respectively (ratio = 13.7). Picrotoxin and ouabain also had strong proconvulsant actions (ratios 97 and 91 respectively), maximal at 15 min like FA. Ouabain had a longer duration of action (at least 4 h) than FA and picrotoxin (1 h). Other convulsants tested (glutamate, homocysteic acid, leptazol and strychnine) were only weakly active immediately (5-60 s) after administration and had low ratios (1.4 to 2.7). In the leptazol infusion test (0.3 mg/min i.v.) in mice all drugs tested except ouabain when administered at up to convulsant ED_{50} values significantly reduced the time from clonus to HLE ($P < 0.05$).

The proconvulsant action of sub-convulsive doses of FA in mice to a strong afferent stimulus which was itself not convulsant was examined by subjecting the mice to an auditory stimulus (110dB, 15 s) from a bell suspended at 70 cm in a box 34 cm diameter and 76 cm high. In mice pre-treated (−15 min) with FA, generalized convulsions (ED_{50} = 2.3 μg) and HLE (2.8 μg) were readily induced. Convulsions occurred in only 4% of mice (n = 90) pretreated with control fluid (i.c.v.).

It is known that repetitive electrical stimulation applied locally to the cortex can act as an epileptogenic focus which will produce an after-discharge (AD). ADs were induced in rats chronically implanted with an electrical connector linked to screw electrodes in the skull (Goff, Miller, Smith, Smith & Wheatley, 1975). Stimulation (100 Hz, 1 ms width, 1 s duration) through a frontal screw induced clonic convulsions accompanied by AD of mean duration 12.1 s (n = 9). When tested 90 min later, FA (10 μg intraventricularly) at 15 min before the second stimulation significantly increased AD duration by 90% (P = 0.001: n = 3). Control fluid (intraventricularly) significantly reduced AD duration by 62% (P = 0.05: n = 3) whereas in untreated rats (n = 8), AD duration was unchanged after the second stimulation.

The results suggest that raised folate concentrations can increase cortical activity and therefore increase the tendency to convulsions.

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Further observations on the change in sensitivity to halothane induced by acute administration of central nervous system depressant drugs in the rat

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In a previous communication we outlined the use of repeated determination of halothane-induced sleeping time as a method for studying changes in the excitability of the central nervous system (CNS) occurring with time (Turnbull & Watkins, 1975). We reported that pre-treatment of rats with sodium pentobarbitone (a total dose of 90 mg kg^{-1} over a period of 10 h) or meprobamate (800 mg kg^{-1} 10 h^{-1}) resulted in the development of a hyposensitivity to halothane which was followed by a rebound hypersensitivity to the anaesthetic. However, we could not be certain that the changes in sleeping time were entirely due to changes in the sensitivity of the CNS. We have therefore measured brain halothane concentrations on awakening in saline and drug pretreated rats and have found the same pattern of change in CNS excitability as was indicated by the sleeping time.

First, we have confirmed that repeated exposure to halothane does not induce hyposensitivity. The brain halothane concentration found on awakening from the last of twelve exposures to halothane was the same (111 ± 10 (6) μg g^{-1} ± s.e. mean) as that found in rats which had been anaesthetized only twice during the same 48 h period (120 ± 6 (6) μg g^{-1}). Secondly, we have shown that the diurnal variation in sleeping time is due to an altered sensitivity of the CNS to halothane, since rats awakened with a higher brain halothane content at 0100 h (167 ± 7 (6) μg g^{-1}) than at 1100 h (126 ± 11 (6) μg g^{-1}).

We have also repeated our experiments in which

halothane sleeping time was determined at intervals after administration of sodium pentobarbitone (90 mg kg^{-1} 10 h^{-1}) or meprobamate (800 mg kg^{-1} 10 h^{-1}) but in addition have determined the brain halothane concentration on awakening in groups of similarly pretreated animals killed at the time of maximum hyposensitivity and hypersensitivity to the anaesthetic. The brain halothane concentration on awakening was significantly higher at the time of decreased sensitivity (control 131 ± 5: pentobarbitone pretreated 157 ± 8; meprobamate pretreated 177 ± 9 $\mu g\ g^{-1}$) and significantly lower at the time of hypersensitivity (control 190 ± 23: pentobarbitone pretreated 125 ± 21, meprobamate pretreated 132 ± 18 $\mu g\ g^{-1}$) compared with the levels found in saline pretreated animals.

In addition, we have assessed the sensitivity of similarly pretreated rats to pentobarbitone by determining the duration of anaesthesia following an i.c.v. injection of 800 μg sodium pentobarbitone. Halothane-tolerant rats were found to be tolerant to i.c.v. pentobarbitone and halothane-sensitive rats slept for significantly longer than control animals. Thus, using three different indices, our results indicate that repeated injection of anaesthetic doses of pentobarbitone or meprobamate leads to the development of a hyperexcitability which is followed by a rebound decrease in the excitability of the CNS. The effect of pretreatment with other centrally active drugs is presently being investigated.

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Is morphine inhibition of the twitch response of the mouse vas deferens mediated via noradrenaline?

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The inhibitory effect of morphine on the mouse vas deferens was first reported by Henderson, Hughes & Kosterlitz (1972). We have confirmed that morphine in low concentrations (0.03-3.0 μM) inhibits the twitch response to field stimulation (0.1 or 1.0 Hz, 1 ms, 150 mA). This action of morphine is antagonized by small doses of the narcotic antagonist, naloxone (50 nM).

Morphine has also been reported to inhibit the output of noradrenaline in this tissue and it was suggested that this was the mechanism by which it inhibited the twitch response (Henderson, Hughes & Kosterlitz, 1972; Hughes, Kosterlitz & Leslie, 1975).

In 5 experiments the output of noradrenaline from 4 vasa deferentia was measured by bioassay (Hughes, 1972). After 120 stimuli at 1.0 Hz it was 52 ± 9 pg (mean ± s.e. mean). When morphine (1.0 μM) was added to the bath in the same experiments the output of noradrenaline was 53 ± 9 pg. After the morphine was washed out 43 ± 13 pg of noradrenaline was released.

In another experiment a control output of 31 pg of noradrenaline was increased by phenoxybenzamine (15 μM) to 391 pg. Here morphine (1.0 μM) still inhibited the response to stimulation but did not reduce the output of noradrenaline (373 pg).

When noradrenaline (0.1-3.0 μM) was added to the bath the twitch was inhibited and this inhibition was reduced by phentolamine (10 μM). The dose response curve for the inhibitory effect produced by morphine (0.1-0.3 μM) was unaffected by phentolamine (10 μM). Conversely, the dose-response curve for the inhibitory effect of noradrenaline was unaffected by naloxone (50 nM) while the same concentration of naloxone displaced the morphine curve to the right.

The motor response of the vas deferens to exogenous noradrenaline or acetylcholine was unaffected by morphine (1.0 μM) thereby excluding an action of the drug on post-synaptic receptors.

In conclusion, these results suggest that the inhibitory effect of morphine on the twitch response of the mouse vas deferens is unlikely to be mediated via noradrenaline.

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