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TITLE: OREXINS (HYPOCRETINS): THE INTERSECTION BETWEEN HOMEOSTATIC AND HEDONIC FEEDING

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Arc, arcuate nucleus; BLA, basolateral amygdala; BMA, basomedial amygdala; CeA, central amygdala; CPP, conditioned place preference; DAMGO, D-Ala2-*N*-Me-Phe ^{4}-gly^{5}-ol-enkephalin; DMN, dorsomedial nucleus; FR20, fixed ratio 20; HFD, high fat diet; HPF, highly palatable food; LHA, Lateral Hypothalamic Area; MPOA, medial preoptic area; NAcc, nucleus accumbens; NI, nucleus incertus; NTS, nucleus of the solitary tract; OB, olfactory bulb; OXR-1, orexin 1 receptor; OXR-2, orexin 2 receptor; PeF-LH, perifornical-lateral hypothalamic area; PFC, prefrontal cortex; POA, preoptic area; PR, progressive ratio; PR5, progressive ratio 5; PVN, paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; VLPO, ventrolateral preoptic area; VMN, ventromedial nucleus; VTA, ventral tegmental area.

Abstract

Orexins are hypothalamic neuropeptides originally discovered to play a role in the regulation of feeding behaviour. The broad connections of orexin neurons to mesocorticolimbic circuitry suggests they may play a role in mediating reward related behaviour beyond homeostatic feeding. Here, we review the role of orexin in a variety of eating-related behaviour, with a focus on reward and motivation, and the neural circuits driving these effects. One emerging finding is the involvement of orexins in hedonic and appetitive behaviour toward palatable food, in addition to their role in homeostatic feeding. This review discusses the brain circuitry and possible mechanisms underlying the role of orexins in these behaviours. Overall, there is a marked bias in the literature towards studies involving male subjects. As such, future work needs to be done to involve female subjects. In summary, orexins play an important role in driving motivation for high salient rewards such as highly palatable food and may serve as the intersection between homeostatic and hedonic feeding.

1. Introduction

Eating behavior is regulated by a number of hormones and neural substrates, including by orexin (Fukushima et al. 2015). Orexin, also known as hypocretin, is a neuropeptide produced by a group of neurons located in the lateral hypothalamic area including the lateral hypothalamus and dorsomedial–perifornical area. It consists of two different forms, orexin A and orexin B, which are synthesized from the precursor prepro-orexin (De Lecea et al. 1998, Sakurai et al. 1998). Although there is a small number of orexin-producing cells in the brain (less than 80,000 neurons in humans and approximately 3000 - 4000 in rats (Mieda 2017) , these cells project extensively throughout the neuraxis including to cortical areas, the limbic system, thalamus, hypothalamus, brainstem and spinal cord (Xu et al. 2013). These widespread connections underscore orexin's involvement in various brain functions which are mediated by the G-protein coupled receptors, orexin receptor type 1 (OXR-1) and orexin receptor type 2 (OXR-2) (De Lecea et al. 1998, Sakurai et al. 1998). The binding affinities of orexin peptides to these receptors differ such that orexin A binds to both OXR-1 and OXR-2 with approximately equal affinity, while orexin B almost exclusively binds to OXR-2 (Sakurai et al. 1998). OXR-1 expression predominates in cortical areas, the bed nucleus of the stria terminalis and the locus coeruleus while OXR-2 are more highly expressed in the nucleus accumbens, central medial thalamus and hypothalamic paraventricular nucleus (Sakurai et al. 1998, Marcus et al. 2001, Trivedi et al. 1998). Differences in receptor distribution and expression pattern indicate that orexin receptors may be involved in distinct neurobiological processes and circuitry underlying orexin's effects.

Orexin peptides have been implicated in numerous behavioural and physiological processes (Mahler et al. 2014). An initial role for orexin was originally found in the regulation of feeding (Sakurai et al. 1998, Xu et al. 2013). In 1998 Sakurai and colleagues showed the expression of orexin in the lateral hypothalamic area, an area in the brain that serves as a feeding centre. Further, when microinjected into the lateral ventricle, both orexin A and B were found to induce feeding in a dose dependent manner (Sakurai et al. 1998). Indeed, the term orexin comes from the Greek word 'orexis' for appetite. However, since this original discovery, orexin neurons have also been found to play a role in other brain functions including arousal and sleep (Xu et al. 2013, James et al. 2017), response to stress (James et al. 2017), regulation of autonomic function (James et al. 2017) and reward related behaviour (Sharf et al. 2010b).

The precise role of orexin signalling in the brain remains elusive given this established role in multiple central processes and behaviours. Recently, it was postulated that the multiple roles of orexin are based on its unifying function in facilitating the transformation of motivational drives into certain adaptive behaviours (Mahler et al. 2014). Current findings suggest that orexin promotes motivation for highly salient reinforcers such as addictive drugs and highly palatable food (Mahler et al. 2012). However, while numerous findings support the role of orexins in drug seeking behaviour and relapse (Hopf 2020), the role for palatable food needs to be further explored. As an example, although some studies report the role of orexins in dysregulated eating that resembles addiction (Mahler et al. 2012), their involvement in other aspects of dysregulated eating such as craving remains a subject of debate due to mixed findings from existing studies (Nair et al. 2008, Martin-Fardon et al. 2018). Therefore, in this review we will give an overview of rodent studies on the role of orexin in eating-related behaviour, with a focus on reward and motivation, and the brain circuitry driving these effects. Specifically, we will review literature on orexin's involvement in feeding, hedonic eating, cue-driven eating related behaviour, motivation for palatable foods, reinstatement of palatable food-seeking, and the connection of the orexin system with the olfactory system. We will also explore sex differences and identify research areas where future studies are required. Thus, the questions that we aim to answer in this review include: 1) to what extent are orexins involved in eating-related behaviour and food reward? 2) what brain regions or circuits are involved? and 3) do sex differences exist in orexin-mediated eating behaviour?

2. Method

We reviewed published studies investigating orexin-related eating behaviour according to the guideline and methodology for conducting systematic scoping reviews developed by Arksey and O'Malley (Arksey & O'Malley 2005) and further modified by Levac et al. (Levac *et al.* 2010).

2.1 Eligibility criteria

All original articles that investigated the involvement of orexin in feeding were included in this review if they a) were conducted in rodents (mice and rat) and b) evaluated behaviours related to eating with a focus on consummatory behaviour indicated by the meal size or food intake, food-motivated behaviour and hedonic or reward-based eating behaviours. We defined hedonic or reward-based eating behaviour as eating for pleasure when caloric needs are already fulfilled (Zheng & Berthoud 2007). Exclusion criteria includes articles that did not provide information on the sex of the experimental subjects, are not written in English and are non-original articles such as reviews, meeting summaries, commentaries, editorials, letters to the editor and conference abstracts. Studies conducted in humans and species other than rodents were also excluded.

2.2 Data sources and search strategy

Three electronic databases including PUBMED, Embase and Web of Science were used to identify relevant studies. We restricted the search to articles written in English language published from 1998 to August 2020. We used MESH terms as the keywords and performed the search in all databases using the following search strategy: (orexin OR hypocretin) AND (eating behaviour OR eating disorder OR binge eating OR binge eating disorder OR feeding OR feeding behaviour OR appetite).

2.3 Study selection, data collection and analysis

Studies identified from databases search were imported to Endnote X8. We evaluated the retrieved articles based on the pre-defined inclusion criteria. After removing duplicates, the titles and abstracts were screened to eliminate irrelevant articles. Conference abstracts, reviews, meeting summaries, commentaries, editorials and letters to the editor were discarded. Then, full text screening was conducted and papers that did not meet eligibility criteria were excluded. All relevant individual publications were reviewed in detail and results were then summarized based on the initial research questions. We also performed an additional search by manually looking at the reference lists of included articles to identify any further relevant literature.

3. Results

3.1 Search results

A total of 4,124 articles were identified from the database search. Eleven additional papers were obtained from the manual search and sources. We discarded 3,931 papers after performing deduplication and screening titles and abstract for irrelevant literature. The remaining 206 articles were assessed during the full text review. Among these, 71 were excluded, retaining 135 studies to be included in this scoping review (Figure 1). These papers were excluded because they did not assess any behaviour related to eating (67 papers), did not provide information on the sex of the experimental subjects (3 papers) or not written in English (1 paper).

