

5-Hydroxytryptamine and Atrial Fibrillation: How Significant is This Piece in the Puzzle?

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Serotonin and Atrial Fibrillation. 5-Hydroxytryptamine, a recent addition to the list of hormonal triggers for atrial fibrillation (AF), may play a pivotal role in the induction of AF related not only to cardiac surgery but also to acute coronary syndromes, valvular heart disease, cardiomyopathies, alcoholism, aging, and conducting tissue disease. This review examines the supporting laboratory and clinical evidence and provides a comprehensive insight into the basic underlying mechanisms involved. It also delves into the potential benefits and limitations of 5-HT₄ antagonists in the prevention and management of this arrhythmia. (*J Cardiovasc Electrophysiol*, Vol. 14, pp. 209-214, February 2003)

atrial fibrillation, 5-hydroxytryptamine, arrhythmia

Introduction

The serendipitous observation that atrial fibrillation (AF) could be successfully treated was arguably made almost 300 years ago, when chincona bark was used to treat malaria and was also noted to correct irregular heartbeat.¹ This most common of arrhythmias currently affects an estimated 2.3 million Americans² and continues to be responsible for significant morbidity and mortality.³ This is a reflection of the complex, heterogeneous, and challenging nature of AF. In humans, the atria are subject to numerous different insults, and the final endpoint is AF. Furthermore, the longer this arrhythmia is present, the more resilient it is to reversal due to anatomic, electrical, and histologic remodeling.⁴⁻⁶ The multiple factors involved in the pathogenesis of AF act either independently or in concert, and a recent addition to this list of factors is 5-hydroxytryptamine (5-HT; serotonin). As early as the 1950s, infusion of 5-HT into humans was known to produce a myriad of unpredictable cardiovascular responses.^{7,8} A sinus tachycardia was consistently induced, and bizarre atrial arrhythmias occasionally were triggered. Over the last decade, significant advances have been made in deciphering and understanding serotonergic mechanisms, not only in the cardiovascular system but also in the central nervous system and gastrointestinal tract. This review concentrates on the serotonergic regulation of the human atria, exploring the chronotropic, inotropic, and lusitropic effects; the basic mechanisms underlying these actions; and a possible explanation for the existence of such a system in humans. The review explains how this system may be more of a hindrance than a benefit, especially in the generation of atrial arrhythmias, particularly AF. It also provides a brief overall view of the role of 5-HT in the regulation of the cardiovascular system as a whole.

Serotonin, Serotonergic Receptors, the Cardiovascular System, and the Human Atria

Serotonin is a fast-acting, small-molecule, indoleamine neurotransmitter that is produced and secreted by serotonergic neurons in the central and enteric nervous systems in humans. It is synthesized by the hydroxylation of the amino acid tryptophan by tryptophan hydroxylase to 5-hydroxytryptophan, which is decarboxylated to 5-HT by aromatic amino acid decarboxylase. Following synthesis, 5-HT is stored in small vesicles in nerve terminals prior to being released. Once released, 5-HT is metabolized by monoamine oxidase (MAO) present in the intestine, liver, and mitochondria in the cytoplasm of serotonergic neurons. 5-HT is also taken up by circulating blood platelets; thus, although platelets do not synthesize 5-HT, they can store and release 5-HT when activated.

Over the last several years, molecular cloning techniques have revealed a vast diversity among 5-HT receptors. These receptors are classified according to their *structural* (primary amino acid sequence), *transductional* (second messenger coupling), and *operational* or *recognitory* (pharmacologic) characteristics.^{9,10} Seven distinct serotonergic receptor classes have been recognized (5-HT₁ to 5-HT₇), each encoded by a separate gene. Furthermore, the 5-HT₁, 5-HT₂, 5-HT₄, and 5-HT₅ classes currently consist of five (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), three (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), four (5-HT_{4A}, 5-HT_{4B}, 5-HT_{4C}, 5-HT_{4D}), and two (5-HT_{5A}, 5-HT_{5B}) subclasses, respectively. The 5-HT_{1C} subclass has been reclassified as the 5-HT_{2C} subtype.⁹ Some of these subclasses are themselves encoded by separate genes, others by variable expression of exon lengths leading to splice variants (e.g., 5-HT₄¹¹ and 5-HT₇¹²). All but one 5-HT receptor subclass, namely, 5-HT₃, belong to the G-protein coupled or seven transmembrane-spanning receptor family.¹⁰ 5-HT₃ receptors are directly coupled to ligand-gated cation channels. It is noteworthy that the existence of receptor (sub)types 5-HT_{1E/1F}, 5-HT_{5A/B}, 5-HT₆, and 5-HT₇ has been generated from molecular biologic techniques, and there are no known agonists/antagonists for them. As such, their functional responses, except coupling to adenylyl cyclase, have yet to be elucidated.⁹ Furthermore and more importantly, different 5-HT receptor subtypes are responsible for similar effector responses across the species barrier. Hence, extreme caution

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must be exercised when extrapolating the operational characteristics derived from other animal species to humans.

