Chapter

Possible Dysregulation of Orexin and Dopamine Systems in Anorexia Nervosa

Marcela Morales-Mulia and Sandra Morales-Mulia

Abstract

Anorexia nervosa (AN) is a psychiatric illness characterized by a lack of motivation and a taste for rewarding food consumption. Mood disorders such as depression and stress are frequently associated with this condition. Abnormalities in several neural systems have been identified in patients with AN, including serotonin, dopamine (DA), appetite-related neuropeptides, and other neurochemical systems. Moreover, the changes that occur between the mesolimbic dopaminergic pathway and the orexin neurons in the lateral hypothalamus (LH) in response to the reduction in food consumption are key in the development of AN. Several studies suggest a functional relationship between orexin and dopaminergic circuits. LH orexin neurons project dense fibers on dopaminergic neurons, potently activating these neurons. DA and orexin neurons regulate negative and positive motivational states, such as drug and food seeking behavior. For this reason, it is important to extend the study of the functional and emotional interactions that exist between both neuronal systems to design new drugs that act at a behavioral and molecular level to treat AN. This chapter provides an overview of the evidence from literature implicating dopamine-orexin systems in AN and discusses recent advances that have contributed to our current understanding of the mechanisms underlying the molecular bases of AN.

Keywords: mesocorticolimbic system, dopamine receptors, reward, mental illness, orexin neurons, motivation, anxiety disorders

1. Introduction

Anorexia nervosa (AN) has been classified as a chronic psychiatric disease since this condition has a strong emotional component. AN belongs to a group of eating disorders and is characterized by extreme body weight loss. AN patients show combination of physical, psychological, and behavioral disturbances that usually have their onset during adolescence. AN is associated with high levels of psychiatric comorbidity including psychosis, hyperactivity, depression, and anxiety. In consequence, this illness has become a major focus of attention in terms of both the research community and the general public. The prevalence of AN is approximately 1% in women and less than 0.5% in men [1]. Patients with AN show a high degree of anhedonia (the reduced capacity to experience reward or pleasure) and have a disturbed body image and an intense fear of weight gain. Standardized mortality ratios show that the rate of death in AN is at least five times greater than that in the general population [2].

Little is known about the etiology and the intrinsic biological alterations of anorexia, but it appears to be the result of different factors, for example, low self-esteem, certain personality traits such as perfectionism, mental illnesses such as depression, anxiety, self-harm, difficulty to manage stress and cope with life. Feelings of obsession and compulsion are also related with AN. Society and communication media play a key role in this pathology, since through them we are constantly told that the image of the body is very important because it reflects our value, as people. While culture, society, and the media exert pressure on women to remain thin, now it is widely accepted that there is a biological basis for this psychiatric disorder. Henceforth, the complexity of AN has limited the development of neuroscience-based treatments, and no medication or other biological treatment has been approved for the disorder. Then, to understand the biology of pathological eating behavior is an important step in the development of appropriate pharmacotherapies that can be used to treat AN patients.

To date abnormalities in several neural systems have been identified in patients with AN, including serotonin and DA, appetite-related neuropeptides, and other neurochemical systems. This chapter will focus especially on the dopaminergic neurons of the ventral tegmental area (VTA) that project the nucleus accumbens (NAc) to form the mesocorticolimbic circuit; and in the orexin neurons localized exclusively in two subregions of the hypothalamus; the perifornical area (PFA) and the LH, where orexin peptide is expressing [3].

Previously, it was thought that the serotonin system was the only or most important neurotransmitter involved in AN, and all research was carried out around its neurotransmission. Subsequently, preclinic and clinic evidence propose that the dopaminergic system could be a key factor in the pathophysiology of eating disorders. The AN is characterized by a reduction in food intake (diet restriction) and hyperactivity. In this sense, decrease in DA content has been observed in hypothalamus, hippocampus, and the dorsal striatum after a restricted diet. Moreover, the motor activity is modulated mainly by dopaminergic circuits. These first data point out for the first time the possible contribution of dopaminergic transmission in anorexia.

