Short Conceptual Overview

Orexin modulates brown adipose tissue thermogenesis

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Abstract

Non-shivering thermogenesis in brown adipose tissue (BAT)
plays an important role in thermoregulation. In addition,
activations of BAT have important implications for energy
homeostasis due to the metabolic consumption of energy
reserves entailed in the production of heat in this tissue. In this
conceptual overview, we describe the role of orexins/hypocre-
tins within the central nervous system in the modulation of
thermogenesis in BAT under several physiological conditions.
Within this framework, we consider potential neural mecha-
nisms underlying the pathological conditions associated with
the absence of the central orexinergic modulation of BAT ther-
mogenesis and energy expenditure. Overall, the experimental
basis for our understanding of the role of central orexin in reg-
ulating body temperature and energy homeostasis provides an
illustrative example that highlights several general principles
and caveats that should help guide future investigations of the
neurochemical regulation of thermogenesis and metabolism.

Keywords: cannabinoid; narcolepsy; obesity; stress;
ultradian rhythm.

Introduction

The regulation of body temperature by the central nervous
system is critical for mammalian survival in a wide variety
of thermal environments. Small variations in core body tem-
perature within the physiological range often occur during
behavior and may be functionally relevant. However, large
deviations in cellular temperature can sufficiently alter a vari-
ety of molecular properties, including enzymatic activities,
diffusion capacity, and membrane fluidity, to impair cellular
function. Severe disruptions in cellular function result in loss
of motor coordination, mental confusion, loss of conscious-
ness, significant respiratory and cardiovascular dysfunction,
and eventual death.

Significant progress has been made in our understanding
of the fundamental central nervous system circuitry that reg-
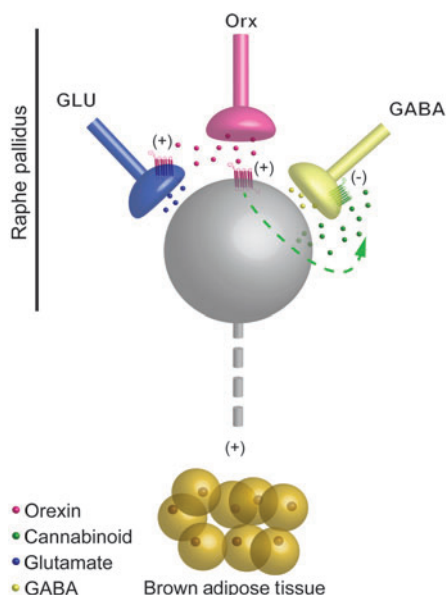ulates body temperature [see refs. (1–4)]. Not surprisingly,
the excitatory amino acid glutamate and the inhibitory amino
acid GABA are the primary neurotransmitters within the
fundamental central neural pathways for thermoregulation.
In addition, body temperature can be influenced by an exten-
sive array of peptides and other central neurotransmitters,
including (but not limited to) hypocretin/orexin, galanin,
melanin-concentrating hormone, neuropeptide Y, oxyto-
cin, glucagon-like peptide 1, cholecystokinin, cocaine- and
amphetamine-related transcript, melanocortins, opioids,
thyrotropin-releasing hormone, corticotropin-releasing fac-
tor, tuberoinfundibular peptide of 39-amino-acid residues
(TIP-39), dopamine, norepinephrine, epinephrine, serotonin,
histamine, insulin, and leptin. However, the precise neuroana-
tomical sites of action and the specific mechanisms by which
many of these neurochemicals influence the fundamental
neurocircuitry for thermoregulation remain unknown. In this
article, we will use an illustrative example the influence of
orexin on thermoregulation, to highlight some of the gen-
eral principles and caveats that should guide experiments to
understand the precise mechanisms by which neurochemicals
may interact to influence thermoeffector activation.

Orexin neurons contribute to the regulation of BAT thermogenesis

Orexins/hypocretins (5, 6) are peptides synthesized primar-
ily by neurons located in the lateral, perifornical, and dorso-
medial areas of the hypothalamus. These orexinergic neurons
have widespread projections in the brain that include many
thermoregulatory areas, such as the preoptic area, dorso-
medial hypothalamus, parapyramidal area (PaPy), and the
rostral raphe pallidus (rRPa) (7–9). The rRPa is especially
relevant to thermogenesis as it is the location of the sympa-
thetic premotor neurons for BAT (10, 11). We have recently
demonstrated a role of orexin in the rRPa in the control of
BAT thermogenesis (9). Transynaptic retrograde virus tracers
injected in BAT as well as injections of the retrograde tracer
cholera toxin subunit-b in the rRPa and PaPy highlighted a
direct projection from orexinergic neurons to rRPa and PaPy
sympathetic premotor neurons controlling BAT thermogene-
sis. Furthermore, nanoinjection of orexin in the rRPa or PaPy,
or nanoinjection of *N*-methyl-D-aspartate (NMDA) in the per-
ifornical area of the lateral hypothalamus containing orexin-
ergic neurons potentiated the ongoing BAT sympathetic nerve
activity (SNA) elicited by mild cooling of core body tem-
perature. However, during a slightly warm condition when
the BAT sympathetic nerve was quiescent, neither nanoinjec-
tion of orexin in the rRPa nor direct activation of orexinergic

neurons by nanoinjections of NMDA in the perifornical area of the lateral hypothalamus increased BAT SNA (9). Thus, orexin appears to serve as a modulator that changes the gain of the central thermoregulatory system to facilitate ongoing sympathetic activity to BAT and BAT thermogenesis.

