



Cardiovascular Pharmacology

Effects of β -adrenoceptor antagonists on anaphylactic hypotension in conscious ratsWei Zhang^{a,c}, Toshishige Shibamoto^{a,*}, Yasutaka Kurata^a, Hiroyuki Kohno^b^a Department of Physiology II, Kanazawa Medical University, Uchinada Ishikawa 920-0293, Japan^b Department of Oncologic Pathology, Kanazawa Medical University, Uchinada Ishikawa 920-0293, Japan^c Department of Pathophysiology, Medical College of Qinghai University, Xining 810001, China

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ABSTRACT

Anaphylactic shock is sometimes fatal or resistant to therapy in patients treated with propranolol, a nonselective β -adrenoceptor antagonist, against cardiovascular diseases. However, it remains unknown which subtype of β -adrenoceptors, β_1 - or β_2 -adrenoceptor, is primarily responsible for the detrimental effects of propranolol on anaphylactic hypotension. Effects of β_1 - and β_2 -adrenoceptor antagonists were therefore determined on the survival rate and systemic hypotension in conscious Sprague–Dawley rats that suffered from anaphylactic shock. Mean arterial pressure and portal venous pressure were simultaneously measured. The control rats showed a decrease in mean arterial pressure and an increase in portal venous pressure, but did not die within 48 h after an injection of ovalbumin antigen. The survival rate of the rats pretreated with propranolol (1 mg/kg; $n = 7$), the selective β_2 -adrenoceptor antagonist ICI 118,551 (0.5 mg/kg; $n = 7$), or adrenalectomy ($n = 7$) was significantly smaller than that with the selective β_1 -adrenoceptor antagonist atenolol (2 mg/kg; $n = 7$). However, the changes in mean arterial pressure and portal venous pressure were similar for 10 min after antigen among any groups, although propranolol and atenolol attenuated the antigen-induced increase in heart rate. Furthermore, bolus injections of epinephrine (3 μ g/kg) at 3 and 5 min after antigen prevented the death of the atenolol-pretreated rats, but only marginally prolonged the survival rates for the ICI 118,551- or propranolol-pretreated and adrenalectomized rats. In conclusion, in rat anaphylactic shock, inhibition of β_2 -adrenoceptor causes more detrimental effects than that of the β_1 -adrenoceptor. These β -adrenoceptor antagonists may exert detrimental effects on rat systemic anaphylaxis via inhibiting beneficial actions of catecholamines endogenously released from the adrenal gland.

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1. Introduction

Anaphylactic shock is a serious allergic reaction that is rapid in onset and is potentially life threatening (Kemp and Lockey, 2002). There are several reports that patients with pre-existing cardiovascular diseases and those treated with propranolol, a β -adrenoceptor antagonist, have increased incidence and severity of anaphylaxis (Mueller, 2007; Lang, 1995). Thus, β -adrenoceptors are probably involved in the pathogenesis and increase in severity of systemic anaphylaxis. β -Adrenoceptors are subdivided into three types: β_1 , β_2 and β_3 . Antagonists and agonists of two basic subtypes of β -adrenoceptors, β_1 - and β_2 -adrenoceptor are currently used. In general, inhibition of β_1 -adrenoceptor causes cardiac depression resulting in bradycardia and decreased cardiac contractility, while inhibition of β_2 -adrenoceptor can induce bronchospasm, increase vascular resistances of coronary and skeletal muscle beds, and decrease vascular permeability (Abdelrahman et al., 1990; Hiatt et al., 1985; Motulsky and Insel, 1982). Most reports of anaphylaxis

and β -antagonist use have involved the noncardioselective agent propranolol which can inhibit both β_1 - and β_2 -adrenoceptors, although cardioselective (selective β_1 -adrenoceptor) agents have also been associated with anaphylactic and anaphylactoid reactions (Lang, 1995). However, it is not known which subtype of β -adrenoceptors, β_1 - or β_2 -adrenoceptor, is primarily responsible for the detrimental effects of propranolol on anaphylactic shock.

It is reported that the liver is partly involved in rat anaphylactic hypotension by producing hepatic venoconstrictive response to anaphylactic chemical mediators (Shibamoto et al., 2005). This anaphylactic hepatic venoconstriction induces portal hypertension which then causes congestion of the upstream splanchnic organs, with resultant decreases in venous return and effective circulating blood volume, and finally augments anaphylactic hypotension. β_2 -Adrenoceptor agonists are suggested to induce dose-dependent decreases in portal pressure and increases in portal tributary blood flow in normal rats (Poo et al., 1992). It is therefore interesting to determine whether β -antagonists augment anaphylaxis-induced hepatic venoconstriction resulting in deterioration of anaphylactic hypotension.

