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.

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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-methane-sulphonate, 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.

Other fish were tested to see if unconditioned behaviour was affected by the drug. This was assessed by two methods *viz.* the number of times that free-swimming fish spontaneously crossed between compartments of the shuttlebox and the time taken to escape from the US. No significant difference was observed in the incidence of spontaneous crossing between chambers of the shuttle box or in the time to escape from the US in controls compared to vinblastine injected fish. The usefulness of spontaneous crossing and shock escape time in detecting behavioural changes was shown in fish immersed in MS222. At a concentration of 20 μg/ml of anaesthetic, fish made significantly fewer spontaneous crossings, and at 33 μg/ml took significantly longer to escape from the US, compared to fish in water alone.

In order to determine whether the effect of vinblastine on avoidances was dose related, other fish were given either 0.5 μg or 2 μg of vinblastine (i.c.). After 5 days, the performance of the two groups was not significantly different but both groups avoided shock significantly less well than controls.

Vinblastine is known to disrupt the integrity of neurotubules, probably by combining with a subunit protein (Itani & Lagnado, 1976). It is speculated that the observed behavioural effects are due to disruption of either neurotubule structure or function, or possibly both. The results obtained are unlikely to be due to general toxic actions since vinblastine injected fish escaped from shock as well as controls and were also just as spontaneously active.

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