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The anticonvulsant activity of ketamine in mice following the inhibition of GABA synthesis by mercaptopropionic acid

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The dissociative anaesthetic, ketamine, has been reported to precipitate epileptiform discharges in the neocortex of the cat (Winters, Ferrar-Allado, Guzman-Flores & Alcaraz, 1972; Wong & Jenkins, 1974) although Celesia & Chen, (1974) have demonstrated that ketamine suppresses focal seizures in the same species. Similar conflicting evidence has been obtained in man (see Ferrar-Allado, Brechner, Dymond, Cozen & Crandall, 1973; Corssen, Little & Tavakoli, 1974). Ketamine is also known to inhibit glutamate decarboxylase (GAD) *in vitro* (Dye & Taberner, 1975) and therefore the effects of ketamine on the convulsions produced by another inhibitor of GAD, mercaptopropionic acid, have been examined.

All drugs were made up in physiological saline and injected i.p. into groups of 8 adult LACG mice of either sex. The time from injection to the first full tonic-clonic seizure was determined. The dose required to produce full seizures in all the mice (CD_{100}) was also determined.

Ketamine alone produced a dose-dependent loss of the righting reflex during which time the mice exhibited random twitching of the limbs. At a dose of 90 mg/kg the mice lost their righting reflex for 19.2 ± 1.8 minutes. Mercaptopropionate alone produced convulsions and running fits within 4 min at doses in excess of 20 mg/kg; the CD_{100} was 35 mg/kg. At this dose all the mice recovered within 30 minutes. The LD_{100} for mercaptopropionate was 140 mg/kg. When ketamine (90 mg/kg) was given simultaneously with the mercaptopropionate the minimum convulsive dose was increased to 168 mg/kg; the CD_{100} to 195 mg/kg and the LD_{100} to over 250 mg/kg. Ketamine did not affect the degree of inhibition of GAD observed *in vivo* following convulsive doses of mercaptopropionate. At the onset of convulsions after 150 mg/kg mercaptopropionate the inhibition was 35-39% compared to control mice. In mice given ketamine plus mercaptopropionate, which were not convulsing, the degree of inhibition was within the same range.

From these results it would appear that, despite the overt excitatory behavioural phenomena observed following hypnotic doses of ketamine, the latter can prevent seizures induced by mercaptopropionate. Also, at this dose, ketamine does not measureably inhibit GAD *in vivo* nor does it prevent the convulsive effects of mercaptopropionate by protecting GAD from inhibition. The results therefore support the view of Chen and his co-workers (Chen, Ensor & Bohner, 1966; Celesia & Chen, 1974) namely, that ketamine possesses anticonvulsant properties.

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Response of identified ventromedial hypothalamic nucleus neurones to putative neurotransmitters applied by microiontophoresis

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Recent physiological studies have indicated that the amygdala exerts a prominent excitatory influence on the majority of HVM neurones, and that HVM neurones have efferent connections to both hypothalamic (median eminence, anterior hypothalamic area) and extrahypothalamic (preoptic area, periaqueductal gray, amygdala and thalamus) areas (Renaud & Martin, 1975b). This study details preliminary results on the responsiveness of HVM neurones, identified through their afferent and efferent connections, to microiontophoretic application of substances which may act as neurotransmitter agents in this region.

Spike discharges from HVM neurones in pentobarbitone anaesthetized male Sprague Dawley rats were recorded with single 3.0 M NaCl filled micropipettes rigidly mounted to an adjacent multibarrelled micropipette filled with the following solutions:– monosodium L-glutamate (0.5 M, pH 7.0); gamma aminobutyric acid (0.5 M, pH 4.5); glycine (0.5 M, pH 3.5); histamine dihydrochloride (0.2 M, pH 4.0); dopamine HCl (0.2 M, pH 4.5); picrotoxin (5 mM, pH 7.5); strychnine sulfate (5 mM, pH 5.5); growth hormone release-inhibiting hormone or somatostatin (5 mM, pH 6.5); thyrotrophin releasing hormone (5 mM, pH 6.5); and luteinizing hormone releasing hormone (5 mM, pH 6.5).

The actions of these substances on the neural activity or excitability of HVM cells are summarized in Table 1.

Of the excitatory substances, the action of glutamate was brisk in onset and termination compared with the slow onset excitant action of histamine, an effect which outlasted the application by several seconds (Haas, 1974). The potent depressant action of GABA and glycine was rapid in onset and termination. Although these effects could be antagonized by picrotoxin and strychnine respectively, only picrotoxin applied either by microiontophoresis or by intravenous injection partially antagonized synaptic inhibition evoked by amygdala stimulation. Only depressant responses were observed with the three hypothalamic peptides tested. Selected HVM neurones displayed marked sensitivity to some peptides but not others (Renaud & Martin, 1975a; Renaud, Martin & Brazeau, 1975). The action of dopamine was never as potent as that of the depressant amino acids, but similar to the weaker depressant responses observed with some peptides.

More detailed study of HVM neurones with specific efferent connections, may indicate cellular populations with receptors for specific substances, and may help to define their biological significance in neural integration and regulation within this important hypothalamic centre.

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Table 1 Pattern of response (no. of cells)

	Increase	*Decrease*	*No response*	*Current range (nA)*
Glutamate	46	0	0	24-80
Histamine	12	20	5	3-25
GABA	0	18	1	5-20
Glycine	0	16	1	8-22
Dopamine	0	18	6	20-50
GH-RIH	0	28	8	5-80
LH-RH	0	13	5	10-30
TRH	0	46	20	10-30