EFFECTS OF THE CAPSAICIN ANALOGUE RESINIFERATOXIN ON THERMOREGULATION IN ANESTHETIZED RATS

N. Okane, T. Osaka, A. Kobayashi, S. Inoue and S. Kimura, National Institute of Health and Nutrition, Shinjuku, Japan.

Systemic administration of resiniferatoxin (RTX) or capsaicin, both of which share a homovanillyl moiety as a structural motif essential for bioactivity and thus are called vanilloids, is known to induce marked hypothermia in mammals. The vanilloid-induced hypothermia results from coordinated heat loss responses such as cutaneous vasodilation, sweating, and panting. In the present study, we studied the effects of RTX (50 μg/kg, s.c.) on heat production and heat loss simultaneously in rats. Adult male Wistar rats were anesthetized with urethan (1.1 g/kg, i.p.) and placed on a heating pad to maintain their baseline body temperature at ~36°C. Administration of RTX induced triphasic changes in O_2 consumption (VO_2): an immediate facilitatory phase with a peak at 50 min, an inhibitory phase with a minimal value at 100 min, and a long-lasting facilitatory phase. The temperature of skin (T_s) also increased immediately after the RTX injection, suggesting cutaneous vasodilation and an increase in heat loss. The temperature of colon (T_c) decreased immediately after the RTX injection and subsequently increased above the baseline level. The biphasic change in T_c can be explained by the sum of heat loss and heat production: the effect of heat loss predominated during the initial 2 h, and that of heat production emerged after the end of the heat loss. In capsaicin-desensitized rats, RTX did not facilitate but inhibited VO_2 to a minimal value at 140 min. T_s and T_c did not change in these rats. Accordingly, the RTX-induced thermal responses were largely mediated by capsaicin (vanilloid) receptors, and the inhibition of VO_2 might be caused by a cell-nonselective action of RTX. However, pretreatment with the VN_2 vanilloid receptor antagonist ruthenium red (10 mg/kg, s.c.) enhanced the RTX-induced increase in VO_2, suggesting attenuation of the inhibitory phase. Thus, the VN_2 receptors may mediate the inhibitory phase of VO_2 and receptors other than VN_2 may mediate the facilitatory phases of VO_2. Ruthenium red also blocked the RTX-induced increase in T_s and decrease in T_c. Therefore, we consider that activation of the VN_2 receptors contributed to the hypothermia by inhibiting thermogenesis and facilitating heat loss, coordinately. Moreover, the results also indicate that the thermogenic responses were not caused by hypothermia. Pretreatment with the VN_1 antagonist capsazepine (10 mg/kg, s.c.), which reportedly reverses 1-mg/kg capsaicin-induced inhibition of thermogenesis in brown adipose tissue, did not affect the RTX-induced responses. Because RTX is 100-1000 times more potent than capsaicin, this amount of capsazepine might not have been sufficient to affect the RTX-induced responses. Accordingly, we could not determine the receptor subtype that mediates the RTX-induced thermogenesis. In rats with adrenal demedullation, the RTX-induced immediate facilitation of VO_2 was significantly attenuated but the long-lasting thermogenic phase remained. On the other hand, administration of the β-blocker propranolol largely attenuated both the immediate and long-lasting phases of RTX-induced thermogenesis. Therefore, the RTX-induced immediate thermogenesis was mediated by catecholamines released from the adrenal medulla; and the long-lasting thermogenesis, by sympathetic nerve activity.

osaka@nih.go.jp