STRESS-PROTECTIVE PROPERTIES OF LITHIUM NICOTINATE, A NEW NICOTINIC ACID DERIVATIVE

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Abolition or, most important, prevention of stress reactions is a vital task in practical psychopharmacology. Psychotropic drugs play the leading role in pharmacotherapy of stress reactions and, in particular, of psychoemotional stress [5-7]. A special place among the psychotropic drugs used to control stress reactions belongs to tranquilizers, the most widely used group of psychoactive drugs [1, 2].

Meanwhile the tranquilizers in current use do not fully satisfy clinical requirements and cannot be used to prevent the development of stress in an individual at work, and needing such preparations, for they give rise to marked side effects. That is why there is an urgent need for the discovery and pharmacologic study of new psychotropic agents with a marked stress-protective action, but free from side effects, especially those such as disturbance of movement coordination, muscle relaxation, and loss of working capacity. These requirements are satisfied most completely by drugs based on natural metabolites. Being related to the body they are highly effective and specific in action, their toxicity is low, they are harmless, do not cause tolerance or dependence, they penetrate easily through cell membranes, and are quickly excreted from the body [9].

The aim of this investigation was to study stress-protective properties of lithium nicotinate, a tranquilizer based on two natural human metabolites, namely nicotinic acid and the trace element lithium. Nicotinic acid possesses psychotropic properties: it causes rapid diminution of symptoms in several psychoses and neuroses and restores normal brain metabolism. Lithium is a generally recognized psychoactive preparation which is highly effective when used to cure and also to prevent effective disorders, neurosis-like states, various kinds of overstrain, and so on. The new preparation organically combines the effectiveness of lithium in regulating the course of nervous processes and the profound effect of nicotinic acid on nerve tissue metabolism, together with its powerful detoxicating action.

EXPERIMENTAL METHOD

Experiments were carried out on 389 noninbred male rats weighing 180-200 g, kept on the standard animal house diet. After preliminary testing [4] the animals were divided into three groups: 1) unemotional, 2) moderately emotional, and 3) highly emotional. The effect of the drug on the behavioral response of rats to stimulus novelty was evaluated [3, 14]. The essence of the method is that a rat is kept for 2 min in a cylinder located in a vessel containing soda. The smooth and high walls of the cylinder do not allow the animal to climb up or jump out. Through the transparent wall the animal sees a net by which it can escape from the vessel. To get out of this situation the rat must make the only correct and possible decision enabling the goal to be reached, namely to dive beneath the cylinder and escape from the water up the net. The animal's state of stress was due to finding itself in the water and partial immobilization (the diameter of the cylinder was 12 cm). The latent period (LP) of the avoidance or escape reaction, the number of attempts at avoidance, the level of defecation (number of boluses), and LP of escape from the stress situation were recorded. Parameters were studied in parallel in control and experimental groups. The physical tolerance of the rats was studied in a cylindrical treadmill 50 cm in diameter, revolving at a speed of 12-15 rpm.

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An electric current of 50-100 mA was applied randomly to metal plates in the floor. The animal's running time until total exhaustion was recorded. The dynamics of cardiovascular function was studied with reference to the following parameters: ECG — the R-R interval with calculation of heart rate (HR), the amplitude of the R and T waves in three standard leads: ballistocardiogram (BCG) — amplitude of the JK wave measured by means of a portable instrument [12]. The arterial blood pressure (BP) was recorded in chronic experiments by an electroplethysmographic method [10] and the velocity of the blood flow (VBF) was measured by the method in [11]. A state of neurosis was produced by the method in [13], in the writers' modification [8]. Lithium nicotinate was injected intraperitoneally in a dose of 10 mg/kg daily for 2 weeks.

EXPERIMENTAL RESULTS

The results showed that lithium nicotinate has low toxicity and a marked tranquilizing action. In a dose of 5-10 mg/kg it reduces tension and aggressiveness of animals and quiets them. In the same dose the compound reduces spontaneous motor activity, and in a dose of 20 mg/kg reduces it by more than half. In a dose of 10 mg/kg lithium nicotinate exhibits marked antagonism against caffeine and amphetamine, and distinct synergism with barbiturates. Even in subtoxic doses, it does not disturb the orienting reactions of animals or their movement coordination and has no muscle-relaxing action. In a dose of 5-10 mg/kg lithium nicotinate accelerates the formation of conditioned defensive reflexes (CDR) but does not affect a stable reflex, unless given in a dose of 100 mg/kg or higher, when it has an inhibitory action on CDR. ED_{50} of the compound by the antimetrazol test is 86 (103.2-71.4) mg/kg.

