Published in final edited form as:

Auton Neurosci. 2013 June ; 176(1-2): 1–2. doi:10.1016/j.autneu.2013.02.004.

Highlights in basic autonomic neurosciences: Central adenosine A1 receptor – The key to a hypometabolic state and therapeutic hypothermia?

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Abstract

The positive outcome that hypothermia contributes to brain and cardiac protection following ischemia has stimulated research in the development of pharmacological approaches to induce a hypothermic/hypometabolic state. Here we review three papers to highlight the role of the adenosine 1 receptor (A1AR) as a potential mediator and physiological regulator of a hypothermic state in both hibernating and non-hibernating mammals. We would like to emphasize the importance of comparative studies between hibernating and non-hibernating species that could lead to important discoveries on the mechanisms inducing hibernation and how they might be translated to induce a clinically useful hypothermic state.

Keywords

Adenosine; Hypothermia; Thermoregulation; Torpor; Ischemic injury

Introduction

There is a growing interest in finding a mechanism to induce therapeutic hypothermia in humans. Deep hypothermia and the resulting hypometabolic state significantly reduce cellular oxygen consumption which would be beneficial during a variety of surgeries and which contributes to cardio- and neuro-protection following traumatic ischemia events like cardiac arrest, myocardial infarction and stroke. Since a deep hypothermia is spontaneously triggered in hibernators, understanding the brain mechanisms regulating the initiation of this process could illuminate a method for its induction in non-hibernating species, including humans.

Jinka, T.R., Toien, O., Drew, K.L. 2011. Season primes the brain in an arctic hibernator to facilitate entrance into torpor mediated by adenosine A(1) receptors. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 31, 10752–10758.

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Article Summary

In this manuscript, the authors explore the role of the adenosine A1 receptor (A1AR) in triggering the entrance into torpor in the arctic ground squirrel (AGS), a hibernating species. Measurements of oxygen consumption (Vo_2) and core body temperature (T_{core}) were used as indirect measures of the metabolic state. In the first experiment, the central administration of the A1AR antagonist, 8-cyclopentyltheophylline (CPT), reversed a naturally occurring torpor, producing an increase in body temperature together with an increase of the Vo_2 consumption. In contrast, the activation of A1AR by the central administration of the adenosine A1 agonist, N^6 -cyclohexyladenosine (CHA), induced a hypothermic and hypometabolic state characterized by reduction of T_{core} and the Vo_2 . However, the induction of torpor by CHA injection was only effective in the middle and early hibernating season of the AGS, but not in the off-season for hibernation. Finally the authors showed that an A3AR agonist failed to induce torpor and that an A2AR antagonist did not reverse naturally occurring torpor. These results led the authors to conclude that the A1AR, but not the A2AR or A3AR, is necessary for the induction of the torpid state in the AGS.

Commentary

This is a well executed study, conducted with the appropriate controls, demonstrating the role of the A1AR in the induction of hypothermic and hypometabolic state that the authors relate to torpor. Although torpor is considered to be a hypometabolic state in which the thermogenesis is strongly reduced, it is a more complicated behavior characterized, not only by the inhibition of the thermogenesis, but also by an altered homeostatic regulation of other physiological and behavioral functions to guarantee the survival of these animals under these challenging conditions. This manuscript demonstrates the involvement of A1AR in the induction of the hypometabolic and hypothermic state in the AGS but does not give a conclusive answer to the question of whether adenosine is the mediator of the physiological torpid state. It remains to be determined if, during the induction of torpor by stimulation of A1AR, the behavioral (sleep homeostasis), cardiovascular and respiratory functions correspond to those occurring during natural hibernation. Furthermore, we do not yet know why the activation of A1AR is not able to trigger torpor during the off-season and which brain areas are involved in the induction of A1AR-mediated hypothermia. Overall, this is an important and innovative paper that should trigger scientific curiosity to understand the important question of how hibernation is regulated centrally.

Muzzi, M., Blasi, F., Masi, A., Coppi, E., Traini, C., Felici, R., Pittelli, M., Cavone, L., Pugliese, A.M., Moroni, F., Chiarugi, A. 2013. Neurological basis of AMP-dependent thermoregulation and its relevance to central and peripheral hyperthermia. *Journal of cerebral blood flow and metabolism* 33, 183–190.

