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Repeated treatment with antidepressant drugs potentiates the locomotor response to (+)-amphetamine

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The therapeutic effect of antidepressant drugs only becomes apparent after about two weeks of treatment. We have found previously that various antidepressants —amitriptyline, imipramine, iprindole, maprotiline, mianserin, nisoxetine, zimelidine, as well as thioridazine and levomepromazine—given chronically but not acutely, potentiate the clonidine-induced aggressiveness in mice, probably via increased reponsiveness of the α_1-adrenergic system (Maj et al 1980, 1981, 1982b). We have also demonstrated that in mice treated chronically (but not acutely) with antidepressants, reserpine stimulates the locomotor activity immediately after its administration (in the phase of amine release) (Maj et al 1983). These results may indicate that noradrenaline (NA] as well as dopamine (DA), i.e. the increased responsiveness of DA system, may be involved in the effects observed after prolonged administration of the antidepressants. Hence, we have examined how given chronically they affect the action of (+)-amphetamine on locomotor activity in mice. According to Spyraki & Fibiger (1981), desipramine given chronically enhances the locomotor hyperactivity induced by (+)-amphetamine or apomorphine. Recently, repeated treatment with citalopram has been found to potentiate the locomotor response to (+)-amphetamine in rats (Hyttel, personal communication).

The antidepressants we tested were chosen for their various pharmacological profiles: imipramine and amitriptyline block the neuronal uptake of NA and 5-HT; maprolitine and (+)-oxaprotiline are selective NA uptake inhibitors (Maître et al 1971; Mishra et al 1981; Delini-Stula et al 1982); (−)-oxaprotiline does not inhibit NA uptake (Mishra et al 1981); zimelidine inhibits 5-HT uptake and, at higher doses, NA uptake also (Ross et al 1981); citalopram and fluvoxamine are selective 5-HT uptake inhibitors (Christensen et al 1977; Claassen et al 1977; Pawłowski et al 1981; Maj et al 1982a); mianserin and iprindole, both atypical, do not inhibit the neuronal uptake of amines (Gluckman & Baum 1969; van Riezen et al 1981). For comparison, cocaine, a monoamine uptake inhibitor, and phentolamine, a NA antagonist, were also studied.

According to Spyraki & Fibiger (1981), chronic desipramine potentiates the locomotor reponse to (+)-amphetamine and apomorphine given in a narrow (low) dose range. We had observed that, given chronically, imipramine and citalopram potentiate the locomotor effect of low doses of (+)-amphetamine, therefore, in

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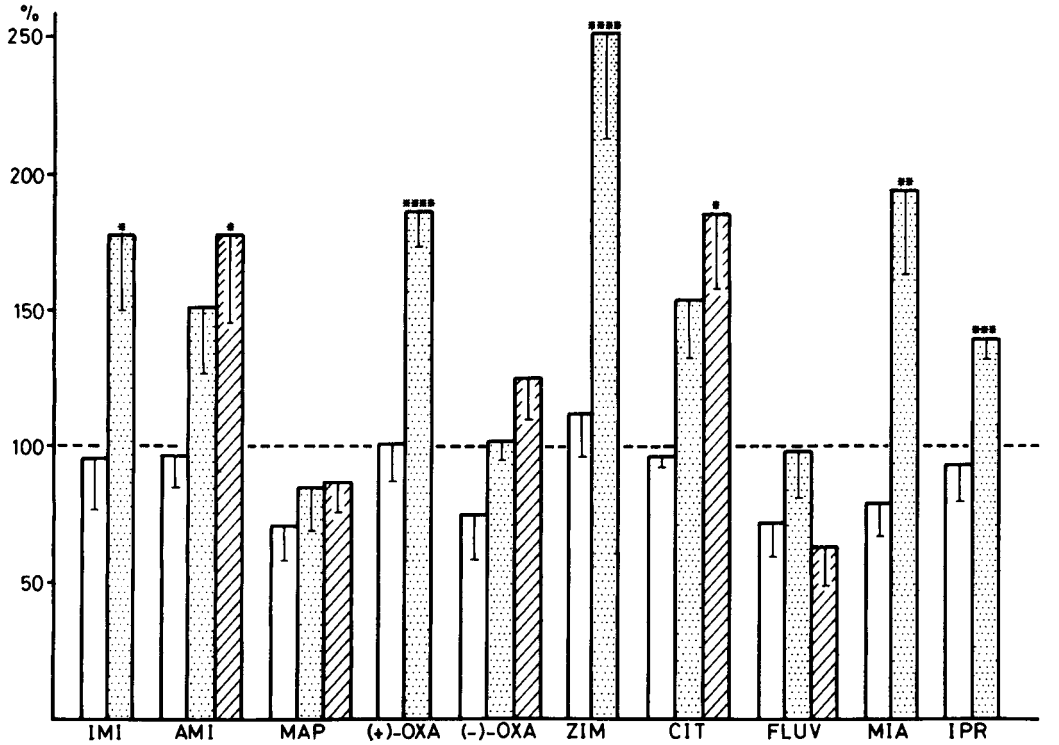

