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Review

Orexin A induces sympathetic and thermogenic activation as a thermoregulatory peptide

M. Monda[1,*], An. Viggiano[2], D. Tafuri[3], E. Viggiano[1], S. Chieffi[1], V. De Luca[4] and G. Messina[1]

[1]Department of Experimental Medicine, Section of Human Physiology and Unit of Dietetics, Second University of Naples, Naples, Italy, [2]Department of Medicine and Surgery, University of Salerno, Salerno, Italy, [3]Department of Motor Sciences, University of Naples "Parthenope", Naples, Italy. [4]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

The hypothalamic peptide orexin A (also called hypocretin-1) was originally named so with the intend of emphasizing its role in promoting food intake. The aim of this brief review is to show that orexin A is an important neuropeptide that primarily controls body temperature through activation of the sympathetic nervous system. The modification of eating behavior due to orexin A could be only secondary to change in the thermoregulatory set-point. Activity of the sympathetic nerves system, brown adipose tissue and central body temperatures, heart rate and food intake were monitored to measure the modifications induced by an intracerebroventricular injection of orexin A on the thermoregulation and eating behavior in various experimental conditions in the rat. We report many experimental evidences derived from our laboratory to demonstrate that orexin A is a thermoregulatory peptide. Our viewpoint is compared with vision of other authors, finding possible agreement or disagreement.

KEYWORDS: sympathetic nervous system, thermoregulation, eating behavior

*Corresponding author: Prof. Marcellino Monda, Department of Experimental Medicine, Section of Human Physiology, and Unit of Dietetics and Sports Medicine, Second University of Naples, Via Costantinopoli 16, 80138 Naples, Italy. marcellino.monda@unina2.it

1. INTRODUCTION

An intracerebroventricular (icv) injection of the hypothalamic neuropeptide "orexin A" is able to induce multiform reactions, as an expression of generalized activation of sympathetic nervous system. Although this neuropeptide is named for its influence on food intake [1], an icv injection of orexin A does not merely affect eating behavior. Rather it also induces an increase in heart rate [2], blood pressure [3], and metabolic rate [4, 5, 6], indicating that this neuropeptide plays a role in the control of vegetative functions [7]. Orexin A also influences body temperature. In fact, an icv administration of orexin A 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 [8]. In addition, the presence of orexin receptors in many cerebral areas suggests that additional functions are played by orexin A [9, 10, 11]. A role for the orexins in sleep regulation has also been demonstrated [12, 13, 14].

The above-mentioned peptide is referred to by the name orexin A and it has also been named hypocretin-1 in the past. The term orexin originates from orexis, the Greek word for appetite and the naming was intended to emphasize the increase in food intake initiated by the peptide, because an icv injection of orexin A induces an increase in food intake in fasted or satiated rats [1].

The aim of this brief review is to report our studies which demonstrate that orexin A is a neuropeptide

that primarily affects body temperature through influences exerted on the sympathetic nervous system. The modification of eating behavior due to orexin A could be only secondary to change in the thermoregulatory set-point. Furthermore, the purpose of this review is to compare our point of view with the view of other authors, so that the agreement or disagreement can be analyzed.

2. EXPERIMENTAL EVIDENCES

The first evidence comes from the reported experiment where the food intake, firing rate (FR) of the sympathetic nerves to IBAT and IBAT and colonic temperatures (T_{IBAT} and T_C), were monitored in 24h-fasting male Sprague-Dawley rats for 15 hours after food presentation during the dark period [15]. Orexin A (1.5 nmol) was injected into the lateral cerebral ventricle 6 hours before food presentation while FR, T_{IBAT} and T_C were also monitored. The same variables were controlled in rats receiving orexin A at the same time of food presentation. Two other groups of control animals were tested with the same procedure, but orexin A was substituted by saline. The results (see Figure 1 and panel A of Figure 5) showed that food intake was significantly lower in the group receiving orexin A 6 hours before food presentation in comparison to all the other groups. FR, T_{IBAT} and T_C were significantly higher in the rats receiving orexin A with respect to rats receiving saline. In this experimental demonstration, the saline groups were tested but not reported in the paper. Food intake of both saline groups was intermediate between orexin-0 group and orexin-6 group. These findings demonstrate that the effects on food intake induced by orexin A depend on the time of food presentation. This prompts us to reconsider the role of orexin A in the control of food intake. The name assigned to this peptide was due to the strong increase in food intake after an orexin A administration, assigning a fundamental role in the induction of food intake [16, 17]. The results of the above mentioned experiment call for a re-discussion of this role, underlining the importance of orexin A in the control of the sympathetic activity and body temperature, which in turn affects food intake. The anorexic effect of substances is better detected in fasted animals. Since this experiment tested a possible anorexic role of orexin A, fasted rats were chosen. In this experiment, an icv injection of orexin A induces an increase in the

