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Mini Review **Open Access**

Role of Orexin System in Obesity

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Abstract

Obesity is a public health disease and its incidence is steadily increasing both in adults and in children especially in the Western World. It is important to understand the underlying mechanisms of obesity and possible treatments as the orexin system with its receptors, which are involved in different physiological processes. In fact, the aim of this mini-review is to consider the importance of the orexin system and the role that orexin plays in the regulation of obesity and physical activity. Furthermore to demonstrate how the orexin and its receptors fit within a network distributed in multiple brain areas, each with specific actions, whose activation and interconnection has been seen to lead to a lower propensity for increase of fat mass, it could thus constitute an important future target for prevention and treatment of obesity.

Keywords: Orexin; Obesity; Energy expenditure

Introduction

The orexin (hypocretin) is an important neurotransmitter in the regulation of sleep-wakefulness and appetite. There are two types of orexin peptides: the orexin-A (OXA or hypocretin 1) and orexin-B (OXB or hypocretin 2). The majority of the orexin peptides are synthesized in neurons located in the lateral and back hypothalamus and they send projections throughout the brain regions [1,2]. These peptides derive from the prepro-orexin (prepro hypocretin) gene, which encodes a precursor (130 amino acids in rodents, 131 residues in humans) that is cleaved into orexin-A (synonymous with hypocretin-1; 33 amino acids) and orexin-B (hypocretin-2; 28 residues (Figure 1).

The orexin binds to two types of receptors, belonging to the class of G protein-coupled receptors: orexin receptor type-1 (OX1R or hypocretin receptor 1) and orexin receptor type-2 (OX2R or hypocretin receptor 2) Both orexin receptors subtypes can bind to OXA and OXB, but with differential affinity; in particular orexin receptor type-1 has a higher affinity for OXA, while orexin receptor type-2 has equal affinity for either orexin peptide [3,4] (Figure 1).

Orexin neurons have a lot of projections related to many and different brain regions, as well as for the orexin receptors that are expressed in several areas of the brain [1,2]. A similar distribution of orexin neurons and their receptors explains how these neurotransmitters are involved in numerous physiological processes, including the modulation of the sleep, the arousal and of the energy expenditure, suggesting an important role in development of obesity [5–8] (Figure 2). In this review we want to highlight that the orexin system can lead to an increase in energy expenditure and so give a contribute to the obesity resistance. We want to provide a synthesis of the current state of knowledge in the regulation of hypothalamic orexin during obesity and provide a platform on which to develop an improved clinical outcomes during obesity in relation to the autonomic nervous system, brown adipose tissue, sleep-wake rhythm, expenditure energy.

The way of the action of the orexin system depends on a series of signals to multiple brain regions, and it is extremely important to understand the anatomy and function of the neuronal network of orexin system. The proof of the fact the orexins peptides are involved into energy metabolism is exemplified in a mouse model that exhibits post-natal loss of orexin neurons [5]. In these mice, the orexin promoter drives expression of the neurodegenerative gene ataxin-3 and leading to progressive loss of the orexin neurons during development. These mice show hypophagia, lower levels of spontaneous physical activity (SPA) and express the appearance of a obesity state when fed a regular diet [5,8,9]. This indicates that an important function of the orexins peptides is to rule energy expenditure and so modulate food intake. A further support for this idea comes from other mouse models in which the results prove that these mice show resistance to high-fat diet–induced obesity, corroborating with the role of orexin in promoting energy expenditure [10,11].

Orexin System and Neural Network
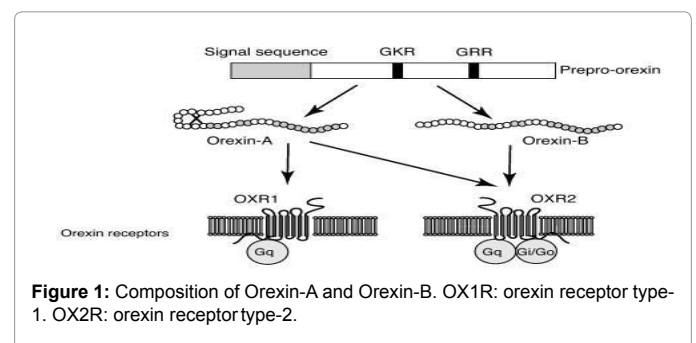
Figure 1: Composition of Orexin-A and Orexin-B. OX1R: orexin receptor type-1. OX2R: orexin receptor type-2.

