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On the Involvement of the Central Cholinergic System in Memory Deficits Induced by Long Term Ethanol Consumption in Mice

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BERACOCHEA, D , T P DURKIN AND R JAFFARD *On the involvement of the central cholinergic system in memory deficits induced by long term ethanol consumption in mice* PHARMACOL BIOCHEM BEHAV **24**(3) 519–524, 1986 — Male mice of the BALB/c strain were given a solution of 12% v/v ethanol as their only source of fluid for 7 months Memory performance was tested after ethanol was omitted from the diet for 3 to 9 weeks, and was compared with performance of control animals (no ethanol) which had been pair-fed or had received tap water The spontaneous alternation task that was used consisted of two forced trials (acquisition) followed, at varying intervals ranging from 30 sec to 6 hr, by a free test trial (retention) Experimental subjects exhibited an accelerated rate of decay of spontaneous alternation, reaching chance level at 6 hours All animals were then tested at this 6-hour interval following injections of either physostigmine or neostigmine that were given before both acquisition and retention (0 05 mg/kg IP) Results showed that physostigmine, but not neostigmine, dramatically improved performance of alcohol-treated subjects Parallel neurochemical analysis showed that chronic ethanol treatment induced a slight (12%) but significant decrease in hippocampal sodium-dependent high affinity choline uptake Though these findings suggest that the observed memory deficits (i e , an accelerated rate of forgetting) might be related to a cholinergic dysfunction, alternative explanations are also proposed

Ethanol Spontaneous alternation Memory Interference Hippocampus Acetylcholine Physostigmine Choline uptake

CHRONIC ethanol consumption in man has been found to result in neuronal damage and associated learning and recent memory impairments [10,31] Though traditionally the pathology has been attributed partially to malnutrition, especially thiamine deficiency [34], the specificity of ethanol in inducing neuroanatomical and functional deficits has been demonstrated in a series of experiments performed in laboratory animals [26] We recently reported that chronic ethanol consumption by mice induced spatial memory deficits which were dependent on the duration of ethanol consumption and which persisted several weeks after ethanol was withdrawn from the diet [6,7] More precisely, a behavioral analysis based on spontaneous alternation (S A) in a T-maze showed an accelerated decay of S A rates as the interval which elapsed between forced trials used as acquisition and a free test trial used as a retention test increased

The present experiment was designed to test whether this observed behavioral impairment might result from an effect of alcohol on the hippocampal cholinergic system Indeed, there is evidence to indicate that cholinergic mechanisms and the hippocampus play a role in memory function [5, 20, 32] and in spontaneous alternation behavior [14] though impairment of S A behavior by systemically administered cholinolytics cannot solely be interpreted as the consequence of a memory deficit (see [30]) Our previous and presently reported results suggest such a memory deficit since experimental subjects were not impaired at short intertrial intervals but were impaired at longer ones relative to controls Furthermore, changes in central cholinergic activity have been observed following both acute and chronic ethanol exposure in both animals [15, 26, 33] and man [2,27]

Accordingly, the purpose of the present experiment was twofold to test whether the impairment of S A observed in alcohol-treated mice might be reversed by physostigmine (a cholinesterase inhibitor), and to study possible changes in hippocampal cholinergic activity by measuring the kinetics of the sodium-dependent high affinity choline uptake (SDHACU) in hippocampal synaptosomes from ethanol-treated mice

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TABLE 1

MEAN DAILY CALORIC INTAKE DURING THE 28 WEEKS OF DIETS ADMINISTRATION AND MEAN BODY WEIGHT (±SEM) AT THE START AND AT THE END OF TREATMENTS

	Body Weights (g)		Caloric Intake/kg				
Groups	1st day	last day	Dry food	Dextri	Sucrose	Ethanol	Total
Water (N=20)	24 4 ± 0 3	33 7 ± 0 9	407 4	—	—	—	407 4
Pair-fed (N=20)	24 6 ± 0 4	35 6 ± 0 8	297 6	157 3	—	—	454 9
Ethanol (N=40)	24 4 ± 0 3	34 4 ± 0 9	297 6	—	61 4	95 9	454 9

