

DISTINCTIVE FEATURES OF THE ACTION OF HYPNOTICS AFTER NOCICEPTIVE STIMULATION OF ANIMALS IN A STATE OF HYPOTHYROIDISM*

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The individual reactivity of the body has recently become the focus of attention of research workers. Its study became possible when experimenters changed over from the investigation of the functions of isolated organs and systems to that of the coordinated activity of the body as a whole.

The modern view of the problem of individual reactivity holds that it is based on a series of factors which ultimately result in differences in the functional state of the nervous system. The importance of individual reactivity clearly arises during investigation of the action of various pharmacological drugs on animals and man [10, 14, 16, 18, 19]. One of the factors changing the functional state of the nervous system and, consequently, the reactivity of the body is pain (nociceptive stimulation).

The influence of nociceptive stimulation on the action of drugs has been investigated in various forms of experiments by many workers; P. A. Ivanov [13], V. V. Zakusov [11, 12], S. G. Kuznetsova [17], S. M. Dionesov [5, 6], S. M. Dionesov and A. G. Usov [8, 9], B. G. Volynskii [4] and others. The experiments of these authors demonstrated that different drugs have an action on the body which differs in intensity (and sometimes in a qualitative respect also), if before the administration and sometimes immediately afterward the animal is subjected to brief nociceptive stimulation. These experiments showed that the action of drugs consequently depends on the individual reactivity of the body.

During a study of the distinctive features of the action of hypnotics on "normal" animals after nociceptive stimulation, creating a temporary functional disorder of the animal, we thought that it would be useful to find out how the same drugs would act after nociceptive stimulation in a case where the functional state of the animal was already altered. As a factor altering the functional condition of the nervous system for a relatively long period of time, and hence the reactivity of the body too, we selected experimental hypothyroidism in which, as has been shown by several authors [1-3, 15 and others], the tonus of the nervous system is diminished.

EXPERIMENTAL METHOD

The experiments were carried out on adult male white mice. A hypothyroid state was induced in them by intragastric injection (for 3 weeks) of a suspension of methylthiouracil in a dose of 5 mg of the drug per day per mouse by means of a tube. For the investigations we selected chloral hydrate and sodium amytal, whose action after nociceptive stimulation we had studied previously [6, 8, 9]. The hypnotic drugs were injected subcutaneously into the mice: chloral hydrate in 3% solution in a dose of 0.3 mg/g, sodium amytal in 0.004% solution in a dose of 0.06 mg/g. The indicator of hypnotic action was the "lateral position." Nociceptive stimulation was applied to part of the animals 5 minutes before the injection of the hypnotics, and lasted for 30 seconds. For stimulation an apparatus constructed by V. V. Levoshin was used, allowing strong compression of the tail of the mice, at the

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base, to be carried out in accurately graded doses. Altogether 1031 experiments were performed.

EXPERIMENTAL RESULTS

Experiments with chloral hydrate. In a previous paper [7] we found a sharp reduction in the hypnotic action of chloral hydrate in mice receiving methylthiouracil for a period of 3 weeks. If in control experiments the "lateral position" was observed in 34% of mice, on the 11th day after the start of administration of methylthiouracil this position was observed in 25% and on the 21st - 22nd day, in only 4% of the animals. Thus chloral hydrate acted considerably less strongly on the hypothyroid animals than on the "normal" animals, and its effect gradually weakened as the duration lengthened (of administration of the drug) blocking the function of the thyroid gland.

We obtained different results after injection of chloral hydrate to hypothyroid animals after nociceptive stimulation. In these experiments the hypnotic action of chloral hydrate was considerably more pronounced; on the 10th-14th day after the start of methylthiouracil administration the "lateral position" appeared in 43% of the animals and on the 21st-22nd day, in 37% of the animals, thereby reaching the level of hypnotic action of chloral hydrate on "normal" intact animals (Table 1).

