*Acta pharmacol. et toxicol.* 1986, **59**, 103–112.

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# Chronic Treatment with Antidepressant Drugs and the Analgesia Induced by 5-Methoxy-N,N-dimethyltryptamine: Attenuation by Desipramine

By

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(Received November 11, 1985; Accepted March 11, 1986)

*Abstract:* The effect of chronic and acute oral or intraperitoneal treatment with the antidepressant drugs, desipramine, amitryptyline, alaproclate and iprindole, upon pain thresholds in the tail flick, hot plate and shock titration tests of nociception in saline- and 5-MeODMT-treated rats was studied. Chronic desipramine treatment increased the pre-test tail flick latencies. In the saline-treated rats, chronic oral desipramine treatment increased tail flick latencies, whereas chronic oral amitryptyline treatment decreased tail flick latencies. In 5-MeODMT-treated rats, chronic oral desipramine treatment attenuated the effects of 5-MeODMT (1 mg/kg) in all three tests of nociception, whereas chronic amitryptyline caused a potentiation in the tail flick and hot plate tests. Chronic oral iprindole treatment attenuated 5-MeODMT-induced analgesia in the hot plate test. Chronic intraperitoneal desipramine treatment attenuated 5-MeODMT analgesia in the tail flick and shock titration tests. In a different chronic treatment experiment, oral desipramine treatment attenuated 5-MeODMT analgesia in the tail flick test and zimeldine did for both the tail flick and hot plate tests, whereas mianserin potentiated 5-MeODMT-induced analgesia in both the tail flick and hot plate tests. In the saline-treated rats, acute treatment with all four drugs, despiramine, amitryptiline, iprindole and alaproclate, elevated the shock thresholds, whereas in 5-MeODMT-treated rats, desipramine and amitryptyline elevated shock thresholds. Two main conclusions can be drawn: chronic desipramine caused a quite consistent attenuation of 5-MeODMT-induced analgesia and the effects of acute treatment differed strongly from that of the chronic treatment. The effects of chronic administration with these antidepressants were compared with other findings using different measures of behavioural and receptor function.

*Key-words:* Antidepressant drugs – chronic – acute – 5-MeODMT – tail flick – hot plate – shock titration – attenuation – potentiation – rats.

Early investigations of the action of tricyclic antidepressants suggested an increased noradrenergic (NA) and/or serotonergic (5-HT) neurotransmission as a basis of the therapeutic effect (Schildkraut 1965; Coppen 1967), due to an inhibition of neuronal reuptake mechanisms. Lately, studies involving chronic administration of antidepressant drugs (ADs) have suggested an opposite mechanism of action (Vetulani & Sulser 1975; Ögren *et al.* 1979; Aprison *et al.* 1982). The evidence concerning the effects of ADs upon 5-HT neurotransmission appears to be rather more complex than that of NA (for reviews, see Sugrue 1983b; Maj *et al.* 1984; Willner 1985). Thus, a decrease in 5-$HT_2$ receptors and a decrease or no change in 5-$HT_1$ receptors, after chronic treatment with ADs, have been reported from binding studies

