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# 5-Hydroxytryptamine uptake inhibitors antagonize the antireserpine effects of noradrenaline uptake inhibitors

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Imipramine is an inhibitor of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) uptake, whereas desipramine, its desmethyl metabolite, mainly inhibits the uptake of NA. The antireserpine action of imipramine does not occur if its metabolism is inhibited by proadifen (Maj et al 1981, 1982a). That negative effect may result from the absence of the desmethyl metabolite and/or from the much increased the brain level of imipramine at which its inhibitive action on 5-HT uptake is brought into prominence and can be an antagonistic factor towards the noradrenergic mechanism. This is supported by the finding that 5-HT uptake inhibitors attenuate the antireserpine action of NA uptake inhibitors (Maj et al 1982c). That action, however, has been observed in the hypothermia test and consequently can be of central as well as peripheral origin. In the present study we have, therefore, taken locomotor activity as a criterion, assuming that its changes should result from central action. In order to simulate the conditions occurring after administration of imipramine we injected concurrently a NA uptake inhibitor and a 5-HT uptake inhibitor. As selective NA uptake inhibitors we used desipramine and maprotiline (Maitre et al 1974) and as selective 5-HT inhibitors, citalopram (Christensen et al 1977; Pawlowski et al 1981), fluoxetine (Fuller et al 1975; Slater et al 1979), fluvoxamine (Claassen et al 1977; Maj et al 1982b) and zimelidine (Ross et al 1976). None of them shows the antireserpine or antitetrabenazine action, but only citalopram and zimelidine were studied in the locomotor activity test.

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*Methods*

The experiments were on Albino Swiss, male mice (25–30 g) having had free access to food and water. The locomotor activity was measured over 1 h when the mice were individually placed in photoresistor actometers. The NA and 5-HT uptake inhibitors were given i.p. singly or together 5 h before the experiments at the doses, generally accepted as effective and chosen on the ground of preliminary experiments. Reserpine (2 mg $kg^{-1}$) was administered s.c. 4 h before the experiment. All drugs were injected as solutions in 0·9% NaCl (saline). There were 8–10 mice to a group. The statistical significance was determined with Student's *t*-test.

Drugs given were: citalopram hydrobromide (Lundbeck), desipramine hydrochloride (Ciba-Geigy), fluoxetine hydrochloride (Lilly), fluvoxamine maleate (Philips-Duphar D.V.), maprotiline hydrochloride (Ciba-Geigy), reserpine (Serpasil-amp., Ciba-Geigy), zimelidine dihydrochloride (Astra).

*Results and discussion*

All the NA or 5-HT uptake inhibitors tested, when given alone (at doses given in Table 1) 5 h before experiment did not affect locomotor activity in normal mice (data not shown).

Desipramine antagonized the reserpine hypoactivity (Table 1). Citalopram, fluoxetine, fluvoxamine and zimelidine were ineffective in this respect. Each of them abolished or much attenuated the antireserpine action of desipramine.

Maprotiline counteracted sedation in reserpinized

Table 1. Effects of 5-HT uptake inhibitors on the action (locomotor activity) of NA uptake inhibitors in reserpinized (2 mg kg$^{-1}$ s.c.) mice. The NA and 5-HT uptake inhibitors were given 5 h before the experiment, reserpine—1 h before the experiment. Locomotor activity was measured over a period of 1 h. Mean value of control group treated with saline only was 156·4 ± 13·9 n = 10. Statistical significances were calculated (Student's *t*-test) as follows: reserpine + desipramine (or maprotiline) versus reserpine; reserpine + 5-HT uptake inhibitor versus reserpine; reserpine + desipramine (or maprotiline) + 5-HT uptake inhibitor versus reserpine + desipramine (or maprotiline).

| | Locomotor activity after NA uptake inhibitors (mean + s.e.m.) | | |
|---|---|---|---|
| 5-HT uptake inhibitor | — | Desipramine 10 mg kg$^{-1}$ i.p. | Maprotiline 10 mg kg$^{-1}$ i.p. |
| Control | 13·5 ± 2·9 | 122·7 ± 31·9** | 65·5 ± 12·8*** |
| Citalopram 10 mg kg$^{-1}$ i.p. | 5·8 ± 2·5 | 14·5 ± 3·5*** | 12·9 ± 2·9*** |
| Fluoxetine 10 mg kg$^{-1}$ i.p. | 8·1 ± 2·9 | 45·6 ± 17·3*** | 17·0 ± 4·9*** |
| Zimelidine 10 mg kg$^{-1}$ i.p. | 7·4 ± 2·6 | 35·9 ± 7·8* | 18·2 ± 5·3*** |
| Control | 10·2 ± 3·0 | 64·9 ± 15·6** | 78·3 ± 20·7** |
| Fluvoxamine 10 mg kg$^{-1}$ | 9·8 ± 3·8 | 23·0 ± 5·9** | 18·5 ± 6·0*** |

* ($P < 0·05$).
** ($P < 0·01$).
*** ($P < 0·001$).

mice (Table 1). Citalopram, fluoxetine, fluvoxamine and zimelidine antagonized the antireserpine effect of maprotiline.

Citalopram, 10 mg kg$^{-1}$ i.p. given 1 h or 3 h after reserpine, 2 mg kg$^{-1}$ s.c. (not 1 h before reserpine as above) also antagonized the antireserpine effect of NA uptake inhibitors (data not shown). These findings allow exclusion of pharmacokinetic origins (e.g. inhibition of absorption) as the source of the antagonistic effect described above.

*m*-Chlorophenylpiperazine (10 mg kg$^{-1}$ i.p. 3 h after reserpine), a 5-HT agonist (Fuller et al 1980; Maj & Lewandowska 1980), is able also to antagonize the antireserpine effect of desipramine or maprotiline (unpublished).

The data indicate that concurrent treatment with an NA uptake inhibitor and a 5-HT uptake inhibitor, simulating the use of imipramine (or other antidepressants that inhibit the uptake of both amines), does not antagonize reserpine-induced locomotor hypoactivity. On the contrary, the antireserpine effect induced by the NA uptake inhibitor is counteracted by the 5-HT uptake inhibitor, as in the hypothermia test (Maj et al 1982c). It can therefore be concluded that: (i) for the antireserpine action of imipramine (and imipramine-like drugs) the noradrenergic mechanism is essential, according to the earlier hypothesis based on body temperature studies (e.g. Garattini & Jori 1967; Slater et al 1979). (ii) the 5-HT uptake inhibition (as well as the 5-HT agonistic activity) is a factor which interferes with the above action.

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