The effect of imipramine of central 5-hydroxytryptamine neurons

SIR,—Ever since Sigg's (1959) discovery that imipramine is capable of potentiating the action of noradrenaline and of sympathetic nerve stimulation, the view has been favoured that a similar action on central noradrenaline is responsible for the antidepressive action of this drug. The peripheral potentiating action is probably due to blockade of an amine-concentrating mechanism located at the level of the cell membrane of the adrenergic neuron (Hillarp & Malmfors, 1964; Carlsson & Waldeck, 1965; Malmfors, 1965). The monomethyl derivatives of imipramine and related agents are more potent inhibitors of this mechanism than their parent compounds. We have investigated central noradrenaline neurons in this respect. The monomethyl derivatives protriptyline and desipramine proved to be active inhibitors of this mechanism in the central noradrenaline neurons (see Carlsson, Fuxe & others, 1966; Carlsson, Corrodi, Fuxe & Hökfelt, to be published). Later, however, imipramine was found to be surprisingly weak in this respect. This is in contrast to the good clinical antidepressive action of this drug. Evidence has recently been obtained that there exist also in the central 5-hydroxytryptamine (5-HT) neurons a reserpine-resistant uptake-concentration mechanism for amines. This mechanism appeared to be resistant to desipramine (Fuxe & Ungerstedt, 1967). We have now observed that imipramine is capable of blocking this mechanism in the 5-HT neurons.

Intraventricular injections of 5-HT (5 μg) were made into the lateral ventricle of rats pretreated with reserpine (12 hr before killing, 10 mg/kg, i.p.) and nialamide (500 mg/kg, i.p., 1 hr before killing). The rats were killed 30 min later (cf. Fuxe & Ungerstedt, 1966, 1967). Imipramine was given in doses of 20–30 mg/kg, intraperitoneally 15 min before the injection. There was a partial blockade of the reserpine-resistant accumulation of 5-HT in many 5-HT cell bodies, non-terminal axons and terminals lying close to the ventricles and the ventral part of the subarachnoidal space.

In another set of experiments rats pretreated with reserpine (10 mg/kg, i.p., 12 hr before killing) and nialamide (500 mg/kg, i.p., 1–6 hr before killing) were given imipramine intraperitoneally in a dose of 5 and 40 mg/kg respectively, 30–40 min before killing. In rats treated only with reserpine and nialamide there is a gradual accumulation of 5-HT in the 5-HT neurons which is maximal after about 4–6 hr, at which time the 5-HT neurons have a strong yellow fluorescence. Only in the highest dose (40 mg/kg) was there any clearcut effect of imipramine. With this dose there was a somewhat less marked accumulation of 5-HT compared to controls in all parts of the 5-HT neurons.

Systemically administered α-methyl-*m*-tyramine and related compounds are capable of reducing brain catecholamine levels, probably by displacement. This action is blocked by protriptyline and desipramine, less so by imipramine (Carlsson, Corrodi & Fuxe, unpublished data; see Carlsson, 1967). Continued work has shown that compounds of this class can also displace central 5-HT. This effect is blocked virtually completely by imipramine in doses of 25 to 50 mg/kg. Thus, the displacing agent alone caused a decrease of 5-HT in mouse brain from 0·40 to 0·18 μg/g. In animals treated with imipramine 30 min before the displacing agent the 5-HT level was 0·37 μg/g.

All these results taken together indicate that imipramine *in vivo* selectively blocks the reserpine-resistant uptake-concentration mechanism at the level of the nerve cell membrane in central 5-HT neurons. This action may be of importance for its antidepressive properties.

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An intravenous catheter for chronic use

SIR,—The use of conscious animals in experiments extending over weeks or months often necessitates the intravenous injection of fluids. Several indwelling catheters terminating in closures attached to the skin have been described but generally these require special machined parts (Khouri, Gregg & Rayford, 1965; Davis, 1966; Goetz & Hanis, 1967). We have designed and used a catheter which is easy to construct and whose components are usually found in research laboratories.

Fig. 1 is a diagram of a section through the catheter and skin-button connector. The connector is built around a No. 1 Record-fitting syringe needle. The needle mount (D) is first cut down to 1 cm in length and filed to an approximately cylindrical external contour. Next, the tapered mount hole is enlarged and a 1 ml serum closure cap (A) inserted. The cap is first cut as in the insert of Fig. 1 along the dotted lines. The closure skirt is then everted over the needle mount and covered with a short length (1 cm) of heat-shrinkable polyethylene tubing.

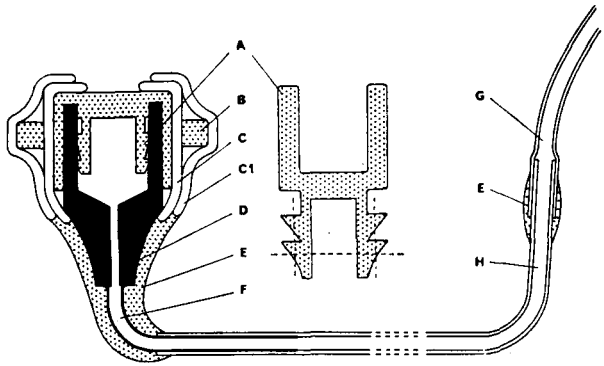

FIG. 1. Diagram of a section through the skin button connector and catheter to show the method of assembly.
A. Serum closure cap. B. Thick-walled rubber tubing. C and C_1, Heat shrinkable polyethylene tubing. D. Needle mount. E. Silicone rubber F. Syringe needle. G. Silicone rubber tubing. H. Teflon tubing.