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بالرسالة صفحات لم ترد بالاصل

EFFECT OF THE CARBAMATE "ALDICARB" ON ACETYL-CHOLINESTERASE EXTRACTED FROM WHOLE AND DIFFERENT PARTS OF RAT BRAIN

THESIS

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ABBREVIATIONS

AChE	= acetyl cholinesterase
BuChE	= butyryl cholinesterase
ACh	= acetyl choline
AThChI	= acetyl thiocholine iodide
CNS	= central nervous system
DTNB	= 5.5' dithio-bis (2-nitrobenzoic acid)
W.B	= whole brain
B.G	= basal ganglia
F.C	= frontal cortex
M.O	= medulla oblongata
P	= pons
Cer	= Cerebellum
DFP	= diisopropyl – flouro – phosphate
PAM	= 2-pyridine aldoxime methiodide
RBCs	= red blood corpuscles
LDH	= lactic dehydrogenase

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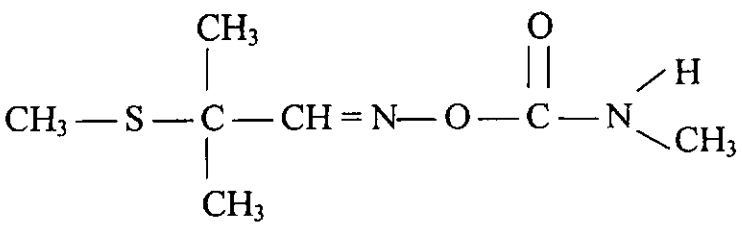
Carbamates

Carbamates are known as inhibitors of cholinesterases. They cause a decrease in RBC cholinesterase and plasma pseudocholinesterase levels.[1]

Carbamate pesticide poisonings tend to be less severe than organophosphates because they bind reversibly to the active site on the cholinesterase enzyme, in contrast to organophosphates that bind irreversibly.[2]

It was reported that carbamates just carbamylate the enzyme exactly as alkylphosphates phosphorylate them.[3] The carbamic acid derivatives inhibit the enzyme acetyl cholinesterase which is directly related to their pharmacological effect.[4,5,6] This inhibition is the basis for their use as insecticides and pesticides but it also leads to toxicosis in a variety of animals including man.[7]

Aldicarb (2 methyl-2 (methylthio) propionaldehyde O- (methyl carbamoyl) oxime) is considered to be the most potent of the commercially available carbamate pesticides.[8] It has a molecular weight of 190, with a chemical formula ($C_7 H_{14} O_2 N_2 S$).

