5-HT receptor subtype-specific drugs and the cardiovascular system

THE SYSTEM for classification of 5-HT receptors set up by Bradley et al.1,2 in 1986 has formed a basis for subsequent 5-HT receptor identification. They proposed the existence of three main types of 5-HT receptors: 5-HT2 and 5-HT3, defined pharmacologically using selective antagonists; and 5-HT1-like, defined with the help of selective agonists and non-selective antagonists. 5-HT1-like binding sites have since been further classified into four distinct subtypes, 5-HT1A, 5-HT1B, 5-HT1C and 5-HT1D, but these sites do not always correlate with the functional heterogeneity of 5-HT1-like receptors3.

However, at a recent symposium* on the multiple effects exerted on the cardiovascular system by 5-HT, it became clear that some of the

*The Cardiovascular Pharmacology of 5-HT: Implications For Drug Therapy, Amsterdam, Netherlands, 4-7 October 1988.
receptors involved do not fit into this classification. Such receptors have been described by the term 'orphan receptor'.

It was also recognized that many of the effects of 5-HT on the cardiovascular system vary from species to species. For example, 5-HT induces bradycardia by activation of 5-HT1 receptors on afferent nerves in the cardiac muscle. But when this bradycardia is inoperative, 5-HT may produce tachycardia – which involves 5-HT3 receptors in the isolated rabbit heart preparation, 5-HT2 receptors in the ganglion-blocked rat and 5-HT1 receptors in the spinal-vagotomized cat (Cohen, Indianapolis). The receptor responsible for the tachycardic response in the pig cannot even be classified: a number of drugs that antagonize the different types of 5-HT receptors do not attenuate the chronotropic response to 5-HT; neither do antagonists at the receptors for adrenaline, acetylcholine, histamine and dopamine (Bom and Verdouw, Rotterdam). It is thus an example of an orphan receptor.

5-HT2 receptors have been identified as being responsible for vascular smooth muscle contraction in a variety of preparations. Currently, this receptor is classified on the basis of antagonism by ketanserin or cyproheptadine; 5-HT3 antagonists such as MDL-72222 must be inactive. Analysis of the pA2 or pKs values in a number of vascular and other smooth muscle preparations has revealed some variations, but these do not as yet form a consistent enough pattern to constitute receptor heterogeneity (Mylecharane, Sydney).

Some of the complications arise from the noncompetitive blockade of the effects of 5-HT by, for instance, ritanserin, methysergide or LY-53857 in the calf coronary and rat tail arteries. This phenomenon can be explained either by allosteric modulation of the 5-HT3 receptors (Kaumann, Welwyn) or by pseudoirreversible inhibition (Clarke, Houston).

5-HT-induced contraction can also be mediated by 5-HT1-like receptors such as those in the dog saphenous vein. The action of the novel and highly selective 5-HT1-like receptor agonist GR-43175 makes it an important new tool for studying this class of receptor. It is a potent agonist at the 5-HT1-like receptors that mediate vascular smooth muscle contraction and inhibit the release of sympathetic neurotransmitter. It is also devoid of agonist or antagonist activity in a range of isolated tissues containing 5-HT2 and/or 5-HT3 receptors (e.g. pig and greyhound coronary artery, dog femoral artery and rat vagus nerve) and even certain 5-HT1-like receptors (e.g. those responsible for vascular or intestinal relaxation) (Feniuk and Humphrey, Ware). The finding that GR-43175 contracts cranial arteries (human basilar artery and feline arteriovenous anastomoses) might be of particular interest to the proposed clinical use of GR-43175 in the treatment of acute migraine (Tfelt-Hansen, Copenhagen).

5-HT and hypertension
5-HT2 receptor antagonists are used clinically to treat hypertension. Ketanserin is one of the best known, although it is recognized that its anti-hypertensive action is at least partly due to its a1 adrenoceptor antagonist activity – to which the 5-HT2 receptor antagonism may contribute. Both ketanserin and the more selective 5-HT2 antagonist ritanserin antagonize the arterial and venous constrictor responses to 5-HT in the human forearm (Blauw and van Brummelen, Leiden).

