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Catestatin and orexin-A influence hamster thermic states during hibernation

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Decreased body temperature during hibernation evokes a neuroprotective effect against the frequent neurodegenerative events of ischemic/reperfusion injuries. This neuroprotection appears to stem from a direct involvement of orexin-A plus the sympathoinhibitory neuroactive peptide catestatin on orexin 2 receptor-dependent feeding and motor behaviors of the facultative hibernating hamster.

Mammalian hibernators undergo profound behavioral, physiological and biochemical variations, which consent them to tolerate low body temperature, ischemia-reperfusion, and reduced energy reserves over days of continuous torpor. At the brain level, the low temperature-dependent energy processes during hibernation require a series of complex transcriptional regulatory mechanisms in order to enhance stress tolerance against aversive environmental conditions with respect to non-hibernators that display a lower tolerability. Hibernation is a physiological condition divided into three phases: entrance in which O_2 consumption drastically drops prior to a gradual decline in core body temperature, hypotensive torpor phase in which body temperature drops to < 5 °C and mean arterial blood pressure falls to 28 mmHg along with a 80–90% reduction of cerebral blood flow, and warming or hypertensive arousal phase in which body temperature rises to euthermic levels (37 °C) and mean arterial blood pressure rising to approximately 403 ± 21% of basal euthermic value.[1]

From the various studies conducted on this physiological paradigm, it appears that orexin 2 receptor (ORX2R) mRNA changes in specific feeding-, motor- and sleep-wake-related limbic regions like the amygdala and the hypothalamus of the facultative hibernator Syrian hamster (*Mesocricetus auratus*) are actively involved with the switching ON/OFF of the different hibernating states.[2] This was the case of the hamster periventricular hypothalamic nucleus infused with orexin-A (ORX-A) and/or the novel chromogranin A-derived peptide catestatin (CST) that accounted for mixed ORX2R expression variations in some limbic regions. In particular, ORX-A alone or in combination (ORX-A+CST) by modifying ORX2R-dependent effects controlled by the supraoptic and ventromedial hypothalamic nuclei, tends to alter feeding plus motor behaviors thus driving hamsters to the entrance phase (**Fig. 1**). For this specific hibernating state, the prevalent occurrence of ORX-A-related events may be consequent to enhanced orexinergic neuronal activities promoting increased energy expenditure processes via the activation of the arcuate orexigenic Neuropeptide Y/Agouti Related Peptide and thus evoking net eating signals plus increased body mass index.[3] Conversely, a CST-dependent upregulation of ORX2Rs in the former hypothalamic nucleus, which elicits oxytocin-related anorexigenic effects,[4] seems to maintain hamsters in an inactive torpor state.[2] As a consequence the sympathoinhibitory component, above all during this hypometabolic phase constitutes a major factor favoring the maintenance of hypothermia, cardiovascular and respiratory functions that are typical of hibernators.[1] Such a hemodynamic relationship seems to be also strengthened during the arousal state by CST-dependent anti-obesity actions[5] via a downregulation of ORX2Rs in the basolateral amigdalar plus arcuate hypothalamic nuclei along with the upregulation in the supraoptic and ventromedial hypothalamic nuclei.[2] Interestingly, both ORX-A alone and in combination with CST by upregulating this orexinergic receptor subtype in mostly the parietal cerebral cortex along with the dorsomedial hypothalamic site lead hibernators to eat more plus execute motor behaviors, which predominantly serve as a major switching ON of the arousal state.[2]

In this context, thermal variations that have been noted as a key element for the activation of ORX2Rs and hence as a vital physiological mechanism allow hamsters to transit between torpor (hypothermia/hypotension) and arousal (hypertension) states in relation to cardiovascular conditions. Concomitantly, hypothalamic neuronal fields enriched with elevated ORX2R expression levels supplied a notable reduction of neurodegenerative signals especially after treatment with CST and this is in good agreement with the results of another study[6] as well as with the longer neuronal survival induced by such an orexinergic subtype in some limbic areas.[2] However, despite the potent sympathoinhibitory and antihypertensive effects of CST causing a marked decrease of blood pressure following infusion into the central amygdalar nucleus, it seems to accomplish such a feature via the major

