EFFECT OF CARBIDINE ON THE GONADS OF RATS DURING CHRONIC ALCOHOL POISONING

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Experiments on rats showed that carbidine,* when injected intramuscularly for 2 weeks in a dose effective for the experimental treatment of alcohol dependence (4 mg/kg), has no gonadotropic action. The drug does not potentiate the adverse after-effects of chronic ethanol poisoning on ovogenesis or spermatogenesis and does not delay the course of repair processes in the gonads after cessation of the ethanol intake. However, carbidine is given during continued consumption of ethanol, further development of the regressive changes in the generative cells of the gonads is observed.

KEY WORDS: carbidine; gonads; ethanol.

The original Soviet psychotropic drug carbidine * has been used with success for the treatment of chronic alcoholism [1,3]. The adverse effect of ethanol on gonad function is generally recognized [4-6,10]. Considering that many psychopharmacological agents can also inhibit the function of the gonads [8,9], and that there is no information in the literature on the action of carbidine on these organs, it was decided to study the effect of this compound on the morphology and functional state of the gonads during chronic administration of ethanol.

EXPERIMENTAL METHOD

Experiments were carried out on 60 noninbred rats (six groups each containing five females and five males) weighing initially 180-220 g. Before the beginning of the experiments all the females had a normal estrous cycle, as shown by daily examination of vaginal smears for 2 weeks. Four groups of rats then received ethanol (a 5% solution for the 1st month and a 10% solution for the 2nd month) for 2 months as the sole source of fluid, whereas the animals of the other two groups received water as usual. The rats were weighed once every 2 weeks and their general condition was inspected. After the end of 2 months, one group of intact rats served as the control (group 1) and the other group received carbidine to determine the effect of the compound on the gonads of intact animals (group 2). The compound was injected intramuscularly once a day for 2 weeks in a dose of 4 mg/kg, which is effective for the experimental treatment of alcohol dependence [2]. Rats receiving ethanol for 2 months were divided as follows: To study the degree of severity and reversibility of the gonadotropic effect of ethanol the animals of one group were killed immediately after ethanol was discontinued (group 3), and those of another group, 2 weeks after the end of alcohol administration (group 4). The remaining animals were given carbidine in accordance with the same scheme as the animals of group 2. Some of the animals continued to receive a 10% solution of ethanol as the sole source of fluid (group 6), whereas the other group received water instead of ethanol (group 5). In the female rats of all groups 2 weeks before the end of the experiments vaginal smears were again studied. At the end of the experiments the animals were decapitated, the ovaries and testes were weighed and their state was studied by morphological methods such as are generally used to assess the gonadotropic action of chemical compounds [7].

EXPERIMENTAL RESULTS

The rats consuming ethanol were found to gain in weight more than the intact animals. The difference was statistically significant as early as 4 weeks after the beginning of the experiment; after 2 months the mean gain in weight of the experimental animals was about twice that of the intact animals (164 and 86 g respectively

*3,6-Dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline dihydrochloride.

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TABLE 1. Number of Generative Elements in Gonads of Rats after Administration of Ethanol and Carbidine (M ± m; n = 5)

Index	Character of treatment					
	control	carbidine	ethanol	withdrawal of ethanol	withdrawal of ethanol + carbidine	ethanol + carbidine
Weight of ovaries, mg/100 g body weight	23,4±1,6	24,0±1,4	13,9±1,4*	15,0±1,0*	11,3±1,1*	9,1±1,1*, †
Primordial follicles	760±42,04	752±25,75	428±20,38*	414±23,61*	421±20,38*	352±21,45* †
Stratified follicles	131±12,61	107±6,43	78±7,51*	101±5,36 †	98±4,29	63±5,36
Ripe follicles	22,5±4,2	250±3,21	12,0±1,7*	10,0±2,14*	14,0±2,14	9,0±1,07
Atretic follicles	705±29,43	837±36,47*	1104±74,05*	780±48,27 †	982±52,56*	802±52,35 †
Corpora lutea	8,7±1,4	14,0±1,5*	5,8±0,86*	5,0±0,86	6,2±1,07	4,4±0,64*
Total number of generative elements	1627±84,08	1723±40,59	1628±82,64	1309±56,42* †	1501±47,58	1230±60,73* †
Weight of testes, mg/100 g body weight	514±8,2	486±37,4	429±15,6*	447±22,8*	410±14,8	440±30,6
Index of spermatogenesis	3,76±0,03	3,71±0,04	3,45±0,05*	3,60±0,03*	3,51±0,03	3,34±0,08
Normal spermatogonia	22,5±1,82	20,0±1,39	9,2±0,98*	15,3±1,31* †	11,2±1,20	8,5±1,36
Desquamation of germinal epithelium, %	0,2±0,21	0,2±0,21	1,8±0,42*	1,5±0,42*	1,8±0,42	2.8±0,42
Tubules with 12th stage of meiosis	2,0±0,42	2,2±0,21	8,8±0,42*	7,0±0,62*	6,8±0,85	7,8±0,64

