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THE EFFECTS OF NEUROTOXIC INSECTICIDES ON CENTRAL CHOLINERGICALLY-MEDIATED HYPERTENSION

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Malathion by itself produced a double-phased blood pressure response in the anaesthetized rat. Immediately after intravenous injection of malathion there was a shortlasting hypotension (up to 90 sec), followed by a prolonged hypertension similar to that observed after intravenous injection of phisostigmine to rats. The hypotensive response is probably due to accumulation of acetylcholine after cholinesterase inhibition by malathion. The hypertensive response to malathion is due to secondary activation of adrenergic mechanisms in the central nervous system.

Malathion coused dose-dependent inhibition of the central cholinergically mediated hypertension in rats produced by intravenous injection of physostigmine. Both the degree and duration of hypertension were equally depressed. These experiments indicate that development of central cholinergically-mediated hypertension is possible only in the presence of functionally competent cholinesterase.

Both lindan and permethrine also depress the central cholinergically mediated hypertension produced by intravenous injection of physostigmine. Thus, all the three neurotoxic insecticides can inhibit transmitter interaction which is the basis of central cholinergically mediated hypertension, but not necessarily by the same mechanisms.

Key words: malathion, lindan, permethrine, physostigmine, central cholinergically mediated hypertension.

INTRODUCTION

Central cholinergically-mediated hypertension (CCMH) was discovered in the early sixties and later described in detail (Varagić *et al.* , 1991). It can be produced only by anticholinesterases which penetrate the central nervous system, but not by quaternary substances which do not pass the blood-brain barrier. Thus, intravenous injection of physostigmine produces accumulation of acetylcholine in the brain and simultaneously increases the total neural activity of the preganglionic sympathetic on the periphery (Stamenović and Varagić, 1970), leading finally to a hypertensive response. Therefore, this type of hypertension

may be due to interaction between the two transmitter systems: adrenergic and cholinergic ("cross-talk"). This type of hypertension can be equally blocked by atropine and by alpha-adrenergic blocking agents, indicating its double origin.

CCMH may be life-saving in the hypovolaemic shock of the experimental animal (Varagić *et al.*, 1996).

Other types of transmitter interactions are also known to function in the central nervous system (Veerasingham and Raizada, 2003).

It was therefore of interest to investigate the action of three well known neurotoxic insecticides (malathion, lindan, permethrin) on CCMH in order to gain a better insight into their molecular mechanisms of action in the central nervous system.

MATERIAL AND METHODS

The experiments involved Wistar rats (300-350 g) kept under standard laboratory conditions. They were fed with rat pellets and offered water ad libitum. They were anaesthetized with urethane (25% solution, 0.7 ml/kg subcutaneously).

The left carotid artery was cannulated for direct recording of blood pressure, whereas the right jugular vein was cannulated for intravenous injections. All the drugs used in the present experiments were injected intravenously. The blood pressure was recorded on an Ugo Basile (Gemini 7070) recording system.

The following substances were used: lindan (Zorka, Šabac), permethrine (Wellcome, London), malathion (Cheminova Agro, Denmark) and physostigmine salicylate (Sigma). Lindan and permethrine were dissolved in absolute ethanol, whereas malathion was dissolved in dimethylsulfoxide (Fluka AG, Buchs).

Statistical analysis was made using a computer programme (Microsoft Excel Version 2000).

RESULTS

Intravenous injection of malathion (80 μg/kg) was found to produce a biphasic response in blood pressure. Immediately after injection the blood pressure dropped, the hypotension lasting up to 90 sec. After this initial response a rise of blood pressure occurred. This hypertension lasted several minutes (up to 10 min). Tachyphylaxis occurred if the same dose of malathion was repeated several times (Fig. 1).

It was also observed that malathion (80 μg/kg) significantly and dose-dependently depressed the central cholinergically-mediated hypertension produced by intravenous injection of physostigmine.A sufficiently high dose of malathion completely blocked this type of hypertension. The results are presented in Figs 2 and 3.

The depressive effect of malathion was evident both from the decrease in the height of the blood pressure response and also in the shortening of its duration, (Fig. 4).

