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LETTERS TO THE EDITOR

Ketanserin—a novel antihypertensive drug?

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There is a current controversy in the literature about the mechanism of the hypotensive action of the new 5-hydroxytryptamine antagonist, ketanserin. The advocates of the drug claim that it acts peripherally by blocking vascular 5-HT_2 receptors (De Cree et al 1981; Van Nueten et al 1981; Wenting et al 1982) which appear to be the same as those 5-HT_2 *binding sites* which have been characterized in the rat brain using radiolabelled ligand binding studies (Peroutka & Snyder 1979). It is further claimed that the efficacy of ketanserin in hypertensive patients is evidence for the pathological involvement of 5-hydroxytryptamine in the aetiology of the disease (De Cree et al 1981; Wenting et al 1982). However it has been shown that in the rat, at least, the hypotensive action of ketanserin is entirely explicable in terms of its additional (but weaker) α_1-adrenoceptor blocking action (Fozard 1982).

We would like to point out that there is now evidence to suggest that the 5-HT_2 *binding site* is similar or identical to the classical so called 'D' receptor in vascular smooth muscle (Cohen et al 1981; see Humphrey 1982). In support of this view we now present data which indicate that a number of clinically available 5-HT antagonists (including ketanserin) have a similar affinity for both the 5-HT_2 *binding site* and the 'D'-receptor (Table 1). If the two sites are similar and in man do mediate 5-hydroxytryptamine's post-junctional action of sensitizing the vasculature to a variety of vasoconstrictor agents (Van Neuten et al 1981) then all of these antagonists should be as effective as ketanserin in producing hypotension.

However, available evidence suggests that other 'D'-receptor antagonists are not indeed hypotensive in animals, at doses which specifically block 'D' receptors in vivo (Fozard 1982; unpublished observations). Unlike methysergide, antagonists like cyproheptadine and pizotifen have no notable agonistic activity (Apperley et al 1976; 1980) which could mask any possible hypotensive action. We therefore conclude that 5-HT_2 receptor blockade itself does not produce hypotension in animals. The question of whether blockade of vascular 5-HT_2 receptors produces hypotension in hypertensive man can only be determined unequivocally by the clinical investigation of a potent specific 5-HT_2 receptor antagonist without significant α-adrenoceptor blocking activity.

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Table 1. Estimates of affinities of various 5-hydroxytryptamine antagonists for 5-HT_2 binding sites and vascular 'D' receptors

	Estimate of −Log [dissociation constant]	
Antagonist	5-HT_2 binding Site[a]	Vascular 'D' receptor[b]
Ketanserin	9·04	8·72 (8·33–9·10)
Methysergide	8·48	8·49 (7·85–9·14)
Cyproheptadine	8·77	8·73 (8·36–9·10)
Pizotifen	8·87	9·42 (8·18–10·66)
Spiroperidol	9·10	8·92 (8·25–9·58)

[a] Mean $-\log K_i$ values calculated from published data derived from [^{3}H]ketanserin and [^{3}H]spiperone binding studies (Leysen et al 1982).

[b] pA_2 value against 5-hydroxytryptamine in rabbit isolated aorta. All antagonists were specific and competitive in their action. Each value (95% confidence limits) is the mean of at least 4 observations. (Apperley et al 1976 unpublished observations).

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