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BRAIN RESEARCH

Research Report

Role of preoptic opioid receptors in the body temperature reduction during hypoxia

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ABSTRACT

Evidence indicates that endogenous opioids play a role in body temperature (Tb) regulation in mammals but no data exist about the involvement of the specific opioid receptors, mu, kappa and delta, in the reduction of Tb induced by hypoxia. Thus, we investigated the participation of these opioid receptors in the anteroventral preoptic region (AVPO) in hypoxic decrease of Tb. To this end, Tb of unanesthetized Wistar rats was monitored by temperature data loggers before and after intra-AVPO microinjection of the selective kappa-opioid receptor antagonist nor-binaltorphimine dihydrochloride (nor-BNI; 0.1 and 1.0 μg/100 nL/animal), the selective mu-opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 cyclic (CTAP; 0.1 and 1.0 μg/100 nL/animal), and the selective delta-opioid receptor antagonist Naltrindole (0.06 and 0.6 μg/100 nL/animal) or saline (vehicle, 100 nL/animal), during normoxia and hypoxia (7% inspired O_2). Under normoxia, no effect of opioid antagonists on Tb was observed. Hypoxia induced Tb to reduce in vehicle group, a response that was inhibited by the microinjection intra-AVPO of nor-BNI. In contrast, CTAP and Naltrindole did not change Tb during hypoxia but caused a longer latency for the return of Tb to the normoxic values just after low O_2 exposure. Our results indicate the kappa-opioid receptor in the AVPO is important for the reduction of Tb during hypoxia while the mu and delta receptors are involved in the increase of Tb during normoxia post-hypoxia.

1. Introduction

Both physiological and pathological conditions may generate a reduction in oxygen availability for living organisms. Physiological situations usually result from hypoxic environments (reduced O_2 partial pressure), such as high altitudes and burrows (Boggs et al., 1984; Kuhnen, 1986; Lechner, 1976; Vargas et al., 2001; Williams and Rausch, 1973). As to pathological situations, obstructive sleep apnea and chronic obstructive pulmonary disease, as well as hemorrhage,

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Abbreviations: AVPO, anteroventral preoptic region; cAMP, cyclic AMP; cGMP, cyclic GMP; CNS, central nervous system; MPO, medial preoptic area; POA, anterior hypothalamus preoptic region; Tb, body temperature; icv, intracerebroventricular

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anemia and traumas are examples of conditions in which patients suffer with hypoxia (Bao et al., 1997; Gordon, 2001; Reissmann et al., 2000).

It is established that hypoxia reduces Tb of endotherms by decreasing heat production and increasing heat loss besides cold-seeking behavior (Barros et al., 2001; Bicego et al., 2007; Gautier et al., 1987; Tattersall and Milsom, 2003). Such response has been called anapyrexia (Barros et al., 2001; Steiner and Branco, 2002) or regulated hypothermia (Gordon, 2001). Recently, it has been proposed that the decrease in the threshold Tb for activation of thermogenesis is a common mechanism for Tb fall associated with physiopathotological hypoxic conditions (Romanovsky, 2004). Moreover, the terms anapyrexia and regulated hypothermia have been suggested to be redefined as the result of changes in the temperature thresholds for activation of thermoeffectors and in the behavioral component of thermoregulation (balance point) instead of changes in a unique thermoregulatory set point (Romanovsky, 2004).

The drop in Tb and metabolic rate reduces the formation of free radicals and tissue edema, as well as the toxicity of many substances, which consists in a protective effect for hypoxic tissues (Gordon, 2001; Katz et al., 2004). The benefits of Tb reduction in hypoxic animals can be evidenced by the increase of survival observed in several species such as rats (Wood, 1995; Wood and Stabenau, 1998), mice (Artru and Michenfelder, 1981), lizards (Hicks and Wood, 1985) and even the *Paramecium caudatum* (Malvin and Wood, 1992).