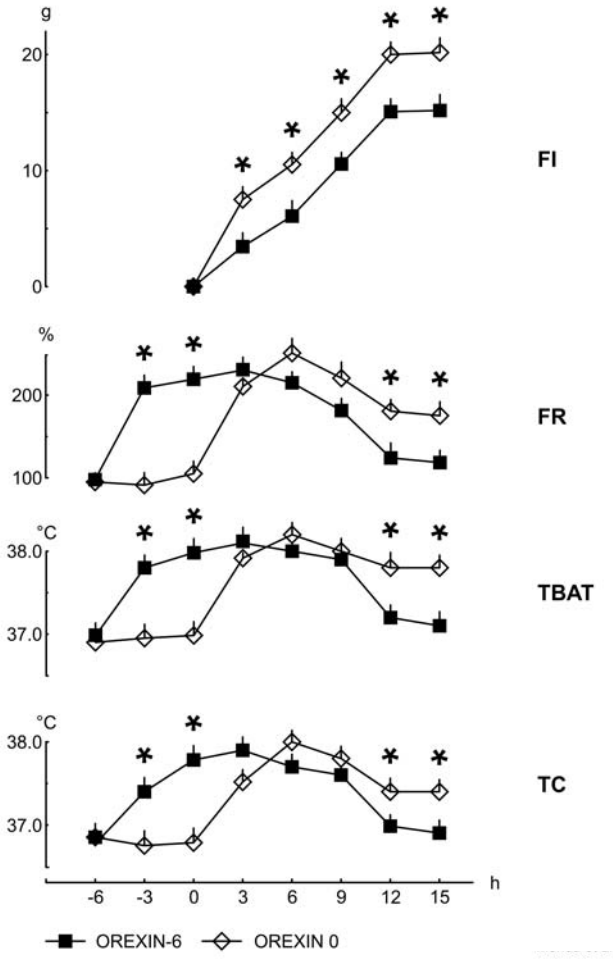

Figure 1. Means ± SE of cumulative change in food intake (FI), firing rate of sympathetic nerves (FR), temperature of brown fat (TBAT) and core temperature (TC). Food presentation was at time 0. Intracerebroventricular injection of orexin A was made 6 h before food presentation (OREXIN-6) or contemporaneously to food presentation (OREXIN-0). The asterisk indicates a significant difference ($p < 0.05$).

sympathetic activity and in the TIBAT independent of food ingestion, that is reduced in the rats with a delayed presentation of food. This suggests that the effects on body temperature are prevalent with respect to eating behavior. Thus, orexin A can induce hyperphagia, but also hypophagia, contradicting the meaning of this name which assigns a primary hyperphagic role to this peptide. Other substances with primary hyperphagic effect, as neuropeptide Y or galanin, induce a reduction of the sympathetic discharge and a decrease in body temperature [18, 19, 20, 21]. Conversely, substances with a primary

hypophagic effect cause an increase in the sympathetic activity. For example, leptin induces reduction of food intake [22, 23], along with an increase in the firing rate of the sympathetic nerves to IBAT and a rise in T_{IBAT} [24, 25]. For this reason, orexin A cannot be considered a substance with a primary hyperphagic effect. The orexin A can induce hypophagia, as in above described experiment, or hyperphagia [16], but it always induces an activation of thermogenesis. We can suppose that this peptide elevates the thermoregulatory set-point, inducing the reactions to reach the new level of body temperature. The increase in food intake in the rats with a non-delayed presentation of food could be a reaction aimed to reach an elevated body temperature. Indeed, food ingestion induces a rise in body temperature due to post-prandial thermogenesis [26, 27, 28, 29]. The hyperphagic effect of orexin A disappears when the body temperature is already increased, so that a reduction in food intake can happen in this condition.

The second evidence comes from the reported experiment where the firing rate of the sympathetic nerves to IBAT, along with IBAT and T_C were monitored in urethane-anesthetized male Sprague-Dawley rats before and 6 hours after an injection of orexin A (1.5 nmol) into the lateral cerebral ventricle [8]. The same variables were monitored in rats with an intraperitoneal administration of lysine acetylsalicylate (100 mg/kg bw), an inhibitor of prostaglandins synthesis. The results (see Figure 2 and panel B of Figure 5) show that orexin A increases the sympathetic firing rate, IBAT and T_C. This increase is reduced by lysine acetylsalicylate (L-ASA). L-ASA reduces the sympathetic activation induced by orexin A, suggesting that PGs have a role in the mediation of this phenomenon. A possible explanation is that orexin A could induce a cerebral synthesis of PGsE, which act on the preoptic area/anterior hypothalamus [30, 31], a very responsive structure to PGsE. On the other hand, we cannot exclude that PGsE could stimulate other hypothalamic areas [32, 33, 34, 35], including the ventromedial hypothalamus [30], which directly controls the activity of nerves to IBAT [36]. The icv injection stimulates thermogenesis and increases body temperature in anesthetized rats, showing that orexin A is involved in thermoregulation independent of eating behavior [32, 37, 38]. Because food intake activates thermogenesis [27, 39], substances affecting

