# Association between Atrial Fibrillation and Adenosinergic System

Subjects: Cardiac & Cardiovascular Systems

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Atrial fibrillation (AF) is a multifactorial sustained cardiac arrhythmia, and it is now considered a real worldwide public health issue. Despite the substantial progress that has been made in the detection and management of AF, the underlying molecular mechanisms associated with the onset of atrial fibrillation and its progression remain still unclear. Among these molecular mechanisms, the implication of the adenosinergic system in AF has increased, since the accumulation of experimental data suggests that the increase in the adenosine blood level and the remodeling expression of the adenosine receptors might be part of the AF pathophysiology. Unfortunately, the adenosinergic system still has a Janus face in cardiac arrythmias, since adenosine can have both antiarrhythmic or proarrhythmic actions, along with adenosine receptors, which can lead to either profibrotic or antifibrotic effects.

adenosine adenosine receptors atrial fibrillation arrhythmia

## 1. Adenosinergic System Signaling

### 1.1. Metabolism of Adenosine

Since Drury and Szent-Györgyi first observed the cardiac effect of adenine compounds in 1929 [1] and Burnstock proposed the concept of extracellular purinergic signaling in 1972 [2], adenosine has emerged as an important signaling molecule with pleiotropic actions, including effects on the cardiovascular system [3][4][5]. This ubiquitous purine nucleoside comes mainly from ATP dephosphorylation when tissue energy requirements increase, such as during hypoxia, ischemia or inflammation [5]. The methionine cycle can contribute to intracellular adenosine formation in the heart by the hydrolysis of S-adenosylhomocysteine [6]. However, ATP hydrolysis is considered the main source of adenosine secondary due to the extracellular dephosphorylation cascade of ATP by the successive action of a membrane-anchored ectonucleoside triphosphate diphosphohydrolase-1 (CD39) and the ecto-5'-nucleotidase (CD73) [7][8][9] (**Figure 1**).

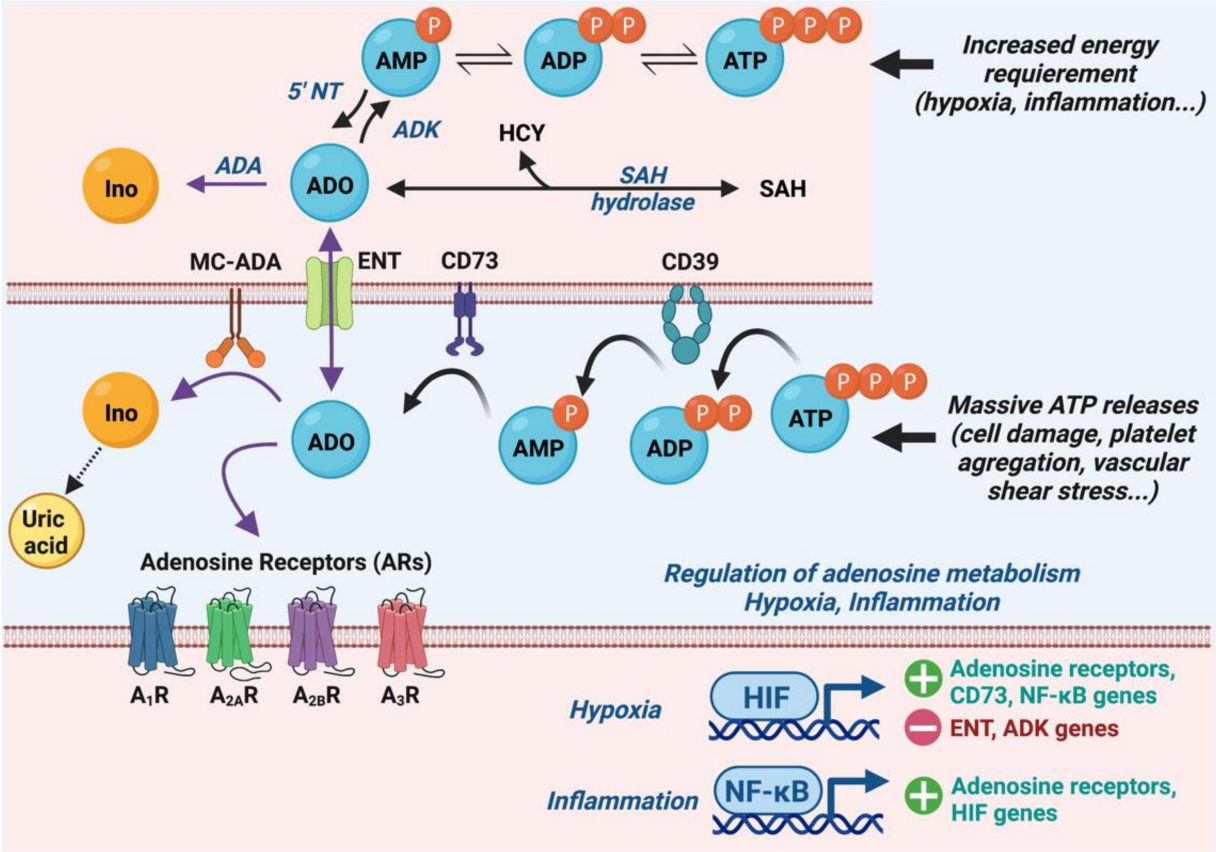


**Figure 1.** Adenosine metabolism. The sources of intracellular adenosine (ADO) come partly from the methionine cycle by the hydrolysis of S-adenosylhomocysteine (SAH) and mainly from the ATP dephosphorylation cascade when cellular energy requirement increases. Massive extracellular release of ATP produces adenosine by the consecutive actions of ectonucleoside triphosphate diphosphohydrolase-1 (CD39) and ecto-5'-nucleotidase (CD73). Adenosine can bind to adenosine receptors (ARs), but it is also reuptake by equilibrative nucleoside transporters ($ENT_{1–2}$) and rephosphorylated by adenosine kinase (ADK). Adenosine is catabolized by adenosine deaminase (ADA) into inosine (Ino) and, finally, joins uric acid metabolism. Hypoxia and inflammation increase the expression of adenosine receptors and the production of extracellular adenosine: HIF promotes the transcription of adenosine receptors and CD73 and NF-kB genes and represses ENT and ADK genes; NF-κB promotes the transcription of adenosine receptors and HIF genes. ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; HCY: homocysteine; HIFs: hypoxia-inducible transcription factors; MC-ADA: mononuclear cell ADA; NF-kB: nuclear factor-kappa B.

