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PHARMACOLOGICAL ACTIVITY AND TOXICITY OF SOME NEUROTROPIC AGENTS UNDER CONDITIONS OF EXPERIMENTAL HYPODYNAMIA

L. T. Kirichek

Translation of "Farmakologicheskaya aktivnost' i toksichnost' nekotorykh neyrotropnykh sredstv v usloviyakh eksperimental'noy gipodinamii", Farmakologiya i Toksikologiya, Vol. 42, No. 3, May-Jun 1979, pp 221-225.

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16. Abstract

Comparison of ED_{50}, the indices of pharmacological range, LD_{50}, risk coefficients, the size of the area of toxic activity, maximal tolerated and absolute lethal doses showed in acute experiments on intact and "hypodynamic" mice that under conditions of a short term tension-producing hypodynamia in the animals, the pharmacological activity of the test neurotropic agents exhibiting a central action undergoes change where as their toxicity remains unchanged.

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PHARMACOLOGICAL ACTIVITY AND TOXICITY OF SOME NEUROTROPIC AGENTS UNDER CONDITIONS OF EXPERIMENTAL HYPODYNAMIA

L. T. Kirichek
Pharmacology Department (Head - Prof. N. S. Kharchenko),
Kharkov Medical Institute

Most of the research done in respect to the effect of hypodynamia on sensitivity to drugs and poisons has been carried out under conditions where animals were kept immobilized for a long time (10-100 days). The purpose of the present work was to study the type and degree of change in pharmacological activity and toxicity of preparations having a central neurotropic effect at the early stages of experimental hypodynamia. /221*

Research Method

The experiments were carried out on 2,600 white mice of both sexes weighing 15-30 g. Hypodynamia was achieved with special box cages that severely restricted animal activity but did not make daily care difficult. The period of hypodynamia was 24 hr at the end of which mouse stress reaction reached its maximal expression (L. T. Kirichek, 1976). The substances studied were sodium oxibutyrate, barbamyl, amizyl, reserpine, morphine, analgine, ethymizol, strychnine, eleutherococcus, ephedrine and melipramine. All preparations, with the exception of sodium oxibutyrate which was administered IP and reserpine which was administered internally, were given subcutaneously, once, in the form of aqueous solutions, reserpine in the form of a suspension in 1% starch paste, in dosages evenly distributed from ineffective to absolutely lethal. Pharmacological activity of the preparations was assessed by the pharmacological effect proper to each (Table I), observed visually or determined instrumentally and toxicity was judged by the demise of the animals. On the basis of the administration of a number of doses by the method of Litfield and Wilcoxson (1949) each preparation was assessed for ED_{50} and LD_{50}, the index of pharmacological effective range (M. L. Belen'kiy, 1963), the risk coefficient at the level of toxic dosage effect (I. P. Ulanova, 1970), the toxic activity zone and likewise resistance and tolerance on the part of the animals to the effect of the medications /224

* Numbers in the margin indicate pagination in the foreign text.

under study judged by the size of maximal tolerable and absolutely lethal doses (V. D. Rozanova et al.,1975). The control group comprised mice kept under conditions of free behavior in the vivarium.

Results

Under conditions of experimental hypodynamia the type of effect of the neurotropic agents studied did not change and their proper effects were clearly manifested both in the intact as well as in the "hypodynamic" mice although the degree of pharmacological activity of the preparations underwent a reliable change (see Table I). Increase in the pharmacological activity of preparations under hypodynamic conditions was regularly associated with an increase in the range of pharmacological effect and decrease in activity with decrease in range.

There was no substantial change in the toxicity of the neurotropic agents studied under hypodynamic conditions (Table II). Only the LD_{50} for ephedrine went down. In hypodynamia there was likewise no change in the degree of risk for the preparations studied, including ephedrine, at the level of their activity in toxic doses. Judged by the criteria proposed by I. P. Ulanova (1970) the risk level was identical in both sets of experiments. The "tolerance" of the animals was steadily maintained when the preparations were administered: the figure for absolutely lethal doses for most preparations was the same as in the control. Mouse "resistance" to the substances under study was more labile under hypodynamic conditions.

Thus, hypodynamia, which induces in animals a condition of fear and stress, changes organic sensitivity in respect to neurotropic drugs.

Conclusions

1. Short term hypodynamia has no effect on the type of action exerted by central neurotropic agents.

2. Under these conditions there is an increase in the pharmacological activity of sodium oxibutyrate, amizyl, reserpine, morphine, analgine, strychnine, eleutherococcus, ephedrine and melipramine, characterized by a drop in the ED_{50} figure and an increase in the range of pharmacological effect. In this context there is a drop in