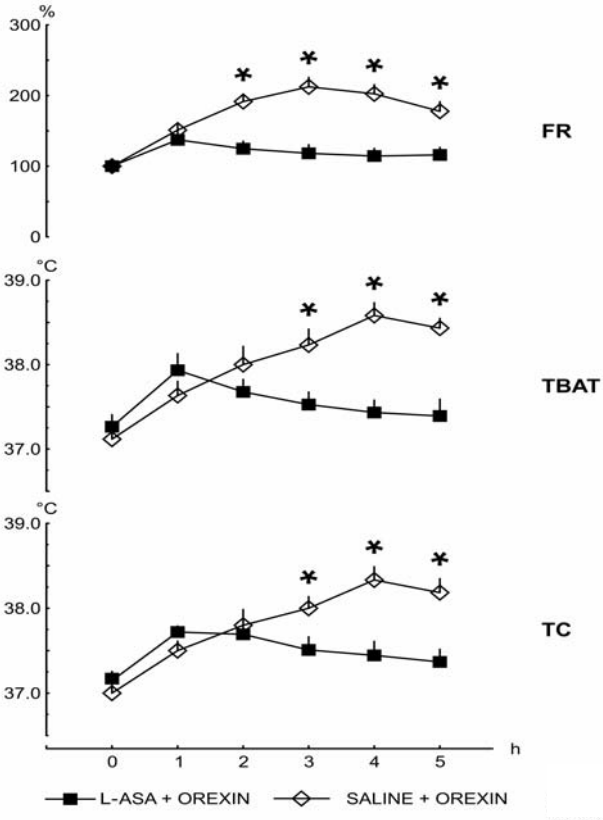

Figure 2. Means ± SE of changes in sympathetic firing rate (FR), in brown fat temperature (TBAT) and in core temperature (TC) of rats with intraperitoneal injection of saline or lysine acetylsalicylate (L-ASA) plus intracerebroventricular injection of orexin A. The asterisk indicates a significant difference ($p < 0.05$).

food consumption induce a secondary influence on body temperature [40]. Since our experiment is carried out in anesthetized animals, the rise in body temperature induced by orexin A is a primary effect of this neurotransmitter. The orexin A affects the temperature of IBAT, which is the most important effector of non-shivering thermogenesis in the rat, illustrating that the rise in heat production is also due to the activation of thermogenesis unrelated to muscle activity. The increase in colonic temperature emphasizes the effect of orexin A on "core" temperature suggesting the inclusion of orexin A among the peptides controlling body temperature. L-ASA injection reduced both temperatures, indicating that these thermic reactions are under the control of PGs, which are classic pyrogens. Further experiments should be carried out to demonstrate definitively an elevation of set-point induced by

orexin A. Since a fever-like hyperthermia is associated with suppression of heat-loss mechanisms, thermocouples fixed on the surface of the tail skin of rats recording tail skin temperature (indicating the presence of vasoconstriction or dilation occurring parallel with an increase in the metabolic rate as indicated by increased brown adipose tissue temperature) could provide proof for a coordinated rise in core temperature that usually characterizes such an elevation of set-point.

The third evidence comes from the reported experiment where the firing rate and cytochrome oxidase activity of the ventromedial hypothalamic neurons, and T_C were monitored in 12 urethane-anesthetized male Sprague-Dawley before and over a period of 2 hour after an injection of orexin A (1.5 nmol) into the lateral cerebral ventricle [2]. The results showed an increase of firing rate in 9 rats, a decrease in 2 rats and no modification of firing rate in 1 rat. In all rats, orexin A induced rise in T_C and cytochrome oxidase activity. A group of 12 rats was used as control and saline, but no orexin A, was injected into the cerebral ventricle. No modifications in firing rate, cytochrome oxidase reactivity and T_C were noted, as reported in Figure 3 and panel C of Figure 5. Furthermore, 12 male rats were anesthetized and lesioned bilaterally in the ventromedial hypothalamus (VMH) with an injection of ibotenic acid (30 nmol into each side), which destroys cell bodies. Sham-lesions were carried out in 12 control rats. After 48 hours, all animals were anesthetized with ethyl-urethane. The firing rates of the sympathetic nerves to IBAT, along with IBAT and T_C were monitored before and over a period of 2 hours after an injection of orexin A (1.5 nmol) or saline into the lateral cerebral ventricle in the lesioned and sham lesioned rats. The results (see Figure 4 and panel D of Figure 5) showed that orexin A increased the sympathetic firing rate, IBAT and T_C in the sham-lesioned rats. These increases were reduced by lesion of the VMH. Saline did not induce any modification. These results strongly indicate that the VMH is involved in the sympathetic and hyperthermic reactions induced by this hypothalamic neuropeptide. The relationship between activation of the ventromedial hypothalamic neurons and thermogenic reaction due to orexin A is demonstrated by the reduction of hyperthermia in the rats with ibotenate lesion.

