MECHANISMS OF HYPOXIA-INDUCED HYPOTHERMIA

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Hypoxia evokes a regulated decrease in body core temperature (Tc) in a wide variety of organisms ranging from protozoans to mammals, a response that has been referred to as anapyrexia, but only recently did the mechanisms responsible for hypoxia-induced anapyrexia start to be suggested. A route mediating the reduction in Tc may be the impairment of central oxidative phosphorylation since intracerebroventricular injection of inhibitors of oxidative phosphorylation such as azide or cyanide reduces the preferred Tc of toads. Moreover, exclusion of glucose from central sites, which could impair oxidative phosphorylation, plays a major role in hypoglycemia-induced hypothermia. However, whether inhibition of oxidative phosphorylation acts directly on neurons to produce anapyrexia or is only a cellular signal for the release of substances that could mediate anapyrexia remains to be determined. Anyway, these data imply that the central nervous system (CNS) plays a central role in the development of anapyrexia. Several putative mediators of anapyrexia have been proposed. Some lines of evidence indicate arginine vasopressin (AVP) as a mediator. However, we recently showed that the blockade of AVP receptors peripherally as well as centrally does not alter the magnitude of hypoxia-induced anapyrexia. Data with Bratleboro rats, which lack AVP producing neurons in the CNS, also support this notion. Besides AVP, many other mediators have also been suggested such as lactate, adenosine and histamine, but none of the possible candidates can trigger a full blown hypothermic response. Recently, the labile gas nitric oxide (NO), by acting in the CNS, has been shown to play a major role mediating hypoxia-induced anapyrexia as well as the decrease in Tc elicited by other stimuli, such as 2-DG, insulin, and systemic arginine-vasopressin, suggesting that NO is a common mediator of hypothermia. This effect is likely to be dependent on the neuronal isoform of NO synthase since treatment with 7-NI, a selective neuronal NO synthase inhibitor, impairs hypoxia-induced anapyrexia, even though some controversy may exist. Furthermore, it is interesting to point out that recent data from our laboratory also points that substances may be formed during hypoxia to counteract the actions of the mediators of anapyrexia and, consequently, to avoid an excessive drop in Tc, similarly to what occurs during fever (pyrogens vs. cryogens). This seems to be the case of endogenously formed carbon monoxide (CO) since inhibition of the enzyme responsible for CO synthesis in the CNS augments the hypoxia-induced anapyrexia. Although progress has been made in the understanding of the mechanisms of anapyrexia, it is important to keep in mind that they still remain little explored and represent a field that needs urgent research.

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