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Over the location in the lateral hypothalamus, which were initially described, the orexin and its receptors have been highlighted in neuronal bodies and positive fibers present in different regions of the central nervous system (CNS) and their position is in connection with the functions performed. Therefore a lot of brain sites join in this regulatory network through a significant number of neurotransmitters (Figure 3). The functions of the orexin system are expressed in different brain regions, they control the same behaviors; in fact many of the brain sites that participate in the SPA network also participate in regulatory networks for food intake and other aspects of energy balance. Several brain regions receive orexinergic input and express the OXR and this instance suggests that the behavioral outcomes of the orexin system are due to simultaneous activation of the OXR in different brain regions connected through projections.

Orexins are produced in a particular area of the hypothalamus, including the caudal lateral hypothalamus and adjacent perifornical area [12] and, from these sites, orexin projects throughout the other areas of the brain. On the basis of anatomical predisposition appears to be valid the hypothesis that the effects of the action of the orexin system derive from a series of parallel signals that come from different brain regions [13]. It is important to know that orexin neurons are in a baseline intrinsic state of depolarized activity [14] and are highly influenced by local conditions in an intralateral hypothalamic local network [15]. The Activation of the OXR causes depolarization and active neuronal firing by four possible mechanisms:

- activation of non-specific cationic currents
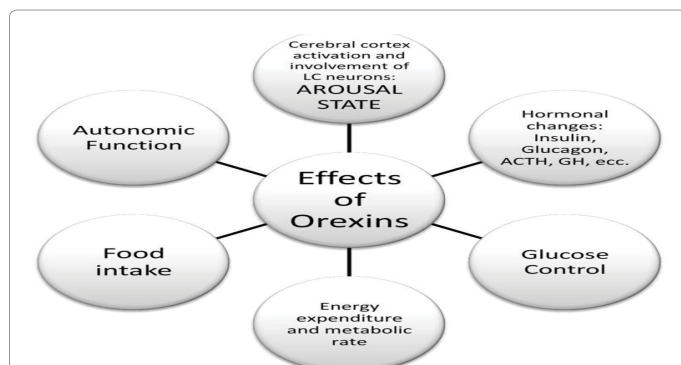- activation of the Na^+/Ca^{2+} exchanger

Figure 2: Effects of orexins in peripheral tissue and central nervous system. and development of obesity. Adapted from Messina et al., [8].
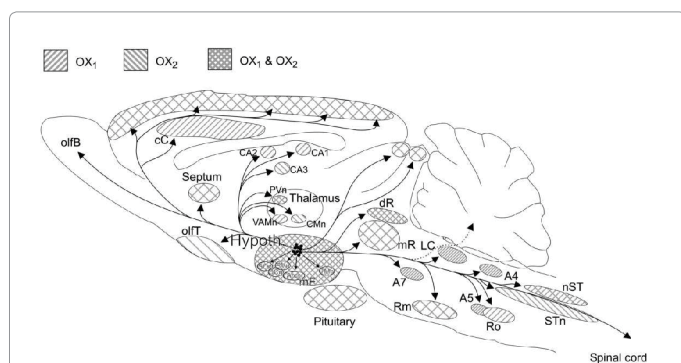

Figure 3: Brain neurotransmitters. OX1R: orexin receptor type-1. OX2R: orexin receptor type-2.

- phosphorylation-dependent inhibition of inwardly rectifying K+ channels
- increase in Ca^{2+} through activation of L- and N-type Ca^{2+} channels [16–20].

The type of mechanism appears to be cell-dependent and both orexin subtypes can couple to many G- proteins that cause neuronal depolarization through many mechanisms cell-specific (Figure 4).

The Role Of Orexin In Brown Adipose Tissue Thermogenesis And Activation Of Sympathetic Nervous System

Orexin system also influences body temperature. In fact, an Intracerebroventricular (icv) administration of orexin system induces an increase in the firing rate of the sympathetic nerves to interscapular brown adipose tissue (IBAT), accompanied with a rise in IBAT and colonic temperatures [21]. In addition, the presence of orexin receptors in many cerebral areas suggests that additional functions are played by orexin system [22]. In general, those experiments demonstrate that an icv injection of orexin system increases the temperature of IBAT, which is the most important effect or of non shivering thermogenesis in the rat [23], illustrating that the rise in heat production is also due to the activation of thermogenesis unrelated to muscle activity. IBAT activity is controlled by the sympathetic nervous system, and factors, which influence thermogenesis, appear to act centrally to modify the sympathetic outflow to IBAT [24]. The increase in colonic temperature emphasizes the effect of orexin system on the "core" temperature confirming the inclusion of orexin system among the peptides controlling body temperature. The rise of the sympathetic discharge induced by orexin system is corroborated by the increase in heart rate, although a possible reduction on the vagal tone cannot be excluded. Since Van Den Pol [25] demonstrated a direct innervation of the intermedio lateral column of spinal cord by orexin-fibers, there might be another direct pathway of the orexin induced activation of the sympathetic nervous system.

