A COMPARATIVE STUDY ON THE PRE- AND POSTSYNAPTIC α-ADRENOCEPTOR ANTAGONIST ACTIVITY OF THE 2R-AND 2S-ENANTIOMERS OF WB4101

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WB4101 (2-(N(2,6-dimethoxyphenoxyethyl) amino-methyl)-1,4-benzodioxane) is a potent α -adrenoceptor antagonist (Mottram and Kapur 1975) exhibiting specificity towards the postsynaptic α-receptor (Kapur and Mottram 1978).

Recently, Nelson et al (1979) have synthesized the 2 R- and 2 S-enantiomers of WB4101 and found the 2 S-enantiomer to be 40-50 times as potent as the 2 R-enantiomer in antagonizing the α -adrenergic response of methoxamine-induced contraction of rabbit aortic strip.

The present study was undertaken to evaluate the relative potencies of the 2 R- and 2 S-enantiomers of WB4101 on the response to noradrenaline induced contractions of the rat vas deferens. This was followed by a comparison of their relative potencies as presynaptic α -adrenoceptor antagonists on clonidine-induced suppression of the twitch response of field stimulated rat vas deferens (Swedin 1971), since previous studies on a series of structurally related benzodioxanes has shown that, though they have widely differing activity as antagonists of the postsynaptic α -adrenoceptor their presynaptic α-blocking activity is remarkably similar (Kapur and Mottram 1978).

Results showed that increasing concentrations of both the 2 R-and 2 S-enantiomers of WB4101 produced parallel shifts of the dose-response curves to noradrenaline, and that calculation of the pA_2 values (Arunlakshana and Schild 1959) revealed that the 2 S-enantiomer was approximately 270 times as potent as the 2 R-enantiomer (Table 1). On the pre-synaptic receptor, however, both the 2 R- and the 2 S-enantiomers proved to be of equal potency having pA_2 values of 6.42 and 6.37 respectively.

Table 1

Receptor Type	Enantiomer	pA_2 value	s.d. (n)	Slope	s.d.	Correlation coefficient
Postsynaptic	2 R	7.55	0.20 (6)	0.92	0.16	0.984
Postsynaptic	2 S	9.98	0.15 (7)	0.96	0.09	0.995
Presynaptic	2 R	6.42	0.08 (7)	1.56	0.13	0.996
Presynaptic	2 S	6.37	0.06 (6)	1.22	0.08	0.998

It is therefore evident from these results, that presynaptic inhibition of clonidine is not only independent of structural alteration of the side chain of benzodioxans, but that variation in spacial arrangement of the side chain likewise has no significant effect on presynaptic blocking activity.

We can therefore conclude that a low degree of structural specificity is required for the antagonism of the presynaptic α- adrenoceptor compared with the postsynaptic receptor. Alternatively these results may be in accord with the recently published observation of Kalsner (1980) who suggested that agonists and antagonists of the α- adrenoceptor may not have a common mechanism or site of action at the presynaptic level. This latter suggestion is borne out by the fact that whilst the 2 R- and 2 S-enantiomers of WB4101 exhibited a classical competitive inhibition of postsynaptic alpha adrenoceptors as shown by the values for slope on the Schild plots (Table 1), the values for slope in the presynaptic studies were indicative of a non-competitive type of blockade.

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