Serotonin (5-hydroxytryptamine, 5-HT) has a wide diversity of actions throughout the body, including the nervous, gastrointestinal and cardiovascular systems. Advances have been made in our understanding of the complexity of its actions with the identification of multiple 5-HT receptors, which have now been divided into seven classes. The cardiovascular actions of 5-HT are mediated by five main sets of receptors, which are proving to be profitable targets for drug development [1]. For example, 5-HT1 receptors, such as sumatriptan, have proved to be effective in aborting acute migraine attacks, by causing vasoconstriction of extracerebral blood vessels. The question of therapeutic potential in the heart has been raised by the actions of serotonin on human atria, where it has positive inotropic and chronotropic actions [2]. The receptor involved has been characterised as the 5-HT1 receptor, which has now been cloned from human atrium [3]. It is not expressed in the ventricle, in contrast to the atrium, but is found in the brain and gastrointestinal tract. It is also species-dependent, being present in the atria of the human and pig, but not in the more common laboratory animals, like guinea-pig and rabbit. The selective localisation of the 5-HT1 receptor to the atria in human raises the possibility that it may have a physiological role in atrial function or a pathological role in the genesis of atrial arrhythmia [2].

The arrhythmogenic potential of serotonin has been demonstrated in isolated human atrial strips, where serotonin-induced arrhythmic contractions were abolished by 5-HT1A antagonists [4]. A possible mechanism of arrhythmia has been demonstrated with an increase by serotonin of the L-type calcium current, ICa, mediated by 5-HT1A receptors in isolated human atrial myocytes [5]. This action was associated with an increase in intracellular cyclic-AMP and was dependent on channel phosphorylation. Arrhythmia may result if the increase in calcium channel conductance leads to intracellular calcium overload, calcium oscillations and triggered activity. A further arrhythmogenic mechanism is suggested in the paper by Pino et al. in this issue [6], which describes the action of serotonin on the hyperpolarisation-activated current, IF, in human atrial myocytes.

IF is an inward current, carried via channels with mixed permeability to K+ and Na+ ions, which is activated by hyperpolarisation and contributes to the pacemaker current in sinus node and Purkinje fibres. It is also present in human atrial cells [7], but is activated at potentials that are sufficiently negative to make it unlikely to play a significant physiological role. The voltage of half-maximal activation for IF in human atrial cells is approximately −90 mV, whereas the maximal diastolic potential in atrial cells is less negative. However, Pino et al. demonstrated that serotonin caused a shift of the activation voltages of IF to less negative potentials, by approximately 11 mV, without change in its maximal amplitude. Such a shift in IF activation voltage in cells of the intact human atrium, in which the normal resting potential is around −70 mV, could result in approximately 40% of maximal IF activation in the presence of serotonin. The resultant inward current may cause spontaneous diastolic depolarisation and arrhythmic activity. Antagonists of 5-HT1A receptors blocked the action of serotonin on IF in human atrial myocytes [6].

There are uncertainties, however, about the potential for IF to generate arrhythmia [8]. The studies of Pino et al. [6], and of others [7], required high extracellular potassium concentration, 25 mM, in order to study IF. With physiological potassium concentrations, particularly at the resting membrane potential, IF is very small [7]. The effect of such a small inward current will be dependent on the opposing outward currents, in particular IK1. This potassium current is absent in spontaneously active sinus node cells, allowing a greater role of IF in the generation of the pacemaker potential, but it may be large in atrial and ventricular myocytes. However, heterogeneity of the relative magnitude of IF and IK1 currents in human atrial cells has been reported, with some myocytes exhibiting predominantly IF [7]. In addition, the relative importance of IF may be...
increased in situations where outward potassium channel density is reduced, for example in heart failure [9] or chronic atrial fibrillation [10]. It may be of note that the dose–response relationship of serotonin for its action on \( I_t \) was similar to that previously shown for \( I_{\text{Ca}} \) [5]. Serotonin, therefore, may be responsible for two potential arrhythmogenic mechanisms, namely automaticity related to \( I_t \) induction and calcium-overload-induced triggered activity secondary to increased \( I_{\text{Ca}} \). The combination may be synergistic, with diastolic depolarisation increasing the likelihood of triggered after-depolarisations reaching threshold.

The actions of serotonin are mediated by positive linkage of the 5-HT\(_4\) receptor to adenylyl cyclase and increased intracellular cyclic-AMP [1]. Similar effects can be observed with catecholamine stimulation; when 5-HT\(_4\) receptors were blocked, isoprenaline caused an increase in \( I_t \), which was indistinguishable from that with serotonin [6]. Interestingly, by contrast, exposure to beta-blockers has been shown to potentiate the actions of serotonin at the 5-HT\(_4\) receptor [4]. This may be related to cross-talk between \( \beta_1 \)-adrenoceptors and 5-HT\(_4\) receptors in the atrial myocyte with changes at the receptors or their coupling to G-proteins. Whether this would increase the importance of serotonin as an arrhythmogenic factor in patients taking beta-blockers is unknown.

A unique feature of serotonin as an arrhythmogenic agent is that it is stored in platelets and released during platelet aggregation. This may have particular relevance to atrial arrhythmias since platelet activation and thrombus formation may occur in dilated atria secondary to structural heart disease. The aggregating platelets release serotonin, which stimulates further aggregation, through platelet 5-HT\(_{2A}\) receptors. Platelet-released serotonin might provoke arrhythmic atrial contractions and the subsequent development of atrial fibrillation. The resultant stasis of blood in the fibrillating atria may be associated with further platelet aggregation, with the possibility that serotonin-mediated effects may perpetuate the atrial arrhythmia. It has been suggested that the positive inotropic effect of serotonin on atria may be detrimental, increasing the likelihood of thrombus being dislodged by atrial contraction with resultant embolic stroke [2], but this may be less of a likelihood in the fibrillating atrium.

In the light of these new data to support the arrhythmogenic actions of serotonin on human atrium, what is the evidence that it is of clinical importance in patients with atrial fibrillation? A case has been made to support serotonin-related arrhythmia [2]. Patients with carcinoid syndrome have high circulating levels of serotonin, which is released together with other vasoactive compounds from the carcinoid tumour, and have an increased incidence of atrial arrhythmias, including atrial fibrillation. However, valvular disease is common in carcinoid syndrome and contributes to the risk of atrial fibrillation. Cisapride, a gastrointestinal prokinetic agent, is a partial 5-HT\(_4\) agonist in the human atrium and has been associated with tachycardia [11], but the incidence is low, and was not confirmed by others [12]. Metoclopramide is also a weak partial agonist and can cause tachycardia but the mechanism is unproven. Thus, the role of serotonin in the development of atrial fibrillation remains an intriguing hypothesis, which will require the continued development of potent 5-HT\(_4\) receptor antagonists, and their evaluation in clinical studies, before it is proven.

References