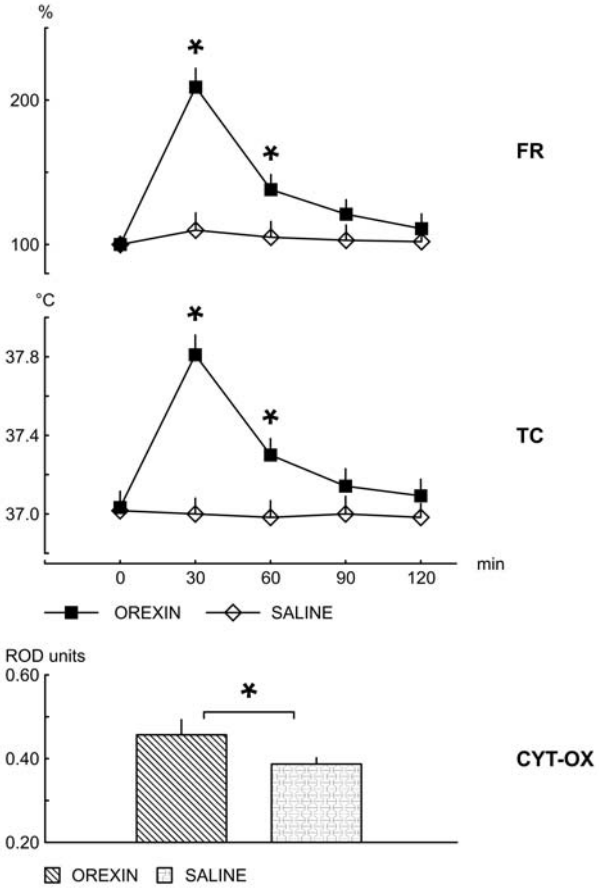

Figure 3. Means ± SE of changes in unit activity of VMH neurons (FR) and in core temperature (TC). The orexin A or saline was injected in a lateral cerebral ventricle (icv) at time 0. In lower panel, means ± SE of values of cytochrome oxidase reactivity (CYT-OX) of VMH, expressed as relative optical density (ROD) units. The asterisk indicates a significant difference ($p < 0.05$).

The findings of the above mentioned experiment indicate that the VMH regulates the discharge of nerves to IBAT in this experimental model, thus demonstrating the agreement of this model to other evidences showing that VMH controls the IBAT activity [41]. Indeed, a lesion of the VMH reduces the IBAT temperature and related metabolic rate in sedentary [27] or trained rats [42]. This experiment emphasizes the influences exerted by orexin A on the VMH that is named "center of satiety". Orexin A increases the activity of ventromedial hypothalamic neurons (as demonstrated by rise in cytochrome oxidase reactivity) with a parallel increase in the sympathetic activity [43, 44]. This demonstration indicates that orexin A exerts a

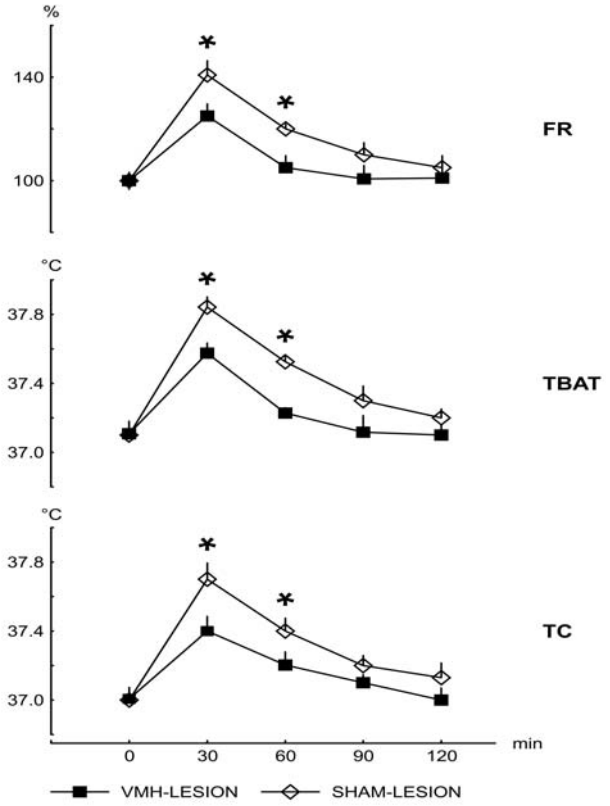

Figure 4. Means ± SE of changes in sympathetic firing rate (FR), in brown fat temperature (TBAT) and in core temperature (TC) of sham-lesioned or lesioned rats with intracebroventricular injection of orexin A at time 0. The asterisk indicates a significant difference ($p < 0.05$).

