

## Neuroleptic Drugs Affect Sympathetic and Thermogenic Reactions to Orexin A

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### Abstract

This review of our literature describes the effects of many neuroleptic drugs on the sympathetic and hyperthermic reactions due to orexin A, a neuropeptide affecting body temperature and food intake by an increase in sympathetic activity. Haloperidol reduces, while clozapine and olanzapine block the hyperthermia induced by orexin A. Risperidone enhances the elevation of body temperature due to orexin A. Quetiapine delays these hyperthermic effects. The implications on human therapeutic strategies are discussed, including the involvement of orexinergic pathway in the induction of obesity, induced by these neuroleptic substances. We summarize our published data in a unique report so to emphasize the influences of these neuroleptic drugs on the control of body temperature, exerted by orexinergic system. This large vision could be also useful to address therapeutic choices.

Patients with serious mental illness are at higher risk of developing metabolic abnormalities (e.g., weight gain, increased blood pressure, and glucose or lipid levels) in comparison to general population. Since the risk increases following initiation of narcoleptic therapy, it must assess carefully risks and benefits when choosing a particular antipsychotic drug.

**Keywords:** Narcoleptic drugs; Orexin A; Sympathetic activity; Body temperature; Body weight

### Introduction

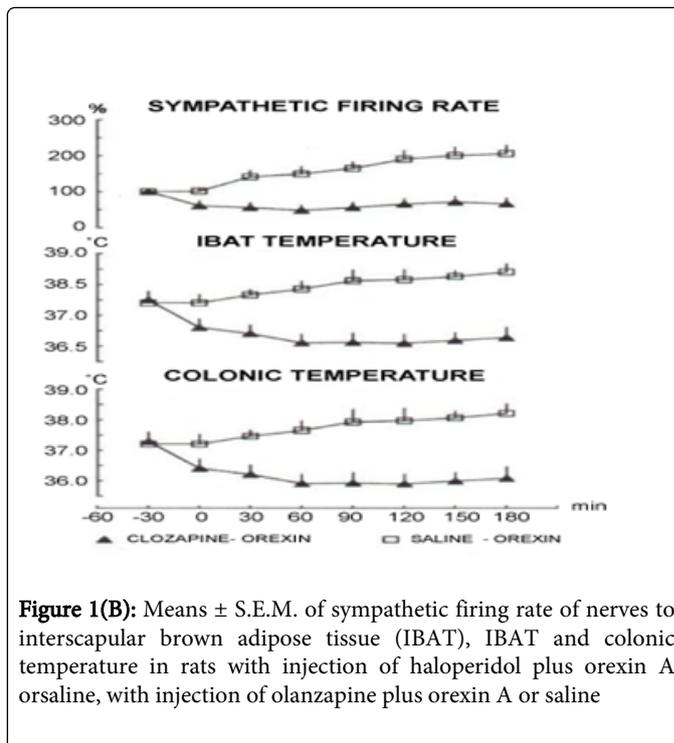
A neuropeptide takes the name of orexin A since this peptide affects food intake [1-3]. Orexin A is synthesized by neurons located in the lateral and perifornical regions of the hypothalamus. Orexin neurons have extensive connections with the prefrontal cortex, limbic structures, hypothalamus, and brainstem, including areas involved in control of arousal, reward mechanisms, and autonomic control, and exert a primarily excitatory effect on neuronal activity via orexin receptors [4]. Orexin A does not influence only food intake, but this peptide also causes an enhancement of heart rate [5], blood pressure [6], and metabolic rate [7,8]. These vegetative changes suggest that orexin A controls many autonomic functions. This peptide also exerts an influence on body temperature. When orexin A is injected intracerebroventricularly, there is an activation of the sympathetic firing rate of nerves to interscapular brown adipose tissue (IBAT). This activation is associated to an elevation of IBAT and colonic temperatures [5]. The contemporaneous tachycardia and hyperthermia after an icv injection of orexin A suggest a generalized stimulation of the sympathetic nervous system. Tonically active sympathetic premotor neurons in the rostral ventrolateral medulla project to the intermediolateral cell column of the spinal cord and provide an excitatory input to sympathetic preganglionic neurons so as to maintain the resting level of sympathetic vasomotor tone [9]. The rostral ventrolateral medulla is the key site for cardiovascular homeostasis. Orexin A-immunoreactive neurons in the lateral