TABLE 1

The "Lateral Position" After Injection of "Normal" and Hypothyroid Mice with Chloral Hydrate in Control Experiments and After Nociceptive Stimulation

Control experiments on "normal" mice			Experiments on hypothyroid mice						Day after begin- ning of administra- tion of methyl- thiouracil
			Control experiments			Experiments with noci- ceptive stimulation			
total number of mice	"lateral position"		total number of mice	"lateral position"		total number of mice	"lateral position"		
	no.	%		no.	%		no.	%	
258	95	37	100	25	25	64	28	43	10—14
			100	4	4	62	23	37	21—22

Experiments with sodium amytal. The hypnotic action of sodium amytal on hypothyroid animals, as shown by our earlier experiments [7], was weaker than in the "normal" animals. In the control experiments, for instance, the "lateral position" was observed in "normal" animals in 51% of cases and in hypothyroid animals on the 21st day after the beginning of methylthiouracil administration in only 9% of cases. After nociceptive stimulation of hypothyroid animals the "lateral position" was observed on the 10th-11th day from the start of methylthiouracil administration in 8% of cases and on the 22nd day - in only 4% of cases. Consequently nociceptive stimulation in practice hardly changed the incidence of appearance of the "lateral position" in the hypothyroid animals. (Table 2).

Neither in the experiments with chloral hydrate nor in those with sodium amytal could we observe any regular feature in the rate of appearance of the "lateral position" and its duration.

In previous investigations [8, 9] we ascertained that after strong nociceptive stimulation the hypnotic action of chloral hydrate is enhanced and that of sodium amytal is diminished. In investigations carried out on hypothyroid mice [7] we found a significant weakening, in comparison with normal, of the hypnotic action of both chloral hydrate and sodium amytal which, in our opinion, is explained by weakening of the process of inhibition as well as that of excitation.

In the present investigation it was discovered that after nociceptive stimulation of hypothyroid animals the intensity of the hypnotic action of both test drugs was affected in the same direction as in "normal" animals; the degree of the changes in intensity of action of these drugs was, however, expressed otherwise. In the control experiments on hypothyroid animals, for instance, the "lateral position" was observed after injection of chloral hydrate in only 4% of animals, but after nociceptive stimulation - 37% of animals. Such a sharp increase in the in-

tensity of the hypnotic action of chloral hydrate is probably explained by the fact that on a background of a sharply lowered tonus of the nervous system a powerful factor such as nociceptive stimulation is capable of causing a considerably larger change in reactivity than when the tonus of the nervous system in the intact animals is "normal", and in its turn this determines the intensity of action of the hypnotic drug. In consequence of this, the increase in the hypnotic action of chloral hydrate observed in our experiments was so great that the "lateral position" was observed as frequently as in the control experiments on "normal" animals.

TABLE 2

The "Lateral Position" After Injection of "Normal" and Hypothyroid Mice with Sodium Amytal in Control Experiments and After Nociceptive Stimulation

Control experiments on "normal" mice			Experiments on hypothyroid mice						Day after beginning of administration of methylthiouracil
			Control experiments			Experiments with nociceptive stimulation			
total number of mice	"lateral position"		total number of mice	"lateral position"		total number of mice	"lateral position"		
	no.	%		no.	%		no.	%	
292	149	51	—	—	—	51	4	8	10—11 21—22
			55	5	9	49	2	4	

In the control experiments on hypothyroid animals sodium amytal elicited the "lateral position" in 9% of the animals, but in the experiments with nociceptive stimulation — in 4% of animals. In this case perceptible changes in the hypnotic action of sodium amytal were practically absent; this was probably due to the fact that in the control experiments on hypothyroid animals the intensity of the hypnotic action of sodium amytal was slight, and so significant changes in its intensity could not be detected even if they occurred. Nevertheless, it must be pointed out that after nociceptive stimulation a tendency was observed for the hypnotic action of sodium amytal to be reduced, i.e., changes in the hypnotic action were brought about in the same direction as in the "normal" animals.

The results which are given in this paper convince us that the individual reactivity of animals under the influence of nociceptive stimulation is modified in the same direction when this stimulation is applied to an animal with "normal" tonus of the nervous system or to one with diminished tonus (during experimental hypothyroidism).

SUMMARY

The sleep-inducing effect of chloral hydrate (0.3 mg/g body weight) and sodium amytal (0.06 mg per g) was studied on white mice with hypothyroidism. The latter was attained by daily (during 3 weeks) administration of methylthiouracil (5 mg per mice) by a stomach tube. Pronounced nociceptive stimulation preceded the administration of sleep-inducing drugs in certain experiments. Sleep-inducing substances caused much less effect on animals with hypothyroidism than on normal animals. After nociceptive stimulation the sleep-inducing effect of chloral hydrate on animals with hypothyroidism was much less than that in normal animals. After nociceptive stimulation the sleep inducing effect of chloral hydrate increased in animals with hypothyroidism more intensely than in normal animals, while the effect of sodium amytal had a tendency to decrease.

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