METHOD

Subjects

The subjects were male mice of the BALB/c strain, approximately 6 weeks old at the time of receipt They were housed in cages of 15 to 20 animals matched for weight and placed in a colony room (ambient temperature 22±1°C, automatic light cycle 8 00 a m to 8 00 p m) Free access to food and water was provided for three weeks before the beginning of ethanol administration

Ethanol Administration

Animals were randomly assigned to one of three groups Subjects of the experimental group were given as their only source of fluid an increasing progression of ethanol solutions as follows 5% (v/v) solution for the first week, 10% for the second week and 12% for the remaining time (7 months) The solutions were mixed from 95% ethanol and supplemented with sucrose (30 g/l) They were available in two 250 ml bottles in each cage Dry food was freely available throughout the experiment Every two days, the subjects were weighed and the quantity of food and ethanol-sucrose solutions consumed was measured Mice in the first control group were pair-fed They received an isocaloric solution of dextri-maltose and dry food that was equivalent to the quantity consumed by the experimental group Animals assigned to the second control group had ad lib access to dry food and tap water After 7 months of treatment, tap water was progressively substituted for ethanol-sucrose (or dextri-maltose) solution by steps of 5% a week Behavioral testing began 3 weeks later

Behavioral Testing

Most of the experiments were run blind All testing was conducted in a T-maze constructed of wood The stem and arms were 35 cm long, 10 cm wide and 25 cm high The starting box (10×12 cm) was separated from the stem by a vertical sliding door Horizontal sliding doors were placed at the entrance of each arm Spontaneous alternation was tested by using two procedures a sequential test procedure, and a discrete trial procedure In the sequential test procedure, mice were given six successive trials as follows To begin a trial, a subject was placed in the start box and after 30 sec, the door to the stem was opened When the animal entered one of the arms, the door to that arm was closed The chosen arm and the time which elapsed between opening the door and closing that of the arm (choice latency) were noted After a 30 sec confinement in the chosen arm, the animal was removed and placed in the starting box for a second trial, etc In the discrete trial procedure, S A was used as a learning paradigm and consisted of two forced trials (aquisition) followed by a free test trial with varying acquisition-test intervals (ATI) During acquisition subjects were forced to enter one of the arms twice, the other being blocked by the sliding door On the test for retention, the animals had free access to both arms

Experimental Design for Behavioral Analysis

All subjects were accustomed to daily handling for 5 days They were then given two free exploration sessions of 5 min in the apparatus on each of three days before being tested for S A with the sequential test procedure (six successive free trials separated by a 30 sec interval) The experiment was then divided into two phases

Phase one Subjects in each group were randomly divided into two subgroups and tested under the discrete trials procedure In the first subgroup (ethanol N=20, pair-fed N=10 and water N=10) each animal was tested for the 30 sec and 1 hr acquisition-test (ATI) intervals, in the second subgroup (the same number of subjects in each group) these intervals were 5 min and 6 hr Each subject was tested four times at each ATI and was forced to enter the left hand arm twice and the right hand arm of the maze twice Under these conditions, it may be assumed that turning biases were eliminated so that the chance rate of alternation was 50% [13,21] Subjects were tested in a random order regardless of the group and ATI Successive tests were separated by two to three days

Phase two The second phase of the experiment was carried out with 31 animals taken randomly from the population used in the 1st phase experimental (N=15), pair-fed (N=8) and water (N=8) Each subject was tested 12 times in the sequential test procedure with an ATI of 6 hours according to the procedure described above Successive tests were separated by two to three days and each animal was successively assigned to one of the two following experimental conditions Testing was conducted under the influence of either physostigmine (P) or neostigmine (N) (i.e , N,P,N,P, or inversely) until each animal was tested 6 times under each of these two drug-conditions Thus, on a given test, the animal received an IP injection of physostigmine sulfate (0 05 mg/kg) 20 minutes before the two forced acquisition trials and 20 minutes before the test trial On the following test, physostigmine was replaced by neostigmine methylsul-

