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An anticholinergic effect of general anaesthetics on cerebrocortical neurones

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The effect of general anaesthetics on the increase in neuronal firing rate produced by the iontophoretic application of acetylcholine and L-glutamate is controversial. Krnjević & Phillis (1963) observed a specific anticholinergic effect (see also Catchglove, Krnjević & Maretić, 1972). But a nonspecific decrease in the post-synaptic sensitivity to all chemical excitants has also been reported (Crawford, 1970; Crawford & Curtis, 1966). It seemed worthwhile therefore to try to eliminate these discrepancies and possibly throw light onto the mechanism of action of general anaesthetics. Rats were anaesthetized with urethane (2.2 g/kg). Electrodes were placed on the exposed cortical surface for ECoG. recording and multibarrelled glass micropipettes inserted into the underlying cortical tissue for recording of single neuronal action potentials and the application of drugs by iontophoresis using the standard techniques.

Under urethane anaesthesia the ECoG. appears as surface positive waves separated by quiescent periods, with the spontaneous activity of cortical neurones occurring during these waves in the ECoG. (Bindman, Lippold & Redfearn, 1964). Monitoring the ECoG. therefore gives a measure of the endogenous drive to the cortex. The iontophoretic application of either L-glutamate or acetylcholine to responsive cortical neurones caused firstly an increase in the number of action potentials falling within the ECoG. waves (presumably representing facilitation of endogenous drive—Forrester, 1975) and then, if the rate of iontophoresis was sufficiently high, evenly spaced action potentials between the ECoG. waves.

When a variety of central depressants (including barbiturates, halothane and benzodiazepines) were systemically administered a decrease in the frequency of the ECoG. waves resulted-without changes in blood pressure (Forrester & Gartside, 1975). Consequently iontophoretically induced excitations which were largely dependent upon the drive to the cortex were reduced. In 5 experiments with halothane (1-2%, inspired) and 8 experiments with thiopentone (5-10 mg/kg, i.v.) both L-glutamate and acetylcholine excitations of this type were reduced.

When thiopentone (5-10 mg/kg, 9 experiments), halothane (1-2%, 12 experiments) and diazepam (1.5-2.0 mg/kg, 10 experiments) were administered to animals where, in the control responses both acetylcholine and L-glutamate induced action potentials between the bursts, then the production of 'interburst action potentials' by acetylcholine was suppressed but those produced by L-glutamate were not.

Hence it is concluded that the general anaesthetics tested antagonize the depolarization of cortical neurones produced by the iontophoretic application of acetylcholine but not that produced by L-glutamate; although depending upon the conditions the increase in neuronal firing rate produced by L-glutamate can be reduced. These results, therefore, support the view that the anticholinergic effect of general anaesthetics may contribute to their anaesthetic effect (Krnjević, 1974).

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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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