Serotonergic regulation of the cardiovascular system as a whole is complex. It involves both central and peripheral mechanisms acting through the numerous receptor subtypes. Centrally mediated mechanisms involve the regulation of autonomic tracts in the brainstem and midbrain by serotonergic neurons originating in the higher centers. Serotonergic neurons located in the raphe obscurus and raphe pallidus project to the autonomic areas of the lower brainstem and spinal cord, whereas forebrain areas involved in cardiovascular regulation receive their serotonergic input from the dorsal raphe.¹³⁻¹⁵ This central regulation of the cardiovascular system is executed predominantly through 5-HT_{1A} (sympathoinhibitory and vagal bradycardia) and 5-HT₂ (sympathoexcitatory) receptor subtypes.¹⁶ Stimulation of 5-HT_{1A} receptors produces a vasopressor and bradycardic effect, which results from a combination of central sympathetic activity inhibition and central stimulation of the vagus nerve. On the other hand, stimulation of central 5-HT₂ receptors results in vasoconstriction and tachycardia due to increased sympathetic discharge.

Peripherally, numerous serotonergic receptors and receptor subtypes modulate a range of cardiovascular functions, including vasoconstriction, vasodilation, platelet aggregation, and positive inotropic, lusitropic, and chronotropic effects. The receptor subtype 5-HT_{1D} has been implicated in vasoconstriction, and its agonist sumatriptan is used in the prevention and treatment of migraine. 5-HT_{1D} receptors have also been identified in human coronary vessels,¹⁷ especially those affected by atheroma,^{18,19} and they likely play a significant role in angina; hence, 5-HT_{1D} receptor agonists such as sumatriptan are contraindicated in patients with atheromatous coronary artery disease. The 5-HT_{2A} receptor antagonist ketanserin offered great promise for the treatment of hypertension,²⁰ but despite its effectiveness at lowering blood pressure it was withdrawn due to its propensity to proarrhythmia. Whether ketanserin's effect of lowering blood pressure is due to its effects on the 5-HT₂ receptor has always been debatable. Ketanserin also has α_1 -adrenoreceptor blocking properties, central sympathoinhibitory properties, and direct vasodilatory properties.²¹ No other selective 5-HT₂ receptor antagonist (e.g., ritanserin and mianserin) effectively lowers blood pressure.²¹ On the other hand, 5-HT₂ receptors play an important role in 5-HT reuptake and platelet aggregation. 5-HT₃ receptors require a special mention, because these unique ligand-gated cation channel receptors are present on human afferent vagal nerve endings and are responsible for the von Bezold-Jarisch reflex in humans.²² This consists of an initial hypotensive response to 5-HT, an effect that results from an abrupt and transient bradycardia (and the consequent decrease in cardiac output) following stimulation of 5-HT₃ receptors on afferent cardiac vagal nerve endings.

In humans, positive inotropic, chronotropic, and lusitropic effects on the atrial myocardium are mediated through 5-HT₄ receptors. The presence of a 5-HT receptor within the human right atrium was first demonstrated in 1989.²³ Subsequent studies on similar right atrial appendage tissue, excised during coronary artery bypass surgery, revealed that this receptor bears a marked resemblance to the rodent cerebral 5-HT₄ receptor.²⁴ Furthermore, 5-HT₄ receptors with characteristics similar to those in the right atrium were found in the left atria of patients with terminal heart failure.²⁵ The exact na-

ture of human sinoatrial 5-HT receptors through which the tachycardia response is mediated is still unknown; however, ample evidence suggests that it is highly likely they are also 5-HT₄ in nature.²⁶ First, in the porcine model, 5-HT induces a tachycardia through receptors that are very similar to human atrial 5-HT₄ receptors.²⁷ Second, in isolated piglet sinoatrial tissue^{28,29} and human atria,²⁴ 5-HT₄ receptors have the same order of potency for agonists and a similar order of antagonist affinity.²⁸⁻³⁰ Finally, cisapride, which is a partial 5-HT₄ receptor agonist for both porcine sinoatrial node²⁸ and human right atrium,²⁴ can also cause sinus tachycardia in humans, presumably through this mechanism.³¹⁻³³

