combination of strophanthin G with calcium that is optimal for manifestation of a cardiotonic effect, possibly as a result of complex formation in the solution and stabilization of the glycoside molecule in the cis position.

The weaker effect of a combination of strophanthin and calcium compared with that of strophanthin alone, added to the ordinary Tyrode solution, may be due to greater intracellular accumulation of calcium, interference with its removal at binding sites, and disturbance of electromechanical coupling processes [10].

The change in contractility of the heart muscles during perfusion with calcium-free solution takes place as the result of a reduction (because of washing out) of the quantity of calcium bound with the sarcolemma, whereas the concentration of nonmetabolic calcium remains constant [9]. Addition of strophanthin to calcium-free Tyrode solution probably increases the quantity of calcium capable of participating in the act of contraction. A combination of strophanthin with low concentrations of calcium is an optimal combination of these substances (possibly as a result of complex formation and conformational changes to the cis form of the glycoside), facilitating interaction between the cardiac steroid and sarcolemmal Ca^{++}-binding sites, and facilitating realization of the inotropic effect. Administration of strophanthin together with calcium preparations with established ratios between the components can be recommended in clinical practice.

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PHARMACOETHOLOGIC ANALYSIS OF THE ACTION OF SOME β-CARBOLINES

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Compounds of the β-carboline group are physiologically active substances with a wide spectrum of pharmacologic action: They simulate effects of serotonin [6], counteract effects of benzodiazepines (BDZ) [7], participate in the formation of dependence on ethanol [1, 3], modify behavior [4], and can induce tremor [3, 6]. The ability of β-carbolines to regulate intraspecific behavior and, in particular, aggression, defense, and sociability, has not been studied previously.

The aim of this investigation was to study pharmacoethologic spectra of the action of β-carbolines and their influence on intraspecific aggression, sociability, and individual behavior.

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EXPERIMENTAL METHOD

Experiments were carried out on 28 male CC57W mice weighing 25-28 g, kept in isolation in individual cages measuring 10 × 12 × 16 cm for 6-9 weeks. For the experiments, 28 of the most aggressive animals among the 50 isolated were chosen. Behavior of the mice was observed by means of a video system — a video camera and television receiver. An "Élektronika L1-08" videotape recorder was used. Behavior of aggressive mice during interaction with a standard partner from the group was analyzed by an ethologic method [2, 5] by means of the "Étograf" apparatus [5] together with an "Élektronika D3-28" microcomputer. Digital information on frequencies and sequences of behavioral acts and postures of the animals was memorized in the magnetic store of the computer, analyzed statistically, and printed out automatically. Frequencies and statistical probabilities of the appearance of each behavioral act and posture and also probabilities of diad transitions from one act into another were calculated. Motivational categories and their behavioral elements are listed in Table 1.

The following β-carbolines, synthesized at the Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, by Professor V. A. Zagorevskii and I. N. Novikova, were administered in doses of 1, 5, 10, and 15 mg/kg 30 min before the experiment: β-carboline-3-carboxyethyl ester (BC-3-CEE), 1-methyl-6-methoxy-dihydro-β-carboline (MMO-DHBC), 1-methyl-6-hydroxy-tetrahydro-β-carboline (MH-THBC), and 1-methyl-6-methoxy-tetrahydro-β-carboline (MMO-THBC). Diazepam, an agonist of BDZ receptors, was given in a dose of 2.5 mg/kg. All substances were injected intraperitoneally. The significance of results was estimated by Wilcoxon's nonparametric TΔ test.

EXPERIMENTAL RESULTS

The experiments showed (Table 1) that BC-3-CEE (antagonist of BDZ receptors) in a dose of 1 mg/kg increased aggression and manifestation of threats, enhanced ambivalence, and depressed intraspecific sociability. BC-3-CEE intensified grooming of the body and reduced the vertical components of individual behavior. In a dose of 10 mg/kg the compound depressed manifestations of threatening, inhibited sociability, and strengthened ambivalence. BC-3-CEE counteracted the activation of sociability by diazepam and restored threatening manifestations and ambivalent behavior inhibited by diazepam. Combined administration of BC-3-CEE and diazepam raised the level of static postures, but vertical activity of standing up on the hind limbs (SHL) was sharply reduced.