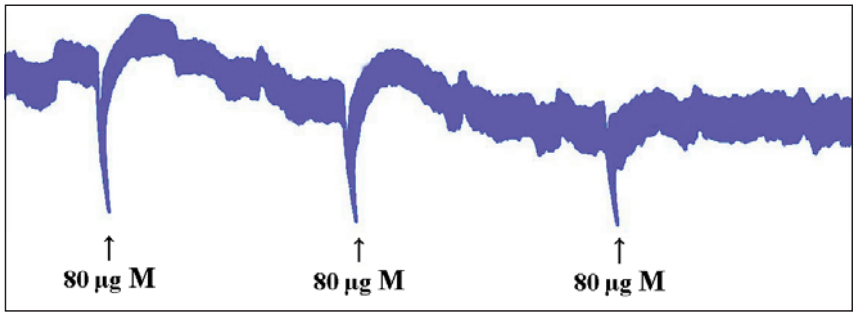

Figure 1. The original tracing of the blood pressure response to repeated injections of the same dose of malathion (M) intravenously (at the arrow).

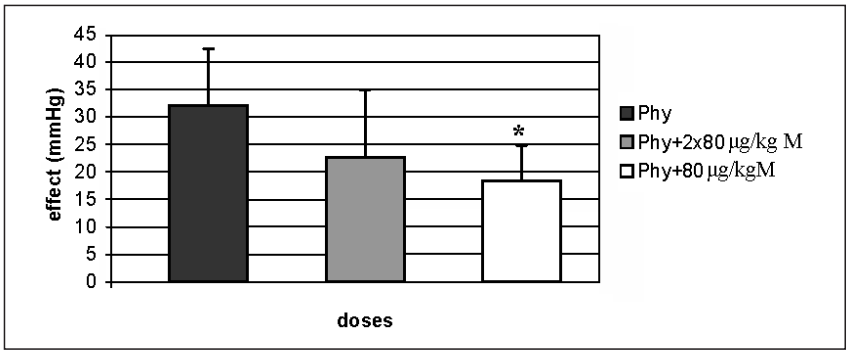

Figure 2. The effect of malathion on the hypertensive response to physostigmine in the rat. The first column shows the effect of physostigmine (80 µg/kg) , whereas second and third columns show the effects of the same dose of physostigmine after previous injection of malathion (M). Combinations are indicated on the right side of the figure. * - $p<0.05$ in comparison with Phy

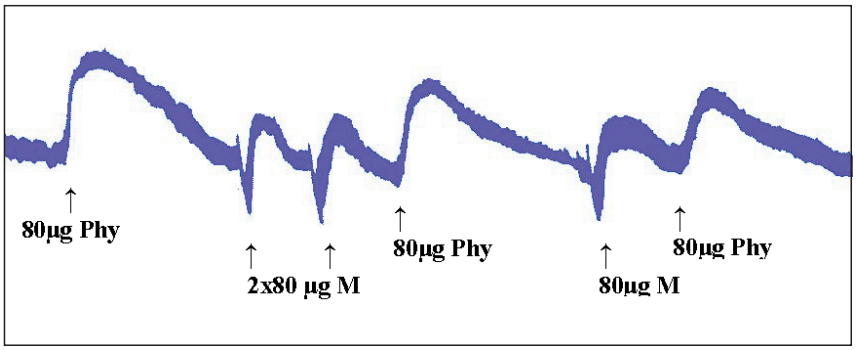

Figure 3. The effect of malathion (M) on the hypertensive response to physostigmine (Phy). Doses are shown below the tracing.

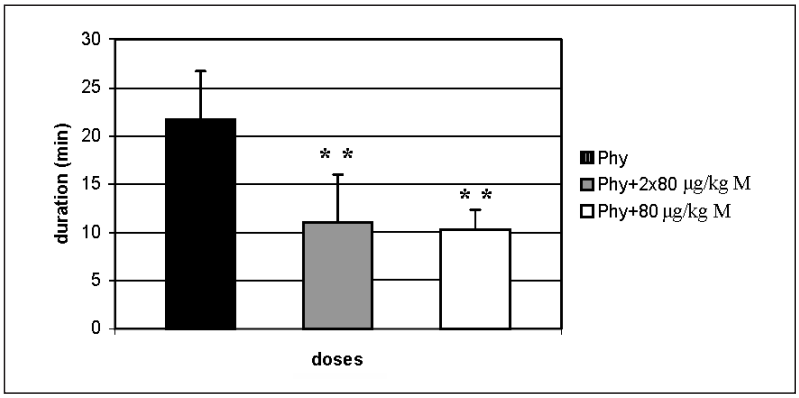

Figure 4. The effect of malathion (M) on duration of the hypertensive response to physostigmine (Phy). * * - $p<0.01$ in comparison with Phy

Lindan by itself, in doses from 8 to 40 μg/kg intravenously, produced only a shortlasting hypotension. In the same range of doses lindan significantly decreased the CCMH produced by physostigmine both in degree and in duration, as shown in Fig. 5.

