previously with *B. pertussis* and incomplete Freund's adjuvant according to the directions of Dieppe *et al.*, (1976). Mice were sensitized by injection into the left hind paw and challenged four days later by injection into the right hind paw with sheep red blood cells (L'Age-Stehr & Diamastein, 1977). The drugs were administered 1 h prior to and 24 h, 48 h, 72 h and 96 h after sensitization and the reaction was monitored by measuring paw thickness after challenge.

Neither drug showed the effect on leucocyte migration observed with conventional anti-inflammatory drugs in non-sensitized rats (Walker, Smith & Ford-Hutchinson, 1976) confirming the absence of anti-inflammatory activity. When the delayed hypersensitivity reaction was superimposed on the sponge reaction significant enhancement of leucocyte migration was observed with both drugs. Similar effects occurred in the mouse, paw thicknesses being significantly increased by levamisole at 24 h and 48 h and by D-penicillamine at 48 h (% increase in paw thickness at 48 h: control 9.0 $\pm$ 3.9 $n = 8$, D-penicillamine 25.6 $\pm$ 7.2 $n = 6$ and levamisole 30.5 $\pm$ 4.5 $n = 5$). Levamisole and D-penicillamine thus enhance delayed hypersensitivity at dosages similar to those used in man. Whether this action in the animal models relates to their common action in rheumatoid arthritis remains to be determined.

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Neuropharmacological studies on the central inhibition of oxytocin release

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The suckling-induced release of oxytocin may be blocked by emotional or stressful stimuli. Such a failure to release oxytocin, and thus eject the milk from the mammary alveoli, has been atrributed to a central inhibition of the reflex (Cross, 1955), and such inhibition possibly involves the cerebral cortex (Taleisnik & Deis, 1964). Moreover, we have recently observed a prominent correlation between the activity of the cerebral cortex and the release of oxytocin in anaesthetized lactating rats.

The electrocorticogram (ECoG) was recorded from bipolar platinum electrodes placed over the frontal lobes of lactating rats, anaesthetized with urethane (1.2 g/kg, i.p.). Typically, the ECoG alternated every few minutes between periods of large amplitude slow-waves and periods of low amplitude fast waves (arousal) (Lincoln, 1969). Within 1–2 min of the young being placed on the nipples, the ECoG changed and a continuous slow-wave pattern persisted for the next hour, or more. Thereafter, the 'cyclic-pattern' of ECoG activity returned. The continuous suckling activity of the young induced a series of reflex milk-ejections characterized by uniform increases in intramammary pressure at intervals of 5–15 min (Lincoln, Hill & Wakerley, 1973). Such milk ejections occurred only during periods of slow-wave ECoG activity and, when the ECoG was of the cyclical pattern, milk ejections were frequently observed 10–15 s after the transition from the 'aroused' to the 'sleep-like' state.

Suppression of cortical activity by the application of KCl to the exposed surface failed to modify the pattern of reflex milk ejection; the mean milk-ejection interval was 10.8 $\pm$ 3.6 (mean $\pm$ s.e. mean) min for controls ($n = 64$) and 10.0 $\pm$ 1.6 min during KCl depression ($N = 64$), and the amount of oxytocin released was similar in both situations. The injection of carbachol (0.1–0.2 μg in 1 μl) or bethanechol (1–2 μg) into the lateral ventricles caused an arousal of the ECoG and a parallel inhibition of the milk ejection reflex. Conversely, the systemic application of atropine (1 mg/kg, i.v.) prevented both the induced arousal and the associated inhibition of the reflex.

Higher doses of atropine (20 mg/kg, i.v.) or hyoscine (30–50 mg/kg, i.v.) promoted a continuous slow-wave ECoG pattern for several hours, and several animals began to eject milk reflexly during this period, when under control conditions they had failed to do so. Reflex milk ejection is subject to inhibition by a central β-adrenergic mechanism (Tribollet, Clarke, Dreifuss & Lincoln, 1977). However, the administration of β-adrenoceptor antagonists failed to alter the pattern of the ECoG irrespective of whether they facilitated the milk ejection reflex or not, and milk ejection was still confined to periods of slow-wave activity.

Thus, in anaesthetized lactating rats, suckling induces a slow-wave pattern of ECoG activity, and only during slow-wave activity is reflex milk ejection observed. Whilst the cortex appears to inhibit the suckling induced reflex during periods of arousal, the basic reflex appears to be entirely fashioned at a sub-cortical level. The cortical inhibition does not appear to be mediated through a β-adrenergic system.

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Piracetam – a non-sedative anxiolytic drug?

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We have previously reported the effects of piracetam, a drug found to improve performance in several learning and memory tests (Wolthuis 1971), on habituation in rats to repeatedly presented tone stimuli (File & Hyde 1977a). The only other drugs we have so far studied which produce a similar pattern of faster within-session habituation are chlordiazepoxide and ethanol (File, 1977), which both reduce anxiety.

We have recently developed a new animal model of anxiety (File & Hyde 1977b) which can distinguish between sedation and the reduction of anxiety. We measure the time that pairs of male rats spend in active social interaction and we have found that this is greatest when the rats are tested in a box with which they are familiar. If the test box is unfamiliar or if the illumination is increased, the active social interaction decreases. Control experiments suggest that it is permissible to interpret the decrease in social interaction that occurs across the test conditions as due to increasing anxiety. Drugs with a sedative action, eg. meprobamate (60 mg/kg) (File & Hyde, unpublished results), ethanol (1.2 g/kg) and acute chlordiazepoxide (5–7.5 mg/kg) (File & Hyde, 1976) decrease social interaction in all test conditions, whereas an anxiolytic action, eg: after chronic administration of chlordiazepoxide (5 mg/kg for five days), is revealed by little change in social intereaction across the four conditions i.e. a significant drug × test condition interaction.

Existing animal models do not distinguish between anxiety and sedation and therefore a compound like piracetam, which has no sedative action, might not have been detected as an anxiolytic. We decided to investigate this possibility using the above test. Rats were randomly allocated to the four test conditions (low light familiar; high light, familiar; low light, unfamiliar; high light, unfamiliar) and 30 min before testing injected i.p. with saline or piracetam (100 mg/kg). The time spent in active social interaction during a ten min period was scored by two observers from a video monitor in an adjacent room.

In the low light familiar test condition there was no difference in the level of active social interaction between the piracetam treated animals and the controls. However, if the box was unfamiliar or when the light level was increased, the rats treated with piracetam showed significantly less of a decline in social interaction when compared with the control animals ($F = 6.218$, $df = 3,56$, $P < 0.001$), thus fulfilling our criterion for a drug with anxiolytic properties.

Whilst not all of the improvements in learning reported with piracetam can be explained simply in terms of an anxiolytic action, this possibility should be borne in mind when interpreting drug results. In some cases, particularly in the geriatric human studies, a reduction of anxiety would be a sufficient explanation for the improved performance in motor tasks.

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