hypothalamus project to the rostral ventrolateral medulla. Microinjection of orexin A into the rostral ventrolateral medulla increases blood pressure and heart rate [10]. In the study by Tupone and colleagues, anatomical tracing and orexin immunohistochemical localization were combined with *in vivo* electrophysiological techniques to elucidate a central neural pathway through which orexin neurons influence IBAT thermogenesis and energy expenditure in rats. Viral retrograde tracing from IBAT and cholera toxin retrograde tracing from the rostral raphe pallidus indicated that a population of orexin neurons in the perifornical region of the lateral hypothalamus is synaptically connected to IBAT via a direct projection from the perifornical region of the lateral hypothalamus to the rostral raphe pallidus. The connection from the perifornical region of the lateral hypothalamus to neurons in the rostral raphe pallidus is important because the rostral raphe pallidus contains sympathetic premotor neurons whose excitatory drive to IBAT sympathetic preganglionic neurons in the thoracic spinal cord determines the sympathetic outflow to IBAT and, in turn, the level of IBAT metabolism and thermogenesis.

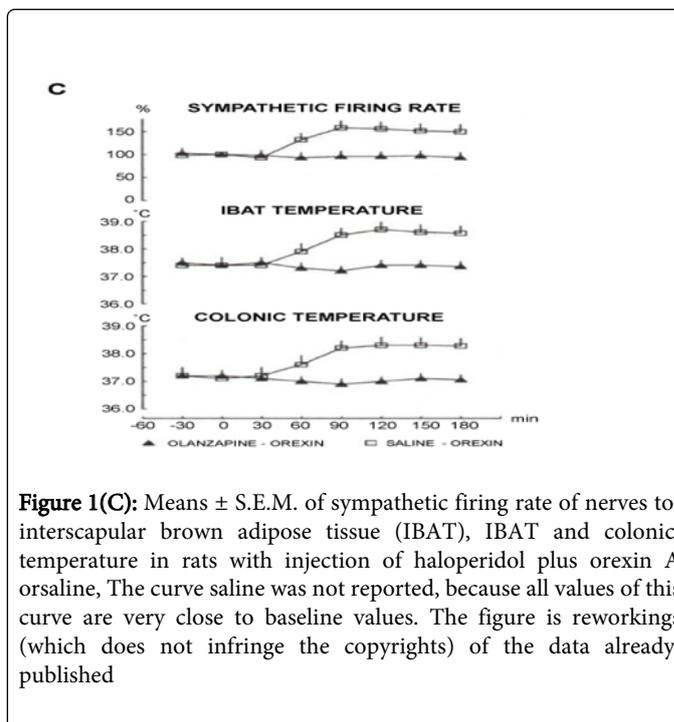
Furthermore, many cerebral areas express orexin receptors. This indicates that orexin A controls various functions [11,12] including regulation of sleep/wake cycle [13]. Neuroleptic drugs, as haloperidol, clozapine, olanzapine, risperidone and quetiapine, can modify body temperature, as showed by various experimental models [14-19]. In the present mini-review, we summarize our published data in an unique report so to emphasize the influences of these neuroleptic drugs on the control of body temperature, exerted by orexinergic system.

## Experimental Evidences

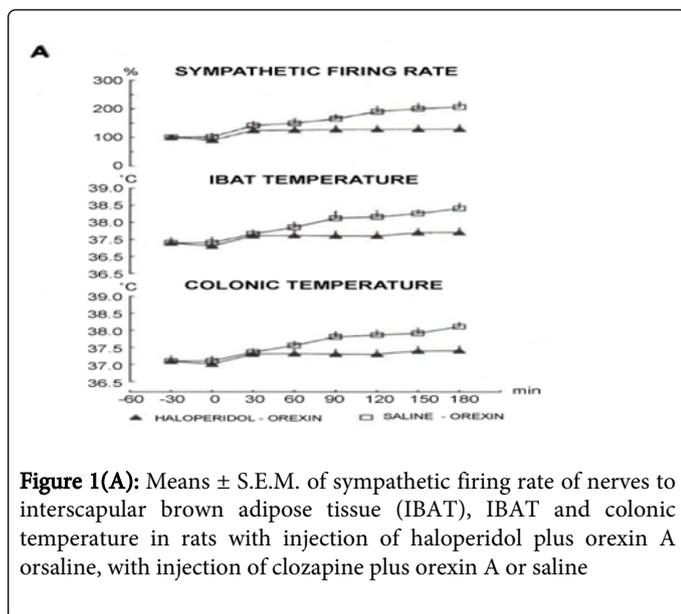
In this section, five our experiments are described in sequence. The sympathetic discharge of nerves to interscapular brown adipose tissue (IBAT), IBAT temperature and colonic temperature were registered in male Sprague-Dawley rats (anesthetized with urethane) before an intracerebroventricular administration of orexin A (1.5 nmol) and during a period of 180 min after this administration. The same variables were registered in rats with an intraperitoneal injection of one of these neuroleptic substance: haloperidol (1 mg/kg bw), clozapine (8 mg/kg bw), olanzapine (10 mg/kg bw), risperidone (50 mg/kg bw), quetiapine (5 mg/kg bw). Haloperidol reduces the hyperthermia and sympathetic activation due to injection of orexin A. These effects are illustrated in the Figure 1-A. Clozapine and olanzapine block the increases in the sympathetic firing rate, IBAT and colonic temperatures induced by orexin A, as reported in the Figure 1-B and 1-C. Risperidone enhances the effects of orexin A, as shown in the Figure 2-A while quetiapine delays the effects of the effects of orexin A on the sympathetic discharge, IBAT temperature and colonic temperature. These delayed effects are shown in the Figure 2-B.



