7. K. M. Reznikov, P. P. Provotorova, and V. I. Sidel'nikova, Farmakol. Toksikol., No. 5, 52 (1982).
8. A. I. Turilova, T. N. Azvolinskaya, and S. A. Kryzhanovskii, Byull. Éksp. Biol. Med., No. 7, 49 (1980).
9. G. G. Chichkanov, A. K. Bogolepov, and D. D. Matsievskii, Kardiologiya, No. 10, 85 (1981).
10. F. B. Duarte, T. Iwasaki, T. Endo, et al., Am. J. Cardiol., 47, 443 (1981).
11. R. D. Reinolds, W. E. Burmeister, R. J. Gorczynski, et al., Cardiovasc. Res., 15, 411 (1981).
12. A. J. Roberts, P. R. Cirpiano, D. R. Alonso, et al., Circulation, 57, 35 (1978).

BEHAVIORAL AND RADIORECEPTOR ANALYSIS OF VILOXAZINE STEREOISOMERS

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A study of drugs with antidepressant action showed that isomers of norzimelidine (an active metabolite of zimelidine) differ considerably (by 7-70 times) in their effects [1]. The same property has been found for isomers of amitriptyline and some of its derivatives [1]. Viloxazine (Vivilan, Vicilan) is an atypical antidepressant, marketed as a racemic mixture, and is a weak inhibitor of monoamine reuptake [7, 11]. Experimentally it has a tranquilizing action. Clinically viloxazine has been shown to have an activating effect in patients with depressive illness.

The aim of this investigation was to compare the effectiveness of viloxazine and its R(+) and S(−) stereoisomers on some behavioral models suitable for the study of antidepressants, and also to analyze the affinity of viloxazine racemate and its stereoisomers for various receptors on brain synaptic membranes.

EXPERIMENTAL METHOD

Tetrahybrid male CBWA mice from the Rappolovo Nursery, Academy of Medical Sciences of the USSR, were used. To assess behavior, known models for detection of antidepressant activity were used: the swimming test as in [12] and the "behavior despair" test as described in [3]. The drugs were injected intraperitoneally in the acute experiments and given perorally (in a volume of 0.3 ml) in the chronic experiments. Each dose was tested on at least six animals. The results were subjected to statistical analysis. Unpurified synaptic membranes of whole brain from CBWA mice and P_2 fractions obtained after shock were used for radioligand analysis. Binding of [^{3}H]imipramine was carried out by the method in [2], of [^{3}H]-dehydroalprenolol as in [14], [^{3}H]-mianserin as in [15], [^{3}H]-spiperone as in [6], [^{3}H]5-HT as in [5], [^{3}H]-WB 4101 as in [15], and [^{3}H]-flunitrazepam as in [4]. Molar aqueous solutions of viloxazine racemate (synthesized at the Pharmaceutical Chemical Research Institute of Bulgaria) and viloxazine R(+) and S(−), synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR, were used. The (+) and (−) isomers of viloxazine were separated by a modified method using O,O^1-dibenzole-(+)-tartaric acid, when the (+)-isomer was isolated through the acid tartrate, and the (−)-isomer through the neutral tartrate [10]. Characteristics of the (+)-isomer were: m.p. 164-165°C, $(\alpha)_D^{25}$ +7.9° (c, 1; water), optical purity 74%; (−)-isomer: m.p. 163-164°C, $(\alpha)_D^{25}$ −10.8° (c, 1; water) optical purity 96%.

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TABLE 1. Effect of Antidepressants on Total Immobilization Time

Substance	Mean duration of immobilization	% of control	Substance	Mean duration of immobilization	% of control
Control	178±12	—	Control	216±18	—
Viloxazine racemate, mg/kg			S(−)-isomer of viloxazine, mg/kg		
90	215±17	121	50	89±12*	41
60	140±9	79	25	71±9*	33
30	92±8*	52	10	60±8*	28
15	87±12*	49	5	181±14	84
10	118±14*	66	1	198±16	92
5	186±16	104			
Control	178±12	—	Control	216±17	—
Imipramine, mg/kg			R(+)-isomer of viloxazine, mg/kg		
5	182±20	102	150	280±19	129
15	136±14*	76	100	250±18	116
30	43±16*	24	50	94±12*	44
60	108±12*	61	25	155±10	72
			10	202±9	94

Legend. Asterisk indicates statistically significant difference from control at $P < 0.05$ level.