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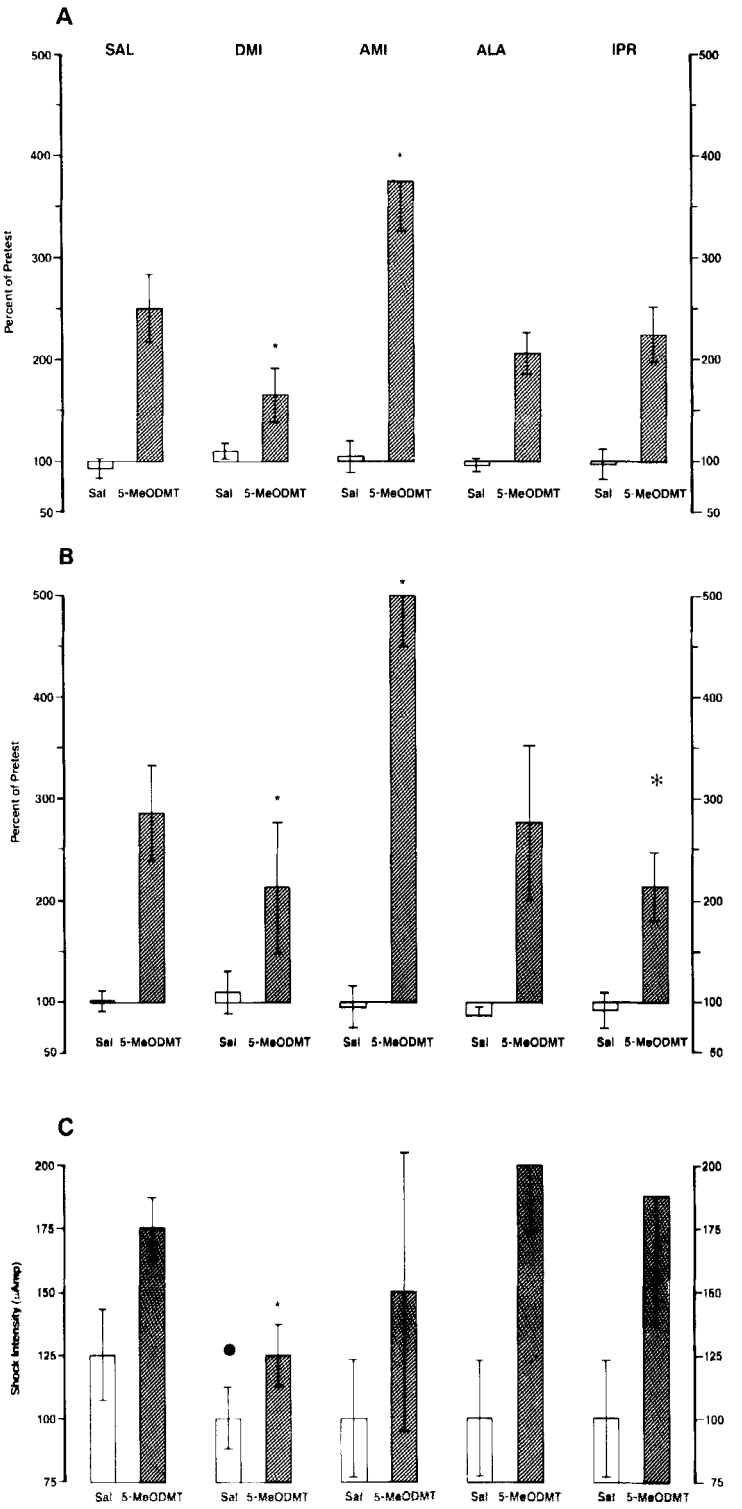



Fig. 1. The attenuation of 5-MeO-DMT-induced analgesia following per oral chronic desipramine treatment and the potentiation of 5-MeODMT-induced analgesia following chronic amitryptyline treatment in the tail flick (A), hot plate (B) and shock titration (C) tests of nociception. Within each AD treatment condition, for each saline and 5-MeODMT group, n = 7 or 8. The values are expressed as medians ± quartiles. Each AD was injected per orally (10 mg/kg) twice daily over fourteen days.
SAL = saline, DMI = desipramine, AMI = amitryptyline, ALA = alaproclate, and IPR = iprindol.
* $P < 0.02$ versus SAL – 5-MeODMT, Mann Whitney U-test.
● $P < 0.02$ versus saline – SAL.

(Goodwin *et al.* 1984), whereas some electrophysiological experiments have indicated increased responsiveness of amygdaloid, lateral geniculate body and hippocampal neurones (de Montigny & Blier 1984), but not others (Rowan & Anwyl 1985). Further, when the effects of ADs on 5-HT-induced stimulation of the second messenger were studied, a decreased responsiveness was obtained (Kendall & Nahorski 1984). In this connection, numerous behavioural studies producing variable results exemplify the disparate methodological considerations (Willner 1985).

The effects of ADs on serotonergic neurotransmission would appear to be of particular importance since many new and potential antidepressants are more or less selective 5-HT uptake inhibitors (Buus-Lassen *et al.* 1975; Doogan 1980; Hyttel 1982; Åberg-Wistedt *et al.* 1984; Ögren *et al.* 1984).

In the present investigation the analgesia induced by acute treatment with 5-methoxy-N,N-dimethyltryptamine (in the tail flick, hot plate and shock titration methods) was selected as a suitable measure of 5-HT function. Also, some clinical implications were considered since in some cases a lowered pain threshold, possibly connected with malfunctions of the 5-HT system, has been reported in depressed patients (von Knorring *et al.* 1984). The ADs studied here included: trycyclic ones such as desipramine (DMI) and amitryptyline (AMI), the atypical ADs iprindol (IPR) and mianserin (MIAN), a new potential AD, the selective 5-HT uptake inhibitor, alaproclate (ALA), zimeldine (ZIM), also a selective 5-HT uptake inhibitor and maprotyline (MAP), a selective NA uptake inhibitor.