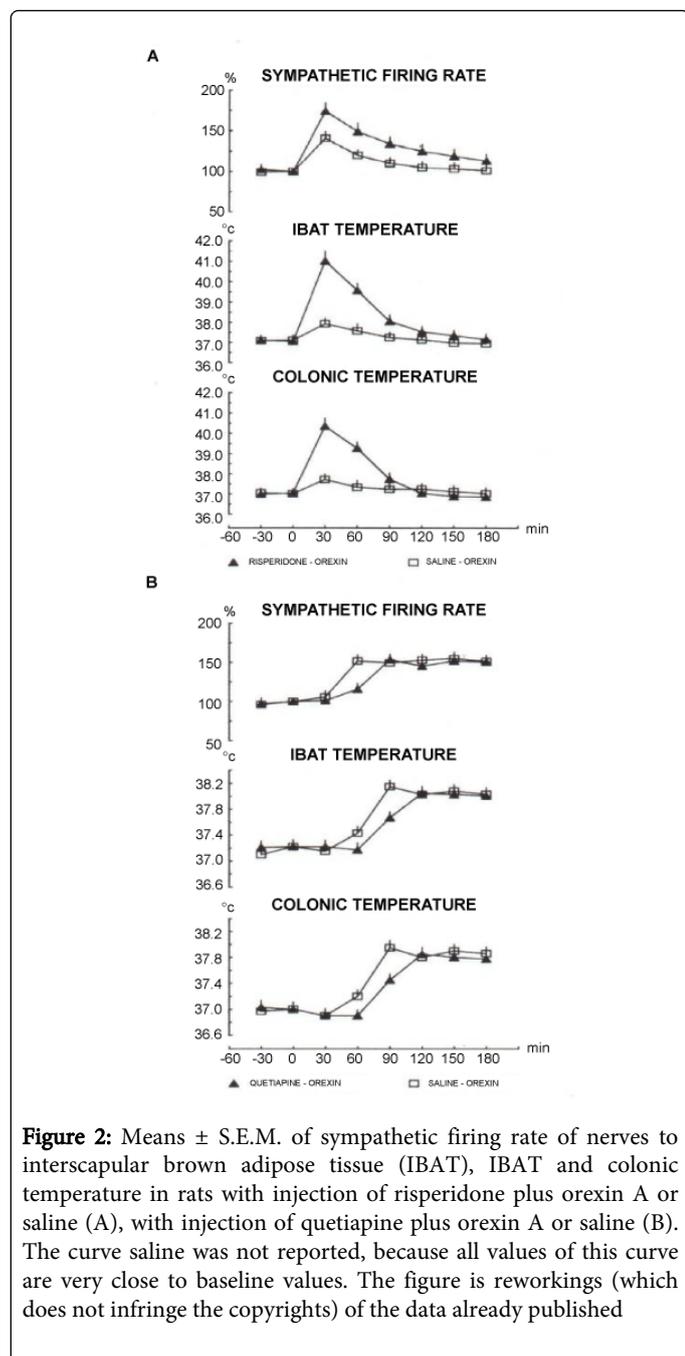
**Figure 1(B):** Means  $\pm$  S.E.M. of sympathetic firing rate of nerves to interscapular brown adipose tissue (IBAT), IBAT and colonic temperature in rats with injection of haloperidol plus orexin A or saline, with injection of olanzapine plus orexin A or saline



