4. Preliminary stimulation of the testes by hCG prevents the stress-induced suppression of the testosterone level in the blood plasma; however, the reaction of the testes to the stimulating effect of hCG is decreased in this case.

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PSYCHOTROPIC PROPERTIES OF OXYTOCIN

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The last few years have witnessed an upsurge of interest in the effect of hormones of the pituitary and hypothalamus on the behavior of animals and on human psychic functioning. Most of the research has focused on the properties of the opioid peptides (endorphins and enkephalins). These have been shown to be capable of activating the brain's pain-suppressing system, of regulating pleasurable and unpleasurable sensations, and of affecting the body temperature and muscle tonus [1-3]. Detailed studies have been made of the antipsychotic effects of the releasing hormones of the hypothalamus: thyroliberin, luliberin, melanostatin, and their analogs [4-6]. Luliberin has a therapeutic effect in senile dementia, thyroliberin and melanostatin are effective in depressive states, and analogs of melanostatin are successfully used to alleviate the depressive syndrome. The neurotropic properties of corticotropin and intermedin have begun to be investigated. Less attention has been paid to the psychotropic properties of oxytocin and vasopressin, which are widely used in clinical practice, specifically in obstetrics and neuroendocrinology. Considerable experience has been accumulated in their use as hormones, but studies of their effect on patients' psychic status have barely begun. The aim of the present investigation was to study the activating effect of oxytocin on the higher nervous activity of animals and to perform a clinical study of the drug for the treatment of patients with the simple form of schizophrenia.

MATERIALS AND METHODS

It proved difficult to study the antidepressive effects of oxytocin because endogenous depressions do not exist in animals, and none of the models of depressive states described

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TABLE 1. Testing and Antidepressive Activity of Oxytocin and its Analogs

Type and number of animals	Test and recorded parameter	Neuropeptide			
		control	oxytocin (200 μg/kg)	4-histidine-oxytocin (200 μg/kg)	7-sarcosine-oxytocin (100 μg/kg)
Mice (20 in control, 12 in each series)	Swimming in cylinder, time, min	29.4 ± 9.1	45.2 ± 6.0*	32.3 ± 7.2	48.7 ± 8.3*
Rats (14 in control, 12 in each series)	Reserpine depression, rectal temperature 1 h after injection, °C	35.3 ± 0.6	38.4 ± 0.5*	36.1 ± 0.7	32.2 ± 0.6*
Rats (10 in control and in experiment)	Ethanol anesthesia, duration min	178.5 ± 17.4	113.2 ± 11.4*	130.2 ± 19.7*	118.3 ± 14.5*
Rats (12 in control and in experiment)	Levomepromazine anesthesia, duration, min	95.1 ± 13.2	74.2 ± 9.6	91.2 ± 8.6	85.3 ± 7.4
Rats (14 in control, 12 in each series)	Amphetamine stereotypy, time, min	32.1 ± 9.6	46.1 ± 12.4	42.5 ± 9.6	51.4 ± 8.3*
Mice (16 in control, 14 in each series)	Haloperidol catatonia, time, min	49.1 ± 12.4	30.4 ± 6.3*	47.2±8.1	42.5 ± 5.6
	Relative activity	±	++	+	+++

Note. The mean values of doubled errors of the means are presented. Reliability of differences from control according to Student test: *) more than 0.99; **) more than 0.95 †. Relative activity of drug taking subjective factors into account: + good, ++ high, +++ very high.
†There are no double asterisks in the original Russian table — Editor.

in the literature can be called completely adequate. It was therefore decided to investigate the antidepressive properties of oxytocin in three different tests [7-9]: a) swimming of albino mice in a narrow cylinder with high walls; b) elimination of reserpine depression in rats; c) a complex of pharmacological assays of the effect of the antidepressant on the duration of ethanol and levomepromazine anesthesia and on the intensification of amphetamine stereotypy in rats, and on the elimination of haloperidol catatonia in mice. The methodological features of these three tests are described in the literature cited.