## Materials and Methods

Male Sprague-Dawley rats weighing 205–215 g, aged 50–55 days at the start of the repeated treatment, were used for chronic administration experiments; rats weighting 280–320 g, aged 65–75 days, were used for acute AD treatment experiments. They were housed in groups of four in a cage under standard laboratory conditions with a 12 hour on/12 hour off lighting schedule in a thermostatically controlled room ($21 \pm 1°$).

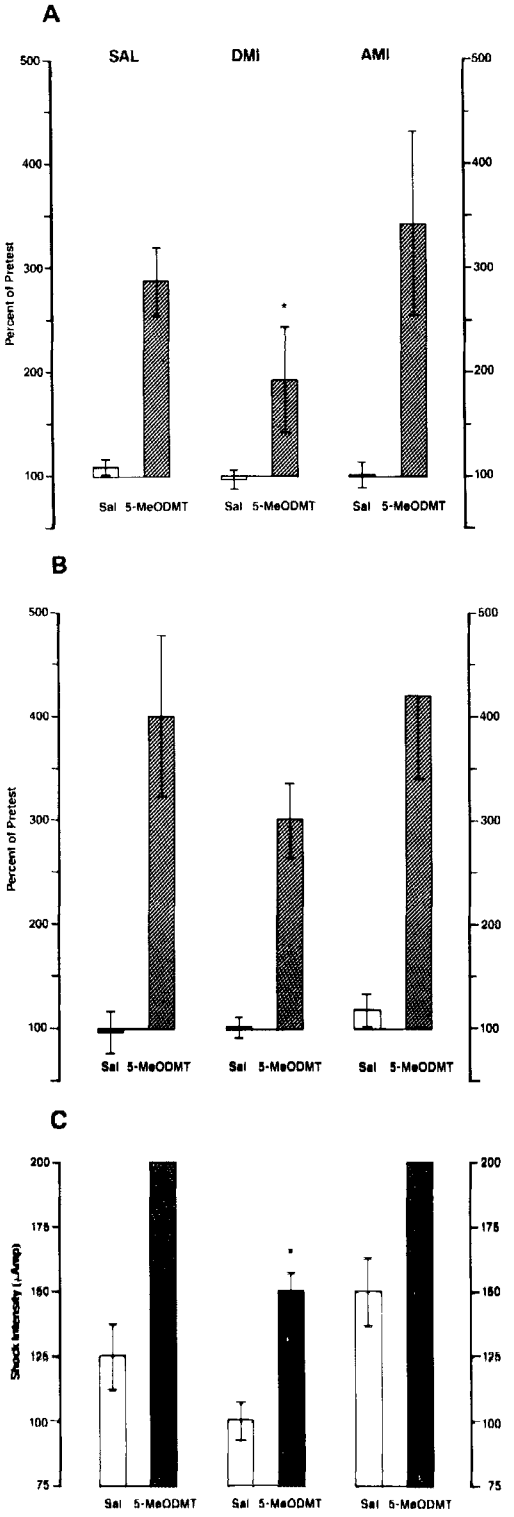
The treatment drugs included: desipramine, DMI, hydrochloride (Ciba-Geigy AG, Basel, Switzerland), amitryptyline, AMI, hydrochloride (WTA, MSD), iprindol, IPR (Wyeth Lab., Philadelphia, P.A., U.S.A.), alaproclate, ALA, hydrochloride (Astra AB, Södertälje, Sweden), maprotyline, MAP, hydrochloride (Ciba-Geigy AG), mianserin, MIAN, hydrochloride (Organon, Oss, Holland), zimeldine, ZIM, dihydrochloride hydrate (Astra AB) and 5-methoxy-N,N-dimethyltryptamine, 5-MeODMT, (Sigma Chemical Co., St. Louis, Mo., U.S.A.). All the compounds were dissolved in saline and injected in a volume of 5 ml/kg.

