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COMMUNICATIONS

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Inhibition of brain cholinesterase activity after the injection of organophosphorus compounds in the rat

B. REIFF (introduced by I. L. NATOFF), *Tunstall Laboratory, Shell Research Ltd., Sittingbourne, Kent*

The intravenous injection into rats of cholinesterase inhibitors which penetrate the blood-brain barrier results in an inhibition of the brain cholinesterase activity and produces a rise in blood pressure which is mediated through the peripheral sympathetic pathways (Dirnhuber & Cullumbine, 1955; Varagić, 1955; Gokhale, Gulati & Joshi, 1965).

Graded doses of different organophosphorus cholinesterase inhibitors were injected intravenously into groups of male rats anaesthetized with urethane. One hundred and fifty seconds after injection, the animals were killed and the brains removed and frozen for subsequent electrometric determination of cholinesterase activity.

The potency of the cholinesterase inhibitors *in vivo* may be regarded as being dependent on two factors: (1) accessibility to the site containing the enzyme, and (2) the " overall inhibitory power " of the compound against the enzyme (Main, 1964).

The accessibility was taken to be a function of the lipid–water partitioning characteristics of the compounds, expressed as *Rm* values [$Rm=\log(\frac{1}{Rf}-1)$; Bate-Smith & Westall, 1950], and measured by reverse phase thin-layer chromatography (stationary phase: kieselguhr-liquid paraffin; mobile phase: water–acetone 1 : 1). The overall inhibitory power was measured *in vitro* using rat brain homogenate as the enzyme source and acetylcholine bromide as the substrate, and expressed as the bimolecular rate constant, k_i (Aldridge, 1950).

The potency was measured as the intravenous dose which produces 50% inhibition of brain cholinesterase activity in 150 s (the ID50). Table 1 shows for each compound the values for k_i, *Rm* and the ID50.

TABLE 1. *Bimolecular rate constants (k_i) for rat brain cholinesterase, the partitioning characteristics (Rm) and the doses of organophosphorus compounds which inhibit brain cholinesterase activity by 50% (ID50) in the anaesthetized rat at 150 s after intravenous injection*

Compound	k_i (in M^{-1} min^{-1})	ID50 (in μmol/kg)	*Rm*	log (k_i . ID50)
Monocrotophos	$1{\cdot}0\times10^4$	25·83	−0·79	5·41
Dichrotophos	$1{\cdot}3\times10^4$	8·76	−0·66	5·06
Mevinphos	$95{\cdot}6\times10^4$	0·51	−0·53	5·69
Dichlorvos	$9{\cdot}1\times10^4$	11·74	−0·29	6·03
Paraoxon	$758{\cdot}8\times10^4$	0·31	−0·27	6·37
Crotoxyphos	$166{\cdot}5\times10^4$	3·00	−0·18	6·70
WL 22864	$70{\cdot}9\times10^4$	2·94	−0·12	6·32
SD 14045	$48{\cdot}6\times10^4$	6·36	−0·09	6·49
Chlorfenvinphos	$37{\cdot}3\times10^4$	28·77	+0·16	7·03

The experimental data could be related by the equation:

$$\log (k_i \text{ ID50}) = 1{\cdot}94\ Rm + 6{\cdot}71$$
$$(\pm 0{\cdot}27) \quad (\pm 0{\cdot}12)$$

The correlation coefficient of the resulting straight line was 0·939 ($n=9$).

The relationship includes a rate constant which implies time dependence, demonstrating that the pharmacological responses *in vivo* during the pre-steady state are related to the physico-chemical characteristics of the organophosphorus compounds. This is in contrast to the steady-state relationships which have often been used as models to correlate chemical structure with biological activity (compare Hansch & Fujita, 1964; Fujita & Nakajima, 1969).

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The release of ^{14}C-glycine from electrically stimulated rat spinal cord slices

JUDY M. HOPKIN and M. J. NEAL*, *Department of Pharmacology, School of Pharmacy, University of London*

Although there is now much electrophysiological evidence that glycine and γ-aminobutyric acid (GABA) are inhibitory transmitters in the central nervous system (Curtis, Hösli & Johnston, 1968; Krnjević & Schwartz, 1967), it has proved difficult