The signals to eat or to stop eating are very complex and extend beyond the control of the homeostatic system that responds to metabolic and satiety signals from the gut. Recently, it has been proposed that mesocorticolimbic dopaminergic system also responds to features of food such as the sight, smell, and taste in addition to cues that predict food intake and override the ingestive behavior [4]. The motivation to eat is key in eating behavior and is regulated by several intrinsic and extrinsic factors. Neuronal and circulating peptides are released in response of internal states, such as hunger or satiety, to stimulate or repress food intake, respectively. Accumulating evidence has pointing out the orexin-containing neurons as central regulators of feeding behavior, energy balance modulation, and metabolic homeostasis.

2. Dopamine neurons

DA is a catecholamine and is a key neuromodulator involved in motivated behaviors. DA-containing neurons are characterized by the presence of tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of catecholamines, and are found throughout the mammalian central nervous system (CNS), including the ventral midbrain (VM) [5]. Midbrain DA-containing neurons are arranged principally in two nucleus: the substantia nigra pars compacta (SNc, also known as the A9 group) and the VTA, or A10 group [5, 6]. Different populations of DA-containing

neurons project to distinct areas and control or modulate specific functions, according to their targets. We will emphasize in the VTA nucleus, which project to ventromedial striatum (NAc) and PFC, forming the mesocorticolimbic system. These DA-containing neurons regulate emotional behavior, natural motivation, reward and cognitive function, and are largely implicated in a range of psychiatric disorders [7–9].

DA acts primly through of two G protein-coupled DA D1 (D1R) and D2 (D2R) receptors [10]. D1R is a postsynaptic receptor that mediates more directly behavior, and the D2R is a presynaptic autoreceptor that regulates DA release in a negative feedback fashion; D1R increases, whereas D2R decreases adenylyl-cyclase activity, and both receptor types are distributed throughout the CNS [11]. A variety of studies indicate that an altered DA function in AN could be implicated. Patients with AN have shown low levels of homovanillic acid in their cerebrospinal fluid (CSF), the major DA metabolite [12]; in addition, a positron emission tomography (PET) study revealed an increase in D2R binding in the anteroventral striatum (NAc in rodents), in a mixed group of women recovered from both restricted-type anorexia nervosa and binge-eating/purging-type [13]. These data suggest that neuronal or synaptic DA may be reduced, but that DA receptors could be increased in number or sensitivity in a compensatory or negative feedback fashion [14]. Thus, a down-regulation of receptor sensitivity might be an important therapeutic goal in AN, to compensate the low levels of DA.

Several hypotheses have been raised about the contribution of DA in AN. On one side, Bergh and Södersten [15] suggest that normal DA responses to hunger and exercise facilitate a progression into AN; in addition, O'Hara et al. [16] proposed that an anomaly in the reward system mediated by the DA leads to the development, maintenance, and resistance to the treatment of the AN.

2.1 Mesocorticolimbic dopamine neurons may facilitate the development of anorexia nervosa

According to Bergh and Södersten [15], dieting, along with high levels of exercise, leads to a stress response that increases cortisol and corticotrophin-releasing factor (CRF) [17–22], which in turn promotes an increase in DA levels in the NAc [23, 24]. In such a way, DA facilitates rewarding behaviors such as diet and exercise to become habits similar to those associated with drug dependency or self-starvation by conditioning this type of reward to initially neutral stimuli [15, 25–28]. In addition, the high CRF levels induced by diet restriction and exercise also facilitate to seek for food, while simultaneously suppressing food intake [29]. However, until now there is no clinical study that compares the DA levels in anorexic subjects before and after developing anorexia that shows chronically high levels of DA before the disease was declared.

2.2 Aberrant concept of starvation in anorexia nervosa

The mentalistic concept of AN assumes that it results from a mental illness. This concept describes this illness as a set of chronic and serious mental disorders with debilitating physical, cognitive, and socioemotional impairments such as anxiety, depression, obsessional traits, and pathological cognitions. Therefore, when the initial care of a patient with anorexia is focused only on cognitive therapies to treat psychological disorders do not usually give good long-time results. Moreover, symptoms such as anxiety and depression also emerge in healthy people during a starvation period [30]. There are many arguments against the hypothesis that an underlying mental disorder causes AN [31]. Recently, it was discovered that AN

and anxiety have different genetic risk factors. Also, almost all mental disorder symptoms observed in anorexics disappear after normalization of eating behavior [31, 32].

