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Orexin System Modulates Resting Energy Expenditure, Autonomic Nervous System and Cardiovascular Disease in Menopause

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Abstract

Menopause is a period of significant physiological change that is largely related to estrogen depletion and subsequent cessation of ovarian function. During menopause period, women tend to gain weight and fat mass. It is not clear whether the increase in adiposity is a consequence of the decline in endogenous estrogen. Cardiovascular disease incidence increases with age in women as well as in men, but in women there is an additional increase due to the menopause. Many researches were conducted to assess the contribution of factors such as estrogen depletion, REE decline, and aging to weight gain. An increase in orexin-A plasma levels, paralleling lower estrogen levels, was found during menopause.

The goal of this review is to provide insight into the biological mechanism governing orexin's role in energy expenditure; autonomic nervous system and cardiovascular risk discuss its significance in the context of menopause. Orexins are hypothalamic neuropeptides recently discovered, involved in the regulation of feeding behaviour, sleep-wakefulness rhythm, and neuroendocrine homeostasis. Orexins might offer the missing link between postmenopausal hypoestrogenism and other manifestations of the menopausal syndrome, including appetite and weight changes and increase in cardiovascular risk.

Keywords: Menopause; Orexin; Fat; Energy expenditure; Cardiovascular disease

Introduction

Menopause is a period of significant physiological change that is largely related to estrogen depletion and subsequent cessation of ovarian function. Menopause is defined as a transition period, characterized by the progressive reduction of estrogens and the classically described signs and symptoms. Sex differences in cardiovascular function are well documented and it is generally considered that women are at reduced risk and rate for adverse cardiovascular events compared to men of similar age and health status. These differences diminish for women at menopause when estrogen levels decrease [1].

The combined effect of ageing and the menopause leads to a sharp increase in the risk of adverse clinical outcomes such as incidence and mortality rates for Coronary Heart Disease (CHD), and bone fracture in women. In fact, these two clinical outcomes are related; low Bone Mineral Density (BMD), a risk factor for osteoporosis, has been associated with cardiovascular endpoints.

Cardiovascular Disease (CVD) incidence increases with age in women as well as in men, but in women there is an additional increase due to the menopause. CHD is the leading single cause of death in women in Northern Europe and North America, but these deaths occur at a later age than in men. In addition to the increasing risk for CHD with ageing, the menopause itself produces a further risk superimposed on the effect of ageing [2]. This is due in part to changes in metabolic risk factors and vascular function which are linked to the loss of ovarian function [3]. Indeed, the menopause results in its own metabolic syndrome [4]. Epidemiological studies show good evidence for both primary and secondary preventive effects of Hormone Replacement Therapy (HRT) in women [5,6].

During menopause period, women tend to gain weight and FM (fat mass) [7]. It is not clear whether the increase in adiposity is a consequence of the decline in endogenous estrogen.

Several studies faced the question by using postmenopausal HRT. If the increase in adiposity is a consequence of the decline in endogenous estrogen that occurs at this time, HRT should prevent or reduce body fat gain. However, existing clinical data addressing this issue are discordant. Anderson et al. [8] showed that short-term (2 months) use of HRT did not alter body mass index (BMI), FM, or fat-free mass (FFM) in postmenopausal women [9]. With long-term use (1 year), Reubinoff et al. [10] found a similar increase in body weight and FM among women taking HRT and those who declined its use.

They did, however, observe that there was a significant shift from gynoid to android fat distribution only in women not taking HRT [11]. A decrease in body weigh was found by Espeland et al. [12] over a 3-year period in women taking HRT compared to women not taking HRT. Conversely, other data suggested that oral estrogen might cause an increase in body fat, possibly by limiting lipid oxidation [9,13]. Thus, whether and how hormone therapy affects body composition in postmenopausal women is still unclear. Ovarian hormones may influence body composition through several potential mechanisms. It has been suggested that estradiol inhibits the action of adipose tissue

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lipoprotein lipase, the enzyme that hydrolyzes circulating triglycerides, allowing for the uptake of fatty acids into adipocytes [11]. Data from rodent models indicate that estrogen acts as an anorectic, decreasing voluntary food intake [14]. Further, weight gain in postmenopausal women may depend on an accelerated resting energy expenditure (REE) decline [15,16]. In this regard, it was found that REE declines by approximately 420 kcal/day in postmenopausal women compared with premenopausal women [17].

