Change in sensitivity to halothane in the rat following administration of sodium barbitone in the drinking water

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We have measured the duration of halothane-induced anaesthesia at intervals during a four week period of administration of sodium barbitone and also after its subsequent withdrawal using the method we have previously described (Turnbull & Watkins, 1975a). Groups of eight female Wistar rats, weighing approximately 130 g at the beginning of the experiment, were used and the sodium barbitone was administered in increasing concentration in the drinking water (which also contained saccharin 125 mg/l) over the period of four weeks. The concentration of barbitone was such that the daily dose increased from approximately 100 mg/kg during the first week to approximately 400 mg/kg during the fourth week. The intended and actual barbitone intakes are compared in Figure 1. Drug withdrawal was effected by substituting saccharin solution for barbitone solution at the end of the fourth week. Control rats received saccharin solution throughout. Halothane-induced sleeping time was measured in treated and control rats at 2–3 day intervals during the period of drug administration and at more frequent intervals after drug withdrawal.

Compared with control animals, the sensitivity to halothane was found to decrease during each of the first three weeks of barbitone administration (Figure 1). Thus, the sleeping time was significantly prolonged when measured on the first occasion each week (days 2, 8 and 15) but by the end of each week (days 7, 14 and 21) the difference between treated and control groups was no longer statistically significant. However, during the fourth week, no such decrease in sensitivity was found, perhaps due to drug cumulation.

Following barbitone withdrawal, a significant decrease in sensitivity to halothane, indicative of an increased excitability of the central nervous system, rapidly developed and lasted for approximately 72 hours. This was followed by a period of hypersensitivity to halothane, but by the sixth day of withdrawal the sensitivity to halothane had returned to control values.

Thus the pattern of change in sensitivity to halothane following drug withdrawal after a four week period of barbitone administration is remarkably similar to that which we have reported to occcur following repeated injections of pentobarbitone for only 10 h (Turnbull & Watkins, 1975b). This suggests that the results obtained with our acute (10 h) experimental model may be predictive of the changes in central nervous system excitability likely to occur on chronic drug administration.

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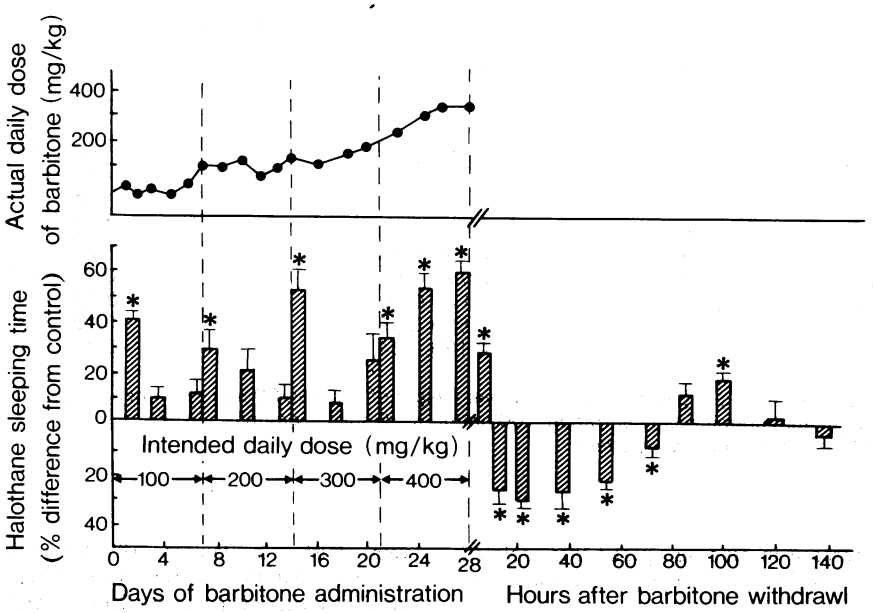

Figure 1 Effect of chronic barbitone administration and withdrawal on the sensitivity to halothane in the rat.
*$P < 0.05$

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Effect of some receptor antagonists on fenfluramine-induced glucose uptake into the isolated rat hemidiaphragm

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We have shown (Kirby, 1974; Kirby & Turner, 1975a,b) that the antiobesity drug fenfluramine in therapeutic concentrations causes a significant and dose related increase in glucose uptake into isolated rat and human skeletal muscle in the presence of insulin.

Using the rat hemidiaphragm preparation and fenfluramine (100 ng/ml), we have investigated the effect of a series of receptor blocking drugs (atropine, haloperidol, mepyramine, methysergide, propranolol and thymoxamine) on this phenomenon. The results (Table 1) show that only the 5-HT antagonist, methysergide, blocked the action of fenfluramine and that this effect was dose related occurring with relatively low concentrations. 10 ng/ml caused approximately 40% inhibition, the maximal response from earlier work being $+2.4 \pm 0.60$ mg of glucose/g wet weight of tissue in 90 min (Kirby & Turner, 1975b).

The results are in agreement with earlier work, in which methysergide was shown to block fenfluramine-induced contractions of human isolated saphenous vein (Kirby & Turner, 1971) and also with the evidence that the central effects of fenfluramine are mediated via 5-HT mechanisms (Garattini, Bizzi, de Gaetano, Jori & Samanin, 1975).

Table 1 Effect of antagonist on fenfluramine-induced glucose uptake into the rat hemidiaphragm

		Change with antagonist when compared with:	
Antagonist	*Concentration (ng/ml)*	*(a) Insulin** *Response*	*(b) Insulin + fenfluramine** *Response*
Methysergide	250	-0.18 ± 0.46	-1.90 ± 0.19**
	50	—	-1.98 ± 0.45*
	10	—	-0.87 ± 0.13*
	2	—	0.15 ± 0.12
Atropine	250	-0.13 ± 0.46	-0.05 ± 0.21
Haloperidol	250	-0.77 ± 0.45	-0.17 ± 0.17
Mepyramine	250	$+0.12 \pm 0.28$	$+0.12 \pm 0.17$
Propranolol	250	-0.58 ± 0.46	-0.18 ± 0.34
Thymoxamine	250	-0.18 ± 0.24	$+0.30 \pm 0.50$

* Change expressed as mg of glucose taken up/g wet weight of tissue in 90 min ± s.e. mean, insulin concentration 100 μu/ml, fenfluramine concentration 100 ng/ml, $n=6$ for all groups.
*$P < 0.01$; **$P < 0.001$ using paired t-test.

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