The main parameter which changed in these experiments as a function of the strength of the influence was time: the duration of anesthesia in the control and after the administration of oxytocin, the duration of catatonia and the stereotypy, and the time from the onset of swimming to mere drifting along. Another objective index was the rectal temperature in the reserpine test. The other characteristics could be described partly subjectively, depending on the personal opinion of the experimenter; therefore, along with the objective indexes of antidepressive effects, we took into account the subjective evaluation of their degree of expression in relative units. The experiment was performed on 114 albino mice of both sexes weighing 18 g, and on 18 male albino rats weighing 180 ± 30 g.

We used oxytocin manufactured by the Gideon Richter Company, in ampules of 5 active units in 1 ml, and the following analogs: 4-histidine-oxytocin and 7-sarcosine-oxytocin, synthesized at the A. A. Zhdanov Department of the Chemistry of Natural Compounds, University of Leningrad. The drugs were injected subcutaneously in doses which produce (as shown by us previously) a local effect [10, 11]. In the control, a 0.9% solution of sodium chloride was also injected subcutaneously in an equivalent volume of 1 ml.

The psychotropic properties of oxytocin were also studied during treatment of 27 men with the simple form of schizophrenia. The patients ranged in age from 27 to 49 years. The disorder had been present for 5 to 19 years. The reasons for their hospitalization were exacerbation of the psychosis in the form of anxiety, phobia, and the development of depressive symptoms; deterioration of the thinking processes as expressed by argumentativeness and paralogical reasoning; the appearance of sleep and behavior disorders.

TABLE 2. Results of the Use of Oxytocin as a Psychotropic Agent

Syndrome	Total patients	Results of treatment			
		alleviation of syndrome	marked improvement	slight improvement	no effect
Asthenodepressive	7	5	2	0	0
Apathodepressive	9	6	3	0	0
Depressive-depersonalizational	2	0	0	1	1
Obsessive-phobic	5	0	0	3	2
Hypochondriac	4	0	1	1	2
Total	27	11	6	5	5

Oxytocin of Gideon Richter manufacture was injected twice daily intravenously with an interval of 6 h between injections. The daily dose was 10 active units and the course of treatment was 7 days. This course of treatment was repeated after an interval of a week. Half of the patients received the drug in the form of a nasal spray, the same dosage being used. Administered by this route, the peptide reached the hypothalamic region bypassing the blood-brain barrier. A comparison, in compliance with international requirements, using the double blind control method, with a group of patients who were administered a placebo (physiological solution) intranasally, showed that, in terms of effectiveness, the intranasal administration of oxytocin is not inferior to the intravenous route. No therapeutic effect of the placebo was noted. The patients did not receive any other drugs during the period of oxytocin therapy.

During the observation period, all the patients underwent a clinical, pathopsychological, and laboratory examination before and after the oxytocin treatment. The patients' own evaluation of their condition was taken into account (0, no change; 1, slight positive changes; 2, positive changes; 3, marked improvement). The pathopsychological testing was carried out by means of the following methods [12, 13]: pictograms, the Luscher color test, remembering ten words, object elimination, and determining the emotional background after Dorofeeva. For enhanced validity of the interpreted findings, patients were selected with the same sociometric (sex, age, occupation) and clinical (course of illness, symptoms) indexes. All the patients had consultations with specialists so as to rule out any concomitant somatic pathology, particularly of an endocrine nature.

The control group consisted of 18 patients with similar clinical symptoms who were being treated with conventional neuroleptic agents.

RESULTS AND DISCUSSION

The results of the animal experiment are summarized in Table 1. When albino mice swam in the cylinder until they developed the depressive syndrome, i.e., listlessly drifted along, it was seen that oxytocin and its analogs exert a positive effect on the state elicited. The most active drug in this test turned out to be 7-sarcosine-oxytocin. This test does not rule out the effect of peptides on physical work capacity. It is also possible that the mice continued their swimming movements for a longer time after an oxytocin injection as a result of intensified locomotor muscle activity. For a correct evaluation, therefore, we were obliged to make a series of subsequent tests in which the dominant role belonged to reserpine depression. A peritoneal injection of reserpine in a dose of 5 mg/kg lowered the rectal temperature 3-4° C. Injection of the antidepressant raised the temperature almost to the normal level.

