A Mechanism Review: Does lack of sleep contribute to obesity?

Coriander Stone BSc

Abstract

A common feature of inadequate sleep is increased and altered appetite, with cravings often featuring high energy foods and continual snacking. Combined with a sedentary lifestyle and low perceived stress, this may lead to obesity.

Obesity is a growing problem particularly in the western world. With nurseries accepting babies as young as 2 months old, children staying in pre-school for up to 11 hours per day and shift work becoming more common, our increasingly busy lifestyles mean inadequate or disrupted sleep is becoming widespread and stress is something most individuals of western societies have frequent experience of. As the mechanisms of obesity are complex and multi factorial, a study on the potential impact of lack of sleep on this disorder seemed timely.

Given the multitude of potential mechanisms concerning sleep deprivation and the link to obesity, this paper focused on one area—the hypocretins (Hcrt) orexins. The literature on these neuropeptides has evolved rapidly since their simultaneous discovery in 1998 by two independent groups, De Lecea et al. and Sakurai et al. Much of the literature is conflicting, reflecting changing discoveries and research throughout the past decade or so.

The overall evidence for the role of hypocretins on appetite dysregulation is strong yet it remains unclear as to how this may affect energy in and output and therefore body weight. Findings are varied reflecting differing methodologies and models used. Future research should focus on controlled human trials modelling stress and perceived stress free environments reflecting more realistic conditions.

Introduction

Obesity is a growing epidemic in western society and countries traditionally considered to have healthy Mediterranean style diets, such as Spain, have seen childhood obesity double in the last 15 years. Obesity poses a severe health problem: as a primary
condition and a risk factor for other serious disorders such as diabetes mellitus, high blood pressure, some cancers, liver disease and cardiovascular disorders.\textsuperscript{5} NHS costs directly related to obesity are estimated at £5.1 billion per year in the UK\textsuperscript{6} and were $147 billion in 2008 in the USA.\textsuperscript{6}

Deaths due to non-communicable diseases (NCD’s) equal an estimated 80% of all deaths in western society and 60% in developing countries.\textsuperscript{7} Shift work resulting in inadequate sleep poses an occupational hazard in the work place and may result in NCD’s. Shift work and inadequate sleep has also been shown to alter appetite and energy levels, resulting in increased appetite via dysregulation of the hormones leptin and ghrelin and reduced energy expenditure.\textsuperscript{1,8} Conditions involving chronic sleep disturbance such as narcolepsy are also consistently associated with an obesity risk and 50-98% of people with chronic sleep apnoea are obese.\textsuperscript{10} It is therefore highly probable that lack of sleep poses a health risk both in terms of its potential impact on obesity and as a contributor to NCD’s. This review will focus on the association between sleep deprivation and dysregulation of the hypocretins and discuss how this may impact on obesity.

**The Hypocretins/Orexins**
The hypocretins, or orexins (referred to as hypocretins hereon), are wake promoting and appetite stimulating neuropeptides derived from the same precursor peptide, prepro-hypocretin, released in the lateral, dorsal and posterior hypothalamus.\textsuperscript{11} They consist of two peptides – Hcrt-1 and Hcrt-2 – which are released by Hcrt neurons in the lateral hypothalamus (LH) and, as with all neuropeptides, bind to G-protein coupled receptors.\textsuperscript{12,13} Whereas neurotransmitters can only signal within their own synapses, neuropeptides diffuse throughout the entire brain, thus imposing a more widespread effect.\textsuperscript{14} They also modify neurotransmitter signals influencing nutrient status in the body.\textsuperscript{14}

Hcrt-1 is a 33 amino acid peptide with two sets of intrachain disulphide bonds and Hcrt-2 is a 28 amino acid C-terminally amidated linear peptide.\textsuperscript{15} The transcript mRNA of their polypeptide precursor, prepro-hypocretin, encodes Hcrt-1 and -2.\textsuperscript{15} Hcrt neurons specifically target those areas of the brain involved in arousal\textsuperscript{11} and in narcoleptic subjects the Hcrt neurons and peptides are almost completely absent or at least, severely dysregulated.\textsuperscript{16} Both narcolepsy and sleep apnoea are associated with Hcrt deficiency.\textsuperscript{10} Hcrt neurons receive input from nuclei within several areas of the brain and also from GABAergic, glutamergic, noradrenergic, serotonergic, histaminergic and cholinergic neurons.\textsuperscript{12,16} In turn, these systems receive information from the peptidergic systems melanin concentrating hormone (MCH) – which increases food intake and decreases energy expenditure\textsuperscript{17}; proopiomelanocortin (POMC), neuropeptide Y (NPY); corticotropin releasing factor (CRF); glucagon-like peptide (GLP) and from metabolic signals via glucose, leptin and ghrelin.\textsuperscript{16} These combined signals lead to raised Hcrt levels and increased arousal as well as increased feeding, though the latter is probably influenced by other Hcrt activated peptidergic systems.\textsuperscript{17}

