TABLE 2. Effect of Anticonvulsants and Antidepressants on Action of Reserpine in Mice (M ± m)

Preparations	Dose, mg/kg	Number of mice	Effect of reserpine 4 h after intraperitoneal injection (2.5 mg/kg)				
			hydrothermia, °C	Δt	P	blepharoptosis	P
Distilled water	—	36	30,2±0,3	—	—	3,8±0,1	—
Sodium valproate	10	36	32,4±0,4	2,2	<0,001	2,8±0,2[a]	<0,001
Imipramine	10	24	33,0±0,4	2,8	<0,001	2,8±0,2[a1]	<0,001
Carbamazepine	50	30	29,7±0,3	—0,5	>0,05	2,9±0,1	<0,001
Sodium valproate	200	30	28,7±0,4	—1,5	<0,01	3,3±0,1	>0,05
Pyrazidol + carbamazepine	10+50	36	32,6±0,3	2,4	<0,001	2,1±0,2 b	<0,001
Imipramine + carbamazepine	10+50	24	33,4±0,3	3,2	<0,001	1,9±0,2 b_1	<0,001
Pyrazidol + sodium valproate	10+200	36	32,4±0,3	2,2	<0,001	2,3±0,2	<0,001
Imipramine + sodium valproate	10+200	12	31,6±0,8	1,4	>0,05	2,4±0,4	<0,001

Note. Differences between a and b and a_1 and b_1 significant at the $P < 0.01$ level.

GABA-ergic action. Under the influence of valproate, a marked increase in the GABA concentration is observed in certain discrete regions of the brain [3, 7]. This effect is evidently insensitive to the action of antidepressants, at least in acute experiments.

This investigation may provide experimental evidence in support of the efficacy of carbamazepine (Finlepsin) in the treatment of affective states.

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CHANGES IN PRESYNAPTIC RELEASE, BUT NOT REUPTAKE, OF BIOAMINES INDUCED BY LONG-TERM ANTIDEPRESSANT TREATMENT

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KEY WORDS: antidepressants; chronic administration; uptake; release; bioamines; brain slices.

The basis of the thymoleptic effect of the tricyclic and many other antidepressants is evidently elevation of the synaptic concentration of noradrenalin (NA) and serotonin (5-HT). This effect is realized both by inhibition of reuptake [5] and intensification of presynaptic release [3] of these monoamines. These changes in function of noradrenergic and serotoninergic synapses are observed after a single dose of antidepressant, but their clinical effect develops only during a course of administration [1]. The retarded development of the therapeutic effect is attributed [2] to adaptive changes in the receptor profile and sensitivity of the nerve cell to monoamines, arising during a course of antidepressant therapy. However,

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TABLE 1. Effect of Long-Term Administration of Antidepressants on Neuronal Uptake and Presynaptic Release of ^{14}C-NA and ^{3}H-5-HT by Rat Brain Slices

