The intracerebral effects of noradrenaline and its modification by drugs in the mouse

SIR,—Imipramine-like antidepressant drugs are known to potentiate the peripheral pharmacological effects of noradrenaline (Osborne & Sigg, 1960; Cairncross, 1965; Jori & Garattini, 1965). The mechanism has been attributed to their ability to inhibit the uptake of the exogenous catecholamine (Axelrod, Whitby & Hertting, 1961; Iversen, 1965) and a similar mechanism has been proposed for imipramine-like drugs in the central nervous system (Glowinski & Axelrod, 1964). However, there is little direct evidence about the effects of imipramine and related drugs on the pharmacological effects induced by noradrenaline administered intracerebrally. The effects of noradrenaline injected intracerebrally in the conscious mouse and their modification by oral pretreatment with imipramine-like antidepressants and other pharmacological agents are now reported.

Noradrenaline was injected intracerebrally (Haley & McCormick, 1957) in male albino mice (Glaxo A_2G strain). The site of injection was within 1 mm of a point on the midline 2 mm rostral to a line joining the anterior bases of the ears. The injection was made with a 22 gauge needle $\frac{1}{8}$ inch long attached to a 0·25 ml Bacton, Dickinson & Co. tuberculin syringe inserted perpendicularly through the skull and into the brain, in volumes of 0·02 ml per mouse. The site was checked by injecting a 1 in 10 dilution of Indian ink in 0·9% sodium chloride solution. Histological examinations reveal particles of ink in the third and fourth ventricles and occasionally along the injection route. Oesophageal temperatures were measured with an electric thermometer and thermocouple (Brittain & Spencer, 1964). In drug interaction experiments the test compounds were orally administered to groups of 5 mice 1 hr before the intracerebral injection of noradrenaline (Acute test). For some drugs, three doses were administered 24, 16 and 1 hr before injection of noradrenaline intracerebrally (Subacute test).

After the intracerebral injection of saline animals remained quiet for 1–2 min before resuming their normal activity when they did not differ from untreated animals. Although a slight and transient fall in body temperature did occur,

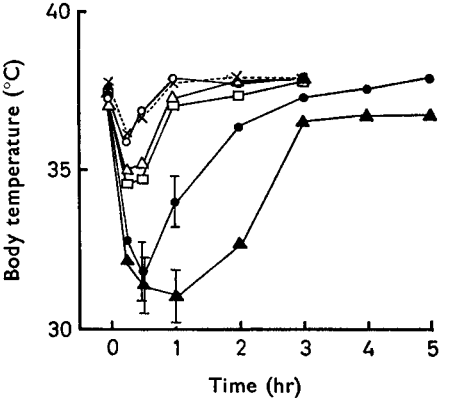

FIG. 1. Changes in body temperature following the intracerebral injection of noradrenaline. Doses μg/mouse: 1 (—○—), 2·5 (—△—), 5 (—□—), 10 (—●—) and 20 (—▲—). Saline control (--X--).

no animal showed residual detrimental effects from the intracerebral injection of saline. In contrast, the intracerebral injection of 10 μg of noradrenaline caused motor inco-ordination and ataxia and after 30 min the animals were sedated and could not be aroused. It was found that the sedation was accompanied by a fall in body temperature. The effect of graded intracerebral doses of noradrenaline on body temperature are shown in Fig. 1.

Pretreatment of animals with imipramine, amitriptyline or nortripytline antagonised the depressive and hypothermic actions of noradrenaline. The effects on body temperature in acute and subacute tests are shown in Fig. 2A and B respectively. The antagonistic effect of imipramine is dose dependent especially in the initial hyperthermia which occurs after noradrenaline injection in pretreated animals.