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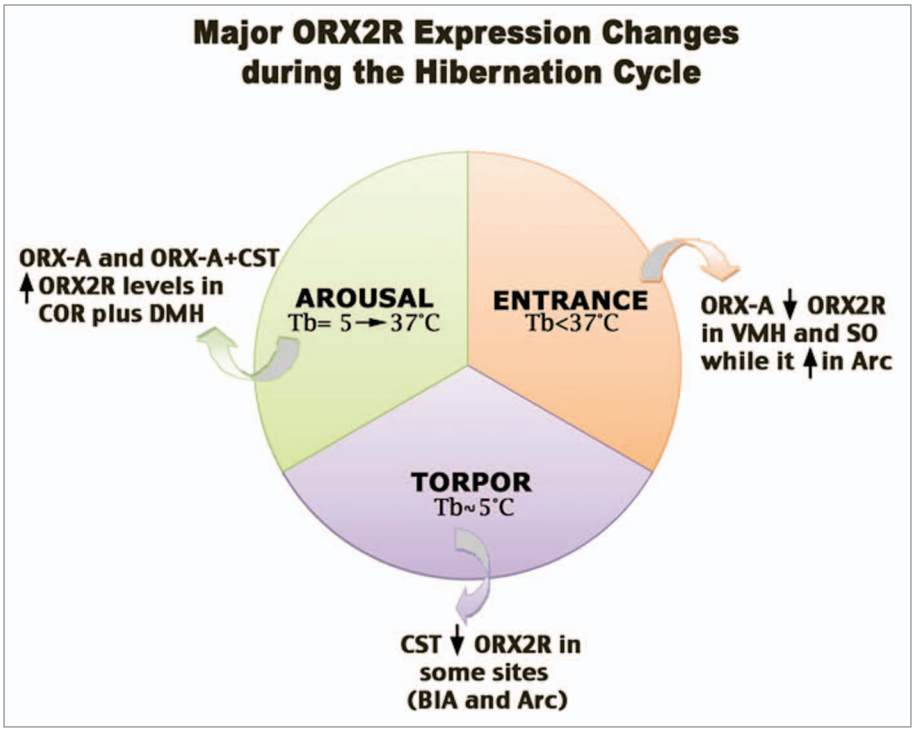

Figure 1. A schematic representation of the three stages featured during the entire hibernation cycle. The text box illustrates the main orexin 2 receptor (ORX2R) transcriptional effects evoked by the different treatments, i.e., the periventricular infusion with ORX-A, CST and ORX-A+CST with respect to ctr animals that were only infused with NaCl. Abbreviations: Arc, arcuate nucleus; BIA, basolateral amigdalar nucleus; COR, parietal cortex; DMH, dorsomedial hypothalamic nucleus; SO, supraoptic nucleus; VMH, ventromedial hypothalamic nucleus.

inhibitory receptor $GABA_A$ complex of this limbic region as illustrated in another hypertensive model, i.e., the spontaneously hypertensive rat.[7] It is noteworthy that chromogranin A-enriched brain areas surrounded by $GABA_A$ interneurons have pointed to this neuroreceptor as an important neuronal element responsible for stress-dependent hemodynamic dysfunctions. In this particular case, the inhibition of $GABA_A$ receptors by its major antagonist bicuculline completely abolishing CST-induced sIPSC along with the chromogranin A-derived peptide neuroprotective effects tend to be responsible for the onset of CST sympathoinhibitory and antihypertensive actions.[2,7] As far as α_1, a main $GABA_A$ receptor subunit is concerned, it seems to guarantee varying degrees of anti-sedative sensitivities during homeostatic events and exerts protection against metabolic-/temperature-dependent sleeping and motor difficulties.

On the basis of indications deriving from these studies, it appears safe to suggest that naturally occurring temperature oscillations are very probably linked to transcriptional variations of certain hypothalamic and limbic neuronal stations operating on orexinergic signals during the different hibernating states in hamsters. In addition, recent results tend to also point to cross-talking mechanisms of other neurosignaling receptor systems operating not only in discrete limbic stations but above all in brainstem regions. Consequently these findings could begin to suggest a series of questions for further studies. First of all, since CST is becoming an important neuropeptide for treating hypertension could its application lead to pleiotropic effects on the basis of animal's ability to compensate for altered blood pressure? Indeed, the amygdalar area of an ischemic tolerating rodent (hamster) showed signs of neurodegeneration after CST treatment, while surprisingly in a hypertensive ischemic model this same treatment evoked a protective effect. So, it would be essentially useful to identify the type of molecular mechanisms operating under these hemodynamic conditions. Furthermore, the results of this study demonstrate for the first time a tight relation between hamster periventricular CST and ORX2R expression levels during the different thermal conditions that may also directly modify wakefulness and energy balance. Overall, the results of our study instead of answering a series of doubts seem to propose other useful questions that are linked with temperature variations of a hibernating rodent model, among which the nature of neuronal responses induced after the interaction of CST with the orexinergic plus GABAergic neuronal systems that may constitute a novel antihypertensive therapeutic alternative for humans.

Disclosure of Potential Conflict of Interests

No potential conflicts of interest were disclosed.

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