Figure 1 illustrates several potential mechanisms by which orexin-mediated facilitation of the activity of BAT sympathetic premotor neurons could occur within the rRPa. Orexin could act by inhibiting GABA release onto BAT sympathetic premotor neurons in the rRPa, consistent with the increases in BAT SNA that can be driven by blockade of GABA$_A$ receptors in this region (12). Interestingly, within the periaqueductal gray, orexin inhibits the release of GABA by cannabinoid-mediated retrograde neurotransmission, in which endocannabinoid, released from the postsynaptic cell in response to orexin receptor activation, diffuses retrogradely to inhibit GABA release from local presynaptic terminals (13). Orexin could also presynaptically potentiate glutamate release onto BAT sympathetic premotor neurons of the rRPa, similar to mechanisms described for the potentiation of muscle tone with microinjection of orexin in somatic motor nuclei (14). In addition, orexin could act directly on sympathetic premotor neurons in the rRPa to alter their responsiveness to synaptic inputs. Although there are no data quantifying the phenotypes of the targets of

orexin terminals within the rRPa, orexin fibers do form close appositions to serotonergic neurons (unpublished observation), consistent with the interesting possibility that the modulatory effects of orexin could be explained by effects on the serotonergic, BAT sympathetic premotor neurons in the rRPa. Indeed, similar to the effect of orexin in the rRPa, activation of serotonergic receptors in the spinal cord changes the gain of the spinal thermogenic network by potentiating glutamatergic excitation of BAT sympathetic preganglionic neurons (15–17).

Role of orexin in the ultradian cycle of BAT thermogenesis

Ultradian rhythms are those with a periodicity of <24 h. Ultradian rhythms in rats have been described for sleep/wake cycles, motor activity, arterial pressure, and heart rate. An ultradian rhythm in BAT thermogenesis has also been demonstrated, with increases in BAT temperature occurring every ~1–2 h (18, 19). A role for orexin in the regulation of the ultradian rhythm of BAT thermogenesis has been suggested (18, 20). Consistent with this hypothesis, injection of orexin into the cerebral ventricles increases BAT SNA and BAT temperature (21), and the activity of orexinergic neurons as well as the levels of orexin in the extracellular fluid of the central nervous system correlate well with the sleep/wake state of the animal, with higher indices of orexin activity during the waking state (22–24). Unfortunately, the presence (or absence) of an ultradian rhythm in BAT temperature in orexin-null mice has not yet been described, although these animals do have disrupted ultradian sleep/wake cycles characterized by shorter bouts of wakefulness compared with control mice (19, 25). We postulate that the ultradian increases in BAT temperature are mediated by the periodic release of orexin in the rRPa and PaPy, resulting in increases in the gain of thermogenic neurotransmission that, in turn, increase body and brain temperatures. What are the functional implications of the ability of orexin to increase the gain of the thermogenic system? An interesting, although untested, hypothesis is that the ultradian rhythm of BAT thermogenesis facilitates neural activity and thereby improves brain function (26). Similarly, given the close correlation of BAT thermogenesis and the resulting increase in body temperature with periods of wakefulness, thermogenesis in this tissue may act to optimize metabolic function during periods requiring enhanced performance in general, and, conversely, low levels of thermogenesis during sleep states may act to conserve limited metabolic resources. Likewise, changing the gain of the excitatory neurotransmitter system driving a thermogenic effector, such as BAT, which consumes energy stores to produce heat, would have clear functional consequences for energy homeostasis (see below).

Figure 1 Schematic diagram summarizing several proposed models of the detailed mechanisms responsible for the modulation of brown adipose tissue (BAT) sympathetic nerve activity and thermogenesis evoked by the actions of orexin in the raphe pallidus.
Orexin peptide released from an orexinergic terminal (pink terminal) in the raphe pallidus may 1) act at postsynaptic orexin receptors on a sympathetic premotor neuron (gray neuron) for BAT to increase its responsiveness to other excitatory synaptic inputs; 2) act at orexin receptors on glutamatergic terminals (blue terminal) to presynaptically potentiate glutamate release onto sympathetic premotor neurons for BAT; 3) act on sympathetic premotor neurons for BAT to stimulate the release of endocannabinoids that subsequently serve as retrograde neurotransmitters to inhibit ongoing GABAergic input (yellow terminal) to sympathetic premotor neurons for BAT.

Role of orexin neurons in the stress-induced increase in body temperature

Zhang and colleagues (27) have demonstrated that the increase in core body temperature evoked by repeated handling stress

is attenuated in mice that lack orexin neurons compared with wild-type mice. Surprisingly, prepro-orexin knockout mice that do not produce orexin peptides have relatively normal stress-evoked increases in core body temperature (27). On the basis of these data, it has been suggested that orexin-containing neurons may be involved in stress-evoked increases in body temperature through the release of neurochemicals other than orexin (e.g., dynorphin or glutamate, which are normally co-expressed in orexin neurons) (27).