Materials and Methods

Animals

Most of the animal studies were conducted on Sprague-Dawley rats, 3 months old and weighing 250–300 g were used in the experiments. The rats were housed in pairs at controlled temperature (22 ± 1°C) and humidity (70%) with a 12:12 h light–dark cycle with light from 07:00 to 19:00 h. The experiments were in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).
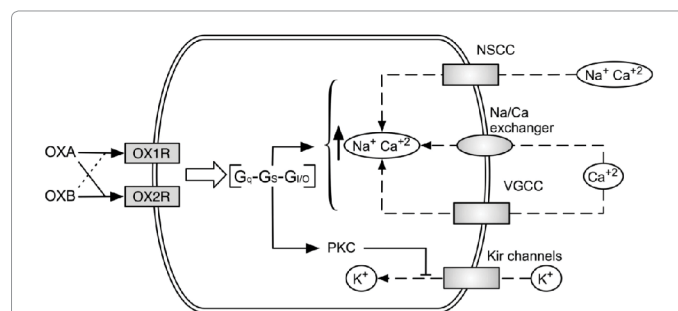

Figure 4: Neuronal depolarization. OX1R: orexin receptor type-1. OX2R: orexin receptor type-2.

Apparatus

A pair of silver wire electrodes recorded the firing rate of nerves to IBAT. The electrical pulses were amplified by a condenser-coupled amplifier and were filtered by band-pass filters (NeuroLog System, Digitimer). The raw pulses were displayed on an oscilloscope (Tektronix) and sent to a window discriminator. Square waves from the discriminator were sent to an analog-digital converter (DAS system, Keithley) and stored on a computer (Personal Computer AT, IBM) every 5 s. A rate meter with a reset time of 5 s was also used to observe the time course of the nerve activity recorded by pen recorder (Dynograph, Beckman). Because signal-to-noise ratio depended on the number of nerve filaments and the condition of contact between nerve and electrodes, the basal burst rates were different for each rat. The threshold level of the event detector was fixed during the experiment at 50% of the peaks of the largest pulses and above background noise. Thermocouples (Ellab) were used to monitor colonic and IBAT temperatures (Tc and TIBAT) and the values were stored on a chart recorder.

Two electrodes applied to the forelegs monitored the heart rate (beats/min). Electrical signals were addressed to a poly- graph (Dynograph, Beckman) to record the electrocardiograph- ic activity on the card and on a computer disk.

Procedure

Usually the animals were anesthetized with ip pentobarbital (50 mg/kg bw) and a 20-gauge stainless guide cannula was positioned stereotaxically above a lateral cerebral ventricle at the following coordinates: 1.7 mm lateral to the midline, 0.4 mm posterior to the bregma, 3.0 mm from the cranial theca. Nerve activity was recorded by small nerve bundles dissected from the intercostal nerves supplying the right side of IBAT. Nerve filaments were isolated from the central cut end of these nerve bundles under a dissecting microscope; the efferent activity was recorded with a pair of silver wire electrodes. The nerve filaments were covered with a mixture of vaseline and liquid petroleum at 37°C to avoid dehydration. At the same time as the nerve activity was recorded the heart rate, Tc and TIBAT were monitored. Tc was measured by inserting the thermocouple into the colon 4 cm from the anus, while TIBAT was monitored by inserting the thermocouple in the left side of IBAT. Orexin was icv injected into the cerebral ventricle in rats which had received a drug or saline alone. The drugs were delivered into the cerebral ventricle by gravity flow over a 2 min interval. The cannula was 0.4 mm longer than the guide cannula.

Concept of obesity and its interindividual variability

Obesity (body mass index ≥ 30 kg of body weight/m^2 of height) is a medical condition characterized by the accumulation of excess free fat [13] that can lead negative effects on health, resulting in a reduced life expectancy and increased health problems. Obesity incidence in adults and children has increased in the last twenty years, especially in developed societies [26,27]. It is related to other diseases, including cardiovascular dysfunction, diabetes mellitus type 2, disorders of the osteo-articular system, stroke, metabolic syndrome and certain types of cancer [28]. Obesity is most commonly caused by a combination of excessive food intake, deficiency of physical activity and genetic suscep-tibility, enough to be considered a multifactorial disease.