## 1.2. Adenosine Receptors and Their Cardiac Effects

Adenosine receptors are subdivided in four G protein-coupled receptors, named $A_1$ ($A_1R$), $A_{2A}$ ($A_{2A}R$), $A_{2B}$ ($A_{2B}R$) and $A_3$ ($A_3R$) receptors, which are classified according to their primary sequence, their associated G-protein and their pharmacological profile (binding affinity of agonists and antagonists) [10][11]. $A_1R$ and $A_3R$ are coupled to the Gi/o proteins leading to the inhibition of adenylyl cyclase (AC), whereas $A_{2A}R$ and $A_{2B}R$ are associated to Gs proteins, which stimulate the adenylyl cyclase and increase the intracellular production of cyclic-AMP (cAMP). $A_1R$

and $A_{2A}R$ have a high affinity for adenosine with a higher binding affinity of $A_1R$. $A_{2B}R$ and $A_3R$ have a lower affinity for adenosine [11][12].

Adenosine receptors are widely distributed in various cells and tissues, including the cardiovascular system [13][14]. All four adenosine receptors have been described in the heart, with distributions varying regionally. Their activations by adenosine have major effects on cardiac function by modulating the sympathetic tone and the conductance of potassium and the calcium current [14][15]. Cardiac $A_1R$ is highly expressed in the atrial myocardium, the sinoatrial node (SAN), the atrioventricular node (AVN) and the His–Purkinje system and presynaptically on adrenergic nerve varicosities but have a lower expression in ventricular myocytes [16]. The activation of $A_1R$ by adenosine induces direct negative chronotropic and dromotropic effects [17] and an indirect anti-β-adrenergic action which can antagonize the positive inotropic effect of catecholamines [18][19][20] (**Figure 2**).

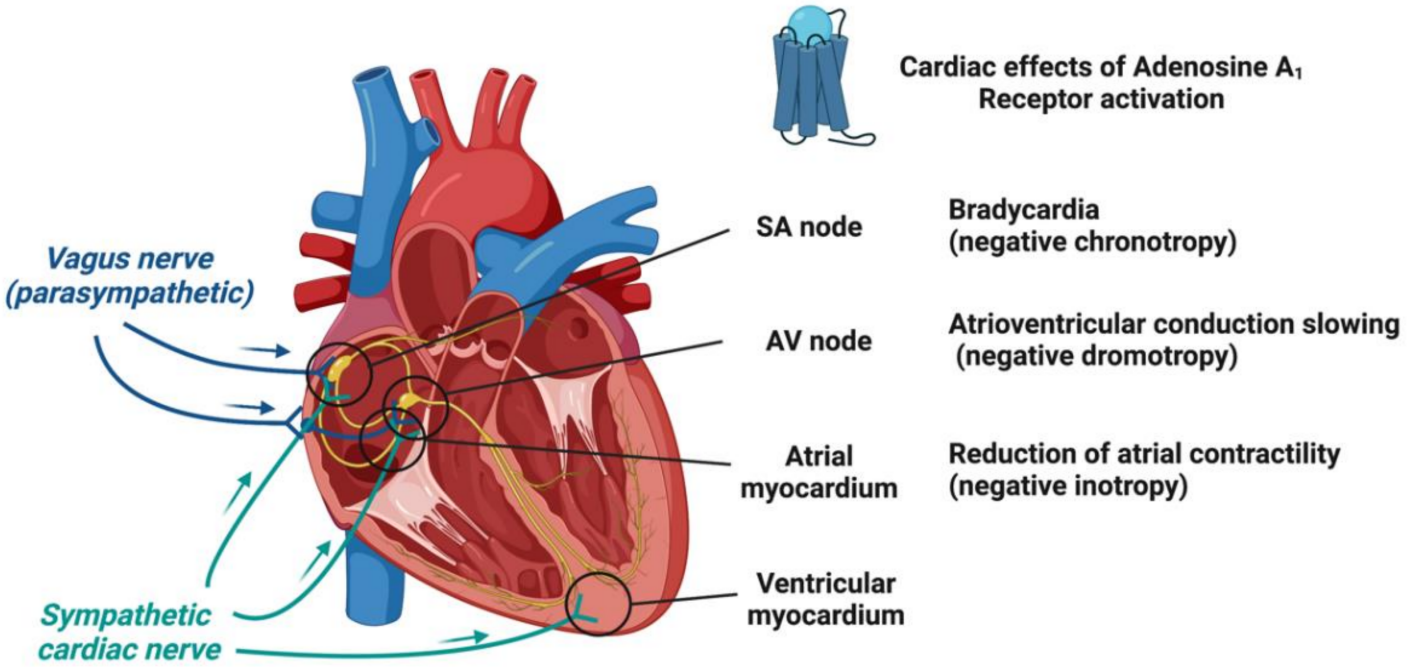


**Figure 2.** Cardioprotective effects of adenosine $A_1$ receptors' activation. Stimulation of the $A_1$ receptors induces bradycardia (negative chronotropy) on a sinoatrial node (SA node), atrioventricular conduction slowing (negative dromotropy) on an atrioventricular node (AV node) and reduced atrial cardiomyocyte contractility (negative inotropy).

## 1.3. Molecular and Ionic Bases of Adenosine Effects in Cardiac Electrophysiology

The electrophysiological action of adenosine in the heart is regionally variable and dependent on the underlying ionic current population, which differ between species [21]. Irrespective of the species, adenosine exerts its cardiac electrophysiological actions mainly through the modulation of potassium, sodium and calcium currents by cardiac $A_1$ and $A_{2A}$ receptors' activation [22][23].

### 1.3.1. Effects of Adenosine on Ionic Currents

Adenosine is believed to induce a cAMP-dependent (indirect effects) anti-β-adrenergic action by a dual mechanism: the activation of the presynaptic $A_1R$ limits the release of norepinephrine [24] and the activation of postsynaptic $A_1R$ blocks the effects of catecholamines by inhibiting adenylyl cyclase activity and then reducing intracellular cAMP levels. This indirect effect subsequently decreased the catecholamine-induced calcium inward current through L-type calcium channels (ICa,L) [25] and the sodium inward current ("funny" current (If) or pacemaker current) through hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [26].