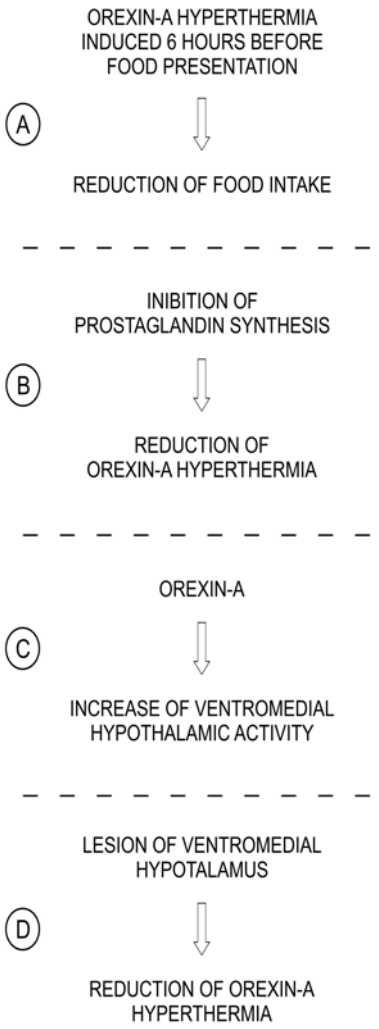

Figure 5. Scheme of the experimental demonstrations (1st: panel A; 2nd: panel B; 3rd: panel C; 4th: panel D).

stimulation of the "center of satiety" with a role similar to other substances, as cholecystokinin. This peptide is able to induce a reduction in food intake and an increase in firing rate of sympathetic nerves to IBAT after injection into the third ventricle or VMH [45]. The above mentioned study supports the hypothesis of a reciprocal relationship between the effects of anorexigenic substances on the thermogenic component of the sympathetic nervous system and food intake [46, 47].

3. DISCUSSION

Several experiments carried out by various authors demonstrate that orexin A is able to increase the sympathetic discharge and body temperature. For example, Berthoud *et al*. [48] have demonstrated that the caudal raphe nuclei in the medulla (known to harbor sympathetic preganglionic motor neurons involved in thermal and cardiovascular regulation) are innervated by orexin A fibers. Since the acute rise in sympathetic activity plays a role in the onset of satiety [39, 49], orexin A cannot be included among the classic orexigenic peptides [50].

Girault *et al.* [51] showed that through the autonomic nervous system, the orexin system plays a key role in the control of glucose metabolism, but it has also been shown to stimulate sympathetic outflow, to increase body temperature. For these authors, the well-known effects of orexin on the control of food intake appear to be more extensive than originally thought, with additional effects on the autonomic nervous system, that is, to increase body temperature and energy metabolism. These authors indicate increase in body temperature as a "crucial effect" of orexin A.

Teske *et al*. [52] emphasized the role of orexins in modulating non-sleep-related energy expenditure with specific focus on the augmentation of whole body energy expenditure as well as hypocretin-induced sympathetic activity, showing a predominant role of hypocretin-1 receptors in the influence on energy expenditure and body temperature. On the other hand, Jászberényi *et al*. [53] reported that orexin A induces hypothermia and they argue that this appetite-regulating peptide might also play a role in thermoregulation.

This orexin-induced hypothermia has not been found by other authors, who instead found that orexin A functions as a key driver of brown adipocyte differentiation through direct actions on brown adipose precursors [54] and orexin A turns up the heat on obesity [55].

In general, the effects of orexin A on the firing rate to IBAT corroborate recent evidences demonstrating the role played by this novel neuropeptide in the control of the autonomic nervous system [8]. Shirasaka *et al*. [3] illustrated that icv injections of orexins increase the activity of the renal sympathetic nerves, which play an important role in the homeostasis of body fluids and the circulatory system.

The orexin A affects the temperature of IBAT, which is the most important effector of non-shivering thermogenesis in the rat [56], illustrating that the rise in heat production is also due to the activation of thermogenesis unrelated to muscle activity. IBAT is the organ responsible for evoking 35-65% of the total increase in metabolic heat production during various experimental manipulations in rodents [57, 58]. 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 [59, 60]. The significant role of IBAT in the hyperthermia induced by orexin A [8, 61, 62, 63, 64] is confirmed by these findings. Throughout our experiment, we report direct evidence of increased sympathetic tone in nerves innervating IBAT after an orexin A injection. This confirms the role of the sympathetic nervous system on IBAT activity.