FIG. 1. Effect of imipramine (IMI), amitriptyline (AMI), maprolitine (MAP), oxaprotiline (+)-OXA, (−)-OXA, zimelidine (ZIM), citalopram (CIT), fluvoxamine (FLUV), mianserin (MIA) and iprindole (IPR) on the action of (+)-amphetamine in the locomotor activity test. – – – (+)-amphetamine (AMPH) 1·25 mg kg^{-1}; open column, antidepressants acute dose 10 mg kg^{-1}) + AMPH; stippled column, antidepressants chronic dose (10 mg kg^{-1} twice daily, 14 days) + AMPH, locomotor activity was measured 2 h after the last dose of antidepressant; and hatched column 72 h after last dose of antidepressant $^{*}P < 0{\cdot}05$; $^{**}P < 0{\cdot}02$; $^{***}P < 0{\cdot}01$; $^{***}P < 0{\cdot}001$.

the present study we used the threshold dose of 1·25 mg kg^{-1}.

Method

Male Albino Swiss mice, 18–22 g, which had free access to food and water, were given the antidepressants, 10 mg kg^{-1} i.p. dissolved in 0·9% NaCl in a volume of 10 ml kg^{-1}, twice daily for 14 days. Cocaine (20 mg kg^{-1}) and phentolamine (5 mg kg^{-1}), similarly administered, were used for comparison. Control animals received solvent. The locomotor activity was measured in photoresistor actometers (two light beams, two photoresistors), 30 min after a s.c. injection of (+)-amphetamine, 1.25 mg kg^{-1}, single animals were placed in actometers and measurements were made over 1 h. (The dose of (+)-amphetamine was regarded as threshold since only in four of 22 experiments with 10 mice per group did it produce a significant increase in locomotor activity, maximally by 40%; in the other groups the motility increased, not significantly, to 120% of controls.) Locomotor activity was measured 2 and 72 h after the last administration of the test drugs. The ambient temperature was 22 ± 1 °C.

Statistical significance was assessed with Student's *t*-test.

Drugs used were: amitriptyline hydrochloride (Polfa), (+)-amphetamine sulphate (Smith Kline & French), citalopram hydrobromide (Lundbeck), cocaine hydrochloride (Roques), fluvoxamine maleate (Philips Duphar B.V.), imipramine hydrochloride (Polfa), iprindole (Wyeth), maprotiline hydrochloride (Ludiomil, Ciba-Geigy), mianserin hydrochloride (Organon), (+)- and (−)-oxaprotiline hydrochlorides (Ciba-Geigy) phentolamine hydrochloride (Ciba-Geigy), zimelidine hydrochloride (Astra).

Results and discussion

The antidepressants in a single dose had no effect on the action of (+)-amphetamine (Fig. 1) nor did (+)-amphetamine itself affect the locomotor activity (0·9% NaCl—327·4 ± 34·9; (+)-amphetamine – 419·1 ± 40·9). Cocaine, too, was without effect (+)-amphetamine: 388·0 ± 39·0; cocaine + (+)-amphetamine: 315·1 ± 31·8, n.s.). But phentolamine revealed a weak antagonistic action ((+)-amphetamine: 425·7 ± 61·5; phentolamine + (+)-amphetamine: 243·1 ± 40·9, $P < 0{\cdot}05$).

None of the drugs, chronically administered alone affected the locomotor activity in mice (data not shown).

In mice treated repeatedly with imipramine, (+)-oxaprotiline, mianserin, iprindole, zimelidine, (+)-amphetamine given 2 h after the last dose of antidepressant intensified locomotor activity (Fig. 1). With amitriptyline and citalopram a statistically significant enhancement was observed 72 h after their last dose. At least, in the case of amitriptyline, the weak effect 2 h after its last dose may be caused by its strong α_1-adrenolytic action (Maj et al 1979a). Maprolitine, (−)-oxaprotiline and fluvoxamine did not change the action of amphetamine at 2 or 72 h after the last dose.

In mice treated repeatedly with phentolamine, (+)-amphetamine given 2 h after the last dose stimulated locomotor activity ((+)-amphetamine: 356·0 ± 44·2; phentolamine + (+)-amphetamine: 695·6 ± 90·5, $P < 0{\cdot}01$); in those treated with cocaine, (+)-amphetamine did not affect the locomotion ((+)-aphetamine: 299·6 ± 27·8; cocaine + (+)-amphetamine: 377·3 ± 42·2, n.s.).

The enhancement of the effect of (+)-amphetamine by the antidepressants may be related, above all, to the increased reponsiveness of the mesolimbic DA system, as proposed by Spyraki & Fibiger (1981) for desipramine and iprindole in rats. A striatal DA system is probably not involved, as repeated administration of the antidepressants enhances neither amphetamine nor apomorphine stereotypy (Delini-Stula & Vassout 1979; Maj et al 1979b; Spyraki & Fibiger 1981); nor do the drugs affect the binding to striatal DA receptors (see: Hall & Ögren 1981; Snyder & Peroutka 1982). It is noteworthy that the sensitivity of cortical DA neurons, as evaluated electrophysiologically, has been reported to increase after a prolonged treatment with antidepressants (Neal & Bradley 1979).

