Some neuropharmacological properties of the new non-barbiturate hypnotic etomidate (R (+)-ethyl-1-(α-methyl-benzyl) imidazole-5-carboxylate)

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Etomidate is a novel short acting hypnotic of great potency and low toxicity. The drug has two optical isomers but only the (+) isomer possesses the hypnotic properties (Janssen, Niemegeers, Schellekens & Lenaerts, 1971). Experiments have been performed in an attempt to elucidate its mode of action.

Both isomers were administered to rats and mice by a variety of routes. Mice were injected intracerebroventricularly by the method of Brittain & Handley (1967) and the ED_{100} for ten minutes loss of righting reflex was determined. For the (+) isomer this was 67.0 ± 9.2 μg, but the (−) was inactive at doses up to 500 μg.

Using the technique of microiontophoresis (Hill & Simmonds, 1973) GABA, glycine and both isomers of etomidate were applied alternately from multi-barrelled micropipettes onto single neurones in the cuneate nuclei of urethane anaesthetized rats. Neurones were found to be readily depressed by GABA, glycine and both isomers of etomidate and, in terms of the applying currents used, the isomers were equipotent and approximately half as active as either GABA or glycine. In the same rats intravenous administration of the (+) isomer (0.25-1.0 mg/kg) produced a pronounced increase in the proportion of slow wave activity in the EEG with concurrent depression of single neurone firing. Topical superfusion of the medulla with solutions of (+)-etomidate in physiological saline (5×10^{-3} M) also significantly depressed neuronal firing. (−)-Etomidate (2 mg/kg; 5×10^{-3} M) was inactive in both of these tests.

In vitro tests of the activity of etomidate were also performed. Respiration of isolated rat brain tissue and mitochondria (Kerkut, Rick & Taberner, 1972) was not depressed by either isomer at concentrations (0.01 mM) in excess of those reported to occur in rat brain following the administration of hypnotic doses (Heykants, 1974). The active uptake of [^{3}H]-GABA and [^{14}C]-glutamate into rat brain slices was also studied (Balcar & Johnston, 1972). This uptake was found to be ouabain sensitive and temperature dependent but was not affected by either isomer of etomidate at concentrations up to 0.2 mM.

It can therefore be concluded that (+)-etomidate is an effective hypnotic at concentrations which do not affect essential tissue metabolism or uptake of putative transmitter substances. The results of the microiontophoretic experiments would suggest that the differing potencies of the two isomers are more likely to be due to the relative ease with which they gain access to their site of action rather than to an intrinsic difference in potency.

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