times were recorded automatically on each trial. The apparatus and training procedures have been described in detail by Ross & Russell (1964). Competing responses in the start box (movements towards positions other than the exit door) during either warning or shock stimuli were recorded as errors. The effects of chlorpromazine (0.25–2 mg/kg), chlordiazepoxide (5–80 mg/kg) and amylobarbitone (2.5–40 mg/kg) on acquisition of CAR in rats were investigated. Training commenced 120 min after subcutaneous dosing with chlorpromazine and 30 min after subcutaneous dosing with chlordiazepoxide or amylobarbitone. Control rats received normal saline. Data obtained in these experiments were analysed as follows. Mean numbers of trials to reach criterion levels of one, two, three, four and five consecutive CAR's were plotted for each dose-group. Training was stopped when the rats reached a criterion of five consecutive CAR's. The slopes of these learning curves provided an index of interactions between drugs and increasing task requirement. In each dose-group, latencies recorded for the individual rats during the five final CAR's were pooled. Latency profiles were analysed by compiling frequency distributions of these latency times for consecutive 0.5 sec intervals of the 3 sec CS warning time. Running time profiles were also analysed in terms of interval histograms. These analyses provided information concerning perceptual ability and motivational changes.

All three drugs impaired learning. Both chlorpromazine and chlordiazepoxide caused more pronounced increases in the slopes of the learning curves than amylobarbitone. Chlordiazepoxide and amylobarbitone increased, whereas chlorpromazine decreased, start box errors. Amylobarbitone differed from the other drugs in having little effect on CAR latencies or running times. Differences in the effects of chlorpromazine, chlordiazepoxide and amylobarbitone on CAR behaviour suggested different modes of action.

REFERENCE

Ross, R. B. & Russell, I. S. (1964). Lateralization and one-trial interhemispheric transfer of avoidance conditioning. *Nature, Lond.*, **204**, 909–910.

The effect of 4-acetamidophenol in reducing fever produced by the intracerebral injection of 5-hydroxytryptamine and pyrogen in the conscious cat

A. S. Milton and Sabine Wendlandt*, *Department of Pharmacology, The School of Pharmacy, University of London*

5-Hydroxytryptamine (5-HT) as well as pyrogen produce a long-lasting rise in rectal temperature when injected into the lateral cerebral ventricles of the conscious cat (Feldberg & Myers, 1964). The action of 4-acetamidophenol, an antipyretic, has been investigated on this effect. Fever was produced in conscious cats by injecting either 5-HT creatinine sulphate (0.125 or 0.5 μ-moles) or pyrogen solution (1 in 200, or 1 in 300 dilution of TAB vaccine) into the right lateral cerebral ventricle through a chronically implanted Collison cannula. All injections were made in a volume of 0.1 ml. and the cannula flushed with 0.05 ml. pyrogen-free 0.9% (w/v) saline solution. The rectal temperature was recorded over a period of 24 hr. 5-Hydroxytryptamine (5-HT) as well as TAB vaccine produced a rise in rectal temperature after a short latent period. The maximum rise, 1°–2° C was reached within 1–3 hr. The temperature remained elevated for 5–15 hr, and in the majority of experiments had returned to the control level in 24 hr. Shivering was observed during the phase of increasing rectal temperature.

An intraperitoneal injection of 4-acetamidophenol (0.33–0.66 m-moles/kg) at the height of the fever abolished shivering almost immediately, and the rectal temperature started to fall within 15 min, reaching the control level in 1–2 hr. The rectal temperature rose again after about 4 hr unless a subsequent dose of 4-acetamidophenol was administered. The response to 4-acetamidophenol was dose dependent. If 4-acetamidophenol was administered before the intracerebral injections of 5-HT or TAB vaccine, the onset of fever was delayed for several hours and could be further delayed by subsequent injections of 4-acetamidophenol. In some animals an intraperitoneal injection of 4-acetamidophenol produced a slight fall in rectal temperature.

In one series of experiments, when injected alone into the cerebral ventricles 4-acetamidophenol (6.6 μ-moles) itself produced a fever similar in degree and time of onset to that produced by both 5-HT or TAB vaccine. This rise in rectal temperature could be reduced or delayed by the intraperitoneal injection of 4-acetamidophenol. In a second series of experiments a slight fall in temperature followed by only a slight rise was observed. When 4-acetamidophenol (6.6 μ-moles) was injected into the cerebral ventricles during fever it produced only a slight and transient fall in rectal temperature.

This work was supported by a grant from the Medical Research Council.

REFERENCE

FELDBERG, W. & MYERS, R. D. (1964). Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. *J. Physiol., Lond.*, **174**, 226–237.

Centrally evoked responses by cholinergic agents and their antagonism by drugs in the conscious mouse

S. I. ANKIER, R. T. BRITTAIN* and SHEILA L. HANDLEY*, *Pharmacology Department, Allen and Hanburys Limited, Ware, Hertfordshire*

Peripheral autonomic actions of imipramine include inhibition of noradrenaline uptake (Axelrod, Whitby & Hertting, 1961) and antagonism of acetylcholine (Vernier, 1961); both mechanisms have been proposed as the basis for clinical efficacy of this drug (Sigg, 1959; Cairncross, Gershon & Gust, 1963). While central inhibition of noradrenaline uptake has been demonstrated (Glowinski & Axelrod, 1964) central anti-cholinergic activity of imipramine has yet to be established. Accordingly, the effects of acetylcholine, carbachol, tremorine and oxotremorine after injection into the cerebral ventricles of conscious mice, and their modification by imipramine and other drugs, have been determined.

Intraventricularly injected acetylcholine, in doses as high as 20 μg/mouse, failed to cause any cholinergic response or change in behaviour. Tremorine (1–20 μg) was also without effect, although very high doses (100 μg) caused some salivation, tremor and hypothermia. However, carbachol (0.5 -5 μg) and oxotremorine (0.1–2 μg) caused salivation, lacrimation, tremor and a fall in body temperature the intensities and durations of which were dose-dependent. The degree of hypothermia afforded a basis for quantitative drug-interaction studies. Because a rise in skin temperature preceded the fall in body temperature, the most likely mechanism of the centrally administered cholinergic agents in causing hypothermia was impairment of central sympathetic outflow.

The effects of peripherally and centrally acting drugs on hypothermia induced by intraventricularly administered carbachol (2 μg) and oxotremorine (2 μg) were next