These results confirm the persistent physiological changes which occur after single doses of hypnotics and emphasize the need for caution in evaluating studies of psychiatric patients receiving night sedation compared to normal controls not taking sleeping-tablets.

REFERENCES

LADER, M. H. & WALTERS, A. J. (1971). Hangover effects of hypnotics in man. *Br. J. Pharmac.*, **41**, 412.

MALPAS, A., ROWAN, A. J., JOYCE, C. R. B. & SCOTT, D. F. (1970). Persistent behavioural and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium. *Br. med. J.*, **2**, 762–764.

Iontophoretic study of the central anticholinergic properties of BRL 1288

G. CLARKE*, J. DAVIES and D. W. STRAUGHAN

Department of Pharmacology, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX

The new anti-Parkinson drug BRL 1288 (2[ethyl-n-propylamino]ethyl-α-α-diphenylglycollate hydrochloride) appears to have new features compared with many existing anti-Parkinson drugs in that it has very little peripheral anticholinergic activity though it abolishes oxotremorine-induced tremors in mice (Hughes & Spicer, 1969; Brown, Hughes & Mehta, 1969; Leslie & Conway, 1970). It thus seemed important to obtain more direct information about the possible anticholinergic activity of BRL 1288 in the central nervous system.

The action of BRL 1288 has been compared with those of atropine and procaine on acetylcholine—and L-glutamate-excited neurones using microiontophoretic techniques. Seven barrelled glass microelectrodes of overall tip diameter 4–10 μm containing the drug solutions were placed in the postcruciate cortex of cats anaesthetized with nitrous oxide-halothane. Extracellular action potentials recorded from one barrel were displayed on an oscilloscope and electronically counted.

BRL 1288 (cationic current 25–100 nA) reduced the excitant action of acetylcholine. However, this action of BRL was not specific for acetylcholine since the excitatory effect of L-glutamate was also reduced. Moreover, BRL 1288 was more effective against glutamate, the EC50 (effective current) being $30{\cdot}5 \pm 9{\cdot}1$ compared with $65{\cdot}0 \pm 17{\cdot}5$ against acetylcholine-induced excitation.

Atropine was at least twice as effective as BRL 1288, on a current basis, in reducing the excitant action of acetylcholine and, unlike BRL, it produced a long lasting effect. However, atropine had only half the activity of BRL 1288 against neurones excited by L-glutamate and recovery was rapid.

Structurally, BRL 1288 has features in common with the local anaesthetic, procaine. Comparisons between these drugs on neurones excited by acetylcholine or L-glutamate showed that both agents often caused a reduction in the amplitude of the extracellular action potential at similar ejecting currents. Furthermore, BRL and procaine were equipotent in antagonizing glutamate excitation although BRL was more effective in antagonizing acetylcholine excitation.

In view of these findings, the local anaesthetic potencies of BRL 1288, procaine and atropine were determined on the isolated frog sciatic nerve. The results obtained indicated that, on a molar basis, BRL was 2–3 times as potent as procaine and one hundred times as potent as atropine.

Though BRL 1288 may have some central anticholinergic properties these are particularly weak on cortical neurones and are probably of little significance. Its main action appears to be a depressant one which is probably related to its local anaesthetic properties.

G.C. is an M.R.C. Scholar.

REFERENCES

BROWN, D. M., HUGHES, B. O. & MEHTA, M. D. (1969). BRL 1288—a new anti-Parkinson drug. *Nature, Lond.*, **223**, 416–417.

HUGHES, B. O. & SPICER, B. (1969). Some anticholinergic activities of BRL 1288—a new anti-Parkinson drug. *Br. J. Pharmac.*, **37**, 501–502*P*.

LESLIE, G. B. & CONWAY, G. E. (1970). Some central actions of benapryzine (BRL 1288). *Pharmac. Res. Comm.*, **2**, 201–204.

Effect of imipramine on unit activity in the midbrain raphé of rats

G. J. BRAMWELL (introduced by D. W. STRAUGHAN)

Department of Pharmacology, The School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX

Intravenously administered lysergic acid diethylamide and other psychotomimetics reduce the firing rate of cells in the dorsal and median raphé nuclei of anaesthetized rats (Aghajanian, Foote & Sheard, 1968; 1970; Foote, Sheard & Aghajanian, 1969). This effect has been attributed to stimulation of central 5-hydroxytryptamine receptors. In the present experiments the action of a drug which affects 5-hydroxytryptamine transmission in another way, *viz.* by blocking the membrane pump for reuptake, has been investigated. Unit activity in the raphé nuclei was recorded in male albino rats (215–275 g) under light anaesthesia (chloral hydrate 350–400 mg/kg i.p.) using tungsten microelectrodes.

All raphé units tested responded to imipramine with a slowing or cessation of firing, though the sensitivity of units varied widely. In preliminary experiments a single dose of 1·25 mg imipramine (approx. 5·0 mg/kg i.v.) caused complete inhibition of firing of raphé units without decreasing the firing rate of control units in the pedunculus cerebellaris superior. The onset of effect was comparable to that of intravenously administered lysergic acid diethylamide; that is maximum effect achieved within 30 s and more rapid than the effect of intravenous pargyline (18·5 mg/kg) which took more than 60 s to reach maximum effect.

In other experiments, imipramine was injected in 0·25 mg doses at intervals of 2 min until an effect was noted, approximately 2 mg/kg producing threshold inhibition and approximately 4 mg/kg giving 100% inhibition. In some cases it was possible to construct cumulative dose-response curves, but in other cases the curve was too steep.

Recovery from imipramine did not occur within 30 min of onset; thus, compared with lysergic acid diethylamide, the effect is persistent and similar to that of monoamine oxidase inhibitors.

The inhibitory effect of imipramine on raphé unit firing appears likely to be related to an increase of 5-hydroxytryptamine, since the inhibitory effect of imipramine given intraperitoneally was seen with a similar dose to that needed to block the reuptake of 5-hydroxytryptamine *in vivo* (Ross & Renyi, 1969). An effect on cate-