The characteristic behavioral effects of apomorphine (2.5 mg/kg) developed in the rats 40 min after injection of galanthamine, i.e., after an interval during which the anticholinesterase action of the reversible inhibitor, significant under the experimental conditions used, was evidently exhausted. This fact, and also observations in which preliminary administration of benactyzine completely prevented antagonism between galanthamine and apomorphine, in agreement with existing views [6], are evidence that the effects of the drugs used, which modified activity of the cholinergic system, were effected through muscarine acetylcholine receptors. These receptors are known to be localized in the mesolimbic structures presynaptically, on DA terminals [8], whereas in the neostriatum, the influence of the cholinergic system on DA mediation is effected through interneurons [5]. The present investigations suggest that the method of separate quantitative analysis of changes in behavioral reactions to apomorphine after preliminary injection of cholinolytics or cholinomimetics can be used to judge the contribution of cholinergic neurotransmitter systems of the various brain structures to the central regulation of movement.

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EFFECT OF GLUCOCORTICOIDS ON FRACTIONAL COMPOSITION AND DERIVATIVES OF HEMOGLOBIN IN RATS

M. V. Nezhentsev, K. A. Averburg, and A. M. Livshin

UDC 612.111.11.014.46:615.357.453

KEY WORDS: glucocorticoids; fractions; derivatives; hemoglobin; rats.

Natural and synthetic glucocorticoid preparations are widely used for the treatment of patients with many diseases, including iron deficiency, hypoplastic, aplastic, and other forms of anemias, and including diseases due to the presence of abnormal forms of hemoglobin [1, 5]. Information on the effect of hormone preparations on the qualitative composition of hemoglobin cannot be found in the literature.

The object of this investigation was to determine the fractional composition and derivatives of hemoglobin in experimental animals after prolonged administration of natural and synthetic glucocorticoids most frequently used in clinical practice.

EXPERIMENTAL METHOD

Experiments were carried out on 48 noninbred male albino rats weighing 180-220 g. Preparations of hydrocortisone and its synthetic analogs were used in doses giving equivalent effects: hydrocortisone acetate 10.0 mg/kg, prednisolone

Department of Pharmacology and Department of Biochemistry, Pediatric Medical Institute, Leningrad.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. G. Baranov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 92, No. 11, pp. 569-571, November, 1981. Original article submitted June 19, 1981.

TABLE 1. Changes in Fractional Composition and Content of Hemoglobin Derivatives (in %) under the Influence of Glucocorticoids (M ± m)

Preparation injected	No. of fractions	Hemoglobin content in fractions			Content of forms of hemoglobin	
		slow	average	fast	methemoglobin	carboxyhemoglobin
Control	4	65,1±1,62	17,6±1,16 11,6±144	5,7±1,14	1,29±0,49	1,92±0,23
Hydrocortisone	3	44,8±2,6	29,2±2,3	26,2±2,39	2,61±0,77	1,82±0,17
P		<0,001	<0,001	<0,001	<0,01	>0,05
Prednisolone	3	37,3±1,33	49,4±1,2	13,06±2,5	2,23±0,92	2,18±0,30
P		<0,001	<0,001	<0,001	<0,05	>0,05
Dexamethasone	3	31,6±2,5	55,5±1,7	12,9±2,8	2,99±0,73	2,26±0,15
P		<0,001	<0,001	<0,001	<0,001	<0,01
Triamcinolone	3	45,7±1,32	31,9±1,4	22,4±1,92	1,72±0,20	2,26±0,10
P		<0,001	<0,001	<0,001	<0,05	<0,01

hydrochloride 2.5 mg/kg, dexamethasone phosphate 0.3 mg/kg, triamcinolone 2.0 mg/kg. Hydrocorticoids were injected intraperitoneally into the animals once daily, in the morning, for 2 months. Rats receiving injections of equal volumes of distilled water served as the control group. On the 14th day the animals were decapitated and heparinized blood was obtained. The erythrocytes were washed with 0.9% NaCl solution and centrifuged. Hemolysis of the erythrocytes was carried out by the addition of an equal volume of distilled water and 0.5 volume of chloroform for 18-20 h at 4°C.

The fractional composition of hemoglobin was studied by electrophoresis in agar-agar gel with Tris-phosphate buffer (pH 7.0, ionic strength 0.03) [3]. Electrophoresis was carried out at 4°C with a current 8-12 mA/cm^2 and voltage 13-14 V/cm for 3 h. Depending on their mobility the separate fractions were designated fast, slow, and average. The hemoglobin in the fractions was determined quantitatively by means of the IE-NA/DDR/323113 densitometer.

The content of hemoglobin derivatives (met- and carboxyhemoglobin) was determined spectrophotometrically [2]. The effect of prednisolone and dexamethasone in a concentration of 10^{-7}-10^{-8} M on met- and carboxyhemoglobin formation in heparinized rats' blood was investigated *in vitro*. Tubes with blood (after addition of the preparations) were incubated at 37°C for 1 h, and the content of the hemoglobin derivatives was determined.

Blood from rats incubated under the same conditions but without addition of the preparations was used for the control.

