Effects of Induction by Pentobarbital Upon Susceptibility of Mice to Insecticides

by R. D. O'BRIEN
Section of Neurobiology and Behavior
Cornell University, Ithaca, New York

Numerous studies have shown that a variety of compounds which are substrates for microsomal metabolism can, if administered to animals for several days, induce an increase in the titre of nonspecific microsomal liver enzymes with a corresponding increase in ability to metabolize not only the inducer, but other substrates (1, 2, 3). Starvation has the reverse effect of such induction (4). Since both organophosphates and carbamates can be metabolized by microsomal systems, with a resultant enhancement or reduction of innate toxicity which varies with each compound, one would expect that starvation or microsomal induction would effect metabolism of these anticholinesterases and hence their toxicity. Similar cases have

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already been shown (5, 6). The present report explores the effect of barbiturate induction on susceptibility of mice to various anticholinesterases.

Methods

Insecticides: The LD_{50} for mice of the following compounds was first measured: dimethoate [O,O-dimethyl S-(N-methylcarbamoylmethyl) phosphorodithioate]; mipafox [N,N-diisopropylphosphorodiamidic fluoride]; dimetilan [2-dimethylcarbamyl-3-methylpyrazolyl- (5) dimethylcarbamate], azinphosmethyl [O,O-dimethyl S-(4-oxobenzotriazinomethyl) phosphorodithioate]; Amiton [O,O-diethyl S-(β-diethylamino)ethyl phosphorothiolate] as the oxalate salt; schradan [tetramethylphosphorodiamidic anhydride] and DIP [diisopropylphenyl methyl carbamate]. The compounds which were soluble in water were dissolved in 0.9% sodium chloride solution and injected intraperitoneally at a rate of 0.2 ml per g. mouse. The compounds which were insoluble in water were made up in propylene glycol and injected intraperitoneally with 0.1 ml per 20 g. mouse. The LD_{50} doses and 95% confidence limits were calculated by computer using an iterative process, involving a weighted linear regression based on probit analysis (7).

In order to induce microsomal enzymes, the mice, 20 g. albino males purchased from the Dan Rolfsmeyer Co., Madison,

Wisconsin, were treated with a 90 mg. per kg. dose of pentabarbitol sodium in 0.9% sodium chloride solution for four days in succession. This solution was administered by intraperitoneal injections of 0.1 ml per mg. of body weight; during this period of treatment the animals were given both food and water. On the fifth day the mice were injected with the LD_{50} dose of the anticholinesterase. They were then kept in retaining jars for 24 hours, and deprived of food and water. During this entire experiment the animals were kept at 72-78°F.

In another investigation the effect of the compounds on animals starved for one or two days was examined. These mice were given water but no food for the specified time. During the starvation period each mouse was kept in an individual retaining jar to prevent cannibalism. The LD_{50} dose of the compound was then administered, and the animals were held for 24 hours with neither food nor water.

Results

Table I shows that induction by pentobarbital increased the toxicity of azinphosmethyl and especially dimethoate; gave slight protection against DIP, Amiton and schradan, and gave marked protection against mipafox and especially dimetilan. For the most extreme cases, the change in LD_{50} was measured: for dimethoate the LD_{50} was decreased from 165 to 111 mg/kg, whereas for dimetilan

it was increased from 12.2 to 18.4 mg/kg.

The effects of starvation were in no case very marked. One is inclined to suspect any increases in mortality as being due to a debilitated state; no significant decreases were observed.

One may conclude that pretreatment of mice with inducers of microsomal metabolism can substantially modify the toxicity of subsequent toxicants. The modification can take the form of enhancement or diminution, depending on whether the role of the microsomes is primarily activation or degradation.

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TABLE 1

Effect of pentobarbital injection upon toxicity of anticholinesterases to male mice

Compound	LD_{50} dose, l.p., mg/kg	Confidence limits (95%)	Vehicle	Mortalities from normal LD_{50} dose after Pentobarb.	Mort. from normal LD_{50} dose after starv. 1 day	2 days
Organophosphates						
Dimethoate	165	129-212	propylene glycol	92%	60%	90%
Mipafox	13.5	11.1-16.3	propylene glycol	15%	40%	80%
Azinphosmethyl	3.4	2.7-4.3	propylene glycol	70%	40%	56%
Amiton	0.62	0.54-0.71	0.9% saline	30%	40%	40%
Schradan	14.8	12.7-17.3	0.9% saline	30%	40%	60%
Carbamates						
DIP	31.1	22.7-42.6	propylene glycol	40%	40%	60%
Dimetilan	12.2	9.1-16.4	0.9% saline	0%	50%	30%

LD_{50}'s after pentobarbital (with confidence limits):

dimethoate 111 (79-157); dimetilan 18.4 (14.9-22.7)

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