O'Hara et al. [16] do not agree with the mentalist concept because this does not assume the normal functions of the neuroendocrine system, which is responsible for regulating the release of peptides that regulate food consumption. The mentalist concept does not take into account the physiological aspects in eating disorders, and this may be the reason why this approach to treating anorexia as a consequence of a mental illness has not led to an effective treatment. O'Hara et al. [16] proposed that an abnormality in the reward system mediated by DA leads to the development, maintenance, and resistance to treatment in the AN.

They suggest that the decrease in dopaminergic activity and the rejection of food intake are key in the development of anorexia. Therefore, they propose increasing DA levels to normalize the consumption of food to reduce the stress generated by starvation, which in turn reduces the release of CRF to gradually increase the consumption of food. However, recent studies suggest that changes in DA found in anorexic patients are due more to a normal characteristic of starvation than to a disease marker.

3. Hypothalamic orexin neurons modulate dopaminergic neurons

Orexin-A and orexin-B neuropeptides were initially identified as endogenous ligands for two orphan G protein-coupled receptors; the OX_1R is coupled entirely to Gq, whereas OX_2R is coupled to both Gi/o and Gq [33]. Both orexins are derived from proteolytic cleavage, of a precursor peptide (pre-pro-orexin), and are produced by a group of neurons in the LH and PFA, a region known as the feeding center (**Figure 1**). OX-A has the same affinity with both receptors, while OX-B has a greater affinity for OX_2R than OX_1R [33, 34]. These receptors are highly expressed throughout the brain including the "dopaminergic reward pathways" (**Figure 1**) [35–39]. Moreover, these

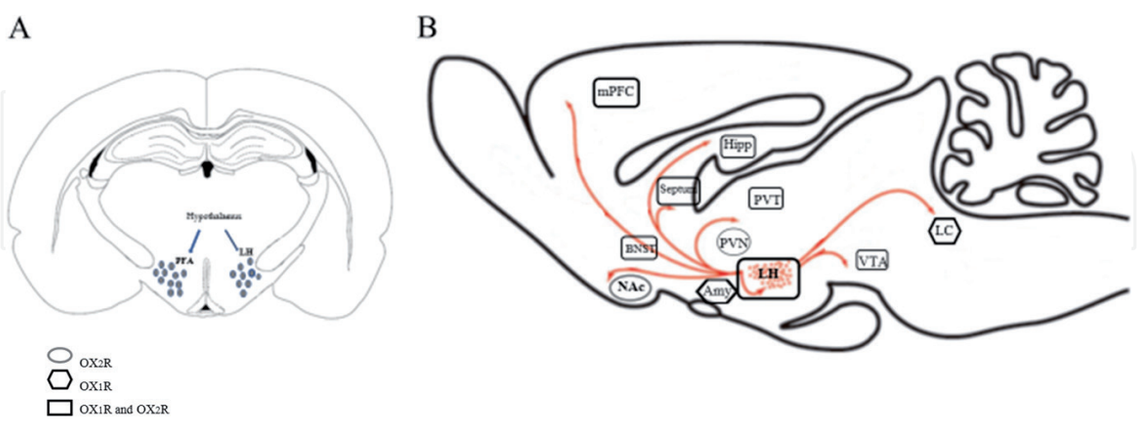

Figure 1.
Schematic representation of the brain areas related to motivated and emotional behaviors. (A) Coronal section of the rat brain showing the lateral (LH) and perifornical area (PEA) of hypothalamus. (B) Representation of the main orexin projections and the expression of orexin receptors 1 and 2 (OX_1R and OX_2R) in these brain regions. The fear circuit comprising the hippocampus (Hypp), medial prefrontal cortex (mPFC), and amygdala (AMY). Areas implicated in anxiety: bed of the stria terminals (BNST), paraventricular thalamus (PVT), and septum. The paraventricular nucleus of the hypothalamus (PVN) regulates stress responses and the hypothalamic-pituitary-adrenal axis hormone cascade. The mesocorticolimbic system modulates the rewarding properties of food and drugs of abuse and comprising the ventral tegmental area (VTA) and nucleus accumbens (NAc). The locus coeruleus (LC) also has dense orexin innervations in concordance with its involvement in arousal and emotional memory. Abbreviation: LH, lateral hypothalamus.

peptides are also regarded as an important factor that regulates feeding behavior, owing to their localization within the lateral hypothalamic area, the classic "feeding center."

