A rapid in vivo test for dependence potential of analgesic drugs

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Collier, Francis, Henderson & Schneider (1974) observed that heroin (1 mg/kg s.c.) reduced the incidence of the quasi-morphine abstinence syndrome (QMAS) produced by giving a single dose of theophylline orally to naive rats. The effect of heroin was removed by the simultaneous administration of naloxone (0.2 mg/kg). More recently, Collier & Francis have shown that whereas levorphanol reduced the quasi-morphine abstinence effect induced by another methylxanthine, 3-isobutyl-1-methylxanthine (IBMX) its stereoisomer dextrorphan had no effect. These results suggested therefore that suppression by narcotic drugs of the QMAS could be used as a rapid *in vivo* method for assessing dependence potential, in a similar way to the conventional single dose suppression test, an example of which was described by Collier & Schneider (1972). Of particular interest in the present series of experiments were the actions of several orally effective drugs commonly used to relieve pain in man, that had differing dependence potential but similar analgesic potency.

The dose-response line for pentazocine suppressing QMAS was shallower that that of codeine, *d*-propoxyphene or pethidine. Rats given an opiate with IBMX and challenged 30 min later by naloxone (0.3 mg/kg) showed a significant dose-related increase in withdrawal jumping, compared with rats given an opiate or IBMX alone. Thus, the physical dependence potential of an opiate may be due to its reducing indirectly, cyclic AMP phosphodiesterase activity in morphine-sensitive neurones.

References

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Sympathetic nerve recording in the conscious rabbit

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The recording of electrical activity from peripheral sympathetic nerves is a useful technique for the evaluation of centrally acting hypotensive drugs. Records of pre- or postganglionic sympathetic activity can be obtained by placing the splanchnic or renal nerve on bipolar electrodes and covering the preparation with mineral oil. However, such recordings can only be made in acute experiments in anaesthetized or curarized animals and such conditions are not ideal for studying centrally acting drugs whose effects may be modified by anaesthesia. Schmitt, Schmitt & Fenard (1974) described implantation of electrodes in the dog and we have adopted this technique for chronic recordings in the rabbit.

Rabbits of 2-3 kg were anaesthetized with halothane and the abdomen opened transversely along the right costal margin. The right greater splanchnic nerve was located anterior to the crus of the diaphragm and a 1.5 cm length cleared of perinephnic fat. The nerve was then transfixed by the two prongs of a bipolar electrode. The electrode tips consisted of 0.3 mm stainless steel wire which had been sharpened electrolytically and mounted in a block of epoxy resin 3 mm apart. Flexible wires from the electrode were led out onto the skin of the back. During implantation electrical activity was monitored via a low level D.C. amplifier and oscilloscope (Tektronix USA) and when a satisfactory signal was obtained the electrode was fixed in position by the application of acrylic dental cement. Several grams of this material were deposited over the nerve and electrode. The abdomen was then closed and an indifferent electrode stitched beneath the skin.

Recordings have been made in the conscious animal up to 30 days after implantation. The pattern of electrical activity is characteristically phasic, bursts of activity being synchronized with