Chronic treatment with ADs consisted of two daily oral injections (10 mg/kg in 5 ml), or one daily intraperitoneal injection (10 mg/kg in 5 ml) over fourteen days. On three consecutive days prior to testing, all the rats (both in the chronic and acute treatment experiments) were adapted (for 20 min./day) to the plexiglas tube used to restrain the animal during the measurement of tail flick latency. In the acute treatment experiment, rats were injected with AD (10 mg/kg, both orally and intraperitoneally) one hour before the test. Nociception testing of the chronically treated rats was performed twenty-four hours after the final dose. In the acute administration experiment, ADs were injected immediately after the pretests. On the test day, each rat was given one pretest on the hot plate and two pretests on the tail flick apparatus. 45–60 min. later, 5-MeODMT (1 mg/kg in 5 ml) or saline (5 ml/kg) was injected subcutaneously and pain thresholds in the hot plate, tail flick and shock titration tests were measured 10 min. later. Shock titration testing was performed in a shock box apparatus ($25 \times 25 \times 30$ cm, Campden Instruments Ltd., London), as described by Archer *et al.* (1985a). Shocks (0.75 sec.) were delivered to the grid floor of the test box by a shock generator and shock scrambler. Shock titrations were continued upwards or downwards depending upon nonresponse or response at the 50, 75, 100, 150, 200, 250, 300, 400 and 500 μA intensities in a stepwise manner, following a 3 min. habituation to the test box. The interval between shocks was 15–20 sec. For tail flick testing, a rheostat-controlled light beam was directed on the tip of the tail (IITC INC. Mod. 33) and the latency to flick was measured, cut-off point 20 sec. For hot plate testing, the surface temperature of the plate was set at 58° (IITC. Mod. 35-D). A pain response was defined as a licking or kicking of the hind legs. The cut-off point was 25 sec. For each rat, the tail flick and pain response latencies at testing were expressed as a percentage of the pretest. For statistical treatment of the data, the Mann-Whitney U-test was employed (Siegel 1956). The values are expressed as medians ± quartiles.

## Results

*Effect of chronic treatment of ADs upon 5-MeO-DMT-induced analgesia. I.*

*Desipramine.* Chronic treatment with DMI antagonized the analgesic effects of 5-MeODMT (1 mg/kg) in all three tests of niciception, when the




chronic route of administration was oral (see fig. 1). With the intraperitoneal route of administration, DMI antagonized significantly 5-MeO-DMT-induced analgesia in the tail flick and shock titration tests, and, although the trend was the same, this effect was not significant in the hot plate test. (see fig. 2).

*Amitryptyline.* Chronic administration with AMI potentiated 5-MeODMT-induced analgesia in the tail flick and hot plate tests when administered orally (see fig. 1), but not intraperitoneally.

*Iprindol.* Orally repeated administration of IPR also attentuated 5-MeODMT-induced analgesia in the hot plate test only (see fig. 1).

*Alaproclate.* No significant effect of chronic alaproclate treatment upon 5-MeODMT-induced analgesia or upon saline-treated rats in the nociception tests was obtained (see fig. 1).

Fig. 1 and 2 present the tail flick, hot plate and shock titration responses to acute 5-MeODMT administration following the chronic oral and intraperitoneal AD treatment. Mann-Whitney U-tests were used to compare the 5-MeODMT group in the SAL condition with those in each of the other chronic treatment conditions. Table 1 presents the pretest values. It will be noticed that desipramine, administered orally, increased tail flick latencies significantly in saline treated rats.

With the chronic intraperitoneal treatment procedure, desipramine increased both the tail flick and hot plate pretest values, whereas amitryptiline did not have any effect.

The pretest values for the hot plate and tail flick tests (see table 1) were the same for all the

Fig. 2. The attenuation of 5-MeODMT-induced analgesia following intraperitoneal chronic treatment with desipramine in the tail flick (A), hot plate (B), and shock titration (C) tests of nociception. Within each AD treatment condition, for each saline and 5-MeODMT group, $n = 7$ or 8. The values are expressed as medians $\pm$ quartiles. Each AD was injected per orally (10 mg/kg) twice daily over fourteen days.
SAL = saline, DMI = desipramine, AMI = amitryptyline.
* $P < 0.02$ versus SAL – 5-MeODMT, Mann-Whitney U-test.

treatment groups with the following exceptions: The DMI repeated treatment groups indicated a higher pain threshold in the tail flick test ($3.50 \pm 0.25$ for the saline condition as opposed to $4.00 \pm 0.35$ for the DMI condition, $P < 0.01$). The DMI-treated rats also displayed an increased irribility and reactivity to handling and restraint in the plexiglass tubes. These rats also showed lowered pain threshold in the shock titration test.

*Effects of chronic treatment of ADs upon 5-MeO-DMT-induced analgesia. II.*

Repeated treatment with ADs caused certain alterations in 5-MeODMT-induced analgesia as follows:

*Desipramine.* 5-MeODMT-induced analgesia was reduced significantly by chronic DMI treatment in the tail flick test only, although a similar, though insignificant, trend was obtained in the hot plate and shock titration tests also (see fig. 3).

*Zimeldine.* Chronic ZIM administration caused a significant attenuation of 5-MeODMT-induced analgesia in both the tail flick and shock titration tests (see fig. 3).