TABLE 2. Effect of Viloxazine and Its R(+)- S(−)-Isomers on Receptor Binding of Some ^{3}H-Ligands

Receptor	Compound		
	Racemate	R(+)	S(−)
β-Adrenoreceptor ([^{3}H]dihydroalprenolol, 2 nM)	13 000	15 000	11 000
Imipramine ([^{3}H]imipramine, 8 nM)	15 000	15 000	15 000
α_1-Adrenoreceptor ([^{3}H]-WB 4101, 9 nM)	20 000	20 000	20 000
α_2-Adrenoreceptor ([^{3}H]mianserin, 8 nM)	20 000	20 000	20 000
Serotonin ([^{3}H]-5-HT, 8 nM)	>24 000	>24 000	>24 000
Dopamine ([^{3}H]spiperone, 0.5 nm, in presence of 10^{-5} M 5-HT)	3 850	3 850	3 850
Benzodiazepine ([^{3}H]flunitrazepam, 6 nM)	>30 000	>30 000	>30 000
	>200 000	>200 000	>200 000

Legend. Table gives mean values of K_i (in nM) based on results of three or four independent measurements:

$$K_I = \frac{IC_{50}}{1 + \frac{L}{K_D}},$$

where IC_{50} is the concentration of the compound inhibiting binding of the ^{3}H-ligand by 50%, L the concentration of the ^{3}H-ligand (in nM), and K_D the dissociation constant of the ligand (in nM).

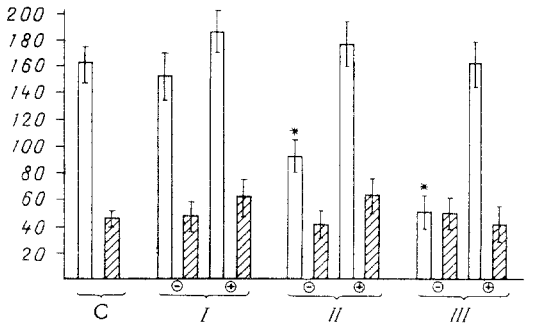

Fig. 1. Effect of chronic administration of viloxazine on avoidance reaction of mice in a shuttle box. Unshaded columns — preshock, shaded — normal. C) Control group; I) after viloxazine treatment for 1 day; II) for 7 days, and III) for 15 days. Ordinate, latency of avoidance of electrical stimulation (in sec). +) Injection of R(+)-isomer of viloxazine; —) injection of S(—)-isomer of viloxazine.

EXPERIMENTAL RESULTS

Effective doses of the test compounds, tested by the method in [12] by a single injection, are given in Table 1. The most effective dose of viloxazine racemate was 15-30 mg/kg, of its S(—)-isomer 10 mg/kg, and of the R(+)-isomer 50 mg/kg. Injection of the (+)-isomer, incidentally, significantly reduced the immobilization time only in one dose, and the effect was 60% weaker than that of the S(—)-isomer. Imipramine was tested as the control. The results agree fully with those published previously [12].

Data showing the effectiveness of the drugs during chronic administration (the "behavior despair" test) are shown in Fig. 1. After peroral administration of a single dose of 10 mg/kg no significant reduction of the avoidance time was observed in a group of preliminarily stressed animals. After 7 days of administration of the S(—)-isomer the avoidance time was significantly reduced, whereas the R(+)-isomer was inactive. After a 15-day course of injections of S(—)-isomer the behavioral parameters reached control levels (the group of unstressed animals), i.e. this viloxazine isomer had a marked "antidepressant" action according to this test. In the case of the R(+)-isomer no specific activity was exhibited. Whereas acute administration of the stereoisomers revealed a fivefold difference in pharmacological activity, the R(+)-isomer was completely inactive when given by a chronic schedule. These results agree with those of an investigation [8] in which the ineffectiveness of the R(+)-isomer was demonstrated in bulbectomized rats in the avoidance learning test. Determination of the action of the stereoisomers on noradrenalin and serotonin release showed no difference.

The results of radioligand analysis are given in Table 2. The affinity of viloxazine and its stereoisomers for imipramine and mianserin receptors, β- and α-adrenoreceptors, and dopamine and benzodiazepine receptors was extremely low and was exhibited in concentrations of no physiological significance. It can thus be concluded that viloxazine does not exhibit specific binding for these receptors. No significant stereospecificity likewise could be found for any of the receptors studied.