Hcrt neurons are generally thought to be excited by several neurotransmitters including glutamate – the most common excitatory neurotransmitter\textsuperscript{18}, CRF, ghrelin, neurotensin, vasopressin and oxytocin whereas serotonin, noradrenaline, dopamine, NPY and leptin inhibit them.\textsuperscript{12,15} These neurons project to various structures within the brainstem particularly those involved in stress, arousal and reward behaviours as well as the limbic system (see Figures 1 & 2). These structures then express one or both Hcrt receptors via
aminergic, noradrenalinergic, histaminergic or serotonergic neurons which lead to cortical arousal. They also project to other cholinergic arousal brain centres, producing acetylcholine.

The sleep regulatory areas of the brain with the densest Hcrt projections are the noradrenergic locus coeruleus (LC), the serotonergic dorsal raphe nucleus, the cholinergic basal forebrain and pedunculopontine nucleus and the histaminergic tuberomammillary nucleus – see figure 3, with the LC exhibiting higher noradrenaline transmissions. The three main groups which impact on arousal are the Hcrt secreting neurons, cholinergic neurons and monoaminergic neurons.

Figure 1: Organisation of Hcrt neuron system (dots) throughout the rat brain. Neurons are found only in the lateral hypothalamus and project to the entire central nervous system.
Figure 2: Hcrt producing neurons (dots) projecting to brain regions involved in stress, arousal and reward behaviour. PFC: prefrontal cortex; NAcc: nucleus accumbens; BNST: bed nucleus of the stria terminalis; Amyg: amygdale; VTA: ventral tegmental area; RN: raphe nucleus; LC: locus caeruleus; LDT/PPT: laterodorsal tegmentum and pedunculopontine tegmentum

Hcrt's bind to two receptors in differing areas of the brain – HcrtR1 and HcrtR2 – with different affinities. Hcrt-1 binds mainly to HcrtR1 whereas Hcrt-2 binds to both receptors with high affinity. HcrtR1 and HcrtR2 are mediated by two G-protein

Figure 3: Schematic representation of the projections of orexin/hypocretin and NPS neurons that may be involved in sleep function. Abbreviations: BF, basal forebrain; LC, locus coeruleus; LH, lateral hypothalamus; TMN, tuberomammillary nucleus; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; Raphe, raphe nucleus
coupled receptors and are very differently distributed in the brain (rats). Within the brain, HcrtR1 mRNA expression is highest in the LC and HcrtR2 mRNA expression highest in the tuberomammillary nucleus (TMN). Both areas are important for arousal states and correspondingly, as sites with the densest concentrations of Hcrt neuron projections, suggests that these brain regions are also major effector sites. See Figure 4 which shows an overview of the Hcrt system.

Interactions between Hcrt’s-1 and -2 depolarise cortical neurons both directly and indirectly via noradrenaline release in the hypothalamic-pituitary-adrenal (HPA) axis.

The Hcrt’s therefore interact with the autonomic, neuroendocrine and neuroregulatory systems including monoamine neuromodulators and the HPA axis. This finding that various neurotransmitter groups interact with the Hcrt’s have led to the hypothesis that the Hcrt’s may be both the target and an essential component of the emotional sympathetic stress response and the Hcrt neuron interaction with the central nervous system (CNS) suggests interaction between this and the arousal/sleep-wakefulness brain centres. Hcrt’s may integrate several transmitter systems, since it has been shown that for long term enhancement of signalling within the hippocampus induced by Hcrt’s, glutamate, GABA, noradrenaline and cholinergic receptors are also required. The Hcrt’s are then regulated by NPY acting at Y1 receptors, GLP via GLP-1 receptor, noradrenaline, CRF via CRF-R1 and cholecystokinin (CCK) via CCKA receptors respectively.

