Journal of Anesthesia & Clinical Research
ISSN: 2155-6148

Messina et al., J Anesth Clin Res 2014, 5:3
DOI: 10.4172/2155-6148.1000395

Case Report Open Access

Role of Orexin in Obese Patients in the Intensive Care Unit

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Abstract

Understanding the regulation of appetite and energy expenditure mechanisms is essential for the health and disease. The recognition that the distribution of these regulatory mechanisms plays a central role in the pathogenesis of obesity and associated metabolic syndrome is not new, and it is even more interesting to understand what happens in an obese patient in the Intensive Care Unit (ICU). This review focuses on the catabolic role of orexin, which paradoxically coexists with its anabolic feeding-inducing role. The goal of this review is to provide insight into the biological mechanism governing orexin's role in energy expenditure, discuss its significance in the context of ICU. Mammals possess a specialized tissue termed Brown Adipose Tissue (BAT) that expends calories to counteract hypothermia. The ability to enhance energy expenditure by manipulating BAT activity is attractive from a therapeutic standpoint, in light of the discovery of metabolically active BAT in adult humans. The finding of a relationship between BAT and orexins levels suggests new research on the possible roles of orexins in many anomalies of energy expenditure, including those of obese patients in the ICU.

Keywords: Obesity; Orexin; Fat; Energy expenditure; ICU

Obesity is a worldwide public health issue with extensive medical, social, and economic consequences [1,2]. Obesity, which is defined by the presence of excess adiposity, negatively impacts health and increases an individual's risk for developing a variety of medical conditions, including cardiovascular disease, certain cancers, diabetes mellitus and adipogenic differentiation [3-7]. Over the past three decades, the prevalence of obesity has doubled in the USA and in Europe country [8-10]. At present, an astounding two-thirds of the US population is overweight and about one-third, or roughly 100 million Americans, are obese [9,11]. And although the most recent data published in the 2005–2006 update of the National Health and Nutrition Examination Survey (NHANES) suggest that obesity rates have stabilized, others project that the obesity 'epidemic' will only continue to worsen, with as many as 75% of Americans and of Europeans potentially being overweight in the year 2020 [12]. Physicians will undoubtedly encounter obese persons in clinical practice and must, therefore, be able to identify and address care needs specific to this patient population.

In the general population, obesity, defined according to the World Health Organization as a BMI >30 kg/m^2, is associated with increased risk for morbidity, mortality. Coinciding with its increasing prevalence in the general population, the number of obese patients in the intensive care unit (ICU) has steadily increased over the years.

Studies looking directly at the effect of obesity on mortality after admission to the ICU had mixed results. Some investigators found that obese individuals had higher mortality during critical illness [13,14], whereas Ray et al. [15] reported that BMI has minimal effects on ICU outcome after patients are admitted to a critical care unit. It has been reported that obesity did not influence outcomes in critically ill patients requiring invasive mechanical ventilation in a medical ICU. Black obese patients had similar outcomes to black non-obese patients, and very obese patients also had similar outcomes to obese patients [16].

Obesity presents the ICU team with a unique set of challenges. Not only does the greater frequency of comorbid diseases in this population lead to increased complexity of care, but the physical aspect of severe obesity makes routine elements of nursing care and diagnostic/therapeutic interventions extremely demanding. Nutrition support is a key component in managing critically ill patients, with early and aggressive feeding interventions shown to improve outcomes favorably. Like other aspects of care, feeding also becomes complicated in the presence of obesity. Calculating daily caloric needs remains controversial in this population, and other issues, such as difficulty obtaining central venous access, frequently limit the provision of adequate nutrition support. Hypocaloric feeding shows great promise as a mechanism for blunting hyperglycemia while promoting favorable changes in body composition, though this approach has yet to be fully validated.

Understanding the regulation of appetite and energy expenditure mechanisms is essential for the health and disease. The recognition that the distribution of these regulatory mechanisms play a central role in the pathogenesis of obesity and associated metabolic syndrome is not new, and it is even more interesting to understand what happens in an obese patient in the ICU.

Resting energy expenditure (REE) accounts for 60–75% of total daily energy expenditure. Various factors contribute to the inter individual variability in REE such as Free Fat Mass (FFM) [17], sympathetic nervous system (SNS) activity [18,19], and endocrine status (e.g., thyroid hormone [20]). REE decreases with age [21,22]. The age related decline in REE could be due not only to the loss of FFM and an alteration in its metabolically active components, but also to reduction in physical activity. It is well known that the reduction in

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Received February 28, 2014; **Accepted** March 27, 2014; **Published** March 29, 2014

Citation: Messina G, Viggiano A, Tafuri D, Palmieri F, De Blasio S, et al. (2014) Role of Orexin in Obese Patients in the Intensive Care Unit. J Anesth Clin Res 5: 395. doi:10.4172/2155-6148.1000395

physical activity leads to a reduction in REE and a decrease in FFM.

