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ALTERED GABAB RECEPTOR THERMOREGULATORY FUNCTION IN RATS WITH DIET-INDUCED OBESITY

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Abstract. *GABAB receptors are G-protein-coupled receptors, playing a very important role in the regulation of many physiological processes. The GABAB signaling pathway could modulate neurotransmission processes at the level of the preoptic area in the anterior hypothalamus, which is thought to function as the thermoregulatory center. The present study was performed to investigate the effects of GABAB agonists and antagonists on core body temperature of rats with normal weight and diet-induced obesity. The results showed that systemic administration of the GABAB antagonist CGP35348 induced significant hyperthermia in rats with normal weight, whereas the GABAB agonist baclofen led to a decrease in body temperature. The effects of baclofen and CGP35348 on body temperature were less pronounced in rats with diet-induced obesity compared with those with normal weight. Presently it remains unclear how obesity affects the GABAB receptor function at the level of the central thermoregulatory system.*

Key words: *GABAB agonist and antagonist, thermoregulation, obesity*

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INTRODUCTION

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS) that activates two types of receptors: the ionotropic GABAA and metabotropic GABAB receptors. Unlike the GABAA receptor that forms ion channels, GABAB is a G-protein coupled receptor that regulates specific ion channels and inhibits adenylyl cyclase which reduces cyclic adenosine monophosphate levels. GABAB receptors are known to control synaptic neurotransmission, playing a very important role in the regulation of many physiological processes [1].

Several studies have shown that GABA and GABA receptor agonists produce hypothermia, whereas GABA receptor antagonists cause hyperthermia [2, 3, 4]. GABA could modulate neurotransmission processes at the level of the preoptic area in the anterior hypothalamus (PO/AH), which is thought to function as the thermoregulatory center. Experiments in rat brain slices demonstrated that GABAA and GABAB agonists decreased dose-dependently the firing rate of warm-sensitive and temperature-insensitive PO/AH neurons, whereas the temperature sensitivity of PO/AH neurons was only changed by ligands of GABAB receptors, and this effect has been restricted to temperature-sensitive neurons [5].

In recent years, there has been considerable interest in the role of the GABAB receptor function in the regulation of feeding behavior and energy expenditure [6, 7, 8]. It has been demonstrated that peripheral administration of the GABAB receptor agonist baclofen significantly reduced food intake and body weight increase in diet-induced obese mice, whereas it had no significant effects on energy balance in the lean controls [9]. The present study was therefore performed to investigate the effects of a GABAB agonist and antagonist on core body temperature of rats with normal weight and diet-induced obesity (DIO).

MATERIAL AND METHODS

- Drugs: CGP 35348, an antagonist at GABAB receptors, and S(−)-baclofen, an agonist of the GABAB receptors, were purchased from Sigma-Aldrich, Germany. The drugs were dissolved in physiological saline solution (0.9% w/v NaCl).
- Experimental animals and diet: Male Wistar rats, 2 months of age, were housed in a group of four per cage and provided with either standard rodent chow (SC) ad libitum or a cafeteria diet (CAF) with two human snack foods (cookies, cereals, waffles, salted peanuts and crackers) varying daily in addition to ad libitum SC. CAF is a robust model of the human metabolic syndrome with concomitant liver and adipose inflammation [10]. Body weight was measured once per week for nine weeks. Rats were maintained on a standard 12 h light/dark cycle (07:00 to 19:00 h) and were cared for in accordance with the ‘‘Principles of Laboratory Animal Care’’ formulated by the National Society for Medical Research and the ‘‘Guide for the Care and Use of Laboratory Animals” Washington DC, National Academy Press.
- Indicators of obesity: We used the body mass index (BMI) for male Wistar rats to assess obesity. The BMI was defined as body weight (g) divided by naso–anal length^2 (cm^2). Values above 0.68 were used as an indicator of obesity [11].
- Monitoring of body temperature: Body temperature was measured with thermistor probes (TX8) inserted rectally to a depth of 6 cm and monitored on multichannel recorder Iso-Thermex 16 (Columbus Instruments, USA). The initial temperature of the animals was determined and then checked at 30-min. intervals up to 120 min. after injection of the experimental substances. The movements of the rats were slightly restricted as previously described [12]. CGP 35348 (5 mg/kg) and baclofen (5 mg/kg) were administered intraperitoneally (i.p.) in an injection volume of 0.2 ml/100g body weight.
- Statistical analysis: The results were analyzed using one-way analyses of variance (ANOVA). The Holm–Sidak post hoc test was used to determine differences between means when a significant change was observed using ANOVA. Results are presented as the mean ± SEM using SigmaPlot software. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