The activation of $A_1Rs$ enhances the IK,Ado thanks to G-protein-coupled, inwardly rectifying K+ (GIRK) channels [27]. After the Gi-protein activation, the $G_i\alpha$ subunits enhance the gating of the GIRK channels, in the same manner as acetylcholine on the muscarinic-2 receptor, which causes a vagally mediated negative chronotropy upon on atrial pacemaker activity [27][28]. The GIRK channels aim to maintain the potassium equilibrium potential (EK+ = −90 mV) and modulate its conductance according to the membrane potential. As other inward rectifiers, they conduct larger inward currents when the membrane potential is negative to the EK+ than outward currents when the membrane potential is positive to EK+ [29][30][31].

On the contrary, like other $G_S$-protein coupled receptors, $A_{2A}R$ stimulation can activate a cAMP-dependent pathway modulating $Ca^{2+}$ handling. However, the precise mechanism of the $A_{2A}R$-induced transduction signal remains controversial. Indeed, some authors report that the stimulation of $A_{2A}Rs$ by a specific agonist (i.e., CGS 21680) did not alter the cAMP level in rat ventricular cardiomyocytes [32], whereas, more recently, others showed that CGS 21680 increased the cAMP content in ventricular cardiomyocytes of transgenic mice overexpressing human $A_{2A}R$ [33].

In the canonical $Ca^{2+}$-dependent pathway, the PKA-dependent phosphorylation might increase the activation of L-type $Ca^{2+}$ channels (LTCC) initiated by membrane depolarization. Following LTCC opening, the inward $Ca^{2+}$ current (ICa,L), in turn, triggers a $Ca^{2+}$-induced $Ca^{2+}$ release (CIRC) from the sarcoplasmic reticulum via the phosphorylated cardiac ryanodine receptors (RyR2) and which is responsible for numerous spontaneous $Ca^{2+}$ release events ($Ca^{2+}$ spark and $Ca^{2+}$ waves) during systole [34][35]. This can lead to the positive inotropic effect of $A_{2A}R$ stimulation in atria and ventricles through the $Ca^{2+}$-induced myofibrilla contraction responsible for the cardiac electromechanical coupling [36]. The structural organization of cardiomyocytes into specific microdomains (i.e., cardiac dyads) favors this cardiac excitation–contraction coupling [37][38]. This is supported by the regional variation of the phosphorylation state of the LTCC [39] and the expression and the activity of the $Ca^{2+}$ handling proteins [38][39][40].

Therefore, the effects of adenosine in the nodal cells (i.e., SAN and AVN), the conductive tissues and in the working myocardium are largely based on the modulation of adenylate cyclase activity, which induces cAMP-dependent PKA signaling, leading to $Ca^{2+}$ handling protein phosphorylation, and to a GIRK-induced potassium outward current (IK,Ado) (**Figure 3**).

