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THE ROLE OF THE CHOLINERGIC SYSTEM IN THE ANTICONVULSANT EFFECTS OF THE BARBITURATES AND OTHER ANTICONVULSANTS

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ABSTRACT

THE ROLE OF THE CHOLINERGIC SYSTEM IN THE ANTICONVULSANT EFFECTS OF THE BARBITURATES AND OTHER ANTICONVULSANTS

The barbiturates are known to affect cholinergic functions but the relationship of this action to the pharmacological effects of these drugs is uncertain. This dissertation describes studies of the role of the cholinergic system 1) in the development of functional tolerance to the sedative-hypnotic effect and 2) in the anticonvulsant activity of the barbiturates.

Rats fed a diet containing phenobarbital (PheB) for six to twelve days had higher brain levels of the drug than controls when they lost their righting reflex in response to a test dose of the drug. These results suggest that a cellular adaptation (functional tolerance) occurred after chronic treatment with PheB. No dose-response relationship for the effect of PheB on high affinity choline uptake (HACU) in rat hippocampus was found and therefore it was not possible to determine whether alteration in cholinergic function was related to the developed functional tolerance to the sedative-hypnotic effect.

Several anticonvulsant drugs were examined for their ability to inhibit high affinity choline uptake (HACU), an indicator of cholinergic nerve activity. In these experiments drugs were administered i.p. to mice, the animals were decapitated, and HACU was measured in

synaptosomes prepared from hippocampus.

Several barbiturates, two benzodiazepines and valproic acid inhibited HACU at doses that correlated well with their anticonvulsant potencies. Several other anticonvulsant drugs (trimethadione, ethosuximide, phenytoin, carbamazepine and clonazepam) did not inhibit HACU. Thus it appears that the ability to inhibit HACU is not common to all anticonvulsants.

To test the hypothesis that inhibition of HACU is responsible for the anticonvulsant effects of some drugs the competitive inhibitor of HACU, hemicholinium-3 (HC-3), was given intracerebroventricularly to rats and mice. One hour after HC-3, the convulsant, picrotoxin, was given i.p.; there was a significant protection against seizures in HC-3 treated animals versus saline treated controls. In another experiment, electrolytic lesions of the major ascending cholinergic pathways to the hippocampus and the cortex were made under pentobarbital anesthesia. The lesioned animals exhibited significant protection from the convulsant effects of picrotoxin versus sham lesion controls.

These experiments demonstrated the involvement of the cholinergic system in picrotoxin seizures and support the hypothesis that some of the anticonvulsant action of the barbiturates and several other drugs is a result of their ability to inhibit the activity of cholinergic neurons.

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