3.2 The role of orexin in eating-related behaviour

3.2.1 Central orexin promotes feeding

Since the discovery of orexin in 1998, an overwhelming body of evidence has accumulated demonstrating a role for orexins in promoting food intake (Table 1). Early studies revealed that blocking endogenous orexins resulted in reduced feeding, as central, but not peripheral administration, of anti-orexin IgG significantly decreased food intake in rats (Yamada et al. 2000, Ida et al. 2000). Moreover, ablation of orexin neurons using either genetic manipulation (Hara et al. 2001) or toxins (Mistlberger et al. 2003) results in hypophagia. On the other hand, acute intracerebroventricular (i.c.v.) injection of orexin A significantly increases food intake (Shiraishi et al. 2000, Crespo et al. 2008, Yamanaka et al. 2000, Edwards et al. 1999, Sakurai et al. 1998, Takano et al. 2004, Akimoto-Takano et al. 2005, Kokare et al. 2006, Li et al. 2015, Sahu 2002, Moreno et al. 2005, Karasawa et al. 2014, Ford et al. 2005, Espana et al. 2002, Monda et al. 2003, Haynes et al. 1999, Zheng et al. 2005, Tsuji et al. 2011, Choi et al. 2010, Jain et al. 2000, Haynes et al. 2000, Alvarez-Crespo et al. 2013, Lubkin & Stricker-Krongrad 1998, Jorgensen et al. 2005, Farr et al. 2005, Asakawa et al. 2002), while continuous infusion into the lateral ventricle increases daily food consumption during daytime hours (Yamanaka et al. 1999, Haynes et al. 1999). Furthermore, intranasal delivery of orexin A produces similar effects (Dhuria et al. 2016). However, a small number of studies report that i.c.v. administration of orexin A has no effect on food consumption (Ida et al. 1999, Ida et al. 2000, Semjonous et al. 2009). Notably, peripheral administration of orexin A does not affect feeding; neither a single intravenous (i.v.) injection nor an 8-day subcutaneous (s.c.) infusion of orexin A increase food consumption (Haynes et al. 1999). These results suggest that central administration of orexin A produces a more robust effect in inducing food intake than peripheral administration.

While studies using i.c.v. administration have provided insight into the broad involvement of orexins in feeding, studies using site-specific injections of orexin A have helped determine the precise brain regions involved in feeding behaviour. Microinjection of orexin A into hypothalamic areas such as the perifornical and lateral hypothalamic area (Sweet et al. 2004, Wang & Kotz 2002, Kotz et al. 2002, Thorpe et al. 2006, Thorpe et al. 2003, Thorpe et al. 2005b, Doane et al. 2007, Sweet et al. 1999, Dube et al. 1999, Kotz et al. 2005), paraventricular nucleus (Dube et al. 1999, Sweet et al. 1999, Gac et al. 2016, Edwards et al. 1999), medial preoptic area (Sarihi et al. 2015), arcuate nucleus (Yang et al. 2018) and dorsomedial nucleus (Dube et al. 1999) result in increased food intake, whereas injection into the ventromedial nucleus (Dube et al. 1999) and ventrolateral preoptic area (Mavanji et al. 2015) has no effect on food intake. Not all studies support these findings as Dube and colleagues (1999) report no effect of orexin A in the medial preoptic area and arcuate nucleus (Dube et al. 1999).

Microinjection of orexin A into extra-hypothalamic sites has also been investigated, with studies finding increased food intake when administered into the nucleus accumbens (Thorpe & Kotz 2005, Sweet et al. 2004, Mayannavar et al. 2014), nucleus incertus (Sabetghadam et al. 2018) and basomedial amygdala (Wang et al. 2018), but not the central amygdala, ventral tegmental area (Dube et al. 1999, Jin et al. 2020, Sweet et al. 1999) and nucleus of the solitary tract (Zheng et al. 2005, Dube et al. 1999). However, pre-treatment with orexin A injected into the nucleus of the solitary tract significantly induces food intake following intake suppression by intraperitoneal (i.p.) injection of cholecystokinin peptide, the intestinal satiation signal (Williams et al. 2020). Overall, hypothalamic nuclei seem to be the primary sites of action for orexin-induced feeding, while some other sites, such as the nucleus accumbens, also play a role.

Further support for the role of orexins in promoting feeding comes from studies using receptor antagonists, with most studies finding that these effects were predominantly mediated by OXR-1 (Table 2). For example, administration of SB-334867, a selective OXR-1 antagonist, reduces food intake in fasted, food restricted, glucose-deprived or sated animals, both when injected peripherally (White et al. 2005, Rorabaugh et al. 2014, Haynes et al. 2000, Haynes et al. 2002, Valdivia et al. 2014, Ishii et al. 2005b, Ishii et al. 2005a, Ishii et al. 2004, Rodgers et al. 2001, Feillet et al. 2017, Otlivanchik et al. 2015) or centrally into the ventricle (Karasawa et al. 2014, Williams et al. 2020, Hsu et al. 2015, Zheng et al. 2007). Other studies investigating the effects of OXR-1 antagonists in specific brain areas found that administration of SB-334867 into the nucleus accumbens (Thorpe & Kotz 2005, Mayannavar et al. 2014), nucleus of the solitary tract (Kay et al. 2014, Williams et al. 2020), hypothalamic paraventricular nucleus (Wang et al. 2018), but not central amygdala (Jin et al. 2020), caused a significant reduction in food intake in rats. Conversely, studies investigating the role of OXR-2 in feeding are rare, with one study finding no effect on food intake after peripheral i.p. administration of the selective OXR-2 antagonist, JNJ-10397049 (Piccoli et al. 2012), whereas microinjection of the OXR-2 antagonist, TCS-OX2-29, into the basolateral amygdala reduced food intake (Rashmi et al. 2015). In addition, intranasal administration of SB-334867, but not TCS-OX2-29, reduced food intake in rats (Lebedev et al. 2020), suggesting that the different compound and route of administration may influence the effect of the drug. Taken together, it is evident that OXR-1 mediates the effects of orexins in promoting feeding while the role of OXR-2 in this field remains unclear. Further research investigating the effects of OXR-2 are needed to elucidate its precise role in feeding.

Unlike orexin A, the role of orexin B in feeding appears to be minimal (Table 3). Although a recent study reported that microinjection of orexin B in the basolateral amygdala could stimulate food intake in rats (Rashmi et al. 2015), it produces no effect when delivered to six intra-hypothalamic areas including the perifornical-lateral hypothalamic area, dorsomedial nucleus, ventromedial nucleus, preoptic area, arcuate nucleus, paraventricular nucleus and to three extra-hypothalamic areas: ventral tegmental area, central amygdala, and nucleus of the solitary tract (Dube et al. 1999, Sweet et al. 1999). Similarly, peripheral delivery of orexin B via acute i.v. injection and chronic s.c. infusion produces no significant effect on feeding (Haynes et al. 1999). However, studies using i.c.v. injections show mixed results. Despite reports that food intake is increased at 2 hours (Sweet et al. 1999, Edwards et al. 1999, Sakurai et al. 1998) and 4 hours (Tsuji et al. 2011, Jain et al. 2000) post i.c.v. injections, others found no effect (Ida et al. 2000, Haynes et al. 1999, Ida et al. 1999, Lubkin & Stricker-Krongrad 1998).

3.2.2 Orexins are involved in hedonic consumption of palatable foods

In addition to a role in feeding behaviour, a number of studies have reported a role for orexins in hedonic or reward-based (non-homeostatic) eating (Tables 2 and 4). This includes overconsumption of food, typically highly palatable food that is rich in fat and sugar in the absence of caloric need and binge-like eating where excessive consumption of food occurs within a discrete, short period of time (Guerdjikova et al. 2017). Knocking out orexin neurons reduces sucrose intake compared to that in wildtype mice (Matsuo et al. 2011) while orexin A administration (i.c.v.) leads to excessive palatable food intake (Rodgers et al. 2001, Rodgers et al. 2000, Benoit et al. 2005, Baird et al. 2009, Furudono et al. 2006). With regards to specific brain regions involved in reward-based feeding, orexin A has been shown to stimulate overconsumption of high fat diet and sucrose when microinjected into the ventral tegmental area (Terrill et al. 2016), the lateral hypothalamic area (Thorpe et al. 2005a), central amygdala (Jin et al. 2020) and posterior thalamic paraventricular nucleus (Barson et al. 2015) and to promote binge-like eating of palatable food when injected into the nucleus accumbens (Castro et al. 2016) or nucleus of the solitary tract (Zheng et al. 2005) while knockdown of OXR-1 in the paraventricular nucleus of the thalamus attenuated overconsumption of high fat diet in sated rats (Choi et al. 2012). Together, these studies highlight the involvement of orexin, in particular orexin A, in mediating reward-based feeding.

It is important to note that orexin does not simply increase consumption indiscriminately; it is the palatability or the salience of these food rewards that seems to be the main factor that drives the behaviour. This is evident from a study by Clegg and colleagues (2002) showing that when given simultaneous access to two diets differing in their palatability, injection of orexin A into the third ventricle resulted in rats consuming a highly palatable food to a significantly greater extent than a less palatable food (Clegg et al. 2002). The higher preference for palatable food is accompanied by a significant increase in orexin gene expression in the perifornical area (Morganstern et al. 2010) and double labelling of orexin and Fos (a marker of neuronal activation) in the lateral hypothalamus (Harris et al. 2005). Mitchell and colleagues (2020) further examined the real-time responses of orexin neurons upon food presentation using fiber photometry and showed that orexin cells produced significantly higher calcium signals when mice approached a chocolate pellet as compared to standard food suggesting that the salience/palatability of food can enhance orexin neuron activity to promote appetitive behaviour (Mitchell et al. 2020).