Orexins were recognized as positive regulators of energy expenditure, thanks to the development of the orexin neuron-deficient mice. Studies conducted in these animals led to propose that orexins promote acute food consumption on one hand and on the other hand prevent the progress of obesity [40]. Since then, numerous pharmacological and genetic studies have supported that these peptides together with their receptors are key regulators of energy expenditure, thus influencing the energy balance.

The activation of the orexin system by means of the microinjection of orexin-A in the hypothalamus has shown that these peptides act as protectors in the development of obesity, by increasing energy expenditure. Also, orexin neurons increase energy expenditure by increasing thermogenesis in brown adipose tissue [40]. On the other hand, it has been observed that overexoression of pre-pro-orexin gene in an animal model promotes resistance to obesity induced by consumption of a high-fat diet [41]

The available anatomical, genetic, and pharmacological evidence supports that the behavioral consequences of the activity of the orexin system are due to parallel signaling to multiple brain regions and neurotransmitter systems such as DA. For example, the NAc is involved in hedonic and motivational aspects of feeding [42] and is an important brain region because endogenous orexin peptides act to modulate DA release [43], which act over hedonic processes associated with food evaluation and consumption. In addition, NAc is involved in the reward of natural behaviors, such as exercise, sex, and, of course food intake.

Orexins in the VTA, the major dopaminergic nucleus, have been implicated in drug and alcohol seeking and reinstatement. as well as food seeking, in highly salient circumstances, food seeking in highly salient circumstances, for example, during hunger, presentation of palatable foods or with exposure to food-related cues, but not in the consumption of regular food [44, 45]. An alternative mechanism by which orexins can stimulate the consumption of highly palatable food is via the paraventricular thalamic nucleus (PVT) because orexin neurons in the hypothalamus also send dense projections to the PVT [37], which in turn regulates DA efflux to the NAc via its glutamatergic projections [46, 47]. It has been reported that orexin actions in PVT promote DA efflux in the NAc, while the inhibition of its receptor OX_1R in this region decreases hedonic intake of palatable foods [48]. Therefore, orexins not only can act directly in the VTA to increase DA [45, 49] but they also increase DA via action in the PVT to promote hedonic food intake [48]. In summary, the control that orexins exert over VTA-NAc circuit is key to modulate motivational behaviors and reward processes related to drug, alcohol, and food seeking.

Functional studies show the relationship between LH orexins and VTA-NAc circuit where orexins exert their actions on the dopaminergic neurons by increasing the firing frequency in VTA neurons in vitro and in vivo [50, 51]. These peptides induce an increase in DA release and its metabolites in both NAc and PFC [4, 49, 52, 53]. Electrical stimulation of the LH nucleus can increase both food intake and accumbal DA turnover [54–56]. In contrast, the inhibition of OX1R reduces DA cells firing [57], as well as significantly decrease in amphetamine, and cocaine-induced DA release in the NAc [57, 58]. On the other hand, the intracerebroventricular administration of OX-A leads to stress-related behavior like grooming, stereotypy, and hyperlocomotion [59], actions that were inhibited by DA D1 receptor (D1R) or DA D2 receptor (D2R) antagonists in rodents [59]. These data provide strong evidence that the orexin system contributes to DAergic neurons regulation in the

mesocorticolimbic pathway and that the action of orexins in these neurons could involve a variety of behaviors that are known to be regulated by DA.

This framework suggests that understanding the function of the orexin requires studying them in a brain region-specific basis, as well as understanding the interactions between different brain regions that receive orexinergic input [40]

