Hypotensive mechanism of adrenergic alpha blockers in cats

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Summary. The hypotensive mechanism of adrenergic alpha blockers is related to their inhibitory effect on the contractile Ca-mechanism in vascular smooth muscles as in nitroglycerin or verapamil.

Considerable evidence is available showing that adrenergic alpha blockers have a typical antagonistic effect on the pressure response produced by adrenergic nerve stimulation or injection of catecholamines[1-6]. But it is not clear whether the blockers have a direct hypotensive action on systemic blood pressure, independent of the action on adrenergic alpha receptors in vascular smooth muscles, or not. To clarify the hypotensive mechanism of the blockers effects of the drugs on systemic blood pressure, Ca-contracture of isolated aortic strips were studied. The effect of known blockers, i.e. phentolamine, phenoxybenzamine, a new quinazoline compound (2-[4-(n-butyryl)-homopiperazine-1-yl]-4-amino-6,7-dimethoxy-quinazoline; E-643), nitroglycerin and verapamil were examined.

Methods. About 40 cats of both sexes were employed. 1. Systemic blood pressure and blood flow of anesthetized cats were determined. 2. A spiral aortic strip was isolated from an anesthetized cat and fixed to a mechanoelectronic transducer system isometrically. Thereafter the strip was suspended in an organ bath containing 10 ml of Tyrode solution bubbled with $CO_2(5\%)+O_2(95\%)$ gas at 20 °C. After equilibration, the bathing solution was replaced with a Ca-free Tyrode solution for 3 min, and then this solution was replaced with a Ca-free K-solution (KCl: 160.4 mM, KH_2PO_4: 0.4 mM, $MgCl_2$: 1.0 mM, $KHCO_3$: 12.0 mM, glucose: 5.0 mM) for 6 min. Finally, when a K-solution containing Ca of 1.8 mM was added, both phasic and tonic contracture were observed.

Results and discussions. As shown in table 1, systemic blood pressure decreased by i.v. administration (2×10^{-8} moles/kg) of all drugs except phenoxybenzamine. The order of maximal pressure fall after the injection was: E-643 > phentolamine > nitroglycerine > verapamil > phenoxybenzamine (0%; in 10-fold doses was 0). 2×10^{-7} moles/kg of phenoxybenzamine showed a typical adrenaline reversal (table 1). Therefore, it is likely that the hypotension in the presence of alpha blockers resulted from an effect other than an alpha adrenergic receptor blockade. The order of the duration of hypotensive effects was: E-643: 90 min, nitroglycerin: 8.6 min, the remnants: shorter than 5 min (table 1).

All drugs of 2×10^{-6} M inhibited the Ca-contracture (phasic and tonic) of depolarized aortic strips. The grade order of inhibition of phasic and tonic components was: nitroglycerin > E-643, dl-verapamil > phentolamine > pamine. Hypotensive potency to the blockers was parallel with their inhibitory potency to the Ca-contracture in the aortic strips (table 2). pA_2 of phentolamine and E-643 to contracture produced by adrenaline in cat aortic strips was 7.8 and 8.2, respectively. It is well-known that nitroglycerin causes a relaxation of vascular smooth muscles by its action on not only Ca-influx but also on the intracellular Ca-sequestration[7], and that verapamil also produces a decrease of Ca-influx across the plasma membranes[8,9].

In conclusion, the present study suggests that the hypotensive action of adrenergic alpha blockers is related to their inhibitory effect on the contractile Ca-mechanism in vascular smooth muscles as in nitroglycerin or verapamil, i.e. the blockers have a direct hypotensive action on the systemic blood pressure independent of the action on alpha receptors in vascular smooth muscles.

Table 1. Blood pressure response of adrenergic alpha blockers, nitroglycerin and verapamil in the anesthetized cats

Drugs (2×10^{-8} moles/kg)	Onset of fall (min)	Time of maximal fall (min)	Return to initial pressure (min)	Extent of systolic fall (mm Hg)	Percent of maximal fall
Phentolamine	0.74±0.11	1.47±0.12	4.39±0.18	52.0±4.60	26.9±2.09
Phenoxybenzamine*	–	–	–	–	–
E-643	0.88±0.40	5.14±0.48	90.92±5.08	60.0±4.00	35.3±0.16
Nitroglycerin	0.59±0.04	1.24±0.01	8.59±0.09	35.3±7.30	19.1±2.90
Verapamil	0.66±0.04	1.15±0.05	2.93±0.21	13.7±1.36	7.5±0.61

* 2×10^{-7} moles/kg.

Table 2. Relationship between the hypotensive action in vivo and the inhibitory effect of adrenergic alpha blockers, nitroglycerin and verapamil on the Ca-contracture in cat aortic strips

Drugs	Hypotensive potency (percent of maximal fall)	Inhibition of Ca-contracture in aortic strips (%)	
		Phasic contracture	Tonic contracture
Phentolamine	26.9±2.09	23.7±5.9	27.7±5.1
Phenoxybenzamine	0	18.2±4.9	19.9±0.6
E-643	35.3±0.16	42.3±8.0	57.0±10.5
Nitroglycerin	19.1±2.09	66.7±2.3	64.2±5.9
Verapamil	7.5±0.61	62.7±9.2	31.1±13.8

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