Editorial

Perspectives of Antiarrhythmic Therapy: New Trails, Challenges and Pitfalls

Cardiac arrhythmia is a leading cause of morbidity and mortality, and the history of anti-arrhythmic drug therapies has been dismal. Development of apparently more and more effective antiarrhythmic agents has been in the focus of interest of drug research during the past few decades, however, neither the ideal compound, nor an optimal strategy has been demonstrated so far. Furthermore, disappointing results have been obtained with several old antiarrhythmic agents, like many class III and class I/C drugs (see e.g. the CAST [1] and SWORD [2] studies). Clearly, the undesired - direct proarrhythmic - side effects of many currently applied antiarrhythmic drugs should not be underemphasized. There are two ways to improve our positions in the antiarrhythmic offensive. One way is the continuous development and refinement of the known structures in order to achieve agents with fewer or less serious side effects. This approach was evaluated in two papers of this issue: providing detailed evaluation of the recent development in class II antiarrhythmic agents (beta-receptor blockers) by Szentmiklósi *et al*. [3] and class IV antiarrhythmics (Ca^{2+}-entry blockers) by Szentandrássy *et al*. [4].

The other strategy is to find new trails, new antiarrhythmic mechanisms, each of them, of course, may also carry its own pitfalls. For instance, manipulation of the ATP-sensitive K^+ channels or utilizing adenosine-related antiarrhythmic mechanisms. Both interventions appear to be a promising approach as discussed in this issue by Muntean *et al*. [5] and Szentmiklósi *et al*. [6], respectively. Similarly to trials, in which the opening probability and the conductance of gap junction channels are pharmacologically modified. Conductance of these connexin-based channels are critically important to modulate longitudinal resistance, and consequently the conduction velocity [7], but they are also responsible for synchronization of the neighboring cells allowing for an effective reduction of beat-to-beat variability of action potential duration [8], a parameter that is currently considered to be a valuable arrhythmia predictor [9, 10]. This is reviewed in the article of Magyar *et al*. [11] in this issue.

Intracellular calcium concentration changes play a pivotal role in both abnormal impulse generation and conduction, since many of the currently known sarcolemmal ion channels are directly or indirectly sensitive to changes of intracellular Ca^{2+}-concentration [12] (e.g. the L-type Ca^{2+} current itself, the Na^+/Ca^{2+} exchange current, Ca^{2+}-dependent Cl^- and K^+ currents - but see also the plethora of publications on the Ca^{2+}-sensitivity of various types of other K^+ currents, including I_{Kr}, I_{Ks}, I_{to} and I_{K1}). Therefore, it is not surprising that two studies in this Special Issue are focused on the problem of intracellular calcium handling, more specifically, what new antiarrhythmic strategies can be built on the elements of this system, including pharmacological manipulation of the ryanodine receptor, or the question of stability of the Ca^{2+}-content of the sarcoplasmic reticulum. The state of art summaries, presented in this issue by Zaza and Rocchetti [13] and Acsai *et al*. [14], may help to understand, and consequently to utilize, these critically important mechanisms, which often appear to be proarrhythmic substrates, but at the same time they may also offer new effective antiarrhythmic strategies.

Activation of inward currents is known to lengthen action potential duration, and consequently increase the propensity of early afterdepolarizations resulting in triggered activity [15]. Analysis of the kinetic properties of late Na^+ current revealed their potential role in generation of early afterdepolarizations. Development of agents (more-or-less) selectively suppressing this current is currently under intensive research, indicating the efficacy of this strategy, as presented in the review article of Bányász *et al*. [16] in this issue.

Since ventricular fibrillation that occurs out of hospital settings usually has a lethal outcome, particular interest has been paid to ventricular electrophysiology. Atrial fibrillation is the most common sustained arrhythmia that has more than 5% prevelance over 65 years of age. Atrial fibrillation directly and indirectly increases mortality by greatly elevating the risk of stroke and heart failure and also substantially impairs the quality of life in the affected population. Furthermore, combination of heart failure with atrial fibrillation requires special attention to these diseases. A common feature in the two pathologies is the marked electrical remodeling seen in their chronic forms. New pharmacological strategies have recently been developed to treat these diseases, as described by the excellent review of Baczkó *et al*. [17].

It is important to accept that better antiarrhythmic results can only be expected after better understanding of the mechanisms that are responsible for the development and persistence of cardiac arrhythmias. Successful drug development requires intensive collaboration between pharmacologists and drug chemists. The major therapeutic strategies - as priorities - are defined by the former, while the optimal sterical structures are designed by the latter. This Special Issue is devoted to those areas of cardiac electrophysiology and pharmacology which are critically important to improve antiarrhythmic drug development. These topics - although focusing primarily on the physiological and pharmacological principles - have important strategic implications for future drug design.