Oxytocin and its analogs were also effective in correcting narcotic states after the administration of ethanol and levomepromazine; they increased the time of amphetamine stereotypy, and corrected haloperidol catatonia in mice. In analyzing the findings, we should note that the weakest antidepressive effect was produced by 4-histidine-oxytocin, a neuro-

peptide which has practically no peripheral hormonal activity. The main achievement of this part of the work may be considered to be the proof offered that there are grounds for using neuropeptides of the posterior pituitary, and primarily oxytocin, for treating depressive states in people.

Curative properties of oxytocin have been noted when the drug has been used clinically as a psychotropic agent: normalization of the emotional background by ameliorating anxiety, alleviating depressive symptoms, increasing the feeling of physical well-being, eliminating asthenic and apathetic states, and normalizing sleep. We did not observe any complications or pronounced side effects which could have given cause to discontinue the drug or lower the dosage. The laboratory indexes did not change appreciably during the process of treatment.

On the basis of the clinical data of the pathopsychological examination and of the patients' self-evaluation, the best results were achieved in treating persons whose predominant symptoms were anergy, asthenia, and apathy combined with emotional disturbances in the form of depressed mood. The results of oxytocin treatment are presented in Table 2, from which we see that the medication most typically has an activating effect, whereas its influence on neurosis-like syndromes is more weakly expressed. The activation produced by oxytocin was also accompanied by a leveling of the emotions.

Previously, these patients had been given neuroleptic therapy, as a result of which remissions were less severe. This corroborates the need to study the spectrum of oxytocin's psychotropic activity.

Upon the completion of the course of oxytocin treatment, the patients were switched to a maintenance therapy with activating doses of neuroleptics (Phrenolone 20-30 mg/day, Stelazine 10-15 mg/day), and after two weeks were referred for outpatient treatment if the remission had stabilized. The catamnetic data were followed up for a year; no cases of aggravated psychotic disturbances requiring hospital treatment were noted.

The outcome of the treatment (according to Sereiskii) in the experimental group was rated as follows: A, 1; B, 18; C, 6; 0, 2. Probably the selection of patients with similar clinical manifestations and acute symptoms accounts in part for such favorable indexes of the therapeutic use of oxytocin. An effect was absent in 2 patients who had suffered the disorder for 16 and 18 years.

The study of the psychotropic properties of oxytocin showed its usefulness in the case of asthenic, apathetic, and anergic symptoms, as well as in moderately depressed moods.

It would be worthwhile to conduct further research to clarify the entire spectrum of the psychotropic activity of oxytocin to enable its differentiated application in neuro-psychotic disorders and to elucidate its role in psychoendocrine correlation.

Earlier, in experiments on animals and in the treatment of patients of nephrological profile, we demonstrated the powerful antiamnestic effect of vasopressin, its analogs, and some analogs of oxytocin [10, 11, 14-16]. Oxytocin has been used in psychiatry for treating states with the predominance of ideational and emotional-volitional disturbances within the framework of schizophrenia, as well as in amnestic disorders [17-19].

Studies of the subtle mechanisms of action of oxytocin have shown that the drug causes the presynaptic activation of the nigrostriatal dopaminergic endings [20], decreases the content of norepinephrine in the hypothalamus, septum, and corpus striatum, but does not alter the dopamine level [21], stimulates the peptidergic neurons of the limbic structures (dorsal septum, dentate gyrus of the hippocampus, dorsal nucleus of the suture), and reaches the receptive zones from the neurosecretory nuclei along the oxytocinergic tracts via the brain ventricles [22]. Oxytocin has been found to play a part in implementing the central nervous system functions related to learning and memory [23].

CONCLUSIONS

1. The neuropeptide oxytocin exerts a pronounced neurotropic effect.

2. The antidepressive effects of oxytocin revealed experimentally were confirmed in the treatment of the depressive syndrome in people.

3. The administration of oxytocin to treat persons with schizophrenia showed that it can be used to normalize the emotional status, to eliminate asthenic and apathetic states, as well as a psychic energizer.

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