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5-brom-2,3-indolindione: its action on isometric contraction and transmembrane action potential duration in guinea-pig papillary muscles

Vida Garalienė[1], Evardas Povilonis[2], Antanas Navalinskas[1]

[1] *Institute of Cardiology, Kaunas University of Medicine, Sukilėlių 17, Kaunas, Lithuania*
[2] *Faculty of Mathematics and Informatics, Vilnius University, Naugarduko 24, Vilnius, Lithuania*

Background. Studies have shown that 5-brom-2,3-indolindione (bromisatin) possesses the positive inotropic properties and preliminary studies indicated that in response to bromisatin the cardiac action potencial (AP) duration increases as well. In the current study we have investigated whether alterations of action potential duration (APD) induced by bromisatin are modified by some ($I_{K1,}$ K_{ATP} and I_K) potassium channels. To evaluate this relation, single doses of $BaCI_2$, dl-sotalol and glibenclamide were used for the blockade of inward rectifier potassium current, $I_{K1,}$ I_{KATP} and the rapid (I_{Kr}) component of the delayed rectifier potassium current. **Methods.** The experiments were carried out on the guinea pig papillary muscles. Isometric contraction and transmembrane potential were recorded using a force transducer and standard microelectrode technique. **Results.** Bromisatin alone resulted in a significant increase in the force of contraction and APD in a dose-dependent manner with an EC_{50} value of 400 ± 80 μmol, and its effect was reverse usedependent. Glibenclamide (10 μmol/l) and sotalol (1.0 μmol/l) intensified the effects of bromisatin and further increased the APD duration by 50%. A 90% and 100% repolarization was induced by bromisatin alone (400 μmol/l). The selective blockade of the I_{K1} by barium (3.1 μmol/l) did not show a substantial influence on bromisatin effects. Bromisatin partially abolished the negative inotropic action induced by glibenclamide, dl-sotalol and barium. **Conclusion**. These findings support the hypothesis that the inhibition of K_{ATP} as well as I_{Kr} contribute to the mechanism of action of the 5-brom-2,3- indolindione and therefore may be beneficial for the prognosis of patients with advanced heart failure.

Key words: 5-brom-2,3-indolindione, isometric contraction, action potential duration, barium chloride, glibenclamide, dl-sotalol, papillary muscle, guinea pig

INTRODUCTION

The number of patients with heart failure is obviously increasing (especially in industrially developed countries) and its prevalence will further increase with the aging of the population (1). Heart failure is frequently associated with cardiac arrhythmias, which represent a significant cause of morbidity and mortality. To improve the hemodynamics and to increase cardiac output in heart failure patients, the positive inotropic agents are used. Conventional positive inotropic agents (β-adrenergic agonists or phosphodiesterase inhibitors) can potentially cause cardiac arrhythmia and increase mortality (2, 3). Based on the current knowledge of the mechanisms involved in cardiac arrhythmias initiation and maintenance (4, 5), it is evident that the pharmacological agents increasing the cardiac action potential duration with multiple electrophysiological actions should be the main strategies for the synthesis and investigations of the novel compounds for the heart failure patients (6).

Our earlier experimental studies have shown that 5-bromisatin (5-bromindole-2,3-dione) (Fig. 1), a derivative of indole-2,3-dione, exert a substantial positive inotropic effect in the papillary muscles of guinea pigs (7). On the basis of the obtained data it was concluded that Ca^{2+} entering through slow calcium channels by both cAMP-dependent and cAMP-independent routs are involved in the mechanism of 5-bromisatin. Besides, the preliminary studies indicated that in response to bromisatin si-

Adress correspondence to: Vida Garalienė, Sukilėlių 17, Institute of Cardiology, Kaunas, 50009, Lithuania. Fax: (8-37) 302 872. E-mail: vida_g@takas.lt

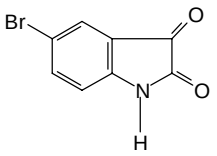

Fig. 1. The chemical structure of 5-brom-2,3-indolindione

multaneously like to isometric contraction the cardiac action potential duration was increased as well. In the current investigation an attempt has been made to find out whether the influence of 5-bromisatin on the lengthening of cardiac action potential was related with some ($I_{K1,}$ K_{ATP} and I_K) potassium channels. To assess that issue, single doses of $BaCI_2$ (3.1 μmol/l), dl-sotalol (1.0 μmol/l) and glibenclamide (10.0 μmol/l) for the blockade of inward rectifier potassium current, $I_{K1,}$ I_{KATP} and rapid (I_{Kr}) component of the delayed rectifier potassium current were used, respectively.