MMO-DHBC (a melatonin derivative), in a dose of 1 mg/kg, reduced the manifestations of threatening, inhibited sociability, and activated locomotion. In a dose of 5-10 mg/kg it inhibited aggression, but activated threatening, pursuit of the partner, and all forms of intraspecific sociability. On the approach of their partner the isolated animals started and repelled their partner. In response to provocation (pushing by the partner) the isolated animals reacted by attacking with biting, i.e., "response aggression" to a high-threshold stimulus was not suppressed by MMO-DHBC. Combined administration of MMO-DHBC in doses of 10 and 15 mg/kg and diazepam prevented activation of sociability by diazepam in aggressive mice. MMO-DHBC in doses of 10 and 15 mg/kg induced tremor — the antiaggressive action of the compound did not appear to be selective.

MH-THBC (a cyclic analog of serotonin), in a dose of 1 mg/kg, increased threatening and ambivalent behavior. In a dose of 10 mg/kg it did not affect aggression and sociability, it enhanced manifestations of threatening and ambivalence, and depressed locomotion. MMO-THBC (a cyclic analog of mexamine), in a dose of 1 mg/kg, enhanced the static elements of behavior but did not affect aggression, threatening manifestations, or sociability. In a dose of 10 mg/kg it significantly depressed aggression and sociability and enhanced static elements of individual behavior.

Blocking BDZ-receptors by BC-3-CEE in a dose of 1 mg/kg thus increased aggression and depressed sociability in isolated mice. An increase in the dose led only to further suppression of sociability without any significant effect on aggressive behavior. BDZ receptors evidently are directly involved in the integration of intraspecific sociability. This is also confirmed by experiments with BDZ agonists: diazepam enhances sociability and depresses aggression, and other BDZ agonists, namely phenazepam and medazepam, have a similar effect [2, 9]. We know that BC-3-CEE binds selectively with BDZ receptors and antagonizes diazepam in many tests [7]. The results of the present investigation show that this antagonism to the effect of diazepam extends also to intraspecific behavior.

TABLE 1. Ethologic Spectra of Action of Some β-Carbolines

Category and elements of behavior	Control		BC-3-CEE 1 mg/kg		BC-3-CEE 10 mg/kg		MMO-DHBC 1 mg/kg		MMO-DHBC 10 mg/kg		Control		MH-THBC 1 mg/kg		MH-THBC 10 mg/kg		MMO-THBC 1 mg/kg		MMO-THBC 10 mg/kg		Control		Diazepam (2.5 mg/kg)		Diazepam (2.5 mg/kg) + BC-3-CEE (10.0 mg/kg)		Diazepam (2.5 mg/kg) + MMO-DHBC (10.0 mg/kg)	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Intraspecific behavior:																												
Aggression:																												
Attacks	19,92	0,086	46,07	0,199*	17,07	0,073	33,85	0,146	0,35	0,001*	19,28	0,083	25,14	0,108	26,50	0,114	16,41	0,070	10,08	0,043*	21,10	0,073	0,60	0,002*	18,9	0,081**	8,16	0,035**
Threatening	19,28	0,083	33,35	0,144*	9,57	0,041*	17,35	0,074*	4,85	0,020*	28,50	0,123	45,28	0,195*	66,57	0,287*	30,75	0,132	12,6	0,054*	33,00	0,142	1,6	0,006*	47,0	0,203**	1,66	0,007
Pursuit	0,78	0,003	0,42	0,001	0,21	0,000	0,78	0,003	0,00	0,000*	0,77	0,003	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,78	0,003	0,0	0,0*	0,0	0,0	0,0	0,0.
Ambivalence:																												
Vibration of tail	12,42	0,053	29,14	0,125*	19,21	0,082*	23,57	0,101	1,85	0,008	24,14	0,104	26,42	0,114	36,57	0,157*	16,08	0,069	8,33	0,035	19,7	0,085	0,0	0,0*	16,4	0,070**	0,75	0,003*
Circulation	1,92	0,008	1,35	0,005	0,92	0,004	0,85	0,003	0,0	0,0	0,0	0,0	0,14	0,0	0,0	0,0	0,83	0,003	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Sociability:																												
Sniffing at nose	4,14	0,017	0,00	0,000*	2,71	0,011*	1,3	0,005*	0,0	0,0*	4,21	0,018	0,78	0,003*	0,64	0,002*	0,83	0,003*	0,91	0,003*	1,3	0,005	20,8	0,089*	14,3	0,061	1,16	0,005*
Sniffing at body	14,42	0,062	2,92	0,012*	3,07	0,013*	6,57	0,028	0,78	0,033*	15,28	0,066	8,07	0,034	8,85	0,038	10,75	0,046	4,25	0,018*	9,2	0,039	40,3	0,174*	3,1	0,013**	5,66	0,024
Sexual sniffing	30,50	0,131	16,92	0,073*	10,14	0,043*	6,85	0,029*	0,0	0,0*	15,92	0,068	13,71	0,059	7,85	0,033	14,83	0,064	6,91	0,029	9,1	0,039	18,5	0,079*	0,2	0,000**	0,83	0,003**
Individual behavior:																												
Sitting	29,85	0,128	13,85	0,059	60,64	0,261*	1,92	0,008*	162,5	0,532*	18,14	0,078	20,0	0,086	16,85	0,072	59,41	0,256*	86,25	0,372*	49,8	0,215	66,9	0,288	85,5	0,369**	81,08	0,350**
Locomotion	20,71	0,089	24,35	0,105	27,57	0,119	51,07	0,220*	57,07	0,246	24,50	0,105	28,28	0,122	13,92	0,060*	29,75	0,128	42,75	0,184*	28,9	0,124	55,3	0,238*	42,0	0,181**	38,08	0,164**
SHL	64,64	0,279	34,78	0,150*	36,00	0,155	70,07	0,302*	6,0	0,025*	53,14	0,229	36,64	0,158*	26,28	0,113*	20,41	0,088	25,08	0,108*	54,8	0,236	26,3	0,113	1,3	0,005**	39,33	0,169
Cleaning, grooming	9,42	0,040	27,07	0,116*	43,71	0,188*	13,21	0,057	2,71	0,011*	26,92	0,116	25,9	0,112	25,64	0,110	26,91	0,116	18,16	0,078	9,4	0,040	0,0	0,0*	0,0	0,0	15,2	0,065**