The objective of this study was to investigate the effects of β_1 - and β_2 -adrenoceptor antagonists on the survival rate and systemic

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hypotension with special reference to hepatic circulation in Sprague–Dawley rats that suffered from anaphylactic shock. To achieve this purpose, systemic arterial pressure and portal venous pressure were directly measured in sensitized rats when the ovalbumin antigen was challenged under the pretreatment with β_1 - and/or β_2 -adrenoceptor antagonists. In addition, a role of the adrenal gland was also studied in rat anaphylactic hypotension. The present experiment was performed in conscious rats, because the sympathetic nervous system, which is closely associated with β -adrenoceptors, is attenuated by the anesthetics.

2. Materials and methods

2.1. Animals

Seventy male Sprague–Dawley (SD) rats (Japan SLC, Shizuoka, Japan) weighing 342 ± 3 g were used in this study. Rats were maintained at 23 °C and under pathogen-free conditions on a 12:12-h dark/light cycle and allowed food and water ad libitum. The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University.

2.2. Sensitization

Rats were actively sensitized by the subcutaneous injection of an emulsion made by mixing complete Freund's adjuvant (0.5 ml) and 1 mg ovalbumin (grade V, Sigma) containing physiological saline (0.5 ml) (Shibamoto et al., 2005). Two weeks after injection, rats were used for the following experiments.

2.3. Surgical preparation

The basic methods for unanesthetized rat experiments were described previously (Zhang et al., 2009). Rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.) and placed supinely on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Japan) that maintained body temperature at 36–37 °C. A polyethylene catheter (ID 0.35 mm and OD 0.55 mm) was inserted into the left femoral artery for measurement of mean arterial pressure and another polyethylene catheter (ID 0.3 mm and OD 0.5 mm) was inserted into the left femoral vein for injections of drugs. Following a midline incision of the abdominal wall, a polyethylene catheter (ID 0.4 mm and OD 0.6 mm) was advanced into the portal vein via the caecal vein with the tip of the catheter just protruding 2–3 cm, for continuous measurement of portal venous pressure. In the experiment with adrenalectomy, adrenal glands were removed bilaterally prior to the caecal vein cannulation. After closure of the abdomen, the catheters were filled with heparinized saline (1000 U/ml) and tunneled subcutaneously to the back. The adrenalectomized rats were given 100 μ g corticosterone (in 100% alcohol, 100 μ l) after surgery and at the following night (Darlington and Tehrani, 1997). All rats regained consciousness within 1 h postoperatively, but more than 48 h was allowed for postoperative recovery.

2.4. Experimental protocol

All experimental protocols were carried out in conscious rats. The exteriorized catheters were connected to a cannula swivel (model TCS2-21, Tsumura; Tokyo, Japan), and the rats were placed in a custom-made plastic cage (L×W×H, 25×21×22 cm) with a free-moving system (Tsumura). Heart rate was measured by triggering the R wave of the electrocardiogram. The mean arterial pressure and portal venous pressure were continuously measured with pressure transducers (TP-400T, Nihon-Kohden, Japan), which were fixed at the level of right atrium at standing position. These vascular pressures and

heart rate were continuously displayed on a thermal physiograph, and also digitally recorded at 20 Hz (PowerLab, AD Instruments).

The following two experimental protocols were employed:

- 1) The effects of β -adrenoceptor antagonists and adrenalectomy on anaphylactic hypotension: either the nonselective β -adrenoceptor antagonist, propranolol (1 mg/kg; 100 μ l; $n=7$), selective β_1 -adrenoceptor antagonist, atenolol (2 mg/kg; 100 μ l; $n=7$), or selective β_2 -adrenoceptor antagonist, erythro-DL-(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol (ICI 118,551, 0.5 mg/kg; 100 μ l; $n=7$) was intravenously administered 20 min before an intravenous injection of the antigen (0.6 mg) dissolved in 300 μ l saline. In the control rats ($n=7$) and the adrenalectomized rats ($n=7$), saline alone (100 μ l) was injected prior to administration of the antigen. The doses of the antagonists were previously shown to be effective in inhibiting relevant β -adrenoceptors (Inagaki et al., 1997; Kitchen et al., 2006; Ishii et al., 2009); actually the dose of propranolol 1 mg/kg is known to inhibit both β_1 - and β_2 -adrenoceptors in rats (Oates et al., 1978). The vascular pressures and heart rate were observed for 2 h after administration of antigen or saline. The survival was evaluated 48 h after antigen.
- 2) The effects of epinephrine on anaphylactic hypotension of the animals pretreated with the β -adrenoceptor antagonists: epinephrine 3 μ g/kg was intravenously administered two times at 3 and 5 min after antigen in the rats pretreated with each β -adrenoceptor antagonist or saline alone. This dose of epinephrine was chosen according to the previous study of rat anaphylactic shock (Dewachter et al., 2007).

