Cardiac electrophysiological studies on the antiarrhythmic and hidden cardiotoxic effects of different compounds

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Summary of Ph.D. thesis

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1. BACKGROUND AND AIMS

1.1. Investigation of the cardiac electrophysiological effects of SZV-270

Cardiovascular diseases remain the leading causes of mortality in the developed world. Approximately 18 million lives are lost annually due to sudden cardiac death, most commonly caused by severe ventricular arrhythmias degenerating into ventricular fibrillation (VF). Following the significant setbacks for pharmacological prevention of ventricular arrhythmias that were provided by the Cardiac Arrhythmia Suppression Trials and the Survival with Oral D-Sotalol trial, where sodium channel blocker Class I/C and potassium channel blocker Class III compounds - instead of improving clinical outcome - increased mortality in post-myocardial infarction patients with reduced ejection fraction, the attention shifted towards potential new antiarrhythmic drugs with more complex ion channel and receptor modulatory effects.

Atrial fibrillation (AF), the most prevalent sustained cardiac arrhythmia, is associated with significant morbidity and mortality, leading to stroke and heart failure. The therapy of AF is not optimal, since pharmacological therapy has limited efficacy and antiarrhythmic drugs exhibit marked proarrhythmic potential due to their cardiac ventricular electrophysiological adverse effects, while AF ablation can lead to complications and recurrence of AF following ablation also occurs.

One promising approach to safer and more effective pharmacological arrhythmia management is the use novel compounds that exhibit more complex actions and modulate several ionic currents. Indeed, amiodarone, a compound affecting a several ionic currents, remains one of the most effective antiarrhythmic drugs both for the management of AF and severe ventricular arrhythmias, however, especially during its chronic application, it exhibits severe extracardiac adverse effect. Class III antiarrhythmic drugs prolong myocardial repolarization and can effectively reduce

re-entry arrhythmias, however, they can also provoke Torsades de Pointes (TdP) tachycardia and D-sotalol increased mortality in post-myocardial infarction patients. Despite its significant QT prolonging effect, amiodarone has a relatively low torsadogenic adverse effect, possibly due to decreased transmural dispersion of repolarization and inhibition of early afterdepolarization (EAD) formation following amiodarone administration, similarly to Class I/B antiarrhythmic drugs. Therefore, the development of novel compounds with complex actions exhibiting combined Class I/B and Class III effects and devoid of severe extracardiac adverse effects, that are effective against both supraventricular and ventricular arrhythmias, is justified.

In this study, a novel compound with complex actions, SZV-270, was investigated regarding its cardiac cellular electrophysiological effects in rabbit and canine atrial and ventricular preparations. Its effects on atrial fibrillation were tested in dogs with chronic atrial tachypacing-induced atrial remodeling.

1.2. Investigation of the possible hidden cardiotoxicity of rofecoxib

Unexpected clinical cardiotoxicity is still the leading cause of discontinuation of clinical trials and the withdrawal of drugs from the market despite great efforts to detect cardiotoxicity in the preclinical phase of drug development programs. Such cardiotoxic effects remain undetected during preclinical and early clinical safety studies and they may manifest in the presence of cardiac diseases e.g., in myocardial I/R conditions; therefore, we termed this phenomenon “hidden cardiotoxicity”. Hidden cardiotoxicity often manifests as ischemia-related lethal myocardial injury and/or as I/R-induced arrhythmias and/or as cardiac dysfunction. Thus, drugs with hidden cardiotoxic properties may present as a serious risk to patients as drugs with overt cardiotoxicity, such as certain cancer treatments. The mechanisms of hidden cardiotoxicity may include the activation of cell death, or pro-arrhythmic processes during