The role of orexin in reward-based consumption of palatable food seems to be largely dependent on OXR-1 activation since OXR-2 antagonism either reduces (Anderson et al. 2014) or has no effect (Piccoli et al. 2012) on binge-like eating. Systemic administration of OXR-1 antagonist, SB-334867, reduces palatable food intake (Buczek et al. 2020) and binge-like consumption of chocolate, sucrose, fructose and saccharine (Rorabaugh et al. 2014, Vickers et al. 2015, Alcaraz-Iborra et al. 2014), and increases feeding latency (Frederick-Duus et al. 2007). When injected into the fourth ventricle, SB-334867 also supresses preference for a palatable food reward as measured by conditioned place preference test (Kay et al. 2014). Other selective OXR-1 antagonists, such as GSK1059865, also reduce binge-like eating for palatable food (Piccoli et al. 2012), while ACT-33582 reduces preference for a high fat / high sugar diet over standard food (Steiner et al. 2013). In particular, site specific studies reveal that injection of SB-334867 into the ventral tegmental area, but not in the medial preoptic area and arcuate nucleus (Sarihi et al. 2015), suppresses high fat diet (Zheng et al. 2007) and sucrose (Terrill et al. 2016) intake. These results support the notion that OXR-1 plays a key role in hedonic intake of palatable food.

3.2.3 The role of orexins in cue-driven eating-related behaviour

Environmental factors such as food-associated cues can stimulate eating and overconsumption of food (Mahler et al. 2012). Orexins have been shown to regulate cue-induced reward-based feeding. In fact, presentation of cues predicting a food reward alone is sufficient to activate orexin neurons (Choi et al. 2010, Harris et al. 2005). A study using the conditioned place preference model found that conditioned animals displaying preference for the food reward spend significantly more time in the reward-paired chamber than non-conditioned animals and this was accompanied by increased Fos expression in orexin neurons in the lateral hypothalamus and medial prefrontal cortex (Harris et al. 2005). Similarly, environmental cues associated with the consumption of chocolate activated orexin neurons in the perifornical area and increased activation of orexin 1 receptor-expressing neurons in the paraventricular thalamus (Choi et al. 2010). In accordance with these findings, orexin neurons are activated during the anticipatory period when rats are expecting their daily food (Mizushige et al. 2006, Choi et al. 2010, Jimenez et al. 2013, Johnstone et al. 2006) and in response to a conditioned stimulus (CS, a tone) associated with a sucrose reward (Hassani et al. 2016). It is proposed that activation of orexin neurons during this anticipatory period of food consumption subsequently drives behaviours required to obtain food (Barson 2018), and once food is available, the activated neurons promote overconsumption of food. In a Pavlovian conditioning study, orexins were shown to mediate excessive feeding stimulated by a learned-food cue in sated rats, as identified by a higher percentage of orexin-Fos double-labelled neurons in the perifornical area (Petrovich et al. 2012). Moreover, systemic or intra-medial prefrontal cortex administration of SB-334867 has been shown to reduces overconsumption of food driven by a food cue. (Cole et al. 2015, Cole et al. 2020) and administration of orexin A into the thalamic paraventricular nucleus has been shown to restore satiety-induced decreases in cue-driven sucrose intake (Meffre et al. 2019). Interestingly, administration of an OXR-2 antagonist, TCS-OX2-29, into this area significantly reduces lever responding for sucrose in hungry rats whereas SB-334867 has little effect (Meffre et al. 2019, Haight et al. 2020), suggesting that OXR-2 in the thalamic paraventricular nucleus play a role in the incentive motivational value of the food cue specifically . In line with this, knocking down OXR-1 signalling in the thalamic paraventricular nucleus did not affect progressive ratio responding for a food reward, but did attenuate unconditioned hedonic feeding where the need for learning and motivation is minimal (Choi et al. 2012), highlighting that orexin receptor subtypes may play a distinct role in cue-induced reward processing. In summary, cues that signal the availability of food reward can activate orexin neurons which subsequently translate them into appetitive behaviours to obtain food. In particular, orexin signalling in certain brain areas such as the medial prefrontal cortex and the thalamic paraventricular nucleus seem to be crucial for the learned associations involved in feeding, such as cue-driven eating-related behaviour.

3.2.4 Orexins drive motivation for palatable foods

A number of studies support the idea that orexin signalling is critical for driving motivation for food rewards. These studies commonly employ an operant self-administration paradigm to assess motivation. In the operant self-administration paradigm, animals learn to make a response (e.g. lever press) to receive a reward. Motivation is measured as the amount of effort an animal should exert before receiving a certain number of rewards. Under a fixed ratio schedule, animals need to make a fixed number of responses to earn a reward. To more specifically assess the level of motivation, a progressive ratio schedule of reinforcement is used. Here, an increasing number of responses is required before the desired reward is given. The upper limit of motivation at which animals stop responding is reflected in the breakpoint value (the final ratio completed). Orexin A administration (i.c.v.) increases motivation to work for a sucrose or high fat pellet in ad libitum fed rats when measured by a progressive ratio schedule in the operant self-administration paradigm (Choi et al. 2010, Kay et al. 2014). Furthermore, microinjection of orexin A into the lateral hypothalamic area not only augments free feeding of sweet pellets but also increases responding on a fixed ratio 20 schedule and breakpoint on a progressive ratio schedule indicating that orexin A increased motivation for food reward (Thorpe et al. 2005a). These effects are likely mediated by OXR-1 since i.p. injection of SB-334867 blocks self-administration of sucrose (Cason & Aston-Jones 2013b, Cason & Aston-Jones 2014, Jupp et al. 2011, Kay et al. 2014), saccharin (Cason & Aston-Jones 2013a), and high fat diet (Nair et al. 2008) and also reduces progressive ratio responding for a palatable diet (Choi et al. 2010, Perello et al. 2010). By contrast, administration of OXR-2 antagonists, JNJ-10397049 and TCS-OX2-29, have no effect on self-administration of saccharin or sucrose (Brown et al. 2013, Shoblock et al. 2011). A recent study by Freeman and colleagues (2020) showed that i.p administration of SB-334867 significantly reduces responding for palatable food in highly motivated animals (i.e. requiring high cost responding) (Freeman et al. 2020). Taken together, these findings suggest that orexin A, through OXR-1, plays an important role in driving motivation for seeking palatable food.

Of interest, orexin signalling seems to selectively modulate willingness to work for palatable food reward but not for less salient food reward such as standard chow. As reported by Borgland and colleagues (2009), the breakpoint in rats lever pressing for a high fat chocolate pellet was significantly reduced after i.p. administration of SB-334867, whereas there was no change in breakpoint for standard chow (Borgland et al. 2009). Although another study reported that SB-334867 reduces progressive ratio responding for standard chow (Sharf et al. 2010a), these animals were food restricted indicating that the effort made to obtain food was likely influenced by their homeostatic need. Moreover, using an effort-based decision-making task, it was found that OXR-1 antagonism reduced the rat's willingness to climb a barrier to obtain a high fat chocolate pellet, highlighting the crucial role of OXR-1 in potentiating motivational drive toward palatable food rewards (Borgland et al. 2009).

3.2.5 Orexins involvement in reinstatement of palatable foods

Studies investigating the involvement of orexins in reinstatement of extinguished operant responding for palatable foods have resulted in mixed findings. In the reinstatement model (considered by some to be an animal model of 'craving'), animals are trained to self-administer food reinforcers by lever pressing or nose poking. Following training, an extinction procedure consisting of multiple sessions is introduced where no reward is delivered, despite continuous lever presses, until animals eventually cease responding. Once the response is extinguished, the reward seeking behaviour is reinstated by presenting certain kind of stimuli such as cues, context or stress (Sharf et al. 2010b). Orexin A injected i.c.v. has been shown to induce reinstatement of lever pressing for high fat food (Nair et al. 2008). Using a model of perseverative reinstatement, where reinstatement sessions were repeated several times, seeking behaviour for palatable food decreased rapidly to extinction level, however there was no association between orexin neuron activation and palatable food suggesting that orexin does not play a role in perseverative seeking behaviour for palatable food (Martin-Fardon et al. 2018).

Studies using antagonists have also provided inconsistent results on orexin's involvement in reinstatement of palatable food seeking behaviour. At a high dose (30 mg/kg), but not lower dose (1-10 mg/kg), i.p. injection of SB-334867 impairs cue-induced reinstatement of sweet solutions (Cason & Aston-Jones 2013b, Cason & Aston-Jones 2013a, Martin-Fardon & Weiss 2014a, Martin-Fardon & Weiss 2014b) in food restricted rats but not ad libitum fed rats (Cason & Aston-Jones 2013b). Furthermore, the dual orexin antagonist, TCS 1102, shows no effect on cue-induced seeking behaviour for palatable food at any fixed or progressive ratio schedule of reinforcement both in hungry and sated rats (Khoo et al. 2018). While one study found that administration of SB-334867 inhibited reinstatement of sucrose-seeking induced by the chemical stressor, yohimbine (Richards et al. 2008), another found that SB-334867 failed to affect reinstatement of high fat food-seeking induced by orexin A, pellet-priming, or yohimbine, even when the dose used was higher (10 and 20 mg/kg) (Nair et al. 2008). These results indicate that orexin receptor antagonists might only be effective in inhibiting reinstatement of palatable food seeking when the dose is high and the reward salience is greater (i.e. in hungry rats). Furthermore, it is possible at higher doses that antagonists are having non-specific effects (Nair et al. 2008). Given the limited and inconsistent literature, further research is needed to investigate the involvement of orexins in driving food seeking behaviour.