The results were subjected to statistical analysis with calculation of confidence limits and determination of the U criterion.

EXPERIMENTAL RESULTS

After administration of glucocorticoids the number of fractions decreased from four to three (Table 1). In rats receiving the preparations the hemoglobin content in the slow fraction showed a statistical significant decrease. A marked decrease (by half; $P < 0.001$) was observed after administration of dexamethasone phosphate, a smaller decrease (by 1.7 times; $P < 0.001$) was observed after administration of prednisolone and triamcinolone, and an even smaller decrease after administration of hydrocortisone acetate (by 1.4 times; $P < 0.001$).

After introduction of hydrocortisone acetone the hemoglobin content in the fast fraction increases by 4.6 times ($P < 0.001$); prednisolone and dexamethasone increase by 2.3 times ($P < 0.001$)

The hemoglobin content in the average fraction was increased statistically significantly after administration of dexamethasone phosphate ($P < 0.001$) and prednisolone hydrochloride ($P < 0.001$), evidently because of the great structural similarity between these glucocorticoids.

There are data in the literature on the redistribution of hemoglobin among its fractions following exposure to oxidizing agents, radiations, etc. [4]. Administration of glucocorticoids also affects hemoglobin composition.

Hydrocortisone acetate and its synthetic analogs led to a statistically significant increase in the methemoglobin content in the blood of the experimental animals (Table 1). Hydrocortisone acetate, prednisolone hydrochloride, and dexamethasone phosphate had a stronger action than triamcinolone. The carboxyhemoglobin level changed only a little after administration of hydrocortisone and prednisolone, but was increased statistically significantly by the action of dexamethasone and triamcinolone.

In the control the methemoglobin contents did not exceed 1.38%. The methemoglobin concentration in the blood was increased statistically significantly after incubation with prednisolone (10^{-7}-10^{-8} M) to 2.4 and 2.77%, respectively ($P < 0.001$). Dexamethasone, in the same concentrations, increased the methemoglobin concentration to 1.17 and 2.75% ($P < 0.001$). This shows that the preparations increased the content of the oxidized derivatives of hemoglobin.

The changes in the fractional composition and content of hemoglobin derivatives under the influence of glucocorticoids described above must consequently be taken into account when a hormone preparation is chosen.

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EFFECT OF CHRONIC ADMINISTRATION OF LITHIUM CHLORIDE ON DEVELOPMENT OF HYPERSENSITIVITY OF DOPAMINE RECEPTORS DURING MORPHINE WITHDRAWAL IN RATS

L. Kh. Allikmets and A. M. Nurk

UDC 615.212.7:547.943/015.156.015.2:615.31:546.34

KEY WORDS: morphine; abstinence syndrome; hypersensitivity of dopamine receptors; lithium.

Prolonged administration of narcotic analgesics increases tolerance to their action and also leads to mental and physical dependence on the drug. Discontinuation of the drug gives rise to a withdrawal syndrome, characterized by various behavioral effects. Meanwhile marked changes are observed in metabolism of CNS mediators.

There is evidence that aggressiveness arising in rats after withdrawal of morphine is connected with a change in the sensitivity of the dopamine receptors [7]. Administration of dopaminomimetic agents (apomorphine, amphetamine) after withdrawal of morphine sharply increase, whereas administration of substances blocking dopaminergic transmission (neuroleptics reduce, aggressive reactions in abstinent rats [5, 7].

Meanwhile hypersensitivity of dopamine receptors developing after withdrawal of chronically administered neuroleptics (haloperidol) can be prevented by giving lithium chloride at the same time [1, 6]. The stabilizing action of lithium chloride on dopamine receptors has been demonstrated in experiments with electrophysiological [4] and behavioral [1] tests and also in experiments on binding of ^{3}H-spiroperidol [6].

The object of this investigation was to study the action of chronic administration of lithium on manifestations of the withdrawal syndrome after discontinuing morphine in rats.

EXPERIMENTAL METHOD

Male Wistar rats weighing 250-280 g were divided into four groups (20 animals in each group). The rats of group 1 received morphine hydrochloride twice a day for 10 days in increasing doses (from 30 to 300 mg/kg intraperitoneally). The rats of group 2 received injections of 0.2M lithium chloride chloride solution in a dose of 2 meq/kg body weight intraperitoneally 1 week before the beginning of the morphine injections, after which the two preparations were given simultaneously for 10 days. Animals of group 3 were given a 0.2M solution of lithium chloride only for 17 days. The animals of group 4 (control) received physiological saline.

The threshold of nociceptive sensation was determined in some of the animals 60 h after administration of the substances ceased by pinching the tail with Hafner's forceps, and their spontaneous and apomorphine-induced (10 mg/kg, intraperitoneally) aggressiveness also was estimated [1]. In another group of animals the dopamine (DA), homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DHPAA) content in the corpus striatum was determined spectrofluorometrically [3].

Department of Pharmacology, Tartu University.

(Presented by Academician of the Academy of Medical Sciences of the USSR M. D. Mashkovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 92, No. 11, pp. 571-572, November, 1981. Original article submitted March 13, 1981.