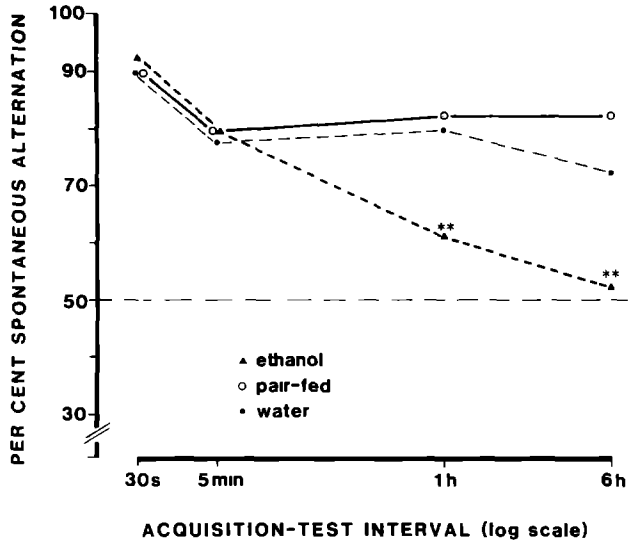

FIG 1 Mean percent spontaneous alternation following two forced acquisition trials as a function of the acquisition-test interval (30 sec to 6 hr) in the experimental and control groups **Significantly different from the two control groups $p<0.01$

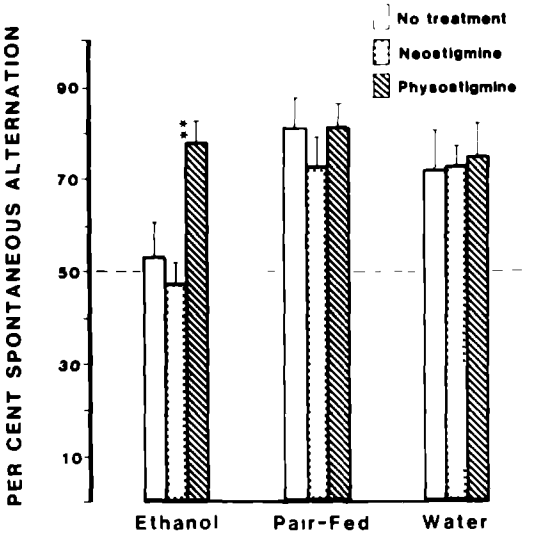

FIG 2 Mean percent spontaneous alternation (±SEM) following two forced acquisition trials followed by a test free trial 6 hours later in the experimental and control groups tested under the influence of either physostigmine, neostigmine or without any treatment Drugs (0 05 mg/kg IP) were given 20 minutes before both the acquisition and test trials **Significantly different from the two other conditions $p<0.01$

fate (0 05 mg/kg) given in exactly the same way as for physostigmine

Neurochemical Analysis

Neurochemical analysis was run blind and was carried out with subjects treated in exactly the same way as the mice used for behavioral analysis, animals were sacrificed in place of being submitted to the 2nd phase of behavioral tests (i e , between 7 and 9 weeks after ethanol was omitted from the diet) Fourteen animals (ethanol N=6, pair-fed N=4, water N=4) were used In addition, six mice still under ethanol treatment for 7 months were sacrificed in order to evaluate a possible recovery after ethanol withdrawal

Sodium-dependent high affinity choline uptake (SDHACU) kinetics were measured in aliquots of resuspended crude synaptosomal (P2) pellets of hippocampi from three different groups of animals The procedure, based on that of Atweh *et al* [4] consists of measuring the difference in the amount of methyl-^{3}H-choline (0 25 μM) taken up by the synaptosomal aliquots over a 4 min period in parallel incubations in sodium-free and normal sodium Krebs Ringer (see [15])

