POSSIBLE INVOLVEMENT OF β_2 -ADRENOCEPTORS IN HYPER-THERMIC EFFECT OF *l*-EPHEDRINE IN RATS

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The experiments were conducted in order to examine the mechanism of hyperthermia induced by *l*-ephedrine in rats. β -Adrenoceptor agonists have been known to enhance normal body temperature. Therefore, the effect of various β -adrenoceptor agonists on body temperature in rats was examined to clarify the mechanism of action of *l*-ephedrine. The results showed that drugs with β_2 -adrenoceptor agonist activity and *l*-ephedrine caused hyperthermia in rats and this effect was selectively inhibited by pretreatment of animals with propranolol (a mixed β -adrenoceptor antagonist) or butoxamine (a selective β_2 -adrenoceptor antagonist). These results suggest that hyperthermic action of *l*-ephedrine may largely be due to its effect on β_2 -adrenoceptors.

Keywords — adrenoceptor; normal body temperature; *l*-ephedrine; hyperthermia; β_2 -adrenoceptor agonist

There have been many reports as to the effect of the central nervous system (CNS) thermoregulatory center and the involvement of various monoamines,^{1–6)} prostaglandins,^{7–9)} γ -aminobutyric acid (GABA)^{10,11)} and anions^{12,13)} in hyperthermia. It is also known that β -adrenoceptor agonists affect temperature regulation in terms of hyperthermia.^{14–16)} The precise mecha-

nism of thermogenic action of β -adrenoceptor agonists involved in temperature regulation, however, has not yet been elucidated. During the course of pharmacological study of Mahuang and *l*-ephedrine, we have previously observed that *l*-ephedrine causes hyperthermia in rats and mice.¹⁷⁾ Therefore, the effects of various β -adrenoceptor agonists and antagonists

TABLE I. *Influence of l-Ephedrine on Normal Body Temperature in Rats*

Compound	Dose (mg/kg, p.o.)	Change in body temperature ($\Delta t^{\circ}\text{C}$)					
		0	1	2	3	4	5 (h)
Normal	—	0	−0.25 ± 0.09	−0.47 ± 0.09	−0.43 ± 0.09	−0.48 ± 0.11	−0.45 ± 0.11
<i>l</i> -Ephedrine	2.5	0	0.52 $\pm 0.12^a$	0.04 ± 0.13	−0.12 ± 0.02	−0.16 ± 0.17	−0.30 ± 0.08
<i>l</i> -Ephedrine	10.0	0	1.74 $\pm 0.24^b$	0.96 $\pm 0.32^a$	0.22 ± 0.17	0.16 ± 0.11	−0.18 ± 0.11
<i>l</i> -Ephedrine	25.0	0	2.21 $\pm 0.18^b$	2.65 $\pm 0.23^b$	2.50 $\pm 0.31^b$	2.13 $\pm 0.37^b$	1.81 ± 0.21
<i>l</i> -Ephedrine	40.0	0	2.20 $\pm 0.24^b$	2.49 $\pm 0.31^b$	2.41 $\pm 0.27^b$	2.20 $\pm 0.21^b$	1.71 $\pm 0.19^b$

Each value represents mean $\pm$ s.e. Significantly different from normal at a) $p < 0.05$, b) $p < 0.01$.

were examined on the control of body temperature in order to clarify the mechanism of hyperthermia induced by *l*-ephedrine.

MATERIALS AND METHODS

Animals used were Wistar male rats (90–110 g in weight), 5 to 10 animals per group. Rectal temperature was measured (Omron, MC-III type) 1 h before the start of experiments, and those animals which had about

36.5 °C were selected for the experiments. Room temperature and humidity were kept at 22 ± 2 °C and $60 \pm 5\%$ respectively. Rectal temperature was measured just before the administration (*p.o.*) of test drugs and measurement was repeated after 1, 2, 3, 4 and 5 h. Each rat was housed individually in wire cage. Antagonists were given 30 min prior to the administration of test drug and doses of the drugs were determined by molarity. Used drugs are as follows; *l*-ephedrine·HCl (Sigma), *d*-pseudoephedrine·HCl (Sigma), *l*-isoproterenol·HCl (Sigma), *dl*-norepinephrine·HCl (Aldrich), epinephrine·HCl (Aldrich), dobutamine (Dobutrex, Shionogi), salbutamol (Venetoline, Allen Hanburys), terbutaline·H₂SO₄ (Buricaniel, Fujisawa), *dl*-propranolol·HCl (Sigma), alprenolol (Aproval, Fujisawa) and butoxamine (Wellcome).

Results are expressed as mean $\pm$ s.e. and statistical significance was analyzed with Student's *t*-test.