Substance	IC_{50} ($\pm S\bar{x} \cdot t$), M				EC_2 ($\pm S\bar{x} \cdot t$), M			
	control		experiment		control		experiment	
	^{14}C-NA	^{3}H-5-HT	^{14}C-NA	^{3}H-5-HT	^{14}C-NA	^{3}H-5-HT	^{14}C-NA	^{3}H-5-HT
Imipramine	$(2,0\pm0,3)\cdot10^{-7}$	$(4,4\pm0,8)\cdot10^{-7}$	$(1,8\pm0,8)\cdot10^{-7}$	$(4,1\pm0,6)\cdot10^{-7}$	$(2,6\pm1,1)\cdot10^{-7}$	$(4,9\pm0,5)\cdot10^{-6}$	$(3,2\pm0,6)\cdot10^{-8}$	$(5,2\pm0,2)\cdot10^{-7}$
Pyrazidol	$(6,7\pm1,7)\cdot10^{-6}$	$(7,9\pm1,1)\cdot10^{-6}$	$(6,5\pm0,8)\cdot10^{-6}$	$(7,6\pm0,8)\cdot10^{-6}$	$(4,5\pm1,6)\cdot10^{-6}$	$(3,4\pm1,2)\cdot10^{-5}$	$(2,4\pm0,8)\cdot10^{-7}$	$(4,0\pm0,6)\cdot10^{-6}$
Harman	$(2,5\pm0,5)\cdot10^{-5}$	$(3,0\pm0,8)\cdot10^{-6}$	$(2,7\pm0,6)\cdot10^{-6}$	$(3,4\pm1,1)\cdot10^{-6}$	$(3,2\pm0,4)\cdot10^{-7}$	$(5,2\pm0,4)\cdot10^{-7}$	$(1,4\pm0,5)\cdot10^{-8}$	$(6,4\pm0,8)\cdot10^{-8}$
C-153	$(2,8\pm0,4)\cdot10^{-5}$	$(3,7\pm0,5)\cdot10^{-6}$	$(3,2\pm1,5)\cdot10^{-5}$	$(3,9\pm1,2)\cdot10^{-6}$	$(4,0\pm0,5)\cdot10^{-7}$	$(4,5\pm0,8)\cdot10^{-7}$	$(5,2\pm0,2)\cdot10^{-8}$	$(2,6\pm0,2)\cdot10^{-8}$
C-307	$(3,8\pm0,6)\cdot10^{-5}$	$(2,7\pm0,5)\cdot10^{-5}$	$(4,0\pm1,2)\cdot10^{-5}$	$(2,5\pm0,6)\cdot10^{-5}$	$(5,0\pm0,8)\cdot10^{-7}$	$(3,2\pm0,4)\cdot10^{-6}$	$(3,6\pm1,1)\cdot10^{-8}$	$(4,4\pm0,5)\cdot10^{-7}$
C-394	$(6,2\pm1,9)\cdot10^{-5}$	$(5,4\pm0,8)\cdot10^{-6}$	$(6,0\pm0,8)\cdot10^{-5}$	$(5,2\pm1,0)\cdot10^{-6}$	$(5,13\pm0,7)\cdot10^{-6}$	$(3,0\pm0,5)\cdot10^{-6}$	$(4,3\pm1,2)\cdot10^{-7}$	$(2,8\pm0,5)\cdot10^{-7}$
C-395	$(2,0\pm1,2)\cdot10^{-5}$	$(7,6\pm1,0)\cdot10^{-6}$	$(2,1\pm0,4)\cdot10^{-5}$	$(7,7\pm0,8)\cdot10^{-6}$	$(3,6\pm0,9)\cdot10^{-6}$	$(4,2\pm0,8)\cdot10^{-5}$	$(1,2\pm0,4)\cdot10^{-7}$	$(2,2\pm0,6)\cdot10^{-6}$

it is not clear what effect these adaptive changes may have on the primary properties of antidepressants: inhibition of reuptake or potentiation of presynaptic release of NA and 5-HT by them.

This paper describes an investigation into the effect of long-term administration of antidepressants on neuronal uptake of NA and 5-HT and on their release induced by electrical stimulation, in rat brain slices.

EXPERIMENTAL METHODS

Experiments were carried out on noninbred albino rats weighing 180 ± 20 g from the Rappolovo nursery, Academy of Medical Sciences of the USSR. Rats of one group were given intraperitoneal injections of 0.2 ml of water for a period of 2 weeks, while animals of the other group received injections of the following antidepressants, also for 2 weeks: imipramine (10 mg/kg), pyrazidol (Pirlindol) (20 mg/kg), harman* (10 mg/kg) and its derivatives — C-153, C-307, C-394, and C-395 (10 mg/kg), which have the properties of potential antidepressants [4]. The rats were decapitated 24 h after the last injection of the test drugs, and thin (200-250 μ) slices of the cerebral cortex were cut by the method described previously [7]. The effects of the test substances on neuronal uptake of ^{14}C-NA and ^{3}H-5-HT by the slices was investigated by the method in [8], and presynaptic release of bioamines by the method in [9]. Methods of studying reuptake and presynaptic release of monoamines were described in detail previously [4]. Values of IC_{50} (the concentration of the substance inhibiting bioamine uptake by 50%) and EC_2 (the concentration of the substance doubling the release of radioactive label compared with its release in response to electrical stimulation of the slice only) were found and compared in the experiments and control.

