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Convulsant activity of thiomalate; a possible metabolite of aurothiomalate

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It has recently been shown that thiomalic acid is a potent competitive inhibitor of glutamate decarboxylase, GAD (Taberner, Pearce & Watkins, 1977). Since other GAD inhibitors, e.g. mercaptopropionic acid, (Lamar, 1970), 4-deoxypyridoxine (Horton & Meldrum, 1973), have been found to possess convulsant activity, and in view of the fact that thiomalic acid, in the form of sodium aurothiomalate (Myocrisin), is used widely in the treatment of arthritis and rheumatism (Gold Therapy in 1975), it was felt that thiomalic acid should be examined for possible convulsant activity.

Thiomalic acid (A.R., Koch-Light Laboratories Ltd.) was converted to the sodium salt by the stoichiometric addition of sodium hydroxide and a 100 mM stock solution prepared and adjusted to pH 7·4 with 50 mM sodium phosphate buffer. Adult LACG mice of either sex were used. Values for the minimum convulsive dose and ED50 of thiomalate were calculated by the methods described previously (Taberner, 1976), and the dose ranges given below represent the 95% confidence limits.

Following intraperitoneal injection, thiomalate was inactive at doses up to 2 mmol (340 mg) kg^{-1}. Higher doses were not tested. After the intracerebroventricular injection of thiomalate, using the method described by Brittain & Handley (1967), the minimum convulsive dose was 0·85 – 0·87 μmol (145 – 150 μg). At higher doses the mice went into running fits within 20–45 s of the injection. Occasional full tonic clonic seizures were also observed. The ED50 for running fits was 1·28 ± 0·10 μmol (220 ± 18 μg) kg^{-1}. The running fits lasted, on average, 8–12 min and the mice fully recovered by 30 min.

Running fits are also a characteristic feature of the effects of mercaptopropionate (Lamar, 1970) suggesting that they may well reflect a common mechanism of action of mercaptopropionate and thiomalate. Both compounds are equipotent as inhibitors of GAD *in vitro* (Taberner & others, 1977) yet the ED50 for mercaptopropionate following intraperitoneal injection in mice is reported to be 0·27 mmol kg^{-1} (Horton & Meldrum, 1973). The lack of activity of thiomalate following intraperitoneal injection therefore suggests that it does not readily cross the blood-brain barrier.

Gold therapy, whilst effective, is subject to an extremely high incidence of side-effects (Girdwood, 1974) although seizure activity has not been reported. The thiomalate moiety has no intrinsic therapeutic value and is only one of several soluble salts with which gold can be combined (Harvey, 1975). A recent report (Danpure, 1976) has indicated that sodium aurothiomalate can react *in vitro* with cysteine to yield free thiomalate. Whilst this reaction may present no risk to patients with a fully-functioning blood-brain barrier, in pathological conditions such as meningitis, when the blood-brain barrier is less effective, there is the possibility that thiomalate may enter the brain and its convulsant properties thus become apparent.

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