Mammals possess a specialized tissue termed brown adipose tissue (BAT) that expends calories to counteract hypothermia [23]. Although the quantity and importance of the BAT in humans is controversial, the ability to enhance energy expenditure by manipulating BAT activity is attractive from a therapeutic standpoint, in light of the discovery of metabolically active BAT in adult humans [24].

It is hoped that stimulating the calorie burning capacity of BAT in humans will help contravene obesity. A large number of resources have therefore now been mobilized to find safe ways to exploit BAT thermogenesis, resulting in discovery of pathways that can potentially be targeted for therapeutic gain [25-32]. Investigations in our laboratory have led to the discovery of an orexin–BAT axis. This review focuses on the catabolic role of orexin, which paradoxically coexists with its anabolic feeding-inducing role. The goal of this review is to provide insight into the biological mechanism governing orexin's role in energy expenditure, discuss its significance in the context of ICU.

Orexins A and B (also known as hypocretins 1 and 2) are hypothalamic neuropeptides, involved in the regulation of feeding behavior, sleep-wakefulness rhythm, and neuroendocrine homeostasis [33-35]. Orexins promote both waking and feeding [36]. In addition to this central role, orexins probably have peripheral effects. This was suggested by the detection of substantial levels of orexins in plasma [37], as well as the demonstration of orexin receptors in several peripheral tissues, including the gastrointestinal tract, endocrine pancreas, adrenal glands, and adipose tissue [38,39]. Snow et al. [40] have demonstrated that plasma orexin levels are one-fifth to one-eighth of orexin cerebrospinal fluid values. It has been demonstrated that orexin-A influences several physiological variables. An intracerebroventricular (ICV) injection of orexin-A induces an increase in heart rate [41], blood pressure [42], and metabolic rate [43], thus, indicating that this neuropeptide plays a role in the control of vegetative functions. The expression pattern of mRNA encoding two orexin receptors (OX1R and OX2R) in the rat's brain has been demonstrated by Trivedi et al. [44]. Within the hypothalamus, expression for the OX1R mRNA was largely restricted in the ventromedial (VMH) and dorsomedial hypothalamic nuclei, while high levels of OX2R mRNA were contained in the paraventricular nucleus, VMH, and arcuate nucleus, as well as in mammillary nuclei [45]. Lu et al. [46] have showed that levels of OX1R mRNA were significantly increased in the VMH of rats after 20 h of fasting. An initial decrease (14 h) and a subsequent increase (20 h) in OX1R mRNA levels after fasting were observed in the dorsomedial hypothalamic nucleus. Levels of OX2R mRNA were augmented in the arcuate nucleus, but remained unchanged in the dorsomedial hypothalamic nucleus and paraventricular hypothalamic nucleus following fasting. The time-dependent and region-specific regulatory patterns of OX1R and OX2R suggest that they may participate in distinct neural circuits under the condition of food deprivation.

These evidences suggest that the two types of orexin receptors are involved in different responses. In addition, the presence of orexin receptors in other cerebral areas suggests that additional functions are played by orexin-A [34]. A role for the orexins in sleep regulation has been demonstrated [47]. Deficiency in orexin neurotransmission results in the sleep disorder narcolepsy in mice, dogs, and humans [48]. Orexin-A also influences body temperature. In fact, an ICV administration of orexin-A induces an increase in firing rate of the sympathetic nerves to interscapular brown adipose tissue (IBAT), accompanied with a rise in IBAT and colonic temperatures [49]. The simultaneous increase in heart rate and body temperature after an ICV injection of orexin-A indicates a generalized activation of the sympathetic nervous system. Few investigations have been performed on the role played by different cerebral areas involved in the induction of the abovementioned tachycardia and hyperthermia [50-52]. The VMH controls thermogenic responses through the autonomic nervous system. Electrical or chemical stimulations of the VMH increase the temperature of IBAT that is the principal effector of non shivering thermogenesis [53].