cardiac I/R, as well as the inhibition of cardioprotective signaling pathways (e.g., ischemic conditioning-induced protection), either of which may be aggravated by the presence of cardiovascular comorbidities. The mechanism of cardiovascular toxicity of cancer treatments is described elsewhere in detail. Nearly 500 medicinal products were withdrawn from the market between 1953 and 2013, the majority of which is related to cardiac adverse events. Moreover, an estimated 197,000 deaths are attributed to adverse drug reactions in the European Union each year. Hidden cardiotoxicity remains undetected in the preclinical and early clinical phases of drug development, since the current guidelines only require the assessment of drug safety in healthy animals. In addition, preclinical and clinical cardiac electrophysiological safety test guidelines advocate the use of healthy animals, tissues, and healthy human volunteers for the assessment of the pro-arrhythmic adverse effects of compounds in development and these tests do not represent patients with increased arrhythmia susceptibility. However, in clinical trials, cardiotoxic adverse events occur in an unpredictable manner, often in patients with cardiac diseases and/or with cardiovascular comorbidities, e.g., hyperlipidemia, hyperglycemia, hypertension, aging, or inflammatory diseases. Indeed, the guidelines for the treatment of heart failure by the American College of Cardiology Foundation/American Heart Association recommend avoiding the use of certain medications in heart failure, e.g., cyclooxygenase-2 (COX-2) inhibitors, since they may exacerbate underlying myocardial dysfunction. Rofecoxib, which is a COX-2 inhibitor, was withdrawn from the market due to an increased risk of cardiovascular prothrombotic events being observed in the VIGOR and APPROVe trials. Later, in a meta-analysis that included 116,094 participants, it was shown that the use of rofecoxib was associated with an increased risk of arrhythmias. Several other mechanism have been proposed for rofecoxib-induced cardiotoxicity, such as the inhibition of protection against I/R injury, prevention of production of epi-lipoxins, increase in blood pressure, and inhibition of vascular

remodeling, however, none of those has been detected during preclinical safety assessment. Nevertheless, according to our definition, rofecoxib showed hidden cardiotoxic properties; earlier and appropriate preclinical tests could have revealed these effects, thus preventing a number of serious adverse events, thereby increasing patient safety. The fact that the cardiotoxic effects of rofecoxib remained hidden in preclinical studies and was only revealed in phase 4 clinical studies and by a following metaanalysis and the enormous costs of long-term cardiovascular outcome trials required to reveal hidden cardiotoxicity suggest that more sensitive screening methods are required for toxicity studies including animal models of myocardial I/R and/or comorbidities. To this end, here we aimed to investigate that hidden cardiotoxicity of rofecoxib, that remained unrevealed during preclinical safety assessment, could have been detected before its authorization in pathological conditions. Our results show that hidden cardiotoxic property of rofecoxib can be revealed with preclinical models of I/R injury. Safety testing of other drugs in the presence of I/R might uncover their hidden cardiotoxicities.

2. Materials and Methods

2.1. Ethical issues

All animal care and the described experiments complied with the Guide for the Care and Use of Laboratory Animals (U.S.A. NIH publication No 85-23, revised 1996) and conformed to the the Directive 2010/63/EU of the European Parliament. The experimental protocols had been approved by the Ethical Committee for the Protection of Animals in Research of the University of Szeged, Szeged, Hungary (I-74-18-2016; I-74-15/2017; I-74-24/2017); and also by the Department of Public Health and Food Chain Safety at

the Csongrád County Government Office (XIII/4227/2016; XIII/3330/2017; XIII/3331/2017).

2.2. Cardiac electrophysiological studies with SZV-270

2.2.1. Action potential measurements from canine atrial trabeculae

Male Beagle dogs (weighing 12-15 kg; n=6) were sedated (xylazine, 1 mg/kg, i.v. and ketamine, 10 mg/kg, i.v.) and anesthetized (pentobarbital, Sigma-Aldrich, 30 mg/kg i.v.), their hearts were rapidly removed through right lateral thoracotomy. The hearts were immediately rinsed in oxygenated modified Locke's solution containing (in mM): NaCl 128.3, KCl 4, $CaCl_2$ 1.8, $MgCl_2$ 0.42, $NaHCO_3$ 21.4, and glucose 10. The pH of the solution was set between 7.35 and 7.4 when saturated with the mixture of 95% oxygen and 5% CO_2 at 37 ºC. Isolated right atrial trabeculae were obtained, individually mounted in a tissue chamber and stimulated as decribed previously. The maximal rate of depolarization (V_{max}), maximum diastolic potential, action potential amplitude, and action potential duration measured at 90% of repolarization (APD_{90}) were evaluated off-line, applying stimulation with a constant basic cycle length (BCL) of 500 ms.

