EFFECT OF HYDIPHEN ON BEHAVIOR AND HEMODYNAMIC MANIFESTATIONS OF EMOTIONAL STRESS

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Hydiphen is an original Soviet tranquilizer (diphenylphosphinylacetic acid hydrazide). In a dose of 120-150 mg/kg hydiphen restores the central baroreceptor reflex regulation of arterial pressure, when depressed in cats during an acute emotional-stress reaction (confrontation with a dog). The compound has an antihypertensive action, reduces tachycardia due to emotional stress, has a selective antiphobic, antiaggressive action, and does not induce ataxia. Behavior was investigated quantitatively in animals during group interaction, using a five-point system.

KEY WORDS: tranquilizer; baroreceptor reflex regulation; emotional stress; antiphobic action.

Hydiphen is a new original Soviet tranquilizer (diphenylphosphinylacetic acid hydrazide), approved by the Pharmacological Committee of the Ministry of Health of the USSR for use in medical practice. The spectrum of pharmacological action of hydiphen was described previously [7, 8]. The object of the present investigation was to establish correlation between the action of hydiphen on behavior and on hemodynamic manifestations of emotional stress. Previous investigations [5] showed that the individual effect of a tranquilizer on hemodynamic components of the emotional stress reaction can be detected only by chronic experiments (without the use of general anesthetics) on animals with simultaneous recording of cardiovascular indices and the character of emotional behavior in a stress-inducing situation.

EXPERIMENTAL METHOD

The spectrum of emotional-behavioral reactivity was estimated in chronic experiments on seven cats under conditions of group interaction [4, 5], after preliminary determination of the type of their emotional-behavioral reactivity. The meaningfulness of response manifestations and quantitative evaluation (in accordance with a five-point system) were based on the use of assessment tables. The hemodynamic indices were recorded on unrestrained animals (five cats). Catheters were inserted beforehand into the aorta (through the carotid artery) and external jugular vein, and a transducer of an electromagnetic flowmeter was applied to the ascending arch of the aorta. The arterial blood pressure (electromanometer), respiration (carbon detector), momentary values of the pulse interval between two systoles (cardiotachometer), and the cardiac output (Nihon Kohden electromagnetic flowmeter) were recorded. The baroreceptor reflex was assessed on the basis of the change in period of cardiac contractions in response to elevation of the blood pressure (intravenous infusion of phenylephrine 0.03-0.04 mg/kg) by methods of regression analysis (for further details of the method, see [2]). An emotional-stress situation was created by placing a dog in a compartment of the chamber, separated by a transparent screen, and by creating a situation of direct interaction between cat and dog after removal of the screen [3]. The baroreceptor reflex was tested in the animals at rest and during emotional stress induced by passive (not allowing direct interaction between the animals) confrontation of the cat with a dog.

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TABLE 1. Effect of Hydiphen on Spectrum of Emotional Behavior in Animals of Different Types

Animals of type I			Spectrum of emotional behavior	Animals of type II		
hydiphen, mg/kg		control		control	hydiphen, mg/kg	
100	50				50	100
0**	0,33±0,40**	1,50±0,44	Fear	2,64±0,47	0,58±0,37**	0
0**	0,50±0,44**	2,00±0,31	Anxiety	2,26±0,48	0**	0
1,00±0,50*	1,58±0,20	1,58±0,37	Aggressiveness	0,57±0,53	0**	0
1,40±0,96**	2,0±0,63*	3,25±0,75	Conflict within the group	2,42±0,78	1,00±0,63**	0
1,90±0,54*	1,75±0,41	1,25±0,68	Manifestations of benevolence	1,21±1,8	1,25±0,41	1,00±0,83
1,00±0,22*	1,33±1,21	1,58±0,86	Hunting	1,57±0,67	0,58±0,58*	0,58±0,80*
2,40±0,54**	1,91±0,20**	0,66±0,81	Benevolent contacts with partners	1,85±0,69	2,16±0,40	2,00±0,89
1,40±0,41**	1,83±0,25	2,25±0,27	Orienting reaction	2,00±0,28	1,16±0,25**	1,50±0*
0,80±0,44**	1,33±0,51	1,66±0,25	Investigation behavior	0,42±1,13	0,66±0,60	1,00±0,44**
1,30±0,27**	1,58±0,20**	2,16±0,40	Motor activity	1,57±0,44	1,08±0,20	1,16±0,25
0,90±0,22*	1,41±0,58	1,83±0,40	Initiative	1,28±0,75	1,00±0,31	1,00±0,35

*P<0.05.
**P<0.01
Legend. Mean value of abundance of manifestation (in points) given; changes significant with respect to Wilcoxon's I nonparametric criterion of difference.