Legend. Mean frequencies (a) and statistical probabilities (b) of appearance of elements of behavior are shown. *) Significant increase or decrease in frequency of act in experiment with the substance compared with control at $P < 0.05$ level by Wilcoxon's TΔ test; **) significance of differences between administration of diazepam (2.5 mg/kg) alone and together with β-carbolines ($P < 0.05$).

The action of BC-3-CEE, moreover, is similar in direction and ethologic spectra to the action of subconvulsant doses of GABA antagonists [9], bicuculline for example. Comparative ethologic analysis suggests that the GABA-BDZ receptor complex plays a role in the realization of complex forms of intraspecific behavior (aggression, for example).

The dihydro-β-carbolines (MMO-DHBC), which closely resemble melatonin, depress sociability but, at the same time, inhibit aggression. Melatonin itself is known to inhibit aggressive behavior in isolated mice [3], and this is explained by the indirect endocrine effects of this substance, and its action is apparently not selective.

It must be emphasized that compounds of the β-carboline group differ in their pharmacoethologic spectra of action; β-carbolines which can bind with BDZ receptors (BC-3-CEE), moreover, increase aggression within a narrow range of subconvulsant doses, whereas those which do not possess this property (MMO-THBC) have no effect or reduce it nonspecifically.

Many effects of β-carbolines can be explained to some degree by their dysphoria-inducing action [1, 6]. A varied degree of dysphoria can determine increased ambivalence (Table 1), reduce motivation for goal-directed intraspecific contacts, and a lowered tendency toward active aggression in aggressive animals. The mechanisms of this dysphoria may be complex and may include antagonism to the action of opiates, and endocrine effects [1, 6]. Against the background of the action of β-carbolines aggression was easily provoked by tactile stimulation, but sociability was not provoked. This may be evidence that the effector mechanisms linked with "response aggression," are not damaged by β-carbolines (MMO-DHBC and MMO-THBC). Data [3, 4] showing blocking of competitive forms of activity in animals by β-carbolines while aggression on the electrode floor, provoked by electric shocks, is preserved, also can be interpreted from this standpoint. Aggression connected with artificial provocation (tactile, painful electrical stimulation), incidentally, is a variant of defensive behavior, which has its own integrative mechanism unconnected with inhibitory control of β-carbolines (MMO-DHBC) and involving DBZ receptors of a different kind.

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