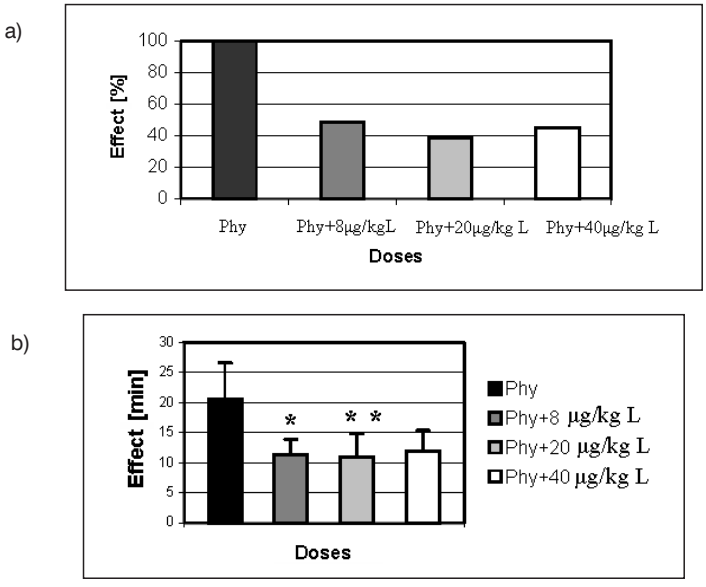

Figure 5. The effects of increasing doses of lindan (L) on the degree (panel a) and duration (panel b) of the hypertensive response to physostigmine (Phy). * - $p<0.05$ in comparison with Phy; * * - $p<0.01$ in comparison with Phy.

Similarly, permethrine (40 to 200 μg/kg) by itself produced only a shortlasting hypotension. Quick development of tachyphylaxis was observed in this type of response to permethrine. In doses from 40 to 200 μg/kg permethrine significantly antagonized the CCMH due to physostigmine both in degree and in duration (Fig. 6).

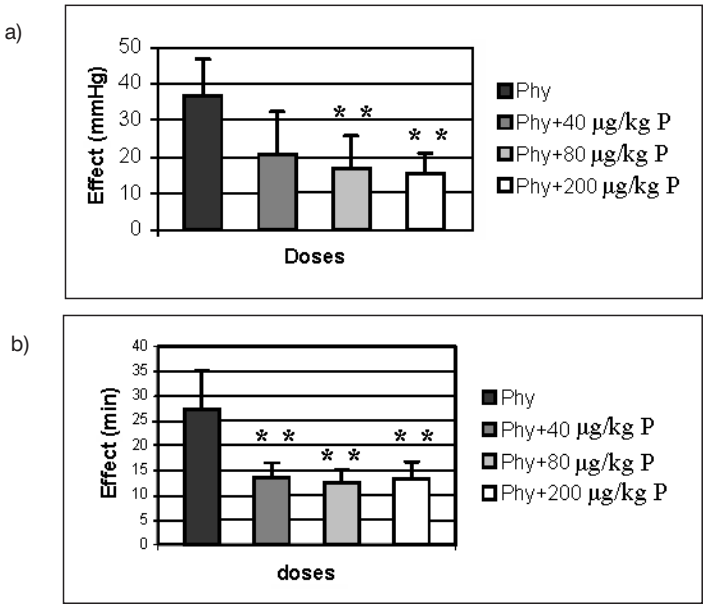

Figure 6. The effects of increasing doses of permethrine (P) on the degree (panel a) and duration (panel b) of the hypertensive response to physostigmine (phy).
* * - $p<0.01$ in comparsion with Phy.

DISCUSSION

Malathion is an anticholinesterase organophosphate which is liposoluble and therefore easily penetrates the central nervous system (Storm *et al.*, 2000; Taylor, 2001). Its action on the blood pressure of the rat is biphasic. The initial shortlasting hypotension lasts only about 90 sec and is followed by a longlasting hypertension which is basically similar to that previously observed and described for physostigmine (Varagić *et al.*, 1991). The initial shortlasting hypotension is probably due to accumulation of acetylcholine, whereas the secondary longlasting hypertension is the consequence of central adrenergic activation.

