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Presynaptic α-block and inhibition of noradrenaline and 5-hydroxytryptamine reuptake by a series of compounds related to mianserin

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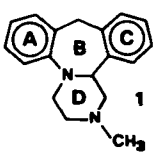
A structure-activity relationship study was undertaken for a variety of structural analogues of the tetracyclic antidepressant mianserin. Presynaptic α-blocking activity in vitro was evaluated measuring the potentiation of depolarization-induced noradrenaline (NA) release from rat cerebral cortex slices. Inhibition of NA and 5-hydroxytryptamine reuptake was measured in rat hypothalamic or striatal synaptosomes, respectively. Presynaptic α-blockade was only found in molecules with an overall bent shape. Flat rigid molecules or flexible ones were not active. Six-membered, chair-formed D-rings (containing the $-NCH_3$ moiety) appeared better than 5- or 7-membered ones. Heteroatom substitution, but not hydroxylation or methylation, of the bridge between the two aromatic rings left presynaptic α-blockade unaffected. *N*-Demethylation and aromatic methyl- or chlorine-subsitution reduced presynaptic α-blockade. In pyridine ring-substituted analogues the localization of the heteroatom appeared to be crucial. 5-Hydroxytryptamine reuptake inhibitory activity was only found in desmethylmianserin. NA reuptake inhibition was found in many mianserin analogues, especially those with an exocyclic $-N(CH_3)_2$ moiety. Structure activity relationships for NA reuptake inhibition differed from those for presynaptic α-blockade and were generally less stringent. For both properties simple additivity relationships appeared to be absent.

The tetracyclic antidepressant mianserin has been shown to possess presynaptic α-adrenoceptor blocking activity (Baumann & Maitre 1977; Harper & Hughes 1979) in addition to noradrenaline (NA) uptake inhibiting properties (Baumann & Maitre 1977; Raiteri et al 1976; Goodlet et al 1977). However, it lacks, 5-hydroxytryptamine (5-HT) uptake blocking properties (Raiteri et al 1976; Goodlet et al 1977). To gain insight into the structural requirements for each of these properties, 32 mianserin analogues were selected and tested for presynaptic α-blockade, noradrenaline uptake-inhibiting properties and 5-HT uptake-blocking activity. The results particularly define the structural requirements for the occurrence of presynaptic α-antagonism, which seems to be strict. Moreover, they show that presynaptic α-blocking properties and NA-uptake inhibition properties are not directly linked and follow different structure-activity relationships.

MATERIALS AND METHODS

Chemistry

The compounds have been synthesized and characterized and the details will be published elsewhere. The pyrrolocompound 17 is known (CIBA/Geigy 1978). The compounds reflect various modifications on the mianserin theme (1).



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The variations consist of: (1) variations in the B ring, i.e. the upper bridge and enantiomerism; (2) variations in the A and C ring, i.e. pyridine and pyrrolo analogues; (3) variations in the D ring, e.g. imidazoline, azepine, piperidine and pyrrolidine analogues; (4) variations in the substitution pattern of the aromatic rings; (5) variation in the substituent on the nitrogen.

Determination of NA and 5-HT uptake blockade

Male Wistar (Cpb:WU) rats (110–130 g) were decapitated and the brains rapidly removed. Corpora striata and hypothalami were dissected, weighed and homogenized, with a Braun homogenizer following Potter-Elvehjem, at 850 rev min^{-1} in 20 volumes of ice-cold 0·32 M sucrose, containing 10 mM glucose and brought to pH 7·4 with Tris. All

* Correspondence.

