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EFFECT OF BUSPIRONE AND BUSPIRONE-LIKE SEROTONIN 1A-AGONISTS ON SYSTEMIC BLOOD PRESSURE

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The role of serotoninergic neurons of the mesencephalic nuclei raphe in the regulation of systemic blood pressure (SBP), which was demonstrated in earlier work [2, 9], remains unclear, for serotonin, injected into the cerebral ventricles, lowers SBP in cats [2], but raises it in rats [9], whereas 8-hydroxy-2-(di-*n*-propylamino)tetraline, which selectively activates serotinin 1A receptors (R_{1A}-5-HT), lowers SBP exclusively both in cats [6, 10] and in rats [3, 4] when applied to the surface of the medulla [6] or injected intravenously [3, 4, 10]. Contradictory results have been obtained with other R_{1A}-5-HT activators, which are derivatives of 1-(2-pyrimidinyl)piperazine (1-FP), such as, for example, buspirone and ipsapirone [7, 10], which (buspirone) have been used or (ipsapirone, hepirone, campirone) studied experimentally and clinically as anxioselective agents.

This paper gives data on the effect of buspirone and some of its structural analogs and the active metabolite 1-PP [5] on SBP levels in rats.

EXPERIMENTAL METHOD

Experiments were carried out on 110 noninbred albino rats weighing 200 ± 20 g, anesthetized with urethane (1 g/kg, intraperitoneally). SBP was measured in the common carotid artery by means of a mercury manometer Before and at various intervals of time after injection of the test drugs, the ECG was recorded in standard lead II on the ÉKP-03 M instrument. In some experiments the frequency and amplitude of the respiratory movements were recorded. Buspirone, ipsapirone (provided by the firm "Troponwerke," West Germany), campirone, levopirone and 1-PP (synthesized at the Institute of Physicoorganic Chemistry and Carbon Chemistry, Academy of Sciences of Ukrainian SSR), which were injected intravenously in doses of 0.1-30 mg/kg and in a volume of 0.1-0.3 ml. Pharmacological analysis of the changes in SBP and the chronotropic function of the heart was carried out with the aid of atropine sulfate, hexamethonium dibromide, cocaine hydrochloride, phentolamine hydrochloride, and metrazol (of USSR origin), picrotoxin (from "Merck," USA), deseryl ("Sandoz," Switzerland), and (±)-alprenolol ("Imperial Chemical Industries," Great Britain).

EXPERIMENTAL RESULTS

The majority of the tested substances modified SBP, depending on its initial level. In normotensive rats (70-120 mm Hg) all the substances tested caused a fall of SPB (Figs. 1 and 2). The effect developed immediately after injection and reached a maximum within 30-60 sec. Its degree and duration (3-40 min) depended on the dose of the drug. Effective doses,

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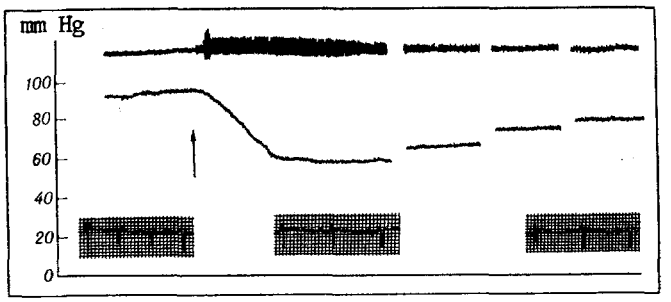

Fig. 1. Effect of campirone (3 mg/kg, intravenously) on respiration, systemic blood pressure (SBP), and heart rate. Kymograms of experiment. From top to bottom: respiration, SBP, ECG, zero line. Arrow indicates time of injection of drug. Intervals between traces 10 min.

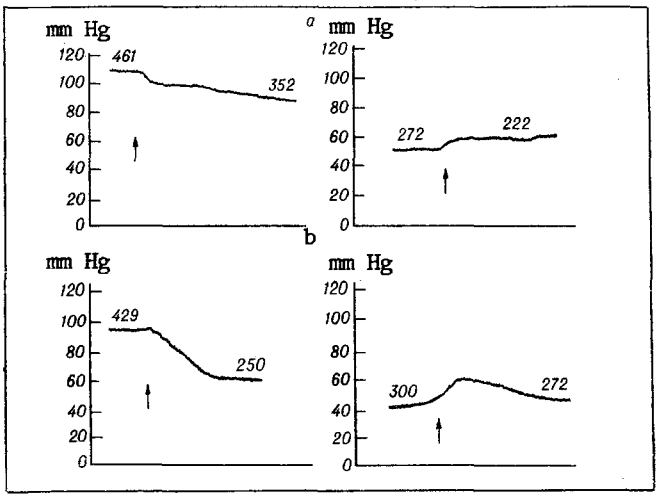

Fig. 2. Effect of buspirone (a) and campirone (b) in a dose of 1 mg/kg on systemic blood pressure in anesthetized rats with different initial pressure levels. Kymograms of experiments on four rats. Arrows indicate times of injection of drugs. Numbers above trace of SBP indicates heart rate, beats/min.

lowering SBP by 30% were identical for buspirone and levopirone, whereas ipsipirone and 1-PP gave the same degree of hypotension in doses half as large, but campirone was only one-third as active (Table 1).