The genetic component in the etiopathogenesis of obesity has as-sumed in last years an important role by identifying an increasing number of genes involved in the disease. The obesity in the humans can depend by different genetic factors [29,30], but the major fac-

tor in determining this variability is physical activity, and specifically a component of total energy expenditure known as nonexercise induced thermogenesis (NEAT) (Figure 4) [31–33]. NEAT includes all forms of energy expenditure not associated with formal exercise and it is related with the concept of spontaneous physical activity (SPA) that is utilized to describe "any type of physical activity that does not qualify as voluntary exercise" [34–42].

Orexin role in sleep regulation and obesity

Many animal studies also support the idea that disordered sleep may contribute to obesity. For example, following weight gain on a high fat diet, obese mice showed increased time spent in slow wave sleep (SWS) [43], while time spent in wakefulness was decreased and the time spent in SWS was increased especially in the dark (active) period. In this model, greater body weight was positively correlated with more time spent in SWS, and negatively correlated with time spent in wakefulness in the dark period. Obesity is associated with decreased levels of orexin [44]. Orexin system regulates and consolidates sleep/wake patterns. Narcoleptic patients, who lack orexin, have altered sleep patterns, highly fragmented sleep and elevated body mass index [45], which highlights the importance of orexin in maintaining normal sleep/wake patterns and energy homeostasis. Thus alterations in orexin levels might be related to disordered sleep regulation observed in obese humans and animal models.

A decade ago Levin and colleagues showed that, when exposed to high fat diet, more than half of out-bred Sprague-Dawley (SD) rats developed diet-induced obesity, while the rest of the rats showed resistance to diet-induced obesity [46]. Previously we showed greater spontaneous physical activity (SPA), orexin sensitivity and orexin receptor mRNA in the lateral hypothalamus of these obesity resistant (OR) rats [47]. Relative to OR rats, SD rats had reduced orexin levels, sleep fragmentation, decreased physical activity and became obese with age [48].

Since obesity has been associated with poor sleep quality, obesity resistance might be associated with better sleep quality, characterized by consolidated sleep/wake states.

Sleep/wake patterns in ORR rats have been associated with elevated orexin receptor profiles in brain regions involved the regulation of vigilance states. In some studies have been measured 24h sleep/wake patterns and orexin receptor mRNA profiles in brain sites involved in sleep regulation, in OR and normally obesity susceptible SD rats at three months of age, an age when their weight gain profiles were significantly different. Obesity resistant rats spend greater time awake primarily during the dark phase, have fewer number of and greater duration of sleep/wake episodes, less frequent transitions between different sleep/wake states, and a lower sleep drive.

These results indicate that during the normal active period, OR rats spent more time awake and had better sleep quality than obesity susceptible SD rats. This study lends additional support to our hypothesis that increased orexin signaling in sleep/wake regulatory sites enhances sleep quality and positively influences obesity resistance.

Orexin role in obesity and resting energy expenditure

Orexin system has a primary role in relation to obesity; in fact some pharmacological studies have demonstrated that icv injections of both orexin types have increased food intake and locomotor activity [49–53]. A polygenic obesity model of rats, the obesity-prone (OP) and obesity-resistant (OR) rats, derived by inbreeding from Sprague Daw-

ley rats, has highlighted the importance of the orexin system in obesity: the results were that OR rats show higher basal levels of SPA and OXA-induced SPA after injections into the rostral lateral hypothalamic area (rLH) than OP rats [42,54-56]. Increased sensitivity to the two subtypes of orexin in OR rats is associated to an increased expression of OX1R and OX2R in the rLH compared to OP rats. It is clear that is not the only orexin to regulate body weight and amount of body fat, but also participate in the response to satiety-promoting other modulators such as leptin or insulin and thus contribute to the polygenic obesity observed in OR and OP rats; indeed the two types of rats have different weight gain profiles despite inconsistently differences in energy intake [54, 57–61]. A very important concept closely related to obesity is the energy expenditure, which is positively influenced by orexin. In general, the total energy expenditure (Total Daily Energy Expenditure) is defined by the sum of different components (Figure 5).

The energy expenditure evaluation assumes great importance because gives us the possibility to determine the nutritional and energy needs allowing to establish the energy balance, understood as caloric share necessary to maintain constant the dimension and body composition, to support physical activity daily and to ensure the long-term health.