Adipose tissue distribution and metabolism is dimorphic in humans, with women exhibiting more extensive body fat mass, as well as greater percentage of subcutaneous adipose tissue compared to men [18]. Estrogens have an indirect role in the regulation of appetite and body fat by acting through other tissues that regulate appetite, energy expenditure or metabolism. Estrogen receptors are widely distributed in the hypothalamus, the primary site in the brain that regulates energy balance, and the effects of estrogens on both energy intake and expenditure are well known [19].

The increase of visceral adipose tissue, occurring in women 3-4 years prior to menopause, correlates with circulating decreasing estrogens and with concurrent increasing serum FSH. These changes have been related to the changes of adipose tissue metabolism. Estrogens influence adipose tissue lipoprotein lipase activity and increase lipolysis [20]. Estradiol can indirectly affect lipolysis by inducing the lipolytic enzyme hormone-sensitive lipase or by increasing the lipolytic effects of epinephrine [21]. Interestingly, it has been shown that estradiol administration attenuates lipolytic response in subcutaneous abdominal adipocytes, but not in adipocytes isolated from the visceral fat depot [22]. On this line estrogens attenuate the lipolytic response through upregulation of the antilipolytic alpha2A-adrenergic receptors only in subcutaneous and not in visceral fat depots and effect which disappears in the menopausal period [22]. On the other hand, a recent longitudinal study in a limited number of menopausal women showed an overall increase of total abdominal fat (both subcutaneous and visceral) without preponderance of visceral fat accumulation [23]. Evidence indicates that estrogens and adipose tissue estrogen receptors are involved in the regulation of energy metabolism pathways from glucose transport to glycolysis [24].

This review reports evidences showing that the orexin modulates REE, autonomic nervous system, and CVD in menopause.

Energy Homeostasis

REE is the main component of daily energy expenditure, accounting for 60-70% of the total energy expenditure in most individuals. Measurements of REE by indirect calorimetry are becoming increasingly popular, because indirect calorimeters are more widely available. REE is influenced by various variables, such as height, weight, gender, health status, and age. Indeed, REE varies during one's life span. It declines during childhood growth and also with advanced age. The age-related decline in REE could be due to the loss of FFM and an alteration in its metabolically active components [25]; however the decline in REE with advancing age cannot be totally due to changes in body composition [26]. Furthermore, studies using doubly labeled water indicated that individuals with higher than recommended BMI ≤ 25 kg of body weight/m^2 of height have a high absolute total energy expenditure compared to individuals with lower BMI [27,28]. It is well known that the reduction in physical activity leads to a reduction in REE and a decrease in FFM. The decline in REE observed in postmenopausal women may depend on aging.

However, REE seems to decrease more during the menopause transition than could be attributed to the aging process [26]. Estrogen depletion probably contributes to accelerated REE decline. Experimental evidence showed that estrogen increases physical activity-related energy expenditure [27,28]. During the menopause transition, the decrease in REE accelerates the gains in FM which, in turn, may contribute to increasing the incidence of obesity-related diseases such as a worsening of cardiovascular risk profile [2,29] and type II diabetes [18]. Also, estrogen depletion by itself seems to increase cardiovascular risk [30-32]. Staessen et al. [33] observed that the incidence of hypertension was significantly higher in hypoestrogenic postmenopausal women when compared with women receiving HRT, after adjustment for age, race, and weight. Comparable findings were reported by Vongpatanasin et al. [34] and Weitz et al. [35] in their studies, concluding that HRT lowered diastolic blood pressure in postmenopausal women. Regarding the metabolic variables evaluated, it was found that postmenopausal women not receiving HRT had significantly higher plasma cholesterol and triglyceride levels than reproductive-age women, but, more importantly, the levels were also higher than in those receiving HRT [36].

The awareness that the distributions 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 menopause. Therefore is extremely important for the health and disease to understand appetite regulation and energy expenditure mechanisms.

Orexins

Orexin A and orexin B (also called hypocretin 1 and hypocretin 2) were first identified in 1998 by two separate groups via two different approaches [37]. The term orexin is derived from the Greek word "orexis," meaning "appetite."