further procedures before incubation were at 0–4 °C. Homogenates were centrifuged (900 *g* for 10 min). The supernatant was recentrifuged (10 000 *g*). The pellet (P_2; crude synaptosoma mitochondrial pellet) was resuspended (10 up-and-down strokes at 400 rev min^{-1}) in the original volume of fresh 0·32 M sucrose containing 10 mM glucose (pH 7·4). This suspension was diluted with 9 volumes of Krebs Ringer (KR) containing (mM) NaCl 118; KCl 4·7; $CaCl_2$ 1·3; $MgCl_2$ 1·2; KH_2PO_4 1·2; Na_2SO_4 1·2; $NaHCO_3$ 25; glucose 11·1; ascorbic acid 1; nialamide $1·24 \times 10^{-5}$ and 0·002% EDTA. (−) −[^{3}H]noradrenaline [^{3}H]NA; New England Nuclear; spec. act. approx. 5·85 Ci $mmol^{-1}$) uptake and [^{3}H]5-hydroxytryptamine [^{3}H]-5-HT; New England Nuclear; spec. act. approx. 21·4 Ci $mmol^{-1}$) uptake was determined in hypothalamic (for NA) and striatal (for 5-HT) synaptosomes. To 1 ml of the synaptosomal suspension, 20 µl of a solution of various concentrations of the drug tested was added after which the incubation was started under an atmosphere of 95% O_2/5% CO_2 at 37 °C. After 2 min [^{3}H]NA (final concentration 1×10^{-7} M) or [^{3}H]5-HT (final concn 1×10^{-7} M) was added in 10 µl and the incubation was continued for 2 min. Synaptosomal[^{3}H]NA or [^{3}H]5-HT uptake was estimated by filtration of 0·5 ml of the synaptosomal suspension over a Millipore filter (Type DA 0·65 µm) after which the filter was washed with 5 ml Krebs bicarbonate buffer (room temperature). Non-specific binding of [^{3}H]NA or [^{3}H]5-HT to the synaptosomes and the filter was determined by adding [^{3}H]NA or [^{3}H]5-HT to a part of the suspension that had been kept at 0 °C. The filters were dissolved in 8 ml Lumagel and counted for radioactivity. Total radioactivity in the incubation medium was determined by counting 0·25 ml of the synaptosomal suspension. Uptake was corrected for non-specific binding. From the log-concentration-response curve (containing 5 concentration points per curve and determined in quadruplicate) of each drug the concentration producing 50% uptake inhibition (IC50) was determined graphically. When a limited number of compounds was retested the IC50 values obtained in the first and second experiment differed by less than a factor of 2. The test was performed in a randomized block design.

Release of [^{3}H]NA from rat cortical slices

Male Wistar rats (Cpb:Wu), 110–130 g were decapitated the brains quickly removed, and parietal cortex slices (about 0·3 mm thick) cut by hand and then chopped into 0·25 × 0·25 mm squares with a McIlwain tissue chopper.

After 10 min preincubation at 37 °C in KR containing ascorbic acid and nialamide, 2·8 µCi [^{3}H]NA (final concentration 0·1 µM; spec. act. 2·83 Ci $mmol^{-1}$) was added. When the tissue (about 120 mg per 10 ml of medium) had been incubated for a further 30 min, the slices were washed 3 times with fresh KR. The slices were then transferred to columns of a modified version of the apparatus described by Mulder et al (1975) and superfusion was with KR (0·5 ml min^{-1}) which was warmed to 37 °C just before entering the column. After 30 min wash-out of non-specifically bound radioactivity, 2-min fractions were collected. After 5 × 2 min the KR was replaced by KR in which the KCl had been increased to 12·5 mM (12·5 K medium) by substituting an equivalent amount of NaCl by KCl. Depolarization-induced stimulation of release due to exposure to 12·5 K medium lasted for 2 × 2 min (S_1). This cycle of 5 × 2 min KR and 2 × 2 min 12·5 K medium was then repeated once (S_2). The last stimulation was followed by superfusion for 5 × 2 min with KR. In experimental columns drugs were added to the media after S_1. After superfusion the tissue was extracted with 5 ml of 2% (w/v) sodium dodecylsulphate in water and removed from the columns. Superfusion fractions, extracts and tissue were mixed with 8 ml of Lumagel (Baker) and counted for radioactivity in a liquid scintillation spectrometer (Packard Tricarb.). Correction for quenching was made by external standardization. The rate of release was expressed as the fractional rate constant (f.r.c.) which was calculated as: (d min^{-1} in superfusion sample)/(d min^{-1} in tissue at beginning of release period × release period (i.e. 2 min)). D min^{-1} in tissue for each release period was calculated as cumulative d min^{-1} in extract and superfusion samples following and including the release period.

