TABLE 1. Pharmocokinetic Parameters of PZ and its Metabolite after Intravenous Injection (0.5 mg/kg)

Serial No.	PZ						MQ	
	$AUC_{0-\infty}$, μmoles/h	$t_{1/2}$, h	CL, liter/h/kg	V_{ss}, liter/kg	V_0, liter/kg	MRT, h	AUC_{0-24}, μmoles/h	V_0, liters/kg
1	12,1	9,6	0,11	0,72	0,16	6,5	22,5	0,015
2	11,1	8,9	0,12	1,15	0,14	9,6	18,1	0,1
3	9,5	9,5	0,14	0,97	0,16	6,9	27,6	0,02

Legend. $AUC_{0-\infty}$) Area under concentration curve of 0 to ∞; AUC_{0-24}) the same, between 0 and 24 h.

It is interesting to compare the data on the pharmacokinetics of PZ, when injected intravenously into rabbits, which we obtained for the first time with corresponding characteristics for man [5]. For instance, the mean values of CL and V_0 in man (0.14 liter/h/kg and 0.15 liter/kg, respectively) are close to their values for the rabbit (Table 1). Other modally independent parameters of the pharmacokinetics are not given in [5], but they can easily be calculated from the parameters of the two-compartment model used to describe the data. It was found that the mean values of MRT and V_{ss} (3.6 h and 0.52 liter/kg, respectively) differ a little from these parameters in rabbits, but are of the same order of magnitude. Rabbits thus constitute a good experimental model with which to study the pharmacokinetics of PZ.

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REGULATION OF ^{3}H-DOPAMINE RELEASE BY PRESYNAPTIC GABA AND GLUTAMATE HETERORECEPTORS IN RAT BRAIN NUCLEUS ACCUMBENS SYNAPTOSOMES*

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The possibility that GABA receptors are involved in the regulation of electrical and secretory activity of dopaminergic neurons in certain mammalian brain formations has been demonstrated previously [4]. The presence of a presynaptic receptor mechanism, sensitivity to GABA and controlling ^{3}H-dopamine (^{3}H-DA) release from nerve endings of the nucleus accumbens of the mesolimbic system of the rat brain was described by the writers previously [2]. Mean-

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TABLE 1. Effect of GABA, Muscimol, and DALA on K^+-Stimulated ^{3}H-DA Release and their Interaction with BC and PT

Substance and dose (in μM)	Number of experiments	Effect of substances, % of control
Control – 30 mM KCl (30)	12	100±8,9
GABA (50)	4	72±12,0***
GABA (50) + PT (50)	4	102±6,7
GABA (50) + BC (10)	4	98±4,3
Muscimol (50)	5	75±6,7*
Muscimol (50) + PT (50)	4	120±26,1
Muscimol (50) + BC (10)	4	114±2,2
DALA (50)	9	131±4,0**
DALA (50) + PT (50)	6	138±10,0*
DALA (50) + BC (10)	5	141±2,8*
PT (50)	7	115±2,2
BC (10)	6	109±10,1

Legend. *P < 0.05, **P < 0.02, ***P < 0.01 compared with control (Wilcoxon–Mann–Whitney test).

while an increasing number of publications is evidence of the existence of several types of GABA receptors, differing in their pharmacological and physicochemical characteristics [1, 5-7, 9].

The aim of this investigation was a neurochemical study of the effect of agonists of different types of GABA receptors – muscimol (type A receptor), baclofen (type B receptor [6]), and δ-aminolevulinic acid (DALA; GABA autoreceptor [7]), and also of GABA itself – on K^+-stimulated ^{3}H-DA release from synaptosomes of the nuclei accumbenes of the rat brain.

EXPERIMENTAL METHOD

Male Wistar rats weighing 150 ± 10 g, kept under standard conditions (temperature 22 ± 2°C, alternation of daylight and darkness every 12 h, food and water ad libitum). The animals were killed by immersion in liquid nitrogen (8 sec) and the brain was quickly removed and the nuclei accumbens isolated (30 ± 5 mg) for homogenization (Teflon–glass, clearance 0.03 mm, number of cycles 10) in 0.32 M sucrose containing (in mM): Na_2HPO_4 – 2.0, KH_2PO_4 – 0.7, EDTA 3.0, pH 7.3. The homogenate was centrifuged (1000g, 8 min, 4°C). The total time required to obtain the unpurified synaptosomes fraction (P_2) did not exceed 15 min. The suspension was diluted in the ratio 1:5 with modified McIlwain's buffer of the following composition (in mM): NaCl – 130, KCl – 1.7, KH_2PO_4 – 1.3, Na_2HPO_4 – 10.4, $MgSO_4$ – 1.3, glucose 11, ascorbic acid 1.1, Na_2-EDTA 0.2, pargyline 0.125 [8].

