β-Adrenergic Stimulation

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β-adrenergic receptor stimulation (β-ARS) is a physiological mechanism that regulates cardiovascular function under stress conditions or physical exercise, producing a positive inotropic (enhanced contraction), lusitropic (faster relaxation), and chronotropic (increased heart rate) effect.

Keywords: β-adrenergic receptor stimulation ; mathematical modelling ; cardiac electrophysiology ; cardiomyocyte

1. Introduction

β-adrenergic receptor stimulation (β-ARS) is a physiological response mechanism that plays a fundamental role in the regulation of cardiomyocyte activity, producing a positive inotropic (enhanced contraction), lusitropic (faster relaxation), and chronotropic (increased heart rate) effect. Such a multifactorial response is triggered via the activation of the β-adrenergic receptors by the sympathetic nervous system, under either stress conditions or physical exercise, and is also known as the “fight-or-flight” response.

β-adrenergic receptors were first described by Lands et al. in the late 1960s [1][2]. They are situated on the cardiomyocyte membrane and react to different neurotransmitters (norepinephrine, epinephrine) and drugs (isoprenaline). When binding with the adrenergic receptor takes place, it starts a reaction cascade where different cellular substrates become phosphorylated, affecting their individual roles in the overall excitation–contraction coupling. As a result, under healthy physiological conditions, the cardiac action potential shortens, while the intracellular calcium transient exhibits an increased amplitude and a faster decay rate as the main manifestations of β-ARS at the cellular level [3][4]. However, the large number of components involved in the β-adrenergic cascade, and the complexity of these subcellular processes and interactions, make β-ARS signalling highly sensitive to cellular changes and to pathological perturbations. As a result, β-ARS plays a main role in a considerable number of heart diseases [5], and it is well established as an important contributor to cardiomyocyte arrhythmogenicity [6][7][8].

In particular, the β-ARS response has direct effects on the ion channels and pumps of the cell membrane (and, therefore, on intracellular ionic concentrations) regulating calcium intake, intracellular calcium handling, calcium extrusion, and cellular repolarisation. Impairments in the balance between these carefully orchestrated processes can affect heart function and render its constituent cardiomyocytes susceptible to proarrhythmic events, such as early and delayed afterdepolarisations (EADs and DADs, respectively). Such afterdepolarisations under β-ARS are common proarrhythmic manifestations in isolated cardiomyocytes from patients of different pathologies, especially those characterised by action potential and calcium transient abnormalities (such as hypertrophic cardiomyopathy [9], long QT syndrome [10][11], or catecholaminergic polymorphic ventricular tachycardia [12]). An overstimulated β-ARS response is also one of the main mechanisms of cardiac hypertrophy, coronary artery disease, or stroke events [13]. The overexpression of the β-adrenergic response has also been linked to the onset of cardiac hypertrophy or the generation of fibrotic tissue [14][15]. The appearance of these structural changes can lead to the creation of re-entry pathways in myocardial tissue, which also contribute to the generation of self-sustained arrhythmias. Induced arrhythmias are also a common manifestation in heart failure. In chronic heart failure, cardiac remodelling at the structural level can affect the pathways involved in the β-ARS response [16]. As a result, the inotropic response of cardiomyocytes to β-ARS is reduced [17][18], while the propensity to arrhythmogenic events increases. β-adrenergic response is also affected by ageing, and an age-dependent impairment between β-ARS and cardiac function has been demonstrated in both healthy and failing hearts [19][20]. β-ARS is altered as well in severe congenital heart disease patients [21]. Finally, recent studies also suggest a hyperactivation of the positive response of β-ARS patients with coronavirus disease 2019 (COVID-19), potentially leading to life-threatening arrhythmic events [22][23].

Refined knowledge of the role that each cellular component has within the β-ARS cascade, and of the consequences that may arise from disturbing its normal functioning, can therefore lead to a better understanding of different pathologies, as well as to the development of new pharmacological targets for their treatment. In these cases, mathematical modelling

and simulation studies of β-ARS can be useful tools for investigating the mechanisms mediating arrhythmic events, assessing their multiscale consequences from the subcellular up to the organ levels, and designing effective treatments [24]. Here, we review the main roles of β-ARS in cellular cardiac electrophysiology, placing our emphasis on the description of the existing mathematical frameworks available for its representation and how insights obtained through experimental approaches have been integrated into these mathematical formulations.