3.2.6 Orexin-mediated eating and olfactory system

The role of orexin in food-seeking behaviour may involve the olfactory system since olfaction can serve as an external cue to stimulate feeding as well as to identify food palatability and sources (Barson 2018). Indeed, orexin activation increases olfactory sensitivity and facilitates the formation of olfaction-based learning and memory (Julliard et al. 2007, Prud'homme et al. 2009, Ferry & Duchamp-Viret 2014). Fasting, as well as microinjection of orexin A into the lateral ventricle, in the presence of food odour has been shown to increase Fos expression in the olfactory bulb (Prud'homme et al. 2009). Furthermore, blocking orexin receptor signalling with the dual orexin receptor antagonist, ACT-078573, reduces sniffing behaviour and Fos expression in the olfactory bulb (Prud'homme et al. 2009). This increased sensitivity in olfaction is associated with the formation of olfaction-based learning and memory in rats (Julliard et al. 2007, Ferry & Duchamp-Viret 2014). Using the conditioned olfactory aversion test with odorized water, i.c.v. injection of orexin A enhanced avoidance performance and reduced intake of the odorized water (Julliard et al. 2007, Ferry & Duchamp-Viret 2014). Thus, orexin seems to influence olfactory sensitivity and olfactory-based learning which is important during food seeking.

3.3 Sex differences in orexin-mediated eating behaviour

In this review, we aimed to examine sex differences in orexin-mediated eating behaviour. Surprisingly, we found that the majority of studies investigating orexin-mediated eating behaviour were conducted using male subjects. Of the 135 papers that we reviewed, 118 studies used only male rodents (Figure 2). Given that females are more susceptible than males in developing eating-related disorders (Guerdjikova et al. 2017), this result clearly highlights the marked underrepresentation of female subjects in this research area.

Among the 11 studies that used both sexes as the experimental subjects, few reported that the effects of orexin in eating behaviour differed between males and females (Calvez et al. 2015, Funabashi et al. 2009, Freeman et al. 2020). Three studies did not report whether or not there was a sex difference (Kaur et al. 2008, Hara et al. 2001, Cole et al. 2020) and the remaining studies found no sex differences (Castro et al. 2016, Buczek et al. 2020, Haynes et al. 2000, Alvarez-Crespo et al. 2013, Zink et al. 2018).

Sex differences in hedonic eating may not be dependent on differences in orexin activation. Buczek et al. (2020) found that female rats consistently ate the same amount of palatable food regardless of hunger/satiety state, whereas male rats typically adjusted their intake according to their satiety level. However, they reported that there is no sex difference in activation of orexin neurons in the lateral hypothalamus between male and female rats following hedonic eating of palatable food (Buczek et al. 2020). Notably, SB-334867 injection reduced hedonic eating in both sexes suggesting that this drug might be an effective treatment for males and females (Freeman et al. 2020, Buczek et al. 2020). Another laboratory examining the hedonic impact of sucrose through "liking" taste reaction test reported that taste reactivity to sucrose was not different between male and female rats after injection of orexin A into the nucleus accumbens (Castro et al. 2016), providing further support to the idea that orexin may play a crucial role for hedonic eating, albeit similarly for both males and females. However, one study reported that difference in orexin system function was associated with the sexually dimorphic hedonic behaviour. Freeman and colleagues (2020) showed that compared to males, female rats had higher intake (demand) for palatable food at low cost but not at higher price suggesting sex differences in hedonic processing but not motivational properties of palatable food. Following the hedonic eating, more orexin-Fos expressing neurons were observed in females than in males (Freeman et al. 2020),

There is a lack of evidence to support the role of orexin in mediating sex differences in motivation and reinstatement of palatable food seeking. SB-334867 injection reduced motivation for palatable food in both sexes (Freeman et al. 2020). Moreover, under a fixed and progressive ratio schedule of reinforcement, SB-334867 injection reduced self-administration of sucrose similarly in food restricted male and female rats (Cason & Aston-Jones 2014, Cason & Aston-Jones 2013b). However, this was not the case for cue-induced reinstatement of sucrose seeking where i.p. injection of SB-334867 disrupted reinstatement of sucrose seeking in male, but not female, rats (Cason & Aston-Jones 2014, Cason & Aston-Jones 2013b) suggesting that OXR-1 may have different roles with respect to cue-induced sucrose seeking in male versus female rats.

Sex differences in orexin-mediated feeding seems to be more prominent when animals are stressed and/or experiencing a negative affective state, such as occurs during fasting. Funabashi et al (2009) showed that fasting induced rebound eating in female, but not male rats, suggesting that females exhibit higher sensitivity to metabolic cues. This was accompanied by increased orexin neuron activation in the lateral hypothalamic area in female, but not male rats (Funabashi et al. 2009). Sex differences also occurred when increased orexin activity was induced by the orexigenic neuropeptide, relaxin-3 (which is known to produce sexually dimorphic feeding pattern), resulting in higher food intake and elevated level of orexin mRNA in female, but not male rats (Calvez et al. 2015). On the other hand, feeding induced by i.c.v administration of orexin A (Castro et al. 2016, Haynes et al. 2000, Alvarez-Crespo et al. 2013) or chemogenetic activation of orexin neurons (Zink et al. 2018) in males and females did not differ under normal conditions although orexin induced an increase in food intake that was dose dependent in female but not in male rats (Haynes et al. 2000). Together, these results suggest that there is little evidence of sex differences in orexin-mediated hedonic feeding and appetitive behaviour toward palatable food, but the limited data suggests that females are more sensitive to the effects of orexin. Although, given the limited literature and lack of replication, further studies examining sex differences in orexin-mediated eating behaviour are required.

4. Discussion

This scoping review aimed to give a general overview about the involvement of orexins in eating-related behaviour with an additional focus on sex differences. The literature strongly supports the involvement of orexins, especially orexin A, in promoting normal food intake and certain forms of dysregulated eating. We also identified several brain regions and neural circuits that are involved in these functions (Figure 3). Of particular interest, we found very few studies examining sex differences in orexin-mediated eating behaviour and that the representation of female subjects in this area of research has been overlooked. Given the potential difference in feeding patterns between males and females (Laviano et al. 1996), we argue that research in this area should accommodate the influence of sex-related variables.

4.1 The role of orexins in homeostatic and reward-based feeding

Orexins not only stimulate homeostatic feeding but also promote overconsumption of food, typically highly palatable food, regardless of hunger and nutritional status. The role of orexins for feeding has been well established. Here, we identified a large number of studies showing that orexin A administration induced an increase in food intake (Table 1). As shown in early studies, orexin neurons are activated under conditions requiring an organism to seek food such as during hypoglycaemia (Cai et al. 2001b, Briski & Sylvester 2001) or restricted feeding (Kurose et al. 2002). Likewise, fasting and food restriction increases the levels of hypothalamic prepro-orexin (Bulbul et al. 2010, Garcia-Luna et al. 2010, Cai et al. 2001a, Cai et al. 1999, Karteris et al. 2005), levels of orexin in the blood (Bulbul et al. 2010, Joibari & Khazali 2013, Komaki et al. 2001) and lateral hypothalamus (Mondal et al. 1999, Cai et al. 2001a, Garcia-Luna et al. 2010), and induces the expression of orexin receptor mRNA and protein in the hypothalamus (Lu et al. 2000, Karteris et al. 2005). Furthermore, a drop in leptin or a rise in ghrelin levels also increases orexin neuronal activity suggesting that orexins interact with feeding-related hormones to control food intake (Yamanaka et al. 2003). In this case, orexin neurons translate peripheral signals of nutrient needs, such as hunger, ghrelin and low glucose level, into appetitive responding for food to maintain nutritional status (Mahler et al. 2014). Under this low energy balance, gene expression of orexin is upregulated (Cai et al. 1999, Karteris et al. 2005, Lu et al. 2000, Sakurai et al. 1998, Griffond et al. 1999) and the activated neurons will then transcribe orexin peptide (Bulbul et al. 2010, Joibari & Khazali 2013, Mondal et al. 1999) to seek food and stimulate feeding (Hagar et al. 2017). In line with the proposed role of orexin in motivational activation, the food seeking in this case is motivated by hunger or metabolic need (Mahler et al. 2014). By contrast, as compared to homeostatic feeding, the level of orexin activation under excessive and binge-like eating of palatable food is found to be higher. Orexin immunoreactivity and gene expression are significantly higher after highly palatable food intake than standard diet (Park et al. 2004, Olszewski et al. 2009) and after saccharin intake as compared to water intake (Furudono et al. 2006). Moreover, using double-labelling with Fos, orexin neuron activation is markedly enhanced after fructose bingeing as compared to standard chow bingeing (Rorabaugh et al. 2014) suggesting that palatability of the food reward influences the level of activation of orexin neurons. Therefore, the metabolic state and the palatability of the food serve to enhance the activation of orexin neurons to promote eating. Indeed, a recent study using in vivo calcium recording showed that orexin cell activity was higher in sated rats approaching a palatable chocolate pellet and in food restricted rats approaching standard food as compared to ad libitum fed rats approaching standard food (Mitchell et al. 2020).

