This in turn may help in the classification of the arrhythmias and identification of the most dangerous. Understanding the effects of drugs is not only a problem of pharmacology (what channel is affected?), but also of nonlinear dynamics (how does this change in ionic properties lead to novel dynamic organization of the heart?).

Both cardiology and nonlinear mathematics deal with the classification of complex dynamics. It is not remarkable that techniques and observations in one discipline are relevant in the other, but rather that both fields have been so independent over the years. □

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Pharmacology

5-HT_3 receptors in the brain?

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THE paper by Kilpatrick, Jones and Tyers on page 746 of this issue[1] presents the first experimental evidence for the existence of the 5-HT_3 subtype of receptors for 5-hydroxytryptamine (5-HT or serotonin) in the mammalian brain. This result could have important, exciting implications for the development of a new class of drugs acting on the brain.

It has long been known that 5-HT is a neurotransmitter in the central nervous system and that it is involved in various physiological functions such as sleep, control of blood pressure, temperature regulation, sexual activity and the perception of pain, as well as playing an important role in psychiatric conditions, for example, disturbances of affective behaviour such as depression and anxiety states. Much of the evidence for the involvement of 5-HT in these conditions comes from knowledge of the pharmacological properties of the drugs which are used in their treatment.

That there is more than one type of receptor for 5-HT was first suggested by Gaddum in 1954 and described in more detail[2] in 1957 when the two subtypes of receptor were designated 'M' and 'D'. Unfortunately, the classification of 5-HT receptors has since become confused, partly by the use of different terminology for the receptor subtypes and, perhaps more importantly, by the use of different criteria for classification. Recent proposals[3,4] for the classification of 5-HT receptors are based on functional criteria, and it seems this classification is being used, although there are alternative proposals[5].

It is generally accepted that there are three different subtypes of receptor for 5-HT and, according to the classification based on functional criteria[3], they are called 5-HT_1-like, 5-HT_2 and 5-HT_3, although the 5-HT_1 receptor has been further subdivided on the basis of data from binding studies. In the central nervous system the 5-HT_1-like receptor is a presynaptic, or autoreceptor, which controls the release of the transmitter from presynaptic nerve terminals. The 5-HT_2 receptor, which seems to correspond to Gaddum's D receptor, is present in the brain and is probably the principal postsynaptic receptor for 5-HT; it mediates the so-called 5-HT behavioural syndrome such as the 'head twitch'[6] and 'wet dog shakes' in rats. The 5-HT_3 receptor, which corresponds to Gaddum's M receptor, has until now been found only on peripheral neurons where it mediates depolarization or release of transmitter. Kilpatrick *et al.*[1] now produce evidence suggesting that the 5-HT_3 receptor exists in the brain.

But there is need for caution. In the past there has been a tendency to assume too readily that a binding site is identical to a functional receptor; it is now recognized that this is not always the case. What Kilpatrick *et al.* have done is to produce evidence for the existence of a binding site in the brain, which shows the appropriate responses to drugs that are selective for peripheral 5-HT_3 sites, both agonists and antagonists, exactly as if it is a 5-HT_3 receptor. However, the only correlation the authors demonstrate between affinity for the binding site and pharmacological potency is for a peripheral 5-HT receptor on the rat vagus nerve (their Fig. 2*b* on page 748). Thus, the final proof that this 5-HT_3 binding site is a functional receptor is still awaited, and the authors go too far both with their title and in their statement "Here we report direct evidence for the existence of 5-HT_3 receptors in rat brain tissue and their distribution . . .". In my view, they should have confined themselves to the term 'binding site' in presenting their otherwise excellent data.

The final demonstration of the existence of functional 5-HT_3 receptors in the brain must come from studies of the central responses to drugs selective for this site. The drug used by Kilpatrick *et al.* in their binding studies, GR 65630, has not been shown to produce any behavioural effects. The closely related compound, GR 38032F, together with MDL 72222 and ICS 205-930, all of which are selective 5-HT_3 antagonists in the peripheral nervous system, and all of which compete for the binding of radioactively labelled GR 65630 in brain, have been reported to produce behavioural effects in rats and primates. However, the currently available data are all contained in abstracts of papers presented at meetings or in short reports which neither provide sufficient detail nor have been fully scrutinized.

What is needed is fully documented and detailed study of the central actions, if any, of GR 65630 and related compounds before the concept of 5-HT_3 receptors in the brain can be fully accepted. Such studies must be carried out with extreme care, first, to ensure that the effects seen are not caused by some peripheral action of the drug which then affects the central nervous system indirectly; and second, that they are not caused by an effect of the drug on some other neurotransmitter system.

The drug ketanserin, for example, is selective for 5-HT_2 receptors but some of its effects result from an action at α-adrenoceptors. It is possible, then, that GR 65630 interacts with neurotransmitter systems in the central nervous system other than 5-HT, despite the fact that ligands for other neurotransmitter receptors were shown to be inactive in the binding studies. If, as suggested by the brief reports[7] of the behavioural effects of GR 38032F, this drug has anxiolytic properties, and if its pharmacological properties are similar to those of GR 65630, a new class of anti-anxiety drugs may appear. But caution is again needed, particularly in interpreting data from animal tests in terms of possible therapeutic actions in humans[8]. The question that remains is "what are the behavioural effects of the agonists and antagonists of 5-HT_3 receptors?". □

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