At 2 months of age, when body weight was not different between the groups, male Wistar rats were randomly assigned to either SC (standard chow)-fed rats or CAF (cafeteria diet)-fed rats. Animals remained on diets for 9 weeks. At the end of the ninth week the CAF group had significantly higher body weight compared to SC-fed rats ($p < 0.001$), but no significant differences were observed in naso-anal lengths between the groups. Therefore, CAF-fed rats had significantly higher BMI compared with SC-fed rats at the end of the dietary period. The BMI of the CAF group was greater than 0.68, which demonstrates a successfully induced model of obesity (Fig. 1).

Core body temperature was similar in both SC- and CAF-fed rats injected with saline. SC-fed rats injected with the GABAB receptor antagonist CGP35348 (5 mg/kg i.p.) exhibited a significantly long lasting increase in core body temperature at the 30th, 60th, 90th and 120th min after application ($p < 0.001$) whereas the hyperthermic response to CGP35348 in the CAF group was moderate and significant only at the 30th and 60th min ($p < 0.001$) (Fig. 2). The temperature response, induced by CGP35348 in SC-fed rats was significantly greater compared to CAF-fed rats ($p < 0.001$). Injection of the GABAB receptor agonist baclofen in a dose of 5 mg/kg resulted in a significant decrease of the core body temperature in both treatment groups (Fig. 3). The hypothermia observed in SC-fed rats was significantly more pronounced at the 30th and 60th min compared to the CAF-fed rats.

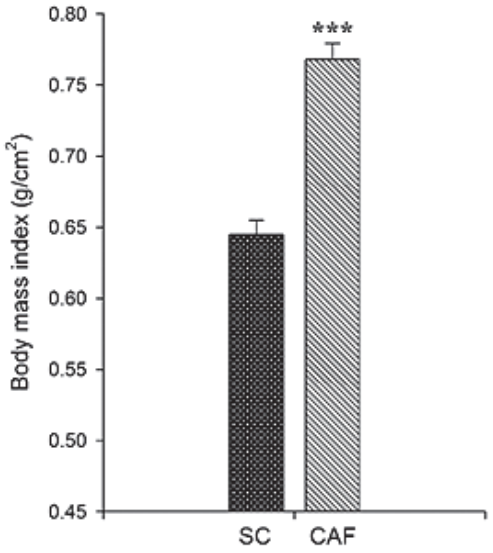

Fig. 1. Changes in body mass index after 9 weeks dieting with a CAF or SC. The BMI of the CAF group exceeds 0.68, which demonstrates a successfully induced model of obesity. ***, p < 0.001 vs. SC-fed group (n = 20 per group). Values represent the mean ± SEM

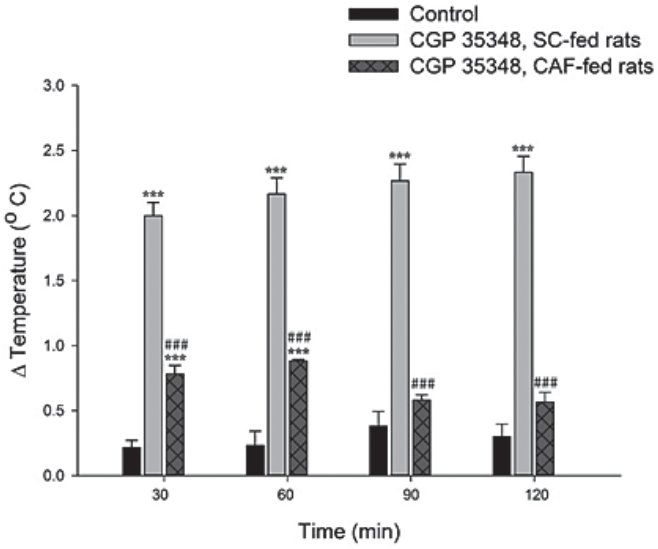

Fig. 2. Effects of CGP35348 on core body temperature in SC-fed rats or CAF-fed rats. Injection of CGP35348 (5 mg/kg i.p.) induced a significant increase in core body temperature. The hyperthermia, produced by CGP35348, was reduced in the CAF group compared with that observed in the SC group. Results are means ± SEM. ***, p < 0.001 vs. control group (SC-fed rats); ###, p < 0.001 vs. CGP35348, SC-fed rats (n = 8 animals per group)