RESULTS

Table I shows that *l*-ephedrine·HCl at 2.5 mg/kg, *p.o.* significantly increased rectal temperature in rats. At 25 mg/kg, *p.o.*, the temperature increased by 2.65 ± 0.35 °C (2 h).

Figure 1 shows the effect of oral administration of adrenoceptor agonists. *l*-Ephedrine·HCl caused hyperthermia. The temperature was also increased by selective β_2 -adrenoceptor agonists, salbutamol and terbutaline by 1.93 ± 0.23 °C (2 h after the administration, 110 mg/kg) and 0.64 ± 0.11 °C (1 h after the administration, 60 mg/kg), respectively. In addition, a maximum increase in temperature of 2.41 ± 0.15 °C was seen 1 h after the administration of *l*-isoproterenol·HCl (a mixed β -adrenoceptor agonist, 63 mg/kg) and a temperature increase of 2.00 ± 0.50 °C was produced 1 h after the administration of epinephrine·HCl (a mixed α - and β -adrenoceptor agonist, 55 mg/kg). *dl*-Norepinephrine·HCl (a mixed α - and preferential β_1 -adrenoceptor agonist, 51 mg/kg), however, did not have any significant hyperthermic effect.

Figure 2 (A)–(C) show the effect of *dl*-pro-

FIG. 1. Influence of *l*-Ephedrine·HCl, Epinephrine·HCl, *dl*-Norepinephrine·HCl, *l*-Isoproterenol·HCl, *d*-Pseudoephedrine·HCl, Dobutamine, Salbutamol and terbutaline on Normal Body Temperature

○—○, normal; ●—●, *l*-ephedrine·HCl, 33 mg/kg; △—△, epinephrine·HCl, 55 mg/kg; ▽—▽, *dl*-norepinephrine·HCl, 51 mg/kg; □—□, *l*-isoproterenol·HCl, 63 mg/kg; ■—■, *d*-pseudoephedrine·HCl, 33 mg/kg; ▲—▲, dobutamine, 60 mg/kg; ▼—▼, salbutamol, 110 mg/kg; ◇—◇, terbutaline, 60 mg/kg.

Each point represents a mean change in body temperature (Δt °C) in 10 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. Drugs were orally administered. Abscissa: time (h) after oral administration of drugs.

FIG. 2. Influence of *dl*-Propranolol Pretreatment

(A) Epinephrine·HCl and *l*-Isoproterenol·HCl Hyperthermia

○—○, normal; ●—●, *dl*-propranolol, 26 mg/kg; △—△, epinephrine·HCl, 55 mg/kg; ▽—▽, *l*-isoproterenol·HCl, 63 mg/kg; ▲—▲, *dl*-propranolol·HCl, 26 mg/kg + epinephrine·HCl, 55 mg/kg; ▼—▼, *dl*-propranolol·HCl, 26 mg/kg + *l*-isoproterenol·HCl, 63 mg/kg.

Each point represents a mean change in body temperature (Δt °C) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. *dl*-Propranolol was orally administered 30 min before Epinephrine·HCl and *l*-isoproterenol·HCl. Abscissa: time (h) after oral administration of these drugs.

(B) Salbutamol and Terbutaline Hyperthermia

○—○, normal; ●—●, *dl*-propranolol, 26 mg/kg; ▽—▽, salbutamol, 110 mg/kg; △—△, terbutaline, 60 mg/kg; ▼—▼, *dl*-propranolol, 26 mg/kg + salbutamol, 110 mg/kg; ▲—▲, *dl*-propranolol, 26 mg/kg + terbutaline, 60 mg/kg.

Each point represents a mean change in body temperature (Δt °C) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. *dl*-Propranolol was orally administered 30 min before salbutamol and terbutaline. Abscissa: time (h) after oral administration of these drugs.

(C) *l*-Ephedrine·HCl Hyperthermia

○—○, normal; ●—●, *l*-ephedrine·HCl, 25 mg/kg; △—△, *dl*-propranolol, 3 mg/kg; ▽—▽, *dl*-propranolol, 13 mg/kg; □—□, *dl*-propranolol, 26 mg/kg; ▲—▲, *dl*-propranolol, 3 mg/kg + *l*-ephedrine·HCl, 33 mg/kg; ▼—▼, *dl*-propranolol, 13 mg/kg + *l*-ephedrine·HCl, 33 mg/kg; ■—■, *dl*-propranolol, 26 mg/kg + *l*-ephedrine·HCl, 33 mg/kg.

Each point represents a mean change in body temperature (Δt °C) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. *dl*-Propranolol was orally administered 30 min before *l*-ephedrine·HCl. Abscissa: time (h) after oral administration of *l*-ephedrine·HCl.

pranolol (a mixed β -adrenoceptor antagonist, 3, 13 and 26 mg/kg) on temperature. Pretreatment with *dl*-propranolol inhibited hyperthermia induced by epinephrine, *l*-isoproterenol, salbutamol, terbutaline and *l*-ephedrine in dose-dependent manner.