However, it seems that different animal species possess different Hcrt polarisations and that noradrenaline, which is usually Hcrt excitatory (depolarising) during the waking period may become inhibitory under sleep deprivation. During normal sleep conditions GABAergic cells in the posterior hypothalamus are activated which inhibit wake promoting signals. Various other regulators of the Hcrt’s may become dysregulated under sleep deprivation, which will be discussed further.

Hcrt levels also fluctuate with the circadian rhythm and forced sleep deprivation has been shown, in some cases, to increase their levels as have many forms of stress: possibly via the activation of the CRF system’s receptors Hcrt neurons express. However, sleep deprivation should in fact inhibit Hcrt neurons to induce sleep and therefore it may be that differing forced wakefulness conditions result in opposing mechanisms. Hcrt neurons have been shown to initiate stress-induced arousal via CRF which in turn also activates the Hcrt’s. Stress-induced activation of the Hcrt neurons leads to reward seeking behaviour (i.e. feeding), possibly via increased glutamate sensitivity.

Hcrt neurons are favourably positioned within the brain to link energy and wakefulness homeostasis; being active during the wake state and becoming inactive during the rest/sleep state. This is logical, considering that feeding and sleep/wake behaviour in animals must be intrinsically linked in order for the animal to actively seek and consume food. In accordance with this, low glucose levels activate the Hcrt’s and high glucose inhibits them, indicating a need to feed or fast respectively. Receptors which regulate appetite are also found on neurons which generate sleep and wakefulness. See figure 5: Hcrt interactions between sleep and metabolism. We know that the Hcrt system shares brain circuits which regulate arousal, metabolism and reward and can be considered “1st order” sensors of metabolic fluctuations which then integrate these factors with other brain pathways to regulate consummatory behaviours. However, the underlying molecular and cellular mechanisms by which they regulate arousal, metabolism and rewards is unknown and where it was previously thought that Hcrt's
regulated feeding – hence their alternative name of orexins – it has been found in some cases that where Hcrt neurons are absent there is no change in feeding behaviour. ¹⁷

Much of the classical methods used to understand the cellular activity and function of the brain is difficult to interpret and may suggest misleading results. This will be discussed further under the “results” section.

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**Figure 4:** The overview of the Hcrt system. (A) Structures of mature Hcrt-1 (orexin-A) and -2 (orexin-B) peptides. The topology of the two intrachain disulfide bonds in orexin-A is indicated above the sequence. Shadow indicates amino acid identities. Mammalian orexin-A sequences thus far identified (human, rat, mouse, pig, dog, sheep, cow) are all identical. (B) Schematic representation of the Hcrt system. Hcrt-1 and -2 are derived from a common precursor peptide, prepro-hypocretin (prepro-orexin). The actions of Hcrt’s are mediated via two G protein-coupled receptors named hypocretin R1/orexin-1 (OX1R) and hypocretin R2/orexin-2 (OX2R) receptors. HcrtR1 is selective for Hcrt1, whereas HcrtR2 is a non-selective receptor for both Hcrt-1 and Hcrt-2. HcrtR1 is coupled exclusively to the Gq subclass of heterotrimeric G proteins, whereas HcrtR2 may couple to Gi/o, and/or Gq. HcrtR1 is abundantly expressed in the locus coeruleus (LC) and dorsal raphe nucleus (DR), while HcrtR2 is abundantly expressed in the tuberomammillary nucleus (TMN), basal forebrain.
cholinergic cells, laterodorsal/pe- dunculopontine tegmental nuclei (LDT/PPT), and dorsal raphe nucleus.\textsuperscript{15}

![Figure 5: Direct interactions between sleep and metabolism illustrating the major anatomical and functional interactions between hunger, feeding, and sleep. Excitatory relationships are indicated by arrow heads while inhibitory interactions are indicated by blunt endings. Circular endings indicate unspecified relationships.\textsuperscript{10}]