All drugs were purchased from Sigma Chemical Company, St. Louis, MO. All drugs were dissolved in saline.

2.5. Statistics

All results are expressed as the means $\pm$ S.E.M. Statistical analyses were performed by the repeated measures analysis of variance and a P value less than 0.05 was considered significant. When a significant difference was obtained, post hoc analysis was performed by the Bonferroni post-test correction method. Comparison among five groups was made by analysis of variance followed by the Bonferroni post-test correction method. Kaplan–Meier survival curves were analyzed by log-rank test. A P value less than 0.05 was considered significant.

3. Results

3.1. Effects of β -adrenoceptor antagonists on anaphylactic hypotension

Table 1 shows the basal levels of hemodynamic variables in control, in the presence of β -adrenoceptor antagonists, and with adrenalectomy. Intravenous injection of the β -adrenoceptor antagonists did not significantly alter the basal levels of mean arterial pressure, or portal venous pressure, but injections of atenolol and propranolol significantly reduced heart rate. Figs. 1A and 2 show the representative recordings and the summary data, respectively, for the time course of mean arterial pressure, portal venous pressure and heart rate after injection of the antigen. In the control rats without β -adrenoceptor antagonists, mean arterial pressure decreased from the baseline of 103 ± 4 mm Hg to 53 ± 3 mm Hg at 4.5 min after the antigen, and portal venous pressure increased from the baseline of 10 ± 1 cm H₂O to a peak level of 33 ± 1 cm H₂O at 1.5 min and then gradually recovered. The changes in mean arterial pressure and portal venous pressure during the initial 10 min after antigen in the groups with β -adrenoceptor antagonists were similar to those of the Control group. In the Control group, heart rate increased from the baseline of 361 ± 14 beats/min to the peak of 505 ± 13 beats/min at

Table 1
Baseline levels of the hemodynamic variables.

Groups	Mean arterial pressure (mm Hg)		Portal venous pressure (cm H ₂ O)		Heart rate (beats/min)	
	Before	After	Before	After	Before	After
Control	103.1 ± 4.1	103.3 ± 4.3	9.2 ± 0.8	10.0 ± 0.6	361 ± 14	362 ± 13
Propranolol	103.6 ± 1.7	108.7 ± 5.0	10.6 ± 0.4	10.3 ± 0.4	391 ± 13	351 ± 10 ^a
ICI 118,551	99.6 ± 4.4	102.5 ± 4.8	9.7 ± 0.7	10.0 ± 1.2	386 ± 8	385 ± 8
Atenolol	101.5 ± 3.3	102.5 ± 5.0	10.4 ± 0.9	9.6 ± 0.9	379 ± 14	344 ± 9 ^a
Adrenalectomy	103.6 ± 1.7	104.4 ± 2.5	10.0 ± 0.8	10.0 ± 0.5	381 ± 10	387 ± 11

Values are means ± S.E.M.; *n* = 7.

^a *P* < 0.05, vs. before injections of β -adrenoceptor antagonists or saline.

10 min after antigen. The increase in heart rate after antigen was significantly attenuated by propranolol and atenolol, as shown in Fig. 2 (bottom). In the Atenolol group, there was no significant increase in heart rate after antigen.

Two hours after the antigen, mean arterial pressure and portal venous pressure recovered to 93 ± 3 mm Hg and 8.8 ± 0.4 cm H₂O, respectively, in the Control group; all rats were alive at 48 h after antigen administration. All seven rats of the Propranolol, ICI 118,551 and Adrenalectomy groups died within 40 min after antigen, as shown in Fig. 3A. In contrast, in the Atenolol group, two rats died between 30 and 40 min, and the other three rats were alive at 120 min. The survival rates of any β -adrenoceptor antagonist groups and the Adrenalectomy group were significantly smaller than that of the Control group, while that of the Atenolol group was significantly greater than that of the Propranolol (*P* = 0.0002), ICI 118,551 (*P* = 0.0012) or Adrenalectomy (*P* = 0.0001) groups.