Lesions of the VMH reduce the sympathetic activation and thermogenic changes induced by various stimuli [54]. The hyperthermia due to sympathetic and thermogenic ICV injection of prostaglandin E1 is reduced by ibotenate lesion of the VMH [51]. Postingestional thermogenesis is lowered by the VMH lesion [55,56]. This evidence indicates that the VMH is involved in hyperthermic reactions induced by several stimulations [57-59]. Orexin-A may partially mediate pressor response by increasing basal sympathetic activity, causing catecholamine release, modulating the vasopressin system [60], and stimulating renal and adrenal orexin receptors [61]. These speculations are further supported by Shiraska et al.'s study [42], where experimental use of orexin-A has been shown to increase heart rate, renal sympathetic activity, catecholamine release, and mean arterial blood pressure.

Orexins have been shown to adversely affect the plasma lipoprotein profile [62] and insulin glucose homeostasis and to stimulate insulin release from pancreatic cells *in vivo* and *in vitro* [63]. Orexin derangements in patients with narcolepsy were associated with an increased BMI [64] and a higher risk of type-II diabetes mellitus [65]. The influence of orexin-A on sympathetic nervous system activity, blood pressure regulation, and metabolic status may contribute to the upsurge in cardiovascular morbidity and mortality in ICU [15,17]. Further, the finding of a relationship between BAT and orexins levels also suggests new research on the possible roles of orexins in many anomalies involving REE.

BAT thermogenesis contributes significantly to energy metabolism. BAT mitochondria uniquely express uncoupling protein 1 that uncouples adenosine triphosphate synthesis from oxidative phosphorylation [64], liberating energy in the form of heat [65]. The heat dissipation in BAT counteracts cold and weight gain during ICU.

Several studies have investigated the relationship between circulating orexin and fat mass and have demonstrated a strong correlation between low plasma orexin and obesity [66,67]. An important question is whether this naturally occurring biological peptide (orexin) has utility in weight management or obesity treatment. Observations made to Dyan Sellayah suggest that peripherally injected orexin activates thermogenesis, without limiting feeding or increasing physical activity [68]. These encouraging observations have paved the way for clinical testing of the thermogenic potential of orexin [69].

Studies suggest a lower mortality in overweight and obese patients, whereas underweight patients appear to suffer from increased mortality. These observations indicate a possible important metabolic role for adipose tissue during critical illness.

Morphologically, adipose tissue of prolonged critically ill patients reveals an increase in newly differentiated. Functionally, adipose tissue of critically ill patients increases its property to store glucose and triglycerides.

The mechanisms by which orexins modulate glucose metabolism through OXR-1 and OXR-2 binding have not been extensively investigated. Existing evidence suggests that orexins induce glucose

production in the liver [70] and facilitate glucose uptake in skeletal muscle [71]. In addition, orexins A and B have been shown to differentially modulate glucagon release from pancreas [72].

Norepinephrine, which is used in large quantities in ICU patients [73] increases non-shivering thermogenesis and body temperature through stimulation of BAT-activity [53]. Furthermore, there is strict relationship between orexinergic and noradrenergic pathways: norepinephrine reuptake inhibitors are utilized in the therapy of orexin-related narcolepsy [74]. Thus, infusion of norepinephrine in ICU patients could influence the effect of orexin. Since starvation in ICU patients is related to higher mortality, the strategy of therapy should be addressed to avoid body weight loss.

In conclusion, orexin should be considered an important peptide in the regulation of energy expenditure in critic patients too. Pharmacological tools should be studied to modulate the orexinergic system in condition as intensive care unit.

A hypothetical therapeutic approach suggests a possible utilization of orexin receptor antagonists. These drugs should induce not only beneficial effects on REM/non REM sleep (which seems to be important in ICU patients), but also reduction of REE to prevent cachexia.

Neuroleptic drugs, as haloperidol, clozapine, olanzapine, risperidone and quetiapine, can modify body temperature. Haloperidol causes significant attenuation of the normal daytime increase of body temperature [75]. An undesirable effect of clozapine is the hypothermia in patients treated with this drug [76]. Quetapine and olanzapine induce a sudden loss of body temperature control during the neuroleptic malignant syndrome [77,78]. There is evidence showing that both hypothermia [79] and hyperthermia [80] are also affected by risperidone.

These neuroleptic drugs modify the effects of orexin A. Indeed, haloperidol [43] reduces sympathetic and thermogenic reactions induced by orexin A, while quetiapine [81] delays this hyperthermic reaction. Olanzapine [82] and clozapine [83] block, and risperidone [84] enhances the elevation of body temperature due to orexin A. In consideration of these influences exerted by neurolectic drugs on body temperature (including also orexin A-induced thermogenesis), neuroleptic substances should be utilized with caution in ICU patients.

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