Stereospecific suppression by opiates of the quasi-morphine abstinence syndrome elicited by 3-isobutyl-l-methylxanthine (IBMX)

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Methylxanthines elicit from otherwise untreated rats several of the behavioural signs seen in the morphine abstinence syndrome (MAS). Heroin readily suppresses the signs elicited by methylxanthines, and naloxone increases their intensity and elicits other signs, such as jumping, to produce a behavioural pattern scarcely distinguishable from the MAS (Collier, Francis, Henderson & Schneider, 1974; Francis, Roy & Collier, 1975). We have, therefore, called the behaviour elicited by xanthines the quasi-morphine abstinence syndrome (QMAS). The present work examines whether suppression by opiates of the QMAS is stereospecific and whether drugs modifying it are effective when injected into a cerebral ventricle.

Drugs were injected into male white Wistar rats (110-200 g) either subcutaneously (s.c.) or, through an indwelling cannula, into the left lateral cerebral ventricle (i.c.v.). The QMAS was elicited with 3-isobutyl-1-methylxanthine (IBMX, 15 mg/kg s.c.) and effects on behaviour were observed 'blind' for up to 15 min after treatment with coded solutions. Fourteen behavioural signs –jumping, teeth chattering, squeak on touch, squeak on handling, diarrhoea, chewing, ptosis, body shakes, head shakes, paw tremor, rearing, restlessness, salivation and licking the penis–were recorded. Total 'quasi-abstinence score' was obtained by counting 1 for presence and 0 for absence of each sign, and was expressed as a median value. The significance of differences between scores was determined by the Mann-Whitney U test.

Heroin (30-300 μg/kg s.c. or 1 and 10 μg/rat i.c.v.) overcame the QMAS in a dose-related way. When the QMAS had been suppressed with heroin (300 μg/kg s.c.), naloxone (10-100 μg/kg s.c. or 0.1-10 μg/rat i.c.v.) reversed the suppression in a dose-related way. Levorphanol (10-100 μg/kg s.c.) also suppressed the QMAS; but dextrorphan was ineffective at 8 mg/kg s.c. These effects were statistically significant at P values ranging downwards from $P = 0.027$ to $P < 0.001$.

That the potent effect of opiates in overcoming the QMAS due to IBMX is stereospecific and is reversed by very small doses of naloxone shows that this is an opiate agonist action. Methylxanthines in turn antagonize opiate agonist actions (Bellville, 1964; Ho, Loh & Way, 1973). This mutual antagonism may provide a clue to the mechanisms of action of both types of drug and to the mechanisms of dependence.

These findings also offer a sensitive *in vivo* method of detecting and estimating the behavioural effects of morphine-like, methylxanthine-like or naloxone-like substances.

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Physiological aspects of the hypnotic properties of steroid hormones

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Although it has been known for nearly half a century that some biogenic steroids possess hypnotic potencies the physiological significance of this effect is still debated. Research in this field was mainly directed towards the development of anaesthetic agents for clinical use and a large number of steroids have been tested for their central depressant activities. They were low in those steroids with high conventional "hormonal activities". However they were very high in some of the hepatic catabolites of steroid hormones which are reduced in ring A and are deprived of