MOLECULAR-BIOLOGICAL PROBLEMS OF PRODUCING DRUGS, AND THE STUDY OF THEIR ACTION MECHANISM

GENETIC DEPENDENCE OF PHARMACOLOGICAL EFFECTS OF CERTAIN PSYCHOTROPIC PREPARATIONS

M. D. Mashkovskii, S. B. Seredenin,
R. A. Al'tshuler, A. A. Vedernikov,
B. A. Badyshtov, and N. I. Andreeva

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In studies carried out during recent years, numerous data have been obtained showing that the interaction processes of the preparations with "targets" and also the transformations of the preparations in the organism proceed by means of enzymic systems, whose activity is to a great extent controlled genetically [1, 2]. The role of the genotype in the pharmacological reactions for chlordiazepoxide and chlorpromazine [3], amphetamine [4] and certain narcotic compounds [5], alcohol, etc., has been demonstrated on inbred animals. More comprehensive studies on the dependence of the action of dithilin [7], phenylzin [8], diphenine [9] on several genetically controlled factors made it possible to rationalize the clinical application of these preparations. The aim of the present work was to study the influence of the hereditary factors on the sensitivity of the animals to the new Soviet-produced preparations sydnocarb (a psychostimulant), phenazepam (tranquilizer) and pyrazidol (antidepressent).

EXPERIMENTAL

The experiments were carried out on male mice of lines C57B1/6 (B6) and BA1B/c (C) with a body weight of 20-22 g. The action of sydnocarb was evaluated from the change in the motive activity of the animals on the "Animex" apparatus (Sweden). The preparation was administered intraperitoneally in doses of 6, 12 and 24 mg/kg. After the injection, the mice were placed in a cage for 10 min, and the motive activity was determined simultaneously in 3 individuals for 10 min.

The influence of phenazepam was studied from the anticonvulsive effect by using the method of titration with corazole. The tranquilizer was introduced intraperitoneally in doses of 0.9, 3.5 and 14 mg/kg. After 30 min, a 2% corazole solution was administered to the tail vein, and the dose causing tonic convulsions was recorded.

The effect of pyrazidole was evaluated from its ability to decrease a tetrabenazine-induced blepharoptosis. The preparation was administered orally in doses of 10, 25 and 50 mg/kg. After 30 min, tetrabenazine was injected intraperitoneally in a dose of 30 mg/kg. The degree of ptosis developing 30-60 min after administration of tetrabenazine was evaluated by the method described in [10]. The statistical processing of the results was carried out by the Student method.

RESULTS AND DISCUSSION

Table 1 shows that the effects of the preparations studied differ appreciably for the B6 and C mice. Thus, in the B6 mice, the administration of sydnocarb in a dose of 6 mg/kg led to an increase in the spontaneous locomotor activity by more than 200%, while administration of the preparation in doses of 12 and 24 mg/kg was accompanied by an inconsiderable increase only in the hyperactivity level attained. In the C mice, sydnocarb in a dose of 6 mg/kg did not substantially change the initial level of spontaneous activity, while when it was administered in doses of 12 and 24 mg/kg, the motive activity of the animals distinctly increased. However, the action of sydnocarb in these doses in both absolute and relative terms was lower than in B6 mice.

TABLE 1. Differences in Action of Sydnocarb, Phenazepam and Pyrazidole in B6 and C Mice

Line of mice	Dose of sydno-carb, mg/kg	Effect of pyrazidole (tetrabenazine antagonism; decrease in value of blepharoptosis, % with respect to initial value)	Dose of phena-zepam, mg/kg	Effect of phenazepam (corazole antagonism; increase in convulsive dose of corazole, % with respect to initial dose)	Dose of pyrazidol, mg/kg	Effect of sydnocarb (hyperactivity; increase in locomotion factor, % with respect to initial factor)
B6	0	(395±60 impulses)	0	(93,3±3,7 mg/kg	0	(2,56±0,19 points
B6	6	221±20*	0,9	+205±11*	10	—9±8
B6	12	+236±22*	3,5	+435±24*	25	—57±7*
B6	24	+291±94*	14	+547±17*	50	—70±19
C	0	(537±77 impulses)	0	(99,9±4,7 mg/kg	0	(1,69±0,19 points
C	6	+22±23	0,9	+121±20	10	—18±14
C	12	+88±26	3,5	+255±14	25	—38±10
C	24	+50±18	14	+366±18	50	—80±8

The protective effect of phenazepam (antagonism to the convulsive action of corazole) was observed well also in the B6 mice, although the sensitivity of mice in the two lines towards corazole was practically the same.

