investigated. Oral pretreatment (1 hr beforehand; doses expressed as mg/kg) with chlorpromazine (5), haloperidol (10), chlordiazepoxide (20), pentobarbitone (20), phenytoin (20), methaqualone (20), phenelzine (20), codeine (50) or morphine (50), or subcutaneous pretreatment (1 hr) with propantheline (20) or atropine methonitrate (20) failed to modify the hypothermic effects of intraventricularly injected carbachol or oxotremorine. Oral pretreatment with imipramine (7.3), amitriptyline (8.5), nortriptyline (11.9), atropine sulphate (2.0) and amphetamine (2.9), however, inhibited by 50% the hypothermia induced by carbachol. Similar results were obtained when the cholinergic agent was oxotremorine. To determine whether the inhibitory action of these drugs was mediated through a central mechanism, they were injected intraventricularly (1–40 μg/mouse) 30 min or 60 min before the intraventricular injection of carbachol or oxotremorine. Only atropine, in doses as low as 0.05–1.0 μg/mouse, markedly inhibited the hypothermia induced by intraventricular carbachol or oxotremorine. In the light of these results it seems improbable that the clinical usefulness of thymoleptic drugs depends on central anticholinergic activity.

† Present address, Department of Pharmacy, University of Aston, Birmingham.

REFERENCES

AXELROD, J., WHITBY, L. G. & HERTTING, G. (1961). Effect of psychotropic drugs on the uptake of H^3-norepinephrine by tissues. *Science, N.Y.*, **133**, 383–384.

CAIRNCROSS, K. D., GERSHON, S. & GUST, I. D. (1963). Some aspects on the mode of action of imipramine. *J. Neuropsychiat.*, **4**, 224–231.

GLOWINSKI, J. & AXELROD, J. (1964). Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. *Nature, Lond.*, **204**, 1318–1319.

SIGG, E. B. (1961). Pharmacological studies with tofranil. *Canad. Psychiatric. Assoc. J.*, **4**, S75–83.

VERNIER, V. G. (1961). The pharmacology of antidepressant agents. *Dis. nerv. Syst.*, **22**, 7–13.

Pharmacological evidence for a cholinergic mechanism in brain involved in a special stereotyped behaviour of reserpinized rats

J. SCHEEL KRÜGER* and A. RANDRUP, *Sct. Hans Hospital, Dept. E, Roskilde, Denmark*

Pharmacological studies have indicated that a cholinergic mechanism is involved in the "paradoxical" stereotyped behaviour in reserpinized rats, described by Schiørring & Randrup (1968).

Male Wistar rats housed in individual cages were treated with reserpine (7.5 mg/kg s.c., Serpasil, CIBA). As expected the general behavioural effect was a strong sedation followed by catalepsy (3 hours after the injection). About 4–4.5 hr after reserpine bursts of co-ordinated activity were observed, consisting of constant sniffing (head movements with nose on cage wires and synchronous breathing) accompanied by forward locomotion. During the locomotion the rats retained the characteristic hunched "bison"-posture. A "rearing" was often also observed (standing on hindlegs and sniffing the upper part of the walls). Since the locomotion and rearing followed a fixed pattern and the sniffing was continuous, the activity was of a stereotyped character. The duration of this activity varied between 2 min and more than 2 hr. Of seventy-one rats studied, forty-nine rats (69%) showed this behaviour 4–5.5 hr after reserpine. At 7, 9–11, and 19–21 hr after reserpine this behaviour declined to 26%.

A complete inhibition of the locomotion, rearing and sniffing was observed after the following central anticholinergic drugs given 5.5 hr after reserpine (each drug s.c. to six rats): scopolamine hydrochloride (5 mg/kg); benactyzine hydrochloride (10 mg/kg);

benzhexol hydrochloride (10 mg/kg); benztropine hydrobromide (10 mg/kg); caramiphen hydrochloride (20 mg/kg), The animals were randomized to avoid identification during the observation period of one hour, which began 10 min after the injection. After (—)-hyoscyamine sulphate (20 mg/kg) a few bursts of activity were observed during the first 20 min. Twelve rats were also given saline and another twelve rats methylatropine nitrate (20 mg/kg s.c.). A high degree of activity bursts were shown in these control groups by eleven and ten rats, respectively.

In accordance with these results preliminary experiments have indicated that cholinergic drugs such as arecoline, oxotremorine, and physostigmine induce, in rats sedated by reserpine, a stereotyped behaviour characterized by locomotion, rearing, sniffing, and gnawing. Further research is in progress to give a more complete explanation for the resemblance between the proposed cholinergically-induced behaviour in reserpinized rats and the amphetamine-induced behaviour (Randrup, Munkvad & Udsen, 1963). These anticholinergic substances given to normal rats provoke the same behaviour changes (Arnfred & Randrup, 1968) as those which are completely inhibited in reserpinized rats by the same anticholinergic substances.

REFERENCES

ARNFRED, T. & RANDRUP, A. (1968). Cholinergic mechanism in brain inhibiting amphetamine induced stereotyped behaviour. *Acta pharmac. tox.*, in the Press.

RANDRUP, A., MUNKVAD, I. & UDSEN, P. (1963). Adrenergic mechanisms and amphetamine induced abnormal behaviour. *Acta pharmac. tox.*, **20**, 145–157.

SCHIØRRING, E. & RANDRUP, A. (1968). "Paradoxical" stereotyped activity of reserpinized rats. *Int. J. Neuropharmac.*, **7**, 71–73.

The effects of (±)-amphetamine sulphate on the self-selected circadian rhythm of activity and rest in the canary

G. WAHLSTRÖM* and E. WIDERLÖV, *Department of Pharmacology, Uppsala University, Uppsala, Sweden*

Canaries were allowed to choose between light and darkness (Wahlström, 1964). The birds (usually males) were put singly in cages, each illuminated separately. The light is on as long as the bird does not use the night perch, one of the two perches in the cage. The recorded circadian rhythm usually consists of one period of light (activity) and one period of darkness (rest). The duration of the circadian period is counted from one waking (leaving the night perch) to the next.

(±)-Amphetamine sulphate (7.5 and 15 mg/kg) was given orally through a stomach tube as a single dose either early (AM) or late (PM) during the activity. This circadian period was counted as No. 0. The average pre-experimental duration of activity and circadian period were obtained from the five circadian periods prior to circadian period No. 0. In each experiment the differences from these averages were calculated for period No. 0 and the three following ones. The means and standard errors, given in Table 1, were calculated on corresponding differences from all experiments.

Table 1 shows two interesting features with regard to changes in activity. The expected increase in duration of activity after amphetamine was seen in the PM series, where the birds did not roost at the expected time and overslept the next morning (seen as an increase in duration of the circadian period). In the AM series, with 15 mg/kg given on an average 9.49 hr before expected roosting, there was no increase in the duration of activity. There