After saturation of the buffer with carbogen the pH was adjusted to 7.3. After preincubation (5 min) of the synaptosomes at 37°C ^{3}H-DA was added to the samples (12.8 Ci/mmole, NEN) to a final concentration of $4 \cdot 10^{-7}$ M. The suspension was incubated at 37°C and at the rate of 0.5 ml/min in the following order: 10 min – normal buffer, 4 min – buffer with the test substance (or substances) in the required concentration, 5 min – buffer with 30 mM KCl and the test substance, 3 min – normal buffer. Two-minute fractions of the superfusate were collected in scintillation flasks.

After the end of the superfusion the filter and samples were dissolved in 8 ml of Bray's scintillator. The effect of the substances on induced secretion was estimated as a percentage of the effect of 30 mM KCl in the course of 5 min, taken as 100%. Radioactivity was measured on a KLB-1210 Ultrobeta counter (Sweden). Statistical analysis was carried out by nonparametric methods [3].

EXPERIMENTAL RESULTS

None of the substances tested changed the basal release of ^{3}H-DA during superfusion in a concentration of 50 μM: bicuculline (BC) and picrotoxin (PT) in concentrations of 10 and 100 μM respectively. The results of the study of the effect of agonists and antogonists of GABA receptors and also of their combination on K^+-induced ^{3}H-DA release are given in Table 1.

GABA and muscimol, agonists of type A GABA receptors, inhibited ^{3}H-DA release to 75% relative to the effect of KCl. BC, a competitive antagonist, and PT, a noncompetitive antag-

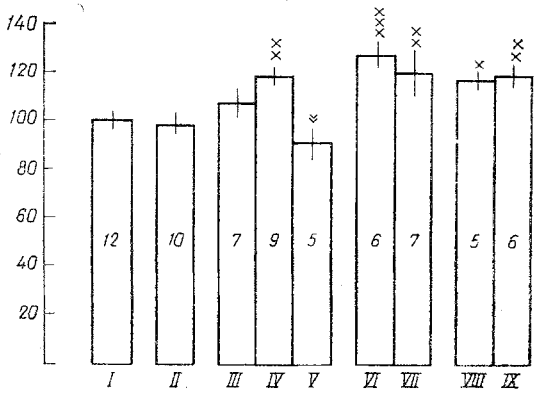

Fig. 1

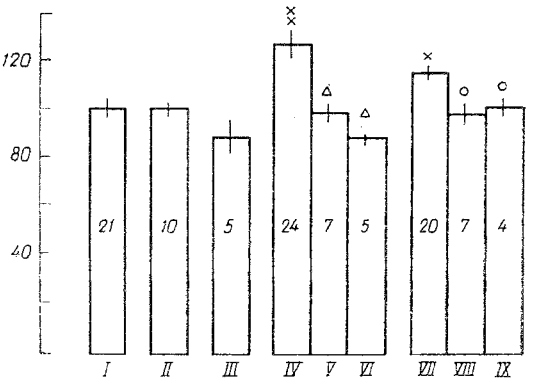

Fig. 2

Fig. 1. Influence of DEEG on effects of L-glutamate, DALA, and baclofen. Ordinate, Effect of substances (50 μM) and their combinations relative to control (30 mM KCl), taken as 100%. Numbers on columns indicate number of independent determinations. I) Control; II) DEEG; III) L-glutamate; IV) L-glutamate (100 μM); V) L-glutamate (100 M) + DEEG; VI) DALA; VII) DALA + DEEG; VIII) baclofen; IX) baclofen + DEEG. *P < 0.05, **P < 0.02, and ***P < 0.01 — significance of differences from I respectively;) P < 0.02 — difference from IV significant.

