In conclusion, it must be pointed out that mice tolerated the injections of liposomes prepared from the diester analog of lecithin badly. The animals became drowsy, developed hypokinesia, and refused to eat. No such phenomena were observed in the case of ordinary egg lecithin.

It can be concluded from all these facts that, in order to create liposomes capable of circulating for a long time in the blood stream, it is necessary to use other lipids, or approaches based on a different principle, on a search for which the authors are currently engaged.

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EFFECT OF PSYCHOTROPIC DRUGS ON RNA SYNTHESIS IN BRAIN CELL NUCLEI

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Changes in the distribution of biogenic amines in the brain were produced by intraperitoneal injection of psychotropic drugs – reserpine (80 μg/100 g) and chlorpromazine (300 μg/100 g) – during chronic experiments on rats. Under these conditions reserpine reduced the endogenous RNA polymerase activity of types I and II of the rat brain cell nuclei on average by 61 and 34%, and chlorpromazine did so by 32 and 38% respectively. In a cell-free system reserpine and chlorpromazine in concentrations of 0.1 and 1 mM had no effect on the RNA-synthesizing activity of isolated rat brain cell nuclei. It is suggested that the action of psychotropic drugs on the genetic apparatus may be mediated through either a decrease in cyclic AMP production or inhibition of RNA-synthesizing activity.

KEY WORDS: RNA polymerase; psychotropic drugs; biogenic amines; rat brain.

Changes in the distribution of biogenic amines in the brain can be produced by means of psychotropic compounds. These changes, in turn, are reflected in behavioral actions [4].

The object of this investigation was to study the role of the genetic apparatus in these phenomena.

EXPERIMENTAL METHODS

Experiments were carried out on male albino rats weighing 100-120 g. Psychotropic drugs – reserpine in a dose of 80 μg/100 g and chlorpromazine in a dose of 300 μg/100 g – were injected intraperitoneally into the rats daily for 3 days. Physiological saline was injected into control animals. On the 3rd day, 2 h after the injection, the rats were killed and the cell nuclei isolated from their brain by the method of Chauveau et al.

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TABLE 1. Effect of Resperine and Chlorpromazine on Endogenous RNA-Polymerase Activity of Rat Brain Cell Nuclei

Psychotropic drugs	Incorporation of [^{14}C]UTP into acid-insoluble material, cpm/100 μg DNA				Inhibition, %	
	control		experiment			
	RNA polymerase type I	RNA polymerase type II	RNA polymerase type I	RNA polymerase type II	RNA polymerase type I	RNA polymerase type II
Reserpine	2381	5362	747	3132	68,7	41,6
	1162	4365	649	3209	44,2	26,5
	800	3576	243	2317	69,7	35,3
Chlorpromazine	1358	4915	982	4021	27,7	18,2
	648	2190	303	1368	53,3	37,6
	1117	2893	820	1141	26,6	60,6
	643	2821	504	1803	21,7	36,1

TABLE 2. Effect of Reserpine and Chlorpromazine on RNA Synthesizing Activity of Isolated Rat Brain Cell Nuclei in a Cell-Free System

Conditions of reaction	Incorporation of [^{14}C]UTP into acid-insoluble material, cpm/40 μg DNA	
	RNA polymerase type I	RNA polymerase type II
Complete system (control)	617	2094
	626	1793
Complete system + reserpine (0.1 mM)	634	1509
	647	2647
Complete system + reserpine (1 mM)	562	1902
	781	2370
Complete system (control)	380	2334
	352	2278
Complete system + chlorpromazine (0.1 mM)	280	2025
	379	2441
Complete system + chlorpromazine (1 mM)	386	2588
	440	2275

