EFFECT OF DI-n-PROPYLACETATE AND γ-ACETYLENIC GABA ON HYPERBARIC OXYGEN-INDUCED SEIZURES AND GABA METABOLISM

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The administration of γ-acetylenic GABA or di-n-propylacetate to mice delayed the onset of hyperbaric oxygen-induced seizures in the animals. The former compound caused large increases in brain GABA content and strong inhibition of glutamate decarboxylase activity, whereas the latter compound brought about only moderate increases in brain GABA level and had little or no effect on the enzyme activity. It is suggested that the GABA system is not involved in the anticonvulsant mechanism of γ-acetylenic GABA but may play a role in the action of di-n-propylacetate.

INTRODUCTION

It has been known for several decades that the breathing of oxygen at high pressure (OHP) induces seizures in both animals and man (1,2). Although the underlying biochemical mechanisms are incompletely understood, substantial evidence has been obtained in support of a role for GABA in the etiology of the OHP-induced seizures (3). Moreover, the administration of a high dosage level of GABA to animals prior to their being exposed to OHP brought about a significant delay in the onset of the convulsions (4). In view of these findings, we deemed it appropriate to test the efficacy of GABA-elevating agents as anticonvulsant drugs against oxygen toxicity.
Two compounds were selected for the investigation: 4-amino-hex-5-ynoic acid (γ-acetylenic GABA, RM 71645), a recently developed inhibitor of GABA catabolism (5), and di-n-propylacetate, a GABA-elevating agent with anticonvulsant properties (6-8) that has gained recognition as a therapeutic agent against petit mal epilepsy (9). The anticonvulsant action of these two drugs against OHP-induced convulsions and the associated changes in GABA metabolism are the subject of this report.

EXPERIMENTAL PROCEDURE

Animals

Male Swiss mice weighing 25–30 g were used in the experiments. All animals were fasted for 24 h prior to the administration of the drugs.

Administration of Drugs

The drugs used in the investigation were di-n-propylacetic acid (ICN-K & K Laboratories Inc., Plainview, New York) and γ-acetylenic GABA (Centre de Recherche Merrell International, Strasbourg). Solutions of the drugs were prepared daily in 0.9% (wt/vol) NaCl, the pH being adjusted to 7.0 immediately before use. The final concentration of the drug was adjusted so that the required dosage was administered in a volume equivalent to 0.5% of the body weight of the animal. All injections were intramuscular, and the injected animals were kept in a laboratory with minimal background noise.

Exposure of Animals to Hyperbaric Oxygen

The mice were exposed to 80 psi (gauge pressure) oxygen, with the apparatus and procedure described previously (10). The animals were placed in individual lucite compartments and were observed throughout the exposure.

Time to Onset of Seizures

The susceptibility of the mice to seizures was placed on a quantitative basis by determining the CT_{50} value. This value, expressed in minutes, denoted the length of exposure to OHP required to produce generalized seizures in 50% of the mice. The CT_{50} value was determined by plotting cumulative percentage convulsed as a function of time on logarithmic probit paper, as described by Paton (11). The mean time ±SEM for the onset of seizures in those animals convulsing is also given in the tables for comparative purposes.

Biochemical Analyses

The animals were decapitated so that the heads fell directly into liquid nitrogen. The brains were excised while still frozen, and GABA-containing extracts prepared as