Like the majority of other 5-HT receptors, 5-HT₄ receptors in human atrial tissue are coupled to G_s proteins, and stimulation causes an increase in contractile force and accelerates the onset of muscle relaxation via increased cyclic adenosine monophosphate (cAMP) levels and cAMP-dependent protein kinase A (PKA) activity³⁴ (Fig. 1). Patch clamp atrial myocyte experiments have demonstrated that this increased contractile force is a result of phosphorylation of membrane-bound and sarcolemmal L-type Ca²⁺ channels (i_{CaL}) by PKA leading to increased atrial cytoplasmic ionized calcium.³⁵ The role of PKA is obligatory in this process.³⁵ The hastened onset of atrial relaxation produced by 5-HT has been attributed to PK-dependent phosphorylation of phospholamban

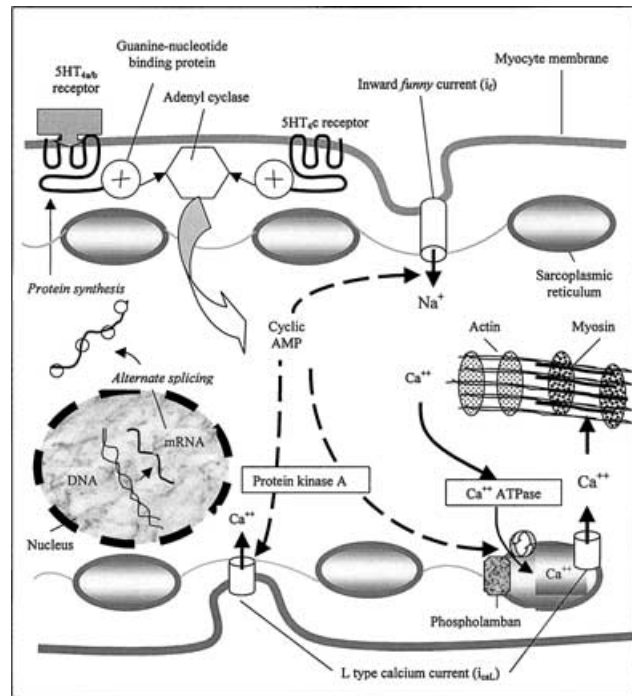


Figure 1. Physiology of 5HT₄ receptor stimulation in cardiac myocytes and its possible role in the generation of atrial arrhythmias. Alternate splicing results in expression of three variants of the 5HT₄ receptor: 5HT_{4a}, 5HT_{4b}, and 5HT_{4c}. Although 5HT_{4a} and 5HT_{4b} isoforms require agonist stimulation, it appears that 5HT_{4c} demonstrates basal constitutive activation to cause a rise in the level of cAMP. cAMP in turn stimulates hyperpolarization-activated "funny" currents (i_f), and protein kinase A activity. Protein kinase A leads to phosphorylation of both L-type Ca²⁺ channels (i_{CaL}) leading to increased cytoplasmic ionized Ca²⁺ and phospholamban, which hastens the onset of atrial relaxation by the resultant acceleration of Ca²⁺ capture by the sarcoplasmic reticulum and/or desensitization of the contractile proteins to Ca²⁺.

and/or troponin I, followed by the resultant acceleration of calcium capture by the sarcoplasmic reticulum and/or desensitization of the contractile proteins to Ca^{2+} .³⁴

Until recently, one exciting observation had been that 5-HT₄ mRNA had not been detected in human ventricular tissue.^{36,37} This implied that any 5-HT₄ receptor antagonists developed would be atrium specific and free of ventricular proarrhythmia. However, Bach et al.³⁸ have demonstrated that 5-HT₄ mRNA is detectable in human ventricular tissue acquired from two patients. Nonetheless, this does not explain why 5-HT did not modify the L-type Ca^{2+} (i_{CaL}) current in human ventricular myocytes or cause positive inotropic effects in ventricular trabeculae when investigated by Jahnel et al.³⁹ Furthermore, there is no record of 5-HT infusions or any experimental 5-HT agonist ever inducing ventricular arrhythmias. Thus, the mere presence of mRNA does not automatically imply translation and expression through a protein product. In addition, gene expression is subject to activation/deactivation depending on genetic predisposition and environmental factors. Clearly, the role of human ventricular 5-HT₄ mRNA requires further investigation.