*Mianserin.* Chronic MIAN administration caused a significant potentiation of 5-MeODMT-induced analgesia in both the tail flick and shock titration tests (see fig. 3).

*Maprotyline.* No effects of chronic MAP treatment upon 5-MeODMT-induced analgesia were obtained. In each case, the repeated saline treatment-5-MeODMT group was compared with the repeated AD treatment-5-MeODMT group. Table 1 presents the pretest values. As in study I, desipramine, administered orally, increased tail flick latencies significantly.

*Effect of acute treatment of ADs upon 5-MeO-DMT-induced analgesia.*

Table 2 presents the effect of acute treatment with ADs upon analgesic responses by 5-MeODMT- and saline-treated rats. In acute 5-MeODMT-treated rats, DMI and AMI, both intraperitoneally administered, heightened the threshold shock intensity. In acute saline-treated rats, oral administration of DMI, AMI, ALA and IPR increased shock thresholds in the shock titration test, whereas intraperitoneal DMI increased reponse thresholds in the tail flick and hot plate tests.

*Table 1.*

The effect of chronic treatment with ADs upon tail flick and hot plate response latencies. The number of animals per treatment (N) is shown in the brackets. Each AD was injected orally (10 mg/kg) twice daily over fourteen days.

| | Values expressed as median ± quartile | | | | |
|---|---|---|---|---|---|
| Oral I. | SAL | DMI | AMI | ALA | IPR |
| (N) | (16) | (15) | (13) | (15) | (15) |
| TF | 3.85 | 4.3* | 3.3 | 4.05 | 3.5 |
| | ±0.4 | ±0.2 | ±0.2 | ±0.6 | ±0.3 |
| HP | 4.25 | 5.5 | 5.0 | 5.0 | 4.25 |
| | ±0.6 | ±1.2 | ±0.5 | ±1.0 | ±0.75 |
| Intraperitoneal | | | | | |
| | SAL | DMI | AMI | | |
| (N) | (16) | (18) | (16) | | |
| TF | 3.25 | 3.95* | 3.5 | | |
| | ±0.3 | ±0.3 | | | |
| HP | 4.0 | 5.25* | 4.0 | | |
| | ±0.25 | ±1.0 | ±0.9 | | |
| Oral II. | | | | | |
| | SAL | DMI | MAP | MAIN | ZIM |
| (N) | (16) | (16) | (16) | (16) | (16) |
| TF | 3.50 | 4.00* | 3.45 | 3.70 | 3.40 |
| | ±0.25 | ±0.35 | ±0.40 | ±0.20 | ±0.20 |
| HP | 4.75 | 5.00 | 4.50 | 5.00 | 5.00 |
| | ±1.5 | ±1.0 | ±1.0 | ±0.75 | ±0.5 |

* $P < 0.02$, Mann-Whitney U-test.

Note: SAL = Saline, DMI = desipramine, AMI = amitryptyline, ALA = alaproclate, IPR = iprindol, MAP = maprotyline, MIAN = mianserin, ZIM = zimeldine, TF = tail flick test, HP = hot plate test.

## Discussion

The present results describe the effects of chronic administration and acute treatment of ADs upon measures of nociception in acute saline-treated and acute 5-MeODMT-treated rats, employing two routes of administration for the ADs, oral and intraperitoneal. Chronic DMI treatment elevated hot plate and tail flick pain thresholds for the intraperitoneal route but only in the tail flick

