NITRIC OXIDE IN THE CONTROL OF BODY TEMPERATURE AND FEVER

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Fever is a phenomenon characterized by a raised thermoregulatory set point that leads to an elevation in body temperature (Tb). It is well known that fever can be initiated by a number of agents including endotoxin (LPS), viruses, yeast and Gram-positive bacteria. Considerable efforts have been made to identify the mechanisms of fever, but they still remain only partially understood. Recently, a new biologically active molecule has been described, *i.e.*, the gaseous compound nitric oxide (NO). This molecule started a revolution in the understanding of the physiological systems and has been shown to participate of several physiological and pathophysiological manifestations, including thermoregulation and fever. A growing body of evidence supports that NO plays a role in thermoregulation under euthermic conditions. In this context, we and others have provided evidence that NO plays different thermoregulatory effects by acting in the periphery and in the central nervous system (CNS). This notion is based on the opposite results obtained by injecting pharmacological modifiers of the NO pathway systemically or intracerebroventricularly. Accordingly, peripheral NO might increase thermogenesis, leading to an increase in Tb, and yet increase heat loss mechanisms (cutaneous vasodilation, panting and sweating), producing a reduction in Tb. The thermoregulatory effect of the systemic inhibition of NO synthesis depends, thus, on the prominent thermoregulatory mechanism in the species tested, ambient temperature, among other factors. Accordingly, systemic inhibition of NO synthesis has been shown to decrease Tb in rats, a fact that seems to be associated with an impaired thermogenesis (Branco *et al.*, 1997; Steiner *et al.*, 1998), whereas systemic inhibition of NO synthesis increases Tb in rabbits, a response which seems to result from a reduced respiratory heat dissipation (Mathai *et al.*, 1997). Moreover, inhibition of NO synthesis in the CNS has been shown to lead to a slight increase in Tb (Branco *et al.*, 1997; Steiner *et al.*, 1998), which is likely to be associated with an increase of the sympathetic tonus. As to fever, evidence has accumulated that peripherally acting NO is likely to be a signaling molecule for the development of fever since it has been reported that systemic administration of inhibitors of NO synthesis impairs fevers induced by LPS in rats and guinea pigs (Scammell *et al.*, 1996), IL-1 in rats (Reimers *et al.*,1994; Roth *et al.*, 1998), MDP in guinea pigs (Kamerman and Fuller, 2000), yeast in rats (Ataoglu *et al.*, 2000) and even psychological stress in rats (De Paula *et al.*, 2000). On the other hand, intracerebroventricular administration of NOS inhibitors enhances fever in rats and rabbits, suggesting that NO is an antipyretic molecule by acting in the CNS (Almeida *et al.*, 1999). Although the summation of NO actions in the CNS results in antipyresis, NO may also be a pyretic molecule in some specific brain regions, such as the OVLT.

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