Imipramine affects dopamine uptake by rat brain

SIR,—We wish to present evidence that imipramine affects the uptake of dopamine by brain aminergic neurons. Our evidence is indirect but is consistent with the evidence that the central action of the tricyclic antidepressants is related to the blockade of a membrane concentrating or uptake mechanism as shown for peripheral nerves (Titus, Matussek & others, 1966). In the central nervous system, antidepressants alter the uptake of intraventricularly injected radioactive noradrenaline (Schanberg, Schildkraut & Kopin, 1967; Glowinski & Axelrod, 1964), to decrease the histochemical fluorescence of intraperitoneally injected precursors of noradrenaline and 5-hydroxytryptamine (5-HT), and to reduce the amount of chemically determined amines (Carlsson, Fuxe & Ungerstedt, 1968; Carlsson, Fuxe & others, 1966). We have shown elsewhere that, after intraventricular injection, less 5-HT is taken up by the brain when it is combined with imipramine than when it is given alone (Pscheidt & Himwich, 1968).

Rats were injected intraventricularly (Noble, Wurtman & Axelrod, 1967) with a constant injection volume of 10 μl. At appropriate times the animals were decapitated and the brains rapidly removed, rinsed with saline, frozen on solid carbon dioxide and subsequently analysed for their content of dopamine. The brains were homogenized and extracted (Mead & Finger, 1961) and the final extract treated with iodine (McGeer & McGeer, 1961) and the apparent dopamine content determined fluorometrically. The dosage and injection schedule is in Table 1.

TABLE 1. DOPAMINE CONTENT OF MOUSE BRAIN (μG/G) AFTER TREATMENT WITH TRANYLCYPROMINE, DOPAMINE OR IMIPRAMINE SEPARATELY OR IN COMBINATION

Dose rate and time given before death	Number of animals	Dopamine content of brain, μg/g $\pm$ standard deviation
None	6	1·7 $\pm$ 0·3
Dopamine (20 μg, i.vent., 30 min)	12	2·4 $\pm$ 0·9
Imipramine (500 μg, i.vent., 30 min)	4	1·6 $\pm$ 0·5
Tranylcypromine (5 mg/kg, i.p., 0 min)	3	2·4 $\pm$ 0·7
Tranylcypromine (5 mg/kg, i.p., 0 min) and imipramine (500 μg, i.vent., 30 min)	3	2·3 $\pm$ 0·2
Tranylcypromine (5 mg/kg, i.p., 0 min) and imipramine (500 μg, i.vent., 30 min) and dopamine (20 μg, i.vent., 30 min)	6	3·5 $\pm$ 1·1
Tranylcypromine (5 mg/kg, i.p., 0 min) and dopamine (20 μg, i.vent., 30 min)	12	9·8 $\pm$ 1·1
Dopamine (20 μg, i.vent., 7½ min)	4	8·7 $\pm$ 4·5
Dopamine (20 μg, i.vent., 15 min)	5	5·0 $\pm$ 1·9
Dopamine (20 μg, i.vent., 60 min)	6	1·7 $\pm$ 0·7

The pertinent findings are the lack of change in brain dopamine with all drug combinations except those of tranylcypromine-dopamine and tranylcypromine-imipramine-dopamine. The former combination elevated brain dopamine content five times above control levels whereas inclusion of imipramine in the intraventricular injection reduced this elevation to only a two-fold increase. We interpret this result as wholly consistent with the view that tricyclic antidepressants are capable of blocking the uptake of dopamine at central aminergic neurons.

Thudichum Psychiatric Research Laboratory,
Galesburg State Research Hospital,
Galesburg, Illinois 61401, U.S.A.

GORDON R. PSCHEIDT
HAROLD E. HIMWICH

July 3, 1968

References

Carlsson, A., Fuxe, K., Hamberger, B. & Lindqvist, M. (1966). *Acta physiol. scand.*, **67**, 481–497.
Carlsson, A., Fuze, K. & Ungerstedt, U. (1968). *J. Pharm. Pharmac.*, **20**, 150–151.
Glowinski, J. & Axelrod, J. (1964). *Nature, Lond.*, **204**, 1318–1319.
McGeer, E. G. & McGeer, P. L. (1962). *Can. J. Biochem. Physiol.*, **40**, 1141.
Mead, J. A. R. & Finger, K. F. (1961). *Biochem. Pharmac.*, **6**, 52–53.
Noble, E. P., Wurtman, R. J. & Axelrod, J. (1967). *Life Sci.*, **6**, 281–291.
Pscheidt, G. R. & Himwich, H. E. (1968). *J. Pharmac. exp. Ther.*, in the press.
Schanberg, S. M., Schildkraut, J. J. & Kopin, I. J. (1967). *Biochem. Pharmac.*, **16**, 393–399.
Titus, E. O., Matussek, N., Spiegel, H. E. & Brodie, B. B. (1966). *J. Pharmac. exp. Ther.*, **152**, 469–477.

Microscopical appearance of some oil-in-water emulsions

SIR,—Barry (1968) has demonstrated the presence of crystalline material in polyhedral particles occurring in emulsions. We find the preparative technique to influence the microscopical appearance of some similar emulsions. Solutions of cetostearyl alcohol (7 g) in liquid paraffin (50 g), and cetomacrogol 1000 or cetrimide (0·5 g) in water (42·5 g) were mixed at 60°. Separate batches of the crude emulsion were (*a*) stirred by hand, (*b*) passed through an automatic pipetting syringe or (*c*) passed through a Q.P. hand homogenizer four times. Samples of each product were examined under a phase contrast microscope and where necessary they were diluted with distilled water.

The relatively gentle shear action of stirring produced emulsions in which we, too, observed globules containing crystalline material.

The syringe technique resulted in a greater degree of globule shearing. Crystals were not visible within the globules but what appeared to be filamentous structures could be seen, either enveloping the globules or dispersed in the aqueous phase (Fig. 1A). These structures were present in the freshly prepared emulsion and did not disappear on ageing or show up under polarized light. They melted when the samples were heated to about 60° on a Leitz hot stage. On cooling, acicular crystals could be seen inside some globules, and filaments were again evident, this time radially orientated at the oil–water interface (Fig. 1B). The orientation effect might have been due to the coverslip but it seems likely that, in general, the interfacial film may act as a template for filament production.

The greatly reduced globule size of the highly sheared homogenized emulsions limited the detail visible by optical microscopy. Aggregates of globules, as noted by Axon (1957) and Riegelman (1962) were apparent in diluted samples. Fig. 1C shows an undiluted emulsion which has been heated to about 60°.

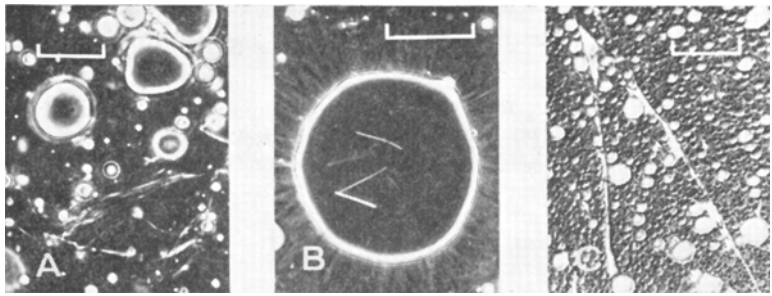

FIG. 1. Photomicrographs of: (A) Emulsion prepared by syringe technique—diluted before examination. One division = 10 μ. (B) As (A) but heated and cooled. One division = 20 μ. (C) Undiluted homogenized emulsion after heating and cooling. One division = 30 μ.