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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The effects of chronic lithium administration on the metabolism of L-tryptophan in the rat forebrain

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We have investigated the effect of lithium (Li^+) on the accelerated production of 5-hydroxyindoles induced by a large dose of L-tryptophan. Male Albino Wistar rats (124) weighing 150-250 g were divided into two groups of 62 animals. One group received an i.p. injection of isotonic (0.15 M) LiCl (0.75 mequiv/kg) each day for 10 days, whilst the control group received injections of saline. Twenty-four hours after the last dose of Li^+ or saline, half of the animals in each group received a single injection of L-tryptophan (100 mg/kg i.p.) whilst others received an equivalent volume of saline. Pairs of animals (one tryptophan treated and one control) from each group were killed 30, 60 and 90 min after the injection of tryptophan or saline, and the forebrain concentration of 5-HT and 5-HIAA measured fluorimetrically (Collard & Roberts, 1974).

Li^+ pretreatment had no effect on the changes in forebrain 5-HT and 5-HIAA measured 30 or 90 min after the injection of L-tryptophan (Table 1). However, the maximum increase in 5-HT concentration which occurred 60 min after the injection, was significantly reduced in the Li^+ group, and the concentration of 5-HIAA was correspondingly increased.

There is evidence that the increase in 5-HIAA concentration induced by a loading dose of L-tryptophan results from the deamination of the increased amount of free cytoplasmic 5-HT which is accessible to monoamine oxidase (Moir & Eccleston, 1968). The results of this study may therefore indicate that Li^+ increases the deamination of free cytoplasmic 5-HT, possibly by inhibiting the transport of newly synthesized 5-HT into, or the binding of 5-HT within the storage compartment of 5-HT neurones. Alternatively, Li^+ may divert the metabolism of L-tryptophan away from the production of 5-HT, and towards the production of 5-hydroxyindolepyruvic acid through the 5-HTP aminotransferase pathway (Millard & Gal, 1971).

Table 1 The effect of Li^+ pretreatment on L-tryptophan-induced changes in forebrain 5-hydroxyindoles measured 30, 60, and 90 min after the i.p. injection of L-tryptophan (100 mg/kg). Results are expressed as the mean ± s.e. of mean 8, 13, and 10 pairs respectively. Statistical analysis is by paired *t* test

	Change in 5-HT concentration (ng/g wet weight)			
Time after L-tryptophan	*Control*	*Lithium*	*Lithium minus control*	*P*
30 min	+ 145 ± 50	+ 142 ± 52	− 3 ± 77	NS
60 min	+ 283 ± 59	+ 132 ± 71	− 151 ± 64	$P < 0.05$
90 min	+ 202 ± 53	+ 72 ± 80	− 130 ± 96	NS
	Change in 5-HIAA concentration (ng/g wet weight)			
Time after L-tryptophan	*Control*	*Lithium*	*Lithium minus control*	*P*
30 min	+ 75 ± 19	+ 117 ± 15	+ 42 ± 24	NS
60 min	+ 201 ± 39	+ 280 ± 23	+ 79 ± 35	$P < 0.05$
90 min	+ 254 ± 30	+ 235 ± 47	− 19 ± 39	NS

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