Finally, following 5-HT₄ receptor stimulation, desensitization of the atrial myocardium occurs to a lesser extent than that reported at other 5-HT₄ receptor sites.⁴⁰ Differences in the potential phosphorylation sites in the sequences of the 5-HT₄ receptor isoforms may account for this finding.¹¹

5-HT₄ Receptors and AF

Theoretically, 5-HT-induced cardiac arrhythmias, particularly AF, can be initiated not only through stimulation of 5-HT receptors peripherally but also through central serotonergic mechanisms. However, at present there is very little direct evidence that the central serotonergic neuronal input upon the autonomic nervous system and its sympathoinhibitory/sympathoexcitatory and provagal influences are involved in the generation of cardiac arrhythmias. In addition, most of the observations of the effects of central serotonergic neurons are based upon a variety of different animal species, and extrapolating these findings to humans should be undertaken with caution.

Peripherally, cardiac arrhythmias can be generated by stimulation of 5-HT₃ receptors on vagal afferents⁴¹ and atrial arrhythmias by stimulation of 5-HT₄ receptors on atrial myocytes.^{40,42} Ventricular arrhythmias have been reported secondary to administration of ketanserin, which is a well-known antagonist of the rapid component of the delayed rectifier K^+ current (i_{Kr}) that prolongs QT,⁴³⁻⁴⁵ but as mentioned earlier it is also a 5-HT₂ receptor antagonist.⁴⁶ There is some evidence that 5-HT₂ receptors play little or no role in ventricular arrhythmias generated by ketanserin.⁴⁷

The mere existence of 5-HT₄ receptors in the human atria begs the teleologic question as to why they exist. It appears that like many other systems in the human body, these receptors may represent a hormonal backup mechanism for dysfunction of the intracardiac conducting system and/or its autonomic influences. Dysfunction of either of these systems invariably generates various bradyarrhythmias leading to hemostasis, platelet activation, and aggregation. In the human cardiovascular system, 5-HT is released from the *dense granules* in activated platelets contributing to vasoconstriction and platelet aggregation as part of the normal physiologic hemostatic process. Platelets activated within the hu-

man atria in response to bradyarrhythmias would have positive inotropic, chronotropic, and lusitropic effects by stimulating 5-HT₄ receptors. How much protection this system offers asymptomatic patients with conducting tissue disease is unknown. There is little doubt, however, that this system could be more of a hindrance than a benefit. There is in vivo, in vitro, and clinical evidence that stimulation of 5-HT₄ receptors, in addition to causing sinus tachycardia, can trigger atrial arrhythmias including AF.

