Different Antagonistic Effects of Bunazosin and Ketanserin on the Norepinephrine-Induced Vasoconstriction in Isolated, Perfused Canine and Simian Skeletal Muscle Arteries

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Abstract—Blocking activities of bunazosin and ketanserin on norepinephrine (NE)-induced vasoconstrictions were investigated in isolated, perfused canine and simian skeletal muscle arteries. NE caused an increase in perfusion pressure in a dose-related manner to almost the same extent in both canine and simian arterial preparations. Bunazosin and ketanserin inhibited NE-induced vasoconstrictions much more readily in simian arteries than in canine arteries. The mechanisms for the different adrenolytic activities of \(\alpha_1\)-antagonists between these two arteries were discussed.

Recently, it was demonstrated that isolated skeletal muscle arteries of dogs were sensitive to \(\alpha_1\)-adrenoceptor agonists but not to \(\alpha_2\)-agonists (1), using the cannula inserting technique which was developed by Hongo and Chiba (2) and modified by Tsuji and Chiba (3). In the present study, we tried to examine blocking effects of bunazosin, a selective \(\alpha_1\)-adrenoceptor antagonist (4, 5), and ketanserin, a 5-HT\(_2\)-receptor antagonist with \(\alpha\)-adrenoceptor blocking activity (6-8), on norepinephrine-induced vasoconstrictions in canine and simian skeletal muscle arteries.

Ten mongrel dogs weighing 7-15 kg and eight Japanese monkeys (Macaca fuscata) weighing 5-13 kg of either sex were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) or ketamine hydrochloride (10 mg/kg, i.m.), respectively. They were sacrificed by rapid exsanguination after treatment with sodium heparin (200 units/kg, i.v.). Muscle branches of the canine femoral artery and the simian deep femoral artery which supply blood flow to skeletal muscle were carefully isolated and cut into several segments (0.5-0.8 mm in outer diameter and 5-8 mm in length). Then, a stainless steel cannula (27 gauge, 0.4 mm in outer diameter and 3 cm in length) with one small hole at a 5 mm distance from the distal sealed end was inserted into each vessel segment and set up for perfusion as reported previously (2, 3). Krebs' solution, gassed with 95% \(\text{O}_2\) and 5% \(\text{CO}_2\) and maintained at 37°C by means of a thermostat pump (Haake EF2), was perfused with a peristaltic pump (Harvard Apparatus 505-1210). The flow rate was kept constant throughout the experiments (0.5-1.5 ml/min). The basal perfusion pressure was between 50-100 mmHg. The change in perfusion pressure was measured with an electromanometer (Nihon Kohden, MPU 0.5 A) and vaso-constriction was recorded as an increase in perfusion pressure. The experiments were started when the arteries had equilibrated for about 60 min. The drug solution was administered into the rubber tubing close to the cannula in a volume of 0.01-0.03 ml by a microsyringe (Terumo Co.) for 3-4 sec.

Drugs used were dl-norepinephrine hydrochloride (Sankyo), bunazosin hydrochloride (Eisai) and ketanserin (Janssen). Results are expressed as means±S.E.M., and significance of the differences between data
was obtained by a Student's t-test for unpaired variates.

A bolus administration of norepinephrine caused an immediate increase in perfusion pressure in a dose-related manner in both canine and simian skeletal muscle arteries. No tachyphylaxis was observed in repetitive injections of norepinephrine in both preparations. The threshold dose of norepinephrine for inducing an increase in perfusion pressure was almost the same in either canine or simian arterial preparations (approximately 0.003 to 0.01 μg), and 1 μg of norepinephrine caused a maximal increase of more than 200 mmHg in perfusion pressure.

A single dose of bunazosin (0.1–10 μg) did not produce any significant vascular response by itself. Bunazosin (0.1 μg), injected bolusly, inhibited the vasoconstrictor responses induced by repeated injections of 0.3 μg of norepinephrine to a similar degree for 15 to 20 min. Thus, dose-response curves were made within 20 min after an injection of each dose of bunazosin in both vascular preparations. The effects of bunazosin on the dose-response curve for norepinephrine are shown in Fig. 1A (dog) and 1B (monkey), respectively. Bunazosin shifted the dose-response curve for norepinephrine in canine arteries to the right in a parallel manner. The dose-response curve for norepinephrine in simian arteries was much more greatly shifted than that in canine arteries; and moreover, the maximum response was markedly depressed by a larger dose (1 or 10 μg) of the antagonist.

Ketanserin (0.1–10 μg), injected bolusly, did not cause any vascular response in both arterial preparations. A dose of 1 μg of ketanserin did not inhibit norepinephrine-induced vasoconstrictions, but it rather potentiated them in canine arteries. On the other hand, in simian arteries, 0.1 μg of ketanserin clearly induced a parallel shift of the dose-response curve for norepinephrine to the right. At 10 μg, ketanserin clearly suppressed norepinephrine-induced vasoconstrictions in canine arteries. Summarized data are shown in Fig. 2.

A small dose of ketanserin may probably have suppressive effects on the inhibitory action of 5-HT on adrenergic transmitter release or uptake blocking effect on adrenergic nerve endings. However, it is not clear

![Fig. 1](image-url)
in this study, because we did not obtain significant potentiating effects. In the present study, it was shown that bunazosin readily suppressed responses to norepinephrine in simian skeletal muscle arteries to a greater extent than in canine arteries. Since these arteries were not sensitive to selective α₂-adrenoceptor agonists, clonidine and xylazine, the density of α₂-adrenoceptors might be low (1). In both arteries, norepinephrine produced almost the same grade of control dose-response curves. Therefore, it is considered that the density of α₁-adrenoceptors in these two different animal's arteries might be high to the same extent, but the sensitivity to α-adrenoceptor blocking agents was clearly different. Hata et al. (5) reported that large differences were found in the maximum binding sites and Kᵦ values of [³H]bunazosin in different tissue preparations, suggesting that there are possibly more than two kinds of α₁-adrenoceptors with different affinities for bunazosin. In this study, we demonstrated that both bunazosin and ketanserin had markedly different α-adrenolytic activity on the same organ of the dog and monkey. The definite mechanisms for the different potencies of α₁-adrenolytic actions of α₁-adrenoceptor antagonists between isolated dog and monkey vessels are not clear in the present experiments, but the following factors can be considered: 1) different affinities of the antagonists, 2) different conformations of the α₁-adrenoceptors, 3) different densities of spear receptors, 4) different diffusion times of the antagonist to reach the adrenoceptors by different anatomical structures, 5) different participations of presynaptic mechanisms and 6) different post-receptor, intracellular changes.

Fig. 2. Effects of increasing doses of ketanserin on norepinephrine (NE)-induced vasoconstrictions in the isolated, perfused skeletal muscle arteries. (A), NE vs. ketanserin in canine arteries (n=7); (B), NE vs. ketanserin in simian arteries (n=7). Values represent the mean±S.E.M.

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