**Leptin**

Leptin is a satiety protein hormone produced in adipose tissue via brain signals, which inhibits neurons in the arcuate nucleus (AN) of the hypothalamus which co-express NPY – a feeding stimulant – and agouti-related peptide (AgRP), which works in synthesis with NPY to increase appetite. It activates POMC neurons which co-express cocaine-and amphetamine-regulated transcript (CART) (Adamantidis & Luis de Lecea 2009).\textsuperscript{20} Both NPY and AgRP sense circulating levels of leptin and ghrelin and respond accordingly.\textsuperscript{10} Leptin also increases energy expenditure via thermogenesis.\textsuperscript{20} As it responds to signals from body fat, the amount of leptin in the body is directly proportional to levels of fat. Leptin deficiency leads to severe obesity from an early age.\textsuperscript{21} Thus leptin is an important regulator of energy intake and output and crucial to maintaining a normal body weight.

**Ghrelin**

Ghrelin is an appetite stimulating hormone produced in the gut with an opposite mechanism of action to leptin: it activates NPY and AgRP and inhibits POMC and CART neurons as well as decreasing locomotor activity and therefore increasing energy conservation.\textsuperscript{20} NPY and AgRP neurons have orexigenic effects and POMC and CART anorexigenic effects. Ghrelin is the first circulating neuropeptide which increases appetite after systemic administration\textsuperscript{13} and levels have been shown to spike at around 3 a.m under normal sleep conditions. It is probable that insufficient sleep dysregulates this spike and consequent daytime levels\textsuperscript{15} (see Figure 6).
Figure 6: Roles of Hcrt in coordination of energy and sleep homeostasis. Hcrt neurons stimulate the hypothalamic nuclei involved in feeding behavior and increase cortical arousal and promote wakefulness through the aminergic nuclei and other sleep-related nuclei. Stimulation of dopaminergic, limbic and cholinergic centres by Hcrt can modulate reward systems, motor activity, and emotional arousal. Peripheral metabolic signals, leptin, ghrelin and glucose and circadian rhythms influence Hcrt neuronal activity to coordinate arousal and energy homeostasis. Abbreviations: ARC: arcuate nucleus; LHA: lateral hypothalamic area; NPY: neuropeptide Y; TMN: tubermammillary nucleus; LC: locus coeruleus; VTA: ventral tegmental area; LDT: laterodorsal tegmental nucleus; PPN: pedunculopontine tegmental nucleus.

Neurons in the arcuate nucleus of the hypothalamus sense circulating leptin and ghrelin levels and transmit signals to the lateral hypothalamus which process them alongside autonomic, endocrine and environmental inputs and then stimulate the relevant behaviours. Hence appetite is the integration of metabolic and hormonal cues in the CNS.

Sleep deprivation has been shown repeatedly to lower leptin and raise ghrelin and glucose levels (see figure 7), leading to low POMC and CART and increased NPY and AgRP stimulation, thus increasing appetite and feeding behaviour. In addition, low leptin and high ghrelin and glucose levels also increase Hcrt excitability, illustrating the close link between these systems and their potential impact on appetite and thus obesity.
Does Lack of Sleep Contribute to Obesity?

Coriander Stone

The Nutrition Practitioner
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Figure 7: Change in daytime levels of leptin, ghrelin, appetite and hunger from 10-hour to 4-hour bedtimes in 12 healthy lean subjects after 2 days of curtailed sleep.¹,⁸

Methodology
A unsystematic preliminary literature search was carried out using terms such as “sleep deprivation and obesity” on google scholar and google search. After reading through the literature a basic diagram theoretically linking sleep deprivation to obesity was developed (figure 8). Further reading was obtained via the same preliminary search strategy to help develop the network diagrams further (figures 9 & 10).

Since Hcrts seemed to be a central part of the mechanism under review this became the focus for subsequent searches. A well defined search term was used in google scholar with the aim to acquire around 250 papers from which, after further reading, the most relevant papers would be selected. The first search: "sleep deprivation" (hcrt OR "hypocretin" OR "orexin") leptin ghrelin ("hpa" OR hypothalamus OR pituitary OR adrenal) obtained 424 results but adding “glutamate” in narrowed this down. The final search: "sleep deprivation" (hcrt OR "hypocretin" OR "orexin") leptin ghrelin ("hpa" OR hypothalamus OR pituitary OR adrenal) glutamate, resulted in 138 papers.

