# TRANQUILIZING PROPERTIES OF SOME β-CARBOLINES AND THEIR POSSIBLE ROLE IN THE CONTROL OF ALCOHOL CONSUMPTION

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Data in the literature indicate that β-carbolines — condensation products of serotonin and some of its metabolites with acetaldehyde — may be formed as the result of alcohol administration [5]. Among compounds of the β-carboline group there are some which can bind highly specifically with benzodiazepine receptors [5], through which the anxiolytic, muscle-relaxing, and anticonvulsive action of the benzodiazepine tranquilizers is probably mediated [5]. Considering that ethanol also possesses marked tranquilizing activity, and that this is one of the factors responsible for addiction to alcohol [4], it was decided to study the possible anxiolytic, anticonvulsive, and muscle-relaxing properties of some derivatives of β-carbolines found in animals and man *in vivo* [5]: 1-methyl-6-oxy-tetrahydro-β-carboline (1 Me-6-O-THBC); 1-methyl-6-methoxy-tetrahydro-β-carboline (1-Me-6-MeO-THBC); 1-methyl-6-methoxy-dihydro-β-carboline (1-Me-6-MeO-DBC); β-carboline-3-carboxyethyl ester (BC-3-CEE).

## EXPERIMENTAL METHOD

To detect the tranquilizing properties of the substances a method which is a variant of a conflict situation was used: the appearance of motivated fighting in a pair of rats for a safe place (platform on an electric floor) [2]. If both rats of a pair ran to the safe platform in the course of 1 min and remained together on the platform for 10 sec this was assessed as evidence of the tranquilizing effect of the substances tested. The criterion of manifestation of a sedative effect was absence of fighting between rats on the electric floor for 1 min. Electric shocks 1 sec in duration were applied every 3 sec to the electric floor: the voltage of the current was 80-90 V and its frequency 50 Hz. Expriments were carried out on 440 noninbred male albino rats weighing 200-230 g. The muscle-relaxing effect was studied by the "revolving rod" method [3] and the anticonvulsant action of the compounds was studied by determining their action on the convulsant effects of metrazol in a dose of 100 mg/kg. The acute toxicity of the compounds and also their general depressant properties were studied by the methods of "potentiation" of the action of thiopental sodium in a subthreshold dose (12.5 mg/kg) and prolongation of the anesthetic effect of thiopental sodium (30 mg/kg). Experiments to study the muscle-relaxing effect, anticonvulsant action, acute toxicity, and general depressant properties were carried out on 1300 noninbred male albino mice weighing 18-20 g. The substances for testing were injected intraperitoneally 50 min before the beginning of the experiments. The results were read in alternative form and processed by the method of Litchfield and Wilcoxon, with calculation of 50% effective doses ($ED_{50}$) [1].

## EXPERIMENTAL RESULTS

The experiments showed (Table 1) that compounds 1-Me-6-MeO-DBC, 1-Me-6-MeO-THBC, and BC-3-CEE had a tranquilizing action for they depressed motivated aggression (fighting for the safe place) in doses 5-10 times less than in the case of unmotivated aggression (fights without any safe place). Compound 1-Me-6-MeO-DBC had the strongest tranquilizing activity (the doses in which it had a similar action were 20 times less than the dose of diazepam which gave a tranquilizing effect). It was found that the tranquilizing properties of the compounds tested are not associated with anticonvulsant activity or a muscle-relaxing effect such as are characteristic of drugs of the benzodiazepine series.

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TABLE 1. Comparative Pharmacological Activity of β-Carbolines

| Compound | Tranquilizing effect ($ED_{50}$), mg/kg | Sedative effect ($ED_{50}$), mg/kg | Muscle-relaxing action ($ED_{50}$), mg/kg | Anticonvulsant properties ($ED_{50}$), mg/kg | Inhibition of diazepam binding by 50%, mM | Acute toxicity ($LD_{50}$), mg/kg | Potentiation of action of thiopental sodium in subthreshold dose (12.5 mg/kg) | Prolongation of anesthetic effect of thiopental sodium in dose of 30 mg/kg |
|---|---|---|---|---|---|---|---|---|
| 1-Me-6-O-THBC | 0 (0,1—65,0) | 25,0 (23,2—28,1) | 0 (0,1—65,0) | 0 (0,1—65,0) | — | 650 (630—680) | 0 (0,01—65,0) | 0 (0,01—65,0) |
| 1-Me-6-MeO-THBC | 0,47 (0,42—0,51) | 2,5 (2,0—3,7) | 0 (0,1—25,0) | 0 (0,1—25,0) | 0,21 | 240 (220—250) | 0 (0,05—25,0) | 0 (0,05—25,0) |
| 1-Me-6-MeO DBC | 0,015 (0,005—0,015) | 0,38 (0,15—0,46) | 0 (0,001—5,0) | 0 (0,001—5,0) | 0,15 | 50 (45—58) | 0 (0,001—5,0) | 20 (10—30) |
| BC-3-CEE | 0,22 (0,17—0,25) | 0 (0,1—13,0) | 0 (0,01—15,0) | 0 (0,01—15,0) | 0,000007 | 125 (120—135) | 0 (0,05—13,0) | 0,01 (0,005—0,02) |
| Diazepam | 0,32 (0,28—0,36) | 1,54 (0,97—2,43) | 2,75 (1,37—5,5) | 0,51 (0,39—0,67) | 0,000004 | 240 (192—300) | 0,66 (0,53—0,8) | — |

Legend. 0) no effect; range of doses of compounds tested is shown in parentheses

Compounds 1-Me-6-MeO-DBC and 1-Me-6-MeO-THBC, which we found to have a tranquilizing action, have no marked ability to bind with benzodiazepine receptors [5]. Hence it follows that the tranquilizing properties of these compounds are mediated by different mechanisms. The existence of independent β-carboline receptors can be postulated, and their role is evidently in the endogenous control of the emotional state, in conjunction with benzodiazepine receptors. The tranquilizing action found in some β-carbolines can modulate alcohol motivation considerably and in particular it can weaken it [4], especially in cases when a craving for ethanol is due to emotional-stress and depressive causes. In other words, the tranquilizing action of ethanol, as one of the factors determining addiction to it may be mediated in particular by β-carbolines.

The pharmacological effect of the compounds tested was shown to appear after 15 min and to continue for 30 min. Meanwhile the compounds did not potentiate the action of thiopental sodium in a subthreshold dose, i.e., they had no general depressant action, evidence of the high specificity of their manifested psychotropic effects.

LITERATURE CITED


1. M. L. Belen'kii, Elements of Quantitative Evaluation of a Pharmacological Effect [in Russian], Leningrad (1963), pp. 86-102.
2. Yu. V. Burov and R. M. Salimov, Byull. Eksp. Biol. Med., No. 5, 64 (1975).
3. K. S. Raevskii, Pharmacology of Neuroleptics [in Russian], Moscow (1978), pp. 83-86 and 96-98.
4. Yu. V. Burov, Vest. Akad. Med. Nauk SSSR, No. 5, 72 (1982).
5. M. M. Airaksinen and I. Kari, Med. Biol., 65, 21 (1981).