[9]. The number of nuclei was judged from the DNA content. The RNA-synthesizing activity of the nuclei (i.e., the ability of the isolated nuclei to synthesize RNA from added substrates) was judged from the incorporation of [^{14}C]nucleoside triphosphates into material precipitated by cold 5% TCA. The incubation mixture (0.25 ml) for determination of endogenous type I RNA polymerase activity of the nuclei contained the following components, in micromoles: Tris-HCl (pH 8.3) 25, $MgCl_2$ 1.5, ATP, GTP, and CTP – 0.1 of each, [^{14}C]UTP 0.017 (0.208 μCi, from Amersham), and nuclei in a quantity corresponding to 40 μg DNA. The incubation mixture (0.25 ml) for determination of type II endogenous RNA polymerase activity of the nuclei contained the following components, in micromoles: Tris-HCl (pH 7.5) 25, $MnCl_2$ 0.825, $(NH_4)_2SO_4$ 62, ATP, GTP, and CTP – 0.1 of each – [^{14}C]UTP 0.017 (0.208 μCi), and nuclei in an amount corresponding to 40 μg DNA. The samples were incubated for 20 min at 37°C. The reaction was stopped by the addition of cold 5% TCA containing 20 mM Na pyrophosphate. The precipitates were transferred to Whatman GF/C glass filters, washed 3 times with cold 5% TCA and 96% ethanol, and dried; the radioactivity of the samples was determined in a liquid scintillation mixture on the SL-30 counter (France).

EXPERIMENTAL RESULTS

The psychotropic drugs were injected in a dose necessary to cause a change in the functional state of the animal. Under these experimental conditions, both reserpine and chlorpromazine had an inhibitory effect on RNA synthesis: Activity of RNA polymerases of both type I and type II was reduced (Table 1). Reserpine, incidentally, proved to be a stronger inhibitor, especially against type I RNA polymerase, the activity of which was reduced under its influence on average by 61%, compared with a mean decrease in activity of type II RNA polymerase of 34%. Chlorpromazine had a similar inhibitory effect on RNA polymerase activity of types I and II, which it reduced on average by 32-38%.

The psychotropic drugs (reserpine and chlorpromazine) reduce the content of biogenic amines in the brain in different ways. The mechanism of action of reserpine, however, has been studied in more detail than

that of chlorpromazine. Reserpine, by reducing the content of biogenic amines in the brain, leads to their increased liberation from the depots. It has been shown to influence processes connected with the uptake of biogenic amines. A decrease in the content of biogenic amines is accompanied by a marked decrease in the content of cyclic AMP in all regions of the rat brain [2].

The action of chlorpromazine is based on its effect on permeability of cellular and subcellular membranes [6]. Besides blocking α-adrenoreceptors, chlorpromazine reduces the permeability of the cell membrane and inhibits active uptake of biogenic amines, preventing their immobilization, and thereby reducing their effect in sympathetic transmission.

To study the mechanism of action of reserpine and chlorpromazine on RNA synthesis (whether or not it is reduced as a result of a decrease in the content of biogenic amines), in the next series of experiments the effect of these drugs on the RNA-synthesizing activity of isolated rat brain cell nuclei in vitro was studied. As Table 2 shows, in a cell-free system reserpine (0.1 mM) and chlorpromazine (1 mM) had no effect on RNA-synthesizing activity.

The absence of any direct action of reserpine and chlorpromazine on isolated cell nuclei in in vitro experiments indicates that their effect must be mediated by a special mechanism connected with the functioning of the genetic apparatus. The action of this mechanism must be connected with biogenic amines. Baru and Kraeva [1] found that subcutaneous injection of reserpine (0.5 μg/kg) into rats caused a decrease in incorporation of ^{32}P (as orthophosphate) into nuclear RNA, whereas it had virtually no effect on cytoplasmic RNA. These facts indicate that psychotropic drugs take part in reactions initiated by cyclic AMP. We know that psychotropic drugs can act on the genetic apparatus by modifying the distribution of biogenic amines [3]. The biogenic amines realize their effects through protein kinase reactions. Protein kinases, in turn, participate in derepression of the genome [7, 8].

It can thus be concluded that the action of psychotropic drugs on the genetic system may be mediated either through a decrease in cyclic AMP production or inhibition of RNA-synthesizing activity in vivo.

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