A 10% inspired hypoxic mixture was demonstrated to change the thermal sensitivity of warm-sensitive neurons located in the POA of anesthetized rats (Tamaki and Nakayama, 1987). Warm-sensitive neurons, profusely distributed through the POA, are known to be tonically active at thermoneutrality (Boulant, 2006; Nakayama et al., 1961; Nakayama et al., 1963). Recent body of evidence (Morrison et al., 2008) indicates that warm-sensitive neurons located in the MPO are inhibited by local temperature decrease and by GABAergic projections from median preoptic nucleus, whose neurons receive afferent inputs from cool-sensitive (and possibly warm-sensitive) cutaneous thermoreceptors, via parabraquial nucleus. Moreover, MPO neurons are demonstrated to influence autonomic thermoeffectors via inhibition of thermogenic pathways that involve the dorsomedial hypothalamus and rostral raphe pallidus.

During the last two decades, some substances have been suggested to play a role in Tb reduction during hypoxia, such as dopamine, serotonin and nitric oxide, by acting specifically in the POA (Branco et al., 2006). Endogenous opioids have also been suggested to be involved in thermoregulation during hypoxia (Mayfield and D'alecy, 1992; Mayfield et al., 1994; Steiner and Branco, 2002) but the specific receptors implicated in this response as well as the site of their action are still unknown. Three major opioid receptors were identified and cloned, kappa, mu and delta, each one presenting different physiological and pharmacological properties (Jordan and Devi, 1998). There is anatomical and electrophysiological evidence for the presence of these receptors in the POA of rats (Coolen et al., 2004; Mansour et al., 1987; Mansour et al., 1994; Mansour et al., 1995; Mansour et al., 1996; Yakimova et al., 1996; Yakimova et al., 1998).

Endogenous opioids are a group of molecules with several effects many of them associated with stress responses, analgesia (Akil et al., 1984) and thermoregulation (Baldino et al., 1980; Benamar et al., 2005; Broccardo and Improta, 1992; Handler et al., 1992; Handler et al., 1994; Mackowiak, 1998; Malvin, 1998; Mayfield and D'alecy, 1992; Mayfield et al., 1994; Salmi et al., 2003; Spencer et al., 1988; Spencer et al., 1990; Yakimova et al., 1996; Yakimova et al., 1998). It was demonstrated that subcutaneous injection of naltrexone (nonselective opioid antagonist) blocks hypothermia occurring after heatstroke in guinea pigs indicating an opioid-mediated mechanism for inhibition of metabolism (Romanovsky and Blatteis, 1996). On the other hand, icv injection of naloxone, another nonselective opioid antagonist, presents a hypothermic effect in guinea pigs (Romanovsky et al., 1994).

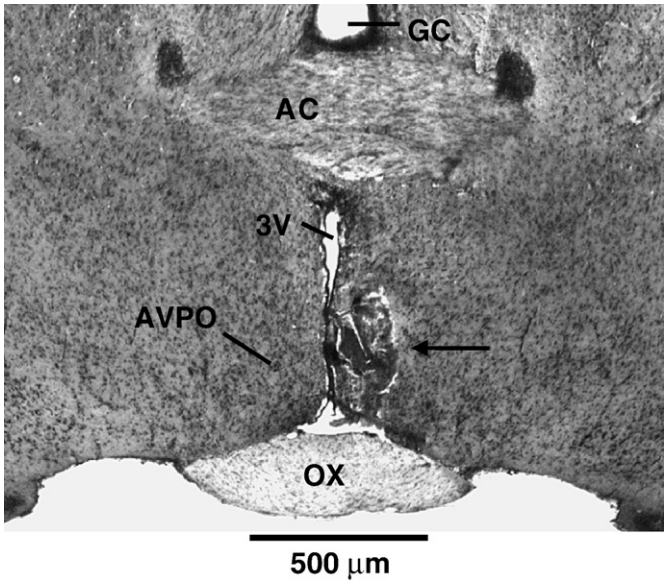

Fig. 1 – Typical site of microinjection in the anteroventral preoptic region (AVPO). Injection site is indicated by the black arrow. [Landmarks: the anterior commissure (CA); the optic chiasm (OX); the third ventricle (3V)]. GC: guide cannula.