Another action of ketanserin is to counteract 5-HT-induced platelet aggregation and amplification of vasoconstrictor responses to other substances (van Nueten, Beerse). The amplification phenomenon seems to be more marked in pathophysiological circumstances like chronic hypertension, atherosclerosis and vasospasm. Another proposed mechanism of action of ketanserin was the reduction of a particular, apparently easily realizable pool of monoamines in peripheral tissues. In hypertensive and senescent animals the pool becomes larger in certain vascular tissues and spleen (Leysen, Beerse).

Reduction of blood pressure can also be achieved via central activation of 5-HT1A receptors. The potent and selective 5-HT1A agonists flesinoxan and 8-OH-DPAT lower blood pressure and heart rate in all species studied so far (Wouters, Weeep; Mir, Basel). The first studies with flesinoxan in hypertensive patients also show that this compound lowers blood pressure in man (de Voogd, Weeep).

5-HT and migraine
Our current understanding of the pathogenesis of migraine is still incomplete, the two hypotheses being that the headache is of cardiovascular or neurogenic origin.

The craniovascular pharmacology of 5-HT supports the first view, but does not necessarily rule out the second. Migraine is associated with a rapid release from platelets and excretion in urine of 5-HT. The resulting reduction in blood 5-HT may cause a combination of arterial dilation, arteriolar constriction and opening of arteriovenous anastomoses. Several drugs effective during migraine attacks, including ergotamine and GR-43175, constrict arteriovenous anastomoses and thereby may restore the blood flow through the cranial circulation (Saxena, Rotterdam).

According to the neurogenic hypothesis of migraine, the activation of the sensory innervation of the cranial vasculature leads to vasodilatation via an axonal reflex mechanism which may involve 5-HT3 receptors located on the trigeminal nerve endings. This hypothesis is primarily based on the positive results reported with the 5-HT3 receptor antagonist MDL-72222 in the acute management of migraine (Fozard, Basel). However, Lataste (Basel) reported that under placebo-controlled double-blind conditions ICS 205-930, another potent and selective 5-HT3 receptor antagonist, is ineffective in aborting migraine. He argued, though, that migraine may result from a cascade of events following the initial release of 5-HT from platelets, and that treatment after onset of an attack may be too late to have an effect. Clinical trials to explore possible prophylactic effectiveness of continuous 5-HT3 receptor antagonism with ICS 205-930 are in progress.
non-selective antagonist methiothepin. Martin (Beckenham) has analysed the interactions of tryptamines with 5 HT receptors and produced 'fingerprints' consisting of affinity and, in the case of agonists, efficacy estimates, and has proposed this approach as a method to extend and improve the current classification scheme. More positive identification of the receptors requires the development of more selective drug tools.

Pharmacological analysis of receptors is, however, only one way to look at the effects of a substance. The isolation and cloning of 5-HT receptors has already revealed a remarkable resemblance between the 5-HT$_1$C receptor and the 5-HT$_2$ receptor, and between the $\beta$-adrenergic receptor and the 5-HT$_{1A}$ receptor (Hartig, Baltimore). This multidisciplinary interest in the 5-HT receptor will ultimately lead to a better understanding of the cardiovascular effects of 5-HT.

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**References**

3 Humphrey, P. P. A. and Richardson, B. P. in Serotonin (Mylchrestance, E. J., et al., eds), MacMillan Press, in press

GR-43175: 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide
ICS 205-936: (3a-tropanyl)-1H-indole-3-carboxylic acid ester
MDL-77222: 1aH, 3a, (5aH-tropan-3-y)3,5-dichlorobenzoate
LY 53857: 4-isopropyl-7-methyl-9-(2-hydroxy-1-methylpropoxy)carbonyl4,6,6a,7,8,9,10,10a-octahydrolindo-(4,3-g)quinoline maleate.