3.2. Effect of epinephrine on anaphylactic hypotension in rats pretreated with β -adrenoceptor antagonists or adrenalectomy

Based on the finding described earlier that inhibition of β_2 -adrenoceptor reduced survival rate as compared with that of β_1 -adrenoceptor, the effects of epinephrine, which has affinity to both

β_1 - and β_2 -adrenoceptors, were examined on anaphylactic hypotension in rats pretreated with β -adrenoceptor antagonists or adrenalectomy. Table 2 shows the basal levels of the hemodynamic variables for the epinephrine experiment, and the finding was essentially the same as the previous experiment (Table 1). When epinephrine was administered at 3 and 5 min after antigen, systemic arterial pressure and portal venous pressure showed a transient increase, but the changes in mean arterial pressure and portal venous pressure of any β -adrenoceptor antagonist groups were similar to those of the Control + Epinephrine group during the initial 10 min after antigen, and no significant differences were observed among groups (Figs. 1B and 4). Thereafter, the levels of mean arterial pressure and portal venous pressure were significantly smaller in the Propranolol + Epinephrine, ICI 118,551 + Epinephrine, or Adrenalectomy + Epinephrine groups than those of the Control + Epinephrine group. The antigen-induced increase in heart rate of each group (Fig. 4) was similar to that without epinephrine administration (Fig. 2), but heart rate in the Atenolol + Epinephrine group significantly increased after antigen. Fig. 3B shows the survival rates of the rats treated with epinephrine. Epinephrine prevented the death of the β_1 -adrenoceptor antagonist Atenolol group, while it increased only slightly, but significantly, the survival rates of the β_2 -adrenoceptor antagonist ICI 118,551, Propranolol and Adrenalectomy groups.

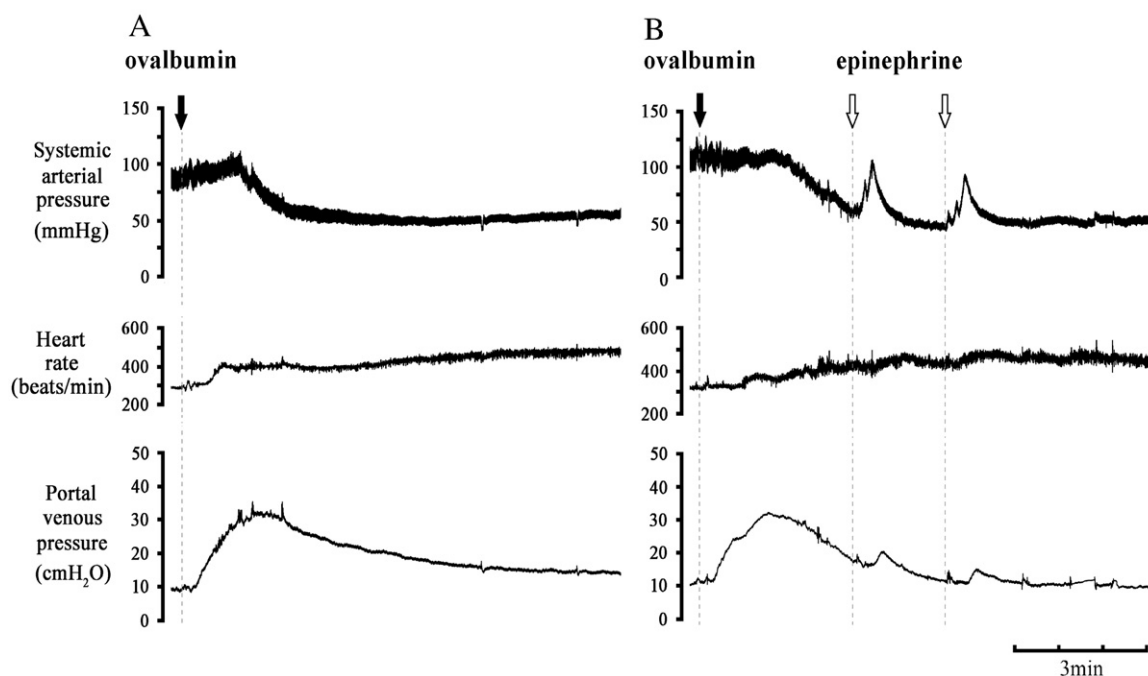


Fig. 1. The representative recordings of systemic arterial pressure, heart rate, and portal venous pressure after an injection of ovalbumin antigen in a control rat (A) and a control rat injected with epinephrine (open arrows) at 3 and 5 min after antigen (B).

