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Antagonism of 5-methoxy-*N,N*-dimethyltryptamine-induced changes in postdecapitation convulsions in rats by repeated treatment with drugs enhancing 5-hydroxytryptamine neurotransmission

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Repeated administration of drugs that increase tryptaminergic neurotransmission antagonized the increase in latency to onset and the duration of postdecapitation convulsions (PDCs) induced by an acute 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) injection; Zimelidine (2×5 mg kg^{-1}), fluoxetine (2×5 mg kg^{-1}), amiflamine ($2 \times 2{\cdot}5$ mg kg^{-1}) and α-ethyltryptamine ($2 \times 2{\cdot}5$ mg kg^{-1}) administered orally over 10 days caused a substantial blockade of the increase in latency to onset and duration of PDCs following 5-MeODMT, whereas alaproclate (2×5 mg kg^{-1}), clorgyline (1×1 mg kg^{-1}) and pargyline ($2 \times 2{\cdot}5$ mg kg^{-1}) caused a lesser blockade. Repeated 5-MeODMT (3×2 mg kg^{-1}) administration blocked the acute effects of 5-MeODMT (2 and 4 mg kg^{-1}) upon PDCs completely. These findings indicate down-regulation of the 5-hydroxytryptamine receptors which mediate the action of 5-MeODMT on the PDCs and offer a simple model system for studying 5-HT receptor sensitivity changes at the spinal level.

Violent tonic-clonic convulsions are observed following the decapitation of rats and mice (Richardson & Jacobowitz 1973); a monoaminergic mechanism was implicated since reserpine administration blocked these postdecapitation convulsions (Eichbaum & Yasaka 1971; Kamat & Sheth 1971). Lesions of the descending noradrenergic system were shown to block the convulsions (e.g. Suenaga et al 1977) whereas tryptaminergic antagonism or depletion caused prolongation of convulsion duration (Thut & Myslinski 1976; Myslinski & Thut 1977; Archer & Tandberg 1984). The direct 5-hydroxytryptamine (5-HT) agonist, 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT), administered from 15 min to 2 h before decapitation, effectively produces some disruption of postdecapitation convulsions (PDCs) by prolonging both the latency and duration of the PDCs (Archer & Tandberg 1984). Since 5-MeODMT causes an increase in functional 5-HT activity in central regions (Andén et al 1971; Fuxe et al 1972; Bradley & Briggs 1974), a useful pharmacological tool is at hand for the investigation of central receptor mechanisms.

A lack of uniformity in the effects of repeated administration of antidepressant drugs upon central 5-HT mechanisms seems apparent. Repeated treatment with antidepressant drugs has been found both to elevate 5-HT response function (de Montigny & Aghajanian 1978; Friedman & Dallob 1979; Stolz & Marsden 1982) and to decrease it (Buus Lassen 1972; Ögren et al 1979; Maj et al 1979; Rényi 1984). The purpose of this investigation was to measure the effects of repeated treatment with antidepressant and potential antidepressant drugs upon the changes of PDCs induced by 5-MeODMT. The 5-HT uptake inhibitors, zimelidine, alaproclate and fluoxetine, as well as the monoamine oxidase inhibitors (MAOIs), amiflamine (Ask et al 1983), α-ethyltryptamine, clorgyline, and pargyline, and the noradrenaline (NA) uptake inhibitor, desipramine, were all administered repeatedly over 10 days.

Methods

Male Sprague-Dawley rats, 250–300 g, aged 55–65 days, were randomly allocated to the different repeated administration treatment conditions (for each group, n = 9 or 10) and were housed in groups of 3 rats under laboratory conditions with a 12 h on/off lighting cycle in a thermostatically controlled room (21 ± 1 °C).

The treatment drugs at dose schedules stated in the text included: 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) (Regis Chemical Co., USA), amiflamine bitartrate, clorgyline hydrochloride (synthesized by Dr L. Florvall, Astra Läkemedel AB, Södertälje, Sweden), pargyline hydrochloride (Saber Laboratories Inc, USA), α-ethyltryptamine acetate (Regis Chemical Co., USA), fluoxetine hydrochloride (Lilly 110 140) *p*-chloroamphetamine hydrochloride (Sigma), zimelidine dihydrochloride hydrate and alaproclate hydrochloride (Astra Läkemedel AB), desipramine hydrochloride (Ciba-Geigy A.G.). When administered twice daily the compounds were given at 0800 and 1600 h or once daily at 1200 h.

Twenty-four hours after the final injection, and 35 min after either acute 5-MeODMT or saline, each rat was decapitated and the trunk placed feet upwards.