The strong influence of orexin A on body temperature, independent of eating behavior, is emphasized by the above-mentioned demonstrations, suggesting that the effects on body temperature are prevalent in comparison to eating behavior. Orexin A can induce both hyperphagia or hypophagia, but it always induces an activation of thermogenesis, contradicting the significance of its name that assigns a primary hyperphagic role to this peptide. We can suppose that this peptide elevates the thermoregulatory set-point, inducing the reactions to reach the new level of body temperature. The increase in food intake, obtained in various experiments, could be a reaction aimed to reach an elevated body temperature. On the other hand, these reactions are different from those observations of the literature that describe the fever-like elevation of core temperature as part of "sickness behavior" regularly associated with anorexia [65]. Probably, a different mechanism is involved in the association between orexin-hyperthermia and food intake. Since it has been recently demonstrated [66, 67] that brain orexin promotes obesity resistance, the orexin A should not be counted among the anabolic neuropeptides [68], but among catabolic peptides [51, 69]. A possible thermoregulatory role for orexin has been proposed by other authors. Cold exposure increased orexin mRNA in the hypothalamus [70]. Transneuronal retrograde transport of pseudorabies virus from the BAT identified the caudal raphe neurons with orexinergic innervation [48] and orexin-containing neurons in the hypothalamus [71]. Orexin knockout mice showed elevated body temperature during sleep [72] and orexin neuron-ablated mice had an attenuated body temperature fluctuation [73]. Also, orexin neurons are indispensable for stress-induced thermogenesis in mice. Indeed, these authors pointed out, for the first time, the possible importance of co-existent neurotransmitter/ modulators in the orexin neurons for stress-induced hyperthermia and the importance of integrity of the orexin neurons for full expression of multiple facets of the fight-or-flight response [74]. Furthermore, the importance of orexin A in the thermoregulation is corroborated by recent studies, showing that the thermosensitivity of orexin neurons may be an important part of maintaining energy homeostasis during fever [75, 76].

In conclusion, the above evidences suggest that orexin A exerts a key role in the thermoregulation.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

