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.

This work was supported by the Medical Research Council and Janssen Pharmaceutical supplied the etomidate.

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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

Table 1 Dose ratios (D.R.) produced by bicuculline (BIC), picrotoxin (PTX), iso-propyl bicyclo phosphate (IPTBO) and mixtures of pairs of these compounds

	Mean D.R.	*Mean D.R. with*	
	Alone	*BIC*	*PTX*
BIC	3.5 (3)	—	10 (1)
PTX	2.5 (3)	10 (1)	—
IPTBO	6.9 (3)	32 (2)	5.0 (3)

Number of experiments shown in brackets.

by PTX (10 μM), BIC (50 μM), IPTBO (100 μM), and mixtures of pairs of these compounds, was expressed as a dose ratio (DR) of shift of the dose response curve to GABA. These values are shown in Table 1.

If two antgonists act competitively at the same site, the DR for a mixture of the two would be expected to be $DR_1 + DR_2 - 1$, but if one of the antagonists were non-competitive it would then be $DR_1 \times DR_2$ (Abramson, Barlow, Mustafa & Stephenson, 1969). From Table 1, IPTBO + PTX gave the former relationship while IPTBO + BIC and PTX + BIC gave the latter, suggesting that PTX and IPTBO share a common mode of action while BIC exerts its antagonism by a different mechanism. This may reflect a difference between competitive and non-competitive antagonism or in this preparation antagonists may be acting at two distinct sites in the sequence of events triggered by GABA.

We wish to thank Dr. J.F. Collins for the IPTBO. S.P. is a Wellcome Research Student.

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The effect of (±)-6-fluorotryptophan on sleep and brain monoamine levels in the rat

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(±)-6-Fluorotryptophan (6-FT) has been reported to be a short-acting, competitive inhibitor of brain tryptophan hydroxylase, with a specificity of action superior to that of the widely-used inhibitor, p-chlorophenylalanine (pCPA) (McGeer, Peters & McGeer, 1968; Peters, 1971). 5-hydroxytryptamine (5-HT) is generally accepted to play an important role in the control of sleep mechanisms (Jouvet, 1972). However, in depletion experiments in the rat using pCPA (Rechtschaffen, Lovell, Freedman, Whitehead & Aldrich, 1973) or 5,7-dihydroxytryptamine (Ross, Trulson & Jacobs, 1976), results have been obtained which are not consistent with this hypothesis. This report describes the effects on sleep of an alternative inhibitor to pCPA.

Male Sprague-Dawley rats (200–250 g) under pentobarbitone sodium anaesthesia (60 mg/kg intraperitoneally) were prepared for EEG recording by implanting electrodes onto the cortical surface (Timo-Iaria, Negrão, Schmidek, Hoshino, de Menezes & da Rocha, 1970). Following surgery, all rats were housed individually for at least one week; food and water *ad libitum*, lights on 0800–2000 h, ambient temperature 20 ± 2°C. In each experiment, recordings were made on 3 consecutive days (pre-drug, drug and post-drug days) from either 1200 to 1600 h ($n=4$) or