No date restrictions were implemented, given only 14 years or so of research on Hcrts exists. Abstracts from all 138 papers were then reviewed and any papers deemed significant to the review were obtained and read in full. Of the papers selected only 10 were inaccessible in full. The authors were contacted in these cases and all but two responded. These last two papers were therefore discarded. The full progression of diagrams can be seen in the appendix. Books were only used for reference and were not included in the review.
Figure 8: version 1 (V1) diagram showing theoretical mechanism linking sleep deprivation to obesity
Figure 9: V2 diagram showing theoretical mechanism linking sleep deprivation to obesity
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**Figure 10:** V3 diagram showing theoretical mechanism linking sleep deprivation to obesity
Results
As mentioned previously, results differed depending on the animal model and type of experiment carried out. Papers are discussed here and conclusions drawn in the next section. The biological clock is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus and it was found that vasopressin plays a prominent role in SCN output. Glucose tolerance and insulin sensitivity increase at the onset of darkness but Hcrt detain this action and feed into the sympathetic liver activity, thus increasing glucose levels. Circulating glucose levels regulate the Hcrt, either by activating (in the case of low glucose) or inhibiting them (in the case of high levels) but sleep deprivation may dysregulate this entire system.

Lack of sleep and light trigger the SCN to send projections to the Hcrt but in sleep deprivation these projections are diminished. The mechanistic explanations for lack of sleep and obesity are not yet fully understood. Under normal sleep and feeding conditions there is a nocturnal rise in leptin levels, yet although ghrelin seems non clock-gene regulated it appears to be triggered nocturnally by sleep in humans. This nocturnal spike is absent in sleep deprivation yet levels rise the following day. Hcrt release is therefore circadian rhythm controlled as it is stimulated by the SCN. As lack of sleep leads to poor insulin regulation and high liver glucose, sleep deprivation can be seen as being a chronic stressor on the body. Stress has long been thought to contribute to obesity via the actions of cortisol, prolactin and insulin and perhaps this is a valid mechanism for the link between lack of sleep and obesity in humans. Raised cortisol also leads to low leptin and high ghrelin levels. However much of the conclusions drawn are theoretical as little is known on the interactions between each system.

In a study on mice by Tsujino et al it was found that a form of cholecystokinin named CCK-8S, neurotensin, oxytocin and vasopressin activated the Hcrt receptors (although the authors also recognised that the Hcrt activity regulatory mechanisms are not fully understood). The underlying mechanisms were studied using calcium (Ca) imaging and slice patch recording. It was found that Hcrt producing neurons project mainly to monoaminergic and cholinergic nuclei and activate monoaminergic neurons, consistent with other findings and that these regulate the sleep and wake cycles. Also consistent with other findings, the authors noted that Hcrt receive regulation (but not necessarily activation or inhibition) from serotonin, noradrenaline, acetylcholine, GABA and glutamate and are also influenced by CRF, GLP-1, NPY, ghrelin, leptin and glucose. Monoaminergic neurons were also found to be active during wakefulness and inactive during REM sleep by Sakurai. Tsujino et al. found that the sulphated octapeptide form of CCK – CCK-8S – acts via two CCK receptor subtypes, CCK_4 and CCK_5 and that the former activates Hcrt neurons. They used Ca activated dye on transgenic mice to show that the dye was expressed in Hcrt via glutamate and that glutamate therefore depolarises Hcrt neurons via ionotropic glutamate receptors. Serotonin was found to hyperpolarise (inhibit) Hcrt.

CCK-8S was seen to bind to both CCK_4R and CCK_5R but only activated the Hcrt via the former and this finding was confirmed using double-label immunofluorescence analysis. The Ca showed that raised levels of CCK-8S increase Hcrt activity. CCK was also shown to suppress food intake and increase sleep when given intracerebroventricularly and this action was suppressed by raised Hcrt levels leading to
increased arousal and feeding, as expected. It was concluded that the action of Hcrt's may be counterbalanced by other CCK actions elsewhere in the brain.