EXPERIMENTAL RESULTS

Data on the effect of hydiphen on the spectrum of emotional behavior of animals characterized by different types of behavioral reaction, according to our classification, are summarized in Table 1. In a dose of 25-50 mg/kg (enterally) hydiphen narrows the original spectrum of emotional reactivity, but even in high doses (100 mg/kg) it does not disturb the adequacy of the behavioral response. No marked general sedative action develops, although initiative and spontaneous motor activity are depressed: the animal tries to assume a comfortable recumbent posture, but orienting activity remains sufficiently high. Neither ataxia nor muscle relaxation is observed.

In animals predisposed to anxiety and fear reactions (type II) hydiphen (25-50 mg/kg) weakens excessive anxiety and changes the character of zoosocial interaction: The animal does not exhibit fear in front of dominant partners in the group and assesses their behavior adequately in accordance with ethologically significant features. The passive form of fear on contact with partners is abolished: During contact with the leader the animal assumes a posture of surbordination, which prevents the possible onset of conflicting interaction. If the dose is increased to 100 mg/kg hydiphen completely abolishes manifestations of fear and anxiety, and benevolent contacts in the group of animals increase. In animals with a tendency toward aggressive reactions (type I) hydiphen, in the same doses, has a definite antiaggressive and anticonflict action.

Under conditions of an emotional-stress situation hydiphen (50 mg/kg intravenously) completely suppressed emotional stress due to the presence of a dog in the neighboring half of the chamber. However, the alerting reaction and orientation toward the dog (turning the ears and head, fixation of the gaze) still remained. The response to closeness and confrontation was significantly changed. In animals with dominance of an anxiety reaction, responding with a passive-defensive reaction (running away, posture of passive subordination), manifestations of fear were suppressed and an active-defensive reaction developed. In aggressive animals affective forms of defensive behavior were weakened. Animals with different types of initial behavioral response to a stress-inducing object thus responded almost identically after administration of hydiphen: A well-oriented preventive-defensive type of behavior developed, with elements of active defense in response to direct contact with the dog, against the background of very slight emotional stress of the mild anxiety type, without any manifestations of fear or aggressiveness.

In tranquilizing doses, hydiphen had no clear effect on the background hemodynamic indices but it considerably reduced the intensity of cardiovascular correlates of the emotional-stress reaction. In waking animals in a quiet state in the experimental chamber (with no contact with the dog) the arterial pressure varied between 70 and 80 mm Hg, the mean period of cardiac contractions was 450-600 msec, and the cardiac output 530-560 ml/min. After intravenous injection of hydiphen (50 mg/kg) a tendency was observed for the systemic arterial

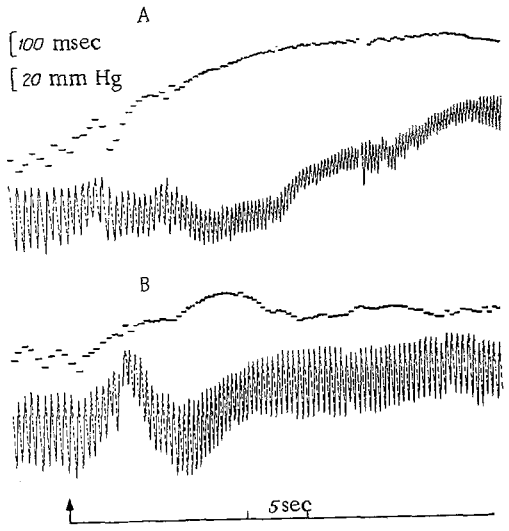

Fig. 1

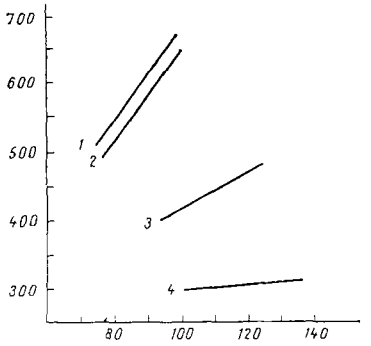

Fig. 2

Fig. 1. Changes in period of cardiac contractions and arterial pressure in cat during confrontation with dog before (A) and after (B) injection of 50 mg/kg hydiphen. From top to bottom: period of cardiac contractions (in msec) and arterial pressure (in mm Hg). Arrow indicates beginning of confrontation. Time marker 5 sec.