Overflow was defined as the increase of radioactivity in release samples during exposure to 12·5 K medium over the estimated basal outflow. It has previously been shown (Dismukes et al 1977; Taube et al 1977) that under comparable conditions the stimulation-induced increase in tritium release almost completely represents [^{3}H]NA.

The drugs were all tested at 10^{-6} M. Drug effects were evaluated by relating S_2/S_1 for both f.r.c. and ^{3}H-NA-overflow in experimental columns (drugs present during S_2) to S_2/S_1 as found in control columns. Under control conditions, generally pre-stimulation and stimulation f.r.c.s are found of 0·005

and 0·10 for S_1 and 0·005 and 0·07 for S_2, resulting in a general S_2/S_1 ratio of $\approx$ 0·7. Under the present conditions the maximal increase of S_2/S_1 (as brought about by e.g. phentolamine 10^{-5} M) is $\approx$ 100% (see also Schoemaker et al 1981).

Effects on K^+-evoked ^{3}H-NA release were rated as follows: 0: no effect, +,++,+++: 10–20, 20–40 and > 40% increase, respectively, of K^+-evoked [^{3}H]NA release.

RESULTS

B-ring variants (Table 1)

The variations include enantiomerism (2, 3), heteroatom substitution (4, 5, 6), substitution on the methylene bridge (7, 8, 9), total omission of the methylene bridge (10) and shortening of the bridge (11). Mianserin itself (1) has been included for reference.

A large difference is found between the activities of the enantiomers (2, 3) of mianserin. The (−)-enantiomer (2) is almost devoid of any activity, the (+)-enantiomer (3) incorporates all of the activity that is found in the racemate itself.

The heterobridged compounds 4, 5 and 6 all display qualitative similar activities as mianserin (1). The nitrogen bridged 6 shows enhanced NA uptake blocking properties relative to 1. In contrast, the methylene bridge variants 7, 8 and 9 are devoid of NA release potentiating properties. The *cis* methyl substituted 8 is the only one in which NA-uptake blocking properties are retained. Finally, the more flexible 10 and the essentially flat 11 also do not retain appreciable activities in the NA release and NA uptake assays.

Table 1. Effect of B-ring variation on presynaptic α-blockade (measured as potentiation of K^+-evoked [^{3}H]NA release), NA uptake inhibition and 5-HT uptake inhibition. For comparison: IC50 of desmethylimipramine under the present conditions for NA-uptake block is approx. 5×10^{-9} M, whereas the IC50 of imipramine for 5HT-uptake block under the present conditions is approx. 4×10^{-6} M.

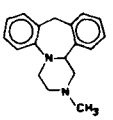
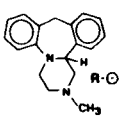
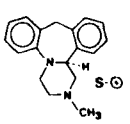
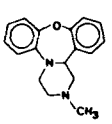
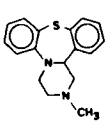
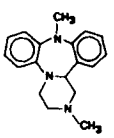
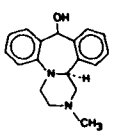
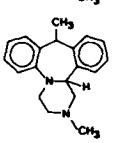
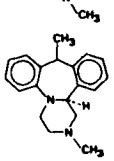
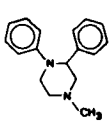
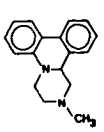
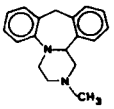
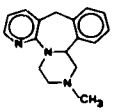
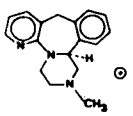
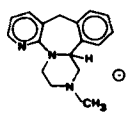
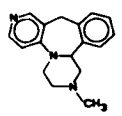
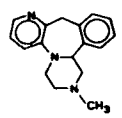
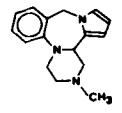
No.	Formula	Effect on NA-release	IC50 (M) NA-reuptake	IC50 (M) 5 HT-reuptake
1		+++	3.10^{-8}	$< 10^{-5}$
2		0	5.10^{-6}	$< 10^{-5}$
3		+++	2.10^{-8}	$< 10^{-5}$
4		+++	2.10^{-7}	$> 10^{-5}$
5		++	2.10^{-8}	$< 10^{-5}$
6		+++	$< 10^{-8}$	$> 10^{-5}$
7		0	$1,2.10^{-6}$	$> 10^{-5}$
8		0	2.10^{-8}	$< 10^{-5}$
9		0	1.10^{-7}	$> 10^{-5}$
10		+	2.10^{-7}	$< 10^{-5}$
11		0	2.10^{-6}	$> 10^{-5}$