The increased responsiveness of the α_1-adrenergic system, which we suggested previously (Maj et al 1981), may be an additional factor, as the noradrenergic stimulation arising from the release of NA by amphetamine intensifies the dopaminergic response; an apparent analogy is seen in the case of the increased hyperactivity after a combined administration of apomorphine and clonidine (Andén 1970).

The possibility that (+)-amphetamine hyperactivity may be enhanced by 5-hydroxytryptaminergic or cholinergic blockade must be ruled out as no enhancement was observed in the acute experiment after mianserin, the 5-HT antagonist, and after the tricyclics which have cholinolytic properties.

The concentration of (+)-amphetamine in the mouse brain after repeated administration of the antidepressants was not determined nor are relevant literature data available. However, in view of the diversity of chemical structures of the antidepressants used, pharmacokinetic interactions do not seem to be responsible for the enhancement of (+)-amphetamine action. Certainly, such interactions do not occur in acute experiments, as the action of (+)-amphetamine was not intensified. Also they have not been found in chronic experiments with desipramine in rats (Spyraki & Fibiger 1981).

From acute experiments it is difficult to find a pharmacological effect common to all the drugs examined that enhanced the action of (+)-amphetamine. It does not seem to be inhibition of NA uptake (although such a possibility is supported, above all, by results of experiments with (+)- and (−)-oxaprotiline, since cocaine is inactive here. But cocaine is a short-acting drug and the twice daily dose may not have been frequent enough. Neither is it the inhibition of 5-HT uptake, as fluvoxamine, studied herein, and fluoxetine, studied by Spyraki & Fibiger (1981), are ineffective. Experiments with phentolamine, amitriptyline and mianserin, might point to an α_1-adrenergic antagonistic effect; such an effect, however, was not apparent with other drugs studied, such as citalopram or iprindole. Therefore it remains difficult to explain the increased response to (+)-amphetamine after repeated treatment with antidepressants.

Two of the antidepressants, fluvoxamine and maprolitine, did not enhance the action of (+)-amphetamine. Flavoxamine, in contrast to maprolitine, was also inactive in our earlier experiments (Maj et al 1982b, 1983) which suggests a difference between it and citalopram, another selective inhibitor of 5-HT uptake. A more striking finding is the lack of action of maprolitine which is related pharmacologically to oxaprolitine and tricyclics; this may be due to some blocking effect of maprolitine on DA receptors (Delini-Stula & Vassout 1979).

In conclusion, prolonged treatment with many antidepressants potentitates the locomotor effect of (+)-amphetamine, probably via the increased responsiveness of DA mesolimbic system, mechanism which may be involved in the therapeutic antidepressive action.

A similar enhancement of the amphetamine-induced hyperactivity was found by us in rats after chronic treatment with imipramine, amitriptyline, mianserin and citalopram, whereas no effect on the amphetamine-induced stereotypy was observed (Maj et al 1985). Also chronic administration of impramine enhances the locomotor hyperactivity in rats, induced by amphetamine given into the nucleus accumbens. The level of DA and its metabolites (HVA, DOPAC, 3-methoxytyramine) remains unchanged (Maj et al in preparation). Therefore continuation of the experiments leads to a conclusion similar to that expressed by us in this paper.

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Time-related effects of benzodiazepines on intestinal motility in conscious dogs

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The effects of diazepam and GABA on intestinal motility were investigated in fasted dogs fitted with strain-gauge transducers. Injected intravenously at 9.00 and 16.00 h, diazepam (0·5 mg kg^{-1}) affected intestinal motility only during darkness i.e. from 19.00 to 7.00 h. These jejunal motor effects which were mimicked by GABA, (0·3 mg kg^{-1} i.v.) corresponded to a disruption of the migrating myoelectric complex (MMC) with an increased contractile activity. These results demonstrate that benzodiazepines affect the intestinal motility in dog and suggest that the effects are related to sleep-stages.

Benzodiazepines have been used in the treatment of gastrointestinal and colonic motor disturbances (Haubrich 1976) however, few experiments have been conducted to analyse their effects on intestinal motility in healthy or ill subjects.

Controversial effects of intravenous diazepam on human lower oesophageal sphincter pressure have been reported (Hall et al 1975; Weihrauch et al 1979) showing that the effects are related to the dose used and the duration of the treatment (Weihrauch et al 1979).

There is now substantial evidence that benzodiazepines act on γ-aminobutyric acid (GABA)-ergic pathways enhancing GABA-ergic transmission by a postjunctional membrane action (Costa & Guidotti 1979) with an interaction between the respective receptors (Tallman et al 1980). In addition, an enhanced binding of [^{3}H] diazepam is obtained when either GABA or one of its analogues is included in the binding assay (Tallman et al 1978; Wastek et al 1978).

GABA is known to stimulate intrinsic inhibitory and excitatory nerves in the guinea-pig intestine (Krantis et al 1980) inducing a contractile response (Inouye et al 1960). Consequently the present work was undertaken to analyse in conscious dogs the effects of diazepam injected intravenously on the motility of the small intestine and to compare these effects with those of GABA.

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