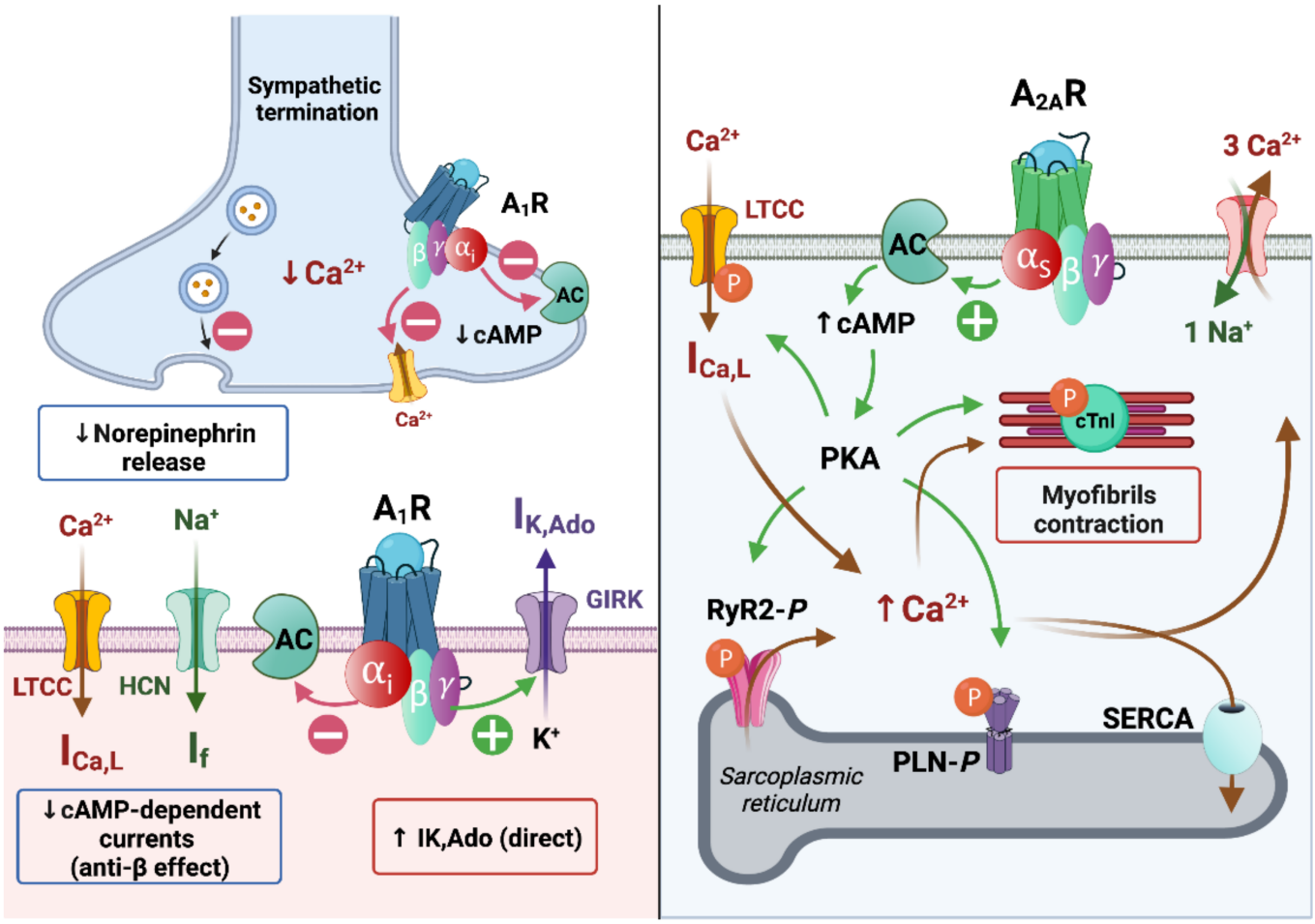


**Figure 3.** Adenosine receptors signaling (**right**: $A_1R$; **left**: $A_{2A}R$). Prejunctional $A_1R$ activation limits the norepinephrine release. Complementarily, $A_1Rs$ reduce the increased adrenergic-induced cAMP elevation and the cAMP-dependent currents (I funny, ICa,L). The main effect of $A_1R$ activation is mediated through GIRK-induced outward K+ current (IK,Ado). $A_{2A}R$ activation increases cAMP and, consequently, activates the PKA. PKA phosphorylates L-type $Ca^{2+}$ channels (LTCC) inducing an inward $Ca^{2+}$ current (ICa,L). Ryanodine receptors' (RyR2) phosphorylation by the PKA allows for the $Ca^{2+}$-induced $Ca^{2+}$ release from the sarcoplasmic reticulum. Cardiac troponin I phosphorylation and cytosolic $Ca^{2+}$ sparks trigger the myofibrils' contraction during systole. During diastole, the phosphorylation of phospholamban (PLN) permits the SERCA to pump $Ca^{2+}$ into the sarcoplasmic reticulum. The $Na^+$: $Ca^{2+}$ exchanger extrudes $Ca^{2+}$ allowing for diastolic relaxation. AC: adenylyl cyclase; cTnI: cardiac troponin I; PKA: protein kinase A.

### 1.3.2. Adenosine Effects on the Action Potential in Nodal Cells and Working Cardiomyocytes

The action potential of the sinoatrial node cells is characterized by a more depolarized (−60 mV) and more labile resting membrane potential than contractile cardiomyocytes due to the almost lack of Kir2-encoded inwardly rectifier potassium currents (IK1) [41][42]. After a previous action potential, when the membrane potential reaches the maximum diastolic membrane potential, the HCN channels' opening allows for the inward Na+ "funny" current (If), which contributes to the automaticity. This spontaneous diastolic HCN-mediated depolarization drives the membrane potential to the action potential threshold (~−40 mV) [43]. This threshold triggers the opening of voltage-

dependent L-type $Ca^{2+}$ channels, which induce a low slope of depolarization (phase 0). Lastly, while the $Ca^{2+}$ channels close, the rapid and slow delayed rectifier current (IKr, IKs) induces outward $K^+$ currents, which are responsible for the repolarization (**Figure 4**A).