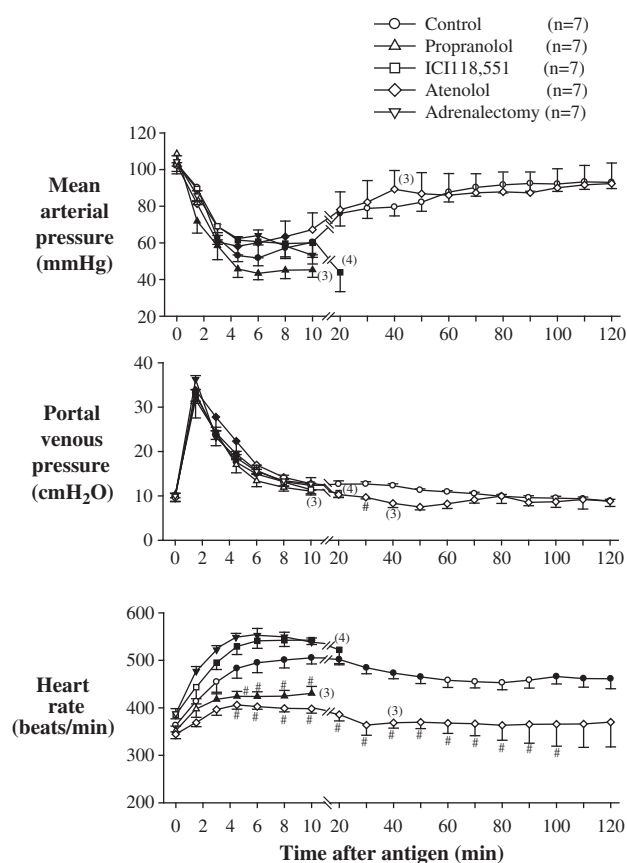


Fig. 2. The summary of mean arterial pressure, portal venous pressure and heart rate after an injection of ovalbumin antigen. Circle, Control group ($n=7$); triangle, Propranolol group ($n=7$); square, ICI 118,551 group ($n=7$); diamond, Atenolol group ($n=7$); inverted triangle, Adrenalectomy group ($n=7$). Values are means $\pm$ S.E.M.; # $P<0.002$, vs. the Control group; closed symbols $P<0.001$, vs. the baseline. The numbers in parentheses indicate the sample numbers of the animals.

4. Discussion

In this study, we determined which subtype of β -adrenoceptor, β_1 - or β_2 -adrenoceptor, is primarily responsible for the detrimental effect of the β -adrenoceptor antagonist on anaphylactic shock in unanesthetized rats. Three major findings were obtained. First, the survival rate of the rats pretreated with the selective β_2 -adrenoceptor antagonist ICI 118,551 was smaller than that with the selective β_1 -adrenoceptor antagonist atenolol, while similar to that with the

nonselective β -adrenoceptor antagonist propranolol. These results indicate that, in rat anaphylactic shock, inhibition of β_2 -adrenoceptor causes more detrimental effects than that of β_1 -adrenoceptor. Second, bolus injections of epinephrine prevented the death of the atenolol-pretreated rats, but only slightly prolonged the survival rate of the ICI 118,551- and propranolol-pretreated rats. Epinephrine has affinity to both β_1 - and β_2 -adrenoceptor; thus, the finding of 100% survival of the Atenolol group suggests that activation of β_2 -adrenoceptor by epinephrine is effective under β_1 -adrenoceptor inhibition. On the other hand, the absence of substantial improvement with epinephrine in the ICI 118,551 group suggests that the activation of β_1 -adrenoceptor by epinephrine is not effective under β_2 -adrenoceptor inhibition. These findings may reinforce more detrimental action of β_2 -adrenoceptor inhibition than β_1 -adrenoceptor inhibition. Finally, the antigen-induced increase in portal venous pressure was nearly the same among any β -adrenoceptor antagonist groups. These findings indicate that anaphylactic portal hypertension is not involved in the detrimental effect of β -adrenoceptor inhibition on rat anaphylactic shock.

The order of detrimental effects on survival rate was atenolol < ICI 118,551 $\leq$ propranolol. Similarity between propranolol and ICI 118,551 may be reasonable, because although propranolol is a nonselective β -adrenoceptor antagonist, this agent is actually more β_2 -selective than β_1 -selective (Hoffmann et al., 2004; Baker, 2005).

