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 meprobamate (60 mg/kg) (File & Hyde, unpublished results), ethanol (1.2 g/kg) and acute chlordiazepoxide (5–7.5 mg/kg) (File & Hyde, 1976) decrease social interaction in all test conditions, whereas an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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Antagonistic effects of two anaesthetics on hypotonic haemolysis

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Many general and local anaesthetics are known to protect erythrocytes against hypotonic lysis, often at concentrations similar to those causing reversible nerve block. For this reason the erythrocyte has in the past been regarded as a good model for the study of the mechanism by which anaesthetics produce their effect. This striking correspondence is consistent with, although it does not prove, the theory that the primary action of anaesthetics is to increase the fluidity of membrane lipids (Seeman, 1972; Strichartz, 1976).

Seeman, in an earlier paper (Seeman, 1966) presented dose-response curves showing the effect on haemolysis of a number of local anaesthetics, including lignocaine. Rather high lignocaine concentrations (above 10^{-2}M) were needed to reduce haemolysis, and it was remarked that the protection in this case might be due to the increased tonicity of the test medium. That this may indeed be the explanation is suggested by a more recent finding (Sheetz & Singer, 1974) that a steady *increase* in haemolysis occurs between 10^{-3} and 10^{-2}M lignocaine. This steady increase is to be distinguished from the steep rise to 100% haemolysis observed at high, 'lytic' concentrations of many anaesthetics (Seeman, 1972).

The experiments reported here were performed as described by Seeman (1966) except that Tris buffer was used instead of phosphate buffer. They were designed to determine whether the haemolysis promoting effects of lignocaine, if confirmed, occurred at concentrations causing local anaesthesia, and if they could be antagonised by an anaesthetic known to decrease haemolysis at nerve-blocking concentrations. Figure 1 shows that lignocaine increasingly promotes haemolysis over the range 1–10 mM. The figures quoted for local anaesthetic concentrations of lignocaine (Strichartz, 1976) fall towards the bottom of this range, or below it, but they did not include figures for total nerve block.

Benzyl alcohol is known to decrease hypotonic haemolysis at local anaesthetic concentrations, and increase it only at much higher concentrations producing lysis even under isotonic conditions. The protective effect is explained by the expansion and fluidization of the membrane (Seeman, 1972). Figure 1 demonstrates that benzyl alcohol readily antagonises the effect of lignocaine; the effect of lignocaine (5 mM) on haemolysis can be balanced by benzyl alcohol (20 mM).

These results suggest that anaesthetics, at concentrations similar to those causing nerve block, do not necessarily protect erythrocytes but may, on the contrary, have antagonistic effects on haemolysis in hypotonic solution.

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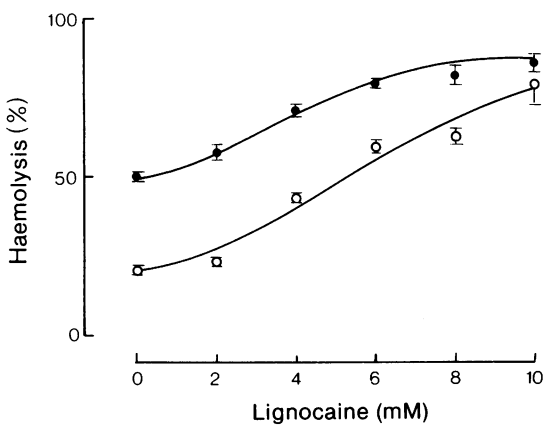

Figure 1 The effects of lignocaine on hypotonic haemolysis in the absence (●) and presence (○) of 20 mM benzyl alcohol.

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