EFFECT OF HYPOTENSIVE AGENTS ON BARORECEPTOR REFLEXES IN WAKING ANIMALS

M. F. Bravkov

UDC 615.225.2.015.4:612.178.6

The effect of α-methyldopa, clonidine, pentobarbital sodium, and reserpine on reflex bradycardia induced by an artificial rise of the systemic arterial pressure (BP) was studied in experiments on waking cats. The substances used, which have a tranquilizing action, led to various changes in function of the baroreceptor reflexes, the initial BP level, and the cardiac frequency.

KEY WORDS: arterial blood pressure; pulse interval; baroreceptor reflex.

Most investigations into the pharmacological regulation of baroreceptor reflexes have been carried out in the form of acute experiments on anesthetized animals, so that it was difficult to assess the effect of hypotensive drugs with central action.

Accordingly the present investigation was carried out in order to study the effect of various neurotropic compounds on baroreceptor reflexes in waking animals.

EXPERIMENTAL METHOD

Experiments (51) were carried out on 24 cats able to move freely in the experimental chamber. Under sterile conditions, 6-7 days before the beginning of the observations, catheters were introduced into the aorta (through the carotid artery) and external jugular vein of the anesthetized animals. The catheters were fixed to the animal's head in special devices [1]. In the course of the experiment the systemic arterial pressure (BP), the pulse interval (PI) between two systoles, and respiration were recorded. The baroreflexes were tested by noting changes in the period of cardiac contractions during a transient rise of BP induced by intravenous injection of phenylephrine in doses of 0.03-0.04 mg/kg [8], using methods of regression and correlation analysis. Mean values of the regression coefficient were taken on the basis of five or six tests of the baroreflex. The drugs for testing — pentobarbital sodium in doses of 1-3 mg/kg, α-methyldopa in doses of 10-20 and 40-50 mg/kg, clonidine in doses of 0.001-0.003 mg/kg, and reserpine in a dose of 0.1 mg/kg — were injected intravenously.

EXPERIMENTAL RESULTS

In waking animals lying quietly on the floor of the experimental chamber BP was 65-85 mm Hg, the mean period of the cardiac contractions was 350-550 msec, and the regression coefficient was 4.2-12.8 msec/mm Hg. These indices remained virtually unchanged during observations for 2-3 months.

The effect of α-methyldopa was estimated 1-1.5 h after injection of the drug (Table 1). In doses of 10-20 mg/kg α-methyldopa caused an increase in the regression coefficient (with corresponding strengthening of the baroreceptor reflexes [8], slight bradycardia, and hypotension. With an increase in the dose of the drug (40-50 mg/kg), besides the appearance of a sedative, tranquilizing effect, strengthening of the baroreflex, and bradycardia, an increase in BP also was observed. The increase in systemic BP was evidently due to the marked peripheral effect of the drug [2]. After repeated injectionof α-methyldopa (in a daily dose of 20 mg/kg for 3 days) BP fell by 8 ± 1 mm Hg and the period of the cardiac contractions increased (by 82 ± 7 msec). The regression coefficient under these circumstances was virtually unchanged.

After the injection of clonidine the cats showed a marked tranquilizing effect and the motor activity of the animals and their response to the experimenter's manipulations were reduced. A dose-dependent increase in the regression coefficient was observed and it correlated with the increase in bradycardia and the fall in the

Department of Experimental Physiology and Pharmacology, Central Research Laboratory, Academician I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 2, pp. 166-168, February, 1979. Original article submitted April 11, 1978.

