Penicillin-induced convulsions and inhibition of glutamate decarboxylase

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Penicillins administered topically to the brains of animals produce epileptiform convulsions possibly by the antagonism of GABA-mediated inhibition (Hill, Simmonds & Straughan, 1973). However, both GABA synthesis and uptake have been shown to be reduced in epileptogenic foci induced by penicillin (Gottesfeld & Elazar, 1975). In view of the fact that inhibitors of GABA synthesis also produce convulsions (Wood, 1975) and that some penicillins produce convulsions after a longer delay than might be expected from a direct interaction at GABA receptors, the present study has compared the relative potencies of a range of penicillins as glutamate decarboxylase (GAD) inhibitors and as convulsants.

Adult LACG mice were used throughout. CD_{50} values were determined following direct intracerebroventricular injection as described previously (Taberner, 1976). GAD activity was assayed in partially purified extracts of whole brain using essentially the radioisotopic method of Roberts & Simonsen (1963) in the presence of excess pyridoxal phosphate. Inhibitor constant (Ki) values were subsequently determined from Dixon plots using varying concentrations of inhibitor and substrate.

The penicillins tested fell into three groups in terms of CD_{50}. Group I (ampicillin, amoxycillin and 6-aminopenicillanic acid) failed to produce convulsions at doses up to the limit of their solubility (>220 nmoles). Group II (penicillin G, penicillin V, flucloxacillin and cloxacillin) were convulsant, with CD_{50}'s between 50 and 80 nmoles. Group III (D- and L-Penicillamine) were far less potent with CD_{50}'s of 1737 and 2139 nmoles respectively. All the compounds listed were inhibitors of GAD activity and competitive with respect to glutamate. The Ki values all fell within the range of 1–10 mM and showed no correlation with relative convulsant potency. Mean latency to convulsions varied between 1.6 min (penicillin V) and 2.8 min (cloxacillin), except D-penicillamine which had a mean latency of 43.5 minutes.

All group I and II compounds contain the β-lactam and thiazolidine rings of the penicillin nucleus whereas D-and L-penicillamine (ββ-dimethylcysteine) consist only of the uncondensed thiazolidine ring in a straight chain form. Since the penicillins and penicillamines were approximately equipotent GAD inhibitors it is unlikely that the β-lactam ring is required for GAD inhibition. The low convulsive potency of Group I compounds may reflect their poor solubility which prevents them from penetrating to their site of action *in vivo*. The average concentration of the group II penicillins in the brain after i.c.v. injection will be well below their Ki values for GAD inhibition, and it is therefore very unlikely to contribute significantly to the convulsant action of these compounds. However, the low potency of D- and L-penicillamine and the long latency exhibited by D-penicillamine suggest that, in this case, GAD inhibition may be responsible for their convulsant activity.

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Some sub-cellular effects of an organophosphorus insecticide, Abate

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Organophosphorus compounds are characterized by their anticholinesterase effects; in addition, they have been found to affect microsomal drug metabolizing enzymes of the liver (Stevens, Stitzel & McPhillips, 1972). In this study the interactions of OOO'-O'-tetramethyl-OO'-thiodi-*p*-phenylene phosporothioate, Abate, with rat liver, brain and blood have been investigated. Rats of the CFHB-remote Wistar strain were given Abate in arachis oil daily by intraperitoneal injection at doses between 10 and 300 mg/kg body weight over periods of 4, 7 and 10 days. Changes in the levels of various enzymes in liver homogenates and sera have been used as indicators of hepatic injury. Of the enzymes determined, Aspartate transaminase, Alanine transaminase, acid phosphatase and the ratio of Lactate dehydrogenase (2oxobutarate:Pyruvate) did not show any significant changes over all dose periods (P=0.05). There were slight reductions in the levels of Glutamate dehydrogenase and aminopyrine demethylase at all dose periods and in the P_{450} in the 7