4. Anorexia nervosa and anxiety disorders: role of orexin and dopamine

4.1 Anorexia nervosa and anxiety disorders

AN is a very complex disease, characterized by a profound dysregulation in neurocircuits related to control eating behavior, anxiety, fear, and reward positive/negative reinforcers. AN is a serious motivated behavioral condition with high morbidity and mortality. Anorexic patients usually have a high comorbidity with severe anxiety disorders, such as obsessive-compulsive disorder (OCD) and social anxiety disorder (SAD) [60]. One characteristic that anorexics share with people suffering from SAD is their fear and concern about how other people perceive them. Elevated neuroticism and perfectionism as well as decreased novelty seeking are anxious personality traits observed in these disorders [60]. Therefore, anxiety disorders and AN are strongly correlated; in both disorders, the fear is organized around an irrational belief associated with heightened vigilance and pronounced anxiety. Another characteristic shared between AN and OCD is compulsivity: to engage in repetitive and stereotyped acts that have unwanted outcomes [61] and arises from a reduced ability to control inflexible yet maladaptive behavior as the starvation, which persists in the face of negative consequences, for example, interfering with academic/occupational/social interests in longer term and the behaviors promoting further, and potentially dangerous, weight loss.

Recently, Lloyd et al. [62] have proposed a central role for anxiety in the development of compulsive starvation; they suggest a dual mechanism by which anxiety could be motivating the initiation of AN and propose that the reinforcement effects of starvation cause excessive repetition of behaviors leading to the buildout of psychological symptoms of AN. They also suggest that starvation becomes compulsive until it has adverse implications for anxiety, which generates the symptoms of AN and which encourages the formation of a vicious circle that guarantees the persistence of an extreme dietary restriction. Stress and distress tolerance have been suggested as important factors in determining the onset and course of AN [61]. Stressful and traumatic events often precede eating diseases. Notably, high levels of anxiety tend to also precede the onset of addiction and OCD.

Dietary restriction has an anxiolytic effect, because women recovered from AN show elevated levels of serotonin (5-HT) metabolites [63], and gene variants linked to more active 5-HT and noradrenaline (NA) systems are implicated in AN [64, 65], supporting the involvement of these neurotransmitter systems in the heightened anxiety that precedes AN. Thus, dietary restriction relieves the anxiety (or negative reinforcement) provided by the dietary restriction that increases with anxiety.

Starvation is a compulsive behavior that over time becomes a habit with a dominant influence in individuals with AN. Surprisingly, in anorexics, there is an imperative need to keep starving [62]. However, this behavior puts your life at risk.

Subjects with AN show an extreme aversive state characterized by high levels of anxiety when eating, that is, when they do not carry out their compulsive behavior of starvation [61, 66]. This is also observed in addiction and OCD, where the execution of compulsions serves to temporarily relieve the negative effects [61, 67–69].

Several studies indicate that the levels of anxiety in anorexics are even higher than before the restriction of food and that this anxious behavior is partially mediated by an increased sensitivity of the 5-HT and NA systems, which results from the reduced consumption of tryptophan and tyrosine, respectively [70, 71].

When starvation becomes necessary to avoid an extremely anxious state, the desire to starve is enhanced given the poor emotion regulation abilities of individuals with AN, which limits the use of alternative strategies to overcome dysphoria [72–74].

Anxiety precedes and coincides with restrictive eating in AN [75–78], which is not the case for individuals without the disorder [77]. Repeatedly engaging in dietary restriction in an anxious state facilitates anxiety to evoke restrictive eating habits, due to a pairing of emotion and behavior.

Thus, several mechanisms likely explain how anxiety promotes engagement in maladaptive dietary restriction habits that have developed during a compulsive illness.

4.2 Dopamine and orexins systems: evidence for an interconnection in anorexia nervosa

Stress and distress tolerance have been suggested as important factors in determining the onset and course of AN. Stressful and traumatic events often precede eating diseases. AN comprises a hyperactivation of the HPA axis [79]. Patients with AN present significantly elevated concentration of plasma cortisol, increased central CRF, and significantly less cortisol suppression after dexamethasone administration than controls [80, 81]. Moreover, hormonal changes also do not seem to be specific for AN and are found in other diseases or in healthy subjects as a consequence of malnutrition and starvation [82]. In general, these data show the need to study other molecules as possible indicators of HPA-axis hyperactivity on the one hand and that regulate emotional states on the other hand. DA and orexins share diverse characteristics at the physiological, psychological, and psychiatric levels, such as the ability to modulate the HPA axis activity, induce drug and food seeking behavior, increase the motivation to obtain food, and regulate emotional states, such as depression and anxiety.