**Figure 1(C):** Means  $\pm$  S.E.M. of sympathetic firing rate of nerves to interscapular brown adipose tissue (IBAT), IBAT and colonic temperature in rats with injection of haloperidol plus orexin A or saline, The curve saline was not reported, because all values of this curve are very close to baseline values. The figure is reworkings (which does not infringe the copyrights) of the data already published



**Figure 1(A):** Means  $\pm$  S.E.M. of sympathetic firing rate of nerves to interscapular brown adipose tissue (IBAT), IBAT and colonic temperature in rats with injection of haloperidol plus orexin A or saline, with injection of clozapine plus orexin A or saline

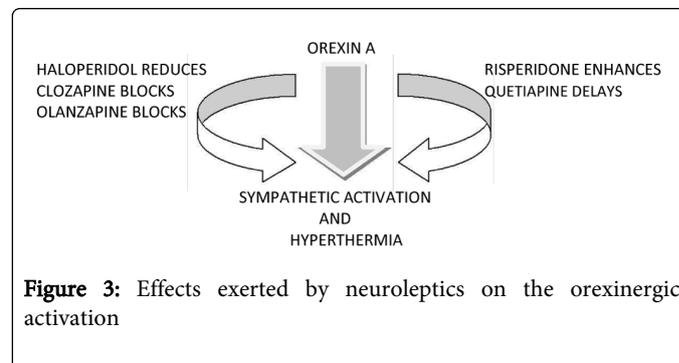


Detailed description of methodological procedure is reported in papers cited in References list.

## Discussion

Haloperidol reduces the sympathetic and thermogenic effects due to an icv administration of orexin A [20,21]. Since the increase in the sympathetic activity induced by orexin A is reduced by haloperidol (antagonist of D2 receptors of the dopaminergic system), an involvement of the D2 receptors can be hypothesized. This indicates that an activation of dopaminergic system could be a possible mechanism of sympathetic and thermogenic stimulation induced by orexin A.

Figure 3 showing the effects exerted by neuroleptics on the orexinergic activation, as reported in five our experiments, which have been already published.



Since clozapine has high affinity for dopamine receptors [22], an involvement of the dopaminergic system can be hypothesized in the block of hyperthermia induced by orexin A [23]. On the other hand, an involvement of serotonergic pathways in the orexin-induced hyperthermia cannot be excluded. Since clozapine is an antagonist of 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors [24,25]. The blockade of these receptors could determine the lack of the hyperthermia due to orexin A.

Furthermore, several laboratories found an even higher affinity for  $\alpha$ <sub>1</sub>-adrenergic receptors [26,27]. Indeed, it was shown that central blockade of  $\alpha$ <sub>1</sub>-adrenergic receptors produces hypothermia [28], and that  $\alpha$ <sub>1</sub>-agonists block the hypothermic effects of clozapine [29]. Then, the central blockade of  $\alpha$ <sub>1</sub>-adrenergic receptors due to clozapine could be responsible for the lack of the body temperature elevation caused by orexin A. Clozapine blocks completely the hyperthermic action of orexin A. This indicate that patients treated with clozapine are non responsive to physiological variations of orexin A. This non-responsiveness to orexin A could induce not only hypothermia, but also body weight gain [30]. Indeed, orexin A is involved in the activation of thermogenesis related to eating behaviour. The thermogenesis due to food intake is an important factor in the regulation of body weight and the lack of this thermogenesis causes the obesity [31,32]. Moreover, the therapy of rare but dangerous hypothermia caused by clozapine should exclude drugs, which affect the orexinergic system to induce an elevation of body temperature.

Since olanzapine is an antagonist of 5-HT<sub>2</sub> and D1-D2 receptors [33], the block of these receptors could cause the lack of body temperature elevation due to orexin A [34, 35]. Since olanzapine exerts also influences on cholinergic, adrenergic and histaminergic pathways, an involvement of these pathways cannot be excluded [36]. The therapy of the rare but dangerous hypothermia caused by olanzapine [37] cannot comprehend substances affecting the orexinergic system to elevate body temperature: this system is blocked by olanzapine. We can suppose that the body weight gain could be caused, at least in part, by a decrease in the thermogenic changes due to orexin A. Because weight gain due to antipsychotic drugs is a frequent reason for noncompliance with pharmacological treatment [38], studies on mechanisms affecting obesity are very important in the management of psychiatric therapy.