REFERENCES

1. Sweet, D. C., Levine, A. S., Billington, C. J. and Kotz, C. M. 1999, Brain. Res., 821, 535-538.
2. Monda, M., Viggiano, A. N., Viggiano, A., Viggiano, E., Lanza, A. and De Luca, V. 2005, Eur. J. Neurosci., 22, 1169-1175.
3. Shirasaka, T., Nakazato, M., Matsukura, S., Takasaki, M. and Kannan, H. 1999, Am. J. Physiol. Physiol., 277, 1780-1785.
4. Lubkin, A. and Stricker-Krongrad, A. 1998, Biochem. Biophys. Res. Commun., 253, 241-245.
5. Messina, G., Viggiano, A., De Luca, V., Messina, A., Chieffi, S. and Monda, M. 2013, Obstet. Gynecol. Int., 2013, 209812.
6. Messina, G., Vicidomini, C., Viggiano, A., Tafuri, D., Cozza, V., Cibelli, G., Devastato, A., De Luca, B. and Monda, M. 2012, Auton. Neurosci., 16, 102-106.
7. Monda, M., Viggiano, An., Viggiano, Al., Viggiano, E., Messina, G., Tafuri, D. and De Luca, V. 2007, Regul. Pept., 139, 39-44.
8. Monda, M., Viggiano, A., Mondola, P. and De Luca, V. 2001, Brain. Res., 909, 68-74.
9. Kukkonen, J. P., Holmqvist, T., Ammoun, S. and Akerman, K. E. 2002, Am. J. Physiol. Physiol., 283, 1567-1591.
10. Ramirez, A. D., Gotter, A. L., Fox, S. V., Tannenbaum, P. L., Yao, L., Tye, S. J., McDonald, T., Brunner, J., Garson, S. L., Reiss, D. R., Kuduk, S. D., Coleman, P. J., Uslaner, J. M., Hodgson, R., Browne, S. E., Renger, J. J. and Winrow, C. J. 2013, Front. Neurosci., 24, 254.
11. Alexandre, C., Andermann, M. L. and Scammell, T. E. 2013, Curr. Opin. Neurobiol., 23, 752-759.
12. Marcus, J. N., Aschkenasi, C. J., Lee, C. E., Chemelli, R. M., Saper, C. B. and Yanagisawa, M. 2001, J. Comp. Neurol., 435, 6-25.
13. Scammell, T. E. and Winrow, C. J. 2011, Annu. Rev. Pharmacol. Toxicol., 51, 243-66.
14. Kantor, S., Mochizuki, T., Lops, S. N., Ko, B., Clain, E., Clark, E., Yamamoto, M. and Scammell, T. E. 2013, Sleep, 36, 1129-1138.
15. Monda, M., Viggiano, A. and De Luca, V. 2003a, Brain. Res., 961, 220-228.
16. Shiraishi, T., Oomura, Y., Sasaki, K. and Wayner, M. J. 2000, Physiol Behav., 71, 251-261.
17. Wolf, G. 1998, Nutr. Rev., 56, 172-173.
18. Szekely, M., Petervari, E., Pakai, E., Hummel, Z. and Szelenyi, Z. 2005, Neuropeptides, 39, 103-115.
19. Egawa, M., Yoshimatsu, H. and Bray, G. A. 1991, American Am. J. Physiol. Physiol., 260, 328-334.
20. Nagase, H., Bray, G. A. and York, D. A. 1996, Brain. Res., 709, 44-50.
21. Patel, S. and Hutson, P. H. 1996, Eur. J. Pharmacol., 317, 197-204.
22. Okamoto, S., Kimura, K. and Saito, M. 2001, Neuroscience Letters, 307, 179-182.
23. Ukropec, J., Sebokova, E. and Klimes, I. 2001, Arch. Physiol. Biochem., 109, 38-51.
24. Haque, M. S., Minokoshi, Y., Hamai, M., Iwai, M., Horiuchi, M. and Shimazu, T. 1999, Diabetes, 48, 1706-1712.
25. Haynes, W. G., Morgan, D. A., Djalali, A., Sivitz, W. I. and Mark, A. L. 1999, Hypertension, 33, 542-547.
26. Tentolouris, N., Liatis, S. and Katsilambros, N. 2006, Ann. N. Y. Acad. Sci., 1083, 129-152.
27. Monda, M., Sullo, A. and De Luca, B. 1997, Physiol. Behav., 61, 687-691.
28. Messina, G., De Luca, V., Viggiano, A., Ascione, A., Iannaccone, T., Chieffi, S. and Monda, M. 2013, Neurol. Res. Int., 2013, 639280.
29. Viggiano, A., Vicidomini, C., Monda, M., Carleo, D., Carleo, R., Messina, G., Viggiano, A., Viggiano, E. and De Luca, B. 2009, J. Diabetes Complications, 23, 119-123.
30. Simpson, C. W., Ruwe, W. D. and Myers, R. D. 1994, Neurosci. Biobehav. Rev., 18, 1-20.
31. Stitt, J. T. 1991, J. Physiol., 432, 99-110.
32. Monda, M., Amaro, S. and De Luca, B. 1994, Brain. Res., 651, 148-154.
33. Monda, M. and Pittman, Q. J. 1993, Am. J. Physiol., 264, R456-459.
34. Monda, M., Amaro, S., Sullo, A. and De Luca, B. 1996, Prostaglandins, 51, 169-178.
35. Monda, M., Sullo, A., De Luca, E. and Pellicano, M. P. 1996, Am. J. Physiol., 271, R1638-1642.
36. Thornhill, J. A. and Halvorson, I. 1994, Can. J. Physiol. Pharmacol., 72, 89-96.
37. Monda, M., Viggiano, An., Viggiano, Al., Fuccio, F. and De Luca, V. 2004, Neuroscience, 123, 567-574.

