INFLUENCE OF ALKALOIDS OF THE PLANT ANABASIS APHYLLA L. ON THE PHYSIOLOGICAL PROCESSES OF ANIMALS

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Annotation.
The article provides an assessment of the effect of the activity of the alkaloids anabasine, anabasamine and lupinine in various doses on apomorphine hypothermia in mice and rats, as well as a study of apomorphine hypothermia in rats as a test for psychotropic drugs and studied the effects of these alkaloids in various doses on physical activity and body temperature of animals. An assessment of the influence of the activity of alkaloids at various doses on the physical excitation induced by phenamine in mice was studied. We analyzed that alkaloids, like antidepressants, significantly counteracted the effects of reserpine and phenamine, but their effect was less pronounced than that of imipramine, and alkaloids reduce physical activity and reduce body temperature. These alkaloids act on adrenergic processes. Decreased phenamine arousal and increased phenamine hyperthermia and group toxicity in mice.

Key words: alkaloids, anabasine, anabasamine, lupinine, physical activity, temperature, hyperthermia, hypothermia, locomotion, standing up, phenamine, caffeine, Anabasis aphylla L.
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Introduction. At present, the number of various diseases is continuously increasing and the priority for the future of every society is to create for the physical health of man. Much attention is paid to the study of psychotropic drugs containing natural compounds for surgery and treatment of diseases. At the world level, scientific research is being conducted to confirm alkaloids isolated from plants as promising sources in the development of drugs for the prevention and treatment of various diseases. Uzbekistan has large resources of medicinal plants. One of the main sources of these plants is the species Anabasis aphylla L.

Anabasis aphylla L. is a succulent flattened-spherical shrub 25–70 cm high, of the family Amaranthaceae [16]. The rhizome is thick, twisted, woody, turning into a powerful taproot, penetrating to the depth of the soil to the occurrence of groundwater (5 - 20 m). Stems numerous, lignified at the bottom, branching. The leaves are almost undeveloped, barely noticeable, devoid of chlorophyll. The flowers are small, inconspicuous, bisexual, solitary, with bracts, form dense spike-shaped inflorescences. Perianth simple, usually cup-shaped, consists of 5 free leaves, 5 stamens. Pistil with upper unilocular ovary, in dense terminal spicate inflorescences. The fruits are rather juicy, round, laterally flattened formations, with a winged, fleshy fruit-bearing [15]. Anabasis aphylla L is recommended as an agricultural raw material that is used in various industries [8, 48-56], including pharmacology.

Of the 3 alkaloids isolated from this plant [11, 292], two belong to the pyridine (anabasine, anabasamine) and lupinine to the norlupinane series. The chemical structure and effects of the alkaloids anabasine, anabasamine and lupinine on various processes of the animal organism have been studied [1, 57-62; 2, 26-33; 5, 19-22; 6, 23-26; 7; 40-44; 9, 147-148; 10, 481; 14, 20-22; 12; 13], however, the effect of these alkaloids on apomorphine hypothermia, physical activity and body temperature in animals, and phenamine-induced physical

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excitation has not been studied in detail. Apomorphine hypothermia in mice, described by I.P. Lapin and M.L. Samsonova [4; 563-567], is used as a test to distinguish between antidepressants, which reduce apomorphine hypothermia, and anticholinergics, which do not affect it.

The aim of the research was to study the effect of these alkaloids on apomorphine hypothermia, locomotor activity and body temperature in animals and to evaluate the effect of alkaloids at various doses on phenamine-induced physical excitation and hyperthermic effect in mice.

Materials and methods of research. Experiments were performed on rats, mice and frogs. The control and experimental groups consisted of at least 7-8 animals each. As in the experiments with reserpine, mice and rats were placed in groups of 7-8 animals in metal boxes, and another similar box was used to measure the physical activity of each animal separately. We used this test in the study of alkaloids. Laboratory temperature in these experiments ranged from 18 to 23°C.

To study the neuropharmacological activity of alkaloids, we decided to test the half-lethal dose (HLD50) of alkaloids when injectedintraperitoneally for mice, rats and subcutaneously for frogs in the laboratory of Namangan State University.

On mice, it was found that their HLD50 does not particularly differ from those established in the conditions of Tashkent [3, 37-44]: anabasine18.8 mg/kg, anabasamine 159 mg/kg and lupinine 263 mg/kg. In HLD50 rats: anabasine20 mg/kg, anabasamine 175 mg/kg and lupinine 250 mg/kg. On frogsanabasine24 mg/kg, anabasamine 400 mg/kg and lupinine over 480 mg/kg. In other studies, the toxicity of these alkaloids in rats and frogs was not investigated.

