trials. The compounds studied were mianserin (4 and 16 mg/kg), amitriptyline (1, 4 and 16 mg/kg), imipramine (1, 4 and 16 mg/kg), methysergide (2.5 and 5 mg/kg) and cinanserin (4 and 16 mg/kg). The two-tailed permutation test was used for the statistical evaluation of the results.

Rats rapidly acquired the avoidance response. Treatment with morphine not only eliminated avoidance responses but also strongly suppressed escape and intertrial responses. Mianserin only slightly reversed the effect of morphine on avoidance behaviour. However, rats given morphine + mianserin showed a significantly larger number of escapes and intertrial responses than morphine + placebo-treated animals. Methysergide and cinanserin also restored the ability of morphine-treated rats to score escape and intertrial responses, although to a lesser degree than mianserin. Amitriptyline and imipramine were ineffective.

Methysergide and cinanserin have been shown to antagonize the antinociceptive action of intracerebrally administered morphine (Yaksh, DuChateau & Rudy, 1976). Like methysergide and cinanserin, mianserin possesses 5-HT receptor blocking properties (Vargaftig, Coignet, de Vos, Grijsen & Bonta, 1971). The ability of these compounds to antagonize the incapacitating effect of morphine on the performance of rats in a shuttlebox supports the idea that 5-HT mechanisms are involved in some of the effects of morphine. The restoration of intertrial responses by mianserin, methysergide and cinanserin suggests that these drugs reversed the morphine-induced akinesia. Restoration of escape responses indicates that antagonism of analgesia may also be involved.

Mianserin, though a clinically effective antidepressant (Murphy, 1975; Wheatley, 1975), was a negative in conventional animal screening tests for antidepressants (Van Riezen, 1972). The finding that amitriptyline and imipramine failed to act like mianserin in the present experiments adds to the notion that the latter compound may be pharmacologically different from tricyclic antidepressants.

References

MURPHY, J.E. (1975). A comparative clinical trial of Org GB 94 and imipramine in the treatment of depression in general practice. *J. int. med. Res.*, **3**, 251–260.

VAN RIEZEN, H. (1972). Different central effects of the 5-HT antagonists mianserin and cyproheptadine. *Arch. int. Pharmacodyn.*, **198**, 256–269.

VERGAFTIG, B.B., COIGNET, J.L., DE VOS, C.J., GRIJSEN, H. & BONTA, I.L. (1971). Mianserin hydrochloride: peripheral and central effects in relation to antagonism against 5-hydroxytryptamine and tryptamine. *Eur. J. Pharmacol.*, **16**, 336–346.

VERHAVE, T., OWEN, JR., J.E. & ROBBINS, E.B. (1959). The effect of morphine sulfate on avoidance and escape behavior. *J. Pharmacol. exp. Ther.*, **125**, 248–251.

WHEATLEY, D. (1975). Controlled clinical trial of a new antidepressant (Org GB 94) of novel chemical formulation. *Curr. Ther. Res.*, **18**, 849–854.

YAKSH, T.L., DuCHATEAU, J.C. & RUDY, T.A. (1976). Antagonism by methysergide and cinanserin of the antinociceptive action of morphine administered into the periaqueductal gray. *Brain Res.*, **104**, 367–372.

The effect of ethanol on a passive avoidance task in rats

GABRIELE BAMMER & G.B. CHESHER
(introduced by HANNAH STEINBERG)

Department of Pharmacology, University of Sydney, N.S.W., Australia

It has previously been shown (Chesher, 1974) that ethanol (1.5 g/kg, i.p.) enhances the learning of an active conditioned avoidance task in rats. This effect was abolished if the animals had been pre-treated with the catecholamine synthesis inhibitor α-methyl-*p*-tyrosine. The task made use of a two-compartment shuttle box; to escape an electric shock, the animals had to learn to change compartments within 5 s of the sounding of a buzzer.

In the experiments to be described the effect of ethanol was tested on a passive avoidance task: instead of running to another compartment, the animals had to refrain from doing so to avoid a shock.

The apparatus, similar to that described by Jarvik & Kopp (1967), consisted of a two-compartment box with an interconnecting opening. The rat was placed into one compartment which was lit by a 25 W incandescent light, and the time before it entered the adjacent, dark compartment was determined. Rats usually prefer the dark when given a choice. A shutter prevented the rat from retracing its steps, and it was given a footshock of 1 mA for 5 seconds. Animals were re-tested in the same apparatus 1 or 7 days later. Male Sprague-Dawley rats (200–390 g) were used.