REFERENCES

[1] Investigators of the Cardiac Arrhythmia Suppression Trial. Preliminary report: Effect of encainide and flecainide on mortality in randomized trial of arrhthmia supression after myocardial infarction. N Eng J Med, 1989; 321: 406-412.

[2] Waldo AL, Camm AJ, deRuyter H, Freidman PL, MacNeil DJ, Pitt B, Pratt CM, Rodda BE, Schwartz PJ. Survival with oral d-sotalol in patients with left ventricular dysfunction after myocardial infarction: rationale, design, and methods (The SWORD Trial) Am J Cardiol, 1995; 75: 1023-1027.

[3] Szentmiklósi J, Szentandrássy N, Hegyi B, Horváth B, Magyar J, Bányász T, Nánási PP. Chemistry, physiology, and pharmacology of β-adrenergic mechanisms in the heart. Why are β-blocker antiarrhythmics superior? Curr Pharm Des 2015; 21(8): 965-76.

[4] Szentandrassy N, Nagy D, Hegyi B, Magyar J, Bányász T, Nánási PP. Class IV antiarrhythmic agents: new compounds using an old strategy. Curr Pharm Des 2015; 21(8): 977-1010.

[5] Muntean DM, Kiss L, Jost N, Baczkó I. ATP-sensitive potassium channel modulators and arrhythmogenesis: an update. Curr Pharm Des 2015; 21(8): 1091-1102.

[6] Szentmiklósi JA, Galajda Z, Cseppentő Á, Gesztelyi R, Susán Zs, Hegyi B, Nánási PP. The Janus face of adenosine: antiarrhythmic and arrhytmogenic actions. Curr Pharm Des 2015; 21(8): 965-76.

[7] Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol Rev, 1989; 69: 1049-1069.

[8] Zaniboni M, Pollard AE, Yang L, Spitzer KW. Beat-to-beat repolarization variability in ventricular myocytes and its suppression by electrical coupling. Am J Physiol Heart Circ Physiol, 2000; 278: H677-H687.

[9] Thomsen MB, Volders PG, Beekman JD, Matz J, Vos MA. Beat-to-Beat variability of repolarization determines proarrhythmic outcome in dogs susceptible to drug-induced torsades de pointes. J Am Coll Cardiol, 2006; 48: 1268-1276.

[10] Hinterseer M, Beckmann BM, Thomsen MB, Pfeufer A, Ulbrich M, Sinner MF, Perz S, Wichmann HE, Lengyel C, Schimpf R, Maier SK, Varro A, Vos MA, Steinbeck G, Kaab S. Usefulness of short-term variability of QT intervals as a predictor for electrical remodeling and proarrhythmia in patients with nonischemic heart failure. Am J Cardiol, 2010; 106: 216-220.

[11] Magyar J, Bányász T, Szentandrássy N, Kistamás K, Nánási PP, Satin J. Role of gap junction channel in the development of beat-to-beat action potential repolarization variability and arrhythmias. Curr Pharm Des 2015; 21(8): 1042-52.
[12] Bers DM, Grandi E. CaMKII regulation of cardiac ion channels**.** J Cardiovasc Pharmacol, 2009; 54: 180-187.
[13] Zaza A, Rocchetti M. Calcium store stability as an antiarrhythmic endpoint. Curr Pharm Des 2015; 21(8): 1053-61.
[14] Acsai K, Nagy N, Márton Z, Oravecz K, Varró A. Antiarrhythmic potential of drugs targeting the cardiac ryanodine receptor Ca^{2+} release channel: case study of dantrolene. Curr Pharm Des 2015; 21(8): 1062-72.
[15] Song Y, Shryock JC, Belardinelli L. An increase of late sodium current induces delayed afterdepolarizations and sustained triggered activity in atrial myocytes. Am J Physiol Heart Circ Physiol, 2008; 294: H2031-H2039.
[16] Bányasz T, Szentandrássy N, Magyar J, Szabó Z, Nánási PP, Chen-Izu Y, Izu LT. An emerging antiarrhythmic target: late sodium current. Curr Pharm Des 2015; 21(8): 1073-90.
[17] Baczkó I, Leprán I, Kiss L, Muntean DM, Light P. Future perspectives in the pharmacological treatment of atrial fibrillation and ventricular arrhythmias in heart failure. Curr Pharm Des 2015; 21(8): 1011-29.

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