REVIEW

Effects of Barbiturates on GABA System: Comparison to Alcohol and Benzodiazepines

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Abstract. Central nervous system depressants, e.g. barbiturates, alcohol and benzodiazepines, have a wide spectrum of activity in humans and animals. Evidence accumulated suggests that some of the pharmacological actions exerted by these agents may be mediated through the GABA system by mimicking GABAergic transmission. This proceeding briefly summarizes the evidence presented in our previous review (Yu S and Ho Ik: Alcohol 7: 261, 1990) as to how the GABA system plays a part in the barbiturate actions and the development of tolerance to and physical dependence on barbiturates. The comparisons of the effects of alcohol, barbiturates and benzodiazepines at different steps of GABA synapse are also discussed. Furthermore, the results which have been reported in the literature are inconsistent. This may be due to differences in (a) animal models used; (b) brain regions used; (c) protocols (dose, duration, form and route of administration, etc.) used in treating animals and/or (d) techniques (pharmacological, biochemical, physiological, etc.) used. (Keio J Med 40 (4): 183–186, December 1991)

Key words: CNS depressants, GABAergic transmission, tolerance

Introduction

Evidence reviewed suggests that some of the pharmacological actions exerted by barbiturates, alcohol and benzodiazepines may be mediated through the GABA system by mimicking GABAergic transmission. However, the mechanisms of the actions of these agents on GABA system remain to be elucidated. Benzodiazepines have been demonstrated to have the receptors which are parts of the GABA_A receptor (GABA-benzodiazepine receptor chloride ionophore complex). Although definitive barbiturate binding site has not yet been identified, evidence available strongly suggests that the barbiturate binding sites and convulsant binding sites are separate but allosterically affect each other. As far as ethanol is concerned, it is likely that multiple neurotransmitter systems are affected. Therefore, it is still unclear how alcohol, barbiturates, and benzodiazepines are functionally associated with the GABA system.

Effects of Barbiturates on the GABA System

Based on the in vitro studies, it is demonstrated that barbiturates alter the transport systems in GABA neurons. This may be due to their hydrophobic character, which modifies the properties of the synaptosomal lipids and/or the hydrophobic segments of proteins. Barbiturates may act on a specific site of GABA_A receptor complex, which is close to the ionophore of the complex, in order to facilitate chloride ion flux, and to modulate the GABA, benzodiazepine, and tert-butylbicyclophosphorothionate (TBPS)/picrotoxin recognition sites allosterically.

Contradictory data exist concerning the acute effects of barbiturates on brain GABA levels in rodents. Glutamate decarboxylase (GAD) activities were increased in rats and mice after acute treatment with pentobarbital. Whereas, the activities of GABA transaminase (GABA-T) were not altered. It has been reported that K^+-stimulated, Ca^{2+}-dependent GABA release was increased in the striatum of the mouse, but it was not altered in the cerebellum. As for the GABA_A receptor, barbiturates were found to increase the GABA binding site in rodents except for one study which showed that phenobarbital had no effect on GABA binding in the cerebellum. Acute injection of pentobarbital has no effects on TBPS binding in various regions of rat brain. However, acute pentobarbital injection has been shown to increase benzodiazepine receptor binding.
in both “ethanol Long Sleep” and “ethanol Short Sleep” mice. Sutton and Simmonds reported a decreased GABA degradation after acute pentobarbital treatment.

The pharmacological and biochemical studies carried out in our laboratory have demonstrated that the acute administration of pentobarbital causes an increase in the brain level of GABA which is associated with pentobarbital-induced narcosis. This was further substantiated by the finding that pentobarbital-induced sleeping time was prolonged when the brain GABA level was elevated by the administration of inhibitor of GABA-T. In addition, the activity of GAD during pentobarbital-induced narcosis was significantly higher than that of the control group. Pentobarbital also increased the release of GABA from mouse striatum.

In summary, acute studies support the electrophysiological and the in vitro biochemical observations that suggest a role for enhanced GABAergic transmission in the anesthetic, but not convulsant, effects of barbiturates.