Article Summary

This manuscript describes the hypothermia following the central administration of adenosine 5'-monophosphate (AMP) in mice and addresses potential mechanisms through which it might be elicited. ICV injection of 30–300 μg AMP in mice elicited a dose-dependent hypothermia of ~40 min duration and of ~2.5 °C maximal amplitude. Since this hypothermia

was almost completely blocked by the adenosine A1 receptor (A1R) antagonist, DPCPX, the conversion within the CNS of exogenous, extracellular AMP to adenosine (Ado) contributes significantly to the hypothermia. Central Ado-induced hypothermia was potentiated by blockade of equilibrative nucleoside transporters (ENTs), responsible for the uptake of Ado. AMP also interacts with A1R to elicit hypothermia since AMP still elicits an A1R-dependent hypothermia following inhibition of 5'-NT, the enzyme that converts extracellular AMP to Ado. AMP added to the bathing solution reduced, via A1R, the spontaneous firing rate of both warm-sensitive and temperature-insensitive neurons in the preoptic area (POA), the latter effect providing a potential mechanism for a reduction in thermoregulatory thermogenesis and cutaneous vasoconstriction that would be expected to underlie the hypothermia elicited by central AMP or Ado. Intraperitoneal AMP could prevent or reverse central PGE2-evoked fever, but not the hyperthermia elicited by i.p. MDMA.

Commentary

This study provides good evidence that activation of central A1R, by Ado and, to a more limited extent by AMP, can produce a potent hypothermia and that the role of 5'-NT in determining the extracellular level of Ado can contribute significantly to the thermoregulatory responses mediated via A1R. The authors acknowledge, however, that the efflux of Ado through ENTs of neurons, rather than the conversion of AMP to Ado is the mechanism of increased extracellular Ado during increased neuronal discharge. The authors have overinterpreted their results from recordings of POA neurons. Not only are most of the thermally-insensitive POA neurons likely to be involved in controlling homeostatic systems other than thermoregulation (sleep, reproduction, osmotic balance, etc), but the finding of A1R-mediated effects on POA neurons does not preclude "the possibility that Ado influences on other neuronal populations in thermoregulatory pathways are responsible for Ado's hypothermic effects." A particular shortcoming of this study is the absence of a test of their hypothesis that blockade of A1R in the POA would eliminate the hypothermic response to AMP administration. Nonetheless, these results make a significant contribution to our appreciation of the significant role of central adenosine and its purinergic receptor systems in the regulation of body temperature and energy homeostasis.

McClure, J.M., O'Leary, D.S., Scislo, T.J. 2011. Neural and humoral control of regional vascular beds via A1 adenosine receptors located in the nucleus tractus solitarii. *American journal of physiology. Regulatory, integrative and comparative physiology* 300, R744–755.

Article Summary

This paper explores the effect of adenosine A1 receptor activation selectively in the nucleus tractus solitarii (NTS) on the regulation of regional vascular conductance via the sympathetic nervous system, adrenal catecholamine secretion, and vasopressin secretion. The main findings are that adenosine A1 receptor activation in the NTS results in an initial transient adrenal-mediated beta-adrenergic vasodilation occurring predominately in the iliac vascular bed followed by a sustained vasopressinergic vasoconstriction in all vascular beds examined (iliac, mesenteric, renal). There was very little contribution of regional

sympathetic vasoconstriction to any of the observed changes in vascular resistance evoked by adenosine A1 receptor activation in the NTS.

Commentary

The authors hypothesized a role for adenosine A1 receptor activation in the NTS in redistributing blood flow from the viscera to skeletal muscle during the hypothalamic defense response (HDR). This hypothesis is a reasonable extension of previous work demonstrating a role for adenosine A1 receptor activation in the NTS in the HDRSt (St Lambert et al., 1997), however it was not supported by the observations that activation of A1 receptors in the NTS had little, if any, effect on the redistribution of blood. Nonetheless, this paper clearly elucidates the mechanisms underlying the robust cardiovascular effects of activation of adenosine A1 receptors in the NTS, results that could have important implications for conditions in which this system may become activated, such as ischemia, hypoxia and severe hemorrhage.

Concluding Remarks

The discussion of these three papers leads to the conclusion that adenosine could be the key molecule for the induction of torpor in hibernating mammals and that brain areas involved in maintaining homeostasis, including those controlling thermoregulation, metabolism, cardiovascular function and respiration, could play a role in the induction of torpor in both hibernating and non-hibernating mammals. Clearly, further experimentation in non-hibernating species, including human, will be required to explore the possibility that central adenosine can trigger a torpor-like state that would be therapeutically useful to reduce metabolic demands of ischemic or injured tissues.

References

St Lambert JH, Thomas T, Burnstock G, Spyer KM. A source of adenosine involved in cardiovascular responses to defense area stimulation. *Am J Physiol.* 1997; 272:R195–R200. [PubMed: 9039009]