Fig. 2. Effect of blockers of GABA uptake on effect of DALA and baclofen. I) Control; II) nipecotic acid; III) DABA; IV) DALA; V) DALA + nipecotic acid; VI) DALA + DABA; VII) baclofen; VIII) baclogen + nipecotic acid; IX) baclofen + DABA. ×, Δ, and o) P < 0.05, and ××) P < 0.02, compared with control, respectively. Remander of legend as in Fig. 1.

onist of GABA receptors reversed the effects of the agonists. The complete range of these effects, namely activation by GABA and muscimol. Antagonism with BC, and participation of the chloride ionophore, sensitive to PT, is a characteristic features of type A receptors [6]. Conversely, DALA stimulated release of the radioactive label, and this was not abolished by BC and PT. Baclofen has a similar action. The similar effect of DALA, considered to be a "selective agonist of GABA autoreceptors" [7] was rather unexpected, having regard to the fact that this amino acid, with its C5 chain, inhibited stimulated release of ^{3}H-GABA from rat cerebral cortical synapses with IC_{50} of 10 μM (IC stands for inhibiting concentration), whereas BC and PT prevented this decrease [7]. The possibility that two types of GABA receptors may exist in the nucleus accumbens — ordinary postsynaptic (presynaptic heteroreceptors [11]) and autoreceptors, with opposite actions on the level of motor activity, has been stated by other workers [14, 15]. In our case, however, the absence of specific antagonism with BC and PT does not allow the nature of this phenomenon to be characterized as GABA-receptor.

Considering the structural similarity between the molecules of DALA and glutamic acid, which is the excitatory amino-acid transmitter in the brain, and also if the results described above are compared with data in the literature on the ability of L-glutamate to potentiate ^{3}H-DA release from slices of the nucleus accumbens, whereas the diethyl ester of glutamate (DEEG) — an antagonist of the glutamate receptor, weakens this increase [12], a series of experiments was carried out to compare the influence of DEEG on the effect of glutamate, DALA, and baclogen (Fig. 1).

Glutamate (50 and 100 μM) has a facilitatory action of ^{3}H-DA release, which although it is not weaker than the effect of DALA and baclofen, is DEEG-sensitive, whereas the effect of DALA and baclofen is unchanged in the presence of this antagonist of glutamate receptors of quisqualate-dependent type [16]. Meanwhile inhibitors of the GABA uptake system namely L-2,4-diaminobutryic acid (DABA) and nipecotic acid, which themselves do not affect tritium release, counteracted the effect of DALA and baclofen (Fig. 2).

The results are thus evident, first, that ^{3}H-DA release from synaptosomes of the mesolimbic system of the rat brain is under inhibitory DABA-receptor control; this control, moreover, is effected by means of presynaptic receptors (postsynaptic heteroreceptors), which exhibit the pharmacological properties of type A GABA receptors; second, that excitatory pre-

synaptic receptors, sensitive to glutamate, and characterized by properties of the qusiqualate subtype, are also present there. The similar effects of DALA and baclofen, an agonist of type B GABA receptors, cannot be classed as receptor-determined because of the absence of a generally accepted specific antagonist of receptors of this type. Meanwhile antagonism of these analogs with blockers of the GABA transport systems suggests the existence of a connection between this system and labeled DA release. The coexistence of functional systems of two neurotransmitters, and in particular, of DA and GABA, demonstrated for the first time in the study, may be confirmed by [10], in which this possibility was demonstrated on the example of discovery of glutamate decarboxylase and tyrosine hydroxylase immunoreactivity in neurons of the olfactory bulbs. It was noted recently that DA is taken up by serotoninergic neurons of the neostriatum [13].

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EFFECT OF SOME DRUGS ON ETHANOL-INDUCED CHANGES IN BLLOD-BRAIN BARRIER PERMEABILITY FOR ^{14}C-TYROSINE

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In the modern view [1] the blood-brain barrier (BBB) is a complex membrane which functions in accordance with general principles that are similar for all membranes, whereas on the other hand, it is complex structural-functional formation that is under various kinds of physiological control and, in particular, under the influence of neurotransmitter systems. It has been shown that ethanol, with its marked membranotropic action [9] and with the ability to interfere with neurotransmitter processes in the brain [2, 3, 5], increases the permeability of the BBB for physiologically active substances, including amino acids, and among them, tryptophan [13] and dopa [8], which are precursors of neurotransmitters. This suggests that changes in permeability of BBB induced by ethanol may evidently be linked with its membranotropic effect and (or) its effect on neurotransmitter processes. This hypothesis is confirmed by data on the ability of chlorpromazine (CP), used as a membrane stabilizer, to reduce the permeability of BBB for albumin following microtraumatic brain damage in rats exposed to ethanol [14], and also on the ability of haloperidol (HP), as dopaminergic antogonist, to prevent the amphetamine-induced increase in permeability of BBB for albumin [15].

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