*P < 0.05 compared with control (group 1).

†P < 0.05 compared with group 3.

for males, 42 and 23 g for females). No significant differences were found in the behavior and state of the experimental and intact animals.

The results of the pathological study of the ovaries and testes are given in Table 1. The histological picture and quantitative indices of the morphology and function of the gonads in the rats of group 1 (control) corresponded to those generally accepted as pertaining to the normal structure of these organs in the rat [7]. The study of the gonads of the rats of group 2 showed that carbidine, in a dose of 4 mg/kg by intramuscular injection for 2 weeks, had no negative gonadotropic action. The compound had no significant effect on the morphology or function of the ovaries, in which, compared with the control, only slight delay in the reduction of the corpora lutea and a small increase in the number of atretic follicles, evidently due to their slower organization, were observed. In three rats, during the first 3 days of administration of carbidine, a disturbance of the sequence of the individual phases of the estrous cycle was noted. In the males of group 2 the indices of spermatogenesis were virtually indistinguishable from those for intact animals of group 1.

Investigation of the gonads of the animals of group 3 showed that ethanol, after 2 months of consumption, had a clearly marked negative effect on ovogenesis and spermatogenesis. In the female rats there was a marked decrease in weight of the ovaries, a decrease in the number of primordial follicles in the ovaries, pointing to their large-scale atresia, and also delay of their development and ripening, as shown by the decrease in the number of stratified (ripening) and ripe (Graafian) follicles. The estrous cycle was disturbed in all the animals, with changes in its duration and in the sequence of the individual phases. In males, evidence of the negative gonadotropic action of ethanol was a decrease in the weight of the testes and in the index of spermatogenesis, and also a decrease in the number of normal spermatogonia in the testis and an increase in the number of tubules with desquamated epithelium and the 12th stage of meiosis.

Changes in the morphological and functional state of the gonads after consumption of ethanol were reversible. For instance, in females of group 4 studied 2 weeks after the withholding of ethanol, a marked increase was observed in the number of stratified (ripening) follicles, the number and structure of which were indistinguishable from those in the control animals of group 1. In the males, all the indices of spermatogenesis studied also were substantially improved, although they had not yet reached the control levels by this time.

Comparison of the indices of ovogenesis and spermatogenesis in the animals of groups 4 and 5 showed that carbidine, when given after the ending of ethanol consumption, not only did not potentiate the adverse consequences of the chronic gonadotropic action of ethanol, but likewise did not delay the natural course of repair. Only in females, besides an increase in the number of ripening follicles, the number of atretic follicles continued to remain high, evidently because of some delay in their organization. Just as in the rats of group 4, in the females of group 5 moderate disturbances of the estrous cycle persisted, and were especially marked during the first days of administration of the compound.

Meanwhile, in the animals of group 6 which received carbidine while ethanol consumption continued, by contrast the further development of regressive changes in the generative elements of the gonads was observed and was particularly marked in the females. In the ovaries of these animals, side by side with a sharp decrease in the number of primordial follicles, signs of delay of their development and ripening also were found. On the whole, the more rapid massive atresia of the follicles followed by their organization led to the development of marked atrophy of these glands, as shown both by a marked decrease in their weight and by a decrease in the total number of structural and functional elements contained in them.

These investigations thus showed that carbidine, if administered for a long time in a dose effective for the experimental treatment of alcohol dependence, has no negative gonadotropic action. The compound does not potentiate the adverse effects of chronic administration of ethanol on ovogenesis and spermatogenesis and does not delay the course of repair in the gonads after ethanol consumption has ceased. However, if carbidine is given while ethanol consumption still continues, regressive changes in the generative elements of the gonads continue.

These results must be taken into consideration when the use of carbidine for the treatment of alcoholism is contemplated.

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