molecules which have a complex interplay with the hypocretin/orexin system, such as the histamine H1 receptor agonists, the histamine H3 receptor antagonists, and the neuropeptide Y receptor antagonists. All this body of research would provide a tremendous opportunity to improve the quality of life of patients with ADHD by means of pathophysiologically oriented treatment.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood onset psychiatric disorders, with an estimated worldwide prevalence of about 5% in school-aged children [1]. According to the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM–IV) [2], ADHD is characterized by a pattern of pervasive, impairing, and developmentally inappropriate symptoms of inattention and/or impulsivity-hyperactivity. Impairing symptoms of ADHD may persist into adulthood in up to 60% of cases [3].

It is well known that ADHD is often associated with other disorders, which contribute to the functional impairment of the patient. Commonly reported psychiatric comorbid disorders include oppositional defiant disorder, conduct disorder, anxiety disorders, depressive disorders, speech and learning disorders [4]. On the other hand, sleep/alertness disturbances and eating disorders associated with ADHD have been quite overlooked in research as well as in the clinical practice. However, increasing empirically based evidence has suggested a significant association between ADHD and sleep/alertness alterations [5,6], as well as abnormal feeding behaviors [7].

A better insight into the mechanisms underlying this association is of relevance for two reasons. First, it may advance our understanding of the pathophysiology underlying ADHD. Second, from a clinical standpoint, it might allow a better and more comprehensive management of patients with ADHD. Since sleep/alertness and feeding alterations associated with ADHD have been quite overlooked in research as well as in the clinical practice. However, increasing empirically based evidence has suggested a significant association between ADHD and sleep/alertness alterations [5,6], as well as abnormal feeding behaviors [7].

In the present paper, we hypothesize that alterations in the hypocretin/orexin system contribute to impaired alertness and abnormal feeding behaviors in patients with ADHD.

Background

The hypocretins (also named orexins) were described by two groups in 1998 and comprise two distinct peptides. Sakurai et al. [8] purified two peptides from rat brain extracts that activated a G-protein-coupled receptor. Because intracerebroventricular injection of these peptides in rats acutely stimulated food consumption, they were named orexin-A and orexin-B after the Greek word ‘orexis’, meaning appetite. Around the same time, de Lecea et al. [9] identified a cDNA encoding two polypeptides in the hypothalamus that they named hypocretins on the basis of their hypothalamic localization and their proposed sequence similarity to the secretin family of peptides. It soon became clear that the peptides isolated by the two groups were, in principle, identical. Therefore, they are commonly referred to as the ’’hypocretin/orexin system’’.

Neurons expressing hypocretins/orexins are located exclusively in the lateral and posterior hypothalamus (perifornical areas) [10]. Although small in number, these neurons have extensive projections throughout central nervous system, including the cerebral cortex, the limbic system (e.g. the amygdala and hippocampus), the hypothalamic nuclei (e.g. the arcuate nucleus and the tuberomammillary nucleus), and the brainstem (e.g. the central gray, locus coeruleus, and raphe nuclei). Throughout these projections, the hypocretin/orexin system can affect a variety of physiologic mechanisms, including sleep/alertness, feeding behaviors, endocrine, and autonomic functions. In order to better understand our hypothesis, we detail here some data on the role of the hypocretin/orexin system in the regulation of sleep/alertness and feeding behavior.

Sleep/alertness

Orexin neurons send their projections to nuclei involved in sleep/wake regulation, including the locus coeruleus, raphe nuclei, tuberomammillary nucleus, pedunculopontine tegmental nucleus/laterodorsal tegmental nucleus, ventrolateral preoptic nucleus, and basal forebrain (BF) cholinergic neurons [10]. The hypocretin/orexin system projections to the limbic system may also play a relevant role, since recent evidence suggests the implication of the limbic system in the generation of arousal [11]. This highlights the role of emotional factors in the regulation of alertness.

The involvement of the hypocretin/orexin system in the regulation of sleep/wakefulness states is supported by the deficiency of hypocretin/orexin neurons in narcolepsy with cataplexy, a debilitating neurological disease characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and sleep onset-associated hallucinations. Several lines of evidence (reviewed in [10]) have confirmed that genetic disruption of the hypocretin/orexin system can cause narcolepsy with cataplexy.

Feeding behaviors

Since the initial demonstration of orexin-induced hyperphagia in rats, a large body of evidence has accumulated in support of the involvement of the
The hypocretin/orexin system in mechanisms of appetite regulation, including motivational aspects of eating, drive to eat, cephalic phase reflexes, mastication, and insulin secretion [12]. The projections of the hypocretin/orexin system to the limbic structures may play a significant role in the regulation of emotional aspects of eating. Several lines of evidence suggest that hypocretin/orexin induced hyperphagia is at least partly mediated through downstream activation of Y1 and Y5 receptors of neuropeptide Y (NPY), and, vice versa, that NPY-induced hyperphagia may in part be mediated through activation of orexin mechanisms [13]. Mounting evidence indicates that the hypocretin/orexin system not only stimulates appetite for food, but also can stimulate an appetite for other rewards such as abused drugs [14].