In another review paper by Parker and Bloom\textsuperscript{14} it was deemed unclear as to whether the Hcrt's impact on appetite directly or indirectly, via their influence on arousal, and thought that they possibly influence feeding via a variety of factors but to identify all these mechanisms is, for now at least, highly complex. It appears from this review that Hcrt's are only orexigenic if activated in the hypothalamus and that HcrtR1 antagonists have no impact on drug or food seeking behaviour, whereas HcrtR2 antagonists do. It was noted that the Hcrt’s activate neurons in MCH and the ventral tegmental area in the midbrain which would impact on sleep and arousal. All the studies reviewed focused on the effects of ghrelin generally yet not whether it was peripherally or centrally derived. Konadhode et al.\textsuperscript{17} found Hcrt's present on neurons involved in chewing, gastrointestinal function, arousal and bladder control and as such must be focused on keeping the animal awake whilst feeding. The TMN histaminergic system via HcrtR2 was also found to increase wakefulness maintenance and in narcoleptic patients there is a high incidence of type 2 diabetes and obesity due to altered energy state, which strongly suggests a role for the Hcrt's in feeding.\textsuperscript{19} In addition to this, the authors found that anti-Hcrt antibody decreased food intake and that a HcrtR1 antagonist reduces food intake and obesity. Injecting Hcrt-1 into the brain increased feeding and starvation induced wakefulness.

Ohno and Sakurai\textsuperscript{3} found that the Hcrt neurons send excitatory signals to monoaminergic neurons to maintain wakefulness and these then send inhibitory feedback signals to the Hcrt neurons.\textsuperscript{3} This mechanism maintains the activity of the monoaminergic neurons yet when their cell activity is disrupted even slightly, it leads to a decrease in the inhibition of Hcrt neurons. Hcrt neurons therefore become aroused and increase their excitatory influence on the monoaminergic cells – thus it can be seen that the feedback mechanism maintains a wake state when disrupted by, for example, lack of sleep, explaining why the Hcrt's have been found to be raised even under sleep deprivation, where usually they would be inhibited. Since the Hcrt neurons remain fairly inactive in the quiet awake state and rise with activity, it is suggested that theoretically, insomnia or sleep deprivation where the subject stays resting may not impact on appetite in the same way that sleep deprived shift work might.

In some studies it has been shown that ghrelin increases body mass and fat but not food intake.\textsuperscript{30} The authors state this is suggestive of low energy expenditure or increased utilisation of carbohydrates for energy, rather than fat and go on to say this suggests ghrelin decreases sympathetic nervous system (SNS) activity. However, this view does not correspond with well-known mechanisms of the SNS, which state that expending carbohydrates in the form of sugars rather than fat is indicative of the stress response, indicating that ghrelin in fact increases SNS rather than decreases it. Enquiries to clarify this position from the authors yielded no response.

Contrary to findings that sleep deprivation may lead to obesity, a study by Galvão et al\textsuperscript{31} using male Wistar rats of 3-4 months of age found that REM sleep deprivation in rats led to increased food intake but weight loss. There was no change in global food intake although diurnal intake increased and the lack of sleep was shown to decrease leptin, testosterone and insulin. They also found an increase in SNS and HPA axis activity through an increase in the stress hormones cortisol and adrenocorticotropic hormone (ACTH) and speculated that increased Hcrt’s may also lead to increased HPA-axis activity. In accordance with other findings, the lack of sleep also showed a rise in
orexigenic NPY and a decrease in anorexigenic POMC and raised leptin inhibited the Hcrts. In spite of the energy content of the diet, leptin still decreased under sleep deprivation, demonstrating a dysregulation of the normal mechanism.

They also found that corticotropin releasing hormone (CRH) increased wakefulness and the SNS response, indicating that stress is another causal factor for both sleep deprivation and perhaps a rise in appetite. Stress hormones were released after just one day of sleep deprivation and the rats began to lose weight on day 2 (of a 4 day experiment). They then re-gained weight to equal the controls, in spite of their food intake progressively rising and seemed also to adapt to the physiological stress of sleep deprivation.

Sleep deprivation (SD) was found to increase Hcrts stimulated by agonists of glutamate ionotropic factor and inhibited by dopamine and dopamine receptor agonists. Thus SD increased glutamate and decreased dopamine, leading to increased Hcrt activity. Hcrt synthesis seemed to be regulated by glucocorticoids, with low levels leading to low Hcrt expression. Figure 11 shows some of their findings.