Table 2. Effect of A- and C-ring variation on presynaptic α-blockade (measured as potentiation of K^+-evoked [^{3}H]NA release), NA uptake inhibition and 5-HT uptake inhibition.

No.	Formula	Effect on NA-release	IC50 (M) NA-reuptake	IC50 (M) 5 HT-reuptake
1		+++	3.10^{-8}	$> 10^{-5}$
12		+++	2.10^{-6}	$> 10^{-5}$
13		+++	7.10^{-7}	$> 10^{-5}$
14		0	5.10^{-6}	$> 10^{-5}$
15		0	3.10^{-6}	$> 10^{-5}$
16		0	3.10^{-6}	$> 10^{-5}$
17		+++	2.10^{-7}	$> 10^{-5}$

A and C ring variants (Table 2)
This series consists of the A-ring aza compounds 12, 15 and 16, the enantiomers of 12, i.e. 13 and 14, and the C-ring pyrrole derivative 17. The 6-aza analogue (12) and its (+)-enantiomer (13) are highly active in potentiating NA-release, but both are devoid of the NA-reuptake blocking properties of mianserin. In contrast, the (−)-enantiomer (14) and the 8- and 9-aza compounds 15 and 16 are hardly active in all assays. As in the A-ring, aza-ring substitution in the C-ring seems permissible, as is reflected by the results of 17.

Compounds with modified D rings (Table 3)
This series can be subdivided as it contains compounds with minor (18 and 19) or major (20—29) changes relative to the mianserin skeleton. Both ring contraction (18) and expansion (19) lower the activity, but in a different way.

The analogues 20, 21 and 22 show the influence of modification of the B–D ring junction. In all these modifications the NA-reuptake blocking properties are lost to the same extent, relative to 1. The piperidine derivative 22 retains a pronounced blocking effect upon presynaptic α-receptors.

Extension of the aliphatic nitrogen outside the ring (23, 24) diminishes potentiating activity on NA release. NA-reuptake blockade, however, gains efficiency when the D ring remains six membered (24). Demethylation of either 1 or 22 gives some overall loss of activities (25 and 26, respectively). The demethylation of mianserin also introduces some 5-HT-reuptake blocking properties (25). Compound 27 is a fairly potent NA-uptake blocker with only weak presynaptic NA-receptor blocking properties. The D-pyrimido derivative 28 is only marginally active compared with its pyrazino isomer mianserin. Its 10-aza analogue 29 has lost all activities.

Substitution of the aromatic rings (Table 4)
The influence of substitution is represented here by a small selection. Methyl substitution at C 7 in mianserin (30) leads to inactivation with regard to effects on release and reuptake of NA. The affinity towards the 5-HT-ergic uptake system rises but remains feeble. A similar effect is observed by 13-chloro substitution (31).

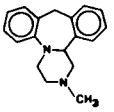
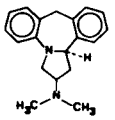
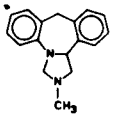
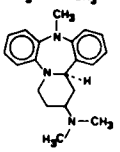
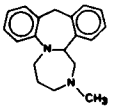
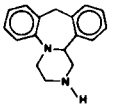
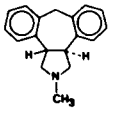
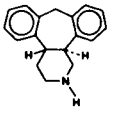
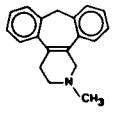
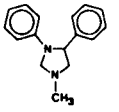
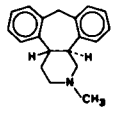
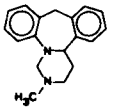
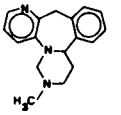
The effects of methyl substitution on the activity of the mianserin analogues 4 and 21 is found in the values for 32 and 33. Here the effect of methyl substitution seems less dramatic for 4 than for mianserin itself.