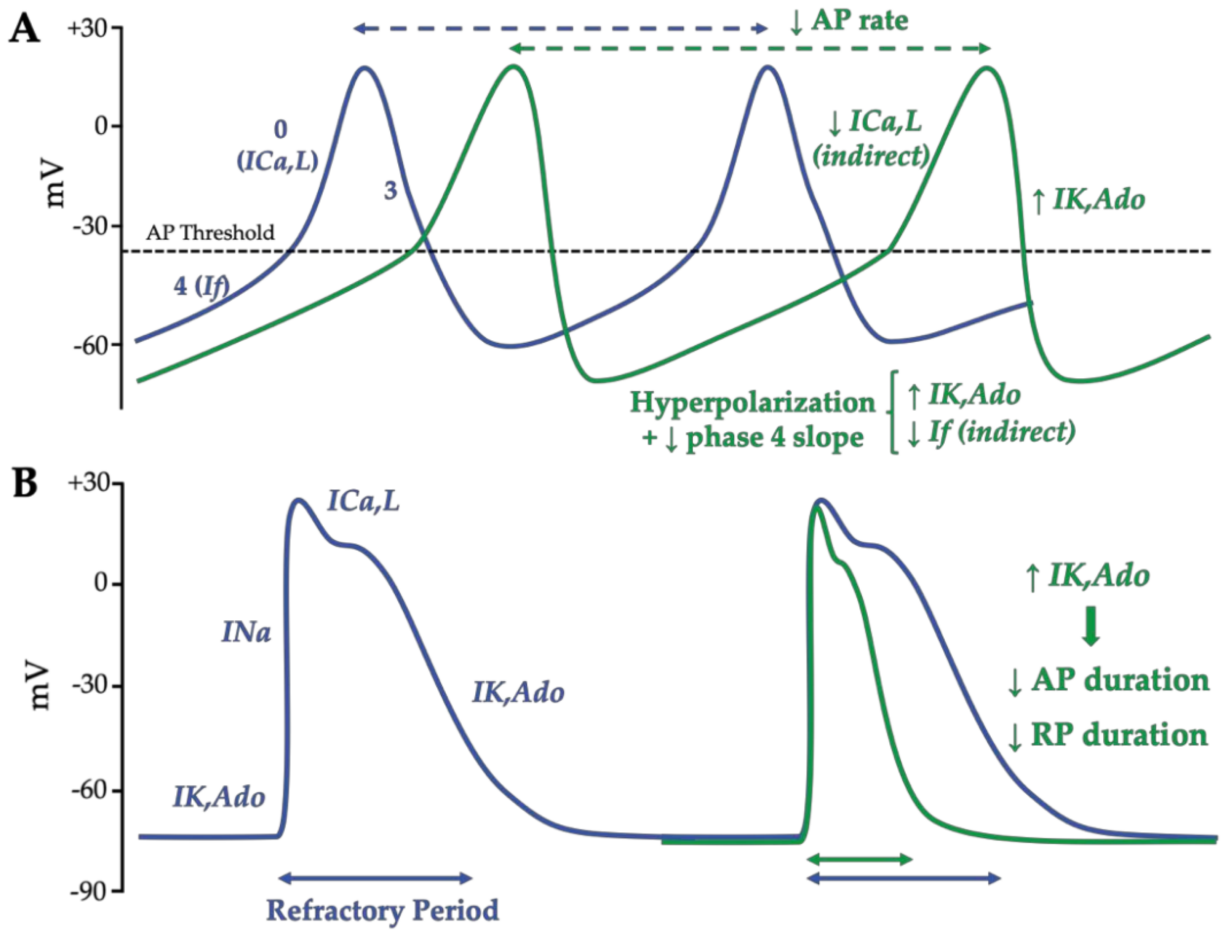


**Figure 4.** Illustrations of the effects of adenosine on action potential in a sinoatrial cell (**A**) and atrial cardiomyocyte (**B**). In a sinoatrial node, adenosine increases the outward IK,Ado current, which induces hyperpolarization and reduces the slope of the diastolic depolarization. Complementarily, adenosine reduces indirectly the inward $Na^+$ pacemaker current (If) and the inward $Ca^{2+}$-dependent depolarization through L-type $Ca^{2+}$ channels (ICa,L). Adenosine incudes negative chronotropy. On an atrial working myocardium, adenosine increases the outward $K^+$ current (IK,Ado) and shortens the action potential duration and the refractoriness, thereby adenosine can reduce atrial contractility. Dotted arrows correspond to the corresponding RR intervals. Solid arrows correspond to the corresponding action potential refractory period.

Conversely to nodal cells, atrial and ventricular myocardium are fast response cardiac tissues with $Na^+$-dependent depolarization (INa) through the voltage-gated sodium channels $Na_v1.5$ [44]. The initiation of the atrial action potential is permitted by a rapid inward $Na^+$ current (INa), followed by an inward $Ca^{2+}$ current due to the opening of L-type $Ca^{2+}$ channels (ICa,L), which finally close during repolarization, while inward rectifier K+ channels open (**Figure 4**B).

# 2. Pathophysiology of Atrial Fibrillation

Atrial fibrillation (AF) is the most common pathologic tachyarrhythmia, defined by the absence of distinct repeating P-waves, irregular atrial activations on surface ECGs and irregular R-R intervals. At the beginning, episodes of sinus rhythm are punctuated by periods of arrhythmia (paroxysmal AF). AF progression leads to more frequent and longer episodes until they last more than 7 days (persistent AF). After one year, in the absence of spontaneous or medical cardioversion, which allow a return to sinus rhythm, AF is then considered as a “long-standing persistent” AF. Finally, AF can be defined as a “permanent” AF when the therapeutic attitude is to consider that no further attempts to control sinus rhythm will be undertaken [45].

The pathophysiology of AF is supported by anatomical and electrophysiological changes in atria for which all of the exact molecular mechanisms are still unknown. Understanding of this complex AF pathophysiology is essential to identify the underlying molecular mechanisms. According to the Coumel triangle, AF pathophysiology first depends on trigger factors, which are rapid focus firing activity, initiating the arrhythmia. Then, the arrhythmogenic substrate are electrophysiological, mechanical and anatomical characteristics of the atria that sustain AF. Further, multiple neuro-humoral dynamic modulators also interfere with the initiation, progression and termination of AF. Therapeutic targets for a rhythm control strategy should consider all aspects of this classification [46].

## 2.1. Atrial Fibrillation Triggers

Repeated atrial ectopias are known to initiate AF and are considered as triggers of AF [47]. They can be localized within the pulmonary veins (PVs) and, less frequently, in others atrial areas (non-PV triggers). Among patients affected by AF, 20% of them exhibit non-PV foci [48], which can be predicted by female gender (odds ratio: 2.00), left atrial enlargement (odds ratio: 2.34) and AF episode prolongation [49][50]. Mapping studies have identified and localized a discrete clustered anatomical area corresponding to non-PV foci in the inferior mitral annulus, the posterior left atrium, the interatrial septum particularly at the fossa ovalis/limbus region, the crista terminalis and Eustachian ridge, the coronary sinus, and the superior vena cava [50].

PV ectopias originate all along the myocardium sleeve of PV and present unpredictable firing with various, intermittent and delayed conduction to the left atrium. They are defined as focal discrete sites of early and centrifugal activation [51]. Compared to the atrial cells, the PV cardiomyocytes have specific action potential properties that predispose to arrhythmogenesis [52]. Indeed, PV cells have a higher resting membrane potential, a lower amplitude of the action potential, a smaller maximum phase 0 upstroke velocity and a shorter action potential duration (**Figure 5**).

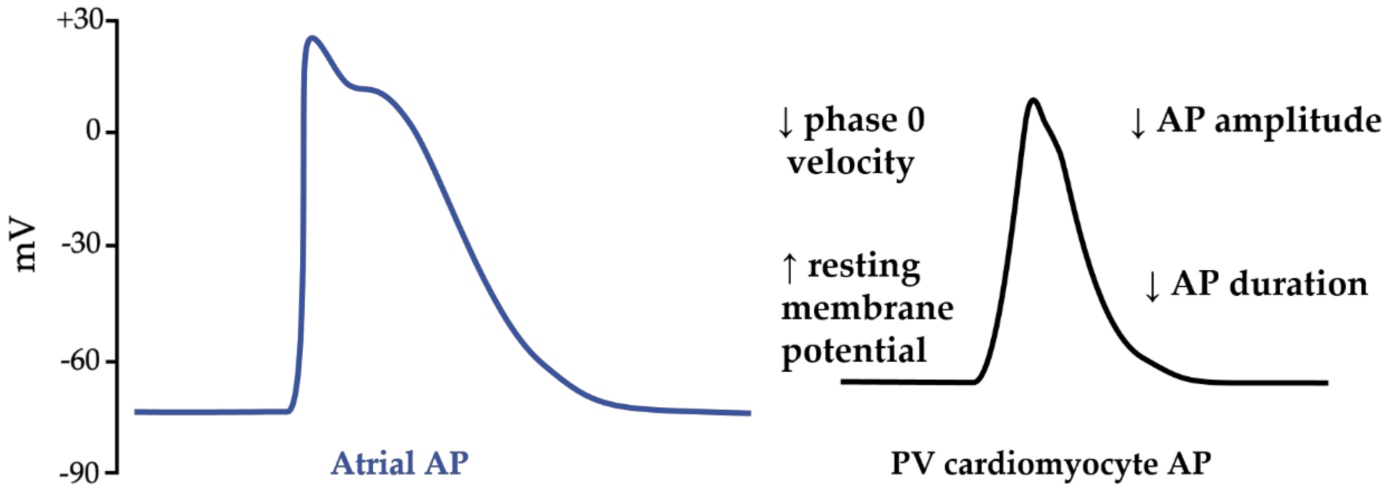


**Figure 5.** Schematic illustration of differences between action potentials (APs) in atrial cardiomyocytes and in pulmonary vein (PV) cardiomyocytes. Action potential of PV cardiomyocytes have a more depolarized resting membrane potential, a lower AP amplitude, a smaller maximum phase 0 upstroke velocity and a shorter action potential duration compared to atrial AP.