**Figure 11**: (A) Body weight change (g) of control (CTL; n = 8) and paradoxical sleep deprived (PSD; n = 8) groups during 4 days of PSD. Body weight was measured daily at 8:00 h and variation was calculated by the equation \[(\text{current weight} - \text{previous weight})/\text{previous weight} \times 100\]. (B) Actual food intakes of CTL and PSD rats were measured twice a day at 8:00 h (estimated nocturnal intake) and at 17:00 h (estimated diurnal intake) after subtraction of the residues collected from the water in the deprivation chamber. The insert shows the total amounts of diurnal and nocturnal food intake. Data are presented as mean SEM. * = significantly different from CTL group at the same time point (p < 0.05); z = significantly different from the other days, within the same group (p < 0.05); ¥ = significantly different from corresponding diurnal food intake (p < 0.05).
Rolls et al also discussed the finding that Hcrt deficiency is common in the elderly and is related to glucose intolerance and insulin resistance and that both the hypothalamus and the Hcrt system affect the stress response.

In their review paper, Mayanji et al discuss that only sleep deprivation studies using rats show weight loss, whereas human studies show weight gain. There may be various reasons a pertinent one being the difference between animal and human studies. Most rat studies use a method called disc over water (DOW) which involves placing the animal on a disc over cold water. If the rat falls asleep they become unbalanced, make contact with the water and therefore wake, re-starting the whole cycle. Evidently this is a highly stressful situation and in addition, the water temperature increases thermogenesis which in turn contributes to weight loss. There is also increased physical activity using the DOW method where the animal repeatedly has to climb out of the water.

There are also differences in the durations of sleep deprivation between animal and human studies. In most of the rat studies, there was chronic and prolonged SD whereas human studies involved a small amount of sleep loss daily, i.e. sleeping 4-6 hours per night instead of 8. It seems that complete sleep loss results in weight loss whereas mild-moderate sleep restriction on daily sleep increases weight gain. Also where moderate sleep restriction combines with the activation of the stress response, it has been shown to lead to weight gain. In rats with only partial SD weight gain also occurred and it may also be that weight gain is more linked to the quality of sleep rather than time spent sleeping.

As Hcrts increase physical activity, it may be that they are the link between metabolism, sleep and obesity and it is also possible that SD activates the HPA axis, SNS and brain metabolism which in turn leads to low leptin, raised ghrelin and therefore, in some cases, obesity. In one study it was found that SD raised Hcrts to beyond normal levels.

A final area of interest, not fully explored due to time constraints, is the link between ghrelin and growth hormone (GH). Ghrelin stimulates GH nocturnally but disturbances to GH (i.e. in decreased nocturnal ghrelin under SD) and cortisol lead to a dysregulation in glucose. SD leads to increased nocturnal GH, raised following evening cortisol and decreased insulin sensitivity the following morning and peripheral tissues exposed to GH for extended periods of time may cause decreased muscular glucose uptake and thus dysregulation. SD also increases inflammatory cytokines which may lead to insulin resistance and diabetes. The HPA axis becomes dysregulated in SD and leptin and cortisol mirror each other’s 24 hour patterns, creating an inverse relationship. This inverse relationship becomes disrupted under SD, where leptin levels stop rising in the early morning when cortisol levels are decreasing. SD leads to a 30% decrease in glucose tolerance but it is also possible that SD leads to low leptin because of the increase in wake time and therefore a simple increased need for calories.

Spiegel discusses that low leptin levels coincide with an increase in sympathovagal balance and that SD results in an increase in Hcrt-1. Leptin release is inhibited by SNS activity which means that SD leads to raised SNS activity and lowered leptin. Even under SD in non-perceived stressful conditions the stress response is activated and SD also lowers levels of thyroid stimulating hormone (TSH), one of the main regulators of metabolism.
Conclusion
It is still unclear which neuropeptides influence feeding and exactly how. We can understand how they activate various brain regions and impact on each other but not clearly deduce how they lead into feeding behaviour. Many neuropeptides are involved in the regulation of appetite but the challenge is discovering which, if any, is the most implicated. If this can be achieved than further trials can be designed to elucidate the mechanisms of action.

In addition to divergent animal study designs involving severe stress and increased physical activity which may account for differences in results, sleep in most human studies is self-reported which is problematic to accurately monitor. Whilst some researchers found that lack of sleep increased Hcrt release, it may be that they did not investigate or report the follow-on mechanisms and inhibitory feedback mechanisms which lead to the Hcrts being inhibited again by disruption of the monoaminergic cell activity.

