The effect of imipramine on central monoamine neurons

SIR,—Imipramine potentiates the action of noradrenaline in the peripheral nervous system (Sigg, 1959). This action, however, is weaker than that of desipramine, its demethylated derivative. This potentiation is because these drugs probably block the uptake-concentration mechanism at the level of the nerve cell membrane of the sympathetic adrenergic neurons (see e.g. Hillarp & Malmfors, 1964; Malmfors, 1965; Carlsson & Waldeck, 1965). The current hypothesis has been that imipramine and related drugs exert a similar blocking action on the uptake-concentration mechanism of the noradrenaline neurons in the central nervous system and that this action may be responsible for their antidepressive properties (see Klerman & Cole, 1965). Evidence (Carlsson, Fuxe & others, 1966; Hamberger, 1967) in support of this view has been given for imipramine-like drugs such as desipramine and protriptyline, but imipramine itself has been found to be only a poor blocker of the uptake-concentration mechanism of the central noradrenaline neurons (Carlsson, Corrodi, Fuxe & Hökfelt, to be published). We now present evidence that imipramine has an effect on the central 5-hydroxytryptamine (5-HT) neurons. Experiments using histochemical (Hillarp, Fuxe & Dahlström, 1966) and biochemical amine analyses have been made and they show that imipramine influences the rate of 5-HT depletion after amine synthesis inhibition (cf. Andén, Corrodi & others, 1966).

Male, Sprague-Dawley rats (200–250 g) have been used. Imipramine (10 or 30 mg/kg) was injected intraperitoneally 15 min before the injection of the tyrosine-hydroxylase inhibitor, the methylester of α-methyltyrosine (H 44/68) or the tyrosine and tryptophane hydroxylase inhibitor, α-propyldopacetamide (H 22/54). In the six histochemical experiments only the highest dose of imipramine was examined. In three experiments H 22/54 (500 mg/kg, i.p.) was used and in another three H 44/68 (250 mg/kg, i.p.). Each histochemical experiment consisted of 4 groups (untreated controls, imipramine alone, imipramine plus inhibitor, inhibitor alone) with 4 rats in each group. Thus, about 100 rats were used in the histochemical experiments. For time-intervals and other details see Table 1. The rectal temperature of the animals was regularly controlled and found to be within normal limits (37–38°).

Histochemically, it was found that in 10 rats out of 12 there was a clear retardation of amine depletion from the 5-HT nerve terminals of the brain, e.g. those of the nucleus suprachiasmaticus, after H 22/54 under the influence

TABLE 1. MONOAMINE CONCENTRATIONS IN WHOLE BRAIN 3¼ HR OR 4¼ HR AFTER IMIPRAMINE (10 OR 30 MG/KG I.P.) GIVEN 15 MIN BEFORE H44/68 (250 MG/KG, I.P.) AND H22/54 (500 MG/KG, I.P.) RESPECTIVELY. The values are given in % of controls. n = number of experiments. Each group represents 4 animals. The statistical analysis has been made according to Student's *t*-test.

		5-HT in %	Noradrenaline in %	Dopamine in %
Untreated controls	(n = 4) ..	100·0 ± 3·5	100·0 ± 2·0	100·0 ± 2·5
Imipramine 30 mg/kg	(n = 4) ..	96·8 ± 14·3	82·7 ± 13·4	100·6 ± 13·8
H 44/68	(n = 4) ..	—	50·1 ± 1·9	28·8 ± 2·2
Imipramine (30 mg/kg) + H 44/68	(n = 4) ..	—	45·4 ± 1·6	32·1 ± 4·0
H 22/54	(n = 6) ..	43·0 ± 2·2[1]	—	—
Imipramine (30 mg/kg) + H 22/54	(n = 4) ..	62·2 ± 4·2[2]	—	—
Imipramine (10 mg/kg) + H 22/54	(n = 4) ..	45·9 ± 3·9	—	—

• Significance between [1] and [2] $P < 0.01$.

of imipramine. In no case, however, was there any observable change in the rate of amine depletion from the central noradrenaline and dopamine nerve terminals after H 44/68. Nor was the number and intensity of the catecholamine and 5-HT nerve terminals affected by imipramine alone. In the biochemical experiments similar results were obtained (see Table 1). There was a significant ($P < 0.01$) retardation of 5-HT depletion after H 22/54 under the influence of imipramine. The effect was not present with the lowest dose used (10 mg/kg). The rate of noradrenaline and dopamine depletion after H 44/68 was not affected nor were the catecholamine or 5-HT levels (Table 1).

The present findings show that imipramine in a dose of 30 mg/kg clearly retards the rate of amine depletion from central 5-HT nerve terminals after inhibition of 5-HT synthesis (H 22/54). Since the rate of amine depletion after inhibition of synthesis is dependent on the nervous impulse flow (Andén & others, 1966; Andén, Fuxe & Hökfelt, 1966) it may be that there is a decreased nervous impulse flow in the 5-HT neurons under the influence of imipramine. If so, this change in nervous impulse flow may be related to the fact that imipramine in a dose of 30, but not 10 mg/kg, which was ineffective also in the present experiments, is probably a blocker of the reserpine-resistant uptake-concentration mechanism of the central 5-HT neurons (Carlsson, Fuxe & Ungerstedt, 1968). This blockade will increase the amounts of 5-HT reaching the postsynaptic receptors and could, thus, initiate a negative feedback on the presynaptic 5-HT neuron. This would result in a decreased impulse flow, which was, in fact, indicated from the results of the present study. It is known from previous studies that desipramine probably has no effect on the 5-HT neurons, since there is no retardation of the rate of 5-HT depletion after amine synthesis inhibition under the influence of desipramine (Corrodi, Fuxe & Hökfelt, 1967) nor is there any observable block of 5-HT uptake (Fuxe & Ungerstedt, 1967). It is proposed that an effect on the 5-HT neurons may be of importance for the antidepressant action of imipramine.

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