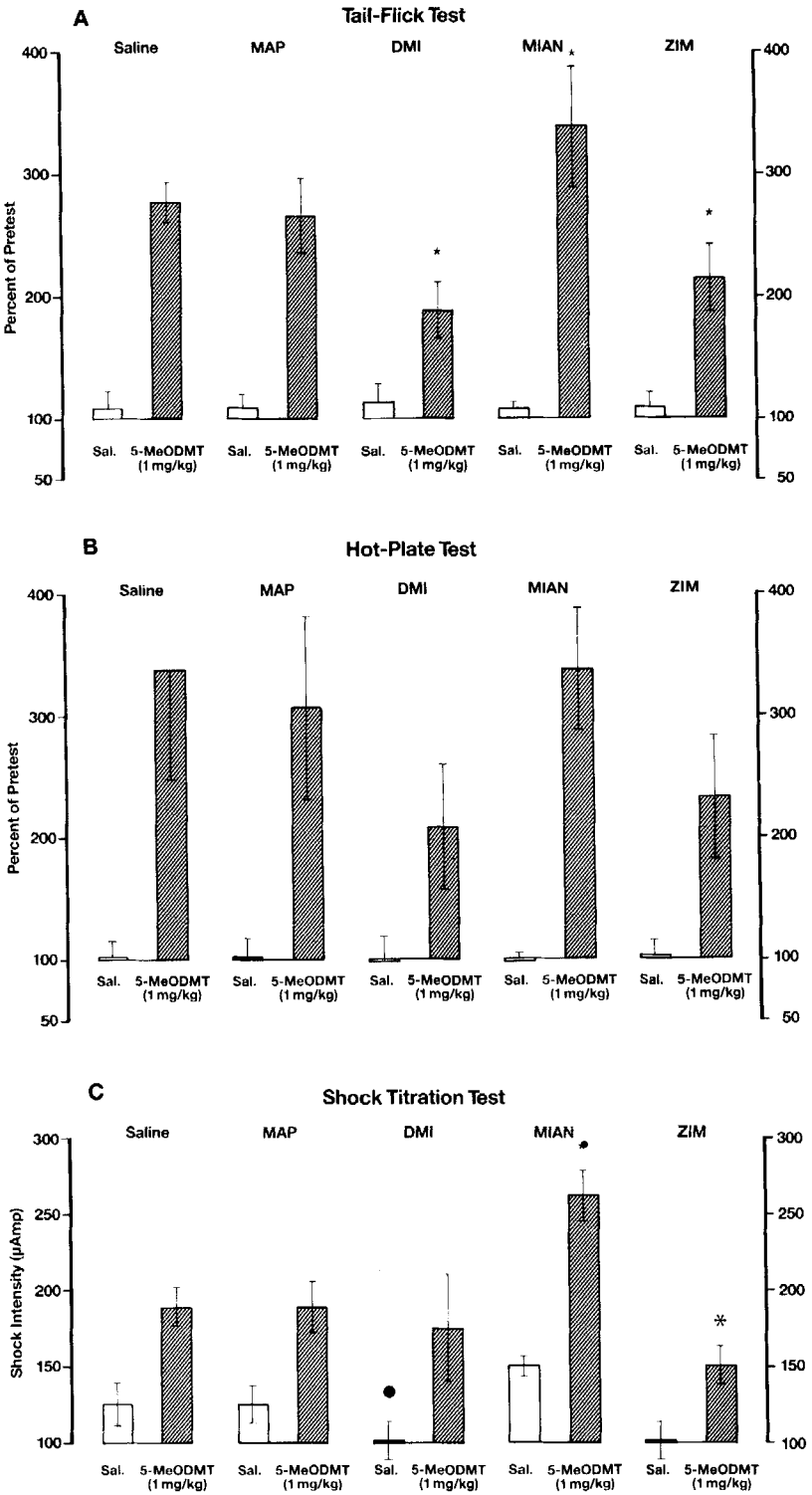



Fig. 3. The attenuation of 5-MeODMT-induced analgesia following per oral chronic treatment with desipramine and zimeldine and the potentiation of 5-MeODMT-induced analgesia following chronic mianserin treatment in the tail flick (A), hot plate (B) and shock titration (C) tests of nociception. Within each AD treatment condition, for each saline and 5-MeODMT group, n = 7 or 8. The values are expressed as medians ± quartiles. Each AD was injected per orally (10 mg/kg) twice daily over fourteen days.
SAL = saline, DMI = desipramine, MAP = maprotyline, MAIN = mianserin, ZIM = zimeldine.
* $P < 0.02$ versus saline – 5-MeODMT, Mann-Whitney U-test.
● $P < 0.02$ versus Saline – SAL, Mann-Whitney U-test.

test for the oral route. Chronic oral AMI treatment lowered pain thresholds in the tail flick test. Chronic treatment with both DMI and AMI affected 5-MeODMT-induced analgesia, although generally in the opposite directions: oral administration of DMI antagonised the action of 5-MeODMT in all the three tests of nociception, whereas AMI potentiated the action of 5-MeODMT in the tail flick and hot plate tests after oral administration. Iprindole attenuated the action of 5-MeODMT in the hot plate test. Intraperitoneal administration of DMI antagonised 5-MeODMT-induced analgesia in the tail flick and shock titration tests but not significantly in the hot plate test. Thus, both routes of administration offer strong evidence for the antagonistic effect of chronic DMI upon the action of 5-MeODMT in the tests of pain sensitivity.

