Chronotropic and Inotropic Effects of 3 Kinds of Alpha-Adrenergic Blockers on the Isolated Dog Atria

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SUMMARY

Using the isolated and blood-perfused dog atrial preparation, chronotropic and inotropic responses to 3 kinds of alpha-adrenergic blockers, phentolamine, phenoxybenzamine, and E-643, were compared.

When phenoxybenzamine was administered into the cannulated sinus node artery, positive chronotropic and inotropic responses were induced in doses of 10–300 μg. Phentolamine also produced positive responses, but at larger doses such as 100 and 300 μg, accompanying initial negative responses.

E-643 usually produced only negative chronotropic and inotropic effects. Positive responses to phenoxybenzamine and phentolamine were significantly suppressed by propranolol, and negative responses to E-643 and phentolamine were not modified by atropine treatment.

From these results and previous reports, it is assumed that sinus tachycardia induced by alpha-blockers in situ may be due to 3 different mechanisms, i.e., 1) reflex tachycardia induced by the hypotension, 2) augmented catecholamine release mediated by the block of the presynaptic alpha-adrenoceptors, and 3) direct catecholamine release from locally innervated sympathetic nerve terminals.

Additional Indexing Words:
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It has been reported that release of norepinephrine elicited by nerve stimulation is regulated through negative feed-back mechanism mediated by presynaptic α-adrenoceptors. Therefore, sinus tachycardia elicited when an alpha-adrenoceptor blocking agent was given intravenously in intact animals may be induced by the reflex mechanism and by the activation of further release of the transmitter due to the alpha blockade on peripheral sympathetic tone. Thus, in isolated myocardial preparations which were completely isolated from extracardiac factors, the influence of the reflex mecha-
anisms and presynaptic alpha-adrenoceptor function should be ruled out and other modifying mechanism may be explicit.

In the present study, we tried to examine actions of three alpha-adrenoceptor blocking agents, phentolamine, phenoxybenzamine, and a new quinazoline compound (E-643, 2-\text{[}4-(\text{n-butyryl}-)\text{-homopiperazine}-1-\text{yl}]\text{-}4\text{-amino-}6, 7\text{-dimethoxyquinazoline hydrochloride}) on the SA nodal pacemaker activity and contractility using the isolated and blood-perfused dog atrial preparation.\textsuperscript{3,4}

**Methods**

Eight mongrel dogs of either sex weighing from 13–18 Kg were anesthetized with sodium pentobarbital, 30 mg/Kg, i.v. The right atrium was quickly excised and immersed in Tyrode solution at 4–10°C. The isolated atrium was perfused with arterial blood through the cannulated sinus node artery. The blood was led from the cartil artery of the heparinized support dog under the constant perfusion pressure of 100 mmHg by aid of a peristaltic pump (Harvard Apparatus 1210). The atrium was suspended in a bath filled with blood at a constant temperature of 37°C. Sinus rate was recorded with a tachometer (Nihon Kohden RT-5), which was triggered by the atrial electrograms. The upper part of the crista terminalis of the isolated atrium was connected directly to the force displacement transducer (Grass FTO3B) by a silk thread, and isometric developed tension was measured. Details of the isolated and blood-perfused canine atrium are described in previous papers.\textsuperscript{3,4} The volume of drug solution injected with microinectors was 0.01–0.03 ml in a period of 4 sec.

Drugs used in this study were phenoxybenzamine hydrochloride (Tokyo Kasei), phentolamine hydrochloride (Ciba), acetylcholine chloride (Daiichi), (\textpm\text{-}propranolol hydrochloride (Sumitomo Chemicals), (\textpm\text{-}norepinephrine hydrochloride (Sankyo), and E-643 (2-\text{[}4-(\text{n-butyryl}-)\text{-}homopiperazine}-1\text{-yl}]-4\text{-amino-}6, 7\text{-dimethoxy-}quazoline hydrochloride) (Eisai).

**Results**

1. **Chronotropic and inotropic effects of phentolamine, phenoxybenzamine, and E-643 on isolated atria**

When a single dose of phentolamine was directly injected into the cannulated sinus node artery, positive chronotropic and inotropic effects were induced at doses of 10–300 µg. However, at relatively large doses, phentolamine also produced negative chronotropic and inotropic effects which were followed by long-lasting positive ones. The threshold dose for inducing negative responses was approximately 100 µg. These responses were repetitively obtained when successive injections were administered as the response to each preceding injection wore off completely.
Phenoxybenzamine also produced positive chronotropic and inotropic effects at a dose range of 10–300 µg. Maximum responses were obtained at about 100 µg, and 300 µg of phenoxybenzamine produced rather smaller responses. Phenoxybenzamine-induced positive responses were usually larger than phentolamine-induced ones, but not significantly. Moreover, phenoxybenzamine never produced a negative inotropic and chronotropic response within the examined doses.

E-643 usually produced dose-relatedly negative chronotropic and inotropic effects, and never induced a positive response. The threshold dose for inducing negative response was approximately 30 µg. The duration of responses to E-643 was 5–10 min at 100 µg, and 10–20 min at 300 µg. Summarized data are shown in Fig. 1.

2. Effects of propranolol and atropine on the responses to alpha-adrenoceptor blocking agents

Positive chronotropic and inotropic responses to 100 µg of phentolamine and 100 µg of phenoxybenzamine were significantly suppressed by treatment with 3 µg of propranolol which inhibited the responses to 0.03 µg of nor-epinephrine (each 3 experiments). Thus, these alpha-blocking agents may cause a release of catecholamine from peripheral adrenergic nerve terminals in the heart.

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Fig. 1. Comparative chronotropic and inotropic responses to phenoxybenzamine (POB, ○—○), phentolamine (PA, ●—●), and E-643 (■—■) in 5 isolated and spontaneously beating dog atrial preparations. Control sinus rate was 106±4 beats/min (mean±SEM) in 5 atria. Vertical bars represent standard errors of the mean.
Negative chronotropic and inotropic responses to 100 μg of E-643 and 300 μg of phentolamine were not influenced by treatment with 100 μg of atropine which completely abolished effects of 0.1 μg of acetylcholine (each 2 experiments).

DISCUSSION

In the present experiments, effects of 3 kinds of alpha-adrenoceptor blocking agents on the heart were compared by use of blood-perfused atrial preparations which were completely isolated from extracardiac factors. Phenoxybenzamine and phentolamine caused slight positive inotropic and chronotropic effects which were significantly suppressed by propranolol. Therefore, these positive effects might be due to a release of norepinephrine from sympathetic nerve terminals in the atrial muscle. Since extracardiac reflex mechanism did not exist in these preparations, the block of the presynaptic alpha-adrenoceptors has no influential role on phentolamine- and phenoxybenzamine-induced tachycardia.

On the other hand, E-643, which was classified into a competitive α-antagonist, produced only negative chronotropic and inotropic effects in all examined oses. E-643-induced negative effects were not influenced by an adequate dose of atropine. Therefore, effects of E-643 were not induced by cholinergic mechanisms. It seems that E-643 has direct cardiac depressant properties and may have no catecholamine-releasing action.

Previously, we reported that phentolamine induced positive chronotropic effect in the in situ SA node preparation of the dog. Thus, we considered that an α-adrenoceptor blocking agent has accelerative properties which may be following three mechanisms, i.e., 1) reflex tachycardia induced by the hypotension, 2) augmented catecholamine release mediated by the block of the presynaptic alpha-adrenoceptors, and 3) direct catecholamine release from locally innervated sympathetic nerve terminals in the heart by some alpha-adrenoceptor blocking agents such as phentolamine or phenoxybenzamine.

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