First, in the early 1950s, direct infusion of 5-HT into humans was noted to trigger bizarre atrial arrhythmias.^{7,8} Second, in isolated human atrial tissue, 5-HT has been shown to induce rate-dependent arrhythmic contractions through 5-HT₄ receptors, particularly in tissue that has been subjected to chronic β -adrenoreceptor blockade.⁴² Third, using rapid atrial pacing to induce atrial flutter and fibrillation in pigs, Rahme et al.⁴⁸ demonstrated that the 5-HT₄ antagonist RS-100302 terminated atrial fibrillation/flutter in the majority of cases and prevented reinduction of sustained tachycardia in all animals. Fourth, the partial 5-HT₄ receptor agonist cisapride, in addition to inducing sinus tachycardias as mentioned earlier, has been reported to induce other supraventricular tachycardias in humans.^{32,33} It is noteworthy, however, that cisapride is also a known antagonist of the rapidly activating delayed rectifier K^+ current (i_{Kr}) and well documented to be responsible for QT prolongation and ventricular arrhythmias.^{49,50} Finally, the clinical association between AF and advancing age, hypertension, ischemic heart disease, valvular heart disease, cardiomyopathies, and coronary artery bypass grafting is well established.³ In all of these conditions except one, there is an abundance of evidence demonstrating that both platelet handling and metabolism of 5-HT are altered. With advancing age, not only is 5-HT uptake by platelets more rigorous⁵¹ and platelet 5-HT levels higher,^{52,53} but platelet sensitivity to 5-HT and hence their tendency to degranulate also are increased.^{52,54} In hypertensive patients, on the other hand, platelet 5-HT levels are decreased⁵⁵⁻⁵⁹ due to a combination of increased release from,^{55,59} and reduced uptake by, platelets.^{57,59} Consequently, plasma serotonin levels in hypertensive patients are higher compared with normotensive controls.^{55,59} In valvular heart disease, sheer stress leads to platelet activation^{60,61} and undoubtedly an increase in plasma 5-HT levels. Similarly, in cardiomyopathies, stasis and turbulence lead to platelet aggregation and would be expected to increase platelet 5-HT release and plasma 5-HT levels, although this has not been formally demonstrated in any study. In acute coronary syndromes, there is platelet activation and increased 5-HT levels across the coronary vascular bed.⁶² A pathogenic role for 5-HT has been implicated in vasospastic angina.⁶³ About 30% of all patients undergoing coronary artery bypass grafting develop AF, usually within 5 days of the procedure.^{64,65} This is a much higher proportion than can be accounted for by existing underlying ischemic heart disease, hypertension, or left ventricular dysfunction. The exact reasons for this finding are unknown.⁶⁴ It is possible that platelet activation and release of 5-HT play the crucial role. Even in alcohol dependency, where the association with AF is well established, there is deranged storage and 5-HT handling by platelets.⁶⁶ Furthermore, diurnal variations in paroxysmal AF are well documented⁶⁷ and previously have been attributed to circadian variation in autonomic activity⁶⁸; however, 5-HT also may be implicated. Not only does platelet aggregation exhibit diurnal variation,⁶⁹ but so do

platelet 5-HT uptake and platelet 5-HT levels.⁷⁰ It has been postulated that the influence of melatonin upon the 5-HT uptake mechanism is responsible for this phenomenon.⁷¹

The case for 5-HT in the pathogenesis of AF across a whole range of different laboratory-based and clinical conditions is overwhelming. However, experience with a low incidence of AF in carcinoid syndrome indicates that elevated plasma levels of 5-HT is only half the story. The other part is the atrial myocardium and expression of 5-HT₄ receptors, not just as a whole, but also of its various subtypes and their affinities to 5-HT under different clinical conditions. However, apart from the observations that up to four different 5-HT₄ receptor isoforms may be expressed in human atrial tissue,³⁷ little information is available on the effects of aging and various other clinical conditions on their expressions and affinities.

The underlying mechanisms involved in 5-HT-mediated AF are similar to other hormonal triggers of AF, namely, catecholamine or excess thyroxine induced.⁷² Two processes have been proposed in attempt to explain the electrophysiopathologic basis of any form of AF. First, from the observation that AF often is initiated or preceded by an atrial extrasystole as determined by ECG evidence, the *focal mechanism theory* proposes that enhanced automaticity in one or more rapidly depolarizing foci within the atria are responsible for AF. Histologically, cardiac muscle cells with preserved electrical properties extend into the pulmonary veins, the predominant site for such enhanced focal automaticity.^{73,74} Foci of enhanced automaticity also occur in the right atrium and infrequently in the superior vena cava or coronary sinus.⁷³⁻⁷⁵ Numerous factors such as autonomic nervous system activity, atrial ischemia, atrial stretch, anisotropic conduction, aging, and fibrosis can be responsible for the generation of such automatic foci.

The second *reentrant circuit theory* of AF proposes that the existence of one or more reentrant circuits within the atria are responsible for AF.^{76,77} Moe et al.^{76,77} proposed that wavefronts of electrical activity fractionate as they propagate through the atria and result in self-perpetuating "daughter wavelets." An increase in the number of these daughter wavelets increases the propensity for continuation of AF. The number of these daughter wavelets is influenced by (1) shortening of atrial effective refractory period (ERP) and increased dispersion of the ERP (ERP_{DISP})^{4,78-80}; (2) decrease in conduction velocity^{79,81}; and (3) increased atrial size or mass.^{79,81}

The 5-HT₄ receptor stimulation in the human atria may trigger focal atrial extrasystoles by calcium overload leading to induction of AF. Various studies have demonstrated that overloading cardiac myocytes with Ca²⁺ can be associated with the generation of arrhythmias,^{82,83} which are thought to be due to generation of Ca²⁺-dependent delayed afterdepolarizations resulting in triggered action potentials.⁸⁴ Pino et al.⁸⁵ also demonstrated that 5-HT₄ receptor stimulation increases the pacemaker (I_f) current in human atrial myocytes via the cAMP pathway. This effect can lead to shortening of atrial ERP and increased dispersion of atrial ERP, which might be responsible for the arrhythmogenic potential of 5-HT in the human atrium. Finally, the effect of 5-HT₄ receptor stimulation on the inward *ultrarapid* component of the delayed rectifier K⁺ current (I_{Kur}) is unknown. These channels are specific to the human atria and are under strong adrenergic influence.^{86,87} As such, they are likely to be affected by sero-

tonin producing atrial-specific effects including arrhythmias, which may be inhibited by potential 5-HT₄ antagonists.