It is likely that orexin's action is more important in the seeking for food rather than the actual food consumption itself. Although orexin activity increased when animals were anticipating and expecting food (Mieda et al. 2004, Akiyama et al. 2004, Kaur et al. 2008), once food was available and the physiological need fulfilled, orexin activity decreased (Cai et al. 2001b). This is supported by studies showing that a rise in glucose level normalized the elevated level of orexin peptide and neuron activity (Burdakov et al. 2005, Funabashi et al. 2009, Yamanaka et al. 2003). Another study, using fiber photometry, found that upon physical contact with food, the activity of orexin neurons rapidly reduced, regardless of the taste, textures and caloric content (Gonzalez et al. 2016). Similarly, Mitchell et al. (2020) report that during the approach to food, orexin activity significantly increased but then reverted to baseline level when food consumption started. Further, they suggest that termination of this orexin activity may be mediated by direct and indirect inhibitory signals from the nucleus accumbens to orexin neurons in the lateral hypothalamus (Mitchell et al. 2020). Together, this raises the possibility that orexin signalling is more crucial for mediating appetitive behaviour rather than the consumption itself. Others argue that orexin effect in promoting food intake may be partly secondary to changes in wakefulness. Yamanaka et al. (1999) showed that increased daytime wakefulness caused by continuous i.c.v infusion of orexin A per se may have resulted in increased food intake (Yamanaka et al. 1999). Thus, it is likely that animals feed more because they are awake, instead of asleep, during the testing period.

Orexin signalling is crucial for driving motivation for a highly salient reinforcer. With regard to reward seeking, orexin signalling has been shown to mediate food-reinforced behaviour especially in the operant responding for palatable food (Tables 2 and 4). This finding fits with the role of orexins in the reinforcing effects of drugs of abuse. Numerous studies have reported a major role of orexin in addictive-like behaviour. Cues associated with drugs of abuse activate orexin neurons (Harris et al. 2005, Martin-Fardon et al. 2018), while blockade of OXR-1 signalling reduces self-administration of opiates, cocaine, nicotine, and alcohol (Mahler et al. 2012). Indeed, current evidence shows that orexin is involved in seeking behaviour for all major addictive drugs (Mahler et al. 2014). However, when it comes to seeking behaviour in the absence of reward, the effects of orexin on motivation for food reward versus addictive drug seem to dissociate. While seeking behaviour of an extinguished response for addictive drugs remained intact in the presence of orexin signalling, orexin's involvement in this behaviour was less evident when a food reward was no longer available (Mahler et al. 2012, Martin-Fardon et al. 2018). Therefore, this poses the question, does orexin's involvement in motivation for addictive substances differ from those for natural food rewards? Apart from this issue, the current evidence implicating orexin receptors in food reward raises the possibility of developing novel therapeutic treatments for eating disorders that target these receptors. Evidence shows that blocking OXR-1 signalling reduced overconsumption and binge-like intake of palatable food, even at low doses (Table 2). Thus, from a clinical perspective, OXR-1 antagonists may be a potential target for treating disordered eating such as binge eating.

4.2 The neural pathways and mechanisms underlying orexin-mediated eating behaviour

The role of orexins in homeostatic versus non-homeostatic feeding seem to be mediated by different neural circuits. Several brain regions have been identified as sites of action of orexins in promoting food intake. Normal eating is predominantly controlled by orexin signalling in intra-hypothalamic nuclei with some additional sites outside of hypothalamus including the nucleus accumbens. On the other hand, overconsumption and binge-like eating of palatable food involves more restricted sites outside of the hypothalamus such as the nucleus accumbens, ventral tegmental area, and paraventricular nucleus of the thalamus. The nucleus accumbens and ventral tegmental area have long been known for their role in reward processing (Thompson & Borgland 2011). Thus, it is not surprising that orexin may mediate its role in hedonic and reward-related eating behaviour via signalling in mesocorticolimbic regions. Indeed, administration of a μ-opioid receptor agonist into the nucleus accumbens induces hedonic intake of palatable food which is completely blocked by injecting the OXR-1 antagonist, SB334867, into the ventral tegmental area, suggesting that a mesolimbic circuit plays a role in orexin-mediated reward-driven consummatory behaviour (Zheng et al. 2007). Notably, orexin signalling in the ventral tegmental area does not preclude the involvement of other sites in stimulating overconsumption of palatable food. The ventral tegmental area contains dopamine and GABA neurons that project to several brain areas involved in positive reinforcement (Fields et al. 2007). Given that orexins excite both the dopaminergic and non-dopaminergic neurons in the ventral tegmental area (Borgland et al. 2006, Korotkova et al. 2003), it is likely that the activity of brain areas other than the nucleus accumbens are also modulated to promote the “liking” and “wanting” of palatable food (Berridge 2009). Despite the fact that several brain regions have been identified as sites of action of orexins, studies investigating the neural circuitry underlying orexin-mediated eating behaviour are limited. Further research should investigate the specific projections of orexin neurons involved in eating-related behaviour in order to gain a deeper understanding of orexin's function in this behaviour.

Orexin's effects in promoting reward-related feeding may involve downstream signalling through other peptides and neurotransmitter systems such as dopamine- or opioid-mediated circuits. Orexin neurons project broadly to the ventral tegmental area and orexin signalling in this region leads to increased dopamine release through projections to the nucleus accumbens and prefrontal cortex to mediate reward seeking (Sharf et al. 2010b). Likewise, orexin activation in the thalamic paraventricular nucleus raises dopamine levels in the nucleus accumbens and medial prefrontal cortex to stimulate hedonic intake of palatable food (Choi et al. 2012) and to increase the motivation to work for sucrose (Meffre et al. 2019), suggesting that in addition to the ventral tegmental area, the thalamic paraventricular nucleus may act as a critical site to mediate orexin action on dopamine circuitry and reward-based feeding. Moreover, orexin projection to the paraventricular nucleus of the thalamus is one of the densest in the brain (Peyron *et al.* 1998) and thus positions this brain region as an important site of action of orexin. Downstream opioid signalling may be important in mediating orexin effects since injection of an opioid antagonist, naloxone, abolished orexin A-induced hedonic feeding (Sweet et al. 2004). In addition, it is worth noting that substance P has been shown to be a direct downstream target of orexins in the paraventricular nucleus of the thalamus to mediate the effect of orexin in ethanol drinking (Barson *et al.* 2017). Further study to investigate whether substance P also mediates the actions of orexins in reward related feeding is warranted. Enhanced synaptic plasticity may also underlie orexin action in reward-based eating. It has been shown that intra- ventral tegmental area orexin A potentiates receptor-mediated excitatory postsynaptic currents, suggesting that orexin A plays a role in long term neural plasticity which may underlie its involvement in reward seeking behaviour (Borgland et al. 2006). Self-administration of highly palatable food but not standard chow pellets enhances glutamatergic synaptic transmission at ventral tegmental area neurons (Borgland et al. 2009). Further, orexin A applied directly to the ventral tegmental area significantly increases potentiation of glutamatergic NMDA receptor evoked EPSCs. Subsequent experiments revealed that this orexin-mediated potentiation of synaptic transmission is due to increased presynaptic signalling and glutamate release. More importantly, arousal and aversive stimuli such as foot shock do not produce the same effect suggesting that potentiation of glutamatergic synaptic transmission mediated by orexin A is selective to highly salient rewarding stimulus (e.g. highly palatable food) (Borgland et al. 2009). In summary, in the involvement of orexins in mediating hedonic and appetitive behaviour towards palatable food appears to involve interactions with dopaminergic, opioidergic and glutamatergic signalling within mesocorticolimbic areas.

4.3 Sex differences in orexin-mediated eating behaviour

It is known that males and females differ in their eating behaviour and susceptibility to eating disorders (Guerdjikova et al. 2017, Fukushima et al. 2015). Considering the key role of orexins in mediating eating behaviour, it is important to understand whether orexin signalling differs in males and females. Unfortunately, current studies on orexin-mediated eating behaviour predominantly use male subjects making it difficult to evaluate sex differences. Though some works highlight sex differences in orexin signalling during feeding and food-related reward behaviour (Calvez et al. 2015, Freeman et al. 2020, Funabashi et al. 2009), other reports have contrasting results (Castro et al. 2016, Buczek et al. 2020, Haynes et al. 2000, Alvarez-Crespo et al. 2013, Zink et al. 2018). In fact, a similar pattern is observed in studies investigating the role of orexins in mediating the effects of addictive substances. While some studies report that OXR-1 signalling mediates alcohol and cocaine seeking in male but not female rats, other reports suggest no sex differences (reviewed in (Hopf 2020)). However, despite these conflicting findings, they provide a precedent for different orexin signalling in males versus females, although a great deal of works remains to be done in this area. Females have significantly more dendritic spine on their orexin neurons than males suggesting that they may receive more excitatory input onto these cells (Grafe *et al.* 2019). The level of prepro-orexin, orexin A, and OXR-1 mRNA is higher in females (Jöhren et al. 2002, Johren et al. 2003), and females show higher orexin system activation compared with male rodents in response to stress (Grafe *et al.* 2017). Future studies should examine whether the sex differences in cell morphology, expression and activity of orexin lead to distinct behavioural phenotypes in males and females, especially when considering that stress itself often triggers addictive behaviour and disordered eating.

5. **Conclusion**

Orexins are involved in promoting regular food intake and contribute to motivation for higher salience rewards such as highly palatable food. Thus, orexin neurons may serve as the interface between homeostatic and hedonic feeding. Evidence for the role of orexin in craving for palatable food is lacking and further investigations are required in this area as well as in investigating the specific circuitry underlying orexin-mediated eating behaviour. We strongly implore that future studies use more female subjects, especially given that eating disorders are predominantly observed in women. Lastly, studies have largely focused on OXR-1 signaling and considering that OXR-2 is also involved in reward related behaviour, further investigation into the role of OXR-2 in eating-related behaviour is warranted.

