The Effect of Acute Ethanol and Gabapentin Administration on Spatial Learning and Memory

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Abstract

Introduction: Patients with epilepsy can have impaired cognitive abilities. Many factors contribute to this impairment, including the adverse effects of antiepileptic drugs like Gabapentin (GBP). Apart from anti-epileptic action, Gabapentin is used to relieve ethanol withdrawal syndrome. Because both GBP and ethanol act on GABAergic system, the purpose of this study was to evaluate their effect and interaction on spatial learning and memory.

Material and Methods: Male Sprague-Dawley rats were trained in the Morris water maze for 5 consecutive days. On the sixth day, a probe test was performed to assess the retention phase or spatial rats’ memory ability. Ethanol (1.5 g/kg i.p.) and GBP (30 mg/kg i.p.) was administered each day 30 and 40 minutes before testing respectively.

Results: Acute ethanol administration selectively impaired spatial memory (p<0.05), yet it failed to impair the acquisition phase (learning). Contradictorily GBP selectively impaired learning on second and forth days.

Conclusion: These findings demonstrate that GBP and acute ethanol impair different phases of learning probably by modifying different neuronal pathways in cognitive areas of the brain.

1. Introduction

Gabapentin (GBP) [1-(aminomethyl) cyclohexaneacetic acid] is a structural analogue of gamma-aminobutyric acid (GABA) proved to be useful for partial seizures treatments in patients with epilepsy (Holmes, 1997).

These patients have cognitive disabilities, and anti-epileptic drug (AED) therapy may contribute to this impairment. This side effect may be attributed to the modulation of GABA neurotransmission in cognitive areas of the brain such as the hippocampus (Taylor, 1998).

Apart from anticonvulsant efficacy, gabapentin is widely used to relieve neuropathic pain (Baillie, JK; Power, I; 2006) and to reduce the ethanol withdrawal syndrome (Bonnet U, 1999). Therefore it’s worth determining the effects of gabapentin on cognitive function in non-epileptic subjects.

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Ethanol potentiates GABA-mediated inhibition in the hippocampus (Givens and Brees, 1997). It has been shown that, acute ethanol administration decreases the quality of learning as well as memory tasks (Mattews, 1999). However, it has been reported that moderate ethanol doses (1.0 and 2.0 g/kg) do not impair the spatial learning performance examined in Morris’ water maze task on rats (Acheson et al., 2001).

The opposing results might be because of the ethanol’s disturbing effects merely on some types of spatial tasks not all of them. Furthermore there is a possibility that ethanol would only impair memory (retention or probe test) not learning (acquisition phase).

To understand this inconsistency better and also to investigate the similarities between ethanol and GBP’s effect on spatial memory, the following study was conducted.

2. Methods

2.1. Subjects

Thirty-two male Sprague-Dawley rats were housed under controlled environmental conditions with free access to food and water and a 12-h light – dark cycle. The test was done on the following groups: GBP, Saline, (control) Acute ethanol, Acute ethanol and GBP.

2.2. Drugs

GBP was kindly provided by Iran- Daru Company (Tehran, Iran). GBP (30 mg/kg) was freshly dissolved in saline and administered intraperitoneally 40 min before the tests. Ethanol (1.5 g/kg 10% w/v in saline) was administered intraperitoneally 30 min before testing.

2.3. Apparatus

The water maze was a circular pool, 150 cm deep and 40 cm high, divided into 4 quadrants. The water temperature (21±2°C) and the external cues in the room were unchanged throughout the behavioral testing. A platform, 10 cm deep, was immersed 2 cm under the water surface at the center of a quadrant. The swim path was recorded by a computerized video-tracking system allowing automatic calculation of swimming distance (cm), swim velocity (cm/s) and time spent in each quadrant. Behavioral testing was conducted during the light phase of the cycle.