Data on the effect of stress and also of a preliminary course of lithium nicotinate on solution of the simplest extrapolation task by the rats, namely escape from the stress situation, are given in Table 1. It will be clear that the shortest LP of the reaction was recorded in unemotional rats (4.4 ± 1.3 sec), in moderately emotional animals it was 10.1 ± 2.5 sec, and the highly emotional rats made no attempt whatever to escape from the stress situation, not only during the assigned 2 min, but also indefinitely, until the animal exhausted its strength and dropped into the water. The number of attempts at avoidance was highest in group 1 (12.6 ± 1.9), whereas in group 3 it was zero. The number of defecations was higher in groups 1 and 3 (4.7 ± 1.1 and 3.0 ± 0.8, respectively), and was lowest in group 2 (1.0 ± 0.2). Although the number of attempts at avoidance in group 1 was high, and in group 3 it was zero, the rats of both these groups failed to escape within the assigned time from the stress situation (LP > 120 sec), and only in group 2 was LP 26.0 ± 3.2 sec. A course of lithium nicotinate essentially changed the animals' behavioral reaction. In group 1 the parameters studied were virtually unchanged, except LP of escape, which was significantly reduced from 120.0 ± 0.0 to 96.0 ± 8.4 sec (by 20%). A much greater improvement of goal-directed performance of the escape task was recorded in group 2 than in group 1. Although LP of the avoidance or escape reaction was reduced to 48.5%, it did not reach statistical significance. Meanwhile the number of attempts at avoidance increased significantly, and LP of escape decreased significantly (from 26.0 ± 3.2 to 14.2 ± 1.8 sec). Lithium nicotinate had its most marked effect on highly emotional rats, in which LP of the avoidance reaction was significantly reduced from an indefinite value to 32.0 ± 4.3 sec. The number of attempts at avoidance increased from 0 to 7.4 ± 1.7 ($P < 0.001$) and LP of escape also decreased to 40.5 ± 5.5 sec ($P < 0.001$).

The next stage of the investigations was to study the effect of a prophylactic course of lithium nicotinate on the physical endurance of unemotional and highly emotional rats. Table 2 gives data for the duration of running of the animals in a cylindrical treadmill. Unemotional animals were physically more resistant than highly emotional animals: their running time was twice as long (45.4 ± 5.2 and 20.3 ± 1.8 min, respectively). Animals of both groups adapted themselves to these conditions: training for 12 days increased physical endurance whereas stress reduced it sharply. Highly emotional animals proved to be more sensitive to stress than unemotional. Whereas the physical endurance of the former was reduced by 2.4 times, that of the latter was reduced by only 1.6 times. A prophylactic course of lithium nicotinate had a normalizing effect on physical endurance of both groups of rats, but this effect was much stronger on highly emotional animals. By the 12th day of administration of the drug the physical endurance of highly emotional rats was increased by 326.6% (from 10.9 ± 1.7 to 35.6 ± 3.0 min; $P < 0.001$), but that of the unemotional rats by only 152.7% (from 39.1 ± 5.0 to 59.7 ± 5.1 min; $P < 0.02$).

TABLE 1. Effect of Course of Lithium Nicotinate on Escape Reaction of Rats from Stress Situation (M ± m)

Parameter	Experimental conditions	Group of animals		
		1-	2-	3-
LP of avoidance or escape reaction, sec	Control	4,4±1,3	10,1±2,5	120,0±0,0
	Experiment	3,8±1,2 (86,4%)	4,9±1,1 (48,5%)	32,5±4,3 (26,7%)*
Number of attempts at avoidance	Control	12,6±1,9	1,0±0,2	0 0
	Experiment	10,4±2,0 (82,5%)	5,4±1,7 (540,0%)*	7,4±1,7 (0)*
Defecation level (number of boluses)	Control	4,7±1,1	1,7±0,3	3,0±0,8
	Experiment	4,5±1,6 (95,7%)	2,1±0,7 (123,5%)	2,7±0,6 (90,0%)
LP of escape from stress situation, sec	Control	120,0±0,0	26,0±3,2	120,0±0,0
	Experiment	96,0±8,4 (80,0%)*	14,2±1,8 (54,6%)*	40,5±5,5 (33,7%)*

Legend. *P < 0.05 compared with control. Here and in Table 3, % of control given in parentheses.