The physical activity of the animals was assessed by two parameters: by locomotion (horizontal component of approximate physical activity) and by standing up (vertical component of approximate physical activity). Physical excitation was used to assess the effect of alkaloids on phenamine-induced stimulation of locomotion and standing up, the vertical component of the physical orienting response. As in the experiments with reserpine, mice were placed in groups of 7–8 animals in metal boxes, and another similar box was used to measure the physical activity of each animal separately.

Locomotion was measured using a keyboard counter by the number of intersections of the rays of the cross drawn on the bottom of the box. At the same time, the number of standing up for 2 minutes was counted. after 15 min. after injection of phenamine. All experimental graded data were processed statistically by Student's t-test.

Results and discussion. As can be seen in Table 1, the alkaloids at the doses tested had no effect on apomorphine-induced hypothermia. Of the 4 experiments of this type, only one exception was made, in which anabasine(3 and 6 mg/kg), anabasamine (25 and 50 mg/kg) and lupinine (40 and 80 mg/kg) significantly reduced apomorphine hypothermia. The tricyclic antidepressant imipramine, taken for comparison with alkaloids, did not significantly reduce the effect of apomorphine in all experiments, so it was decided to repeat these experiments on rats. As can be seen from Table 2, imipramine in rats counteracted apomorphine hypothermia in 100% of cases. Another antidepressant, demethylimipramine, similarly to imipramine, relieved apomorphine hypothermia in rats, but did not always have an effect on it in mice. Therefore, we can conclude that the antagonism of antidepressants with apomorphine in the hypothermia test is more reliable to assess in rats. The same applies to new drugs. In mice, the effect of the new drug can be missed in this test.

Subsequently, we continued the study of apomorphine hypothermia in rats. However, alkaloids at tested doses: anabasine 1 and 2

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mg/kg, anabasamine 5 and 12.5 mg/kg and lupinine 10 and 20 mg/kg (when injected 30 minutes before apomorphine), as well as anabasine 3 mg/kg ,anabasamine 25 mg/kg and lupinine 40 mg/kg (injected 1 hour before apomorphine at a dose of 5 mg/kg) had no effect on hypothermia.

Table 1.

Effect of alkaloids on apomorphinehypothermia in Mice

1 st. injection		Temperaturechange[x]	Dose of apomorphine in mg/kg	Hypothermia (-Δt°)[xx]
drugs	lose,mg/kg			Cumulativeindicesfor 30+60 min.
30 min. afterinjection				
H_2O	-	-1,6	-	0,6±0,18
H_2O	-	-1,3	5	9,9± 1,50
ANB	1,5	-1,3	5	9,1± 1,73
ABM	12,5	-1,9	5	7,5±0,45
Lup	20	-0,5	5	10,8±0,72
Im	12,5	-2,0	5	4,5±0,60*
60 min. afterinjection				
H_2O	-	-1,0	-	+1,1±0,18
H_2O	-	-1,6	5	4,8±0,56
ANB	3	-0,4	5	4,3±1,09
ABM	25	-2,1	5	5,0±0,80
Lup	40	-0,5	5	5,4±0,95
Im	12,5	-0,5	5	1,9±0,65*
H_2O	-	-1,3	-	+1,7±0,27
H_2O	-	-1,4	5	5,7±0,42
ANB	6	-1,4	5	7,1±0,38
ABM	50	-5,0	5	3,5±0,82
Lup	80	-1,6	5	7,0± 1,11
Im	25	-1,4	5	2,8±0,36**

Note: ANB –anabasine, ABM –anabasamine, Lup–lupinine, Im– imipramine, [x]– fromthe initial temperature, [xx] - from the temperature before the injection of apomorphine, * P<0,05; ** P<0,01. In each group, 7 mice - females. All drugs were injectedintraperitoneally.

Along with alkaloids, 10 antidepressants were investigated: imipramine, demethylimipramine, amitriplitine, nortriptyline, maprotiline, chlorimipramine, noveril, aponal (all at a dose of 5 mg/kg). All the tested antidepressants, with the exception of the new antidepressant iprindole, which differs from others in its weak adrenogenic effect, significantly reduced apomorphine hypothermia in outbred rats and Wistar rats. Azafen had the least pronounced effect.