Once initiated by whatever mechanism (5-HT related or another), AF also may be maintained by 5-HT. Ample evidence exists that AF leads to platelet activation.^{88,89} This is a result of irregular atrial wall motion,⁹⁰ endothelial damage,⁹¹ and/or reduced plasma adenosine levels⁹² seen in AF. This leads to 5-HT release and stimulation of 5-HT₄ receptors in the atria, potentially perpetuating the fibrillation. However, the altered expression of the various 5-HT₄ receptor isoforms could be pivotal in this process. Blondel et al. demonstrated that the human 5-HT₄ receptor subtype (c) exhibits basal constitutive activation of adenylyl cyclase resulting in an increased basal cAMP level³⁷. Furthermore human 5-HT₄ receptor isoforms (a) and (b) express similar basal constitutive activation of adenylyl cyclase when over expressed³⁷.

The discovery of 5-HT₄ receptors in the human atria and their possible role in arrhythmia generation has led to the development of a number of 5-HT₄ receptor antagonists.⁹³ Theoretically, such agents could influence management in all cases of atrial arrhythmias where the onset is associated with platelet activation, including acute coronary syndromes, conducting tissue disease, cardiomyopathies, and valvular heart disease. However, the presence of a number of other contributing variables in these conditions, such as hyperadrenergic drive and electrical/histologic remodeling of the atria, means that the overall therapeutic benefit of 5-HT₄ receptor antagonists in these settings is likely to be minimal. The biggest impact of these agents probably will be in the prevention and management of postoperative AF, particularly after cardiac surgery. Use of these agents would eliminate undesirable side effects such as negative inotropism and chronotropism associated with other antiarrhythmic drugs used in this setting. 5-HT₄ receptor antagonists may prove to be a welcome addition to our current arsenal of antiarrhythmic drugs, especially if the risk of ventricular proarrhythmia is confirmed to be negligible.

The excitement surrounding the potential benefits of 5-HT₄ receptor antagonists has been to the detriment of 5-HT₄ receptor agonists. Such agents have the potential to be effective not only in symptomatic sinus bradycardias and certain conducting tissue diseases but also in the clinical minefield of autonomic dysfunction and vasovagal syncope. However, the proarrhythmic potential of such agents through their effects on the *funny* (I_f) current, the L-type calcium current (I_{CaL}), and their potential effect on the inward *ultrarapid* component of the delayed rectifier K⁺ current (I_{Kur}) means they are unlikely to become available for clinical use in the short to medium term. Nevertheless, such compounds still can provide invaluable information about the distribution, functions, and affinities of the different 5-HT₄ receptor subtypes.

Conclusion

The account of the role of 5-HT in the initiation and maintenance of AF outlined here provides a most plausible development to our understanding of the causes of AF; however, a number of important questions remain unanswered. First, what the exact distribution of 5-HT₄ receptors across the entire human myocardium? Second, what is the exact nature of these 5-HT₄ receptor subtypes, and what impact does aging and other factors predisposing to AF have on their expression and affinities? Third, what effect, if any, do the changes in

5-HT₄ receptor and/or isotype expression have on anatomic, electrical, and ionic remodeling? Finally, like all the other contributing factors to AF, what is it about the atrium that renders certain individuals susceptible to the influence of 5-HT? This account highlights that not all the underlying mechanisms responsible for AF have been resolved. Furthermore, for every possible contributing factor, a thorough understanding of the basic science is essential for maximal clinical impact. The war against AF may be 300 years old, but there appears to be no shortage of new battlefronts over which to try and make a real impact. With an ever-aging population in the West and the prediction that the prevalence of AF is likely to increase 2.5-fold in the next 50 years,² such that between 5.0 and 6.3 million Americans will likely be affected by 2050, no effort should be spared in the attempt to win this war.

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