

## Reactions of morphine-dependent rats to changes in their usual daily dose

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Rats that are maintained on large, once daily doses of morphine, eat, drink and are active for up to 6 h after injection. During the next 18 h they eat and drink less, defecate more, lose weight and become less active (Kumar, Mitchell & Stolerman, 1971); these are all signs of morphine abstinence (Martin, Wikler, Eades & Pescor, 1963). We have tested how such rats respond to abrupt changes in the size of their usual daily dose of morphine. Male hooded rats ( $n=12$ ) were injected intraperitoneally with increasing doses of morphine-HCl once a day at 10 h and were then maintained on 100 mg/kg for 48 days. Then, instead of the usual daily dose, test doses of morphine 0, 25, 50 and 100 mg/kg were given in counterbalanced order at weekly intervals and measurements of food and water consumption were made at intervals during the next 24 h; defecation was measured by the number of boluses deposited and locomotion was tested during a 3 min test in a Y-maze 2.5 h after the dose. Between tests rats received the usual daily dose of morphine. Analyses of variance were performed on the scores and assessments of linear trend tested for dose-related changes. Over the 24 h there were dose-related falls in eating and drinking, increases in defecation and in weight loss; locomotion was also reduced ( $P<0.001$  in all cases). Without morphine the signs of abstinence were most intense and occurred mainly during the first 6 h after injection.

In the second experiment, male hooded rats ( $n=12$ ) were maintained on 100 mg/kg of morphine for 78 days and were tested using the same general procedure as above. However, the weekly test doses in this experiment were increased from 100 mg/kg to 125, 150 and 200 mg/kg of morphine. The main consequence was a dose-related reduction in the intensity of abstinence signs between 6–24 h after injection. The nightly falls in eating and drinking, the defecation and weight loss were all mitigated (linear trend significances:  $P<0.01$ ). There were depressant effects on eating and defecation of the raised doses during the first 6 h after injection but drinking and locomotion were unaffected. On the next day, however, 6–24 h after the usual daily dose of morphine, there were some increased signs of abstinence as a function of the previous day's test dose—the rats drank less ( $P<0.001$ ), defecated more ( $P<0.05$ ) and lost more weight ( $P<0.001$ ); for example, after 200 mg/kg, mean fluid consumption fell from 16.0 ml to 7.8 ml, defecation increased by 21% and weight loss rose from 11.1 g to 22.7 g. Therefore, interpolating even a single large dose can temporarily alter the level of morphine dependence.

## References

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## Effect of vinblastine sulphate on the acquisition of a conditioned avoidance response in the goldfish

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The alkaloid colchicine is known to disrupt neurotubules (Banks & Till, 1975). It has been suggested that neurotubular integrity is necessary during learning since intracranial (i.c.) injections of colchicine in goldfish (*Carassius auratus*) interfere with the acquisition of an active shock avoidance learning paradigm (Clingbine & Heading, 1977). Other drugs which disrupt neurotubule integrity e.g.

the *Vinca* alkaloid vinblastine sulphate (VLB) (Wooten, Kopin & Axelrod, 1975) may cause similar behavioural effects.

Goldfish (6–8 g) were injected with vinblastine (1 µg, i.c.) while anaesthetized with MS222 (tricaine-methanesulphonate, Sandoz) at a concentration of 200 µg/ml. They were allowed to recover for 6 h in their home tanks prior to initial training. They were then trained at 18°C in a two-way shuttlebox to associate a light (CS) with an electric shock (US) by being given 20 trials per day over 5 days. Performance was judged by the number of responses to the CS and analysed by ranking tests (values of  $P<0.05$  were taken as significant). After 5 days, the performance of fish injected with vinblastine (1 µg) was significantly lower than controls receiving vehicle (10 µl of Young's Freshwater Teleost Ringer solution). Controls significantly improved over 5 days but vinblastine injected fish did not.