Acute treatment produced a different set of results: acute intraperitoneal DMI elevated pain thresholds for the hot plate and tail flick tests in saline-treated rats, and the pain threshold for shock titration in 5-MeODMT-treated rats. Intraperitoneal AMI potentiated shock thresholds in 5-MeODMT-treated rats. Oral administration of DMI, AMI, ALA and IPR elevated shock thresholds in saline-treated rats. Pharmacokinetic problems could possibly account for some of the discrepancies between intraperitoneal and oral routes of administration. Only oral administration of AMI potentiated 5-MeODMT analgesia and it is possible that the active metabolite, nortryptiline, was involved in the administration of this compound. The present results (study II) also demonstrated an attenuation of 5-MeODMT-induced analgesia in the tail flick test following chronic treatment with DMI and ZIM over 14 days. ZIM also produced a similar attenuation in the hot plate test, as well. In contrast, chronic MIAN treatment potentiated the effects of 5-MeODMT in the tail flick and hot plate tests. MAP was without effect in both respects.

The investigated changes of 5-MeODMT-induced analgesia may appear to reflect changes of serotonergic receptor sensitivity following chronic administration. However, the characteristics of the receptors involved in this effect (5-$HT_1$ or 5-$HT_2$, Peroutka & Snyder 1981) remain obscure. Some data suggest the involvement of 5-$HT_1$ receptors, at least in the tail flick test (Schmauss *et al.* 1983), but also in the hot plate test (Ögren & Berge 1985). The behavioural effects of 5-MeODMT that have been studied most often in connection with chronic treatment with ADs are components of the "serotonin syndrome" (Trulson & Jacobs 1976). Characteristically, some components of this behaviour are enhanced when the test is performed 24 hours or more after the final dose of the AD, but attenuated if this time interval is shorter (Stolz & Marsden 1982; Goodwin *et al.* 1984; Willner 1985). The present results may indicate a "down-regulation" of 5-HT receptors after chronic DMI and, perhaps IPR, treatment, whereas the opposite was found for AMI. However, the variable nature of the results obtained with the different ADs suggests that this effect may not have been obtained. Also, it should be noted that no change in the locomotor response to RU 24969 (5-$HT_1$-mediated) was obtained after chronic DMI treatment (Green *et al.* 1984). The down-regulation of 5-HT receptors is not found for all ADs; regional variations and 5-HT binding sites are not necessarily correlated with functional changes (Willner 1985).

It should be considered whether the attenuation of 5-MeODMT-induced analgesia by DMI could be due to some "down-regulation" of adrenoceptors in the descending NA pathways. Down-regulation of receptors refers to laboratory studies indicating that various antidepressant and potential ADs, if administered on a clinically relevant time basis, down-regulate the NA receptor-coupled adenylate cyclase system in the brain (*cf.* Sulser 1982). It is likely that chronic DMI causes some receptor adaptation in adrenoceptors when post-decapitation convulsions are measured (Archer *et al.* 1984; Archer *et al.* 1985b). Sugrue (1982) compared chronic DMI treatment with that of IPR and MIAN to measure parameters of $\alpha_2$-adrenoceptor subsensitivity using acute low doses of clonidine to lower concentration of the NA metabolite, 3-methoxy-4-hydroxyphenylethyleneglycol sulfate (MHPG-$SO_4$). Chronic DMI treatment only was associated with the induction of central $\alpha_2$-adrenoceptor subsensitivity, whereas chronic MIAN could possibly have induced

*Table 2.*

The effect of acute treatment with various antidepressant drugs upon responses in the tail flick, hot plate and shock titration tests in 5-MeODMT- and saline-treated rats. For each rat, tail flick and hot plate responses are expressed as a percentage of the pretest, shock titration is expressed in μAmp intensity.

| | Treatment | Tail flick (median ± quartile) | Hot plate (median ± quartile) | Shock titration |
|---|---|---|---|---|
| SAL[1] | Sal | 99.5 ± 6 | 100.0 ± 17 | 150.5 ± 12 |
| | 5-MeODMT | 327.0 ± 85 | 325 ± 66 | 225.0 ± 25 |
| DMI (p.o.) | Sal | 123.5 ± 43 | 85.5 ± 19 | 175.0 ± 43[a] |
| | 5-MeODMT | 351.5 ± 72 | 250.0 ± 123 | 200 ± 62.5 |
| AMI (p.o.) | Sal | 124.0 ± 18 | 77.5 ± 18 | 175 ± 19[a] |
| | 5-MeODMT | 275.0 ± 103 | 284.0 ± 124 | 287 ± 56 |
| ALA (p.o.) | Sal | 103.0 ± 17 | 71.0 ± 9 | 250 ± 25[a] |
| | 5-MeODMT | 342.5 ± 87 | 319.5 ± 89 | 300 ± 31 |
| IPR (p.o.) | Sal | 100.0 ± 2.5 | 120.0 ± 24.5 | 200 ± 12.5[a] |
| | 5-MeODMT | 353.0 ± 1 | 267.0 ± 12.5 | 200 ± 62.5 |
| DMI (i.p.) | Sal | 136.0 ± 17[a] | 133.0 ± 12.5[a] | 150 ± 0 |
| | 5-MeODMT | 242.5 ± 81 | 330.0 ± 74 | 300 ± 0[b] |
| AMI (i.p.) | Sal | 89.5 ± 10 | 110.0 ± 18 | 125.0 ± 12.5 |
| | 5-MeODMT | 258.5 ± 53.5 | 270.0 ± 90 | 425.0 ± 81[b] |