When tested 30 min after ethanol (1.5 g/kg, i.p.) rats ($n=45$ per group) entered the dark compartment on both trial 1 and trial 2 with a significantly shorter

latency than saline controls (trial 1, saline mean latency 12 ± 1 s, ethanol 7 ± 1 s; trial 2, saline 137 ± 11 s, ethanol 23 ± 7 s; $P < 0.001$). Dose response relations could be demonstrated in both trials for doses of ethanol between 0.9 and 2.0 g/kg ($n = 15$ or 20 per group). If rats were not shocked in the dark compartment at trial 1, latencies at trial 2 did not differ significantly from trial 1. Pre-treatment with α-methyl-*p*-tyrosine (80 mg/kg, i.p.) 3.5 h before ethanol or saline did not affect the ethanol induced changes at either trial ($n = 17$ per group).

The test procedures in both kinds of experiment described depended on the initiation of movement. In the active avoidance task ethanol led to quicker learning, and this effect was abolished by pre-treatment with α-methyl-*p*-tyrosine, which suggests that a newly synthethized catecholamine may have been involved. In the passive avoidance task ethanol hindered learning and this was not affected by α-methyl-*p*-tyrosine.

Although the effect of ethanol on the performance of both these tasks in rats can be described as 'stimulating' movement, each is presumably mediated by different neuronal pathways.

References

CHESHER, G.B. (1974). Facilitation of avoidance acquisition in the rat by ethanol and its abolition by α-methyl-*p*-tyrosine. *Psychopharmacologia*, **39**, 87–95.

JARVIK, M.E. & KOPP, R. (1967). An improved one-trial passive avoidance learning situation. *Psychological Reports*, **21**, 221–224.

Effect of iontrophoretic and intravenously administered atropine on the acetylcholine-discharges of lateral geniculate neurones

JEAN-MARIE GODFRAIND (introduced by R.G. CASTEELS

Laboratoire de Neurophysiologie, Université Catholique de Louvain, UCL-5449, avenue Hippocrate 54, 1200 Bruxelles, Belgium

In the present study, acetylcholine (ACh) sensitivity of lateral geniculate cells was re-examined after iontophoretically and intravenously administered atropine under different experimental conditions.

Conventional techniques for extracellular recording with 5-barrel micropipettes and iontophoretic drug application were used (Krnjević & Phillis, 1963). The outer barrels were filled with the following substances: ACh (1 M, pH 4.9), atropine sulphate (10 mM in 165 nM NaCl, pH 5.5), mecamylamine HCl (10 mM in 165 mM NaCl, pH 6.6) and L-glutamate (1 M, pH 7–7.4). Geniculate neurones of lamina A were identified by the visual evoked response and by the neuronal sensitivity to L-glutamate and ACh. Subsequently, dye deposition was achieved to mark recording sites and to permit the histological reconstruction of electrode tracks (Godfraind, 1969, 1976; Godfraind & Meulders, 1969). All animals, except one, received an injection of atropine methylnitrate (4 mg/kg, i.v.), and were paralyzed with an intravenous infusion of succinylcholine at an approximate rate of 1 mg/min.

In an anaesthetized cat (fluothane 1%), and in a non-anaesthetized midpontine pretrigeminal preparation, the observations made were in agreement with previous descriptions: neuronal discharges induced by ACh were depressed either by atropine or by mecamylamine applied by iontophoresis, as well as after an intravenous injection of atropine sulphate (3 mg/kg) (Curtis, 1966; Curtis & Crawford, 1969; Marshall & McLennan, 1972).

Different results were observed under α-chloralose (80 mg/kg, i.v.; 3 cats) and urethane (1 g/kg, i.v.; 2 cats) anaesthesia. Under these conditions, discharges evoked by ACh (15–45 nA, 10–20 s) were also prevented or greatly reduced by iontophoresis of either atropine (10–20 nA, 40–50 s) or mecamylamine (10–30 nA, 30–65 s). However, after atropine sulfate i.v. administration (3 mg/kg), neuronal discharges could still be induced by ACh applied with similar iontophoretic parameters. Tests with cholinergic antagonists applied by iontophoresis were again performed on the same units to analyse the pharmacology of these 'remaining' ACh responses. These appeared to be more resistant to iontophoretically applied atropine than before the i.v. atropine sulphate injection. Indeed, after atropine had been iontophoretically reapplied with the same parameters, some of the ACh responses were comparable to the control, while others were slightly delayed by about 3 to 5 s. On the contrary, mecamylamine was a good antagonist: 7 to 30 nA mecamylamine for about 30–65 s was sufficient to depress ACh induced activity (20–45 nA ACh for 10–20 s). This antagonism was shown to be reversible provided a small dose of mecamylamine was applied.