Recently, Harris et al. [14] have proposed a functional dichotomy for the hypocretin/orexin neurons, suggesting that hypocretin/orexin neurons located in perifornical and dorsomedial hypothalamic areas are involved in arousal and waking, whereas those located in the lateral hypothalamus are primarily involved in reward processing, including feeding behaviors.

Deficit of alertness in ADHD

According to the hypoarousal theory of ADHD, children with ADHD (or at least a subgroup of them) may actually be sleepier than controls and may use motor hyperactivity as a strategy to stay awake and alert, in order to counteract the tendency to fall asleep [15]. In a seminal study using the multiple sleep latency test (MSLT, an objective procedure used to assess daytime sleepiness) Lecendreux et al. [16] confirmed that children with ADHD are sleepier than controls. This result was subsequently replicated by Golan et al. [17] in a sample of adolescents with ADHD. In line with these findings, a more recent study by Miano et al. [18], using a novel approach (analysis of the cyclic alternating pattern rates), supported the hypothesis of the existence of a hypoarousal state in children with ADHD.

Abnormal eating behaviors in ADHD

According to a recent review of the literature by our group [7], available evidence suggests that binge eating or eating disorders with bulimic behaviors occur at higher than expected rates in subjects with ADHD.

The mechanisms involved in the so called “reward deficiency syndrome” may play a significant role to explain the association between ADHD and binge eating. The “reward deficiency syndrome” is characterized by an insufficient dopamine-related natural reward that leads to the use of ‘unnatural’ immediate rewards, such as substance use, gambling, risk taking and, remarkably, binge eating [19]. Several lines of evidence suggest that a subset of patients with ADHD may present with behaviors consistent with the “reward deficiency syndrome” [20,21].

The hypothesis

Since the hypocretin/orexin system is involved in the control of alertness and reward seeking, including feeding, and given that patients with ADHD may present with a deficit of alertness as well as with binge eating or other behaviors aimed to provide unnatural immediate rewards, we speculate that patients with ADHD (or at least a subgroup of them) have an alteration in the hypocretin/orexin system. In particular, we hypothesize that hypocretin/orexin neurons located in perifornical and dorsomedial hypothalamic areas (involved in the control wakefulness) are hypoactivated, while those located in the lateral hypothalamus, involved in reward processing, are overactivated in patients with ADHD. Since one can suppose that a normal level of alertness is required to adequately control and regulate eating behaviors, we further speculate that the deficit in alertness contributes to aggravate the abnormal feeding patterns associated with ADHD.

Interestingly, the hypocretin/orexin system has been shown to stimulate locomotor behaviors in animal models [22]. It has been suggested that such a stimulation is required to support feeding seeking [22]. Therefore, we speculate that increased motor activity in ADHD might be a mechanism coupled to an overstimulation of feeding behaviors due to a hyperactivation of the hypocretin/orexin system in the lateral hypothalamus.

To our knowledge, the functioning of the hypocretin/orexin system has never been investigated in patients with ADHD.

Electrophysiological studies in animal models of ADHD aimed at quantifying the firing of hypocretin/orexin neurons in perifornical, dorsomedial, and lateral hypothalamic areas could provide a first support to our hypothesis.

Functional neuroimaging studies assessing the activity of the perifornical, dorsomedial, and lateral hypothalamic of patients with ADHD during tasks evaluating feeding behaviors and alertness would be pivotal to confirm our hypothesis.

Dosing the cerebro-spinal fluid levels of hypocretin/orexin in patients with ADHD, as previously
done, for example, in patients with narcolepsy-cataplexy [23] or restless legs syndrome [24], could provide further strong evidence in favour of our hypothesis.

Finally, studies of the hypocretin/orexin genes or their receptors in animals and humans could allow us to discover possible genetic alterations underlying the putative dysfunctions of the hypocretin/orexin system.

Given the role of the limbic system in the control of alertness and eating behaviors, as previously pointed out in this paper, we believe that future research aimed at understanding the role of the hypocretin/orexin system in ADHD should focus in particular on the projections of this system to the limbic structures.

**Implications**

If confirmed by future studies, our hypothesis could lead to further refinement in our understanding of the central mechanisms involved in alertness and reward seeking behaviors, including abnormal eating behaviors, in patients with ADHD. Since the molecular underpinnings of these impairing behaviors associated with ADHD are still unclear, research in this field should be encouraged.