2. Mathematical Models of β-ARS

Several mathematical formulations, with varying degrees of complexity and physiological detail, have been proposed to date to describe different aspects of β-ARS in cardiac myocytes. In particular, special attention has been given to the modelling of β-ARS in mammalian ventricular electrophysiology, while studies on atrial electrophysiology are considerably lagging. **Table 1** summarises the main β-ARS computational frameworks discussed in this section as landmark studies underlying the foundation of these modelling efforts.

In general terms, cardiac myocytes present three different subtypes of β-adrenergic receptors (β-AR): β1-AR, β2-AR, and β3-AR [25], the former two being the most prevalent and important. Many of the existing mathematical models of β-ARS describe the binding of an agonist, usually isoproterenol (ISO), to β1-AR and β2-AR and the subsequent phosphorylation cascade. In particular, the binding with β-ARs activates the receptor-bound stimulatory G protein, which enhances the production of 3′-5′-cyclic adenosine monophosphate (cAMP), activating protein kinase A (PKA). PKA phosphorylates key cellular substrates that affect the functioning of several channels and ion pumps. The main targets located on the sarcolemma are the L-type calcium channels (I_{CaL}) [26], slow delayed rectifier potassium (I_{Ks}) channels [27], fast sodium current (I_{Na}) channels [28], the cystic fibrosis transmembrane conductance regulator (I_{CFTR}) [29][30], and the sodium–potassium pump (I_{NaK}) [31]. At the subcellular level, PKA also phosphorylates the ryanodine receptors (RyRs) and phospholamban (PLB) [26][32], both located on the sarcoplasmic reticulum, as well as troponin I (TPNI) [33], myosin binding protein-C [33], and titin [34], these located on the myofilaments. A graphical representation of the main PKA phosphorylation cascade is presented in **Figure 1**.

Table 1. Landmark studies in the mathematical modelling of β-ARS in cardiac electrophysiology.

Model (Year)	Species	β-ARS Isoform	Signalling	Substrates	Main Model Advances
Zeng and Rudy [35] (1995)	Guinea Pig	Generic	None	I_{CaL}; I_K; PLB; I_{NaK}; I_{Na}	Simulation of the isoproterenol effect by increasing conductances and parameter shift
Saucerman et al. [36] (2003)	Rat	β1	cAMP; PKA	I_{CaL}; PLB	Dynamic target phosphorylation integrated with cell signalling
Greenstein et al. [37] (2004)	Dog	Generic	None	I_{CaL}; PLB; I_{Kr}; I_{Ks}	Introduction of a binary population-based approach for target phosphorylation
Iancu et al. * [38] (2007)	Guinea Pig	β1	cAMP	N/A	Cellular signalling compartmentation
Soltis & Saucerman [29] (2010)	Rabbit	β1	cAMP; PKA	I_{CaL}; I_{Ks}; PLB; RyR; TnI; I_{CFTR}	Integration with dynamic CaMKII regulation
Hiejman et al. [39] (2011)	Dog	β1, β2	cAMP; PKA	I_{CaL}; I_{Ks}; I_{Kur}; PLB; I_{NaK}; I_{Na}; RyR; TnI	Two different β isoforms; population-based approach with four different populations
Bondarenko [40] (2014)	Mouse	β1	cAMP; PKA	I_{CaL}; I_{Na}; I_{NaK}; RyR; I_{Kur}; I_{to}; I_{K1}; PLB; TnI	Compartmentalised mouse model with new L-type calcium channel subpopulations
Khalilimeybodi et al. * [41] (2018)	Mouse	β1, β2	cAMP; PKA; GSK3β; ERK	N/A	Addition of new molecular signalling pathways (GSK3β and ERK)

* Models focused only on signalling (not directly considering substrate phosphorylation). N/A: not applicable.

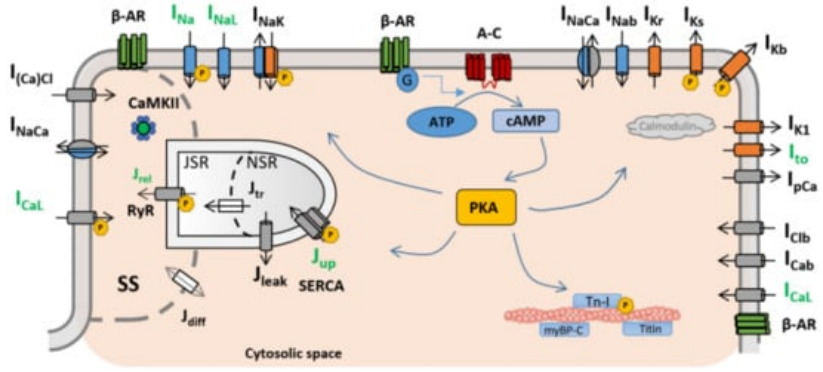

Figure 1. Schematic representation of the ionic currents and subcellular targets considered in modelling studies of β-ARS and the subsequent PKA phosphorylation cascade. The currents marked with an encircled P represent the different PKA targets. Adapted from [42] under the Creative Commons Attribution (CC BY 4.0) license.