The inhibitory effect of clonidine (10^{-4} M) and of 5-HT (10^{-5} M) on presynaptic release of ^{14}C-NA and ^{3}H-5-HT also was studied in brain slices from intact rats and rats treated for 2 weeks with antidepressants. The results were subjected to statistical analysis by the usual methods.

RESULTS

All the antidepressants studied intensified presynaptic release of ^{14}C-NA and ^{3}H-5-HT in rat brain slices. Concentrations doubling ^{14}C-NA release induced by electrical stimulation of brain slices from rats of the control group differed significantly in the case of different antidepressants, and varied from $(2.6 \pm 1.1) \times 10^{-7}$ M with imipramine to $(5.13 \pm 0.7) \times 10^{-6}$ M with C-394 (Table 1). Stimulation of presynaptic release of ^{3}H-5-HT by imipramine was observed in a concentration of $(4.9 \pm 0.5) \times 10^{-6}$ M. Presynaptic release of ^{14}C-NA and ^{3}H-5-HT was doubled in rats receiving long-term treatment with imipramine (10 mg/kg) when its concentrations were an order of magnitude higher: $(3.2 \pm 0.6) \times 10^{-8}$ and $(5.2 \pm 0.2) \times 10^{-7}$ M respectively. A similar effect was observed during long-term administration of pyrazidol and of harman or its derivatives (C-153, C-307, C-394, and C-395).

Preliminary administration of antidepressants for several days, however, did not change the ability of these compounds to inhibit neuronal uptake of ^{14}C-NA and ^{3}H-5-HT. Determination of IC_{50} 24 h after the final dose of the drugs revealed no significant changes in the

*1-Methyl(9H)pyrido(3,4-b)-indole.

ability of the various compounds to inhibit reuptake. For instance, IC_{50} for imipramine, which inhibits ^{14}C-NA uptake by brain slices from intact animals during repeated administration of the antidepressant also, was $(2.0 \pm 0.3) \times 10^{-7}$ and $(1.8 \pm 0.8) \times 10^{-7}$ M respectively. Clonidine (10^{-4} M), an agonist of presynaptic α_2-adrenoreceptors, and serotonin (10^{-5} M), an agonist of presynaptic 5-HT-receptors, inhibited by 43.8 and 38.7%, respectively, release of radioactive label from slices of cerebral cortex, preincubated with ^{14}C-NA and ^{3}H-5-HT, induced by electrical stimulation. The inhibitory effect of clonidine and serotonin in the same concentrations on release of ^{14}C-NA and ^{3}H-5-HT was significantly weakened in experiments on brain slices from rats receiving repeated doses of these antidepressants.

The results thus suggest that long-term administration of antidepressants has a modulating effect on presynaptic mechanisms, aimed at increasing the active concentration of bioamines in the synapse. The increase in the concentration of mediators in aminergic synapses may arise from two causes: an inhibitory effect on neuronal uptake and a stimulating action on presynaptic release of monoamines. Systems responsible for the mechanism of release, but not of neuronal reuptake of bioamines are affected by these adaptive changes. Administration of a course of antidepressants for several days leads to considerable potentiation of neurotransmitter release, induced by electrical stimulation, from axon terminals of monoaminergic neurons and significantly diminishes the inhibitory effect of clonidine and serotonin on presynaptic release of ^{14}C-NA and ^{3}H-5-HT.

The modulating effect of repeated doses of antidepressants on presynaptic pulsed release of neurotransmitters by noradrenergic and serotoninergic brain neurons may be due to a change in the density of presynaptic autoreceptors. Direct radioligand investigations [6] have shown that chronic imipramine administration is accompanied by the neurochemical changes mentioned above.

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