Post-decapitation convulsions (PDCs) were measured according to the procedure described by Archer et al (1984), as follows: two stopwatches were started at the time of decapitation. One of these was stopped as soon as the first of the biclonal kicks was observed; this time was taken as the latency of onset. The time of the clonal movement was recorded by the second stopwatch. The difference between the two measurements was taken as the duration of PDCs.

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Prediction of the last kick with the reasonable certainty was based on experience (see Archer et al 1984). Experimental bias was eliminated by dividing the procedure: the experimenter responsible for administration and group allocation was not involved in the time-keeping.

Results

Repeated treatment with uptake inhibitors. As reported previously (Archer & Tandberg 1984) a single dose of 5-MeODMT (2 mg kg^{-1} i.p.) prolonged significantly the PDC latency of onset and the duration of PDCs when the rats were decapitated 35 min after the injection. Rats that received repeated doses of the selective 5-HT uptake inhibitors zimelidine, alaproclate or fluoxetine, all at 2 × 5 mg kg^{-1} p.o., daily for 10 days, showed significantly shorter PDC latency of onset following acute 5-MeODMT injected 24 h after the last dose of the uptake inhibitor (Table 1). The noradrenaline uptake inhibitor desipramine (2 × 5 mg kg^{-1} p.o. daily) did not have this effect but, in contrast to the 5-HT uptake inhibitors, did itself prolong the latency and the duration of PDC as reported previously (Archer et al 1984). Only zimelidine reduced the prolonged duration of PDC induced by 5-MeODMT.

Repeated treatment with monoamine oxidase inhibitors. Repeated administration of the selective and reversible MAO-A inhibitors amiflamine or α-ethyltryptamine both at 2 × 2·5 mg kg^{-1} p.o. daily for 10 or 11 days, significantly shortened the latencies to onset of PDCs after acute 5-MeODMT compared with saline-treated rats. The irreversible but selective MAO-A inhibitor clorgyline, given once daily at 1 mg kg^{-1} i.p. for 10 days, also antagonized the increased latency to onset of PDCs induced by 5-MeODMT. The non-selective MAO inhibitor pargyline (2 × 2·5 mg kg^{-1} p.o. for 10 days), also significantly reduced the prolongation of the latency of onset of PDCs produced by 5-MeODMT but the effect was less than that of α-ethyltryptamine. Of the MAO inhibitors studied, only amiflamine caused a significant antagonism of the increased duration of PDC induced by acute 5-MeODMT.

Repeated treatment with 5-MeODMT or p-chloroamphetamine. Repeated 5-MeODMT (3 × 2 mg kg^{-1} i.p.) administered over 10 days, abolished the prolonged latency to onset of PDCs caused by acute 5-MeODMT (2–4 mg kg^{-1}) 24 h after the last dose, even when an acute dose of 4 mg kg^{-1} 5-MeODMT was administered just before decapitation (Table 1). This treatment significantly antagonized the prolongation of the duration of PDC caused by acute 5-MeODMT. A threshold dose of *p*-chloroamphetamine (PCA) (2×1 mg kg^{-1} p.o.) for release of 5-HT, administered to rats over 10 days did not change the prolongation of the latency of PDC onset or its duration after acute 5-MeODMT injected 24 h after the last PCA dose (data not shown).

Discussion

The observation that an injection of the direct-acting 5-HT receptor agonist 5-MeODMT (Andén et al 1971; Fuxe et al 1972) to rats prolongs the latency to onset and the duration of PDCs indicates that inhibitory 5-HT receptors are involved in the instigation of this type of convulsions (Archer & Tandberg 1984), which are absolutely dependent on an intact noradrenergic system in the spinal cord (Suenaga et al 1977; Archer et al 1984). In order to demonstrate that the effects of 5-MeODMT on PDCs are selective for 5-HT receptors, we have recently tested the ability of several 5-HT antagonists in blocking the 5-MeODMT effects (Archer & Tandberg, unpublished observations). The 5-HT antagonists mianserin, methergoline, cianserin and

Table 1. The effect of repeated treatment with antidepressant and potential antidepressant drugs upon the 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) (2 mg kg^{-1})-induced changes of latency to onset and duration of postdecapitation convulsions. Rats were treated over 10 days; repeated treatment, n = 20.

