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Mianserin, danitracen and amitriptyline withdrawal increases the behavioural responses of rats to L-5-HTP

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Trulson et al (1976a,b) demonstrated that after lesion of the central 5-hydroxytryptamine (5-HT) nerve terminals in rats supersensitivity to 5-HT precursors and agonists occurred. Such supersensitivity was not observed after a chronic inhibition of the 5-HT synthesis or a chronic blockade of 5-HT receptors by methysergide (Trulson et al 1977). On the other hand, Klawans et al (1975, 1977) found an enhanced behavioural response to D,L-5-hydroxytryptaphan after a chronic treatment of guinea-pigs with methysergide.

The present study was undertaken to determine whether a repeated administration of mianserin and danitracens, both antidepressant drugs that block 5-HT receptors (Kähling et al 1975; Maj et al 1976a, b; Van Riezen 1972), affected the response to 5-HTP. For comparison we also examined amitriptyline, the classical tricyclic antidepressant regarded as an inhibitor of the 5-HT and noradrenaline (NA) uptake. The 'wet-dog' shake behaviour reflecting the activity of the central 5-HT system (Bedard & Pycock 1977) was used to test the responsiveness to L-5-HTP.

Male Wistar rats (180–210 g) were placed individually in wire mesh cages and immediately after injection of L-5-HTP ethyl ester HCl (dissolved in 0·9% NaCl, injected i.v. in a constant volume of 1 ml kg^{-1}, 12·5 mg kg^{-1}, the dose producing about 20 shakes per 30 min) wet dog shakes were recorded for 30 min. Shakes began about 3 min after L-5-HTP injection, reached a peak about 10–15 min later and lasted for almost 45 min. Apart from the shakes, the rats occasionally displayed reciprocal forepaw treading (rhythmical dorsoventral movements of the forelimbs), forepaw crossing, grooming with the forepaws and hind limbs as well as sporadic yawning. The animals were treated with a vehicle or drugs injected once or twice a day at 9 a.m. and 6 p.m. for 4 or 10 days. The last drug dose (except for amitriptyline, the last dose of which was given 72 h before) was administered 24, 48 or 72 h before injection of L-5-HTP ethyl ester.

A single dose of mianserin (2 mg kg^{-1}) (Fig. 1A) 24, 48 and 72 h before L-5-HTP did not affect the number of L-5-HTP-induced shakes. A 4-day administration (Fig. 1B) markedly elevated the number of shakes 48 and 72 h after withdrawal. A 10-day treatment (Fig. 1C) significantly reduced the number of shakes when the last dose of mianserin was administered 48 h before L-5-HTP, and increased it markedly when mianserin was given 72 h before.

A single dose of danitracen (3 mg kg^{-1}) (Fig. 1A), 72 h before L-5-HTP, elevated (by about 50%) the number of shakes. A similar but much stronger effect was observed after 72 h with 4- and 10-day danitracen injections (Fig. 1B and 1C). In this 4- and 10-day treatment the number of shakes was reduced significantly after 24 h in the latter regimen. After 48 h the results did not differ from the control values.

A single dose of amitryptyline (10 mg kg^{-1}) (Fig. 1A) 72 h before the test had no effect on the L-5-HTP-induced shakes, whereas 4- and 10-day treatment significantly increased the number of shakes (Fig. 1B and 1C).

The results indicate that mianserin and danitracen in doses blocking 5-HT receptors, e.g. blocking the head shake response to L-5-HTP (Maj et al 1976a; 1978) enhance this response when they are administered chronically. Since the enhanced response to L-5-HTP occurs particularly 72 h after withdrawal of mianserin, danitracen, and not 24 h after, it may be assumed that it does not result from the effect of the examined drugs on pharmacokinetics or the L-5-HTP metabolism. It seems, therefore, that this response may be due to a prolonged (4- or 10-day) blockade of 5-HT receptors, as was observed with methysergide (Klawans et al 1975). The lack of an enhanced response to L-5-HTP in the initial period (especially after 24 h), or even its weakening (after a 10-day danitracen administration)

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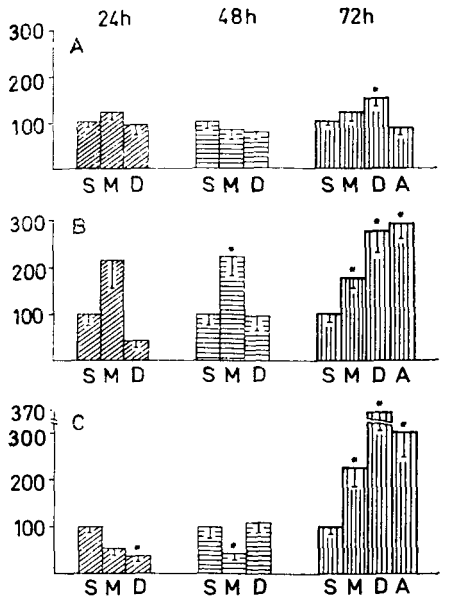

FIG. 1. Effect of single injection (A) 2 × day for 4 days (B) and 2 × day for 10 days (C) treatment with saline (S) or various antidepressants on wet-dog shakes (ordinate: wet-dog shake per 30 min) response in rats induced by L-5-HTP. L-5-HTP ethyl ester (12·5 mg kg^{-1} i.v.) was given 24, 48 or 72 h after the last dose of mianserin (M) (2 mg kg^{-1} i.p.) or danitracen (D) (3 mg kg^{-1} i.p.) or 72 h after the last dose of amitriptyline (A) (10 mg kg^{-1} s.c.). Shakes were recorded for 30 min following L-5-HTP injection. The results are means with s.e.m. of data obtained from 8 rats; they are expressed as a percentage of control (S) values which in the case of a single treatment (A) were 24, 48 or 72 h after injection 17·6 ± 1·9, 20·4 ± 3·3 or 19·9 ± 1·6 respectively; in the case of a 4-day treatment (B) 28·0 ± 7·0, 26·0 ± 6·0, 20·0 ± 3·7; in the case of a 10-day treatment (C) 30·6 ± 4·2, 21·4 ± 4·9, 18·4 ± 2·7. * $P < 0.05$ (*t*-test).

may be caused by a permanent presence of the drug blocking the 5-HT receptors in the brain.

Withdrawal of amitriptyline after chronic dosage also results in an enhanced response to L-5-HTP. Although amitriptyline is an inhibitor of 5-HT uptake, its single dose also prevents the head shake response to L-5-HTP (Fuxe et al 1977; Nakamura et al 1976), its ED50 values in this test being 5·5 and 1·3 mg kg^{-1} in rats and mice respectively (Maj et al 1979). This drug also antagonizes the stimulation of the hind limb flexor reflex in the spinal rat induced by 5-HT-mimetics (Maj et al 1979). It is likely, therefore, that irrespective of its effect on 5-HT uptake, amitriptyline also has a blocking action on 5-HT postsynaptic receptors, the latter property appearing to be relatively more potent (Fuxe et al 1977).

In conclusion, the enhanced response to L-5-HTP after a chronic administration of mianserin, danitracen and amitriptyline may provide further evidence for their action blocking the brain 5-HT receptors.

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