Particular caution is warranted when interpreting genetically driven ablation and knockout models as there is always the possibility for developmental changes or compensatory mechanisms, as well as unintended consequences on additional cell populations beyond those specifically targeted [e.g., due to developmental expression patterns that differ from those in adult animals; see ref. (28)]. This may also be true in the case of orexin. Orexin is required for the development and differentiation of BAT, and orexin administration during gestation in orexin-null dams rescues this developmental defect in the newborn pups (29). The placenta may be the source of the orexin required for BAT development (29). However, how could this defect explain the differences observed between prepro-orexin knockout mice and orexin neuron-ablated mice? As the source of the functionally important orexin may be the placenta, the genotype of the dam could determine the development of BAT in the offspring. The prepro-orexin knockout mice were generated by breeding heterozygotes (27); therefore, the dams will produce orexin as adults (30). Unfortunately, it is not clear from the methodological description of the generation of orexin neuron-ablated mice whether the dams are devoid of orexin (the specific genotype of the dams is not stated) (27). However, if orexin neuron-ablated dams were used, then the differential expression of orexin in the placenta of the dams would be expected to result in differences in the development of BAT that could contribute to a difference in the stress-evoked increase in body temperature that is independent of alterations in the central nervous system of the pups. There is also an apparent controversy concerning the UCP-1 expression levels in orexin knockout mice [compare, for instance, Figure S1E in ref. (29) to Figure 3 in ref. (27)]. Obviously, additional insights are necessary to resolve these issues.

Role of orexin in obesity

Narcolepsy is a neurological disorder principally characterized by altered sleep/wake cycles, in most cases attributable to reduced orexin neurotransmission (30–32). In addition to the disturbances in sleep/wake cycles, there is a well-recognized association between narcolepsy and obesity in human patients and animal models of the disease (33–38). The increase in body weight in human patients with orexin deficiencies occurs despite a reduced caloric intake (39) and a normal total physical activity compared either with healthy control subjects (40) or with patients with idiopathic hypersomnia (34). Similarly in mice that lack orexin, weight gain occurs despite reduced food intake; however, in mouse models,

a decrease in spontaneous motor activity likely contributes to the weight gain (41). Impaired thermogenesis in BAT has also been suggested to play a role in the propensity for weight gain in orexin-null mice (29). There are currently no studies demonstrating a role for diminished activation of BAT in the increased incidence of obesity of narcoleptic patients; however, this hypothesis would be consistent with the recent demonstrations of an inverse relation between the activity of BAT and body mass index in adult humans (42–45). Conversely, augmented orexin activity prevents diet-induced obesity and could contribute to a lean phenotype (46).

Highlights

1. Orexin has pleiotropic effects on thermogenesis in brown adipose tissue. These include synergistic contributions to the development and differentiation of brown adipocytes and to the neurally regulated activation of this tissue under various physiological conditions. In addition, orexin neurons may contribute to thermogenesis through the release of neurotransmitters other than the orexin peptide.

2. Neurochemicals may act as modulators, which by themselves may be insufficient to drive thermoeffector systems, but instead act to change the gain of neural activity driven primarily by other neurotransmitters.

3. Because neurons express multiple neurotransmitters, neurochemical phenotyping may have limited utility until the unique and the 'interactive' roles of each neurochemical in target cell regulation have been addressed. This is especially important when using genetic methods to specifically alter a 'neurochemically specific' cell population as the important neurotransmitter under a given condition may indeed differ from the genotype used to target the cell.

4. 'Knockout' models must be interpreted with caution owing to developmental compensation and/or potential for changes in development.

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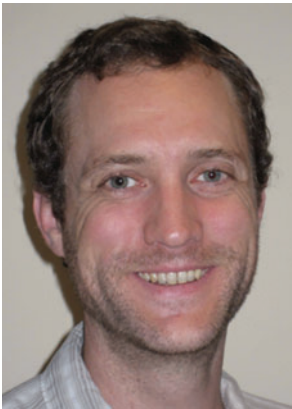
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Dr. Domenico Tupone obtained his PhD in Neurophysiology in 2010 from Alma Mater Studiorum, University of Bologna, Bologna, Italy. He was honored by the Italian Sleep Research Society (SIRS) with the annual "Igino Fagioli" award for the best doctoral thesis in basic sleep research, for his neurophysiological studies on the relationship between REM sleep and central regulation of metabolism. Dr. Tupone is currently a postdoctoral fellow in the laboratory of Prof. Shaun F. Morrison, in the Department of Neurological Surgery at the Oregon Health and Science University, where he studies the central neural regulation of body temperature. Dr. Tupone's principal research interest is the pharmacological manipulation of the central autonomic circuits controlling body temperature for the development of clinical approaches to controlled hypothermia. His studies implement in vivo, electrophysiological and anatomical approaches in anesthetized, awake head-restrained and free-behaving rats.

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