## 2.2. Mechanisms of AF Perpetuation

Two major mechanisms of perpetuation supported by anatomical and/or electrophysiological changes are described by the multiple wavelets hypothesis [46][53] and the localized (focal or reentrant) AF drivers.

The multiple-wavelet phenomenon hypothesizes that multiple random wavefronts propagate through the atria until depolarizable tissue is available. Secondary to AF, atrial enlargement increases the critical atrial mass that is required to self-perpetuate this mechanism [54]. Within a same critical atrial mass, a short refractory period and delayed conduction velocities increase the theoretical number of wavelets.

AF drivers are defined as a localized source of fast and repetitive activity during AF episodes from which activation propagates and breaks down into fibrillation of the rest of the atria [55]. The drivers are considered to be focal when the wavefront activation originates from a focal site with centrifugal activation and as reentrant when the waves fully and continuously rotate around an anatomical or functional pivot point [56]. As ectopias, because of the electrophysiological characteristics of PV cells and the brutal change in PV orientation fiber, the drivers are mostly located in the PV antral and adjacent regions [56][57]. With a longer AF duration, the complexity of the AF drivers increases, and they are located at extra-PV sites [56].

Anatomical reentries are defined by the presence of an unidirectional slow conduction area or block resulting in a fixed cycle length and localization circuit. Atrial fibrosis favors these slow conduction areas [58]. The nonuniform anisotropic conduction within a fibrosis area is an important substrate for reentrant tachycardia [53]. Functional reentries are defined by an absence of an underlying substrate and/or anatomical obstacle. **Figure 6** illustrates the formation of a functional reentrant circuit due to the heterogeneity of the atrial potential duration at the PV junction.

Then, the functional reentry can be schematized as a central refractory area maintained by centripetal waves moving around [59] or a propagation of spiral wave reentry or “rotor” around a core area at which the depolarization and the repolarization curves join each other [60].

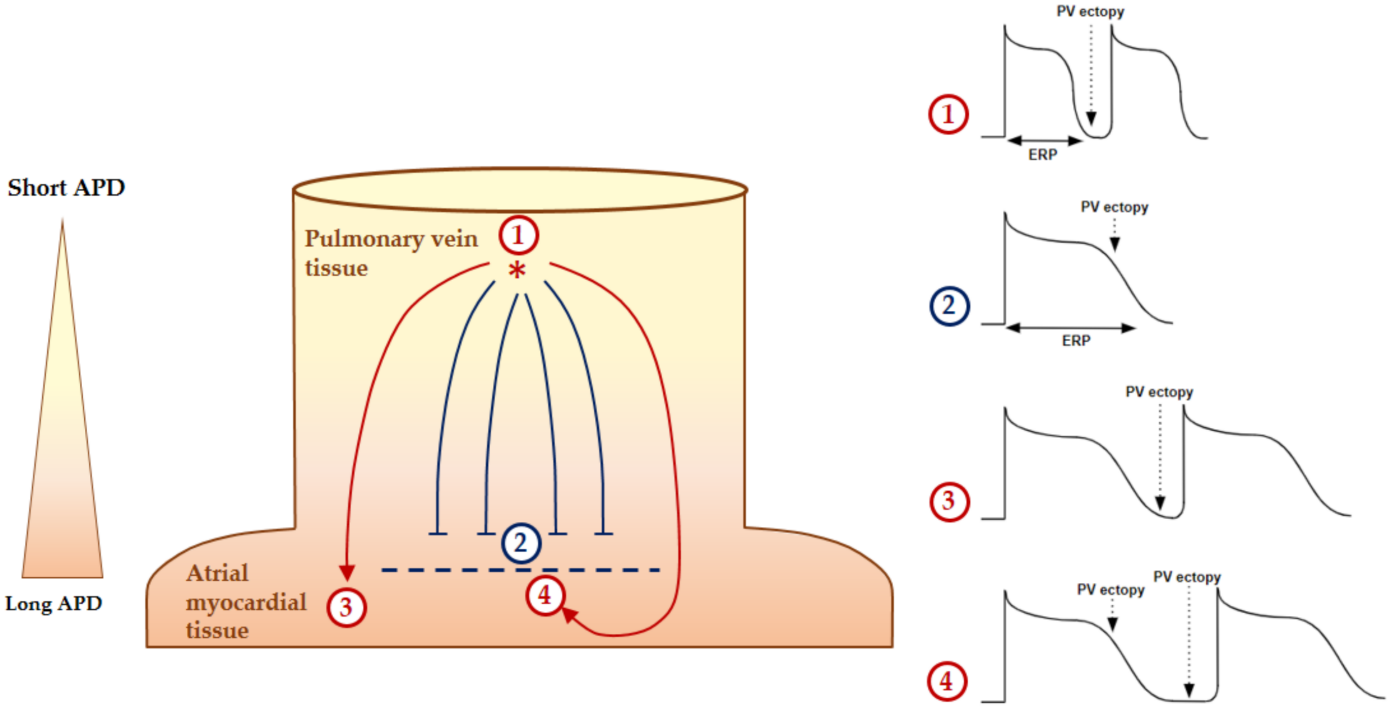


**Figure 6.** Formation of a functional reentrant circuit due to the heterogeneity of the atrial potential duration at the pulmonary vein (PV) entrance. The delay after depolarization in area no. ① initiates a PV ectopy within the PV sleeve, where the action potential duration (APD) is shorter, with a subsequently shorter effective refractory period (ERP) and propagates toward the PV junction where the APD is longer. The ectopic beat blocks are in area no. ② because of the refractory tissue. However, the impulse propagation continues laterally until the APD tissue is out of the refractory time (area no. ③.). Finally, the PV ectopic beats move around the functional refractory area and then across the previous refractory region of the block in area no. ④, which is now out of the refractory time. The dotted line represents the functional unidirectional refractory area, the solid arrows represent the propagation of the action potential and the star represents the initiation of the ectopic focus.