2.2.3. Action potential measurements from canine and rabbit right ventricular papillary muscles and in canine Purkinje fibers

Male Beagle dogs (weighing 12-15 kg; n=7) and white rabbits (weighing 2-3 kg; n=6) were used for the experiments. Right ventricular papillary muscle tips were obtained, mounted and stimulated using the conventional microelectrode technique. The preparations were stimulated (HSE stimulator type 215/II) initially at a constant cycle length of 500 ms (canine Purkinje fibers) or 1000 ms (canine and rabbit papillary muscle), with rectangular constant current pulses 2 ms in duration. The current pulses were isolated from ground and delivered through bipolar platinum electrodes. Transmembrane potentials were recorded with the use of conventional 5–20 MΩ, 3 M KCl-filled microelectrodes connected

to the input of a high-impedance electrometer (Biologic Amplifier VF 102, Claix, France). The first derivative of transmembrane potential (dV/dtmax) was obtained electronically with a Biologic DV-140 (Claix, France) differentiator. At least 60 min. was allowed for each preparation to equilibrate during continuous superfusion with modified Locke's solution, warmed to 37˚C before the experimental measurements commenced. The following types of stimulation in the course of the experiments were applied: stimulation with a constant cycle length of 1000 or 500 ms (1 or 2 Hz); stimulation with different constant cycle lengths ranging from 300 to 5000 ms taking the measurements after the 25th beat. The preparations were then superfused with the solution containing 1 μM SZV-270 for 40–60 min. before the pacing protocol was repeated and the parameters were measured again, then superfusion continued with 5 μM SZV-270 for another 40-60 min. and measurements were repeated. Efforts were made to maintain the same impalement throughout each experiment. In case an impalement became dislodged, however, adjustment was performed and the experiment continued if AP characteristics of the re-established impalement deviated less than 5% from the previous measurement.

2.2.4. Whole cell patch-clamp studies

Isolated ventricular cardiomyocytes were obtained from male rabbits (weighing 2-3 kg) by enzymatic dissociation as described previously (Major et al., 2016). A drop of cell suspension was placed into a transparent recording chamber mounted on the stage of an inverted microscope (Olympus IX51, Olympus, Tokyo, Japan), and myocytes were allowed to settle and adhere to the bottom of the chamber for at least 5 minutes before superfusion was initiated. HEPES buffered Tyrode's solution was used as the normal superfusate. This solution contained (in mM): NaCl 144, NaH_2PO_4 0.4, KCl 4.0, $CaCl_2$ 1.8, $MgSO_4$ 0.53, Glucose 5.5, and HEPES 5.0 at pH of 7.4. Patch clamp micropipettes were made from borosilicate glass capillaries using a P-97 Flaming/Brown micropipette puller

(Sutter Co, Novato, CA, USA). The electrodes had 1.5-2.5 MΩ resistances when filled with pipette solution that contained (in mM): KOH 110, KCl 40, K_2ATP 5, MgCl2 5, EGTA 5, GTP 0.1 and HEPES 10, during K^+ current measurements. Aspartic acid was used to adjust the pH of the pipette solution to 7.2. The L-type calcium current ($I_{Ca,L}$) was recorded in HEPES-buffered Tyrode's solution supplemented with 3 mM 4-aminopyridine. A special pipette solution was used containing (in mM: KOH 40, KCl 110, TEACl 20, MgATP 5, EGTA 10, HEPES 10 and GTP 0.25, pH was adjusted to 7.2 by KOH.

Ionic membrane currents were recorded with the Axopatch 200B patch-clamp amplifier (Molecular Devices, Sunnyvale, CA, USA) using the whole cell configuration of the patch clamp technique. Membrane currents were digitized and recorded under software control (Digidata 1440A, pClamp 10, Molecular Devices, Sunnyvale, CA, USA) after low-pass filtering at 1 kHz. The inward rectifier (I_{K1}), transient outward (I_{to}), rapid (I_{Kr}) delayed rectifier potassium currents were recorded in rabbit ventricular myocytes. 1 μM nisoldipine was included in the bath solution to block $I_{Ca,L}$. When I_{Kr} was recorded, I_{Ks} was inhibited by using the selective I_{Ks} blocker HMR1556 (0.5 μM). All experiments were performed at 37°C.

2.2.5. Statistical analysis

The incidence of arrhythmias was calculated and compared by using the χ^2 method. All other data are expressed as mean ± SEM. Statistical analysis was performed using ORIGIN 8.1 (Microcal Software, Northampton, MA, USA). Differences between means were compared by ANOVA followed by Student's t-test (paired or unpaired, as appropriate). Data were considered as statistically significant when $p<0.05$.

