The GABA-mimetic action of etomidate

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Etomidate is a potent stereoselective hypnotic drug, the (+)-isomer having considerably greater hypnotic activity than the (−)-isomer (Janssen, Niemegeers, Schellekens & Lenaerts, 1971).

We have found that (+)-etomidate (5–50 μM) produced depolarization of primary afferent terminals and hyperpolarization of motoneurones as recorded from dorsal and ventral roots of the isolated spinal cord of the frog. At similar concentrations (+)-etomidate produced depolarization of postsynaptic neurones of the rat isolated superior cervical ganglion. On both these preparations (+)-etomidate was 20 times more potent than (−)-etomidate and the responses produced were slower in onset and of longer duration than those produced by similar applications of GABA. The levels of (+)-etomidate used were within the range found in rat brain following hypnotic doses (Heykants, 1974).

Responses of these *in vitro* preparations to etomidate were specifically antagonized by bicuculline (25 μM) or picrotoxin (50 μM) as were responses to GABA, whereas strychnine (1 μM) antagonized hyperpolarizing responses of frog motoneurones to β-alanine but not responses to (+)-etomidate or GABA.

A similar pharmacological specificity was also observed on caudal medulla neurones of the halothane anaesthetized rat *in vivo*. Iontophoretic application of bicuculline methobromide (10–40 nA) antagonized the depression of firing rate produced, by iontophoretic application of GABA (0–20 nA) or (+)-etomidate (20–50 nA), but when glycine (0–20 nA) and (+)-etomidate were compared, iontophoretic application of strychnine (0–10 nA) antagonized only responses to glycine.

All these results indicate that the depressant effect of etomidate is produced by a GABA-mimetic action and this is unlikely to be the result of endogenous GABA release since (+)-etomidate has been shown not to affect uptake of [^{3}H]-GABA by rat brain slices (Hill & Taberner, 1975).

Pentobarbitone and other barbiturates have also been shown to have a GABA-mimetic action (Nicoll, 1975). We have compared these actions of pentobarbitone with those of (+)-etomidate on the *in vitro* preparations above and it is interesting that their relative molar potencies for GABA-mimetic action correspond closely to their relative hypnotic potencies.

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Interactions of GABA antagonists on the isolated frog spinal cord

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Picrotoxin (PTX) and bicuculline (BIC) are now well established as antagonists of the central action of GABA (Curtis & Johnston, 1974). Recently isopropyl bicyclo phosphate (IPTBO) has been shown to be a potent GABA antagonist on the isolated rat superior cervical ganglion and the hemisected isolated frog spinal cord (Bowery, Collins, Hill & Pearson, 1976). However, very little is known about the precise mechanism of action of these compounds in the CNS. To investigate this further d.c. recording from a dorsal root of the frog spinal cord preparation (Bowery *et al.*, 1976) was used and superfusion of GABA in Tris buffered Ringer was found to give dose dependent depolarizations. The antagonism produced