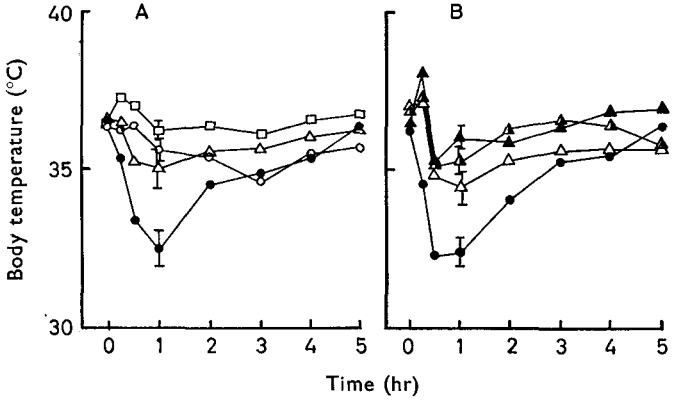

FIG. 2. Effects of imipramine-like antidepressants on hypothermia induced by intracerebrally injected noradrenaline (10 μg/mouse). A. Imipramine (—△—), amitriptyline (—○—) and nortriptyline (—□—) each at 5 mg/kg orally 1 hr prior to noradrenaline. Noradrenaline control (—●—). B. Imipramine, 3 oral doses each at 5 mg/kg (—△—), 10 mg/kg (—▲—) or 20 mg/kg (—▲—) before noradrenaline. Noradrenaline control (—●—).

The effects of other drugs have been investigated in this procedure. The drugs listed below did not prevent noradrenaline-induced hypothermia nor depression in doses (mg/kg orally) up to those given in brackets after each compound: chlorpromazine (2), chlordiazepoxide (25), diazepam (25), haloperidol (25), pentobarbitone (25), phenytoin (25), benzhexol (10), atropine (10), chlorpheniramine (10) and homochlorcyclazine (10). Higher doses of atropine (20) and benzhexol (20) were weakly active in preventing the noradrenaline-induced hypothermia by about 50%. Amphetamine (2) almost completely prevented the intracerebral effects of noradrenaline. Phenelzine (5) had little effect on the noradrenaline response but sub-acute administration of this drug (3 × 5 mg) potentiated the hypothermia and sedation.

The mode of action of the imipramine-like antidepressants in antagonising the central effects of noradrenaline is not known. Preliminary experiments in which uptake of tritrated noradrenaline has been studied indicate that very small amounts (1·8–2·8%) of the injected noradrenaline are taken up by the

brain tissue. Furthermore imipramine, in doses which antagonized the depression and hypothermia produced by noradrenaline, had no significant effect on this very low uptake. Thus it is impossible at this time to reconcile the observed antagonism of noradrenaline by imipramine-like antidepressants in the mouse with the current concept that these agents may facilitate central adrenergic mechanisms in the same way as they do at the periphery by inhibiting the uptake of noradrenaline into neurone transmitter stores (Axelrod & others, 1961; Iversen, 1965; Jori, Paglialunga & Garattini, 1966).

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On the mechanism of the hyperglycaemic effect of chlorpromazine

SIR,—Chlorpromazine shows hyperglycaemic properties in several animal species including man. Previous experiments suggested that this drug interferes with the peripheral utilization of glucose (Chagovets & Shtutman, 1963; Jori, Bernardi & Garattini, 1964) as supported by the fact that chlorpromazine reduces glucose tolerance (Bhide, Tiwari & Balwani, 1965; Jori & Bianchetti, 1966). However, several mechanisms may be involved (Bonaccorsi, Jori & Garattini, 1964). In high doses, chlorpromazine may induce hyperglycaemia by activating adrenals and sympathetic nerve endings (Mraz & Triner, 1963).

Chlorpromazine also released adrenaline from adrenals *in vitro* (Weil-Malherbe & Posner, 1963) and it increased the urinary excretion of catecholamines *in vivo* (Johnson, 1964). Furthermore chlorpromazine impaired the uptake

TABLE 1. EFFECT OF β-ADRENERGIC BLOCKING AGENTS ON THE HYPERGLYCAEMIA INDUCED BY CHLORPROMAZINE AND BY ADRENALINE

Treatment mg/kg i.p.	Blood glucose (mg %) after chlorpromazine 15 mg/kg	Blood glucose (mg %) after adrenaline 100 µg/kg
Saline	137 ± 9	146 ± 3
MJ 1999 5 × 2	102 ± 2·6*	109 ± 2·4*
Propanolol 5 × 2	99 ± 5*	96 ± 4*
Pronethalol 5 × 2	116 ± 6·1*	112 ± 7·4
D-(−)-INPEA 10	108 ± 2*	106 ± 5*

Blood Glucose was measured 1 and 2 hr after adrenaline and chlorpromazine respectively.

* P <0·01 for saline treatment.

Untreated animals show a blood glucose level of 70 ± 5 mg %. β-Blocking drugs were given 1 hr before and 15 min after the administration of chlorpromazine or adrenaline. D-(−)-INPEA was given only 1 hr before the hyperglycaemic agent.