2.4. Spatial Training and Testing

For acquisition, rats were given four trials on each day for 5 consecutive days. Start positions, were randomly selected for each rat. The following positions were achieved a clockwise movement. The rat was given 60 sec to find the escape platform and 10 seconds to rest on the platform after each trial. If the animal failed to reach the platform in 60 sec, it was placed on the platform manually. On the sixth day, 24 h after the last day’s training, the rats underwent a 60 sec probe trial to test their retention levels, during which the platform was removed and the rat’s searching behavior was recorded.

3. Results

3.1. Spatial Learning

In the acquisition phase of Morris water maze, animals learned the spatial location of the platform during training based on the latency. Global analysis of the latency time to find platform in Gabapentin group indicated a significant difference between groups [ANOVA, F (3,120) F=5.855 p<0.001]. Tukey’s post hoc test showed significant difference, p<0.01 on day 2 and p<0.001 on days 3 and 4. However, acute ethanol administration (1.5 g/kg) did not produce performance deficits on spatial learning (Fig.1).
3.2. Spatial Memory

Results of the probe-trial test are presented in Fig. 2. The time spent in the training quadrant was significantly decreased by ethanol use and ethanol gabapentin groups compared with the control group (p<0.05) but this comparison was not significant for gabapentin group.

4. Discussion

Acute ethanol administration and GBP produced ataxia. The ataxic effects of this study might alter the swimming abilities in the animals, thereby confounding the latency data reported. Hence the impaired spatial memory performance might be due to a nonspecific motor impairment. Although, the ataxic effect was identical between ethanol and GBP groups, the impairment effect was not similar. Acute ethanol administration inhibited spatial learning, while GBP impaired only spatial memory. Therefore, we conclude that the impairment in spatial performance is probably not due to nonspecific motor impairments.

It has been reported that acute ethanol administration, impairs performance on spatial learning tasks that use elevated radial arm mazes (Matthews at al.,1995) but does not impair spatial performance on Morris water maze task (Acheson et al.,2001). However, this study’s data clearly demonstrate that acute ethanol administration make difficulties in performance in adult rats.

One potential explanation for the conflicting results may be that acute ethanol administration does not impair spatial learning, whereas it does impair spatial memory. Our data confirms this hypothesis. However, it has been reported that 2.0 g/kg of ethanol also impairs spatial learning in Morris water maze (Shimizu et al., 1998).

It is possible that ethanol disturbs the learning process according to the dose. More researches are needed to clarify this issue.

It is still unknown which neurotransmitter system(s) are involved in acute-ethanol induced impairment of spatial performance. Acute ethanol administration potentiates GABA A receptor function (Mehta et al., 1998) and Inhibits NMDA receptors (Lovinger et al 1989). Theses two effects of ethanol have been shown to mediate inhibition of hippocampal long term potentiation (Schummers 2001). Long term potentiation of synaptic transmission in the hippocampus is the leading experimental model for the synaptic changes that may underlie learning and memory (Malenka et al 1999).

The exact mechanism of gabapentin is actually unknown, but the enhancement of GABA neurotransmission could be a factor. Gabapentin does not interact with GABA receptors, nor does it inhibit GABA uptake or prevent the degradation of GABA (Taylor et al 1998). However, in vivo, gabapentin increases GABA accumulation in rat brain (LOscher et al 1991).

Figure 2. The effect of acute ethanol and gabapentin on Retention phase. The time spent in the training quadrant was significantly decreased in the acute ethanol and ethanol / GBP groups but was not significantly changed for GBP group.
This study revealed impairment in spatial memory by acute moderate dose of ethanol and impairment in spatial learning by gabapentin. Different doses of ethanol, effect different neurotransmission systems that may underlie memory deficits. Blockade of the NMDA receptors in the hippocampus could be the best candidate, though the cholinergic system may also be involved. It has been suggested that the cholinergic system may be involved in memory impairment after chronic ethanol consumption in mice (Matthews et al 2000). Further research should address the involvement of cholinergic system in acute ethanol administration. The increase of GABA in cognitive areas of the brain may lead to learning impairment caused by Gabapentin.

In conclusion, we have demonstrated that, moderate dose of acute ethanol and gabapentin may cause memory and learning malfunctions.

References


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