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Differential mode of antagonism of 5-hydroxytryptamine-induced pressor effects by (+)- and (−)-mianserin in pithed rats

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Mianserin is an effective antidepressant agent used clinically (review by Brogden et al 1978). It differs from the tricyclic antidepressants both in chemical structure and pharmacologically. The drug's action in depressive illness is not fully understood but it is known as a moderate inhibitor of noradrenaline re-uptake and a weak inhibitor of 5-hydroxytryptamine (5-HT) re-uptake (Kafoe & Leonard 1973; Raiteri et al 1976; Baumann & Maître 1977; Zis & Goodwin 1979; Nickolson & Wieringa 1981). In the peripheral and central nervous system mianserin displays potent anti-5-HT and antihistamine activity (Vargaftig et al 1971; review by van Riesen et al 1981). The most significant peripheral effect of mianserin on noradrenergic transmission is blockade of the neuronal uptake of noradrenaline while α-adrenoceptor antagonism can only be determined with higher concentrations (Cavero et al 1980; Docherty & McGrath 1980). Mianserin is the racemic mixture of the (+)-*S*- and the (−)-*R*-enantiomers, the (+)-isomer being the more active, as shown by tests predictive for antidepressant activity (Schoemaker et al 1980; Nickolson et al 1982). Kalkman et al (1983) recently reported that the stereo-selectivity of (+)- or (−)-mianserin for blocking either α_1- or α_2-adrenoceptors is not particularly pronounced, whereas the (+)-isomer only, showed moderate tyramine uptake-blocking activity in pithed rats. To characterize the individual isomers of mianserin in more detail the present communication describes the interaction of (+)- and (−)-mianserin with 5-HT-induced increases in diastolic blood pressure in pithed rats.

After induction of anaesthesia with hexobarbitone (150 mg kg^{-1}, i.p.), male normotensive Wistar rats (200–250 g) were pithed and immediately artificially respirated. Arterial pressure was recorded from the right carotid artery. After stabilization of cardiovascular functions, drugs were injected via the cannulated right jugular vein. Bolus injections of 5-HT in 0·9% NaCl (saline) were given in a volume of 0·5 ml kg^{-1}, 15 min after saline or the dose of (+)- or (−)-mianserin (1 ml kg^{-1}). ED50 (dose relating to half maximal activity) of the pressor response to 5-HT in control and pretreated pithed rats were calculated by means of log-probit analysis, and the lines tested for parallelism (Tallarida & Jacob 1979).

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The diastolic blood pressure of the pithed normotensive rats ranged between 35 and 45 mm Hg, and the heart rate between 290 and 350 beats min^{-1}. Pretreatment with either (+)- or (−)-mianserin did not alter basal diastolic blood pressure or heart rate. Intravenously administered 5-HT caused a biphasic pressure response (Fozard & Leach 1968), i.e. after an initial increase, diastolic blood pressure fell below preinjection values to a minimum of about 20 mm Hg. The (+)- and (−)-isomers of mianserin dose-dependently antagonized the vasoconstrictor component of the 5-HT response (Figs 1 and 2). Both isomers shifted the dose-response curve to the right in a parallel fashion, since the slopes of the consecutive log-probit lines did not differ significantly ($P > 0.05$).

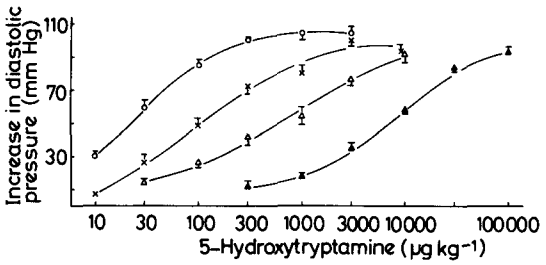

FIG. 1. Log dose-response curves for the 5-HT-induced increase in diastolic blood pressure of pithed rats, 15 min after saline (○——○), and of (+)-mianserin (×——× 0·01; △——△: 0·03 and ▲——▲, 0·1 mg kg^{-1}). Symbols are presented as mean values ±s.e.m. (n = 7–10).

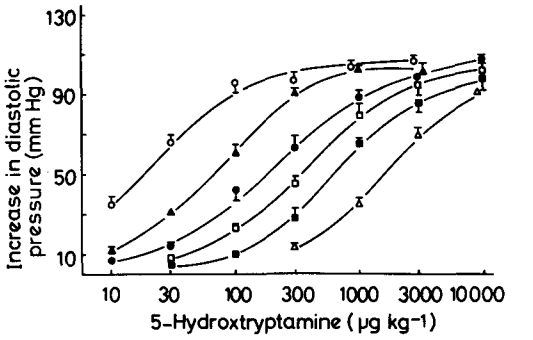

FIG. 2. Log dose-response curves for the 5-HT-induced increase in diastolic blood pressure of pithed rats 15 min after saline (○——○) and of (−)-mianserin (▲——▲ 0·1; ●——● 0·3; □——□ 1; ■——■ 3 and △——△ 10 mg kg^{-1}). Values are mean ± s.e.m. (n = 7–10).

The (−)-isomer was about 100 times less potent in inhibiting 5-HT-induced increases in diastolic blood pressure than the (+)-isomer (Fig. 2). This conclusion is based on the almost similar (100-fold) shift of the 5-HT dose-response curve after 0·03 and 3·0 mg kg^{-1} of (+)- and of (−)-mianserin respectively. Consecutive shifts of the log dose-response curves after pretreatment with increasing doses of (+)-mianserin gradually became greater. This could indicate, either an increasing effectiveness of the antagonist or a decreasing activity of the agonist. Other potent 5-HT antagonists, methysergide and cyproheptadine, also exhibit this peculiar antagonism towards vasopressor 5-HT in-vivo (authors' unpublished observations). A possible explanation is offered by Fozard & Leach (1968) that since 5-HT is thought to act on both the lung and the peripheral circulation, extreme vasoconstriction in the lung would dramatically diminish the blood flow to the heart and thereby appreciably reduce the output. A marked decrease in cardiac output would then counteract the increase in diastolic blood pressure brought about by vasoconstriction of the peripheral resistance vessels. In fact, during the depressor phase of the 5-HT response in pithed rats, a reduction in cardiac output is indeed seen (authors' unpublished observations). We cannot provide an explanation for the observation that (−)-mianserin the less effective antagonist of 5HT-induced vasoconstriction has a different mode of action from that of (+)-mianserin, cyproheptadine or methysergide.

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