DISCUSSION

The results obtained with the 32 selected mianserin analogues provide some insight in the structural factors that, within this series of compounds, govern presynaptic α-receptor blockade on one side and NA- and 5-HT-reuptake blocking properties on the other.

Presynaptic α-receptor blockade
The present results suggest that an overall bent shape of the molecule, which is also found in classical tricyclic antidepressants like amitriptyline (also active as a presynaptic α-blocker, Hughes 1978) is a gross prerequisite for presynaptic α-receptor blockade.

Table 3. Effect of D-ring variation on presynaptic α-blockade (measured as potentiation of K^+-evoked [^{3}H]NA release), NA uptake inhibition and 5-HT uptake inhibition.

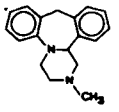
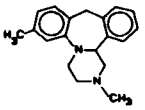
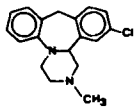
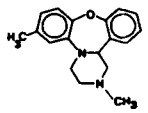
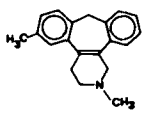
No.	Formula	Effect on NA-release	IC50 (M) NA-reuptake	IC50 (M) 5 HT-reuptake	No.	Formula	Effect on NA-release	IC50 (M) NA-reuptake	IC50 (M) 5 HT-reuptake
1		+++	3.10^{-8}	$> 10^{-5}$	23		+	5.10^{-7}	$> 10^{-5}$
18		++	9.10^{-7}	$> 10^{-5}$	24		0	$< 10^{-8}$	$> 10^{-5}$
19		0	4.10^{-7}	$> 10^{-5}$	25		++	6.10^{-8}	6.10^{-6}
20		0	4.10^{-7}	$> 10^{-5}$	26		++	4.10^{-7}	$> 10^{-5}$
21		+	3.10^{-7}	$> 10^{-5}$	27		+	6.10^{-8}	$> 10^{-5}$
22		+++	2.10^{-7}	$> 10^{-5}$	28		+	3.10^{-7}	$> 10^{-5}$
					29		0	3.10^{-6}	$> 10^{-5}$

A flexible molecule like 10 and an essentially flat molecule like 11 do not qualify. A comparison of the bent molecules 1, 18 and 19 shows preference of the presynaptic α-receptor for a molecule with a six-membered D-ring, as far as ring size is concerned.

The D-piperidino isoster of mianserin (i.e. 22) appears to also display optimal stereochemical requirements for the blockade of presynaptic α-receptors. Its D-pyrrolidino analogue 20 is inactive, however. Within the series of highly active molecules 1, 3, 4, 5, 6, and 22 common conformational relationships exist, i.e. they all appear to contain almost perfect chair-formed D-rings with equatorial substituents. This is evidenced by (i) the results of an X-ray crystallographic study on (+)-mianserin hydrobromide (van Rij & Feil 1973) and (ii) the results of n.m.r. spectroscopic investigations concerning the conformations of mianserin and its major analogues in solution (Funke 1976). Whilst care is needed in extrapolating these results to the situation at the receptor in situ, all results point in the same direction.

Compounds 25 and 26, *N*-demethylated analogues of mianserin and of 22, respectively, still display appreciable affinity to the presynaptic α-receptor. For 25 it is known that, with an overall shape similar to mianserin, its nitrogen lone pair seems to be equatorial in the chair formed D-ring (n.m.r. evidence, Funke 1976)) in contrast to what has been found for mianserin. For 26, it is known that its pK_a value is one unit higher than that of 22 (8·6 vs 7·5). These observations suggest that changes in the position of the lone pair and in the pK_a apparently have only small effects on presynaptic α-blockade,

Table 4. Effect of aromatic substition on presynaptic α-blockade (measured as potentiation of K^+-evoked [^{3}H]NA release), NA uptake inhibition and 5-HT uptake inhibition.