RESULTS

Calorie Intake and Body Weights

During the 28 weeks of ethanol administration, the mean daily calorie intake as ethanol was 95 9 cal/kg As shown in Table 1, the mean weight of dry food consumed daily by the ethanol and pair-fed groups was less than that consumed by the water group No between-group differences were observed for body weights either at the end of the period of diet administration or at the time of testing

Behavior

There were no significant between-group differences in the rates of S A in the sequential test procedure (six successive trials separated by a 30 sec interval) 78 5%, 81 0% and 77 0% respectively, for the ethanol, pair-fed and water groups Moreover, there were no differences in choice latencies

Figure 1 summarizes the results obtained with the discrete trial procedure at varying acquisition-test intervals (ATI) When compared to the pair-fed and water groups, ethanol-treated mice exhibited an accelerated decay of S A rates as the ATI increased Thus, while there were no differences for short delays, significant differences were observed at 1 hr, $F(2,37)=4.48$, $p<0.01$, and 6 hr, $F(2,37)=5.43$, $p<0.01$ Finally, at both the 1 hr and 6 hr ATI, experimental subjects had significantly lower rates of S A than control mice, $t(38)=3.02$ and 3 18, $p<0.01$ in both cases Choice latencies of the groups did not differ significantly at any of the ATIs used

Effects of Physostigmine

The results are summarized in Fig 2 Performances recorded under neostigmine were similar to those obtained in the first phase of the experiment (without treatment) and confirmed the disruptive effect of ethanol at the 6-hr interval (controls vs ethanol $t(29)=4.23$, $p<0.001$) As can be seen in this figure, physostigmine dramatically improved performance in alcohol-treated subjects (from 47 8±4 5% to 74 5±4 3, $t(14)=4.12$, $p<0.01$) No effect was observed on choice latencies Physostigmine had no effect on the performance of control groups While one might think that the lack of an effect of physostigmine on the performance of control animals could be due to a ceiling effect, it should be pointed out that performance of long ITIs was poorer than

TABLE 2

KINETICS OF SODIUM-DEPENDENT HIGH AFFINITY CHOLINE UPTAKE IN HIPPOCAMPAL SYNAPTOSOMAL FRACTIONS IN ETHANOL-TREATED MICE AND IN THE WATER AND PAIR-FED CONTROL GROUPS

Groups	Water (N=4)	Pair-Fed (N=4)	Ethanol† (N=6)	Ethanol‡ (N=6)
SDHACU p mol/4mn/ mg prot	17 39 ± 0 35	17 21 ± 0 20	15 25 ± 0 27*	14 04 ± 0 33*

*Significantly different from the two control groups, $p=0\ 005$
†Seven to 9 weeks after ethanol was omitted from the diet
‡Still under ethanol treatment

that at short ITIs, and yet physostigmine did not affect performance at the longer ITIs

Neurochemical Analysis

Results of the neurochemical analysis are summarized in Table 2 The kinetics of SDHACU in hippocampal synatosomal fractions were significantly lower in alcohol-treated mice 7 to 9 weeks after withdrawal than in either the water or pair-fed groups (−12%, $p=0\ 005$ in both cases) The same phenomenon was observed in subjects still under the influence of ethanol which exhibited a slight but non-significantly lower SDHACU than the ethanol-withdrawn group, $t(10)=1\ 99$, n s

DISCUSSION

Our main findings are as follows (1) the first phase of the experiment shows that the ethanol treatment procedure leads to memory deficits which are not dependent on caloric intake, (2) physostigmine, but not neostigmine, given 20 min before both acquisition and test trials reverses the behavioral deficit exhibited by the experimental group, (3) our biochemical experiment reveals a disruption of the hippocampal cholinergic activity, measured by Sodium Dependent High Affinity Choline Uptake (SDHACU)