Orexins play an important part in the regulation of food intake, body weight and energy metabolism [38-40]. It was found that orexin levels were down-regulated in the hypothalamus of obese rodent subjects [41-44]. In addition, clinical, decreased plasma orexin-A (OX-A) levels in obese individuals were also reported [45-47] and lower OX-A plasma levels were increased during body weight loss [48]. However, these reports showed contrary results. Higher plasma OX-A levels were found in obese individual [49], and could not be decreased by reduction in body weight [50]. These controversial clinical and animal studies showed orexin was closely associated with obesity. Orexin was known to increase food intake [51] and chronic intracerebroventricular administration of OX-A to rats increased food intake in daytime [52].

Accordingly, it was seemingly paradoxical that OX-A, as a matter of fact, acts to decrease body weight in this study [53]. Orexin was able to increase food intake, however, it also robustly increased the physical activity levels and energy expenditure at the same time. In addition, orexin was suggested to maintain a long, consolidated waking period that facilitated search and intake of food which is essential for an animal's survival [54]. Furthermore, it has been suggested that orexins could physiologically stimulate sympathetic outflow since intracerebroventricular (ICV) orexin injections increase blood pressure and heart rate, and these effects are abolished by the administration of drugs that block α or β-adrenoceptors [55]. As a result, it is reasonable that genetic ablation of mice's orexin neurons lead to obesity although eating less [56] and narcolepsy patients have a decreased caloric intake but an increased body mass index [57,58].

OX-A and orexin B (OX-B) are hypothalamic neuropeptides, derive from the prepro-orexin (preprohypocretin) gene, which encodes a precursor (130 amino acids in rodents, 131 residues in humans) that is cleaved into OX-A (synonymous with hypocretin-1; 33 amino acids) and OX-B (hypocretin-2; 28 residues).

Mammalian (human, pig, dog, rat, mouse) prepro-orexin, composed of 130–131 amino acids, is highly conserved with 75% amino acid sequence identity. The human prepro-orexin gene is localized on chromosome 17q21. The mRNA of this precursor is abundantly and specifically expressed in the lateral hypothalamus and adjacent areas important in the central regulation of feeding behavior and energy homeostasis [59].

Orexin A is a 33-amino acid peptide of 3562 Da. It consists of an N-terminal pyroglutamyl residue, two intramolecular disulfide bridges between Cys^{6}-Cys^{12} and Cys^{7}-Cys^{14}, and a C-terminal amidation. The primary structure of orexin A is completely conserved among several mammals (human, rat, mouse, dog, cow, sheep, and pig). On the other hand, Orexin B is a 28-amino acid linear peptide of 2937 Da with a C-terminal amidation. Human orexin B differs by one amino acid from pig and dog orexin B and by two amino acids from rat and mouse orexin B. Orexin B shares 46% sequence identity with orexin A. The similarity in amino acid sequence lies mainly in the C-terminus, whereas the N-terminal half is more variable. The free N-terminal can be related to the rapid metabolism and shorter action of orexin B as compared to orexin A. In contrast, post-translational modifications of both termini and two intrachain disulfide bonds may render orexin A more stable and readily available in CSF. Orexin A also shows higher lipid solubility than orexin B which makes it more blood–brain barrier permeant [60].

These peptides cooperate with two G-protein-coupled receptors, orexin receptor-1 (hypocretin receptor-1) and orexin receptor-2 (hypocretin receptor-2). The orexin receptor- 1 selectively binds orexin A 100 times more avidly than orexin B, which is bound preferentially to the orexin receptor-2. It has been observed that in postmenopausal women, plasma OX-A levels were significantly higher, paralleling the significantly lower estrogen levels [36]. This aspect was found by El-Sedeek et al. [36] who assessed plasma orexin-A levels and estradiol in a group of postmenopausal women not receiving HRT and compared the values with a group on HRT and a group of reproductive-age women. The results showed that postmenopausal women not receiving HRT had the highest levels of plasma OX-A. Conversely, postmenopausal women on HRT had orexin-A levels that were comparable with the control group. However, it should be noted that the determination of plasma OX-A levels presents evident difficulties being such levels extremely low.