No.	Formula	Effect on NA-release	IC50 (M) NA-uptake	IC50 (M) 5 HT-uptake
1		+++	3.10^{-8}	$> 10^{-5}$
30		0	5.10^{-7}	9.10^{-6}
31		0	3.10^{-7}	8.10^{-6}
32		++	8.10^{-8}	$> 10^{-5}$
33		+	2.10^{-6}	$> 10^{-5}$

but the apparent preference for an equatorial lone pair may be marginal (Katritzky et al 1975; Lambert et al 1975).

Substitution of mianserin in the A- or C-ring with a methyl or chlorine substituent at the 7 or 13 position (30, 31) is detrimental for affinity to the presynaptic α-receptor. In the oxygen-bridged series, the effect seems to be less dramatic (32, the maleate of which is known as Org GC 94, Anselmi et al 1976). Methyl-substitution or hydroxylation of the carbon bridge results in loss of activity. The effects of substitution of the A-phenyl ring by a pyridine ring are interesting. The orientation of this ring is critical (cpds 12, 15 and 16). In this particular series, which contains a pyridine A-ring, the enantiomers of 10 (13, 14) have also been investigated and the activity appears to reside in the dextrorotatory isomer 13. The same was observed for the enantiomers of mianserin (see text and Nickolson et al 1980; Schoemaker et al 1981).

NA and 5-HT-reuptake blockade

The distribution of NA- and 5-HT-reuptake blocking properties among the series investigated also gives rise to several interesting observations.

5-HT reuptake is hardly influenced by the compounds mentioned. To some extent blockade is found in 30, 31 and 25. The IC 50 value of 25 (desmethylmianserin) is the same as that for imipramin (measured in the same expt). Compound 25 thus displays a mixed profile of uptake inhibition, but it is also active as presynaptic α-receptor blocker. In this respect it resembles drugs like amitriptyline, although, in contrast to most tricyclic antidepressants, it is devoid of anticholinergic activity (unpublished results.)

The efficiency of the compounds in blocking NA-reuptake shows wide variation. Only two (6, 24) reach the potency of desipramine (of which the IC 50 in a similar expt is approx. $5 \cdot 10^{-9}$ M). The so called *exo* compound 24 is totally devoid of effects on 5-HT-reuptake and NA-release and therefore represents a selective NA-uptake blocker of high potency, but it has shown signs of cardiotoxicity. The mianserin analogue 6 is of similar potency as a NA-reuptake inhibitor and, like 24, it also possesses a N-CH_3 bridge. Its profile, however, is different from 24 in that it has pronounced presynaptic α-receptor blocking properties.

The difference between 8 (*cis*) and 9 (*trans*) is interesting with regard to NA-reuptake blockade. In 8, the affinity towards the NA-reuptake system is retained relative to mianserin, whereas in 9 it is not.

Spectroscopic evidence (Funke 1976) shows that 8 has a mianserin-like conformation, the bridge methyl is equatorial with respect to the azepine B-ring, pointing *away* from the nitrogen at position 2. In 9 the overall mianserin-like conformation is also present, but the bridge methyl group takes an axial position in the B-ring, pointing *towards* the nitrogen at position 2. Apparently this addition bulk is undesirable for optimal NA-reuptake blockade.

The flexible molecule 27 is also a fairly potent NA-reuptake blocker. Relative to its rigid analogue 18, the potency is enhanced. A simple additivity relationship for NA-reuptake blockade is *not* present as 1 is more potent than its analogue 18, whereas the reverse is true for their open analogues 10 and 27. Absence of simple additivity is also evidenced by the effect of 7-methylation, which results in a strong decrease in NA-uptake blocking activity when applied to mianserin (1 vs 30), whereas an increase is found for the *O*-bridged variant (4 vs 32).

In conclusion, the results show that amongst the compounds closely related to mianserin a variety of neurochemical profiles exists, ranging from potent mixed- or selective-uptake blockers to presynaptic α-blockers lacking NA- or 5-HT-uptake inhibitory activity. Clinical evaluation of the latter type of compounds may give an answer to the question

whether mianserin's antidepressant effect is solely related to its presynaptic α-blocking properties, or is also based on the blockade of NA-reuptake.

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