--Human subjects --
Involves human subjects:
If yes: Informed consent & ethics approval achieved:
=> if yes, please ensure that the info "Informed consent was achieved for all subjects, and the experiments were approved by the local ethics committee." is included in the Methods.

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Figure legends

Figure 1. Study flow diagram adapted from Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement.

Figure 2. The number of articles based on the sex of the experimental subjects

Figure 3. Schematic image of brain regions involved in various eating-related behaviour mediated by orexins action based on published literature. Arc, Arcuate nucleus; BLA, basolateral amygdala; BMA, basomedial amygdala; CeA, central amygdala; DMN, dorsomedial nucleus; LHA, lateral hypothalamic area; MPOA, medial preoptic area; NAcc, nucleus accumbens; NI, nucleus incertus; NTS, nucleus of the solitary tract; OB, olfactory bulb; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; VTA, ventral tegmental area.

Cover image caption

We review the role of orexin in eating-related behaviours, with a focus on reward and motivation, and the neural circuits driving these effects. Orexins are involved in homeostatic feeding as well as hedonic and appetitive behaviour toward palatable food. Normal feeding is predominantly controlled by orexin signalling in intra-hypothalamic nuclei with some additional sites outside of hypothalamus. Hedonic feeding involves more restricted sites outside of the hypothalamus known to play a role in reward processing. This review provides a new insight that orexins may be a potential target for treating disordered eating.

Table 1. Involvement of orexin A in promoting food intake

Route	Subjects	Sex	Outcome	Reference
Non-specific administration				
i.c.v.	Wistar rats	Male	Increased food intake	(Shiraishi et al. 2000, Crespo et al. 2008, Yamanaka et al. 2000, Edwards et al. 1999, Sakurai et al. 1998, Takano et al. 2004, Akimoto-Takano et al. 2005)
	Sprague Dawley rats	Male	Increased food intake	(Kokare et al. 2006, Li et al. 2015, Sahu 2002, Moreno et al. 2005, Karasawa et al. 2014, Ford et al. 2005, Espana et al. 2002, Monda et al. 2003, Haynes et al. 1999, Zheng et al. 2005)
	Wistar rats	Male	No effect on food intake	(Ida et al. 1999, Semjonous et al. 2009)
			Increased food intake and reduced feeding time	(Tsuji et al. 2011)
			Continuous infusion increases daily food intake	(Yamanaka et al. 1999)
	Long-Evans rats	Male	Increased food intake	(Choi et al. 2010)
	Sprague Dawley rats	Male	No effect on food intake	(Ida et al. 2000)
	Genetically obese Zucker (*fa*/*fa*) rats	Male	Increased food intake	(Jain et al. 2000)

	Sprague Dawley rats	Male + Female	Increased food intake	(Haynes et al. 2000, Alvarez-Crespo et al. 2013)
	C57BL/6J mice	Male	Increased food intake	(Lubkin & Stricker-Krongrad 1998, Jorgensen et al. 2005)
	CD-1 mice	Male	Increased food intake	(Farr et al. 2005)
	ddy mice	Male	Increased food intake	(Asakawa et al. 2002)
intranasal	Sprague Dawley rats	Male	Increased food intake	(Dhuria et al. 2016)
i.v. and s.c.	Sprague Dawley rats	Male	No effect on food intake	(Haynes et al. 1999)
Site-specific administration				
Hypothalamic regions				
PeF-LH	Sprague Dawley rats	Male	Increased food intake	(Sweet et al. 2004, Wang & Kotz 2002, Kotz et al. 2002, Thorpe et al. 2006, Thorpe et al. 2003, Thorpe et al. 2005b, Doane et al. 2007, Sweet et al. 1999, Dube et al. 1999)
	Fischer 344 rats	Male	Increased food intake	(Kotz et al. 2005)
PVN	Sprague Dawley rats	Male	Increased food intake	(Dube et al. 1999)
			No effect on food intake	(Sweet et al. 1999)
	Balb/c mice	Male	Increased food intake when co-injected with dynorphin	(Gac et al. 2016)
	Wistar rats	Male	Increased food intake	(Edwards et al. 1999)
DMN	Sprague Dawley rats	Male	Increased food intake	(Dube et al. 1999)
VMN	Sprague Dawley rats	Male	No effect on food intake	(Dube et al. 1999)
VLPO	Sprague Dawley rats	Male	No effect on food intake	(Mavanji et al. 2015)
MPOA	Wistar rats	Male	Increased food intake	(Sarihi et al. 2015)
	Sprague Dawley rats	Male	No effect on food intake	(Dube et al. 1999)
Arc	Sprague Dawley rats	Male	No effect on food intake	(Dube et al. 1999)
	Wistar rats	Male	Increased food intake	(Yang et al. 2018)
Extra-hypothalamic regions				
NI	Sprague Dawley rats	Male	Increased food intake	(Sabetghadam et al. 2018)
NAcc	Sprague Dawley rats	Male	Increased food intake	(Thorpe & Kotz 2005, Sweet et al. 2004)
	Wistar rats	Male	Increased food intake	(Mayannavar et al. 2014)
NTS	Sprague Dawley rats	Male	No effect on food intake	(Zheng et al. 2005, Dube et al. 1999)
	Wistar rats	Male	Increased food intake after intake suppression by cholecystokinin	(Williams et al. 2020)
BMA	Wistar rats	Male	Increased food intake	(Wang et al. 2018)
VTA	Sprague Dawley rats	Male	No effect on food intake	(Sweet et al. 1999)
CeA	Sprague Dawley rats	Male	No effect on food intake	(Dube et al. 1999)
	Wistar rats	Male	No effect on food intake	(Jin et al. 2020)

Arc, arcuate nucleus; BMA, basomedial amygdala; CeA, central amygdala; DMN, dorsomedial nucleus; MPOA, medial preoptic area; NAcc, nucleus accumbens; NI, nucleus incertus; NTS, nucleus of the solitary tract; PeF-LH, perifornical-lateral hypothalamic area; PVN, paraventricular nucleus; VLPO, ventrolateral preoptic area; VMN, ventromedial nucleus; VTA, ventral tegmental area.

Table 2. Effects of peripheral and central orexin receptor antagonism in eating-related behaviour

Antagonist	Route	Subjects	Sex	Dose	Outcome	Reference
OXR-1 SB-334867	i.p.	Osborne-Mendel (OM) and S5B/Pl (S5B) rats	Male	30 mg/kg	Reduced food intake	(White et al. 2005)
		Long-Evans rats	Male	5, 10 mg/kg	Decreased yohimbine induced reinstatement of sucrose seeking	(Richards et al. 2008)
				10, 20 mg/kg	Decreased self-administration of palatable food but no effect on food reinstatement	(Nair et al. 2008)
				10, 20 mg/kg	Decreased HFD intake in sated rats and the total number of responses under a PR schedule for sweet high fat pellets	(Choi et al. 2010)
				20 mg/kg	Reduced cue-induced feeding in sated rat	(Cole et al. 2015)
		Sprague Dawley rats	Male	30 mg/kg	Reduced food intake and fructose bingeing	(Rorabaugh et al. 2014)
				20 mg/kg	Blocked hypoglycemia-induced blunting of CPP	(Otlivanchik et al. 2015)
				20–30 mg/kg	Blocked operant self-administration of saccharin and cue-induced reinstatement of extinguished saccharin-seeking in both sated and food restricted rats	(Cason & Aston-Jones 2013a)
				10–30 mg/kg	Decreased self-administration and cue-induced reinstatement of sucrose seeking in food-restricted rats.	(Cason & Aston-Jones 2013b)
			Male + Female	30 mg/kg	Reduced food intake in sated and fasted rat at the dark phase	(Haynes et al. 2000)

	Male + Female	20 mg/kg	Reduced HPF intake in sated and hungry rats	(Buczek et al. 2020)
	Male + Female	30 mg/kg	Reduced low and high cost intake of palatable food	(Freeman et al. 2020)
	Female	30 mg/kg	Decreased self-administration but not cue-induced reinstatement of sucrose seeking in food-restricted rats.	(Cason & Aston-Jones 2014)
Wistar rats	Female	3, 10, 30 mg/kg	Reduced chocolate bingeing dose dependently	(Vickers et al. 2015)
Genetically obese (ob/ob) mice	Female	30 mg/kg/day for 7 days then twice daily for 7 days	Significantly reduced cumulative 24 h food intakes between days 3 and 14.	(Haynes et al. 2002)
C57BL/6 mice	Male	20 mg/kg	Impaired operant responding for food reinforcement under the variable ratio and progressive ratio schedules of reinforcement	(Sharf et al. 2010a)
C57BL/6J mice	Male	5 µg/g	Reduced HFD intake	(Valdivia et al. 2014)
		20,30 mg	Reduced binge-like consumption of sucrose and saccharin	(Alcaraz-Iborra et al. 2014)
		10 µg/g	Blocked ghrelin-induced acquisition of CPP and increased breakpoint in the operant conditioning task for HFD	(Perello et al. 2010)
Lister hooded rats	Male	30 mg/kg	Reduced palatable mash intake and accelerated behavioural satiety sequence	(Ishii et al. 2005b, Ishii et al. 2004, Ishii et al. 2005a)
		30 mg/kg	Reduced food intake	(Ishii et al. 2005a)
		3,10,30 mg/kg	Decreased intake of palatable wet mash	(Rodgers et al. 2001)
C57BL/6J and Rev-Erbα KO mice	Male	20 mg/kg	Reduced chocolate intake	(Feillet et al. 2017)

