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BRAIN RESEARCH

Research Report

Transforming growth factor-beta in the brain enhances fat oxidation via noradrenergic neurons in the ventromedial and paraventricular hypothalamic nucleus

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ABSTRACT

We have previously reported that intracisternal administration of TGF-beta induces an increase in fat oxidation and that intracisternal administration of anti-TGF-beta antibody partially inhibits an increase in fat oxidation during treadmill running in rats. These results indicate a regulatory role of that TGF-beta in the brain on fat oxidation during exercise. However, it is not clear how TGF-beta in the brain enhance fat oxidation. We hypothesized that TGF-beta in the brain elicits its regulatory effects on fat oxidation via hypothalamic noradrenergic neurons, because some reports have demonstrated the important role of hypothalamic noradrenergic neurons in the regulation of fat oxidation during and after exercise. To examine this hypothesis, we measured the extracellular noradrenaline (NA) levels in the paraventricular hypothalamic nucleus (PVH), ventromedial hypothalamic nucleus (VMH) and lateral hypothalamic area, which are especially important in the regulation of energy metabolism, after intracisternal administration of TGF-beta by using an in vivo brain microdialysis. Microdialysis study revealed that intracisternal administration of TGF-beta3 caused increases in the NA levels in the PVH and VMH. Then, we investigated the impact of impairment of noradrenergic neurons in the PVH and VMH by neurotoxin 6-hydroxydopamine microinjection (NA-lesion) on the action of intracisternal administration of TGF-beta. The NA lesion completely abolished the regulatory effect of TGF-beta on fat oxidation. These results suggest that TGF-beta in the brain enhances fat oxidation via noradrenergic neurons in the PVH and VMH.

1. Introduction

We have previously reported that the concentration of activated transforming growth factor-beta (TGF-beta) increases in the cerebrospinal fluid of rats during swimming exercise (Inoue et al., 1999), and intracisternal administration of TGF-beta induces an increase in fat oxidation (Yamazaki et al., 2002). We have also reported that the changes observed on an encephalogram after intracisternal TGF-beta administration were similar to those after swimming exercise (Arai et al., 2002) and that TGF-beta in the brain can partly regulate fat oxidation in the whole body during treadmill exercise (Ishikawa et al., 2006). These results led us to postulate that TGF-beta in the brain largely participates in fat oxidation that is regulated by the central nervous system (CNS) during and after exercise.

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During endurance exercise, the energy substrate shifts from carbohydrate to fat (Hurley et al., 1986), and during the post-exercise phase, fat continues to be the preferred energy substrate (Binzen et al., 2001). How is the increase in fat oxidation during and after exercise advantageous? The increase in fat oxidation during exercise is considered to contribute to performance enhancement because the preferential use of fat leads to the sparing of glycogen, which is an important energy source for every exercise. Body fat stores are enormous, but body carbohydrate stores are limited (Hermansen et al., 1967). In addition, fat can produce twice as much energy as carbohydrate. Thus, the preferential use of fat during exercise implies a more efficient production of energy and sparing of carbohydrate as an energy substrate. Increase in fat oxidation after exercise also provides an indirect support for glycogen synthesis and its restoration. Therefore, an increase in fat oxidation during and after exercise could be regarded as a part of the defensive system that alleviates fatigue and avoids exhaustion.

Thus, we speculate that TGF-beta present in the brain plays a certain role in this mechanism through enhancing fat metabolism. Another effect of intracisternal TGF-beta administration was depression of the spontaneous motor activity in experimental

Table 1 – Effect of 6-hydroxydopamine (6-OHDA) microinjection into the hypothalamus on the noradrenaline (NA) level in the hypothalamic tissues of the rats

Pg/mg (wet weight)	NA-lesioned	Sham	
PVH	653±187.3	1182.7±232.1	$P=0.114$
VMH	231±33.4	1386.3±232.3	$P=0.00116$
LHA	777.9±129.1	874.6±73.8	

The experimental rats were injected 6-OHDA (1 μL, 10 μg/μL) into the hypothalamus bilaterally. The sham-operated rats were injected saline (1 μL). The NA levels in each hypothalamic region were measured using high-performance liquid chromatography (HPLC). The values are expressed as mean±S.E.M ($n=5, 6$).