Although metabolic abnormalities are associated with almost all second generation antipsychotics, clozapine and olanzapine appear to be most consistently associated with the development of metabolic syndrome. In the retrospective-prospective cohort comparison study

[39], the difference between first generation antipsychotics and second generation antipsychotics-treated patients disappeared when patients on clozapine and olanzapine were removed from the analysis. Olanzapine has also been associated with significant weight gain. In the CATIE study, patients in the olanzapine group gained more weight than with any other drug (mean weight gain was 0.9 kg monthly), and 30% of patients in the olanzapine group gained 7% or more of their baseline body weight (compared with 7-16% in the other groups) [40]. Similarly, other studies have reported significant increase in body weight, serum leptin levels, and percentage of body fat [41] and new onset diabetes [42] in patients treated with olanzapine.

Risperidone is an atypical neuroleptic substance which is an antagonist of 5-HT<sub>2</sub> receptors. This antagonism is accompanied by a milder antagonism of dopamine D<sub>2</sub> receptors [43]. An administration of risperidone potentiates hyperthermic reactions due to orexin A [44] suggesting that these thermic effects involve serotonergic and dopaminergic pathways. This seems to demonstrate that a 5-HT<sub>2</sub> receptor antagonism is higher than a D<sub>2</sub> receptor antagonism in the induction of the amplified hyperthermia caused by orexin A. Since rare cases of strong fever have been described in the subjects treated with risperidone, an involvement of orexinergic system in the fever due to risperidone is plausible.

Quetiapine delays (but it does not reduce) the activation of the sympathetic discharge. Furthermore, hyperthermia is the same caused by the injection of orexin A alone [45]. Because quetiapine is an antagonist of 5-HT<sub>2c</sub> and (in rather weak manner) D<sub>2</sub> receptors [46], the block of these receptors could cause the delayed elevation of the body temperature. Since quetiapine affects adrenergic and histaminergic pathways, these systems could be involved in delayed responses to injection of orexin A, [46,47]. Since quetiapine does not block the orexinergic system, drugs affecting orexinergic pathway could be utilized in the therapy of rare but dangerous hypothermia due to quetiapine.

The experiments described in this mini-review are based on exogenously applied orexin A. No conclusion can be drawn on the endogenous orexin system. For this reason, it is desirable that researchers perform further experiments on how to investigate the effect of the endogenously released orexin ligands in interaction with neuroleptics.

Although we cannot conclude much from these experiments with regards to the endogenous orexin system and its role, these experiments demonstrate that an icv administration of orexin A causes an increase in temperature of IBAT, that is strongest effector of unrelated-shivering thermogenesis in the rat [48-50], showing that the increase in heat production is also caused by a stimulation of non-shivering thermogenesis [48,51-53]. The sympathetic nervous system controls the IBAT activity and factors, which affect thermogenesis, exert an action centrally to induce modification of the sympathetic discharge to IBAT [54,45,55].

The described experiment indicates that orexin A affects body temperature, independently of food intake. The name taken to orexin A, named primarily hypocretin-1 [56], was due to the hyperphagic behavior after injection of this neuropeptide, assigning a principal role in the eating behavior [57]. These results indicate that orexin A causes high elevations of body temperature in anesthetized rats. Thus, this hyperthermia is unrelated to eating behavior [53,59,60].

There are a variety of binding-sites linked with temperature modulation (controlled by the autonomic nervous system) and

metabolic syndrome that are present. The autonomic nervous system is involved in the control of eating behavior through influences exerted on the production and loss of heat [1,61]. Thus, the control of body temperature is strictly associated with the control of body weight; this is in accord with the "thermoregulatory hypothesis" of food intake [62]. On the other hand, the metabolic balance is controlled by the autonomic nervous system, so that the vegetative influences affect the storage and the consumption of energy. The consequences of this hypothesis are that subjects with a high set-point of body temperature and/or low sympathetic activity are induced to eat a high quantity of food to elevate the sympathetic discharge and body temperature. Conversely, subjects with a low thermal set-point and/or a high sympathetic tone need to introduce a lower quantity of food to reach a prefixed thermal set-point. On the other hand, alterations of postprandial thermogenesis due to a reduced response of sympathetic activation can play an important role in inducing obesity. In other words, subjects with a low postprandial sympathetic activation need to introduce a higher quantity of food to reach a prefixed body temperature. Patients with serious mental illness are at higher risk of developing metabolic abnormalities (e.g., weight gain, increased blood pressure, glucose or lipid levels) in comparison to general population. Since the risk increases following initiation of neuroleptic therapy, it must assess carefully risks and benefits when choosing a particular antipsychotic drug [63].

In conclusion, this report emphasizes the influences of neuroleptic drugs on the control of body temperature, exerted by orexinergic system. This large vision (see summary scheme) could be also useful to address therapeutic choices.

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