During evaluation of the ability of corazole to eliminate the tetrabenazine-induced blepharoptosis, we should take into account the fact that the effect in B6 mice was $1^{1}/_{2}$ times more intense than in the C mice. However, also under these conditions, judging from the degree of decrease in the initial value of the blepharoptosis, pyrazidole in a dose of 25 mg/kg acted more strongly in the B6 mice (P < 0.05), while in doses of 10 and 50 mg/kg, its effect for both lines of animals did not statistically differ (P < 0.05).

We can assume that the increased sensitivity of the B6 mice towards the psychotropic compounds studied is due to the fact that in this line of mice the rate of xenobiotic metabolism is lower than in mice C. At the same time, it is also probable that the formation of unequal responses in the animals of these lines is due to the fact that the B6 and C mice differ appreciably with respect to the endogenic noradrenaline metabolism [11], the activity of monoaminoxidase and catechol-O-methyltransferase [12], and also with respect to other neurochemical parameters [13]. However, the action of sydnocarb, pyrazidole and tetrabenazine on the central nervous system is mainly caused by their influence on the monoaminergic systems of the brain [14-16]. As far as phenazepam is concerned, it is known that its tranquilizing action depends on the initial state of the animal, in particular, on the nature of the stress reaction. It has already been shown [17] that in the B6 mice which actively react to stress, phenazepam administered in a dose of 0.05 mg/kg causes a decrease in the behavioral indices in the "open field" test, while in the C mice, in which during a stress situation, the fear reaction predominates, the preparation in the same dose caused a behavioral activation. The role of the central mechanisms in the tranquilizing effect of the benzodiazepine derivatives is indicated in the studies of [18] where it was found that rats specially selected according to emotional reactivity to stress contain different numbers of diazepam receptors, and that there are more in animals with low fearfulness.

Thus, from our experiments we can conclude that hereditary factors play an important role in the pharmacological effect of the psychotropic preparations studied. Clarification of the specific reasons for the genetically dependent types of reaction to sydnocarb, phenazepam and pyrazidole demands further neurochemical analysis of experimental phenomena and work on the pharmacokinetics and metabolism of these preparations in animals of different genotypes.

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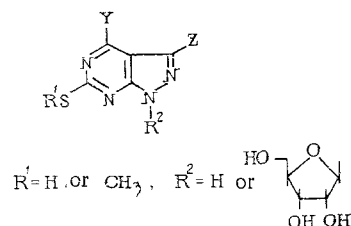
CYTOTOXIC AND ANTIVIRAL ACTIVITY OF 4- AND 3,4-SUBSTITUTED
6-METHYLTHIOPYRAZOLO[3,4-d]PYRIMIDINES AND THEIR RIBOSIDES

Ya. V. Dobrynin, T. A. Bektemirov,
T. P. Ivanova, É. V. Chekunova,
O. G. Andzhaparidze, I. A. Korbukh,
Yu. B. Bulychev, N. G. Yakunina,
and M. N. Preobrazhenskaya

Pyrazolopyrimidine analogs of purines and their nucleosides are known to include natural and synthetic compounds with valuable biological activity: the antitumor and antiviral antibiotic formycin, 3-(β-D-ribofuranosyl)-4-aminopyrazolo[4,3-d]pyrimidine [1]; allopurinol, 4-hydroxypyrazolo[3,4-d]pyrimidine, a preparation used in hyperuricemia [2]; 1-(β-D-ribofuranosyl)-4-aminopyrazolo[3,4-d]pyrimidine and several other 4- and 3,4-substituted pyrazolo[3,4-d]pyrimidine nucleosides, which have cytotoxic and antitumor activity [3].

4- and 3,4-Substituted 6-mercapto- or 6-methylthiopyrazolo[3,4-d]pyrimidines and their ribosides with the general formula

$R^1 = H$ or CH_3, $R^2 = H$ or

have been synthesized in the Laboratory of Chemical Synthesis of the Oncological Scientific Center of the Academy of Medical Sciences of the USSR [4].

Our intention in the work described here was to examine the cytotoxic and antiviral activity of the synthetic compounds toward herpes simplex virus HSV-1 and smallpox vaccinia virus and to study structure—activity correlation in this series of compounds. Robins has shown correlation of structure and biological activity for 4-substituted pyrazolo[3,4-d]pyrimidines [5], while Panzica et al. have done this for 4- and 3,4-substituted pyrazolo[3,4-d]pyrimidine ribosides. The antiviral effect of pyrazolo[3,4-d]pyrimidines and their nucleosides