سامية محمد مصطفى

شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

سامية محمد مصطفى

شبكة المعلومات الجامعية

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التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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بعض الوثائق الأصلية تالفة

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بالرسالة صفحات لم ترد بالأصل

BIOCHEMICAL AND NEUROENDOCRINOLOGICAL STUDIES ON THE EFFECT OF DELTAMETHRIN IN NORMAL AND INTOXICATED RATS

A Thesis

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by

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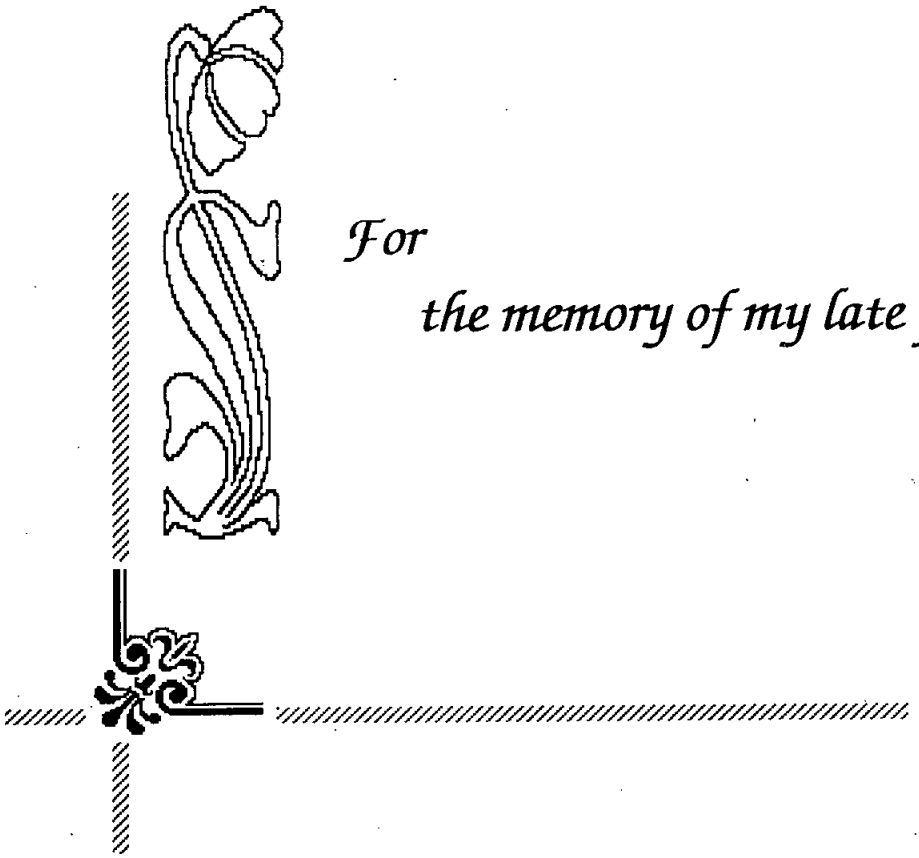
«قالوا سبحانك لا علم لنا إلا ماعلمتنا إنك أنت العليم الحكيم»

"صدق الله العظيم"



For

the memory of my late father

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INTRODUCTION AND REVIEW OF LITERATURE

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A. Pyrethroid Insecticides

Pyrethroids are widely used neurotoxic insecticides which may have detrimental effects on behavioral, autonomic and neuro-endocrine functions of mammals, including man. Two distinct symptoms of poisoning by pyrethroid insecticides have been described in rats. Animals poisoned with non-cyano pyrethroids (type I) elicit a tremor (T) syndrome whereas animals poisoned with alpha cyano pyrethroids (type II) elicit choreoathetotic writhing and profuse salivation (CS) syndrome (Verschoyle and Aldridge, 1980). The CS syndrome results in electroencephalogram changes indicative of CNS involvement. Also, a direct correlation between the levels of deltamethrin in the brain and the onset of CS symptomology has been determined (Rickard and Brodie, 1985). These and many other results indicated that the primary site of action of pyrethroids in mammals is within the CNS.

The lipophilicity of pyrethroids enables rapid access to tissues, including CNS. The *in vitro* activity of many pyrethroids is very high, and *in vivo* very small doses are also required in the nervous system to produce biological effects. Thus, from an intraperitoneal dose to rats of deltamethrin (5 to 8 mg/kg), the concentrations of parent compound were in blood 2.4 to 3.4 nmol/g, in brain 0.12 to 0.45 nmol/g, and in spinal cord 0.23 to 0.38 nmol/g (Rickard and Brodie, 1985). These concentrations indicate a rather biologically highly active molecule, albeit, the effective concentration in the

region of sodium channels is unknown. It is probable that the large variety of signs, symptoms, biochemical and physiological changes are consequences of a primary interaction of pyrethroids with sodium channels (Vijverberg and Van Den Bercken, 1990). It is therefore concluded that by virtue of the molecular action of pyrethroids on the sodium channels, pyrethroids will exert a toxic effect on the nervous systems of many species. Such toxicity will be dependent on interaction of pyrethroids at the molecular target within the sodium channels.