2.3. Cardiac electrophysiological studies with rofecoxib

2.3.1. In vitro simulated ischemia/reperfusion injury study

For isolated papillary muscle experiments, male Wistar rats weighing 200–250 g were used. The rats were anesthetized with pentobarbital intraperitoneally (30 mg kg^{-1}), followed by rapid excision of the heart via thoracotomy. Left ventricular papillary muscle preparations were mounted in a tissue chamber (volume together with solution reservoir: 50 mL) and they were then continuously perfused with oxygen–saturated, HEPES-buffered Tyrode's solution (in mM: NaCl 144, NaH_2PO_4 0.4, KCl 4, $MgSO_4$ 0.53, $CaCl_2$ 1.8, glucose 5.5, HEPES 5 at pH 7.4, 37 ◦C). The preparations were stimulated (Hugo Sachs Electronik stimulator type 215/II, March-Hugstetten, Germany) at a cycle length of 1000 ms (frequency: 1 Hz), while using 2 ms-long rectangular constant voltage pulses that were isolated from ground and delivered across bipolar platinum electrodes in contact with the preparation. Transmembrane potentials were recorded while using the conventional microelectrode technique. Microelectrodes that were filled with 3 M KCl and exhibiting tip resistances of 5–20 MΩ were connected to a high impedance electrometer (type 309, MDE Heidelberg GMBH, Heidelberg, Germany) coupled to a dual beam oscilloscope (Tektronix, Beaverton, OR, USA). Altogether, 54 animals were included in the ex vivo experiments. Papillary muscles of 6 animals/group were superfused with oxygen–saturated HEPES-buffered Tyrode's solution (normoxic solution) and were allowed to equilibrate for 60 min. before baseline measurements were taken. Throughout the experiments, measurements were taken every 2 min. Following the 60-min. equilibration period, groups of preparations were superfused with normoxic solution containing either vehicle, 1 or 10 μM rofecoxib (Normoxia groups) dissolved in DMSO for 90 min. The concentration of 1 μM was chosen for rofecoxib based on the peak plasma concentration (C_{max}) measured after a single, 5 mg kg^{-1} oral dose of rofecoxib in rats. The highest final concentration of

DMSO following the application of 10 μM rofecoxib was 0.2% in the solution. Following the 60-min. baseline superfusion, groups of preparations were superfused with normoxic solution for 30 min. then with nitrogen-saturated and HEPES-buffered solution (ischemic solution, in mM: NaCl 144, NaH_2PO_4 0.4, KCl 4, $MgSO_4$ 0.53, $CaCl_2$ 1.8, 2-deoxy-D-glucose 5.5, HEPES 5 at pH 6.9, and 37 ◦C) for 30 min., and then with normoxic solution for 30 min., all containing either vehicle, 1 or 10 μM rofecoxib (sI/R groups) to induce simulated ischaemia/reperfusion (sI/R). In additional groups of preparations, simulated ischemic preconditioning (sIPC) was performed before 30 min. ischemia by using the following protocol: three times 5-min. simulated ischemia with intermittent 5 min. reperfusion periods. Before index ischemia, the last reperfusion lasted 15 min.

Unbiased evaluation of action potential parameters was achieved by automatic evaluation while using software that was developed in Department of Pharmacology and Pharmacotherapy, University of Szeged (Hugo Sachs Electronic-Action Potential Evaluation System): V_{max}, CT, RMP, APA, APD at 75 and 90% of repolarization (APD_{75} and APD_{90}, respectively). The maintenance of the same impalement throughout each experiment was attempted. However, in case an impalement was dislodged, electrode adjustment was performed, and the experiment was terminated and all data were excluded from analysis if the action potential characteristtics of the re-established impalement deviated by more than 5% from the previous measurement.

2.3.2. Statistical analysis

The difference between treatment groups was evaluated while using two-way ANOVA or one-way ANOVA followed by Fisher LSD post hoc tests with multiple comparisons. We used GraphPad Prism (version 6.0, GraphPad Software, California, USA) and R (version 3.4) with the lme4 library. We claimed that the differences were statistically significant if $p < 0.05$.

3. RESULTS ANS DISCUSSION

3.1. SZV-270 has combined Class I/B and Class III effects

In this study, the cardiac cellular electrophysiological and in vivo antiarrhythmic effects of SZV-270, a novel compound with a structure that features Class I/B and Class III structural elements (of D-sotalol and mexiletine), were investigated in dogs and rabbits, two species used frequently in arrhythmia research.

