PYRIDOXAL PHOSPHATE-UNRELATED INHIBITION OF HIPPOCAMPAL GLUTAMIC ACID DECARBOXYLASE BY CONVULSANT PYRIDOXAL SULPHATE

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Previous studies from this laboratory have shown that pyridoxal-5'-sulphate, the synthetic analogue of pyridoxal phosphate, causes epileptic seizures including tonic-clonic convulsions. These seizure activities are prevented or reversed by GABA or muscimol. In an attempt to delineate the biochemical basis of these seizure processes further, we have studied and shown that pyridoxal sulphate is a competitive inhibitor of glutamic acid decarboxylase. In addition, the chronic administration of pyridoxal sulphate was shown to reduce the concentration of pyridoxal phosphate in the cerebellum, the cerebrum, and basal ganglion, but not in the hippocampus. The activity of hippocampal glutamic acid decarboxylase was reduced after 1, 3, and 5 days of chronic application of pyridoxal sulphate. The inhibition was demonstrated, whether glutamic acid decarboxylase was assayed in the presence or absence of its coenzyme pyridoxal phosphate. Unlike findings in the hippocampus, the activity of glutamic acid decarboxylase in other brain regions was unaffected following chronic application of pyridoxal sulphate. The selective toxic effects of pyridoxal sulfate to the hippocampus, a brain area well known for its high susceptibility to seizure discharges, deserve additional indepth investigation.

INTRODUCTION

Without minimizing the significance of other neurotransmitters, investigators have advanced a major role for \( \gamma \)-aminobutyric acid (GABA) in the pathophysiology of seizure disorders (see 1–3 for reviews). Supporting...
this suggestion is indirect evidence of disturbances in GABA neurotransmission in epilepsies. For example, the concentration of GABA in the cerebrospinal fluid of epileptic patients is lower than in normal non-epileptic subjects (4). Glutamic acid decarboxylase (GAD) has been detected in a number of brain regions whose neurons have been classified as GABAergic in nature (5, 6). In addition, the activity of GAD and the density of GAD positive terminals are reduced at epileptic foci (7, 8). Furthermore, the number of neurons in the hippocampi of epileptic patients is lower than in those of controls (9).

Inhibiting the synthesis of GABA, or the administration of GABA antagonists, produces convulsions simulating epileptic seizures (10). Conversely, drug-induced convulsions can be opposed and/or reversed by enhancing the concentration of GABA in the brain. Finally, many clinically effective and useful antiepileptic drugs, such as benzodiazepine derivatives, are thought to exert their antiepileptic effects through facilitation of GABA-mediated transmission (2, 11, 12).

Pyridoxine plays a definite but unexplained role in the prevention, as well as the production, of convulsive seizures (13 for review). Antimetabolites of pyridoxal phosphate (PLP), such as 4-deoxypyridoxine, or compounds which deplete PLP, such as isonicotinic acid hydrazide, cause seizures in experimental animals (14), which can be interrupted by the administration of pyridoxine. Furthermore, the frequency of seizures in epileptic humans increases when they are treated with the tuberculostatic drug isoniazid (15), which is known to inactivate PLP biochemically by interacting with it to form a hydrazone. Earlier investigators attributed these seizure disorders to the unavailability of PLP as a coenzyme for GAD. However, recent evidence has shown that convulsions are not always associated with a reduction in the concentration of PLP. For example, Hammad et al. (16) studied the convulsive effects of allyglycine, mercaptopurine, picrotoxin, and bicuculline on the concentration of PLP in rats during preictal, early ictal, and late postictal periods. The results of these studies have shown that alterations in the concentration of PLP occur independently of these events and are unrelated to either the cause, the time of onset, or the severity of seizure activities in the areas of the brain tested. In fact, the known association between PLP and convulsive seizures became obscure when Kouyoumdjian and Ebadi (17) reported that the intracerebroventricular (icv) injection of pyridoxal phosphate caused epileptic seizures, including tonic-clonic convulsions. These effects were selective for pyridoxal phosphate and could not be produced by pyridoxine, pyridoxine phosphate, pyridoxamine, pyridoxamine phosphate, or their metabolite, 4-pyridoxic acid. In addition to naturally occurring PLP, its synthetic analogue pyridoxal sulphate produces convul-