Pyrethroids have a very good record of safety in application. Since they are readily detoxified by esterases in mammals, there should be a very high safety factor for concentrations in the environment and consumption of treated agricultural produce. When no precautions are taken when spraying and repeated and prolonged exposure occurs, the lipophilic pyrethroids will be absorbed. This can lead not only to local skin effects but also to sufficient absorption to cause systemic toxicity. Several publications have appeared that extend the original work of Bradbury *et al.* (1983) who showed that mephensin, a muscle relaxant, provided substantial protection against poisoning by cismethrin and deltamethrin. This was in contrast to the poor protection afforded by ether and pentobarbital, diazepam and phenobarbital, atropine plus diazepam (Ray and Cremer, 1979; Gammon *et al.*, 1982; Bradbury *et al.*, 1983).

Due to its short half-life *in vivo*, the mephensin treatment was only of academic value, other substances have now shown more protection. Experimental treatment schedules developed using the rat as the experimental model and methocarbamol have been shown to be effective against poisoning with

fenvalerate, cypermethrin and permethrin. Mephensin and methocarbamol appear to be more effective against pyrethroids containing the alpha cyano group than others (Bradbury *et al.*, 1983; Hirmori *et al.*, 1986). Pretreatment with diphenylhydantoin, a sodium channel blocker, has also led to equivocal results. Although diphenyhydantoin is reported to attenuate both DDT and permethrin-induced tremor, it failed to alleviate toxic signs induced by either cismethrin or deltamethrin (Bradbury *et al.*, 1983), and it also failed to block the proconvulsant effects of permethrin and deltamethrin on pentylenetetrazole-induced seizure thresholds (Devaud *et al.*, 1986). All treatments are targeted to prevent or reduce some of the secondary consequences of the primary interaction of pyrethroids for a sufficient time to allow removal of the parent pyrethroid by metabolism and to a lesser extent by redistribution. The structural similarities between effective substances suggest a common mechanism, but it is still uncertain what it is.

1. Cholinergic effects of pyrethroids

Aldridge *et al.* (1978) reported that decamethrin was found to decrease the acetylcoline (ACh) content in rat brain parts including cerebellum. Similar to decamethrin, type II pyrethroids were appeared to interact with nicotinic ACh receptor channel sites, however, they were slow acting since their effects were significantly higher at longer incubation periods (Abbassy *et al.*, 1983).

Pyrethroids stimulate calcim-dependent neurotransmitter release in mammalian brain slices indicative of a direct depolarizing action of these agents on presynaptic nerve terminals (Eells and Dubocovich, 1988). In contrast, the

actions of pyrethroids on radiolabeled sodium influx and on neurotransmitter release in mammalian nerve terminal preparations have been reported to be dependent upon sodium channel activation (Bloomquist and Soderlund, 1988) or on potassium induced membrane depolarization. The pyrethroids increased the spontaneous release of (^{3}H) ACh from rat brain synaptosomes as further evidence of the depolarizing actions of these insecticides on nerve terminal membranes. Pyrethroid-induced release of ACh was tetrodotoxin-sensitive and occurred over the same concentration range as membrane depolarization. Comparison of ACh release from rat brain slices (Eells and Dubocovich, 1988) revealed a remarkable similarity in pyrethroid actions in two different *in vitro* neuropreparations. Furthermore, these data showed that deltamethrin-induced alterations in synaptosomal membrane potential is a sensitive measure of pyrethroid action on the sodium channel and of pyrethroid toxicity (Eells *et al.*, 1992).

Interestingly, activation of dopamine D_2 receptors in neostriatal tissue of the rat induced an almost complete inhibition of the release of ACh, whereas under similar conditions in the nucleus accumbens ACh release was inhibited for only 50% (Wedzony *et al.*, 1988). However, a clear inhibitory effect of dopamine on the ACh release in most parts of the striatum has been reported, suggesting a close relation between cholinergic neurons and dopaminergic terminals in these striatal areas (Henselmans and Stoof, 1991).

ACh is synthesized from choline and acetyl CoA in a reaction catalyzed by choline acetyltransferase. Mammalian brain, unlike liver, can not synthesize choline; thus central cholinergic neurons largely depended on the blood for their supply of ACh precursor. Precursor availability has previously