An important consideration in energy expenditure deserves the spontaneous physical activity (SPA). It is neither a part of basal metabolism nor a part of physical exercise and was defined as a component of energy expenditure [62, 63]. Zurlo et al. [64] showed that levels of SPA are similar between relatives of the same family, could help explain propensity for weight gain in males, configuring the SPA as a hereditary trait. This idea has recently been corroborate by Levine et al., in his study showing that lean humans stand and ambulate for approximately two hours daily more than obese, which is not affected by weight loss or weight gain, in the obese and lean respectively [49]. Although great differences in body fat, energy intake and body size, OR and OP rats consume a similar number of absolute kilocalories [47]. This could mean that OR rats are less efficient in their calorie use, as they are expending a large amounts of calories to support their smaller energy needs. This supports the idea that elevated in SPA in OR rats contrib-

utes to their obesity resistant phenotype. Indeed, it was seen that injections of orexin A in multiple brain sites increase levels of SPA with a consequent increase of the food intake, which should lead to a condition of obesity. Instead, the activation of the orexin system increases energy expenditure and has a protective effect against obesity. To demonstrate this, has been performed studies on rats through the implantation of cannulae into RLH were given graded dose of OXA. After postinjection were measured SPA and food intake and, as expected, the result was that both components increased. At this point OR rats maintained a lean phenotype, suggesting that the negative caloric benefit of OXA-induced SPA appears to outweigh the positive calories due to OXA-induced hyperphagia. Furthermore, other studies have shown that OR rats have higher endogenous SPA and are more sensitive to other SPA-promoting stimuli and appear to be intrinsically protected from treatments that lower SPA, such as high-fat diet feeding. Then, while OP rats manifest lower SPA levels after high-fat diet consumption, OR rats maintain high basal SPA levels and have greater OXA-induced SPA after high fat diet feeding [65]. Finally, it is worth remembering that over the orexin, other neurotransmitters are able to influence SPA levels, such as cholecystokinin, corticotrophin releasing hormone and leptin, but orexin is the most consistent across all brain sites and types of stimulation.

Conclusion

Orexin system leads to an increase of energy expenditure and SPA levels. A fundamental point of this review is the evidence that higher orexin signaling provides resistance to the development of obesity and this is possible through different mechanisms like an increase in synthesis or release of orexin peptides or changes in expression of the orexin receptor. It is important to understand the concept of orexin and its role in obesity resistance to find new therapeutic and preventive solutions against the excess body weight, in fact the stimulation of orexin receptors may be a valid therapeutic approach together with appropriate low-calorie diet, frequent physical exercise and psychological proposal in order to build the foundation for preventive and curative therapy against obesity.

Figure 5: Components of total daily energy expenditure (TDEE). BMR = basal metabolic rate; NEAT = non-exercise activity thermogenesis; TEF = thermic effect of food; EAT exercise activity thermogenesis; REE = resting energy expenditure; NREE = non-resting energy expenditure. Adapted from Maclean et al. [63].

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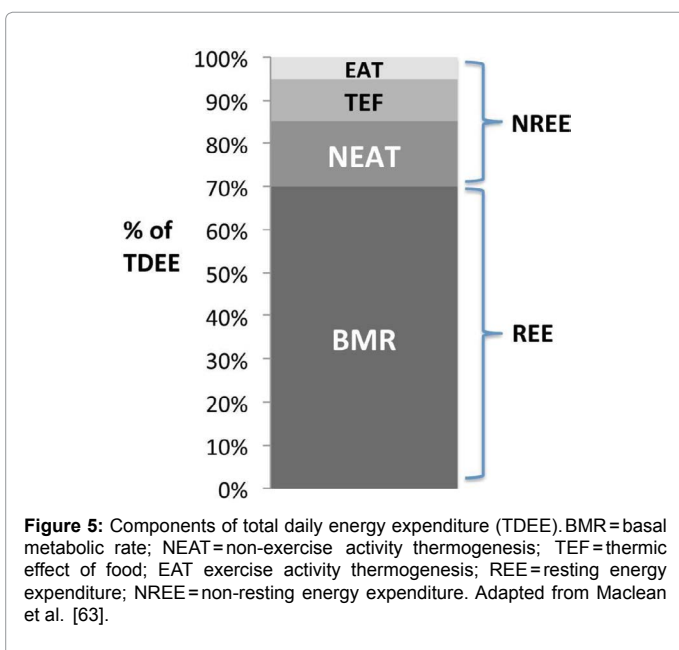
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