Further, the authors found that plasma OX-A levels were directly correlated with some cardiovascular risk factors, namely, blood glucose, and lipid profile, arterial blood pressure (ABP), and BMI. It has been suggested that plasma OX-A levels parallel plasma estradiol levels as orexin is a central metabolic fuel detector, and physiological mechanisms that control energy balance are reciprocally linked to those that control reproduction. Further, OX-A seems to play an important role in the control of the hypothalamic pituitary-gonadal axis [61], and gonadotropin releasing hormone neurons in the hypothalamus have been found to be receptive to orexin modulation [62]. Experimental evidence suggests a mutual regulation of orexin and sexual steroids secretions. It has been reported that ICV administration of OX-A stimulates LH secretion in castrated female rats primed with estradiol and progesterone and inhibits LH secretion in unprimed rats. This dual effect may be due to a steroid regulation of the orexin receptors in selected areas, as the hypothalamus and the adenohypophysis [63,64].

Role of Obesity and Metabolic Syndrome in Postmenopausal

Obesity is a condition defined by a chronic excess of body fat [65] and is positively correlated with shorter life expectancy, metabolic syndrome, type 2 diabetes, and CHD [66]. Obesity has become a public health issue, as its incidence in adults and children has increased in the last two decades across both developed and underdeveloped societies [67-69].

Obesity has been shown to increase after surgical menopause and to be increased in women who started HRT within 12 months of amenorrhea [70]. These investigators also found that the incidence of obesity in women is associated with increases in free androgen index and reductions in sex hormone binding globulin. There is also evidence that even if women do not gain additional weight after menopause, there is a redistribution of body fat favoring an increase in abdominal fat gain rather than lower hip weight gain [71]. Weight that accumulates in the abdominal area is associated with a higher incidence of cardiovascular disease than weight that is accumulated in the lower body [72]. The mechanisms by which weight gain or obesity cause hypertension are not clear.

Increased body weight due to increased fat feeding in dogs increases BP that is prevented if the renal nerves have been severed [73], suggesting a Sympathetic Nervous System (SNS) influence on the increase in BP with weight gain.

Whether body weight alone or the combination of obesity and parameters of the metabolic syndrome, such as insulin resistance, hyperglycemia, hyperlipidemia, and hypertriglyceridemia, increase the risk of cardiovascular and renal disease and contribute to increased BP as well is controversial. Comparison of data from the Framingham Offspring, Atherosclerosis Risk in Communities, and Cardiovascular Health cohorts over more than 8 years, showed that abdominal obesity alone in these cohorts was not significantly associated with increased risk (odds ratio) of cardiovascular disease [74]. However, inclusion of 1-2 parameters of metabolic syndrome and diabetes did significantly increase the odds ratio of contracting cardiovascular disease in both men and women, suggesting that the presence of metabolic abnormalities and diabetes are more indicative of CVD risk than abdominal obesity alone.

Therefore the importance of maintaining body weight in mid-life cannot be underestimated for women where age, menopausal status and BMI are risk factors for CVD. Hodson et al. [75] have shown that an equal BMI and waist circumference in post- compared with premenopausal women is associated with a significantly lower REE and a tendency for lower energy intake. However, the maintenance of BMI in this way has the potential for compromised bone health in postmenopausal women; postmenopausal women spent less time performing moderate exercise and this was associated with a lower BMD. However, the main lifestyle determinant of BMD in postmenopausal women was dietary fatty acid composition (lower dietary n-6:n-3 ratio) and for premenopausal women, REE predicted BMD.

The Role of Orexin in Cardiovascular Function and Sympathetic Nervous System

The distribution of orexins, and orexin receptors, in the

cardiovascular regulatory centers, as well as functional studies indicate a crucial role of orexin in the regulation of autonomic function.