38. Monda, M., Viggiano, A., Viggiano, A., Fuccio, F. and De Luca V. 2004, Brain. Res., 1018, 265-271.
39. Bray, G. A. 2000, Int. J. Obes. Relat. Metab. Disord., 24, 8-17
40. Bray, G. A. 2011, Med. Clin. North. Am., 95, 989-1008.
41. Monda, M., Viggiano, A., Caserta, L. and De Luca, V. 2002, Neuroscience, 115, 79-83,
42. Monda, M., Amaro, S. and De Luca, B. 1993, Physiol. Behav., 54, 1057-1061.
43. Mondola, P., Ruggiero, G., Serù, R., Damiano, S., Grimaldi, S., Garbi, C., Monda, M., Greco, D. and Santillo, M. 2003, Brain. Res. Mol. Brain. Res., 110, 45-51.
44. Viggiano, A., Nicodemo, U., Viggiano, E., Messina, G., Viggiano, A., Monda, M. and De Luca, B. 2010, Neuroscience, 166, 416-421.
45. Yoshimatsu, H., Egawa, M. and Bray, G. A. 1992, Brain. Res., 597, 298-303.
46. Monda, M., Messina, G., Mangoni, C. and De Luca B. 2008, Clin. Nutr., 27, 657-659,
47. Monda, M., Messina, G., Vicidomini, C., Viggiano, A., Mangoni, C. and De Luca, B. 2006, Nutr. Neurosci., 9, 141-145.
48. Berthoud, H. R., Patterson, L. M., Sutton, G. M., Morrison, C. and Zheng, H. 2005, Histochem. Cell. Biol., 123, 147-156.
49. Viggiano, An., Viggiano, Al., Monda, M., Turco, I., Incarnato, L., Vinno, V., Viggiano, E., Baccari, M. E. and De Luca, B. 2006, Exp. Neurol., 199, 354-361.
50. Szekely, M., Petervari, E. and Szelenyi, Z. 2004, Front. Biosci., 9, 2746-2763.
51. Girault, E. M., Yi, C. X., Fliers, E. and Kalsbeek, A. 2012, Prog. Brain. Res., 198, 47-64.
52. Teske, J. A., Billington, C. J. and Kotz, C. M. 2010, Acta Physiol. (Oxf)., 198, 303-312.
53. Jászberényi, M., Bujdosó, E., Kiss, E., Pataki, I. and Telegdy, G. 2002, Regul. Pept., 104, 55-9.
54. Sellayah, D., Bharaj, P. and Sikder, D. 2011, Cell Metab., 14, 478-90,
55. Seale, P. 2011, Cell. Metab., 14, 441-442,.
56. Cannon, B. J., Houstek, J. and Nedergaard, J. 1998, Ann. N. Y. Acad. Sci., 856, 171-187.
57. Monda, M., Amaro, S., Sullo, A. and De Luca, B. 1994, Neuroreport, 6, 135-139.
58. Richard, D. and Picard, F. 2011, Front. Biosci., 16, 1233-1260.
59. Monda, M., Amaro, S., Sullo, A. and De Luca, B. 1995, Brain Res. Bull., 37, 575-580
60. Silva, J. E. 2011, Front. Biosci., 3, 352-371.
61. Monda, M., Viggiano, A., Viggiano, A., Mondola, R., Viggiano, E., Messina, G., Tafuri, D. and De Luca, V. 2008, Peptides, 29, 120-126.
62. Monda, M., Viggiano, A., Viggiano, A., Viggiano, E., Messina, G., Tafuri, D. and De Luca, V. 2006, Neuropeptides, 40, 357-363.
63. De Luca, V., Viggiano, E., Messina, G., Viggiano, A., Borlido, C., Viggiano, A. and Monda, M. 2008, Psychiatry Investig., 5, 203-208.
64. Monda, M., Viggiano, A., Viggiano, A., Fuccio, F. and De Luca, V. 2004, Physiol. Res., 53, 507-513.
65. Elmquist, J. K., Scammell, T. E. and Saper, C. B. 1997, Trends Neurosci., 20, 565-570.
66. Kotz, C. M., Nixon, J., Butterick, T., Perez-Leighton, C. E., Teske, J. and Billington, C. J. 2012, Ann. N. Y. Acad. Sci., 1264, 72-86.
67. Perez-Leighton, C. E., Butterick-Peterson, T. A., Billington, C. J. and Kotz, C. M. 2012, Int. J. Obes. (Lond.), 10, 1038.
68. Szekely, M., Petervari, E. and Balasko, M. 2010, Front. Biosci. (Schol Ed)., 2, 1009-1046.
69. Teske, J. A. and Mavanji, V. 2012, Vitam. Horm., 89, 91-109.
70. Ida. T., Nakahara, K., Murakami, T., Hanada, R., Nakazato, M. and Murakami, N. 2000, Biochem. Biophys. Res. Commun., 270, 318-323.
71. Oldfield, B. J., Giles, M. E., Watson, A., Anderson, C., Colvill, L. M. and Mckinley, M. J. 2002, Neuroscience, 110, 515-526.
72. Mochizuki, T., Klerman, E. B., Sakurai, T. and Scammell, T. E. 2006, Am. J. Physiol. Regul. Integr. Comp. Physiol., 291, 533-540.
73. Zhang, S., Zeitzer, J. M., Sakurai, T., Nishino, S. and Mignot, E. 2007, J. Physiol., 581, 649-663.
74. Zhang, W., Sunanaga, J., Takahashi, Y., Mori, T., Sakurai, T., Kanmura, Y. and Kuwaki, T. 2010, J. Physiol., 588, 4117-4129.
75. Parsons, M. P., Belanger-Willoughby, N., Linehan, V. and Hirasawa, M. 2012, J. Physiol., 590, 4707-4715.
76. Rusyniak, D. E., Zaretsky, D. V., Zaretskaia, M. V. and Di Micco, J. A. 2011, Neurosci. Lett., 498, 162-166.