Moreover, our hypothesis may also set the basis for the study of novel molecular targets for the development of drugs aimed at increasing wakefulness and reducing binge eating and other abnormal reward seeking behaviors in patients with ADHD. This would provide a tremendous opportunity to improve the quality of life of these patients by means of pathophysiologically oriented treatment.

Interestingly, it has been suggested that the effect of orexin on wakefulness is largely mediated by activation of the histaminergic system through hypocretin/orexin receptor 2, while signaling through hypocretin/orexin receptor 1 is important for the regulation of abnormal eating behaviors [22].

Therefore, we speculate that hypocretin/orexin receptor 1 antagonists might have a role in the treatment of abnormal eating behaviors, while hypocretin/orexin receptor 2 agonists might be useful to enhance alertness in patients with ADHD.

With regard to molecules potentially useful for abnormal eating behaviors, it has been reported that the first hypocretin/orexin receptor 1 antagonist (1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl urea hydrochloride (SB-334867)) inhibits both natural food intake and feeding induced by central administration of hypocretin 1 in rats, accelerates the transition between feeding and resting, and reduces the occurrence of several activity-related behaviors. Furthermore, SB-334867 has been shown to reduce feeding, body weight and fat in ob/ob obese mice [25].

As for the treatment of the deficit of alertness, it has been demonstrated that the replacement of central hypocretin by either pharmacologic (intracerebroventricular injection of hypocretin-1) or genetic (ectopic expression of hypocretin in the brain) manipulations allows for the rescue of the narcolepsy-cataplexy phenotype in animal models (mice) [25]. Unfortunately, so far, no published data are available for hypocretin receptor agonists [25]. Research in this field could lead to important therapeutic options to promote wakefulness in ADHD patients, with potential effects on attention and hyperactivity (as expected according to the hypoarousal theory of ADHD).

It would also be worthwhile to assess the role of molecules which act in association with or colocalize with the hypocretin/orexin system. We suggest here some potential avenues of research.

- Recent studies have pointed out that the hypocretin/orexin system and the histaminergic neurons may cooperate in the regulation of sleep/alertness and feeding [26]. In particular, as for the regulation of wakefulness, activation of histaminergic neurons by orexins might be important for modulation of the arousal [27]. The histamine 1 receptor (H1R) play an important role in the regulation of alertness, because H1R agonists decrease all phases of sleep, whereas H1R antagonists increase sleep [26]. With regard to the control of feeding, it has been reported that food intake is depressed by activation of H1R receptors, whereas either treatment with H1R antagonists or inhibition of histamine synthesis increases feeding [26]. Therefore, we believe that the role of H1R agonists deserves special attention in patients with ADHD, because they might be useful to both increase alertness and reduce abnormal feeding behaviors. Thus, the use of just one molecule would allow to manage at the same time two impairing conditions for ADHD patients.

- It is also well-known that the antagonists of the autoinhibitory histamine 3 receptor (H3R) promote wakefulness [28]. Interestingly, H3R antagonists are under investigation for ADHD itself [29]. Therefore, these agents may be of special interest in patients with ADHD, addressing not only the core symptoms of this disorder, but also the associated alterations of alertness and feeding behaviors.
As previously mentioned, it has been pointed out that hypocretin/orexin stimulated feeding may occur at least partly through NPY pathways [13]. This peptide has scarcely been studied in ADHD. Since an NPY-Y1 receptor antagonist (BIBO3340) is now available and it has been shown that it inhibits food intake, research on the role of NPY in abnormal eating behaviors associate with ADHD should be encouraged.

Another potentially interesting line of research could focus on the role of the cocaine and amphetamine regulated transcript (CART). It has been reported that administration of CART inhibits both normal food intake and orexin-A-stimulated food intake in goldfish [30]. Given the implication of the CART in drug reward, research on CART and its interactions with the hypocretin/orexin system in ADHD could provide a tremendous opportunity for the treatment not only of abnormal eating behaviors, but also of other reward seeking behaviors, such as substance abuse disorder, which represents one of the most impairing comorbidities in adolescents and adults with ADHD.

Other molecules which deserve further exploration in ADHD are leptin, ghrelin, dynorphin and galanin, which have a complex interplay with the hypocretin/orexin system in the control of feeding and appetite [31]. To our knowledge, the role of these molecules in the pathophysiology of ADHD has not been addressed.

All this body of research that we propose could provide further evidence in favour of the complexity of the pathophysiology of ADHD, confirming that this is a neurobiological disorder which affects several functions, not only the cognitive or the motor ones. Furthermore, the therapeutic implications of this research could lead to pharmacological options which might significantly improve sleep, eating, and substance abuse disorders of patients with ADHD, ameliorating their quality of life.

Conflict of interest statement

The authors declare no sources of financement.

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