Table 2

Reproducibility of the antihypothermic effect of imipramine and demethylipramine in rats and mice

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Species	Significant antagonism with apomorphine (number of groups)	
	imipramine (5 mg/kg, i.p.)	**demethylimipramine (5 mg/kg, i.p.)**
Rats	8/8	2/2
Mice	4/15	14/24

Each group contains 6-8 animals. Apomorphine was injected at a dose of 5 mg/kg intraperitoneally or subcutaneously.

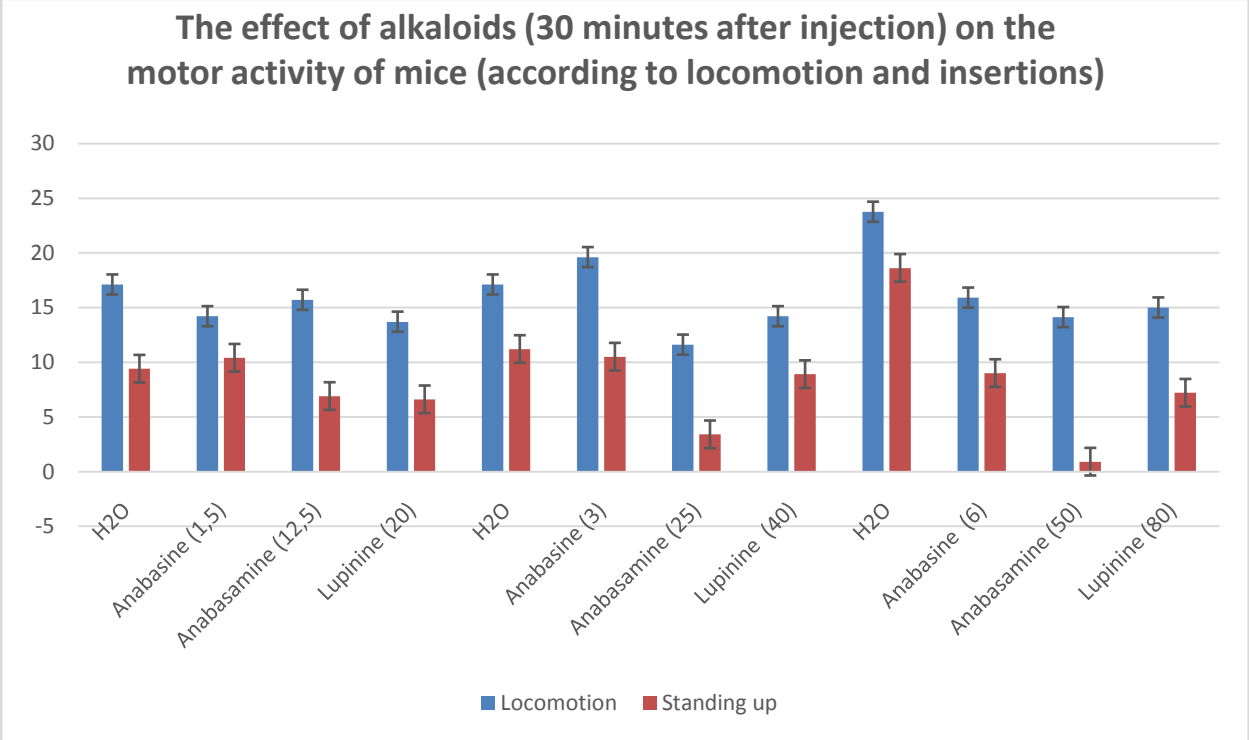
Adrenopositive drugs had a strong antihypothermic effect: AW (5 mg/kg), cocaine (5 mg/kg), and phenamine (0.5 mg/kg). Very low doses of antipsychotics also had an antihypothermic effect: haloperidol and mazheptil (0.002 mg/kg), chlorprothixene and triftazine (0.1 mg/kg), etaperazine (0.01 mg/kg) and chlorpromazine (1 mg/kg).

Of the 4 cholinolytics used, only scopolamine at a dose of 5 mg/kg significantly reduced apomorphine hypothermia, but at this dose it itself causes a significant increase in temperature. Atropine, amizil and pentafen had no effect on apomorphine hypothermia.

To studyphysical activity, alkaloids were tested in doses: anabasine(1.5; 3 and 6 mg/kg), anabasamine (12.5; 25 and 50 mg/kg) and lupinine (20, 40 and 80 mg/kg) or 1 /12, 1/6 and 1/3 LD50. 30 minutes after injection, alkaloids only in high doses significantly inhibited both components of the physical activity of mice (diagram 1). These doses of alkaloids did not change physical activity after 1; 2; 3 and 4 hours after injection in another series of experiments.