Treatment daily dose (mg kg^{-1} p.o.)	Postdecapitation convulsions: Saline		5-MeODMT	
	Latency to onset (s)	Duration (s)	Latency to onset (s)	Duration (s)
	(n = 10)		(n = 10)	
Saline 2 × 5 ml kg^{-1}	1·10 ± 0·08	17·5 ± 0·3	2·80 ± 0·30	25·1 ± 0·6
Zimelidine 2 × 5	1·08 ± 0·07	17·9 ± 0·7	1·40 ± 0·05[a]	21·7 ± 0·5
Alaproclate 2 × 5	1·07 ± 0·07	18·9 ± 0·5	2·00 ± 0·10[b]	22·8 ± 0·6
Fluoxetine 2 × 5	1·00 ± 0·06	18·8 ± 0·1	1·35 ± 0·15[a]	23·2 ± 0·7
Desipramine 2 × 5	1·80 ± 0·10[b]	20·1 ± 0·6[b]	3·10 ± 0·10	26·6 ± 0·3
Amiflamine 2 × 2·5	1·02 ± 0·04	16·8 ± 0·1	1·30 ± 0·08[a]	20·9 ± 0·1[b]
α-Ethyltryptamine 2 × 2·5	1·00 ± 0·03	17·9 ± 0·1	1·30 ± 0·04[a]	22·8 ± 0·7
5-MeODMT 3 × 2 s.c.	1·00 ± 0·04	18·0 ± 0·4	1·01 ± 0·06[a]	20·6 ± 0·06[b]
Clorgyline 1 × 1 i.p.	1·02 ± 0·04	18·0 ± 0·5	1·92 ± 0·08[b]	25·0 ± 0·6
Pargyline 2 × 2·5	1·00 ± 0·05	17·4 ± 0·3	1·95 ± 0·10[b]	23·3 ± 0·7

Values are expressed as means ± s.e.m.
[a] $P < 0·001$, [b] $P < 0·01$, Tukey's test, versus saline condition.

methysergide antagonized the 5-MeODMT induced prolongations of latency to onset of convulsions substantially, and to a lesser extent the prolongation of duration. The efficacy of the 5-HT antagonists for blocking 5-MeODMT changes of PDCs was roughly of the order mianserin > cianserin > methysergide > methergoline. On the other hand, pirenperone, the 5-HT_2 antagonist, and pimozide, the dopamine receptor antagonist did not antagonize the 5-MeODMT induced changes. The results obtained in the present study confirm and extend the idea that spinal tryptaminergic transmission also regulates the PDCs. Hence, elevated tryptaminergic transmission during 10 days produced by repeated administration of the selective 5-HT uptake inhibitors zimelidine, alaproclate and fluoxetine (but not by the selective noradrenaline uptake inhibitor desipramine) or by the monoamine oxidase inhibitors amiflamine, α-ethyltryptamine, clorgyline and pargyline, antagonized the prolonged latency to onset of PDCs induced by 5-MeODMT to varying degrees (see Table 1). This antagonism indicates a compensatory down-regulation at the 5-HT receptors involved in the PDCs. It is possible that chronic treatment with antidepressants influences the pharmacokinetics of 5-MeODMT. Since the chronic treatment with antidepressants influenced mainly the latency to onset rather than the duration of the convulsions, some evidence to favour this hypothesis may be indicated.

Although the duration of the behavioural effects of 5-MeODMT in rats is relatively short (1 or 2 h for the 2 mg kg^{-1} dose), repeated administration of 5-MeODMT to rats has been shown to block almost completely the behavioural changes induced by an acute dose of 5-MeODMT when given 48 h after the last dose (Rényi 1984). In the present study 5-MeODMT was given three times day at the dose 2 mg kg^{-1} i.p., which is above the threshold for inducing behavioural changes. The complete antagonism of the increased latency to onset of PDCs induced by 5-MeODMT 24 h after the last dose of 5-MeODMT shows that the down-regulation of the 5-HT receptors responding to 5-MeODMT also occurs at the spinal level. Since 5-HT_1 but not 5-HT_2 receptors have been detected in the spinal cord (Hall, unpublished data) it seems reasonable to assume that it is the former type which responds to 5-MeODMT-induced changes observed in the PDC test. It remains to be elucidated whether this down-regulation of 5-HT receptors in the spinal cord can be detected in the radioactive ligand binding studies.

Only three of the compounds examined (zimelidine, amiflamine and 5-MeODMT) antagonized significantly the prolonged duration of PDC induced by acute 5-MeODMT. Thus, as we have observed previously (Archer & Tandberg 1984), the latency to onset of the PDC is a more reliable measure than the duration of PDC measure applicable in this type of repeated administrations study; this is probably due to a generally greater variation in the duration of the convulsions. It is suggested that measuring the effect of acute 5-MeODMT on the latency to onset of PDCs in rats is a simple method that can be used in conjunction with behavioural tests to study the 5-HT receptor sensitivity at spinal level; this procedure may be a useful complement to the behavioural tests currently in use.

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