Table 1. *Effects of diazepam on "winning" behaviour of rats in the Grossmann tunnel test of dominance.* The animals encountered once in 10 trials the same opposing animals for five days. Treatment was the fifth day subcutaneously 30 min before testing.

Diazepam dose mg/kg, s.c.	Administered to	No of diazepam treated rats winning	No of reversals of 8 pairs
Placebo	Winner rats	—	0
2	Winner rats	7/8	1
6	Winner rats	8/8	0
Placebo	Loser rats	—	0
2	Loser rats	2/8	2
6	Loser rats	4/8	4
Placebo	Both rats	—	0
2	Both rats	—	2
6	Both rats	—	2

the cotton substitute. This probably means that the method has only a limited value for determining dominance reversal in drugged animals. It cannot be used to demonstrate the taming effect—as "winners" are not made "losers"—of anxiolytic compounds and is probably no measure of aggression for drugged animals.

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A comparison of Mg pemoline and (+)-amphetamine effects upon avoidance behaviour and the amine pump

Reserpine depresses conditioned avoidance behaviour in rats for up to 72 h. However, this depression can be partially reversed by treatment of the reserpinized rats with (+)-amphetamine (Rech, 1964). We have found that conditioned avoidance behaviour is also depressed by Ro 4-1284*, a short-acting reserpine analogue. Moreover, this depression is prevented by pretreatment of the animals with either (+)-amphetamine or Mg pemoline. While the two stimulants can both prevent Ro 4-1284 depression, they are dissimilar in their effects upon the amine pump, suggesting that they may antagonize Ro 4-1284 by different mechanisms.

Male Swiss-strain mice were trained to a 95% level of shock avoidance. Groups of animals ($n \geqslant 8$) were then dosed intraperitoneally with saline, methylcellulose (vehicle for Mg pemoline), (+)-amphetamine (0·5, 1·0, 2·0 mg/kg), or Mg pemoline (25, 50, 100 mg/kg). Thirty min after drug, a five trial testing session was given. Neither (+)-amphetamine nor Mg pemoline altered avoidance behaviour at this time. Immediately after the testing session, an intraperitoneal dose of Ro 4-1284 (2 mg/kg) was given to all the mice. These groups were then tested with five trial avoidance sessions at 30, 60, and 90 min after Ro 4-1284.

* (2-Hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo(a)-quinolizine).

There were no significant differences between the saline and methylcellulose controls, so these data were pooled. However, all groups of animals receiving either (+)-amphetamine or Mg pemoline were significantly different from controls at 30, 60, and 90 min after the dose of Ro 4-1284 ($P > 0{\cdot}01$, χ^2 Test). These results are summarized in Table 1. Since (+)-amphetamine is known to be a potent inhibitor of the amine pump (Rutledge, 1970; Leitz, 1970), both stimulants were then tested for their ability to inhibit noradrenaline uptake in the following system.

Slices of cerebral cortex (0·5 mm thick) were prepared from freshly decapitated mice. One slice was taken from each brain and incubated in five ml of Krebs-Ringer solution supplemented with 0·1% glucose. The concentration of [^{14}C]noradrenaline (Amersham Searle, 40 mCi/mM) was 1×10^{-6} M. Each brain slice was incubated in a shaking water bath under room atmosphere at 37°. For these studies the slices were incubated for 30 min in the presence of drug, and then noradrenaline was added and incubation continued for a further 30 min.

The uptake of noradrenaline was linear for 60 min and reached a concentration in the slices of 10–20 fold that in the medium. However, part of the radioactivity in the slices enters by passive diffusion. It is necessary to make a correction for this process because it is not drug-sensitive. This can be done by incubating a control at 0° in the absence of glucose, or by adding a thousand-fold excess of non-radioactive noradrenaline. The percentage of control active uptake is then calculated from the equation:—

$$\% \text{ Uptake} = \frac{(C_x - C_d)}{(C_c - C_d)}$$

where C_x is the concentration of noradrenaline observed in the experimental slices, C_d is the concentration of noradrenaline entering by diffusion (cold incubation), and C_c is the concentration of noradrenaline in the drugless incubations.

The results are listed in Table 2. Imipramine, a tricyclic antidepressant known to be a potent inhibitor of the amine pump, is included for comparison. Both imipramine and (+)-amphetamine are potent inhibitors in this system, with 50% inhibition

Table 1. *Effect of (+)-amphetamine and Mg pemoline on the suppression of conditioned avoidance behaviour by Ro 4-1284.* Ratios given are the number of avoidances divided by the total number of trials per session. Drugs were injected (i.p.) immediately after the −30 min testing session; Ro 4-1284 (2 mg/kg, i.p.) was injected immediately after the 0 min testing session.

Drug (mg/kg)	Time (min) relative to Ro 4-1284 injection −30	0	+30	+60	+90
Ro 4-1284 only (Controls)	120/120	119/120	20/120	6/120	31/120
Ro 4-1284 plus (+)-amphetamine					
0·5	40/40	39/40	38/40*	27/40*	22/40*
1·0	39/40	39/40	39/40*	40/40*	36/40*
2·0	39/40	39/40	38/40*	39/40*	36/40*
Ro 4-1284 plus Mg pemoline					
25	40/40	39/40	36/40*	35/40*	35/40*
50	40/40	40/40	39/40*	38/40*	40/40*
100	39/40	40/40	39/40*	37/40*	38/40*

* Indicates a significant difference between drug and control groups (no drug, but 2 mg/kg Ro 4-1284 at time = 0) for any time period (χ^2 Test, $P > 0{\cdot}01$).

Table 2. *Inhibition of the uptake of [^{14}C]noradrenaline in mouse brain slices by drugs.* Each value is the mean ± standard error of five determinations of the uptake relative to an internal control. Drugs are preincubated with slices for 30 min before the addition of noradrenaline, after which incubation continues in the presence of noradrenaline for an additional 30 min.

Compound	Fraction of control uptake concentration of drug in incubation 10^{-6} M	10^{-5} M	10^{-4} M
Mg Pemoline	—	—	0·94 ± 0·23
(+)-Amphetamine	0·39 ± 0·10	0·14 ± 0·04	0·08 ± 0·04
Imipramine	0·34 ± 0·10	0·14 ± 0·05	0·06 ± 0·02

occurring at concentrations less than 1 μmol/litre. Mg pemoline is virtually inert, with more than 100 μmol/litre required for 50% inhibition.

(+)-Amphetamine is known to release endogenous noradrenaline from central and peripheral pools. Although the amount of noradrenaline available for release in reserpinized animals is undoubtedly much smaller than in non-reserpinized mice, the released neurotransmitter may be dramatically potentiated by (+)-amphetamine's ability to prevent its reuptake into nerve terminals. Thus inhibition of the amine pump could be a significant factor in the indirect central action of amphetamine observed by Stein (1964) in reserpinized animals. However, the failure of Mg pemoline to exert any significant effect upon the amine pump suggests that this stimulant may antagonize Ro 4-1284 by a different mechanism than (+)-amphetamine.

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