Similar results were obtained in rats: anabasine(6 mg/kg), anabasamine (50 mg/kg), and lupinine (80 mg/kg) 1 hour after injection significantly inhibited both components of physical activity, and after 2; 3 and 4 hours after injection did not influence.

Diagram 1.



Thus, alkaloids have an insignificant and short-term effect on physical activity. On mice, they (at a dose of 1/3 LD50) only after 30 minutes.afterinjection, physical activity was reduced. Therefore, in further studies of the interaction of alkaloids with other drugs, measurements were taken 1 hour and

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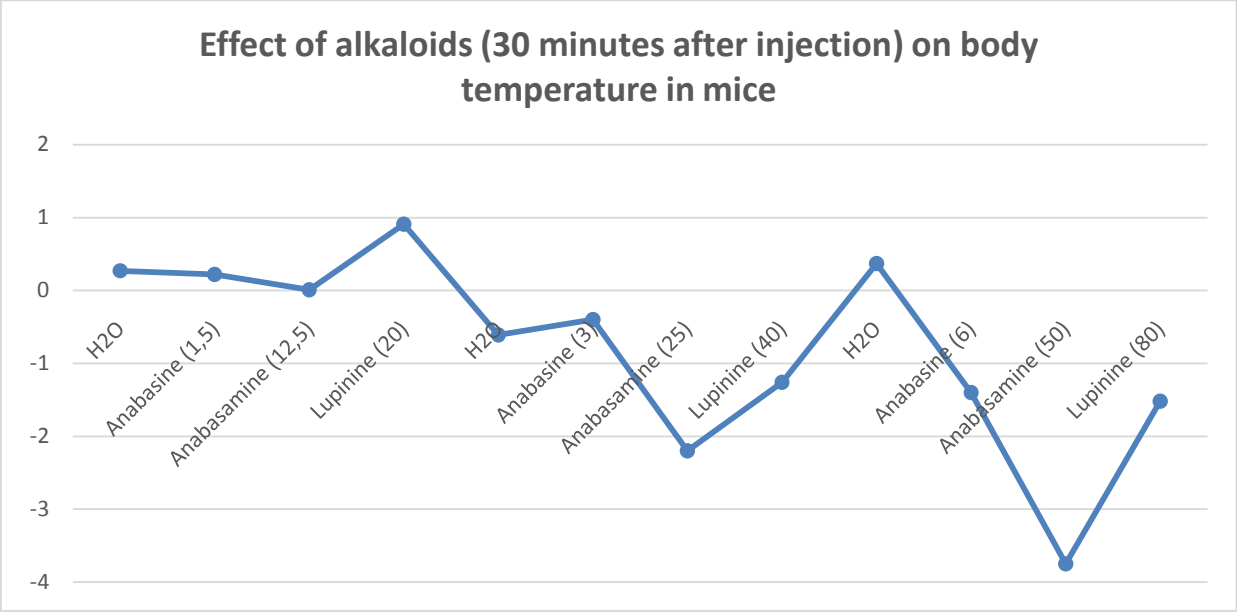
later after the injection of alkaloids, when their sedative effect had already passed (with the exception of some experiments).

On mice after 30 min. after injection, anabasine (6 mg/kg), anabasamine (25 and 50 mg/kg), and lupinine (80 mg/kg) significantly reduced body temperature. At the other doses tested, they did not influence (Diagram 2).

Diagram 2



The second diagram shows the results of one of the 4 experiments of this series (laboratory temperature was 18 - 22 °C). A significant decrease in temperature persisted only after 1 and 1.5 hours after injection, and after 2; 3 and 4 hours the temperature was restored to normal. Similar results were obtained in rats.

Thus, alkaloids cause hypothermia, and this is more pronounced in anabasamine. Our results are in good agreement with the data of I.S. Khazbievich (1973), who found that anabasamine in doses of 25 and 50 mg/kg reduces the temperature in white mice by 1,5 – 2,0 °C and 4,0 – 5,0 °C, respectively.

It turned out that the physical excitation induced by phenamine manifested itself only in increased locomotion, while the number of standing up did not increase. Anabasineat a dose of 6 mg/kg, anabasamine at doses of 25 and 50 mg/kg, and lupinine at doses of 40 and 80 mg/kg significantly reduced the excitation of locomotion caused by phenamine (table 3).