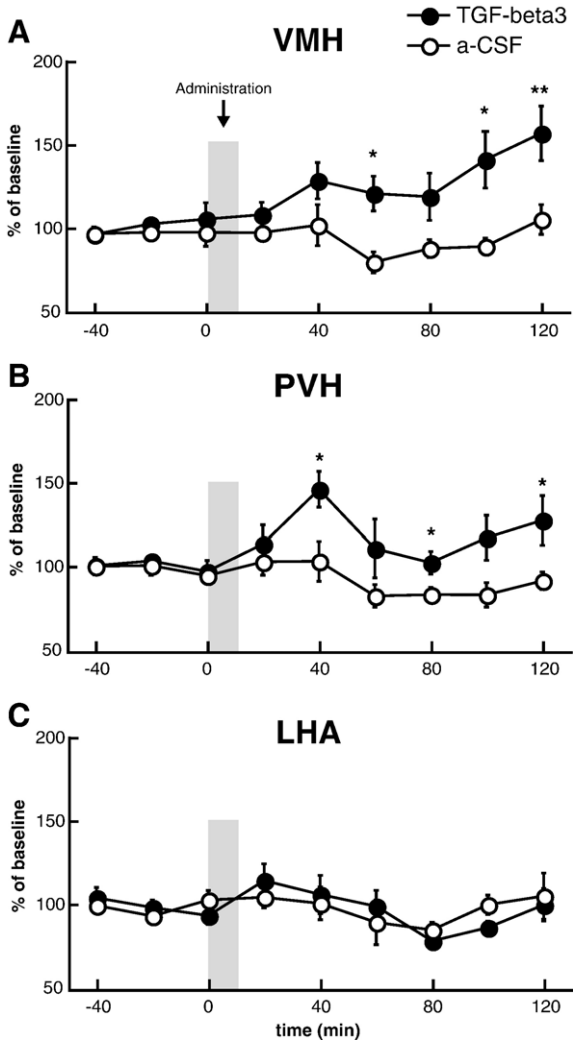

Fig. 1 – Effects of intracisternal TGF-beta3 administration on extracellular noradrenaline (NA) levels in the ventromedial hypothalamic nucleus (A), paraventricular hypothalamic nucleus (B), and lateral hypothalamic area (C). Transforming growth factor-beta (TGF-beta3; 40 μL, 1 ng/μL) or artificial cerebrospinal fluid (a-CSF; 40 μL) was injected into the cisterna magna (at 0–10 min) after establishing the baseline NA levels. The average NA level of 3 samples collected before administering TGF-beta3 or a-CSF was defined as the baseline level (100%). The gray area indicates the period of TGF-beta3 or a-CSF administration. The values are expressed as mean±S.E.M. ($n=5–7$). **, $P<0.01$; *, $P<0.05$; significantly different from the a-CSF group.

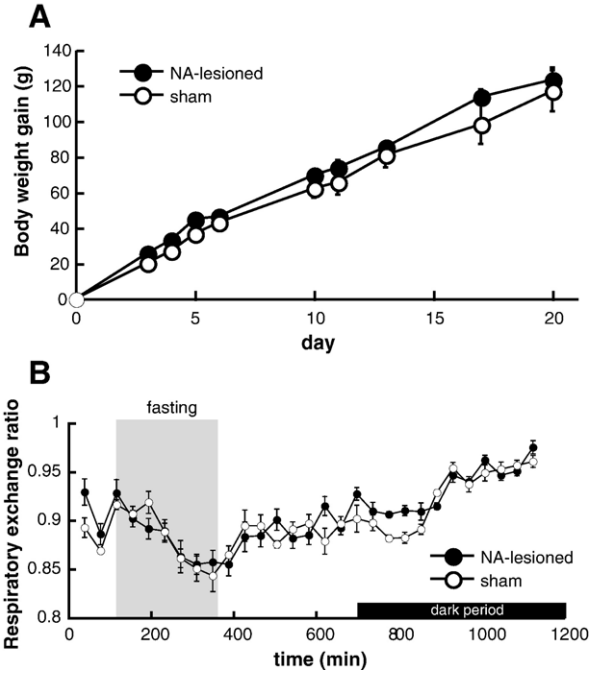

Fig. 2 – (A) Body weight changes after 6-hydroxydopamine microinjection into the hypothalamus. The values are expressed as mean±S.E.M. ($n=5–7$). (B) Respiratory exchange ratio of the noradrenaline (NA)-lesioned rats and the sham-operated rats maintained in a sedentary condition. The RER was measured for 20 h from the onset of the light cycle. After 2 h of the onset of the light cycle, the rats were deprived of food for 3 h and then re-fed. The gray area indicates the fasting period. The values are expressed as mean±S.E.M. ($n=5–7$).