TABLE I. PHARMACOLOGICAL ACTIVITY OF NEUROTROPIC AGENTS IN HYPODYNAMIA

Preparation	Recorded effect	ED_{50}, mg/kg			Index of pharmacological activity range		
		Control	Hypodynamic	P	Control	Hypodynamic	P
Sodium oxibutyrate	Depressant	275 (233,1÷324,5)	250 (213,7÷292,5)	>0,05	10,8 (8,64÷13,5)	10,6 (8,31÷13,5)	>0,05
same	Analgesic	1700 (1416,7÷2040,0)	550 (297,3÷1017,5)	<0,05	1,71 (1,35÷2,16)	4,83 (2,77÷8,39)	<0,05
Barbamyl	Sleep	52 (26,7÷101,4)	61 (34,8÷106,8)	<0,05	2,62 (1,54÷4,45)	2,28 (1,29÷3,82)	>0,05
Amizyl	Midriasis	8,6 (7,0÷10,7)	0,65 (0,41÷1,07)	<0,05	21,5 (16,1÷28,1)	243,1 (150,1÷393,8)	<0,05
Reserpine	Hypothermy	0,75 (0,59÷0,95)	0,7 (0,54÷0,91)	>0,05	4,3 (2,9÷6,3)	5,9 (3,3÷10,4)	>0,05
same	Dyspepsia	12 (5,0÷28,8)	5,1 (3,2÷8,2)	<0,05	0,27 (0,14÷0,53)	0,8 (0,41÷1,56)	<0,05
Morphine	Analgesic	7 (2,06÷23,8)	2,27 (0,53÷5,55)	<0,05	91,0 (11,2÷42,7)	114,5 (58,7÷223,3)	<0,05
Analgine	Lower body temp.	16,6 (8,1÷34,0)	4,35 (3,06÷6,18)	<0,05	138,6 (78,3÷245,3)	528,7 (352,5÷793,1)	<0,05
Ethymizol	Sedative	8,5 (6,6÷11,0)	16,6 (12,5÷21,1)	<0,05	18,8 (12,9÷27,5)	10,8 (8,12÷14,4)	<0,05
same	Respir. stimul	26,5 (17,1÷41,1)	112,6 (59,3÷213,9)	<0,05	6,64 (3,57÷10,2)	1,6 (0,94÷2,72)	<0,05
Strychnine	Higher reflex sensitivity	0,45 (0,23÷0,88)	0,05 (0,046÷0,055)	<0,05	2,56 (1,44÷4,56)	15 (10,9÷20,6)	<0,05
Eleutherococcus	Antihypnotic	0,15 (0,07÷0,35)	0,0000028 (0,000002÷0,000004)	<0,05	793,3 (417,5÷1507,3)	$56 \cdot 10^6$ ($40 \cdot 10^6$÷$73 \cdot 10^6$)	<0,05
Ephedrine *	same	0,042÷0,001	0,00001÷0,000002	<0,05	5 238 (2 680÷10 214)	$8\,300 \cdot 10^3$ ($4\,900 \cdot 10^3$÷$14\,027 \cdot 10^3$)	<0,05
Melipramine	same	35 (12,5÷98)	0,0024 (0,001÷0,006)	<0,05	5,2 (2,67÷10,14)	79 167 (41 667÷150 417)	<0,05

* ED_{50} of ephedrine calculated by the Kerber method.

TABLE II. ACUTE TOXICITY OF NEUROTROPIC AGENTS IN HYPODYNAMIA

Preparation	LD_{50}, mg/kg			Risk coefficient			Resistance		Tolerance		Toxic activity zone	
	C(ontrol)	H(ypodynamic)	P	C	H	Eval.	C	H	C	H	C	H
Sodium oxibutyrate	2960 (2465,5÷3433,6)	2660 (2216,7÷3192,0)	>0,05	0,0003	0,0003	Мало-опасный	2250	1750	4000	4000	1:1,8	1:2
Barbamyl	136 (121,4÷152,3)	139 (119,3÷161,9)	>0,05	0,007	0,005	То же	125	125	175	250	1:1,4	1:2
Amizyl	183 (152,5÷219,6)	158 (140,0÷178,5)	>0,05	0,004	0,005	» »	125	125	250	200	1:2	1:1,6
Reserpine	3,25 (2,39÷4,42)	4.1 (2,41÷6,97)	>0,05	0,055	0,033	» »	0,1	0,25	50	75	1:500	1:300
Morphine	153 (69,5÷336,6)	260 (157,9÷429)	>0,05	0,0003	0,002	» »	10	150	650	650	1:65	1:3
Analgine	2300 (2 000÷2 668)	2300 (1 933÷2 737)	—	0,0003	0,0003	» »	1500	1500	3000	3000	1:2	1:2
Ethymizol	160 (120,3÷212,8)	180 (170÷190,8)	>0,05	0,004	0,004	» »	100	100	250	300	1:2,5	1:3
Strychnine	1,15 (0,92×1,44)	0,79 (0,55×1,02)	>0,05	0,65	0,78	Опасный	0,75	0,25	1,5	1,5	1:2	1:6
Eleutherococcus	119 83,2÷170,2)	156 (136,8÷177,8)	>0,05	0,004	0,004	Мало-опасный	50	100	250	250	1:5	1:2,6
Ephedrine	220 (122,2÷396,0)	83 (57,2÷120,4)	<0,05	0,002	0,002	То же	25	5	700	700	1:28	1:140
Melipramine	182 (125,5÷263,9)	190 (140,7÷256,5)	>0,05	0,004	0,004	» »	100	100	400	250	1:4	1:2,5

the pharmacological activity of barbamyl and ethymizol.

3. The toxicity of the preparations studied having a central neurotropic effect showed no change in an acute experiment with mice subjected to short term hypodynamia as compared with the control.

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