As can be seen from table 4, anabasamine at a dose of 25 mg/kg significantly reduced the effect of phenamine in the first 15 minutes. and after 1 and 2 hours, it slightly increases the effect of phenamine on locomotion (not significant). The alkaloid itself did not change physical activity.

Our next task was to clarify how alkaloids affect the stimulating effect of caffeine. It was found that anabasine (6 mg/kg) and anabasamine (25 and 50 mg/kg) significantly reduced the effect of caffeine on locomotion in mice. Anabasine at a dose of 3 mg/kg and lupinine at both doses used had no effect. Caffeine itself did not affect getting up (table - 5).

Table - 3

Effect of alkaloids on the excitatory effect of phenamine in mice

№	**Drugs**	Dose, mg/kg (i.p.andins.)		Locomotion	Standing up
1	H_2O+H_2O	-	-	16,20±1,81	14,1±2,05
2	H_2O+Ph	-	10	30,00±2,21**	13,2±2,08

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3	ANB +H_2O	3	-	18,50±1,38	19,2±1,69
4	ANB+Ph	3	10	25,2±3,48	15,4±2,10
5	ABM+H_2O	25	-	17,5±2,98	15,6±2,68
6	ABM+Ph	25	10	18,8±2,12^{xx}	8,6±1,98
7	Lup+H_2O	40	-	17,2±1,88	20,4±2,06
8	Lup+Ph	40	10	21,4±3,22^{x}	15,0±3,87
9	H_2O+H_2O	-	-	20,3±1,29	15,5±1,66
10	H_2O+Ph	-	10	33,2±2,77**	17,5±1,16
11	ANB +H_2O	6	-	19,0±1,76	15,7±2,02
12	ANB +Ph	6	10	19,0±2,26^{xx}	8,4±3,06^{x}
13	ABM+H_2O	50	-	16,7±3,07	8,4±2,35*
14	ABM+Ph	50	10	15,6±3,55^{xx}	9,9±3,27
15	Lup+H_2O	80	-	15,2±2,22	12,4±3,58
16	Lup +Ph	80	10	18,6±2,59^{xx}	11,4±2,62

Note: ANB – anabasine, ABM – anabasamine, Lup – lupinine,Ph –phenamine. The drugs were injected 1 hour before phentermine.i.p. –intraperitoneally, ins. –inside.Each group has 8 mice.$^{(*)}$ - difference compared to the group H_2O+H_2O: *P<0,05, ** P<0,001. $^{(x)}$difference compared to the groupH_2O+Ф: ^{x}P<0,05,^{xx}P<0,01.

Table - 4

Effect of anabasamine on the excitatory effect of phenamine in mice

№	**Drugs**	Dose, mg/kg		After 15 min.		After60min.		After 120min.	
				Locomotion	Standing up	Locomotion	Standing up	Locomotion	Standing up
1	H_2O+H_2O	-	-	15,62±1,48	10,25±2,06	9,25±1,56	9,00±1,79	4,50±1,59	4,12±1,66
2	H_2O+Ф	-	2,5	21,37±2,56	3,62±1,06*	16,75±2,93	4,13±1,04	16,87±2,16**	9,50±1,99
3	ABM+H_2O	25	-	12,12±3,36	5,37±2,31	9,00±1,45	5,25±1,98	5,50±0,75	2,87±0,81
4	ABM+Ph	25	2,5	10,75±2,60^{x}	3,75±2,27	22,25±3,45*	4,75±1,54	28,25±5,05**	6,62±1,10

Note: ABM-anabasamine, Ph –phenamine. Each group contains 8 female mice. (*) - difference compared to the corresponding control: *P<0,05, ** P<0,01. $^{(x)}$difference compared to the groupH_2O+Ph: ^{x}P<0,05.

Table - 5

Influence of alkaloids on the excitatory effect of caffeine in mice

№	Drugs	Dose, mg/kg (i.p. and ins.)		Locomotion	Standing up
1	H_2O+H_2O	-	-	17,25±2,75	12,6±2,52
2	H_2O+C	-	20	35,71±3,98*	17,7±1,54
3	ANB+H_2O	3	-	21,5±3,65	15,6±1,98
4	ANB+C	3	20	28,4±4,01	17,3±1,12