It seems that noradrenaline is an excitatory influence on the Hcrts via cortical arousal under normal sleeping conditions which becomes inhibitory under SD, increasing sleepiness. This seems a plausible explanation since most regulatory feedback loops consist of an element (in this case noradrenaline) which turns on a mechanism (Hcrts) and turns off again after a certain time period or under certain conditions – i.e. SD. Results would depend on the experiment design and response of the feedback loop under those particular conditions.

The Hcrt system interacts closely with circadian and environmental factors to act as a sensory system for metabolism. It also senses signals from circulating leptin, ghrelin or glucose and acts accordingly as an arouser. This results in a positive feedback loop between Hcrt sensor and effector properties which may result in obesity in SD. The Hcrts probably also increase food intake partially via the NPY pathway.

Under normal sleep circumstances it seems that Hcrts do not induce over feeding but chronic SD almost certainly dysregulates the Hcrt system in the same way as chronic calorie restriction does, which may lead to overeating. In calorie restriction, there is a down expression of prepro-Hcrt mRNA in the LH which may signal an alarm state whereby Hcrts prepares the body for disaster. This could logically result in an increase in feeding behaviour in preparation for the supposed disaster.

If SD is a stressor (which it appears to be) then under sedentary conditions this would logically lead to weight gain as stress requires an increased necessity for food for increased physical expenditure. Cortisol is also linked to increased appetite and cravings. It might also be that Hcrts increase food-seeking behaviour via various mechanisms under increased arousal (i.e. SD) in order to encourage the animal to seek new grazing pastures, which would also be a logical stress response. If the current environment is stressful and therefore a potential danger it is plausible that an alternative environment may be sought and the animal in question may be encouraged to do so via the Hcrt system.

Another question regarding studies is what type of sleep deprivation is important to this mechanism? REM, non-REM, stressful or sedentary conditions all trigger different responses and mechanisms and would therefore impact on results. Also narcolepsy and sleep apnoea indicate Hcrt deficiency and are associated with obesity which implies that increased Hcrt’s could lead to weight loss. These are all questions that well designed specific trials may be able to answer.
In addition, the association between obesity and Hcrt may be linked with glucose intolerance. As discussed previously, the mechanisms are multi factorial and current understanding makes it possible only to theorise. The consensus seems to be that the HPA axis activation is linked to obesity via increased food intake rather than the Hcrt themselves.

The absence of the sleep to wake transition (i.e. in total sleep deprivation) eliminates the usual morning cortisol spike\textsuperscript{28}, however, in partial sleep loss this spike is amplified. This is an important dysregulation which could have been further investigated if time permitted. As sustained elevated cortisol leads to low leptin and high ghrelin, this is potentially of great relevance to this mechanism. Ghrelin levels usually spike at night under normal sleep conditions yet decrease nocturnally and rise in the daytime under SD. Future reviews could therefore look at the link between SD and the stress response, particularly in relation to cortisol and other catecholamines and their impact on the appetite hormones. Figures 12 & 13 illustrate some of these potential mechanisms underlying SD and obesity.

![Diagram](image_url)  
**Figure 12**: potential roles of Hcrt in SD related obesity
Does Lack of Sleep Contribute to Obesity?

The Nutrition Practitioner
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Coriander Stone

Figure 13: Schematic of positive energy balance in which energy intake is greater than energy expenditure which would result in weight gain. Numerous endogenous and exogenous factors can influence both sides of this balance, and sleep has been associated with both endogenous and exogenous factors.

In as far as nutrition may be of use in combating SD related obesity there may be limited impact. Certainly, reducing glucose levels may help reduce the risk of insulin intolerance and diabetes mellitus and adrenal support may diminish the effects of a chronic stress response. However, much of the literature allures to differing mechanisms and the evidence base for nutritional intervention is sparse. As with any condition the individual must be considered in order to try and target mechanisms for a personalised approach and the real challenge lies in changing lifestyle sufficiently to avoid SD and thus reduce the probability of related disorders.

About the Author
Coriander graduated from CNELM with a first class honours in Nutritional Therapy. She lives in Madrid where she practices from a busy central clinic offering both face-to-face and Skype consultations. She also does nutrition writing in her spare time.