	F344/Brown Norway F1 hybrid rats	Male	3, 30 mg/kg	Increased feeding latency/decreased feeding response to palatable food	(Frederick-Duus et al. 2007)
	Inbred alcohol-preferring (iP) rats	Male	5 mg/kg	Reduced sucrose self-administration	(Jupp et al. 2011)
intranasal	Wistar rats	Male	0.5 mg/ml, 20 µl	Reduced food intake	(Lebedev et al. 2020)
i.c.v.	Sprague Dawley rats	Male	50 nmol	Blocked food intake induced by somatostatin agonist	(Karasawa et al. 2014)
			30 nmol	Blunted food intake induced by ghrelin	(Hsu et al. 2015)
			30, 60, 100 nmol	Reduced HFD intake	(Zheng et al. 2007)
	Wistar rat	Male	20 nmol	Reduced active lever press, breakpoint and number of reinforcers in the PR responding for sucrose (decreased responding and breakpoint), reduced HFD CPP	(Kay et al. 2014)
			10 nmol	Reduced total number of licks for chocolate and food intake	(Williams et al. 2020)
i.v.	Sprague Dawley rats	Male	10 mg/kg	Reduced 5-thio-D-glucose (5-TG) glucoprivation induced feeding	(Otlivanchik et al. 2015)
NAcc	Wistar rats	Male	3, 6 ng	Reduced food intake	(Mayannavar et al. 2014)
	Sprague Dawley rats	Male	1, 3, 6 ng	Reduced food intake	(Thorpe & Kotz 2005)
NTS	Wistar rats	Male	5, 10 nmol	Supressed food intake	(Kay et al. 2014)
MPOA	Wistar rats	Male	10 nmol	No effect on food intake	(Sarihi et al. 2015)
VTA	Wistar rats	Male	10 nmol	Suppressed sucrose intake when administered bilaterally (5 nmol/side) but not unilaterally	(Terrill et al. 2016)
	Sprague Dawley rats	Male	15 nmol/side	Reduced HFD intake induced by DAMGO injection in NAcc	(Zheng et al. 2007)
PVT	Sprague Dawley rats	Male	15 nmol/side	No effect in HFD intake induced by DAMGO injection in NAcc	(Zheng et al. 2007)

				15 µg/300 nl	Reduced sign-tracking behaviour	(Haight et al. 2020)
		Long-Evans rats	Male	15 µg	No effect on cue-induced sucrose seeking in hungry rats	(Meffre et al. 2019)
	PVN	Sprague Dawley rats	Male	1 nmol	Reduced orexin-induced feeding	(Wang et al. 2018)
	Arc	Sprague Dawley rats	Male	15 nmol/side	No effect in HFD intake induced by DAMGO injection in NAcc	(Zheng et al. 2007)
	CeA	Wistar rats	Male	5 µg	Reduced HFD but not food intake	(Jin et al. 2020)
	Medial PFC	Long-Evans rats	Male	2 µg/ul	Reduced cue-induced feeding	(Cole et al. 2020)
ACT-33582	oral	Wistar rats	Male	300 mg/kg/day for 4 weeks	Reduced rat’s preference for HPF over standard food	(Steiner et al. 2013)
GSK1059865	oral	Sprague Dawley rats	Female	10, 30 mg/kg	Reduced binge eating toward HPF	(Piccoli et al. 2012)
OXR-2						
JNJ-10397049	i.p.	Sprague Dawley rats	Female	1, 3 mg/kg	No effect on HPF intake	(Piccoli et al. 2012)
	s.c.	Wistar rats	Male	1, 3, 10 mg/kg	No effect on saccharine self-administration	(Shoblock et al. 2011)
TCS-OX2-29	BLA	Wistar rats	Male	10 µg	Reduced food intake	(Rashmi et al. 2015)
	PVT	Long-Evans rats	Male	15 µg	Suppressed cue-induced sucrose seeking in hungry rats	(Meffre et al. 2019)
		Sprague Dawley rats	Male	15 µg/300 nl	Reduced sign-tracking behaviour and reinforcing properties of reward cue	(Haight et al. 2020)
	i.c.v.	Alcohol preferring rats	Male	100, 300 µg	No effect on sucrose self-administration	(Brown et al. 2013)
	intranasal	Wistar rats	Male	0.5 mg/ml, 20 µl	No effect on food intake	(Lebedev et al. 2020)
Dual Receptor SB-649868	oral	Sprague Dawley rats	Female	3 mg/kg	Reduced binge eating toward HPF	(Piccoli et al. 2012)
Anti-orexin IgG	intra-cisternal	Sprague Dawley rats	Male	4.5, 15, 45 µg	Decreased food intake dose dependently	(Yamada et al. 2000)
	i.p.	Sprague Dawley rats	Male	1.5, 4.5, 15, 45 µg	No effect on food intake	(Yamada et al. 2000)
	i.c.v.	Sprague Dawley rats	Male	1 mg	Reduced food intake	(Ida et al. 2000)

Arc, arcuate nucleus; BLA, basolateral amygdala; CeA, central amygdala; CPP, conditioned place preference; DAMGO, D-Ala2-*N*-Me-Phe ^{4}-gly^{5}-ol-enkephalin; HFD, high fat diet; HPF, highly palatable food; MPOA, medial preoptic area; NAcc, nucleus accumbens; NTS, nucleus of the solitary tract; PFC, prefrontal cortex; PR, progressive ratio; PVN, paraventricular nucleus paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; VTA, ventral tegmental area.

Table 3. Involvement of orexin B in promoting food intake

Route	Subjects	Sex	Outcome	Reference
i.c.v.	Sprague Dawley rats	Male	Increased food intake	(Sweet et al. 1999)
			No effect on food intake	(Haynes et al. 1999, Ida et al. 2000)
	Wistar rats	Male	Increased food intake	(Edwards et al. 1999)
			No effect on food intake	(Ida et al. 1999)
			Increased food intake	(Tsuji et al. 2011)
			Increased food intake	(Sakurai et al. 1998)
	C57BL/6J mice	Male	No effect on food intake	(Lubkin & Stricker-Krongrad 1998)
	Genetically obese Zucker (*fa*/*fa*) rats	Male	Increased food intake	(Jain et al. 2000)
i.v. and s.c.	Sprague Dawley rats	Male	No effect on food intake	(Haynes et al. 1999)
PVN, DMN, PeF-LH, ARC, VMN, POA, CeA, NTS	Sprague Dawley rats	Male	No effect on food intake	(Dube et al. 1999)
VTA, PVN, PeF-LH	Sprague Dawley rats	Male	No effect on food intake	(Sweet et al. 1999)
BLA	Wistar rats	Male	Increased food intake	(Rashmi et al. 2015)

Arc, arcuate nucleus; BLA, basolateral amygdala; CeA, central amygdala; DMN, dorsomedial nucleus; NTS, nucleus of the solitary tract; PeF-LH, perifornical-lateral hypothalamic area; POA, preoptic area; PVN, paraventricular nucleus of the hypothalamus; VMN, ventromedial nucleus; VTA, ventral tegmental area.

Table 4. The involvement of orexin A in hedonic and appetitive behaviour toward palatable food

Route	Subjects	Sex	Outcome	Reference
i..c.v.	Long-Evans rats	Male	Increased appetitive and consummatory feeding behaviour toward sucrose in sated rat	(Benoit et al. 2005)
	Sprague Dawley rats	Male	Increased meal size (consummatory feeding) and meal frequency (appetitive feeding) of sucrose solution (in freely fed rats)	(Baird et al. 2009)

	Lister hooded rats	Male	Increased intake of palatable wet mash (in freely fed rats)	(Rodgers et al. 2001, Rodgers et al. 2000)
	Long-Evans rats	Male	Induced reinstatement of palatable food	(Nair et al. 2008)
	Long-Evans rats	Male	Increased HFD intake over low fat food	(Clegg et al. 2002)
	Wistar rats	Male	Increased saccharine intake compared to water	(Furudono et al. 2006)
	Long-Evans rats	Male	Increased breakpoint responding for sucrose pellet	(Choi et al. 2010)
	Wistar rats	Male	Orexin A increased active lever presses, breakpoint and number of reinforcers in the PR responding for sucrose and HFD intake	(Kay et al. 2014)
VTA	Wistar rats	Male	Increased HFD and sucrose intake but no effect on operant responding for sucrose pellet	(Terrill et al. 2016)
PVT	Long-Evans rats	Male	Increased lever pressing for sucrose in sated rats	(Meffre et al. 2019)
LHA	Sprague Dawley rats	Male	Orexin A augmented free feeding of sweet pellet, increased response rate under FR20 schedule and breakpoint under PR5 schedule. Effect was higher in food deprived rats.	(Thorpe et al. 2005a)
NTS	Sprague Dawley rats	Male	Increased HFD intake in sated rats	(Zheng et al. 2005, Kay et al. 2014)
CeA	Wistar rats	Male	Increased HFD intake	(Jin et al. 2020)
NAcc	Sprague Dawley rats	Male + Female	Increased liking reaction to sucrose and binge-like intake of sweet chocolate	(Castro et al. 2016)

CeA, central amygdala; FR20, fixed ratio 20; HFD, high fat diet; LHA, lateral hypothalamic area; NAcc, nucleus accumbens; NTS, nucleus of the solitary tract; PR5, progressive ratio 5; PVT, paraventricular nucleus of the thalamus; VTA, ventral tegmental area.