To elucidate the mechanisms underlying the ventricular antiarrhythmic effects of SZV-270, action potential measurements were performed in rabbit and dog right ventricular papillary muscle preparations, and several ionic currents were also measured in isolated rabbit right ventricular cardiomyocytes. The compound lengthened the effective refractory period, APD_{50}, APD_{75} and APD_{90} in a concentration dependent manner in ventricular preparations in both species. Furthermore, SZV-270 significantly inhibited the I_{Kr} tail current at relatively low concentrations of 100 and 500 nM. These Class III antiarrhythmic effects were supplemented by Class I/B effects of SZV-270 in the present study. In right ventricular preparations isolated from dogs and rabbits, the larger investigated concentration of SZV-270 significantly reduced V_{max} at stimulation cycle lengths shorter than 1000 ms. In addition, the larger concentration of SZV-270 prolonged APD_{90} in a lesser degree and significantly shortened APD_{50} (depressed the plateau phase) in dog Purkinje fibers. These effects can decrease repolarization heterogeneity in the ventricle, resembling a similar effect of amiodarone. Even high concentrations of SZV-270 did not affect I_{K1}, I_{to} and $I_{Ca,L}$ in rabbit right ventricular cardiomyocytes.

Based on the results of this study, SZV-270 exhibits combined Class I/B and Class III antiarrhythmic actions. What makes this combination beneficial? Class III drugs prolong repolarization and the effective refractory period and are especially effective against re-entry arrhythmias. However, Class III compounds possess marked proarrhythmic activity: they promote

EAD formation and subsequent development of TdP polymorphic ventricular tachycardia. Drugs with Class I/B actions, however, can reduce EAD formation and have been shown to suppress TdP induced by pure Class III agents. Also, the combination of the Class I/B drug mexiletine and the Class III compound sotalol prevented ventricular tachyarrhythmias in dogs with myocardial infarction. Luderitz et al. also suggested that the combination of mexiletine and sotalol was able to suppress ventricular arrhythmias more effectively than either compound alone. These results strongly suggest that a compound with combined Class I/B and III effects can prevent re-entry arrhythmias with reduced risk of provoking TdP arrhythmia.

In a conscious dog model of atrial fibrillation that is based on chronic right atrial tachypacing-induced atrial electrical remodeling, SZV-270 significantly reduced the incidence of burst-induced AF and prolonged the AERP. In canine right atrial trabeculae, SZV-270 prolonged the APD_{50}, APD_{75} and APD_{90} in a concentration dependent manner. The effects of SZV-270 on AF in this model were comparable to those of the selective I_{Kr} blocker dofetilide, which is known as an effective compound for rhythm control in AF. Dofetilide also reduced AF incidence and increased AERP in the present study, and was shown to prolong atrial APD in atrial trabeculae isolated from dogs with chronic tachypacing induced atrial remodeling. The beneficial effects of dofetilide in AF were attributed to its atrial repolarization and AERP prolonging effects. The AF incidence reducing effects of SZV-270 is also probably due to its atrial APD prolonging effects in this study.

3.2. Ischaemic preconditioning prevents the hidden electrophysiological cardiotoxic effects of rofecoxib

In vitro sI/R and sIPC experiments were performed on isolated rat left ventricular papillary muscles in order to analyze the effect of rofecoxib on cardiac action potential parameters. Rofecoxib treatment did not change any of the investigated electrophysiological parameters, including APD_{90} in normoxic conditions. As expected,

the 30 min. simulated ischemia significantly shortened APD_{90} in all groups that were subjected to ischemia when compared to the respective normoxic groups. However, importantly, in the presence of sI/R rofecoxib dose-dependently increased APD_{90} upon reperfusion following the 30 min. simulated ischemia. In the sIPC group, these effects of rofecoxib on APD were not seen during reperfusion. Based on the present results, rofecoxib might further exacerbate the differences in APD between normoxic and ischemic myocardium, further increasing the arrhythmia substrate in I/R. Simulated ischemia (30 min.) resulted in an increase of CT in all groups, while V_{max} was significantly reduced in the rofecoxib treated groups, which only suggested an additional reduction of sodium channel function by rofecoxib in sI/R conditions, further decreasing the already slowed impulse conduction in depolarized ischemic myocardial tissue. These data suggest that adverse effects of COX-2 inhibitors may occur only in the presence of cardiac I/R.