Simultaneously with hypotension, the substances caused bradycardia (Fig. 1), the severity of which depended on dose (Table 1) only with some of the drugs (Ipsapirone, 1-PP). Hypotension and bradycardia are elements in the Bezold–Jarisch reflex, the 3rd component of which, namely transient apnea, was not produced by the test drugs. On the contrary, simultaneously with hypotension, they increased the amplitude and frequency of respiration (Fig. 1).

In initially hypotensive rats, whose SBP did not exceed 60 mm Hg, all the test drugs except ipsapirone gave a pressor response up to 10 min in duration (Fig. 2).

The hypotensive effect of buspirone and its analogs and 1-PP is not directly connected with the bradycardia induced by these substances, for the latter condition (like hyperpnea) is produced also in hypotensive rats responding to injection of the test drugs by elevation of SBP. Atropine (3 mg/kg), which abolishes the negative chronotropic effect of buspirone and buspironelike substances, did not change their hypotensive effects. Since, after decentralization of the vessels, by preliminary injection of hexamethonium (5 mg/kg), buspirone, campirone, levopirone, and 1-PP only raise SBP, it is logical to conclude that their hypotensive action is central in origin Picrotoxin (3 mg/kg), metrazol (20-30 mg/kg), and deseryl (1

TABLE 1. Degree of Hypotensive and Negative Chronotropic Action of Buspirone, Its Metabolite, and Its Structural Analogs

Substance	Number of animals	Hypotensive activity, ED_{30}, mg/kg	Changes in heart rate (% of initial value) after injection in dose of (mg/kg)		
			1	3	10
Buspirone	9	4,17±0,8	77±6,2	74	76
Ipsapirone	5	1,79	64	51	—
Campirone	14	13,18	75	72	70
Levopirone	9	6,11	69	64	61
1-PP	9	1,99	100	89	76

mg/kg) did not change the hypotensive effects of levopirone and campirone (3 mg/kg), but alprenolol (10 mg/kg) significantly lowered the hypotension arising after injection of 3 mg/kg of buspirone or levopirone. The pressor effect of clofelin (0.1 mg/kg), which is easily reproduced after preliminary injection of hexamethonium, was completely prevented by campirone (10 mg/kg), and pyrimidinyl-piperazine (10 mg/kg), and was partially reduced (by 15-20%) by levopirone (3 mg/kg).

The absence of any effect of picrotoxin, metrazol, and deseryl on hypertension induced by these drugs is evidence that $GABA_A$- and serotonin-2 receptors are not involved in this effect. The ability of alprenolol to reduce significantly the hypotension caused by buspirone, campirone, or levopirone, is probably due to blockade of serotonin-1 receptors, for which alprenolol has high affinity [8]. Considering that hypotension is induced not only by buspirone and campirone, acting on 1A and subtypes 1B of serotonin receptors [1], but also by ipsapirone, which exhibits affinity in radioligand [7] and functional [1] investigations exclusively for 1A-serotonin receptors of brain neurons, it can be concluded that it is the latter which mediate the central hypotensive effect of buspirone and its structural analogs However, the hypotensive properties of buspirone and buspironelike substances may be partly due to blockade of the muscular α_2-adrenoreceptors of the vessels, as is indicated by inhibition of the pressor effects of clofelin by campirone, levopirone, and 1-PP.

To analyze the pressor component of the action of buspiron, levopirone, and 1-PP it was reproduced after preliminary injection of hexamethonium (5 mg/kg). It has been shown that cocaine (5 mg/kg) does not influence the pressor effects of these substances, phentolamine (0.5 mg/kg) reduced them by half, but deseryl (1 mg/kg) completely abolishes the hypertension caused by levopirone, buspirone, and 1-PP. The pressor effect of buspirone and its structural analogs and 1-PP is evidently due to activation predominantly of serotonin-2 receptors of the vascular smooth muscles. Involvement of serotonin-3 receptors (ganglionic neurons) in the pressor effect is unlikely, for cocaine does not change this effect of the substances tested.

Thus buspirone, its structural analogs, and 1-PP, with their dual effect on systemic blood pressure, cause hypotension as a result mainly of activation of serotonin-1A receptors of brain neurons, but their pressor effect is due to activation predominantly of serotonin-2 receptors of vascular smooth muscles.

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