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An antagonistic effect of esmolol on beta-3 adrenoceptor in brown adipose tissue in rats

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Esmolol is used in clinical practice as a beta-1 adrenergic antagonist in Europe and North America, but it is still under investigation in Japan. It has a high specificity for beta-1 adrenoceptors relative to the beta-2 subtype. When the antagonizing effect to isoproterenol-induced increase in heart rate (beta-1) or bronchodilation (beta-2) is calculated, the ratio of esmolol is reported to be 42.7, which is higher than that of propranolol (0.85) [1]. Based on its high specificity for beta-1 adrenoceptors, esmolol can be used for the treatment of tachycardia in patients with bronchial asthma. Another adrenoceptor subtype, the beta-3 receptor, was found, and its molecular structure was reported by Emorine et al. [2] in 1989. Beta-3 adrenoceptors play roles in thermogenesis, lipolysis, anti-obesity function, and anti-diabetic function, and their genetic variation has been correlated with hereditary obesity and diabetogenesis [3]. Furthermore, their functions in the cardiovascular system have recently been studied [4]. Although the affinities and effects of various drugs affecting beta-adrenoceptors on the beta-3 subtype have been investigated, the effect of esmolol has not been reported, to our knowledge. Beta-3 adrenoceptors are distributed in adipose tissues with a high density, and beta-3 adrenergic agonists increase temperature to a greater extent in the interscapular brown adipose tissue than in the rectum in rats [5,6]. In the present study, we investigated the effect of esmolol on the beta-3 adrenoceptors by studying the temperature difference between the interscapular brown adipose tissue and the rectum in rats.

The study was approved by our Institutional Animal Care Committee. Forty-five Wistar rats, weighing 200–300 g, were used. The rats were anesthetized with pentobarbital, 50 mg·kg^{-1} i.p. A polyethylene catheter (0.9-mm-diameter) was placed in the femoral vein. Thermistor probes were inserted into the interscapular adipose tissue (THR PT-S001; Shibaura-Denki, Tokyo, Japan and ATB-1100; Nihon-Kohden, Tokyo, Japan) and the rectum (CTM-303; Terumo, Tokyo, Japan). The rats were placed in a plexiglas tube, which was surrounded by warm water, and their rectal temperature was maintained within 37.0 ± 0.5°C. Heart rate was measured with an electrocardiograph (WT 685G; Nihon-Kohden). The drugs employed were dissolved in normal saline and administered intravenously. The volume of bolus injection was adjusted to 0.5 ml. BRL 37344, a selective beta-3 adrenoceptor agonist, was purchased from Sigma (St. Louis, MO, USA), and esmolol was a gift from Maruishi Pharmaceutical Company (Osaka, Japan). The effects of the drugs on the heart rate and the temperature difference between the interscapular adipose tissue and rectum were measured.

The heart rates and the temperature difference between the adipose tissue and the rectum were measured at the time of bolus administration of the drugs, and 2, 5, 10, 15, and 20 min later. The temperature difference was expressed as the change from that at the time of bolus administration of drugs in each rat.

In group A animals ($n = 12$), 50 μg·kg^{-1} of BRL 37344 was administered in order to confirm the rationale for the present model. For investigating the agonistic effect of esmolol on the beta-3 adrenoceptor, esmolol, 10 mg·kg^{-1} and 100 mg·kg^{-1}, was administered to group B ($n = 9$) and group C ($n = 4$), respectively. Then the

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antagonistic effect of esmolol on beta-3 adrenoceptors was investigated in two additional groups. Because the half-time of esmolol is short [7], esmolol was infused in order to investigate whether it antagonized the effects of BRL 37344. Esmolol was infused intravenously at a rate of 1.5 mg·kg^{-1}·min^{-1}, and 10 min later, normal saline (group D; $n = 9$) or 50 μg·kg^{-1} BRL 37344 (group E; $n = 11$) was administered. Values are presented as means ± SD. The statistical significance of differences among measurements was tested using two-way analysis of variance and Bonferroni's correction. Variables were compared with the value at time 0 in each group (intragroup comparison). Variables in group E were also compared with those in groups A and D at the same time points (intergroup comparison). We accepted $P < 0.05$ as significant.

At the time of drug administration, there were no differences among groups in the rectal temperature (37.1 ± 0.3°C; mean ± SD in all groups), the adipose tissue temperature (37.0 ± 0.3°C), or the heart rate (384 ± 36 min^{-1}). BRL 37344 increased the temperature difference from 10 min after administration, but did not affect heart rate in group A (Fig. 1 and Table 1). Esmolol did not affect the temperature difference, and decreased heart rate 2 min after administration in groups B and C. The infusion of esmolol prevented the BRL 37344-induced increase in the temperature difference in group E.