Fig. 2. Effect of hydiphen on baroreceptor reflex regulation of heart rate under normal conditions and during emotional stress. Abscissa, systolic arterial pressure (in mm Hg); ordinate, pulse interval (in msec). Tangent of angle of slope of each straight line to abscissa represents averaged coefficient of linear regression for all experiments. 1) Baroreceptor reflex at rest, 2) the same after injection of 50 mg/kg hydiphen, 4) baroreceptor reflex during confrontation of cat with dog, 3) the same after injection of 50 mg/kg hydiphen.

pressure to fall, although not statistically significantly (by 6±1 mm Hg). The heart rate did not change significantly and the cardiac output rose a little (to 590-600 ml/min) on account of an increase in stroke volume. During the period of emotional stress (approach of the dog and confrontation) the arterial pressure rose on average by 27±1 mm Hg and the heart rate increased (the intersystolic interval was shortened by 240±11 msec) (Fig. 1A). In a dose of 50 mg/kg, hydiphen reduced the pressor response of the arterial pressure during the period of confrontation by 13±2 mm Hg (Fig. 1B). The tachycardia diminished (shortening of the pulse interval was reduced by 73±7 msec). These changes correlated with the development of the tranquilizing action of the drug on the animals' behavior.

The coefficient of regression characterizing the level of the central baroreceptor reflex regulation of the heart rate at rest (which varied in different animals from 9.4 to 12.4 msec/mm Hg), was unchanged by hydiphen (Fig. 2). In the period of emotional stress accompanied by elevation of the arterial pressure (confrontation without direct interaction between the animals) the coefficient of regression fell to 0-2.5 msec/mm Hg, evidence of depression of the function of the baroreceptor reflexes (cardiac component). Under the influence of hydiphen, besides the tranquilizing effect and depression of the cardiovascular responses to emotional stress, the previously depressed baroreceptor reflex recovered. The coefficient of linear regression increased to 4.2-7.2 msec/mm Hg (Fig. 2). Restoration of baroreceptor reflex activity was not simply the result of the tranquilizing action of the drug, for the central muscarinic cholinolytic metamizil (methyldiazine), in a dose of 0.1-2 mg/kg, did not affect baroreceptor reflex regulation of the hemodynamics in acute emotional stress, although it did exhibit a tranquilizing action. The study of the pharmacological properties of hydiphen showed that it has a central nicotinic cholinolytic, antiadrenergic, and antiserotonin effect, and differs in its action from benzodiazepine tranquilizers and central muscarinic cholinolytics.

Depression of the function of the baroreceptor reflexes in repeated emotional-stress states is one mechanism of development of chronic hypertensive states [1]. Activation of the diencephalic mechanisms, in connection with the development of emotional stress, weakens the antihypertensive action of the baroreceptor reflex mechanisms [8, 9]. Accordingly, improvement of the central baroreceptor reflex regulation accompanied by a simultaneous decrease in the pressor reflex and tachycardia due to emotional stress, is a valuable manifestation of the autonomic effect of hydiphen which must be taken into account when it is used clinically.

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ROLE OF GABA-ERGIC STRUCTURES IN THE MECHANISM OF ACTION OF HALOPERIDOL

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The effect of haloperidol on convulsions induced in mice by bicuculline and thiosemicarbazide and on recovery cycles of the primary sensomotor cortical response in rats was studied. In a dose of 0.3-0.5 mg/kg, giving a tranquilizing effect, haloperidol had a protective action against convulsions induced by blockade of GABA receptors through the action of bicuculline, and potentiated depression of the testing response in the recovery cycle of the primary sensomotor cortical response in rats, i.e., within this dose range haloperidol potentiates GABA effects. With an increase in the dose of haloperidol to 1-2 mg/kg its effectiveness in both tests disappeared. On the basis of these results and data in the literature it is suggested that the postsynaptic GABA-positive effect plays an important role in the mechanism of the tranquilizing action of haloperidol and of other neurotropic agents.

KEY WORDS: haloperidol; tranquilizing effect; GABA.

The presence of a linear group between the rings in the structure of aminobutyrophenones, similar in its structure and spatial distribution of charges to the molecular of γ-aminobutyric acid (GABA) [9, 11], was the basis for the assertion that these substances can simulate the effects of GABA [14]. However, butyrophenones, including their most typical representative, haloperidol, have not hitherto been investigated on models of GABA-ergic effects, which could confirm or refute this suggestion. The only investigation to provide convincing evidence of the GABA-positive action of another representative of the butyrophe-

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