The Oxytonic Contraction

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The oxytonic contraction: in our model of cold stress, the extreme low temperature increases Oxytocin receptor (Oxtr) in PVN and at the tissue levels in the soleus muscle but drive the decrease of Oxytocin (Oxt) in plasma. The increase of Oxt in bone balance the decrease of plasmatic Oxt. This mechanism triggers the oxytonic contractions that potentiate the slow-twitch muscle to ensure the proper physical reaction to challenging situations.

Keywords: Oxytocin ; Oxytonic ; Skeletal muscle ; Prader Willy Sindrome ; Cold Stress ; Bone ; Brain ; Contraction

1. Cold Stress Triggers the Oxytonic Contraction

Oxt regulates the physiological adaptation of the organism to challenging stimuli [1][2]. The lack of Oxtr leads to impaired thermogenesis with decreased core body temperature after acute exposure to cold [3]. Thermogenic challenge highlights c-Fos immunoreactivity of Oxt neurons in PVN [4]. Expression of c-Fos, or other immediate early gene products, by specific neurons is used as a marker of cell activation, making staining of these proteins a useful technique for functional anatomical mapping of neuroendocrine systems, such as Oxt, in response to specific stimuli [5]. Normal cold-induced thermogenesis was rescued in Oxtr−/− mice by reinserting Oxtr in hypothalamus with an adeno-associated virus-Oxtr vector [6].

Since Oxt is involved in thermoregulation, which is essential in energy balance and in the etiology of obesity [7], we measured the mRNA levels of Oxt and Oxtr in brain, bone, and brown adipose tissue of mice exposed to short time 6 h (6 h) and 5 days (5 d) cold stress (CS).

The evidence that Oxtr is upregulated consistently after short- and long-term CS in brain suggests that Oxt plays a main role in this tissue in response to CS challenge. Gene expression analysis shows that Oxt mRNA is upregulated in bone after 5 d CS, this indicate that Oxt is adaptive and important in restoring the homeostasis of the body in brain and bone. *Oxt* gene significantly decreased in BAT after 6 h CS but increased in bone after 5 d, supporting the concept that Oxt modulates energy and bone [1][8][9][10]. Oxt regulates the coordinated gene response to the paradigm of CS possibly acting as a master gene [1].

Interestingly, CS challenge for 6 h induced a significant increase of food intake in cold-stressed mice vs control mice but no changes in abdominal fat pad and body weight of the animals was observed. After a longer cold exposure for 5d, the abdominal fat pad weight was significantly decreased while food intake was enhanced by threefold in cold-stressed mice vs control mice. After an initial drop of body weight, it returned to control values. This means that cold-stressed mice are in good health and regained their body weight. The enhancement of food intake following CS is linked to Oxt signaling in brain as this factor is involved in the regulation of food consumption [1][11]. For example, Oxt levels in plasma decreased in obese mice after high-fat diet but increased in synaptotagmin-4-deficient mice, which protects against diet-induced obesity [12].

The evidence that Oxt KO mice develop obesity and impaired cold-induced thermogenesis without a change in food intake suggests that the lack of Oxt may reduce metabolic rate [3][4][8]. Nevertheless, administration of central Oxt reduces food intake in rats, an effect that is reversed by Oxt antagonist implying that Oxt may regulate appetite and energy intake [13][14][15].

Oxtr regulates the coordinated gene response to CS through a feed-forward loop in brain [16]. This is supported by the fact that in a regression study upon elimination of Oxtr expression gene data in brain, we report a loss of correlation in gene expression of mice at thermoneutrality versus gene expression of cold-stressed mice [1].

2. Oxytonic in Skeletal Muscle Physiology

Understanding of Oxtr regulation in metabolically active tissues and outside of pregnancy is of interest since the peptide displays potential antiobesity properties [17]. Recent studies have demonstrated a growth-regulating effect of Oxt mediated by Oxtr in different cell types like myoepithelial cells in mammary gland and uterine smooth muscle cells [18][19][20]. Oxtr is the unique receptor subtype expressed in a clonal culture of human myoblast and its activation by agonist binding stimulates the rate of myoblast fusion, and Oxt appears to be a paracrine/autocrine agent that might regulate the differentiation of human skeletal muscle cells. *Oxt* gene is also expressed by cultured myoblasts which suggests the presence of an intrinsic Oxt/Oxtr system [21]. Oxt appears to be a paracrine/autocrine agent that might regulate the differentiation of human skeletal muscle cells.

