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Research Report

Regulatory mechanism of body temperature in the central nervous system during the maintenance phase of hibernation in Syrian hamsters: Involvement of β-endorphin

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ABSTRACT

We have shown previously that intracerebroventricular (icv) injection of naloxone (a non-selective opioid receptor antagonist) or naloxonazine (a selective μ1-opioid receptor antagonist) at the maintenance phase of hibernation arouses Syrian hamsters from hibernation. This study was designed to clarify the role of β-endorphin (an endogenous μ-opioid receptor ligand) on regulation of body temperature (T_b) during the maintenance phase of hibernation. The number of c-Fos-positive cells and β-endorphin-like immunoreactivity increased in the arcuate nucleus (ARC) after hibernation onset. In contrast, endomorphin-1 (an endogenous μ-opioid receptor ligand)-like immunoreactivity observed on the anterior hypothalamus decreased after hibernation onset. In addition, hibernation was interrupted by icv injection of anti-β-endorphin antiserum at the maintenance phase of hibernation. The mRNA expression level of proopiomelanocortin (a precursor of β-endorphin) on ARC did not change throughout the hibernation phase. However, the mRNA expression level of prohormone convertase-1 increased after hibernation onset. [D-Ala^2,N-MePhe^4,Gly-ol^5] enkephalin (DAMGO, a selective μ-opioid receptor agonist) microinjection into the dorsomedial hypothalamus (DMH) elicited the most marked T_b decrease than other sites such as the preoptic area (PO), anterior hypothalamus (AH), lateral hypothalamus (LH), ventromedial hypothalamus and posterior hypothalamus (PH). However, microinjected DAMGO into the medial septum indicated negligible changes in T_b. These results suggest that β-endorphin which synthesizes in ARC neurons regulates T_b during the maintenance phase of hibernation by activating μ-opioid receptors in PO, AH, VMH, DMH and PH.

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1. Introduction

For animals living in a habitat, where food and environment vary with the change in weather throughout the year, some hibernate before the ambient temperature drastically decreases with food scarcity. Hibernating animals exhibit profound physiological changes including low body temperature (T_b), respiratory depression (Kayser, 1961), bradycardia, analgesia, and attenuated general metabolism (Heldmaier et al., 2004; Milsom et al., 1999; Storey, 2003). Typical hibernating mammals, such as the Syrian hamster and the ground squirrel, tend to lower their T_b to near ambient temperatures during hibernation (Barnes, 1989; Tamura et al., 2005). It is widely recognized that this process is under strict neuronal control involving the hypothalamus, preoptic area and hippocampus (Heller and Colliver, 1974; Sallmen et al., 2003; Wunnenberg et al., 1976). Of about 4070 species of mammals, more than 200 species are known to hibernate (Kawamichi et al., 2000). As such, hibernation is not a special adaptation feature of certain mammals rather it is a universal system that enables the relevant animals to generate the life-maintenance energy required to sustain homeothermism and survive through a hostile and energy-deprived period. Although knowledge regarding neurochemical mechanisms of hibernation is accumulating (Jinka et al., 2011; Tamura et al., 2005), it has not yet been fully elucidated.

The endogenous opioid peptide has been classified into three families: i) endorphins, ii) enkephalins and iii) dynorphins. These opioid peptides have relatively high binding affinity for μ-opioid, δ-opioid and κ-opioid receptors, respectively. In our previous work, we have observed that intracerebroventricular (icv) injection of naloxone (a non-selective opioid receptor antagonist) or naloxonazine (a selective μ-opioid receptor antagonist) at the maintenance phase elevated T_b and interrupted hibernation in Syrian hamsters (Tamura et al., 2005). These results suggest that T_b during the maintenance phase in Syrian hamsters is regulated by certain endogenous μ-opioid receptor ligands. β-Endorphin is an endogenous μ-opioid receptor ligand, and has an important role in nociception, regulation of body temperature and locomotor activity (Tseng et al., 1980). Moreover, the arcuate nucleus (ARC) within the hypothalamus is an important site for syntheses of various opioid peptides, including β-endorphin (Kawano and Masuko, 2000; Liotta et al., 1984; Sofroniew, 1979). Interestingly, perikarya in the ARC contain either β-endorphin or enkephalin, but not both peptides (Bloom et al., 1978; Lantos et al., 1995). Therefore, we attempted in this study to show if β-endorphin played a role in T_b regulation of Syrian hamsters during the maintenance phase in hibernation. Furthermore, we endeavored to locate the site of β-endorphin action in the brain.

2. Results

2.1. Changes in c-Fos-positive cell counts

It is well known that c-Fos serves an index for neuronal activity. Therefore, we investigated if changes in c-Fos-positive cell counts occurred between before (accommodated in a hibernation-inducible environment for 30 days, where their T_b was ca. 37 °C) and after (1 h after hibernation onset, where T_b of hamsters registered ca. 34 °C) hibernation onset.

Unlike other sites that showed either marked decreases or insignificant changes, c-Fos-positive cell counts significantly ($p<0.01$) increased only in ARC after hibernation onset (closed column; Fig. 1).

2.2. Immunohistochemistry

As endogenous μ-opioid receptor ligand β-endorphin-producing cells are localized in ARC, the dynamic perspectives of β-endorphin were investigated by immunohistochemical procedures. Changes of β-endorphin-like immunoreactivity in ARC (Fig. 2) revealed that ß-endorphin-like immunoreactivity was observed mainly in the cell bodies of controls (Fig. 2A). 'Controls' imply those untreated intact hamsters maintained at an ambient temperature of 23 °C in a room illuminated with an alternating 12-h light–dark cycle. When c-Fos-positive cell counts increased 1 h after hibernation onset, ß-endorphin-positive cell counts elevated as well (Fig. 2B).

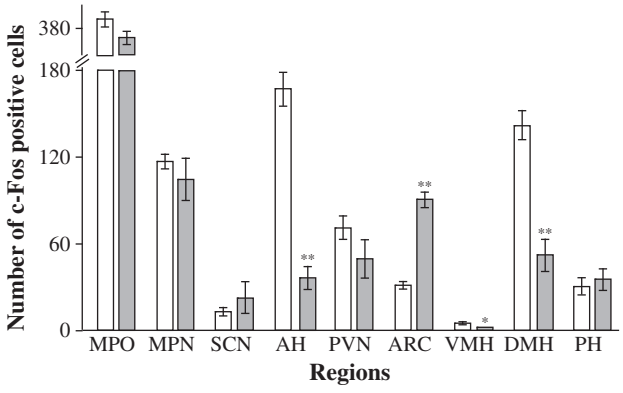

Fig. 1 – Comparison between the c-Fos-positive cell counts before and after hibernation onset in hibernating Syrian hamsters. Open and closed columns represent the numbers of c-Fos-positive cell counts before and after hibernation onset, respectively.Each bar represents the mean ± SEM. of six hamsters. Differences where $p<0.05$ (*) or <0.01 (**) compared with prehibernation values were considered significant using the Kruskal–Wallis test followed by the Mann–Whitney *U*-test.