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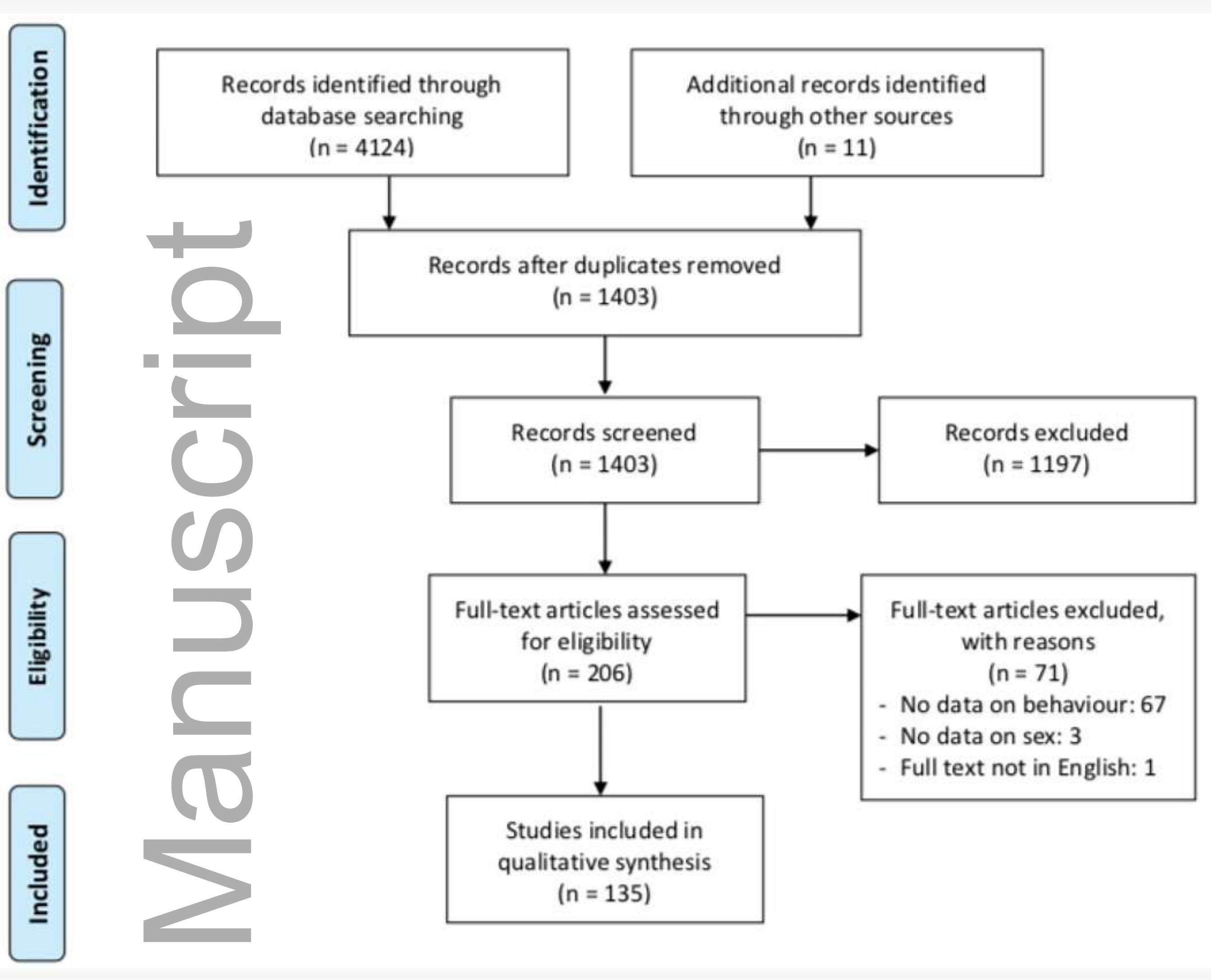

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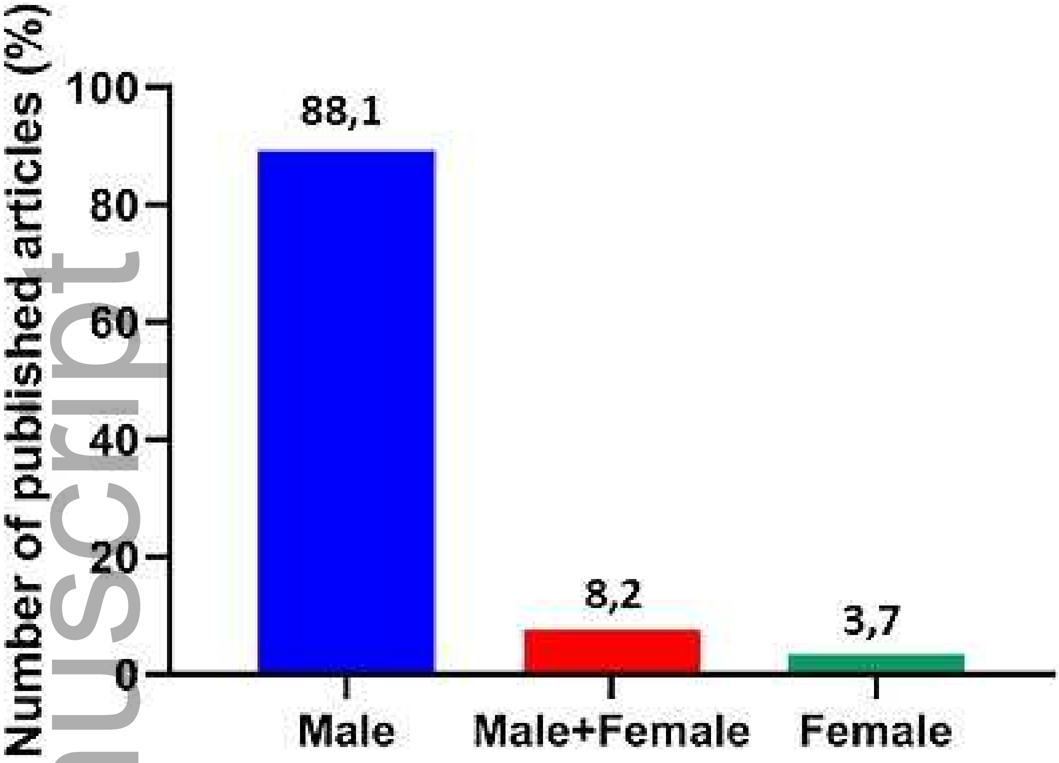

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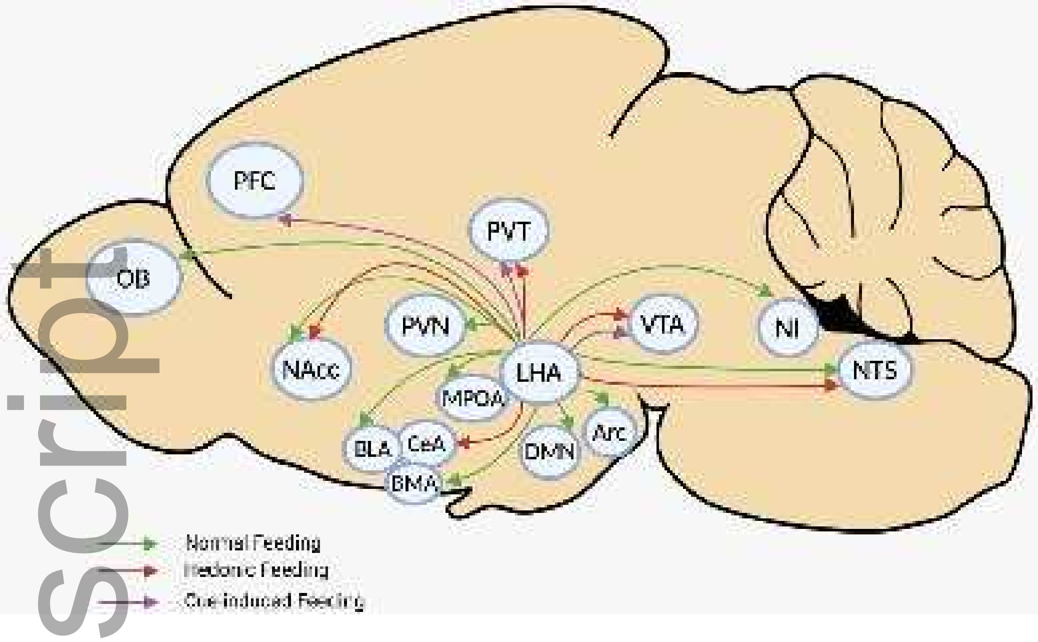

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