The mechanism for the deterioration of the survival in anaphylaxis of the rats by β_2 -adrenoceptor inhibition is not known. β -Adrenoceptor antagonists may exert detrimental effects on anaphylaxis by inhibiting the beneficial action of intrinsic β -adrenoceptor agonists or endogenously released epinephrine on anaphylaxis-induced changes. In this respect, we examined the role of endogenously released catecholamines by using the adrenalectomized rats. In response to antigen, the adrenalectomized rats showed a smaller survival rate than the intact rats. This finding strongly suggests that catecholamines endogenously released from the adrenal gland exert the beneficial effects on rat anaphylaxis. Indeed, activation of the sympathetic nervous system, which could account for the increased release of catecholamines from the adrenal gland, immediately follows the onset of anaphylactic hypotension in anesthetized rats (Potas et al., 2004).

Several possible explanations for the beneficial roles of β_2 -adrenoceptor could be pointed out. First, β_2 -adrenoceptor agonists inhibit mediator release from activated human mast cells in vitro (Church and Hiroi, 1987; Chong et al., 2002; Butchers et al., 1979; Hughes et al., 1983; Peters et al., 1982). Thus, β_2 -adrenoceptor antagonists might have increased the release of anaphylactic mediators, enhancing the anaphylactic responses. In rats, however, it is unlikely because β -adrenoceptor agonists did not exhibit potent inhibition of mediator release from mast cells (Inagaki et al., 1992; Marquardt and

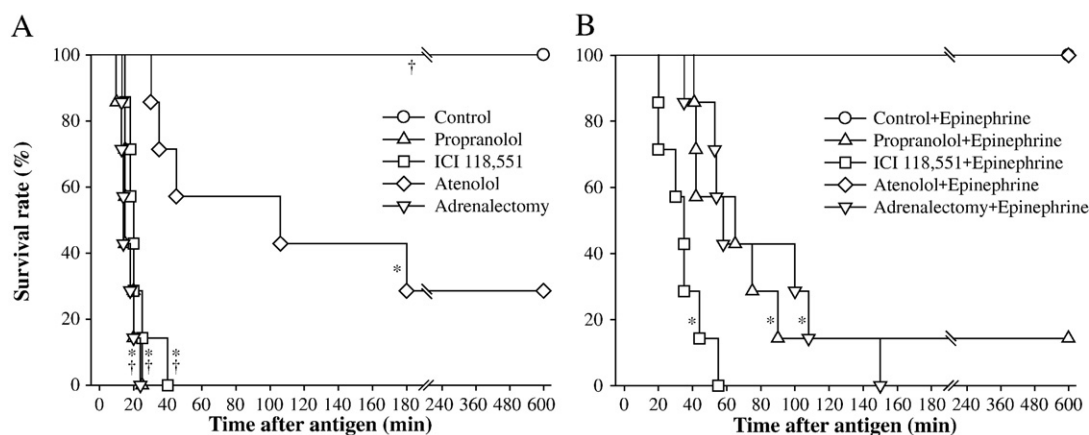


Fig. 3. The survival rates after an injection of antigen. A, without epinephrine; B, with epinephrine. * $P<0.05$, vs. the Control or Control+Epinephrine group. † $P<0.05$, vs. the Atenolol group.

Table 2
Baseline values for the epinephrine experiment.

Groups	Mean arterial pressure (mm Hg)		Portal venous pressure (cm H ₂ O)		Heart rate (beats/min)	
	Before	After	Before	After	Before	After
Control + Epinephrine	109.7 ± 1.8	108.4 ± 2.2	10.0 ± 0.7	10.0 ± 0.6	358 ± 11	353 ± 7
Propranolol + Epinephrine	109.4 ± 2.4	111.9 ± 2.7	9.7 ± 0.5	9.0 ± 0.4	360 ± 19	302 ± 5 ^{ab}
ICI 118,551 + Epinephrine	107.2 ± 2.6	108.8 ± 2.7	9.4 ± 0.3	9.2 ± 0.6	349 ± 11	348 ± 17
Atenolol + Epinephrine	106.5 ± 1.5	100.1 ± 1.9	10.0 ± 0.6	9.2 ± 0.8	343 ± 5	306 ± 5 ^{ab}
Adrenalectomy + Epinephrine	113.6 ± 1.6	112.4 ± 2.0	9.8 ± 0.6	9.5 ± 0.5	391 ± 7	387 ± 9

Values are means ± S.E.M.; n = 7.