TABLE 2. Effect of Adaptation, Stress, and a Prophylactic Course of Lithium Nicotinate on Duration (in min) of Physical Endurance in Rats (M ± m, n = 10)

Group of animals	Experimental conditions	Number of times animals lapsed on treadmill, corresponding to days of investigation				
		1-st day	3-rd day	6-th day	9-th day	12-th day
1-	1. Control	45,4±5,2	46,7±5,5	50,9±6,2	53,1±5,0	57,4±4,3
	2. Stress	27,4±1,9*	29,0±3,0*	34,5±3,5*	35,1±4,3*	39,1±5,0*
	3. Stress + lithium nicotinate	—	—	42,6±4,1	50,2±4,5†	59,7±5,1†
3-	1. Control	20,3±1,8	22,4±3,5	25,6±4,1	24,7±4,1	29,1±2,7
	2. Stress	8,3±0,9*	10,2±1,6*	13,4±1,2*	12,0±1,0*	10,9±1,7*
	3. Stress + lithium nicotinate	—	—	25,0±3,3†	29,4±2,9†	35,6±3,0†

Legend. *P_{1-2} < 0.05, †P_{2-3} < 0.05.

TABLE 3. Dynamics of Changes in Cardiovascular Function of Rats during Chronic Stress and also During Stress after Preliminary Course of Lithium Nicotinate (M± m, n = 22)

Parameter tested	Stress (7 days)		Stress + lithium nicotinate	
	control	experiment	control	experiment
BP, mm Hg	103,1±4,49	123,3±3,40 (119,6%)*	103,5±4,84	105,4±5,10 (101,8%)
VBF, sec	10,5±0,77	13,6±0,71 (129,5%)*	11,2±0,79	12,4±0,80 (110,7%)
ECG: R-R, sec	0,32±0,031	0,22±0,020 (68,7%)*	0,33±0,029	0,31±0,023 (93,9%
HR, beats/min	187,5±10,5	272,7±13,2 (145,4%)*	181,3±11,7	193,5±12,3 (106,7%)
R, mm	9,18±0,53	7,70±0,40 (83,9%)*	8,61±0,52	8,75±0,51 (101,6%)
T, mm	2,53±0,18	2,02±0,12 (79,8%)*	2,50±0,23	2,55±0,20 (102,0%)
BCG: JK, mm	9,63±0,81	7,54±0,56 (78,3%)*	9,56±0,59	9,70±0,39 (101,5%)

Legend. *P < 0.05 compared with control.

It is generally known that one of the most serious disturbances in chronic stress is a change in function of the cardiovascular system, which often leads to severe diseases. Accordingly it was deemed useful to study the effect of stress and prophylactic administration of lithium nicotinate on cardiovascular function. It will be clear from Table 3 that chronic stress led to a significant increase in BP (by 20%) and to an increase in the VBF time (by 30%). The R-R interval on the ECG was reduced, and this led to a significant increase in HR (by 45%) and a decrease in amplitude of the R (by 16%) and T (by 20%) waves. The contractile function of the myocardium was impaired, as is shown by a significant (by 22%) decrease in amplitude of the JK wave on the BCG. The combination of these changes is clear evidence that stress, as a systemic manifestation, affects the most widely different bodily functions. This view is confirmed by the changes discovered in brain energy metabolism under these conditions [8].

Prophylactic administration of lithium nicotinate virtually prevented disturbances of cardiovascular function caused by chronic stress. After administration of the drug there was no change in BP, and myocardial contractility and electrical excitability, and conduction of of the heart muscle remained the same as before, as shown by the unchanged ECG and BCG parameters.

The data given above thus indicate that lithium nicotinate has a marked stress-protective action. It improves physical endurance and working capacity and, at the same time, improves the animals' orientation in a stress situation and facilitates their escape. This is manifested most clearly in highly emotional animals, on which stress had a paralyzing action. The normalizing effect of lithium nicotinate on autonomic functions and, in particular, on function of the cardiovascular system is particularly valuable. The facts described above show conclusively once again that the stress-protective action of a course of lithium nicotinate consists of restoration of normal metabolic processes when disturbed by stress.

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