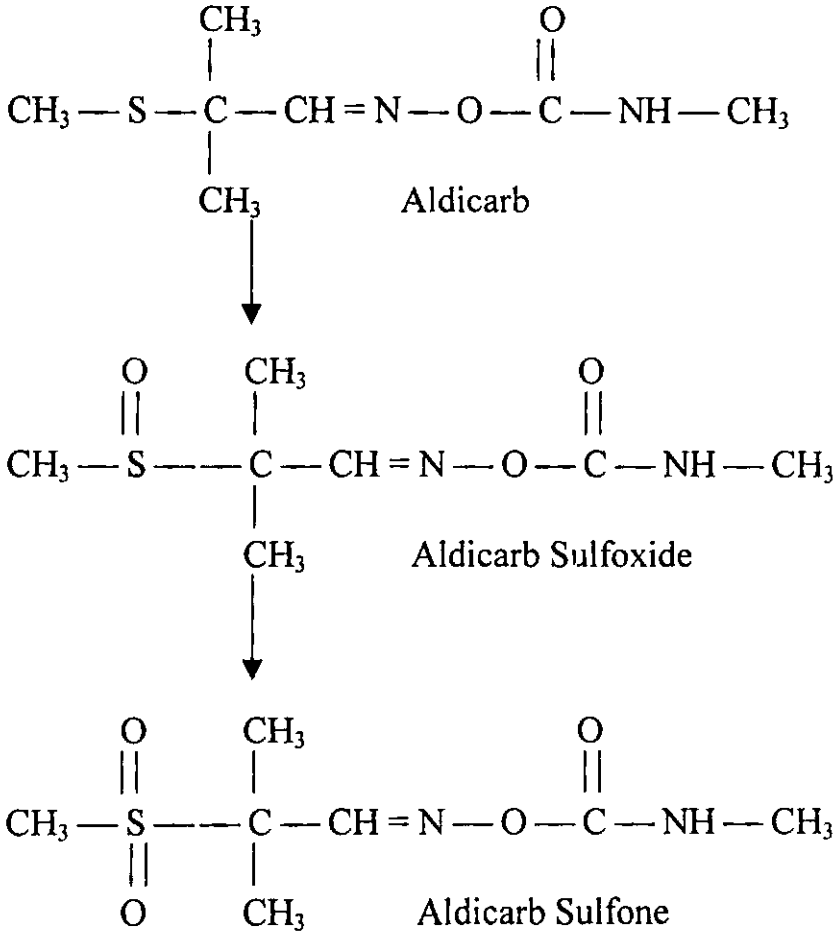


It is an unusual source of acute human poisonings and it is used as a treatment incorporated into soil against nematodes and mites. It is also found to be taken up systemically by plants.[9]

It breaks down rapidly to several metabolites with different toxicities.[10] Since aldicarb is highly toxic, with an oral LD_{50} of 1 mg/KBW,[7] the largest dose administered was 0.1 mg/KBW. At this dose, all tissue samples taken had a significant decrease in AChE activity. Its effect persisted in maternal and fetal blood of rats 24 hours after administration of aldicarb at doses of 0.10 and 0.01 mg/KBW.

The carbamates or their active metabolites apparently reach several tissues very quickly when given orally. Aldicarb is absorbed through the skin, lungs and gastro-intestinal tract. In human trials, doses of 0.1 mg/kg produced symptoms[11], and doses of 0.02 mg/kg demonstrated the lowest observed effect level for cholinesterase inhibition.[12]

Aldicarb is rapidly absorbed via the gastrointestinal tract. After large doses, symptoms occur as quickly as 5 minutes. It is rapidly metabolized to aldicarb sulfoxide then aldicarb sulfone which are pharmacologically active.[13]



It has a short half-life, and in 24 hours, 80-90% of an ingested dose in rats is excreted in urine.[14] Cholinergic symptoms like muscle fasciculations and breathing difficulty were encountered after ingestion of crops treated with aldicarb.[15] Nausea, vomiting and abdominal cramps were also reported. It was found that local gastrointestinal cholinesterase effect can cause illness at dosage levels below those causing significant blood enzyme depression.[16,17]

Cholinesterases

In 1914 Sir Henry Dale[18] suggested that an enzyme which degrades the esters of choline played a role in neurotransmission within the autonomic and somatic motor nervous systems and that this enzyme, acetylcholinesterase, was the target of action of the drug, physostigmine (eserine). In the intervening 85 years, inhibition of the enzyme has been used to augment both the nicotinic and muscarinic actions of acetylcholine. Cholinesterase inhibitors are frequently used as therapeutic agents and are employed worldwide as insecticides.

Over 30 years ago Jean Massoulié and François Reiger uncovered an unusual structural polymorphism in the cholinesterases.[19] Subsequent studies have shown that the polymorphism is reflected in multiple modes of attachment of the enzyme to the outside surface of the cell. Accordingly, the precise localization of cholinesterases within synaptic junctions and the high catalytic potential of the enzyme are both critical to the fidelity of cholinergic synaptic function. Within the last 15 years primary structures of several cholinesterases have been determined, and this has enabled investigators to ascertain the structural basis of the polymorphism and the organization of the genes encoding the cholinesterases.

Cholinesterases may be classified as acetylcholinesterase and butyrylcholinesterase on the basis of differential specificity for acetylcholine and butyrylcholine hydrolysis. Several inhibitors have also been shown to be selective for one of the two enzymes. The AChEs are