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5	ABM+H_2O	25	-	21,0±2,44	14,1±2,67
6	ABM+C	25	20	24,3±1,11^{x}	11,1±1,29
7	Lup+H_2O	40	-	13,8±2,55	10,3±2,60
8	Lup+C	40	20	27,4±4,42	20,5±3,00
9	H_2O+H_2O	-	-	17,6±2,14	13,2±1,00
10	H_2O+C	-	20	30,7±1,53*	15,0±0,62
11	ANB+H_2O	6	-	18,8±2,23	15,4±1,84
12	ANB+C	6	20	19,6±2,25^{xx}	14,3±1,64
13	ABM+H_2O	50	-	16,3±3,20	9,0±1,73
14	ABM+C	50	20	18,8±2,21^{xx}	14,6±3,26
15	Lup+H_2O	80	-	20,8±1,59	16,2±1,74
16	Lup+C	80	20	23,9±2,99	15,5±1,85

Note: ANB-anabasine, ABM-anabasamine,Lup-lupinine, C-caffeine. The preparations were injected 1 hour before caffeine, i.p. - intraperitoneally, ins. – inside. In each group 7 - 8 mice. (*) - difference compared to the H_2O+H_2Ogroups: *P<0,01. (x) difference compared to the H_2O+C groups: ^{x}P<0,05, ^{xx}P<0,01.

Anabasineand anabasamine reduce the stimulating effect of not only phenamine, but also caffeine. The decrease in phenamine excitation under the influence of large doses of alkaloids may be due to the nonspecific inhibitory effect of alkaloids. A similar explanation has been proposed for the antagonism of γ-aminobutyric acid derivatives with phenamine and other stimulants. Antagonism with phenominum is the first short phase of the action of anabasamine (possibly other alkaloids). In the second phase, anabasamine and other alkaloids enhanced all three effects of phenamine studied: physical excitation, hyperthermia, and group toxicity.

It was found on mice that 30 minutes after the injection of anabasine (1,5 and 3 mg/kg), anabasamine (12,5 and 25 mg/kg) and lupinine (40 mg/kg) significantly potentiated the hyperthermic effect of phenamine (table - 6).

Table - 6

Effect of alkaloids on the hyperthermic effect of phenamine in mice

№	Drugs	Dose, mg/kg		Hyperthermic + Δt◦
1.				Cumulativeindexfor 30 + 60 min.
2.	H_2O + Ph	-	10	0,47±0,29
3.	ANB+ Ph	1,5	10	2,75±0,34***
4.	ABM + Ph	12,5	10	1,70±0,27**
5.	Lup+ Ph	20	10	0,77±0,35
6.	Im+ Ph	12,5	10	1,00±0,49*
7.				Через 30 мин. измерения
8.	H_2O + Ph	-	10	1,24±0,52
9.	ANB+ Ph	3	10	3,01±0,67*
10.	ABM + Ph	25	10	4,01±0,59**
11.	Lup+ Ph	40	10	3,33±0,37**
12.	Im+ Ph	25	10	2,09±0,48**

Note: ANB-anabasine, ABM-anabasamine, Lup-lupinin, Im-imipramine, F-phenamine. *P<0,05, ** P<0,01, *** P<0,001. All drugs were injectedintraperitoneally. In each group, 8 mice - females.

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Lupinin at a dose of 20 mg/kg had no effect on the effect of phenamine. Tested for comparison in the same experiment, the antidepressant imipramine (12.5 and 25 mg/kg), in contrast to the alkaloids, not only did not enhance, but even perverted the hyperthermic effect of phenamine. In table - 6, we could not provide cumulative indices for 2 hours of temperature measurement, because anabasamine (25 mg/kg) and lupinine (40 mg/kg) increased the group toxicity of phenamine in the first 60 minutes, and anabasine (1.5 mg/kg kg) anabasamine 12.5 in the second 60 minutes after the injection of phenamine and caused the death of animals. The table shows the results of one of the 3 experiments in this series.

Thus, alkaloids, like antidepressants, significantly counteracted the effects of reserpine and phenamine, but their effect was less pronounced than that of imipramine. Alkaloids did not affect the effects of the reserpine-like drug Po-4-1284 and the hypothermic effect of apomorphine.

Alkaloids reduce physical activity and lower body temperature. Since they act this way only in high doses (about 1/3 LD50) and in the first 15-30 minutes, the inhibitory effect can be regarded as weak and short-lived. True, antidepressants, which have a tranquilizing and sedative effect in patients, also reduce physical activity in doses close to the doses of alkaloids, 1/3 LD50.

The alkaloids anabasine, anabasamine and lupinine act on adrenergic processes. Decreased phenamine arousal and increased phenamine hyperthermia and group toxicity in mice. Thus tested alkaloids interfere with the nervous system of animals.

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