## 2.3. Substrate of Atrial Fibrillation and Atrial Cardiomyopathy

The AF perpetuation is caught in a vicious circle. The triggers and perpetuation mechanisms are dependent on multiple underlying electrical remodeling and atrial fibrosis which are also induced by AF. This vicious circle is supported by the fact that a complete electrical reverse remodeling occurred within weeks after medical or electrical cardioversion [61][62]. Then, the structural alterations can also partially or completely reverse within months after cardioversion [61][62].

Atrial cardiomyopathy has been defined as “any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations” [63].

Thus, any initial electrostructural changes secondary to AF should be considered as an atrial cardiomyopathy. As a consequence, AF should be considered as a risk factor of atrial cardiomyopathy. All other atrial aggressions (i.e., diabetes, hypertension, aging, heart failure, valvular diseases, amyloidosis, granulomatosis and inflammatory infiltrates) primarily responsible for atrial changes, such as fibroblast or noncollagen deposits, are risk factors of AF.

### 2.4. Pejorative Modulators of Atrial Fibrillation

The onset and the termination of AF episodes are likely related to dynamic modulators, which interact with both the trigger and substrate of AF. They exhibit multiple timescales and sites of action, including immediate and long-term electrophysiological atrial changes, ion channel conductance and homeostasis, and local and general inflammation status as well as fibrosis promotion [64]. Nonexhaustive modulators of AF are the autonomic nervous system, obstructive sleep apnea, electrolytes and plasma glucose levels, gastroesophageal reflux disease, ischemia, inflammation, thyroid diseases and advancing age [64].

## 3. Arrhythmogenic Effects of the Adenosinergic System

### 3.1. Adenosine Level and Expression of Adenosine Receptors in AF Patients

High adenosine plasma levels have been found in the left atria of patients during episodes of paroxysmal AF and in persistent AF [65]. The adenosine plasma concentrations then normalized after spontaneous or electrical cardioversion in sinus rhythm [65]. Moreover, the adenosine plasma concentrations in peripheric blood circulation were also higher in permanent AF compared to paroxysmal AF and controls [65]. The high adenosine plasma concentrations could be attributed to peripheral hypoxemia caused by the decrease in the left ventricular output in AF [65][66].

A high adenosine plasma concentration could also be a consequence of energy use in specific underlying cardiovascular conditions, including hypertension [67][68], chronic heart failure [69][70] or vagal syncope [71][72]. These are especially known to be AF risk factors. Interestingly, AF initiation has been described during the strong release of adenosine or the use of extrinsic adenosine injection [73][74].

### 3.2. Implication of $A_1$ Receptors in AF

In Langendorff preparation of rat hearts, the injection of a specific $A_1R$ agonist (CCPA) produced a profound negative chronotropic effect, whereas the selective $A_1R$ antagonist (PSB36) produced a nonsignificant positive chronotropic effect [75]. The increased concentration of both agonist and antagonist produced runs of repetitive atrial ectopy. This clinical effects appears to be mainly driven by a shortening of the action potential and effective refractory period durations, resulting in an increasing AF susceptibility due to the $A_1R$ activation [75]. Indeed, the activation of $A_1R$ through IK,Ado modulation induces a resting membrane potential hyperpolarization, a reduction of the action potential duration and a shortened effective refractory period (ERP) on atrial cardiomyocytes [27] (**Figure 7**).