^a P < 0.01, vs. before injections of β_2 -adrenoceptor antagonists or saline.

^b P < 0.001, vs. the Control + Epinephrine group.

Wasserman, 1982). Second, β_2 -adrenoceptor agonists possess anti-allergic and anti-inflammatory properties. In systemic anaphylaxis, plasma extravasation due to increased vascular permeability may result in reduction of effective circulating blood volume and then anaphylactic hypotension (Wither et al., 1998; Leng et al., 1989). β_2 -Adrenoceptor stimulation has an inhibitory effect on the extravasation of plasma proteins through increased microvascular leakage induced by anaphylaxis and anaphylactic mediators (Svensjo et al., 1977; Ohuchi et al., 1987; Bolton et al., 1997; Wither et al., 1998; Tokuyama et al., 1991). β_2 -

Adrenoceptor antagonists might have blocked the inhibitory effect of β_2 -adrenoceptor activation on vascular permeability and plasma extravasation. Third, the activation of β_2 -adrenoceptor in the presynaptic terminals of the sympathetic nerves can facilitate the release of norepinephrine in systemic circulation (Nedergaard and Abrahamsen, 1990). Therefore, inhibition of β_2 -adrenoceptor should decrease the release of norepinephrine from sympathetic fibers and thereby reduce the vasomotor tone and cardiac activity, resulting in augmentation of anaphylactic shock. Fourth, β_2 -adrenoceptor activation may exert beneficial effects via preventing bronchospasm. Bronchospasm is a common symptom of systemic anaphylaxis (Pumphrey and Roberts, 2000; Brown et al., 2006) and can induce hypoxemia, resulting in aggravation of anaphylactic shock. Because β_2 -adrenoceptor activation causes bronchodilation (Broadley, 2006), β_2 -adrenoceptor antagonists may augment anaphylaxis-induced bronchospasm and result in deterioration of anaphylaxis (Inagaki et al., 1992; Marquardt and Wasserman, 1982). However, whether bronchoconstriction augmented by β_2 -adrenoceptor antagonists plays a significant role is uncertain in the SD rats of the present study; although allergic bronchoconstriction is observed in the Brown Norway rat (Hele et al., 2001), it seems weak in anesthetized SD rats (Sun et al., 1992). Finally, pulmonary circulation may be involved in the beneficial role of β_2 -adrenoceptor. We have recently shown, using anesthetized rats sensitized to ovalbumin in the same manner as the present study, that although the antigen challenge induced no significant increase in pulmonary arterial pressure, pretreatment with either propranolol or ICI 118,551, but not atenolol, unmasked substantial increases in pulmonary arterial pressure and pulmonary vascular resistances (Zhang et al., 2010). This pulmonary vasoconstriction may account for, at least in part, the detrimental action of β_2 -adrenoceptor antagonist: pulmonary vasoconstriction increases the right heart overload, and decreases venous return, resulting in systemic hypotension.

In the present study, the selective β_1 -adrenoceptor antagonist atenolol also exerted a detrimental effect on anaphylaxis as evidenced by a smaller survival rate of the atenolol-pretreated rats than that of the control rats. This finding observed in unanesthetized rats is consistent with a clinical report of unusually severe anaphylaxis in association with selective β_1 -adrenoceptor antagonists (Zaloga et al., 1986). The mechanism for reduced survival rate by atenolol may be firstly related to its action on the heart, in which β_1 -adrenoceptors are rich in distribution. Actually, the heart is one of the target organs of systemic anaphylaxis. Cardiac dysfunction characterized by increased coronary vascular resistance and decreased left ventricular contractility was reported during cardiac anaphylaxis in isolated rat hearts perfused with blood-free solutions (Sun et al., 1992). β_1 -Adrenoceptor inhibition, reducing the heart rate and cardiac contractility aggravates cardiac dysfunction due to anaphylaxis and then decreases survival rate. Second, β_1 -adrenoceptor is involved in the release of renin from renal juxtaglomerular cells (Oates et al., 1978). The inhibition of renin release by β_1 -adrenoceptor antagonists can reduce the formation of angiotensin II and its cardiovascular and sympathomimetic functions. The final