It is of interest that repeated injections of the same dose of malathion produce progressvely lesser and lesser effect. This tachyphylaxis might be associated with increasing acetylcholine esterase inhibition in the brain of the rat. These data indicate that the central cholinergically-mediated hypertension might be produced only in the presence of functionally competent acetylcholinesterase

in the brain. The higher the inhibition of the enzyme in the brain, the lower the hypertensive response to malathion.

This idea is further supported by the finding that malathion inhibited the hypertensive response to physostigmine in the rat. Sufficiently high doses of malathion produce a very high degree of acetylcholinesterase inhibition and simultaneously almost complete block of the hypertensive response to physostigmine, thus leaving the possibility that physostigmine stimulates the muscarinic receptors which is manifested by hypotension (Varagić *et al.*, 1968).

It was also found in the present experiments that both lindan and permethrine, in doses used as already described, produced depression of central cholinergically-mediated hypertension. The mechanism of this action is unknown. The clinical data indicate that the toxicity of permethrine can be manifested by symptoms from the central nervous system (convulsions, coma, confusion) as well as from the cardiovascular system (arrhythmia, shock) (Yang *et al.*, 2002). It has been also found that permethrine produces behavioral changes as well as changes in the content of acetylcholine and cholinergic receptors (Abou-Donia *et al.*, 2001). The same symptoms were also observed in war veterans from the Persian Gulf (Abou-Donia *et al.*, 2001).

Earlier data show that deltamethrine, a substance very close to permethrine, produces a change in the polyamine content in various regions of the brain (Husain *et al.*, 1975). Thus, it is possible that these changes affect the cholinergic-adrenergic interaction which precedes the central cholinergically-mediated hypertension. The final result of this action might be depression of central cholinergically-mediated hypertension, as found in our experiments.

Chronic action of small amounts of lindan from the human environment might produce symptoms of excitation of the central nervous system, including convulsions particularly in children (Nordt and Chew, 2000). Chronic exposure to lindan also produces toxic effects in the cardiovascular system (Amand *et al.*, 1995).

In conclusion, all the three neurotoxic insecticides (malathion, lindan, permethrin) antagonize the central cholinergically-mediated hypertension produced by intravenous injection of physostigmine. This does not necessarily mean that all three insecticides act by the same mechanism. Malathion probably acts by irreversible inhibition of acetylcholinesterase in the central nervous system. The other two substances produce changes in the functions of neurons, the interaction of neurotransmitters being one of them. One of these interactions produces central cholinergically-mediated hypertension, which is inhibited by neurotoxic insecticides.

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DEJSTVA NEUROTOKSIČNIH INSEKTICIDA NA CENTRALNU HOLINERGIČKI-POSREDOVANU HIPERTENZIJU

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SADRŽAJ

Malation prouzrokuje dvofazni efekat na arterijski krvni pritisak anestetizaranih pacova. Neposredno posle intravenske injekcije, malation prouzrokuje kratkotrajnu hipotenziju (do 90 sec.), posle čega nastaje produžena hipertenzija slična onoj koja je zapažena posle intravenske injekcije fizostigmina pacovima. Hipotenzija prouzrokovana malationom najverovatnije nastaje usled nagomilavanja acetilholina posle inhibicije holinesteraze malationom. Hipertenzivni efekt malationa nastaje usled sekundarne aktivacije adrenergičkih mehanizama u centralnom nervnom sistemu.

Malation prouzrokuje dozno-zavisnu inhibiciju centralne holinergički-posredovane hipertenzije kod pacova izazvane intravenskom injekcijom fizostigmina. Kako stepen, tako i trajanje hipertenzije bili su podjednako deprimirani. Ovi eksperimenti ukazuju da je razvoj centralne holinergički-posredovane hipertenzije moguć jedino u prisustvu funkcionalno kompetentne holin-esteraze.

Lindan i permetrin takođe deprimiraju centralnu holinergički-posredovanu hipertenziju izazvanu intravenskom injekcijom fizostigmina. Prema tome, sva tri neurotoksična insekticida prouzrokuju inhibiciju interakcije neurotransmitera koja je osnova za razvoj centralne holinergički-posredovane hipertenzije, ali je moguće da to čine različitim mehanizmima.