Behavioral testing, especially during chronic administration, thus revealed differences in activity of viloxazine stereoisomers, confirming data in the literature [8]. However, the stereospecificity of the action of viloxazine as revealed by behavioral tests is not connected with its action on any of the receptors studied. It can be postulated either that the target for the pharmacological action of viloxazine is certain other receptors (histamine, acetylcholine), or, like norzimelidine [9] and imipramine [13], it has specific binding sites of its own.

LITERATURE CITED

1. M. D. Mashkovskii, N. I. Andreeva, and A. I. Polezhaeva, Pharmacology of Antidepressants [in Russian], Moscow (1983).
2. V. V. Rozhanets, D. Yu. Rusakov, and A. V. Val'dman, Byull. Éksp. Biol. Med., No. 10, 42 (1982).
3. H. Anissman, I. Irwing, and L. S. Sklar, Psychopharmacology, 64, 163 (1979).

4. H. B. Bosmann, D. P. Penney, K. R. Caze, et al., FEBS Lett., 87, 199 (1978).
5. C. S. Cascio and J. Kellar, Neuropharmacology, 21, 1219 (1982).
6. S. Clements-Jewery and P. A. Robson, Neuropharmacology, 20, 1295 (1981).
7. D. T. Greenwood, J. Int. Med. Res., 3, 18 (1975).
8. D. T. Greenwood, J. D. Kemp, and D. N. Middlemiss, J. Pharm. Pharmacol., 34, 38 (1982).
9. H. Hall, S. Ross, S. O. Ogren, et al., Eur. J. Pharmacol., 80, 281 (1982).
10. R. Howe, T. Legh, B. S. Rao, et al., J. Med. Chem., 19, 1074 (1976).
11. R. M. Pinder, R. N. Brogden, T. M. Speight, et al., Drugs, 13, 401 (1977).
12. R. D. Porsolt, A. Bertin, and M. Jalfre, Nature, 266, 730 (1977).
13. R. Raisman, M. S. Briley, and S. Z. Langer, Eur. J. Pharmacol., 61, 373 (1980).
14. V. H. Sethy and D. W. Harris, Eur. J. Pharmacol., 75, 53 (1981).
15. B. Spyra and K. M. Pirke, Brain Res., 245, 179 (1982).

EFFECT OF CORDARONE ON CARDIOMYOCYTE ULTRASTRUCTURE IN EXPERIMENTAL MYOCARDIAL INFARCTION

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KEY WORDS: cordarone; amiodarone; ultrastructure; myocardium; infarct.

Cordarone (amiodarone) is widely used in the clinical treatment of ischemic heart disease (IHD). The mechanism of its antianginal action has been a frequent subject of research [2, 3, 5, 10, 14]. After the discovery that the drug had antiarrhythmic properties [8] indications for its use in the treatment of IHD widened considerably. However, despite many biochemical and electrophysiological investigations, the fine structural changes in the myocardium during the action of cordarone remain virtually unstudied.

The aim of this investigation was to study the dynamics of ultrastructural changes in muscle cells of the peri-infarct zone of the heart under the influence of cordarone at different times after acute experimental coronary occlusion.

EXPERIMENTAL METHOD

Experiments were carried out on 30 cats weighing 3-4 kg and divided into two groups: group 1 (control) — animals with experimental myocardial infarction (EMI) caused by ligation of the anterior descending coronary artery at the junction between its middle and lower thirds; group 2 consisted of cats with EMI receiving cordarone in a dose of 10 mg/kg intramuscularly, twice a day. The ECG of animals of both groups was recorded in standard lead II on the 3rd, 7th, and 15th days, after which the heart was removed under pentobarbital anesthesia (40 mg/kg, intravenously) for electron-microscopic investigation. Pieces of left ventricular myocardium were taken from the peri-infarct zone, fixed in 1% OsO_4 solution, dehydrated, and embedded in Araldite. The number of glycogen granules was determined morphometrically in electron micrographs obtained on the JEM-100B microscope.

EXPERIMENTAL RESULTS

Electron-microscopic investigation of the peri-infarct zone of myocardium in animals treated with cordarone revealed some differences in cardiomyocyte ultrastructure observed on the 3rd, 7th, and 15th days after ligation of the coronary artery.

Considerable degenerative changes were found in the structure of the cardiomyocytes on the 3rd day after acute coronary occlusion in the control animals. The muscle cells were edematous, the myofibrils separated, the myofilaments partially fragmented and, in some cases, in a state of over-contraction. The mitochondria were swollen and the cristae were vacuolated

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