Title : ANTICONVULSANT EFFECT OF HALOTHANE AND ENFLURANE

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Introduction. Cerebellar control of muscle movement is mainly provided by the deep cerebellar nuclei and cerebellar cortex. The degree of inhibitory output of the cerebellar cortex via Purkinje cell (PC) axons on the deep cerebellar nuclei is thought to be determined by the balance between excitatory and inhibitory input, via climbing and mossy fibers, converging upon the PC. It has been shown that the major mediator of the inhibitory input in cerebellar cortex is gamma-aminobutyric acid (GABA) and that a decrease in the rate of GABA synthesis or a blockade of GABA receptors is associated with a rise in cyclic 3',5'-guanosine monophosphate (cGMP) content of cerebellar cortex. Increased cGMP content in cerebellar cortex has been demonstrated with isoniazide, an inhibitor of GABA synthesis, and picrotoxin, a GABA receptor blocker, both of which produce ataxia, tremor and convulsions. Compounds which prevent the rise of cGMP content in cerebellar cortex, such as diazepam, have been shown to have a strong anticonvulsant effect against isoniazide and picrotoxin (1). Halothane and enflurane are known to alter cyclic nucleotide content in the brain and halothane, in particular, to decrease cerebellar cGMP content (2). Therefore, a model utilizing isoniazide- and picrotoxin-induced convulsions was used to test whether halothane and enflurane have anticonvulsant effect and whether such an effect is associated with a change in cGMP content. The effect of volatile anesthetics on this type of convulsions was compared to their effect on convulsions induced through a different mechanism (glycine receptor blockade by strychnine) and also with the effect of phenobarbital at anesthetic equipotent dose.

Methods. Male mice, weighing 25-30 g, were used. First, the anesthetic dose required to abolish righting reflex in 50% of the animals ($ED_{50}RR$) was determined. Unrestrained mice were placed in rotating cages (10 rpm) inside a chamber with two restrained mice with rectal temperature probe. The temperature of the chamber was adjusted to maintain rectal temperature at 37 C. A continuous flow of the anesthetic in air through the chamber was maintained for 60 min at concentrations sufficient to abolish righting reflex in most of the animals. Subsequently, the concentration was lowered gradually and maintained at each concentration for a minimum of 30 min, or until the righting reflex response was reproduced three times. Results did not differ when the reverse sequence, from lower to higher concentration, was used. Anesthetic concentration in the effluent gas from the chamber was measured with a Narkotest-M analyzer. ED_{50} of convulsive agents ($ED_{50}C$) was determined according to Ipsen (3) in the absence and presence of each anesthetic at $ED_{50}RR$ concentration. For cGMP determination, the mice were killed with a microwave beam of 2.8 KW focused to the head for 3 sec. Cyclic GMP content was measured by radioimmunoassay, according to Steiner (4).

Results. $ED_{50}RR$ of halothane, enflurane and phenobarbital were 0.7, 1.01% (v/v) and 102 mg/kg ip, respectively. $ED_{50}C$ of isoniazide, picrotoxin and strychnine were 150.2 ± 14.2, 2.5 ± 0.6, and 0.8 ± 0.3 mg/kg sc. In the presence of halothane at $ED_{50}RR$ the $ED_{50}C$ of isoniazide and picrotoxin were markedly increased, 425.8 ± 29.7, 6.2 ± 1.2 mg/kg sc ($P < 0.05$), while that of strychnine was not changed. Similarly, enflurane at $ED_{50}RR$ exerted an anticonvulsant effect against isoniazide and picrotoxin ($ED_{50}C$ 282.8 ± 54.7, 6.6 ± 1.6 mg/kg sc, $P < 0.05$) and did not provide protection against convulsions induced by strychnine. Phenobarbital, on the other hand, at an anesthetic equipotent dose ($ED_{50}RR$) protected against convulsions induced by all three agents. Isoniazide, 200 mg/kg sc, increased cGMP content in cerebellar cortex from a control value of 6.39 ± 1.10 to 13.50 ± 1.90 ($P < 0.01$) pmol cGMP/mg protein and halothane 1%, v/v, decreased cGMP content by 83.5%, to 1.12 ± 0.16 ($P < 0.005$) and prevented the rise caused by isoniazide, 1.33 ± 0.16 ($P < 0.001$) pmol/mg protein, as determined 45 minutes after exposure to the drugs.

Discussion. The $ED_{50}RR$ of halothane and enflurane are comparable to those reported by Smith (5). At these concentrations both volatile anesthetics have anticonvulsant effect against compounds reducing the rate of GABA synthesis (isoniazide) or blocking GABA receptors (picrotoxin) but not against strychnine, which induces convulsions through a different mechanism. Compared to the effect of phenobarbital at anesthetic equipotent dose, halothane and enflurane appear to have a selective protective effect against convulsions associated with reduced GABAergic inhibitory action and rise in cGMP content in cerebellar cortex. The results suggest that the observed anticonvulsant effect of halothane and enflurane may be due to a depression of cGMP response in cerebellar cortex by the two volatile anesthetics.

References.

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