4. CONCLUSIONS AND NOVEL FINDINGS

1. SZV-270 significantly reduced the incidence of atrial fibrillation and prolonged atrial effective refractory period in a conscious dog model of atrial fibrillation.
Our cellular electrophysiological investigations revealed that SZV-270 exerted its antiarrhythmic effects via combined Class I/B and Class III actions.

2. We demonstrated, that the hidden cardiotoxicity of rofecoxib can be revealed by preclinical cardiotoxicity testing while using experimental I/R models. Moreover, IPC might protect against the hidden cardiotoxic effects of rofecoxib in vitro. These results show that cardiac safety testing with simple preclinical models of I/R injury uncovers the hidden cardiotoxicity of rofecoxib and might reveal hidden cardiotoxicity of other drugs.

PUBLICATIONS

List of publications related to the subject of the thesis

Full length papers

1. Varga RS, Hornyik T, Husti Z, Kohajda Zs, Krajsovszky G, Nagy N, Jost N, Virág L, Tálosi L, Mátyus P, Varró A, Baczkó I. Antiarrhythmic and cardiac electrophysiological effects of SZV-270, a novel compound with combined Class I/B and Class III effects, in rabbits and dogs. Canadian Journal of Physiology and Pharmacology, 2021, 99(1): 89-101. doi: 10.1139/cjpp-2020-0412; PMID: 32970956.
Impact Factor (2020) = 2.273 Q3 (Pharmacology - 168/769)

2. Brenner GB, Makkos A, CsT, Onódi Zs, Sayour NV, Gergely TG, Kiss B, Görbe A, Sághy É, Zádori ZS, Lázár B, Baranyai T, **Varga RS**, Husti Z, Varró A, Tóthfalusi L, Schulz R, Baczkó I, Giricz Z, Ferdinandy P. Hidden Cardiotoxicity of Rofecoxib Can be Revealed in Experimental Models of Ischemia/Reperfusion. Cells, 2020, 26;9(3):551. doi: 10.3390/cells9030551. PMID: 32111102.
Impact Factor (2020) = 6.6, Q1 (Medicine(Miscellaneous))

Published abstracts

1. Varga R, Hornyik T, Husti Z, Juhász V, Mátyus P, Varró A, Baczkó I. Antiarrhythmic and cardiac electrophysiological effects of SZV-270, a novel compound with combined Class I/B and Class III effects, in rabbits and dogs.
6th Meeting of European Section and 7th Meeting of North American Section of the International Academy of Cardiovascular Sciences (IACS), Kragujevac, Serbia (2019) p. 242

2. Husti Z, **Varga RS**, Brenner G, Bencsik P, Giricz Z, Görbe A, Shulz R, Varró A, Ferdinandy P, Baczkó I. Ischaemic

preconditioning prevents the hidden electrophysiological cardiotoxic effects of Rofecoxib
6th Meeting of European Section and 7th Meeting of North American Section of the International Academy of Cardiovascular Sciences (IACS), Kragujevac, Serbia (2019) p. 178 Paper: P38

3. Husti Z, **Varga R**, Brenner G, Bencsik P, Giricz Z, Görbe A, Shulz R, Varró A, Ferdinandy P, Baczkó I. The hidden electrophysiological cardiotoxic effects of rofecoxib are prevented by ischaemic preconditioning.
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CARDIOLOGIA HUNGARICA 49: Suppl.B pp. B26-B26. (2019)

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1. Kohajda Zs, Virág L, Hornyik T, Husti Z, Sztojkov-Ivanov A, Nagy N, Horváth A, **Varga R**, Prorok J, Szlovák J, Tóth N, Gazdag P, Topal L, Naveed M, Árpádffy-Lovas T, Pászti B, Magyar T, Koncz I, Déri Sz, Demeter-Haludka V, Aigner Z, Ördög B, Patfalusi M, Tálosi L, Tiszlavicz L, Földesi I, Jost N, Baczkó I*, Varró A*. In vivo and cellular antiarrhythmic and cardiac electrophysiological effects of desethylamiodarone in dog cardiac preparations. *British Journal of Pharmacology*, 2022, published online: Feb 1. doi: 10.1111/bph.15812.
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IF (2016) = 2.806; Q1 (Multidisciplinary – 10/111)

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