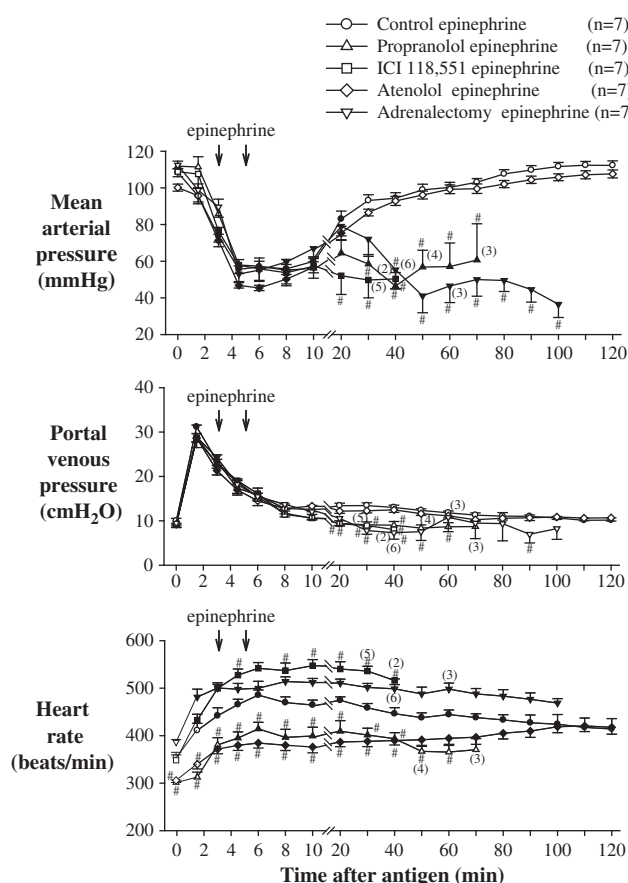


Fig. 4. Effect of bolus injections of epinephrine on mean arterial pressure, portal venous pressure and heart rate after an injection of ovalbumin antigen. Circle, Control + Epinephrine group (Control epinephrine; n = 7); triangle, Propranolol + Epinephrine group (Propranolol epinephrine; n = 7); square, ICI 118,551 + Epinephrine group (ICI 118,551 epinephrine; n = 7); diamond, Atenolol + Epinephrine group (Atenolol epinephrine; n = 7); inverted triangle, Adrenalectomy + Epinephrine group (Adrenalectomy epinephrine; n = 7). Values are means ± S.E.M.; #P < 0.002, vs. the Control + Epinephrine group; closed symbols P < 0.001, vs. the baseline. The arrows indicate injections of epinephrine.

explanation may be its slight β_2 -inhibitory property. Actually atenolol has an affinity to β_2 -adrenoceptor, which is about one fourth to that of β_1 -adrenoceptor (Baker, 2005).

Any β -adrenoceptor antagonists studied in the present study did not affect the antigen-induced increase in portal venous pressure. This finding indicates that enhancement of anaphylactic portal hypertension does not account for the decreases in the survival rate in the presence of β -adrenoceptor antagonists, and that hepatic venoconstriction induced by anaphylactic chemical mediators is not modulated by β -adrenoceptors. This finding of the absence of significant roles of β -adrenoceptors in anaphylactic hepatic venoconstriction is unexpected; β_2 -adrenoceptor agonists are reported to induce a decrease in portal pressure and an increase in portal tributary blood flow in normal rats (Poo et al., 1992).

We studied the effects of acute exposure to β -adrenoceptor antagonists. However, patients are usually taking β -adrenoceptor antagonists on a chronic basis, with all the adaptative mechanisms, such as desensitization, that are likely to occur but were not captured by the present study design. Further study may be required using animals with chronic administration of β -adrenoceptor antagonists, like patients treated with β -adrenoceptor antagonists.

In summary, we determined which subtype of β -adrenoceptors, β_1 - or β_2 -adrenoceptor, is primarily responsible for the detrimental effects of β -adrenoceptor antagonists on anaphylaxis in unanesthetized rats. The survival rates of the rats pretreated with the nonselective β -adrenoceptor propranolol and the selective β_2 -adrenoceptor ICI 118,551 are smaller than that with a selective β_1 -adrenoceptor atenolol. Furthermore, bolus injections of epinephrine dramatically inhibited the death of the Atenolol group, but not the Propranolol or ICI 118,551 group. The detrimental effects of adrenalectomy on anaphylaxis were similar to those of propranolol and ICI 118,551, suggesting that endogenous catecholamines from the adrenal gland activates these β -adrenoceptors, exerting beneficial effects on rat anaphylactic hypotension. In conclusion, in rat anaphylactic shock, inhibition of β_2 -adrenoceptor causes more detrimental effects than that of the β_1 -adrenoceptor.

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