MECHANISM OF RESPONSES OF THE HYPOTHALAMICO-HYPOPHYSEO-ADRENAL SYSTEM TO STRESS

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Administration of chlorpromazine (2.5-3 mg/kg) increased the cortico-steroid level in the blood plasma of intact dogs, inhibited the adrenocortical response during development of anaphylactic and blood transfusion shock, and modified the response of the adrenal cortex in the course of traumatic shock and hypothermia.

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The theory of the hypothalamico-hypophyseal system as the sole mechanism responsible for the integration and correlation of endocrine functions has recently been established and developed. According to this theory, an important role is attached to physiological interaction between the bulbar reticular formation and the hypothalamus [3, 6, 10, 11, 13-15]. In this connection it is interesting to attempt to modify the response of the hypothalamico-hypophyseo-adrenal system to stress situations in a particular direction by administration of pharmacological agents affecting the function of the reticular formation. Investigation of the ability of drugs of the phenothiazine series to suppress the responses of the pituitary and adrenals to stimuli of various types has yielded conflicting results. Some workers have reported the blocking action of chlorpromazine and its analogs on the formation of the stress reaction [7, 8, 12], while others have shown that chlorpromazine does not inhibit the secretion of corticotropin and glucocorticoids in response to stress agents [2, 3, 9, 16].

To continue the study of the regulatory mechanisms of the adrenocortical system, in the present investigation observations were made on responses of the adrenal cortex to shock-producing stimulation during the action of chlorpromazine.

EXPERIMENTAL METHOD

Experiments were carried out on 84 noninbred male dogs. Anaphylactic, blood-transfusion, and traumatic shock and hypothermia were produced in unanesthetized animals. Anaphylactic shock was produced by intravenous injection of horse serum in a dose of 1-2 ml/kg body weight into dogs sensitized with the same serum, 15-21 days after the 3rd sensitizing injection. Blood-transfusion shock was caused by transfusion of human (donors') or rabbit blood in doses of 10 or 3 ml/kg body weight respectively. Traumatic shock was produced by crushing the soft tissues of the thigh. Hypothermia was produced by immersing the animal in an ice bath. The arterial pressure in the carotid artery and the tracheal respiration were recorded on a kymograph. Chlorpromazine in a dose of 2.5-3 mg/kg was injected intramuscularly 30-40 min before stimulation. The index of function of the hypophyseo-adrenal system was the concentration of 17-hydroxycorticosteroids (17-HC) in plasma obtained from blood taken from the inferior vena cava at the level of the orifices of the lumbo-adrenal veins, determined by the method of Silber and Porter as modified by Yudaev and Pankov. Blood for analysis was taken through a polyethylene catheter introduced into the femoral vein.

EXPERIMENTAL RESULTS

Chlorpromazine lowered the arterial pressure from 140-160 to 110-130 mm Hg and in most cases caused a moderate increase in the 17-HC concentration in the blood plasma.

Injection of a reacting dose of serum after injection of chlorpromazine led in every case to severe shock, terminating in death in 6 of the 13 experiments. Meanwhile the response of the adrenal cortex was

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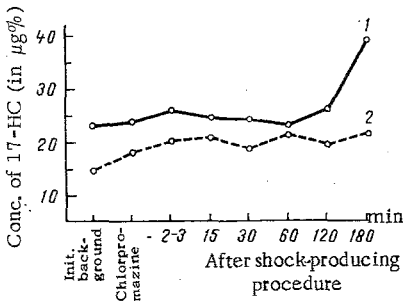

Fig. 1. Concentration of 17-hydroxycorticosteroids in plasma (in μg%) during anaphylactic (1) and blood-transfusion (2) shock in animals receiving chlorpromazine.

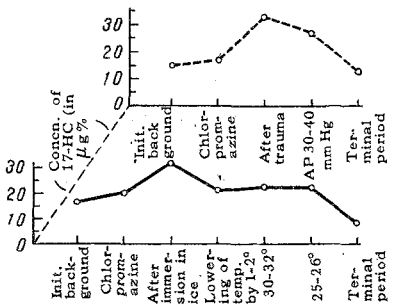

Fig. 2. Concentration of 17-hydroxycosteroids in plasma (in μg%) during traumatic shock and hyperthermia in animals receiving chlorpromazine.

TABLE 1. Concentration of 17-Hydroxycorticosteroids (in μg%) in Plasma of Dogs with Anaphylactic, Blood-Transfusion, and Traumatic Shock and Hypothermia

Pathological process	Initial background	Time after stress procedure					
		2–3 min	15 min	30 min	60 min	120 min	180 min
Anaphylactic shock	23.3±2.17	34.1±6.56	59.8±6.72	58.8±6.77	35.4±4.73	46.3±8.08	58.0±7.28
Blood-Transfusion shock	12.5±1.87	17.5±3.02	30.6±4.93	29.0±5.02	42.3±5.14	25.9±3.23	25.0±4.09

Traumatic shock	Initial background	Erectile phase	At arterial pressure of 60-80 mm Hg	At arterial pressure of 30-40 mm Hg	Terminal period
	15.1±2.16	31.8±2.48	20.1±3.16	45.7±6.24	38.26±5.62

Hypothermia	Initial background	After immersion in ice	With body temperature lowered 1-2°	30-32°	25-26°	Terminal period
	12.3±2.03	22.0±2.44	22.7±4.17	24.6±5.32	32.3±4.16	14.6±4.05

virtually absent during the 2 h after the reacting injection (Fig. 1), distinguishing it sharply from the reaction before injection of chlorpromazine (Table 1).