It can be also seen in Fig. 3 (A)–(C) that pre-

treatment with a selective β_1 -adrenoceptor antagonist, alprenolol (25 mg/kg), did not have any significant effect on hyperthermia induced by these drugs.

Butoxamine, a selective β_2 -adrenoceptor antagonist, however, inhibited hyperthermia induced by *l*-ephedrine (Fig. 4).

FIG. 3. Influence of Alprenolol Pretreatment

(A) Epinephrine·HCl and l-Isoproterenol·HCl Hyperthermia

○—○, normal; ●—●, alprenolol, 25 mg/kg; △—△, epinephrine·HCl, 55 mg/kg; ▽—▽, l-isoproterenol·HCl, 63 mg/kg; ▲—▲, alprenolol, 25 mg/kg + epinephrine·HCl, 55 mg/kg; ▼—▼, alprenolol, 25 mg/kg + l-isoproterenol·HCl, 63 mg/kg.

Each point represents a mean change in body temperature (Δt $^{\circ}\text{C}$) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. Alprenolol was orally administered 30 min before epinephrine·HCl and l-isoproterenol·HCl. Abscissa: time (h) after oral administration of these drugs.

(B) Salbutamol and Terbutaline Hyperthermia

○—○, normal; ●—●, alprenolol, 25 mg/kg; ▽—▽, salbutamol, 110 mg/kg; △—△, terbutaline, 60 mg/kg; ▼—▼, alprenolol, 25 mg/kg + salbutamol, 110 mg/kg; ▲—▲, alprenolol, 25 mg/kg + terbutaline, 60 mg/kg.

Each point represents a mean change in body temperature (Δt $^{\circ}\text{C}$) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. Alprenolol was orally administered 30 min before salbutamol and terbutaline. Abscissa: time (h) after oral administration of these drugs.

(C) l-Ephedrine·HCl Hyperthermia

○—○, normal; ●—●, alprenolol, 25 mg/kg; △—△, l-ephedrine·HCl, 33 mg/kg; ▲—▲, alprenolol, 25 mg/kg + l-ephedrine·HCl, 33 mg/kg.

Each point represents a mean change in body temperature (Δt $^{\circ}\text{C}$) in 7 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. Alprenolol was orally administered 30 min before l-ephedrine·HCl. Abscissa: time (h) after oral administration of l-ephedrine·HCl.

DISCUSSION

l-Ephedrine was reported to act as agonists α - and β -adrenoceptors,¹⁸⁻²²⁾ and β -adrenoceptor agonists were known to enhance normal body temperature.¹⁴⁻¹⁶⁾ In order, therefore, to clarify the mechanism of the hyperthermic action of l-ephedrine, the effects of β -adrenoceptor agonists and antagonists were examined on the rectal temperature in rats.

In the present investigations, l-ephedrine caused a significant hyperthermia. In addition, epinephrine (which has a mixed α - and β -adrenoceptor agonist effect), isoproterenol (a mixed β -adrenoceptor agonist) and salbutamol and terbutaline (β_2 -adrenoceptor agonist) caused a significant increase in rectal temperature. It is important to note that all these drugs have an agonistic effect on β_2 -adrenoceptors.

Norepinephrine (a mixed α - and β_1 -adrenoceptor agonist), however, did not show any hyperthermic effect. These results strongly suggest that the activation of β_2 -adrenoceptors is involved in the hyperthermia. The results also showed that β_1 -adrenoceptor antagonist, alprenolol, did not prevent hyperthermia induced by *l*-ephedrine, epinephrine, isoproterenol, salbutamol and terbutaline. The hyperthermia induced by *l*-ephedrine and the other drugs, however, was inhibited by a mixed β -adrenoceptor antagonist,

propranolol. The hyperthermic effect of *l*-ephedrine was inhibited by a selective β_2 -adrenoceptor antagonist, butoxamine. These results strongly suggest that the hyperthermic effect of *l*-ephedrine is related to its agonistic action on β_2 -adrenoceptors.

FIG. 4. Influence of Butoxamine on *l*-Ephedrine·HCl Hyperthermia

○—○, normal; △—△, butoxamine, 27 mg/kg; ●—●, *l*-ephedrine·HCl, 33 mg/kg; ▲—▲, butoxamine, 27 mg/kg + *l*-ephedrine·HCl, 33 mg/kg.

Each point represents a mean change in body temperature (Δt °C) in 5 rats. Vertical lines show s.e. Significance of difference from normal, a) $p < 0.05$, b) $p < 0.01$. Butoxamine was orally administered 30 min before *l*-ephedrine·HCl. Abscissa: time (h) after oral administration of *l*-ephedrine·HCl.

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