Regarding the role of GABA system in barbiturate tolerance and dependence, our laboratory reported that chronic administration of pentobarbital resulted in a decrease of both GABA and glutamate levels. There was a concomitant 30% decrease in GAD activity, which was confirmed by the finding that the rate of brain GABA accumulation induced by amino-oxyacetic acid (AOAA) administration in tolerant or withdrawn mice was lower than that in control animals. In addition, the involvement of the GABA system in pentobarbital-dependent mice has been studied. GABA levels in these dependent animals were significantly lower than those of the placebo-implanted mice. A further decrease in GABA level was also observed in dependent mice that convulsed after administration of pentylentetrazol, as compared with those that did not convulse. In addition, the activity of GAD measured in convulsed, dependent mice was significantly lower than in nonconvulsed, dependent mice. Chronic administration of pentobarbital resulted in a decrease of spontaneous [3H]-GABA release from striatum. The spontaneous release of [3H]-GABA from the striatum remained at significantly lower levels after abrupt withdrawal from pentobarbital; a decrease in [3H]-GABA release was also observed in the cerebellum.

Barbiturate tolerance and withdrawal also appear to affect GABA_A receptor binding, but the nature of the change has not been consistently observed. Either alteration or no change has been reported in the binding of GABA ligands in brains of barbiturate-tolerant animals. Sivam et al. showed that, whole brain [3H]-muscimol binding to synaptic membranes was increased in pentobarbital-tolerant animals. It was still elevated, but to a lesser degree, at 1 day after withdrawal, and had returned to control by three days after withdrawal. No change in the number of binding sites but a decreased affinity of the high-affinity [3H]-GABA binding site has also been observed during barbital withdrawal. Chronic administration of barbiturate has also been reported to cause changes in benzodiazepine binding. Both pentobarbital- and GABA-stimulated benzodiazepine binding were decreased in pentobarbital-treated cultured neurons. It has been reported that different types of benzodiazepine receptors and their distribution in brain were differentially affected by barbiturates. In the cerebellum, the predominantly type I benzodiazepine receptors were decreased during chronic exposure to phenobarbital. While in the cortex, a decreased number of type II benzodiazepine binding sites was observed in phenobarbital chronically treated mice. In TBPS binding studies, there was an increased density of binding with no change in the apparent affinity in the cerebella of pentobarbital-tolerant rats. Twenty-four hours after the withdrawal of pentobarbital, the frontal cortex, substantia nigra, and cerebellum had a significant increase in the density of [35S]-TBPS binding sites, which correlates with the reduced latency of onset in the pentylenetetrazol-induced twitch response in pentobarbital withdrawn rats.

In summary, it appears that decreases in GABAergic transmission occur with chronic administration of barbiturates. The GABA level, GAD activity, GABA release, and the binding of benzodiazepines have been reported to be decreased, while the binding of TBPS recognition sites was increased in various regions of the brain.

Comparison on the Effects of Alcohol, Barbiturates and Benzodiazepines on GABA Synapse

The literature concerning the effects on the GABA synapse of in vitro, acute, and chronic treatment with alcohol, barbiturates, and benzodiazepines was reviewed. In the in vitro studies, alcohol and benzodiazepines as well as barbiturates enhanced chloride ion flux. Increased binding of [3H]-GABA to GABA receptors was only observed in fresh brain membranes for alcohol and diazepam. On the other hand, GABA levels were increased by alcohol. GABA release was decreased in benzodiazepine-treated preparations.

Levels of the GABA have been found to be increased in brains of animals treated acutely with alcohol, barbiturates or diazepam. However, the effect of alcohol to decrease GABA release was different from that of barbiturates. As in the case of barbiturates, the turnover rate of GABA was inhibited after acute alcohol treatment and the binding of [3H]-muscimol to the GABA_A receptor was enhanced after acute diazepam exposure.

Following chronic benzodiazepine treatment, ligand binding to benzodiazepine receptors was inhibited in
the lorazepam-tolerant mice or diazepam-treated cultured neurons, and the TBPS binding was increased in the brains of mice which were withdrawn from the lorazepam. Alcohol was reported to decrease GABA release during chronic treatment in mice cerebral cortex. GAD activity, was increased during chronic alcohol administration in contrast to the effects of chronic barbiturate treatment.

Conclusions

The evidence summarized demonstrates that the GABA synapse plays an important role in the pharmacologic effects of barbiturates, alcohol and benzodiazepines. There are similarities and differences in the effects of these CNS depressants on the pharmacology and biochemistry of the GABA synapse. The effects of alcohol, barbiturates and benzodiazepines on GABA synapses are different in different brain regions. Furthermore, the results which have been reported in the literature are inconsistent. This may be due to differences in: (a) animals models used (b) brain regions used (c) protocols (dose, duration, form and route of administration, etc.) used in treating animals and/or (d) techniques (pharmacological, biochemical, physiological, etc.) used.

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