A similar blocking effect of chlorpromazine on the hypothalamico-hypophyseo-adrenal system was observed after transfusion of heterogenic blood. Differences in the course of blood-transfusion shock in animals receiving chlorpromazine are worthy of attention. Whereas after transfusion of donors' blood to intact dogs, the shock hypotension was slight or absent, in animals whose reactivity was modified by chlorpromazine, in every case shock developed with, in some cases, a secondary lowering of arterial pressure. The 17-HC concentration in the plasma fluctuated within narrow limits, remaining almost at the background level (Fig. 1).

Traumatic shock in the dogs receiving injections of chlorpromazine was characterized by an ill-defined erectile phase and by rapid progression of the hemodynamic disturbances. The initial response of the adrenal cortex to mechanical trauma corresponded to the changes observed in intact animals after trauma (Fig. 2). Whereas, however, in the animals without premedication, profound shock was accompanied by the highest increase in the 17-HC level and death occurred when the blood corticoid concentration was high, the torpid phase of traumatic shock in animals receiving chlorpromazine was characterized by a progressive decrease in the 17-HC concentration, parallel to the fall of arterial pressure. The animals died with a subnormal 17-HC level. It can accordingly be concluded that chlorpromazine prevents the

secondary rise in 17-HC concentration characteristic of profound shock in unanesthetized dogs. This conclusion was confirmed by the study of the adrenocortical response in the course of hypothermia preceded by administration of chlorpromazine. While not preventing the primary response of the adrenal cortex to cold trauma, chlorpromazine prevented a further increase in the plasma corticosteroids during changes in the body temperature (Fig. 2).

Hence, the study of the effect of chlorpromazine on development of the reaction of animals to stress showed that the drug selectively blocks the stressor effect of several stimuli but is ineffective in situations connected mainly with the creation of exteroceptive information (mechanical and cold trauma).

To investigate the mechanism of action of chlorpromazine on various components of the hypothalamico-hypophyseo-adrenal system, in the next group of experiments the effect of the compound was studied on the secretory activity of the adrenal cortex and its ability to respond to specific stimulators (corticotropin and adrenalin) against the background of chlorpromazine administration. Data in the literature concerning the character of this effect of chlorpromazine on the glucocorticoid function of the adrenal are conflicting, although most workers [1, 6, 9, 10] consider that chlorpromazine increases production of corticosteroids. The results now obtained showed that 30 min after intramuscular injection of chlorpromazine the 17-HC concentration in plasma from peripheral venous blood was increased from 3.35±0.47 to 5.74± 0.56 μg% ($P < 0.001$).

Intravenous injection of 20 i.u. ACTH 30 min after injection of chlorpromazine increased the corticosteroid concentration by 4-5 times. Chlorpromazine thus does not prevent the response of the adrenal cortex to exogenous ACTH, so that, consequently, the absence of adrenocortical response to certain types of stressor stimuli against the background of chlorpromazine is independent of the direct action of the drug on the adrenal cortex, but is associated with disturbance of the adrenocorticotropic function of the pituitary. To study the mechanisms responsible for inhibition of ACTH secretion under the influence of chlorpromazine, a function test was performed in which adrenalin [4] was injected against the background of chlorpromazine.

Injection of 4 μg/kg adrenalin into intact dogs increased the plasma 17-HC concentration by 2-4 times 30-40 min after subcutaneous injection. Injection of adrenalin against the background of chlorpromazine, however, did not change the plasma corticosteroid concentration or lowered it. Analysis of these results suggests that the disturbance of the pituitary adrenocorticotropic function by administration of chlorpromazine is connected with the blocking action of the drug on the adrenergic activating mechanisms of the reticular formation and hypothalamus, the existence of which has recently received factual confirmation [5].

LITERATURE CITED

1. M. S. Kakhana, Pathophysiology of the Hypothalamus [in Russian], Kishinev (1961).
2. M. G. Kolpakov, in: Abstracts of Proceedings of a Scientific Conference on "The Action of Pharmacological Agents on Endocrine Glands" [in Russian], Leningrad (1965), p. 37.
3. V. E. Ryzhenkov, in: Action of Pharmacological Agents on Endocrine Glands [in Russian], Leningrad (1965), p. 37.
4. G. L. Shreiberg, in: Clinical and Experimental Investigation of the Functional State of the Adrenal Cortex and Sympathico-Adrenal System [in Russian], Moscow (1963), p. 25.
5. G. L. Shreiberg, in: Physiology and Pathology of the Hypothalamus [in Russian], Moscow (1966), p. 30.
6. A. I. Yakovleva and N. G. Shakhnazarova, Farmakol. i Toksikol., No. 3, 52 (1957).
7. E. Anderson, R. Bates, et al., Recent Progr. Hormone Res., 13, 21 (1957).
8. E. Aron et al., Bull. Acad. Nat. Med. (Paris), 137, 417 (1953).
9. D. Betz and W. Ganong, Acta Endocrinol. (Kobenhavn), 43, 264 (1963).
10. R. H. Egdahl and J. B. Richards, Am. J. Physiol., 185, 235 (1956).
11. G. W. Harris, in: The Reticular Formation of the Brain [Russian translation], Moscow (1962), p. 191.
12. A. Laborit and P. Huguenard, Hibernotherapy (Artificial Hibernation) in Medical Practice [Russian translation], Moscow (1956).
13. H. Magoun, The Waking Brain [Russian translation], Moscow (1965).
14. J. Mason, J. Clin. Endocrinol., 16, 914 (1957).
15. G. Sayers, Ciba Found. Colloq. Endocrinol., 9, 138 (1957).
16. M. Slusher and V. Critchlow, Proc. Soc. Exp. Biol. (N. Y.), 101, 497 (1959).
17. R. L. Smith, R. P. Maickel, and B. B. Brodie, J. Pharmacol. Exp. Ther., 139, 185 (1963).