At first it was thought that orexins participated in the consumption of food because orexin central administration produces food seeking, and food deprivation increases orexin mRNA [83, 84]. In addition, orexin neurons are excited by peripheral signals of nutrient needs (e.g., ghrelin), inhibited by satiety signals (e.g., glucose) and interact with feeding peptides to promote food consumption and seeking [85–89]. Notably, orexin neurons are active during hunger and help to translate peripheral hunger signals into increased appetitive responding for food and cues associated to consumption of food. Thus, orexins facilitate food seeking especially in motivationally charged circumstances.

Orexins orchestrate various aspects of stress responses. For example, acute (but not chronic and predictable) stress is associated with orexin neuron activation [90]. The orexins help to organize the response to stress, but only when it assumes a motivated and adaptable behavior to cope with stress, that is, when you can escape the stressor. In contrast, when a stressor is chronic, predictable, and impossible to escape, the activity of orexin system decreases, and this hypoactivity can produce motivational symptoms similar to depression.

In the case of DA, it is involved in motivational but not consummatory aspects of feeding. The blocking of mesocorticolimbic dopaminergic system decreases the response for motivational tasks associated with obtaining food [91]. DA depletion

or administration of DA receptor antagonists in NAc reduces the motivation to consumption high palatable food [92–95]. The motivation to eat is a key factor to maintain a normal feeding behavior.

Dysfunction of the OXs and DA systems may contribute to the pathology of anxiety and addiction to food and drugs of abuse, which is commonly associated with anxiety and/or defective fear processing, depression, and cognitive impairment as well as other comorbid conditions. Increase in orexin mRNA levels has been observed in animals exposed to different stressors such as immobilization [96], cold stress [96], or hypoglycemia [84], while that both acute and chronic stress promote major changes in DA signaling in the mesocorticolimbic pathway such as increases in DA release in the striatum, NAc, and PFC [97–99]. D2R receptor knockout mice display anxiety and depression-like behaviors upon chronic stress [100]. Repeated restrain stress produces increases and decreases in DA receptor densities within the mesoaccumbens and nigrostriatal systems in two different strains of mice [101]. So, these results suggested that stressful conditions could be augmented the vulnerability to develop psychiatric illnesses as AN. So, any decline in the transmission of DA and orexins can generate a lack of motivation to consume food. However, there are few studies about the participation of DA receptors in the PFA/HL areas on the control of food drinking. Studies suggest that ethanol intake and excessive food consumption could be similarly affected by DA in the PFA/HL areas, with increases in both ethanol and food intake after D1 receptor activation and decrease in both consumptions after the activation of D2 [100].

Considering that the anxiety induces specific reduction of the D2R in the NAc and that DA attenuates several addictive behaviors in animals [100], it is difficult not to think that DA may act as an anxiolytic agent through the D2R activation. On the other hand, the decreased release of orexins could promote low food consumption, that is, the dysfunction of the orexin system could be accentuating the lack of motivation for the search and consumption of food in anorexics. In this way, the stimulation of orexin receptors together with DA could reduce the stress generated by starvation and, at the same time, increase the motivation for food consumption.

5. Conclusion

Considering on the one hand that AN is a compulsive disorder, and on the other hand that starvation is the result of a negative reinforcement, it is suggested that the dysfunction of DA and orexins in the mesocorticolimbic system is key to the successful treatment of AN. The model can justify the use of existing and planned prevention and treatment programs but may also guide the development of novel interventions to favorably affect the incidence and recovery rates of a life-threatening condition.

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Conflict of interest

The authors declare that they have no conflict of interest.

Nomenclature

AN	anorexia nervosa
HPA axis	hypothalamic-pituitary-adrenal axis
CNS	central nervous system
CRF	corticotrophin-releasing factor
DA	dopamine
D1R	dopamine D1 receptor
D2R	dopamine D2 receptor
LH	lateral hypothalamus
mRNA	messenger ribonucleic acid
NA	noradrenaline
NAc	nucleus accumbens
OCD	obsessive-compulsive disorder
OX_1R	orexin 1 receptor
OX_2R	orexin 2 receptor
PVT	paraventricular thalamic nucleus
PFA	perifornical area
5-HT	serotonin
SAD	social anxiety disorder
SNc	substantia nigra pars compacta
TH	tyrosine hydroxylase
VM	ventral midbrain
VTA	ventral tegmental area

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