Mann-Whitney U-tests: [a]versus SAL-Sal, [b]versus SAL-5-MeODMT } $P < 0.02$. n = 7 or 8 animals in each group.

[1] p.o. and i.p. SAL treatments pooled.

supersensitive $\alpha_2$-adrenoceptors. With regard to the attenuation of 5-MeODMT analgesia by chronic DMI, it has been demonstrated recently that the $\alpha_2$-adrenoceptor antagonist, yohimbine, blocked completely the analgesic effects of 5-MeODMT in the hot plate and tail flick tests of nociception (Danysz *et al.* 1986). Further, it has been conclusively demonstrated that treatments, *e.g.* the application of neurotoxins like DSP4 or 6-OHDA, severely and selectively depleting NA in the descending system, abolish the analgesia induced by 5-MeODMT or 5-HT or other 5-HT agonists (Archer *et al.* 1985a; Archer *et al.* 1985b; Minor *et al.* 1985; Post *et al.* 1986). These investigations (*e.g.* Archer *et al.* 1985a & b) firmly demonstrate the necessity of considering direct NA – 5-HT interactions at spinal levels. It is evident that adrenoceptor subsensitivity ought to be considered as a possible mechanism involved in the effect of chronic treatment of DMI upon 5-MeODMT-induced analgesia, but a note of caution is required since maprotyline, a more selective NA uptake inhibitor, did not cause the same effect as DMI following chronic treatment.

The present findings do not show any common, homogenous action of the ADs administered chronically upon the sensitivity of 5-HT receptors (as reflected by 5-MeODMT-induced analgesia). The main conclusion derived from these experiments is that 5-MeODMT-induced analgesia is influenced in a presently unknown, manner by the compounds administered. Although chronic DMI produced a reasonably consistent attenuation, this test model is probably not suited for the prediction of long-term receptor changes after antidepressant treatment. The pattern of data obtained here may suggest that changes in 5-HT receptor functioning (at least of that population of these receptors involved in nociception) may not be responsible for the therapeutic effect. It is unclear whether the above findings reflect adaptive mechanisms. AMI has been shown to be a blocker of 5-HT receptors. ALA, a selective uptake inhibitor of 5-HT, and IPR possessed no receptor blocking or uptake inhibitor properties (Hall & Ögren 1981). AMI potentiated 5-MeODMT analgesia, IPR caused an attenuation in the hot plate test, and ALA had no effect. On the other hand, ZIM

was a selective 5-HT uptake inhibitor and MIAN blocked 5-HT receptors; ZIM caused an attenuation in the hot plate and tail flick tests whereas MIAN potentiated the 5-MeODMT-induced analgesia. Both the 5-HT blockers, AMI and MIAN, produced a similar result. The mechanism of the action of chronic DMI needs to be clarified also, although others have obtained similar results using other behaviour parameters (Smith & Meyerson 1984). The influence of chronic AD treatment upon agonist-induced behavioural or physiological responses is generally accepted as possible evidence of alterations of receptor sensitivity (Davis 1982). If so, subsensitivity of 5-HT receptors may be suggested after DMI and ZIM treatment, and an increased sensitivity after AMI or MIAN. Alternatively, hindbrain or spinal adrenoceptor subsensitivity may be obtained at presynaptic sites leading to a diminished response to 5-MeODMT-induced analgesia. 5-MeODMT may exert some behavioural effects via stimulation of 5-$HT_2$ receptors (Lucki & Fraser 1985), but in the case of the antinociceptive properties of 5-MeODMT, it seems probable that this characteristic of the 5-HT agonist is related to 5-$HT_1$ receptors (Schmauss *et al.* 1983).

In conclusion, the present results indicate that various ADs differentially affect 5-HT and/or NA receptors following chronic treatment. The existence of a common mechanism was questioned previously (Sugrue 1983a) and several aspects of the observed changes, not least of all, their test dependency, serve to underline those conclusions.

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