0007-4888/79/8702-0149$07.50

TABLE 1. Changes in Initial Values (in % of Regression Coefficient (B), the Systemic BP, and PI under the Influence of Neurotropic Drugs (M ± m)

Drug	Dose, mg/kg	Time after injection of drug, h	B	BP	PI
Methyldopa	10—20	1—1,5	128±6	96±2	106±2
	40—50		151±8	122±2	113±1
Clonidine	0,001	0,5	109±3	96±1	107±1
	0,003		133±3	83±1	118±2
Pentobarbital sodium	1	0,5	71±3	104±2	98±1
	3		63±3	105±1	88±2
		1	82±4	120±3	108±1
Reserpine	0,1	4—5	136±5	84±1	106±1
		24	117±5	89±1	107±1

Note. Values before administration of drugs taken as 100%.

initial systemic BP, changes in BP occurred in two phases: a transient rise (at 3-7 min) immediately after injection of the drug was followed by a long period (several hours) of hypotension (Table 1).

The hypotensive effect of clonidine (catapresan) and α-methyldopa is known to be due ultimately to activation of the adrenoreceptors of the CNS [3,4,6,7,9]. Potentiation of baroreflex bradycardia after administration of α-methyldopa and clonidine is probably attributable to activation of α-adrenoreceptors in the region of the nucleus of the tractus solitarius [7]. This mechanism may perhaps lie at the basis of the hypotensive effect of the drugs, for the hypotensive effect of catapresan disappears after destruction of the nucleus of the tractus solitarius [5].

Pentobarbital sodium also had a sedative action. However, autonomic manifestations after administration of this drug were opposite to those resulting from clonidine. In a dose of 1 mg/kg, pentobarbital caused virtually no change in the initial BP and cardiac frequency, despite a fall in the regression coefficient. After administration of the larger dose of pentobarbital (3 mg/kg) an even greater decrease in baroreflex bradycardia was accompanied by elevation of the systemic BP and an increase in the heart rate (Table 1).

The effect of reserpine on baroreceptor reflexes was investigated in each experiment for 24 h (1, 4-5, and 24 h after injection of the drug). Distinct correlation was found between the regression coefficient and BP during the first hours after administration of the drug. The behavior of the animals 1 h after injection of reserpine was outwardly unchanged, but a decrease in the regression coefficient was accompanied by raising of the BP by 15 ± 2 mm Hg. Marked inhibition of the animals was observed after 4-5 h: The cats lay on the floor of the experimental chamber, their muscles relaxed, and their responses to the experimenter's actions were sharply reduced. Meanwhile the regression coefficient was increased and BP was lowered by 12 ± 1 mm Hg. Practically no sedative effect of reserpine was observed 24 h after its injection, but the baroreceptor reflex remained increased while the hypotension was reduced (Table 1).

The drugs tested, which had a tranquilizing action, thus caused different changes in the function of the baroreceptor reflexes, the initial BP, and the heart rate. It can be concluded from these results that the principal role in the hypotensive action of drugs with a central adrenopositive effect (clonidine, α-methyldopa) and of drugs interfering with monoamine metabolism in the brain (reserpine) is played by the direct effect of the compounds on the mechanisms regulating the activity of vasomotor neurons.

LITERATURE CITED

1. O. S. Medvedev, Fiziol. Zh. SSSR, 60, 1473 (1974).
2. B. M. Altura, Proc. Soc. Exp. Biol. (New York), 145, 129 (1974).
3. M. Henning, A. Rubenson, and G. Trolin, J. Pharm. Pharmacol., 24, 447 (1972).
4. W. Kobinger and A. Walland, J. Pharm. Pharmacol., 2, 155 (1967).
5. J. Lipski, J. Przybylski, and E. Solnika, J. Pharm. Pharmacol., 38, 19 (1976).
6. H. Schmitt, H. Schmitt, J. R. Boissier, et al., J. Pharm. Pharmacol., 9, 340 (1968).
7. H. Schmitt, H. Schmitt, and S. Fenard, J. Pharm. Pharmacol., 14, 98 (1971).
8. H. S. Smyth, P. Sleight, and G. W. Pickering, Circulat. Res., 24, 109 (1969).
9. R. Starke and K. P. Altmann, Neuropharmacology, 12, 339 (1973).