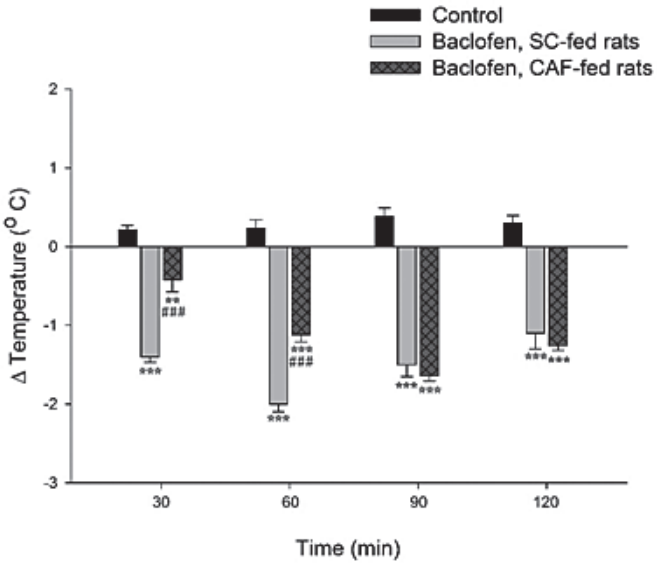

Fig. 3. Effects of baclofen on core body temperature in SC-fed rats or CAF-fed rats. Injection of baclofen (5 mg/kg i.p.) resulted in a significant decrease in core body temperature. The temperature response caused by baclofen was reduced in the CAF group compared with that seen in the SC group. Results are mean values ± SEM. **, p < 0.01; ***, p < 0.001 vs. control group (SC- fed rats); ###, p < 0.001 vs. baclofen, SC-fed rats (n = 8 animals per group)

DISCUSSION

The results of this study show that systemic administration of the GABAB antagonist CGP35348 induced significant hyperthermia in SC-fed rats, whereas the GABAB agonist baclofen led to a decrease in body temperature. The effects of baclofen and CGP35348 on body temperature were less pronounced in rats with DIO compared with those in rats with normal weight.

Sato et al. [9] first reported that the effects of baclofen on food intake and body weight are clearly dependent on whether mice are obese or not. The key behavioral findings were that in both db/db and DIO mice, but not in lean control mice, baclofen treatment significantly reduced food intake and body weight and increased O_2 consumption without affecting motor activities. They suggested that baclofen has the potential to work downstream of leptin receptor and thereby reduce food intake and increase energy ex-

penditure in obese subjects [9]. These findings may explain the observed decrease of baclofen-induced hypothermia in our experiments with obese rats.

Few studies have demonstrated that high-calory diet can alter GABA-ergic signaling in the brain. Sandoval-Salazar et al. [13] have shown that a high fat diet reduced GABA levels in the frontal cortex and hippocampus of rats, suggesting that the lower neurotransmitter levels in these brain regions could impair the inhibitory processes underlying feeding behavior. Furthermore, Corwin et al. [14] found that binge-type eating disrupts dopaminergic and GABA-ergic signaling in the prefrontal cortex and ventral tegmental area in rats. Binge eating is defined as repeated, discrete, intermittent bouts of consuming unusually large amounts of food. They demonstrated that either GABA-ergic inactivation or D2-like receptor activation within the prefrontal cortex increased consumption in bingeing rats, but not controls. It has been shown that exposure to a high fat diet during the perinatal period in rats alters GABA-ergic activity within brainstem neural circuits controlling gastric functions, which may contribute to the dysregulation of homeostatic reflexes, including appetite and metabolic regulation [15].

CONCLUSION

In conclusion, we have demonstrated that temperature responses, produced by a GABAB agonist and antagonist, are altered in obese rats. Presently it remains unresolved how obesity affects the GABAB signaling pathway at the level of the central thermoregulatory system.

Compliance with Ethical Standards

This study was performed in accordance with the „Principles of Laboratory Animal Care“ formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” Washington DC, National Academy Press.

Conflict of interest:

The authors declare no conflict of interest.

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