The SNS plays a crucial role in the regulation of circulation and BP [76-78], and many neuronal groups in the lateral hypothaluamus and brainstem are critically involved in such regulation. It is known, that in vivo, electrical or chemical stimulation of the perifornical nucleus of the hypothalamus increases BP and heart rate (HR) and activates neurons of the lateral paragigantocellular area [79,80]. Soon after orexin and orexin receptors were discovered in 1998, many studies started to examine if orexin in the lateral hypothalamus participation in the regulation of cardiovascular and sympathetic functions [54,81,82]. In vitro, orexin in a dose-dependent manner depolarizes neurons that are involved in the regulation of blood pressure and sympathetic nerve activity (SNA), e.g., neurons in the hypothalamic paraventricular nucleus and the rostral ventrolateral medulla [83-85], as well as spinal cord sympathetic preganglionic neurons [86]. In both anesthetized and unanesthetized normotensive animals, central administration of OX-A or OX-B activates sympathetic activity and increases both ABP and HR [54,82,86-93]. In conscious rats and rabbits [81,82,94] central administration (ICV) of orexin increases ABP [54,82], and SNA [81,82] in a dose dependent manner, and the increased ABP, HR and SNA induced by orexin is accompanied by an increase in plasma catecholamines [81,82]. Intravenous injection of a ganglionic-blocking agent, pentolinium, can abolish OX-A induced increases in ABP and plasma epinephrine concentrations, which suggests that the pressor response induced by the ICV injection of OX-A can be attributed primarily to enhanced sympathetic outflow [82]. Other studies also directly and indirectly support orexin's role in the regulation of blood pressure and SNA, e.g., intrathecal injection of OX-A elicits a dose-dependent increase in ABP, HR [86,92], and sSNA [92], and the effects can be partially attenuated by either β-adrenergic or α-adrenergic receptor antagonists [86] in anesthetized rats. Microinjection of OX-A into the medullary raphe significantly increases ABP, HR, and body temperature in unanesthetized rats [95]. It is well known that orexins are excitatory neuropeptides that also promote locomotion such as chewing and grooming [81,96,97]. To exclude the possible effects of increased locomotion on the changes in ABP, HR and SNA induced by the exogenous orexin in conscious rats, Shirasaka et al. [81] injected OX-A ICV in both anesthetized and conscious rats and tested them under the same experimental conditions. They found that OX-A induced a similar significant increase in ABP, HR and SNA in both anesthetized and conscious conditions in these rats [81], which suggests that the sympatho-excitatory effects induced by exogenous orexin in the cortico-spinal neurons are not due to the activation of locomotion. Also orexin is involved in the cardio-respiratory responses to acute stress, e.g., panic and fear [98-102].

Physiological evidence indicates that orexins affect ventilation. Icv administration of orexin increases breathing frequency and tidal volume [103]. In addition, microinjection of orexin A into the pre-Bötzinger complex and microperfusion into phrenic motoneurons results in the increase of diaphragm electromyographic activity [104]. Furthermore, Shahid et al. [105] looked at the direct effects on phrenic nerve activity (PNA) following microinjection of orexin A into the RVLM. Orexin A in the RVLM causes a long lasting increase of PNA, and the effect is attenuated by OX_1R antagonist and reproduced by OX_2R agonist [105].

Conclusion

The orexin system, like other neuropeptidergic systems, exerts integrated control of homeostasis and adaptive responses via widespread projections to the paralimbic cortex, amygdala, hypothalamus, and brainstem autonomic nuclei. Whereas the activity of orexin neurons is fundamentally dependent on sleep wake state, studies on animal models indicate that the orexin system is not only involved in arousal and sleep state stabilization, but also in control of cardiovascular function, thermoregulation, and energy metabolism via the autonomic nervous system [106]. Carefully controlled clinical studies on patients, like the ones described above, may provide further insight into the involvement of the orexin system in autonomic control both in normal physiology and inmneurologic psychiatric disorders and menopause.

This feedback loop between estrogens and orexins might open the door for further research, particularly in stress-induced derangements and those involving abnormalities in feeding energy homeostasis. Orexins might also offer the missing link between postmenopausal hypoestrogenism and other manifestations of the menopausal syndrome, including appetite and weight changes, sleep disturbances, vasomotor symptoms and increased cardiovascular risk profile.

The current trends of weight loss strategy development include the concepts of patient clinician interaction and of multidisciplinary approach. Epidemiological surveillance of obesity should be refined in order to provide evidence about critical points in life, especially childhood, pregnancy and menopause. The advent of menopause, a critical stage in every woman's life posits not only health concerns, but also the question of quality of life, a key concept in geriatric medicine. The clinician should actively challenge the so-called 'obesogenic' environment through an effort to strategically build correct dietary habits and structured exercise programmes. Furthermore, the effort should be persistent in order for weight loss to be maintained. Patient follow-up should exceed the standard proposed two years and it should include lifelong strategic planning.

This review emphasizes aspects regarding the complex relationship between the autonomic nervous system and body weight, and cardiovascular risk in menopause. These findings could be useful in the elucidation of pathologic mechanisms related to feminine obesity. In conclusion, orexin should be considered an important peptide in the regulation of energy expenditure, cardiovascular risk in menopause too. Pharmacological tools should be studied to modulate the orexinergic system in condition as menopause.

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