Activities of narcotic and narcotic-antagonist analgesics following the intraventricular injection of various substances

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Altered transmitter levels in the central nervous system can affect the activity of narcotic analgesics in animals (Saarnivaara, 1969 a, b; Harris, 1970 and references cited therein). Also the narcotic antagonists which are analgesic in man but inactive in the commonly used animal nociceptive tests, become active in the presence of peripherally administered physostigmine (Harris, Dewey, Howes, Kennedy & Pars, 1969). We have investigated further the effects of centrally administered monoamines, and cholinergic substances, on morphine and some narcotic antagonists.

Groups of ten male mice of the A_2G strain were used. Substances were dissolved in normal saline, and injected subcutaneously, or intraventricularly by the method of Haley & McCormick (1957). Antinociceptive activity was determined using a tail-flick test similar to that of D'Amour & Smith (1941). Results were compared using Student's '*t*'-test.

Intraventricular noradrenaline (NA) (0·5–20 μg) or dopamine (DA) (5–200 μg) did not prolong the reaction time. Indeed, DA caused a brief hypersensitivity to the heat stimulus at doses of 50 μg or above. When injected 30 min after morphine (5 mg/kg subcutaneously) both NA and DA reduced ($0{\cdot}005>P>0{\cdot}001$) the antinociceptive activity of morphine.

Intraventricular 5-hydroxytryptamine (5-HT) (10–20 μg) produced a brief prolongation in reaction time. When injected 15 min after morphine (2·5 mg/kg subcutaneously) 5-HT produced a potentiation ($0{\cdot}05>P>0{\cdot}025$) of the morphine antinociceptive effect.

Subcutaneous injection of nalorphine (20 mg/kg) or pentazocine (20 mg/kg) produced only marginal elevation of the reaction time in the tail-flick test, while naloxone (20 mg/kg) was without effect. The activities of these compounds were not modified by the intraventricular injection of NA or DA. Also, the prolongation in reaction time produced by 5-HT alone was abolished by the antagonists.

Physostigmine (2–4 μg intraventricularly) prolonged the tail-flick reaction time. A dose of 1 μg was without effect alone, but potentiated ($P<0{\cdot}001$) the antinociceptive effect of morphine (2·5 mg/kg subcutaneously) nalorphine (20 mg/kg subcutaneously) ($0{\cdot}005>P>0{\cdot}001$) and pentazocine (20 mg/kg subcutaneously) ($0{\cdot}05>P>0{\cdot}01$). However, the naloxone plus physostigmine combination was without effect on the nociceptive threshold.

These results, using the mouse, have confirmed results previously obtained in the rat (Sparkes & Spencer, 1969), in that 5-HT injected into the cerebral ventricles potentiates the antinociceptive activity of morphine. However, 5-HT does not potentiate the narcotic antagonist analgesics, and is itself antagonized by them. In addition in both species, intraventricular NA (and in the mouse, DA also), antagonizes morphine.

Physostigmine, on the other hand, potentiates both morphine and the narcotic antagonist analgesics, nalorphine and pentazocine, but not naloxone, which is devoid of agonist activity.

These results may reflect a difference between the ways in which narcotic analgesics and narcotic antagonist analgesics interact with central tryptaminergic and cholinergic systems in bringing about their antinociceptive effects.

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Alterations in sleep/wakefulness cycle in rats following treatment with (+)-lysergic acid diethylamide (LSD-25)

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In behavioural studies (Loew, Depoortere & Vigouret, 1970) LSD-25 modified the composition as well as quality of sleep in rats. In particular, the drug appeared to change the quality of paradoxical sleep (PS). In this study, electroencephalographic recordings have been undertaken in order to confirm or refute the results of our earlier experiments.

LSD-25 tartrate (1 mg/kg, calculated as the salt) was injected intraperitoneally into adult male Wistar rats bearing chronically implanted electrodes for recording brain and muscle activity. Recordings were made in habituated rats during a 6 h period following injection. Control recordings were taken from the same animals on the day before drug administration.

Analysis of the total 6 h recordings revealed a 43% ($P<0.05$) increase in wakefulness which was associated with a reduction of 51% ($P<0.05$) in PS and of 18% ($P<0.05$) in slow wave sleep (SWS). More detailed analysis of the results showed that the increase in wakefulness was most prominent in the first hour. This effect gradually declined until hour 4, whilst in hours 5 and 6 no significant changes in the percentages of wakefulness and sleep were seen.

Qualitatively, the recordings showed that the time course of the drug effect was biphasic. In the first phase, lasting up to 2 h, ' aberrant behaviour ' (Dixon, 1968) was accompanied by a pattern of cortical arousal. The stereotyped head movements were preceded by short spindle bursts in the cortex and lateral geniculate body. The second phase began with the appearance of SWS and PS. In this phase, continuous spindle activity in cortical and lateral geniculate recordings during SWS, was most prominent during the third hour. The PS was associated with enhanced phasic activity in the visual system and increased rapid eye movement compared with that seen in control recordings.