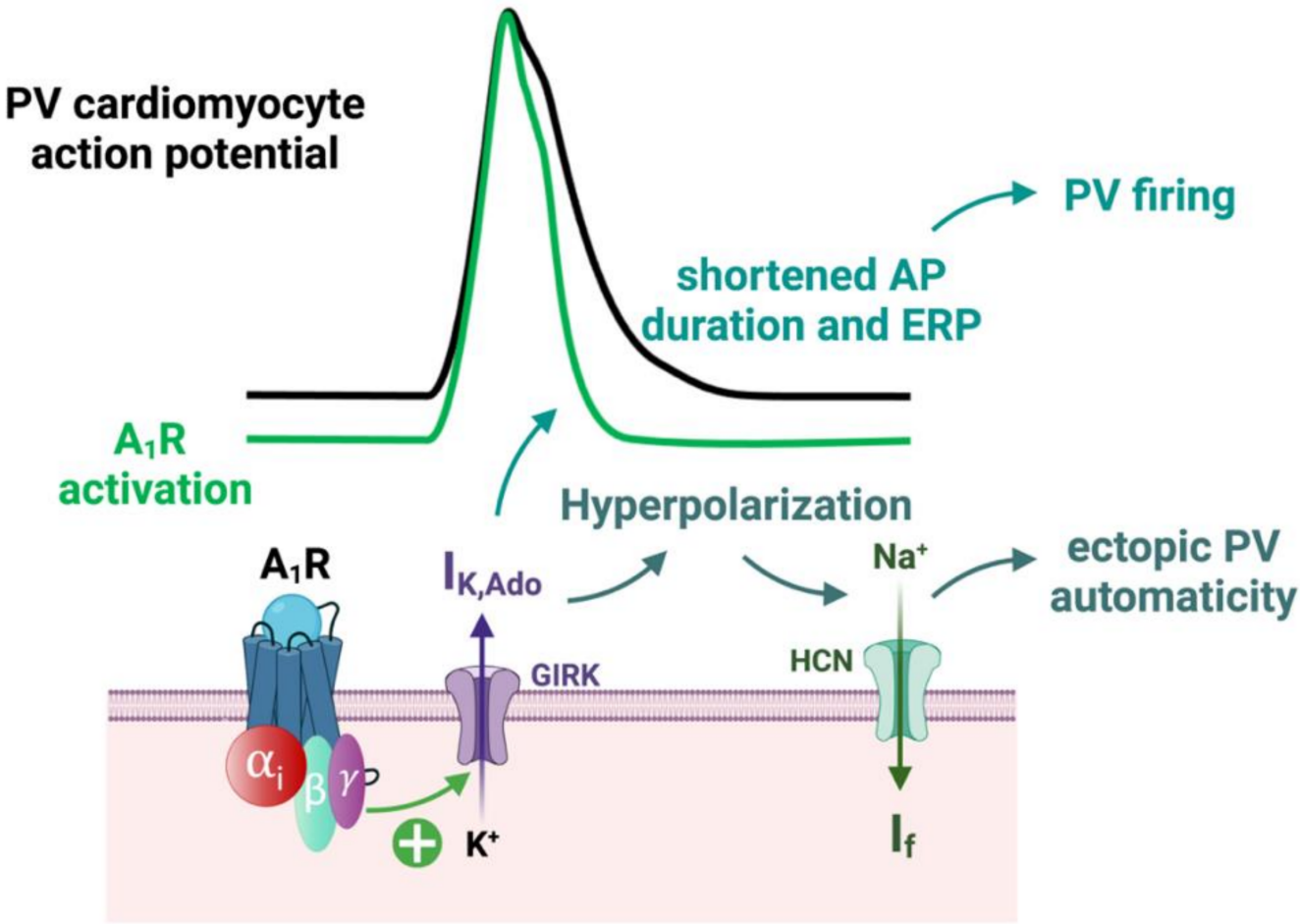


**Figure 7.** Effects of $A_1R$ activation by adenosine on pulmonary vein (PV) action potential (AP). AP: action potential; ERP: effective refractory period; PV: pulmonary vein. In PV sleeves of AF patients, $A_1R$ activation opens GIRK channels, which are responsible for an outward potassium current (IK,ADO). This current shortens the atrial AP duration and effective refractory period (ERP). This enhanced PV firing follows PV ectopy. Furthermore, the outward potassium current is also responsible for a resting membrane potential hyperpolarization which reactivates the If current, increasing PV automaticity.

## 3.3. Implication of AR in the Remodeling of Calcium Handling

In atrial cardiomyocytes, a reduced L-type $Ca2^+$ current (ICa,L) density [76] and increased spontaneous $Ca^{2+}$ release from the sarcoplasmic reticulum through the ryanodine receptor [77] are implicated in the cytosolic $Ca^{2+}$ overload responsible for delayed afterdepolarization (DAD), which promotes AF [78][79]. These effects on calcium remodeling are consistent with adenosine receptor signaling. Despite $A_1R$ activation inducing a c-AMP-dependent decrease in ICa,L, it has limited or no effect on the action potential duration [80]. Indeed, most studies report the major role of $A_{2A}R$ in $Ca^{2+}$ handling remodeling in AF.

## 3.4. Modulation of Atrial Fibrosis by $A_{2B}$ Receptors

The activation of $A_{2B}R$ has an important role in cardiac fibroblast homeostasis, but the role of $A_{2B}$ in fibrosis is controversial, since both profibrotic [81][82][83][84] and antifibrotic effects are reported [85][86][87][88][89]. In cardiac fibroblasts, the increase in cAMP production following $A_{2B}R$ activation plays an essential role in the inhibition of angiotensin-II-induced collagen production [86]. However, activation of the $A_{2B}R$ increases the production of collagen and increases the release of IL-6 in human cardiac fibroblasts, resulting in a profibrosis state [84][90].

## 4. Association between Atrial Fibrillation Risk Factors and the Adenosinergic System

Dysregulation of the autonomous nervous system are characterized by an excessive sympathetic activation, and a diminished parasympathetic influence is central to the pathogenesis of cardiovascular diseases, including heart failure, hypertension and AF [71]. Combined sympatho-vagal activation reflects the equilibrium between the release of epinephrine/norepinephrine, which activate the adrenergic receptors, and the release of acetylcholine, which induces the activation of the muscarinic receptors.

Atrial sympathetic innervation is controlled by adrenergic receptors, which are divided into three major subfamilies: α1-, α2-, and β-adrenergic receptors. They are all coupled to different classes of heteromeric G proteins. The α1 and α2 receptors are coupled to Gq/11 and Gi/o, respectively. β-Adrenergic receptors are coupled to Gs. The α1 and α2 receptors induce a strong extracellular ATP release, while the β-adrenergic receptors activate cAMP production [7]. The activation of the β-adrenergic receptors by isoproterenol leads to the phosphorylation of nonjunctional RyR2 and L-type $Ca^{2+}$ channels (LTCC) and is responsible for large increases in the $Ca^{2+}$ flux [38]. Interestingly, after the use of an $A_{2A}R$ agonist, the increase in the heart rate was attenuated by a β-blocker. Thus, Wragg et al. demonstrated a direct activation of the sympathetic nervous system by $A_{2A}R$ stimulation [91].

In parallel, atrial parasympathetic innervation is controlled by muscarinic receptors ($M_2Rs$). As with $A_1R$ stimulation, $M_2R$ activation leads to the opposite effect on β-adrenergic stimulation. The $M_2R$ stimulation activates inhibitory G proteins, subsequently reduces the activity of the HCN and LTCC and leads to decreased automaticity and conduction velocity in the nodal cell. $M_2R$ also activates the GIRK channel responsible for hyperpolarization [92].

Sympathovagal activation is a strong modulator of AF. Interestingly, hypertension, sleep apnea and heart failure are known to induce sympathetic tone activation and specific atrial remodeling [45][93][94][95][96]. Moreover, all three AF risk factors also induce specific adenosinergic system remodeling. Especially in patients suffering from essential hypertension, an $A_{2A}R$ overexpression was described in PBMCs [68]. Because of the vasodilator effect of $A_{2A}R$, it was hypothesized that the $A_{2A}R$ overexpression was a compensatory mechanism of high blood pressure [96]. However, the chronic release of adenosine in the peripheral cardiovascular system during high blood pressure may also induce atrial remodeling of adenosine receptors. In the same manner, in sleep apnea or heart failure, the associated hypoxia may contribute to the atrial adenosinergic system's remodeling and induce a pro-arrhythmogenic environment.

As the $A_1$R stimulation induces GIRK activation, the question remains whether $A_1$R remodeling and its activation by adenosine can also contribute to arrhythmogenic effects through a similar pathway.

The stimulation of the adrenergic and parasympathetic tone alone or combined can predispose to the AF onset [97]. Sequential combined stimulations had a synergic effect rather than vagal or sympathetic drive alone [97]. Interestingly, heart rate variability analyses before the occurrence of AF showed that AF patients have specific sympathetic and parasympathetic patterns [98]. Furthermore, prolonged atrial pacing in dogs induced sympathovagal activation and increased the risk of AF. Interestingly, the cryoablation of both autonomic nerves prevents the occurrence of AF [99]. However, the exact interaction between the adenosine receptors and cardiac autonomic innervation, as facilitator or inhibitor, is still unclear.

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