The first modelling approach for the consideration of β-ARS in cardiac electrophysiology described the effects of β-ARS by upscaling the magnitude of the most significantly upregulated ion channels during the β-adrenergic response (notably I_{CaL} and I_{KS}) or by shifting the activation curves of these currents [35][43]. Despite its simplicity, such an approach is sufficient to replicate to a good extent the main steady-state effects of β-ARS at the cellular level, such as action potential shortening, increased calcium transient amplitude, or a potentiated arrhythmogenicity. A more complex model developed by Greenstein et al. [37] accounted for these changes using a population-based approach, i.e., treating phosphorylation as a binary process independent of channel gating. This assumption implies that, at each time step, ionic concentrations and ionic currents or fluxes can be expressed as the sum of their phosphorylated and nonphosphorylated cellular parts. However, the steady-state nature of the abovementioned models imposes limitations for investigating transient behaviours in the activation of β-ARS or in dissecting the contribution to the β-ARS response of subcellular targets of PKA phosphorylation.

Saucerman et al. were the first authors to develop, in the early 2000s, a dynamic formulation of β-ARS [36][44]. The model incorporated a complete phosphorylation cascade of the L-type calcium channel and PLB in a rat ventricular myocyte electrophysiological model. The authors considered an extensive validation against published experimental data, including the temporal response of cAMP to ISO [45], PKA activation levels as a function of the concentration of cAMP [46], and PLB phosphorylation to ISO [47], together with experimental recordings of whole-cell patch-clamp I_{CaL} current, calcium transients, and action potentials [48]. This seminal model of β-ARS has been expanded in multiple subsequent studies. Soltis and Saucerman added dynamic phosphorylation by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), in combination with the previously described PKA phosphorylation, to rabbit ventricular cardiomyocytes [29]. Phospholemman phosphorylation was also included in later works [49]. The model was also expanded by Negroni et al. to present an integrated framework of β-ARS and cardiac mechanical contraction [30]. More recently, Meyer et al. investigated a quasi-steady-state approximation of the Soltis and Saucerman model, demonstrating that their reduced-order formulation captured many of the features of the complete model while providing an efficient approximation over a broad range of parameter conditions [50].

The next landmark in β-ARS modelling was provided by Iancu et al., who proposed a new model considering cellular compartmentation of cAMP [38]. This led to a β-ARS model response dependent on local cAMP and PKA concentrations in the different cellular domains. The model response was compared to published measurements of cAMP activity under β-ARS [51]. The compartmentation introduced by the model provided a mechanistic explanation of how the high concentrations of cAMP as measured in experiments can modulate PKA activity.

The ideas described in the Saucerman and Iancu models were further developed by Heijman et al. [39]. In their work, they developed a compartmental model of β-ARS of the canine ventricular myocyte, including a dynamic β-ARS response integrated with CaMKII signalling. The main novelties of the model were the consideration of β1 and β2 isoforms in β-ARS stimulation and the use of a population-based approach with four different populations (phosphorylated by PKA, phosphorylated by CaMKII, phosphorylated by both, and nonphosphorylated) to represent the phosphorylation of its targets. The model was calibrated and validated using a wide range of canine and rodent experimental data, from measurements of molecular signalling (cAMP levels, adenylyl cyclase activity, PKA substrate [52][53]) to the complete cellular response (action potential duration, calcium transients [54]). The Heijman model has also been modified in later works, especially in terms of adjusting its underlying conductances and time constants to mimic the β-ARS response in other species, including humans [55][56].

A later model of β-ARS in mouse myocytes was developed by Bondarenko [40]. The model included some of the elements of the Heijman model, such as the compartmentalisation of the β-ARS system, but considered two types of L-type calcium channels and a different localisation of the RyRs in the compartmentalisation. The model matched experimental data from mice and showed how the different locations of some PKA phosphorylation targets can significantly affect action potential duration and calcium transients.

Recently, Khalilimeybodi et al. [41] formulated a model for β-adrenergic-induced cardiac hypertrophy in rat myocytes. The model included new molecular pathways that ended with the phosphorylation of the GSK3β and ERK molecules, which mediate gene expression in cardiac hypertrophy. The modelling results highlighted the significant contribution of these pathways in regulating cardiac hypertrophy in rats.

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