Even phenotypically diverse skeletal muscles show similar regulation of Oxtr in obese phenotype, suggesting a direct effect on these organs [22]. Interestingly, Oxtr is differentially expressed in various tissues according to the degree of obesity [17]. Elevated Oxtr protein determined by immunoblot was observed in epididymal adipose tissue of obese Zucker rats but was downregulated in subcutaneous fat with no change in retroperitoneal fat. In lean control, Oxt expression showed no changes between fat depots analyzed [22]. Differently in skeletal muscle, fiber type composition are determinants of Oxtr expression. In the skeletal muscle, the variation in Oxtr levels in quadriceps and soleus is related to fiber type composition and reflects different metabolic characteristics that exist among individual skeletal muscles [18][20]. An independent study showed that while quadriceps is highly oxidative in nature due to high mitochondrial content, soleus exhibits a more glycolytic phenotype [18]. This means that Oxt action in skeletal muscle is also associated with regulation of glucose other than lipid metabolism. Oxt is an age-specific circulating hormone, the absence of age-dependent changes of Oxtr in skeletal muscle is consistent with data obtained from gastrocnemius muscle [17]. In addition, cardiac muscle is an Oxt target organ [17][23]: Oxt is involved in the activation of cardioprotective mechanisms, inhibiting the development of hypertrophy, fibrosis, and inflammation in the myocardium, and Oxtr is expressed in cardiac muscle. A recent study showed that an animal model with leptin receptor defect, db/db mice, produces a state of obesity associated with reduced expression of cardiac Oxtr. Chronic treatment with Oxt prevents cardiomyopathy associated with obesity in these mice independently of hyperglycemia and hyperinsulinemia which suggests that Oxt has a direct effect on the cardiac muscle prioritized to obesity [24]. These data are consistent with our hypothesis of a direct effect of Oxt on skeletal muscle and heart that come prior to the effect on metabolism and food intake.

3. Oxytonic in Human Studies

Interestingly, studies on human subjects support the concept that low Oxt levels are associated with a loss of “body tonicity” [3][8][11][25]. For instance, in a cohort of overweight or obese African American veterans, urinary Oxt levels were associated with measures of glycemic status with higher value favoring a healthier metabolic phenotype. Moreover, several interesting associations in the cohort were observed with low Oxt being associated with increased impulsiveness and difficultness in social interactions. The levels of serum Oxt in obese subjects were also lower than those in normal weight subjects. Serum Oxt levels are negatively correlated with different metabolic parameters such as total cholesterol and triglycerides among others [12][26]. The mechanisms underlying decreased Oxt levels in obesity and T2DM remain unknown. This study on human subjects is limited by its cross-sectional design and does not explain the physiological reason of low plasma Oxt in the metabolic syndrome [27]. Nevertheless, a similar study in obese and diabetic children confirms the concept that low Oxt characterizes this metabolic profile. Serum Oxt level was significantly decreased in obese children compared with controls and also lower in obese children with metabolic syndrome compared with those without. These studies in children are consistent with those on adult subjects. Oxt level in obese children is inversely proportional to the severity of metabolic phenotype. Decreased Oxt levels lead to impaired thermoregulation and increased food consumption in obese children [28].

Both adipose and muscle tissue contribute to the establishment of metabolic phenotype. Young female athletes are considered in a higher energy expenditure state than nonathletes. Oxt is a signal for energy availability and is associated with other measures of energy homeostasis in young athletes. Oxt secretion is positively correlated with measures of energy availability as weight and body mass index and energy expenditure in amenorrheic athletes, that is considered the highest energetic state. These subjects have a higher lean mass and skeletal muscle functionality than eumenorrheic athletes or nonathlete consistent with our hypothesis that Oxt augments the muscular functions. Interestingly, no significant relationship was shown between Oxt levels and energy measures in nonathletes young women [15][29].

However, postprandial peripheral Oxt levels in females are lower compared to fasting levels of Oxt independently of menstrual cycle or meal size because endogenous Oxt levels are a satiety signal and Oxt plays a role in the regulation of food intake [30].

Amenorrheic athletes in whom nocturnal levels of Oxt are lower than in eumenorrheic athletes or nonathletes showed impaired bone microarchitecture at the tibia and radius, particularly at the nonweight-bearing radius, although these evidences can be biased by the low estrogen levels of amenorrheic athletes since estradiol stimulates Oxt secretion [31]. Oxt KO mice show high bone mass consequent to the obesity and high leptin, while only intraperitoneal administration of Oxt may be anabolic to bone for its tissue-specific effects [9][32][33]. Recent studies show that Oxt increases acutely in male and female athletes after intense/endurance training, showing, e.g., an evident increase in Oxt plasmatic levels after marathon [34][35][36].

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