In the present experiments with mice, chronic ethanol treatment resulted in behavioral deficits even after ethanol was omitted from the diet for several weeks Our behavioral analysis shows that experimental subjects exhibited an accelerated rate of decay of to-be-remembered information The fact that no deficits were observed in either the sequential test procedure (6 trials at a 30 sec interval) or at short intervals (30 sec and 5 min) of the discrete trial procedure suggests that both the encoding of information and the mechanisms which reduce the tendency to repeat a recent experience functioned normally [28] Consequently, the decline in spontaneous alternation as a function of time may be ascribed to a progressive unavailability of the memory trace relative to events occurring on acquisition trials [6,7], such a conclusion is congruent with observations made by Walker and Hunter [35] in alcohol-treated rats However experiments with amnesic Korsakoff patients do not demonstrate such an accelerated rate of forgetting [17,18] except for memory tasks employing commonly used words [17] In the present experiment, subjects were repetitively tested in the same maze, a situation in which the information to be remembered was highly familiar As a consequence, one can suppose that, as for frequent words, this is a condition which would provide substantial potential for proactive interference

The finding that physostigmine (but not neostigmine) reversed the behavioral deficit suggests that the behavioral deficit could be due to a dysfunction of the central cholinergic system The cholinergic system has been implicated in amnesia and memory processes in other research [5, 20, 32] However, one might be cautious about the interpretation of such findings According to the multipathway hypothesis of memory formation physostigmine may only be compensating for a functional deficit related to brain damage induced by the long-term ethanol treatment, but unrelated to the presently observed but apparently limited cholinergic dysfunction More precisely, we have found that the same ethanol treatment induced neuronal loss in the median mammillary nucleus in mice [23], and experimental lesions of this nucleus result in a similar accelerated rate of decay in delayed spontaneous alternation [8] It is possible that the activation of a cholinergic channel by physostigmine compensates for a deficit which is not related to a cholinergic dysfunction However, our results are congruent with some clinical observations showing that physostigmine treatment improves memory performance in amnesic patients [22] For this reason, we studied in the present experiment the effects of the long-term ethanol treatment on SDHACU activity in the hippocampus

It was found that chronic ethanol treatment resulted in a slight (12%) but significant decrease in the kinetics of SDHACU It may be noted that this apparently limited reduction in high affinity choline uptake may result from one of three possible causes (1) a straight-forward decrease of 12% in acetylcholine turnover rate without any accompanying reduction in neuronal density, (2) a decrease in cholinergic neuronal density of 12% without alteration of acetylcholine turnover rate or (3) a reduction of greater than 12% in neuronal density and affecting a large proportion of cholinergic terminals but with a concomitant acceleration in the acetylcholine turnover rate of the surviving neurones, via a homeostatic compensation mechanism, in an attempt to maintain cholinergic tone This latter phenomenon, which has been observed in central dopaminergic neurones undergoing degeneration (e g , in Parkinsons' disease or following 6-hydroxydopamine lesions) [1, 9, 16], highlights the necessity of using dynamic techniques (e g , SDHACU) which give an index of the state

of activity of cholinergic neurones *in vivo* This is especially pertinent since simple measures of enzymatic activity (e g , choline acetyltransferase, ChAT) in case (3) would have indicated an apparent hypofunction of cholinergic transmission of greater magnitude than might actually exist

Our results are congruent with clinical observations of Korsakoff amnesic patients, who exhibited a decrease in brain choline acetyltransferase activity [2,27] and a decrease in muscarinic cholinergic receptors associated with neuronal loss in the nucleus basalis of Meynert [3] However, as suggested by one reviewer of this paper, the functional significance of such a limited (but significant) reduction of the SDHACU activity is not clear This diminution could be compensated for by homeostatic mechanisms in an attempt to limit this cholinergic dysfunction, such as an increased sensitivity of muscarinic cholinergic receptors which has been observed after chronic ethanol treatment [33] This highlights the necessity of studying complete cholinergic synapse after long-term ethanol consumption in order to clarify the effects of such a treatment on the cholinergic transmission

While the present pharmacological and biochemical experiments support the cholinergic hypothesis of memory deficits induced by a chronic ethanol consumption, such an hypothesis must be strengthened by further experiments as suggested in the text

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