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Review

Anapyrexia during hypoxia

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Abstract

Reducing body temperature has been found to improve survival not only due to hypoxia (the main focus of this review) but also to ischemia, shock, and many other types of insults. Under these conditions, there is a reduced oxygen delivery to the brain. To compensate the hypoxia, a regulated hypothermia (anapyrexia—Glossary of terms for Thermal Physiology, Commission for Thermal Physiology, 2001) takes place, which has been reported as a beneficial response since the drop in body temperature causes a reduced oxygen demand. The objective of the present article is to review the current knowledge of the mechanisms of hypoxia-induced anapyrexia, focusing on its neurochemical control mainly at the preoptic region of the anterior hypothalamus.

Keywords: Hypothermia; Serotonin; Dopamine; Nitric oxide

Contents

1. Introduction

Aerobic organisms rely essentially on oxygen as the final acceptor of electrons from oxidative metabolism, being crucial for maintaining electron flow through the respiratory chain as well as ATP synthesis and therefore cell function. In this scenario, it is clear that hypoxia can put at risk life of all aerobic organisms which employ a number of compensatory responses, such as anapyrexia, in order to alleviate the hypoxic stress (Wood, 1991, 1995; Steiner and Branco, 2002).

It is well established that hypoxia affects thermoregulation, causing a reduction in Tb of endotherms by means of a decreased heat production and increased heat loss (Gautier et al., 1987; Barros et al., 2001; Tattersall and Milsom, 2003). This is thought to be a regulated response rather than a lack of control to low oxygen availability, and thus it is consistent with the notion of a downward resetting of the thermoregulatory set point, as previously

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suggested (Barros et al., 2001; Tattersall and Milsom, 2003). However, the mechanisms responsible for the hypoxic anapyrexia are still poorly understood. Recently, some advances have been made about its mediators (cf. Steiner and Branco, 2002). Adding to this scenario, adenosine, dopamine, serotonin, nitric oxide (NO) and carbon monoxide (CO) have been suggested as putative mediators and represent the main focus of this review article.

2. Anapyrexia as a beneficial response

The way anapyrexia exerts its protection against low oxygen availability may be by means of three main mechanisms. Firstly by the Q10 effect (oxygen consumption decreases about 11% per °C drop in Tb). In mammals, however, this is true for anapyrexia since it is not accompanied by a thermogenic and oxygen consuming response, a fact observed during forced hypothermia, emphasizing the difference between anapyrexia and hypothermia (cf. Glossary of Terms for Thermal Physiology, Commission for Thermal Physiology, 2001). Secondly by a leftward shift in the oxyhemoglobin dissociation curve with a resulting increase in oxygen loading in the lungs. And thirdly, evidence from ectotherms indicates that both the ventilatory and cardiovascular responses to hypoxia, which are oxygen consuming, are impaired at lower Tb values (cf. Wood, 1991).

The argument that anapyrexia increases survival of hypoxic species, together with the fact that this response is extremely widespread among taxa, provides evidence that it is an adaptive response. Lizards, toads and even the *Paramecium* present higher survival rates under hypoxic conditions when hypothermic, usually close to the Tb chosen by these species in a thermal gradient under hypoxia (Wood and Malvin, 1991; Malvin and Wood, 1992). Moreover, in a variety of rodent species like rats, mice, hamsters and squirrels the thermoneutral zone has been reported to be shifted to lower temperatures during hypoxia exposure (Dupre et al., 1988; Gordon and Fogelson, 1991; Barros et al., 2001) suggesting that hypoxia-induced anapyrexia is indeed a regulated response. The correlation between hypoxia and anapyrexia has also been reported in hypoxic rats in which the drop in Tb has been shown to come into effect through inhibition of caspase activation, thereby preventing apoptotic cell death (Zhu et al., 2004). Even cognitive functions were reported to be preserved after severe hemorrhage (which represents an oxygen limiting situation) when combined with anapyrexia (Alam et al., 2005).

3. Neurochemical control of anapyrexia

It is currently acceptable that the thermoregulatory set point is given as a balance between warm- and cold-sensitive neurons located in the preoptic region of hypothalamus (POA) (Boulant, 2000). However, it is important to mention that the set-point concept has recently been reevaluated and a new proposition including more than one thermoregulatory set-point has been suggested (Kazuyuki et al., 1998). Thus, according to this new hypothesis, both fever and anapyrexia are brought about by shifts in the thermal balance as the result of changes in the temperature thresholds for activation of thermoeffectors and in the behavioral component of thermoregulation (Romanovsky, 2004). Data supporting the notion that the drop in Tb caused by hypoxia is consequence of a downward resetting of the thermoregulatory set point exist (cf. Barros et al., 2001). Additionally, Tamaki and Nakayama (1987) reported that thermosensitivities of preoptic warm-sensitive neurons are indeed modified by hypoxia. These findings point at the brain as a major site involved in the anapyrexia. In corroboration, it has been shown that hypoxia-induced anapyrexia results partially from the impairment of oxidative phosphorylation in the CNS (Branco and Malvin, 1996), and that exclusion of glucose from central sites, which could impair oxidative phosphorylation by reducing the availability of metabolic substrate, also causes a reduction in Tb (Branco, 1997). Taken together, these results imply that a reduction in oxidative phosphorylation in the CNS is important for the development of anapyrexia.

As to the thermoeffector neuronal pathways in anapyrexia, it has been suggested that the inhibition of cutaneous vasoconstriction (Janig et al., 1983) and/or inhibition of non-shivering thermogenesis (Mortola and Naso, 1997) take part in the mechanisms underlying the thermoregulatory response to hypoxia. Recently, peripheral chemoreceptor-evoked inhibition of brown adipose tissue (BAT) sympathetic nerve activity was reported to directly contribute to the hypoxia–anapyrexia (Madden and Morrison, 2005). However, further research is still needed. For instance, the neuronal pathways responsible for regulating Tb during hypoxia have not demonstrated any effects on behavioral thermoregulatory pathways particularly in mammals.

As previously mentioned, we will focus on new data about the mediators involved with regulated anapyrexia during hypoxia.

3.1. Nitric oxide

NO synthase (the enzyme responsible for NO endogenous production) is encountered in various tissues involved in Tb control. In this context, there is evidence that NO plays differential thermoregulatory roles by acting in the periphery and in the CNS (Steiner and Branco, 2001). This notion is based on the opposite results obtained by injecting pharmacological modifiers of the NO pathway systemically or intracerebroventricularly. Studies on rats in their thermoneutral zone have shown that the systemic nonselective inhibition of NO synthesis elicits a decrease in Tb, despite the fact that L-NAME should decrease cutaneous heat loss because it causes vasoconstriction in