The present study shows that BRL 37344 increased the temperature difference between adipose tissue and rectum, which indicates that the present model could evaluate a function of beta-3 adrenoceptors. The finding that esmolol itself did not increase the temperature difference in groups B and C indicated that esmolol did not have an agonistic action on the beta-3 adrenoceptors. The infusion of esmolol prevented the increase in temperature difference in group E. This result indicated that esmolol had an antagonistic effect on the beta-3 adrenoceptors. The present study could not investigate the mechanism of the antagonistic effects of esmolol on the beta-3 adrenoceptors, such as whether esmolol binds to the receptors or has an antagonistic effect through any other pathways. A binding assay using radioisotopic ligands will clarify this issue.

The beta-3 adrenoceptors have a role in the cardiovascular system. Although negative inotropic and positive chronotropic actions of BRL 37344 have been reported [4], group A did not show any significant change in heart rate, and we did not measure blood pressure in the present study. A role of for beta-3 adrenoceptors at different stages of heart failure, and

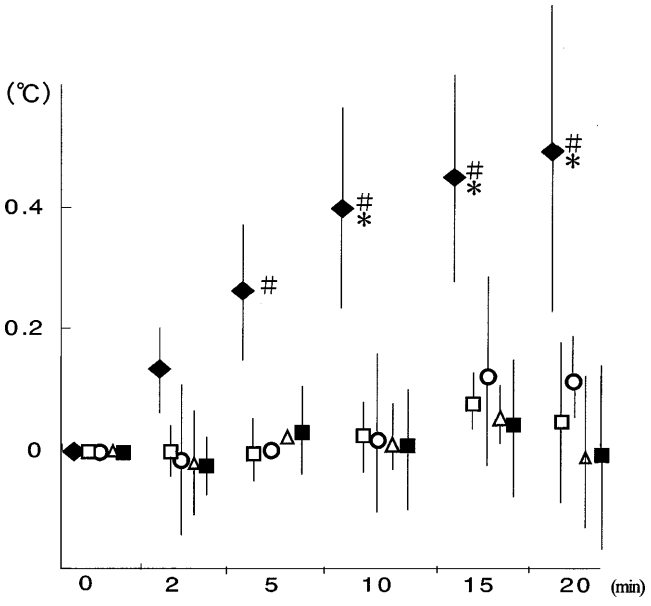

Fig. 1. Changes in temperature difference (°C). The temperature differences between adipose tissue and rectum were calculated and were expressed as changes from that at the time of the boluds administration of drugs, time 0. Values are means ± SD. Rats in each group received the drugs i.v. at time 0; 50 μg·kg^{-1} of BRL 37344 in group A, 10 mg·kg^{-1} of esmolol in group B, 100 mg·kg^{-1} of esmolol in group C, and normal saline (group D) or BRL 37344 (group E) was administered 10 min after esmolol infusion at 1.5 mg·kg^{-1}·min^{-1}. #$P < 0.05$ vs time 0; *$P < 0.05$ vs group E. *Diamonds*, Group A ($n = 12$); *open squares*, group B ($n = 9$); *open circles*, group C ($n = 4$); *open triangles*, group D ($n = 9$); *closed squares*, group E ($n = 11$)

Table 1. Changes in heart rate (beats·min^{-1})

Group	Time after bolus administration of drugs (min)					
	0	2	5	10	15	20
A	368 ± 52	407 ± 59	397 ± 74	386 ± 63	380 ± 52	378 ± 50
B	403 ± 39	363 ± 17*	372 ± 26	380 ± 45	385 ± 36	397 ± 43
C	361 ± 21	317 ± 9*	345 ± 14	360 ± 18	380 ± 16	386 ± 15
D	362 ± 18	369 ± 21	371 ± 29	376 ± 29	371 ± 25	375 ± 29
E	377 ± 23	384 ± 41	397 ± 41	401 ± 38	406 ± 36	405 ± 28

*$P < 0.05$ vs time 0
Values are presented as means ± SD

the possibility of beta-3 adrenoceptor antagonists being preferable agents in the late stage of heart failure have been proposed [4]. However, esmolol has an antagonistic action on beta-1 adrenoceptors, and the dose used in the present study was larger than that used in clinical practice. Esmolol is usually given as a bolus injection in clinical practice, but is not infused, as in the present study. Furthermore, the densities of beta-3 adrenoceptors differ in different species of animals [4]. The clinical significance of the beta-3 adrenoceptor antagonistic action of esmolol shown in the present study should be investigated in the future.

In conclusion, the present study showed that esmolol does not have an agonistic action, but has an antagonistic action on the beta-3 adrenoceptors in rat adipose tissue.

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