MATERIALS AND METHODS

Isolated guinea-pig papillary muscles

The experiments were carried out on guinea-pig papillary muscles. The present investigation conformed to the Guide for the Care and Use of Laboratory Animals published by Lithuanian Food and Veterinary Service (Publication No. 4-300, 1998, revised 2002). Briefly, animals of either sex were stunned with a blow on the neck. The heart was quickly excised and placed in gassed Tyrode solution containing 144 mmol/l NaCl, 1.8 mmol/l $CaCl_2$, 1 mmol/l $MgCl_2$, 4 mmol/l KCl, 10 mmol/l TrisCl and 5-mmol/l glucose at room temperature, pH 7.3–7.4. Thin ventricular papillary muscle was isolated and inserted into an organ bath containing Tyrode solution continuously gassed with 100% oxygen at a temperature of 37 °C. Each papillary muscle was connected to an isometric force transducer (6MX2B, Moscow, Russia) and electrically stimulated (ESU-2, Kursk, Russia) by square-wave pulses of 5-ms duration at a voltage 20% above the threshold at 0.3–1.5 Hz through carbon electrodes. The basic stimulation rate was 1.0 Hz. The maximal perfusion value of the preparation was approximately 4.5 ml/min. All measurements were obtained following no less than 60-min equilibration period when contraction of papillary muscles had reached a steady state. Each experiment was performed on the papillary muscle prepared from different guinea pigs.

Isometric contraction and transmembrane potential duration

In parallel to the recorder of isometric contraction, the transmembrane potential was detected using a standard microelectrode technique. The microelectrodes were made from borosilicate glass capillaries (GC150F-10, Harvard Part No. 30-0057) and filled with 3 mol/l KCl.

The both signals (inotropic response and transmembrane action potential) were digitised at a minimum sampling rate of 10 kHz with a 12-bit A/D converter (Digidata 1200, Axon Instruments, USA) and recorded with a computer. The signals were preserved there and analysed to obtain maximal contraction amplitude and the action potential duration (APD) at 50%, 90% and 100% repolarisation (APD_{50}, APD_{90}, APD_{100}), respectively.

For the calculation of the EC_{50} values from the concentration-dependent curves, bromisatin was added to the bath cumulatively. The calculated EC_{50} value was used for the other tests as a single concentration. Every heart preparations were perfused for 20 min with either drug.

Drugs

All reagents were of the highest obtainable purity. Glibenclamide and dl-sotalol were obtained from the Sigma chemical company (Germany). 5-Bromisatin was synthesized at the Institute of Cardiology, Kaunas Medical University.

The test compounds, glibenclamide and sotalol, were dissolved in DMSO so that in a final testing solution the concentration of DMSO did not exceed 0.1%. This concentration of DMSO did not affect the contractile force and action potential duration.

Statistical analysis

Data are presented as a mean ± SE. The significance of the difference between the means was analysed by the Student's t test. A level of $p < 0.05$ was adopted as critical for the significance.

RESULTS

Isometric contraction and action potential duration

Data presented in Table 1 have shown that 5-bromisatin in isolated guinea pig papillary muscles proved a synchronous concentration-dependent increase of isometric contraction and transmembrane action potential duration. The minimally effective concentration was 100 μmol/l, which caused a slight increase in the force of contraction by 10.3% at 20 min.

Under these conditions, small changes in AP duration were observed as well. For instance, AP duration at full repolarization (APD_{100}) increased by

Table 1. **Effect of cumulative doses of bromisatin on cardiac action potential duration and contraction force in isolated papillary muscles of guinea pig hearts**

Compound	Concentration, mol/l	Contraction force, %	Action potential duration, ms		
			APD_{50}	APD_{90}	APD_{100}
Pre-drug value		100.0	215.0 ± 4.3	243.6 ± 6.7	265.0 ± 7.2
Bromisatin	1×10^{-6}	99.6 ± 1.2	213.7 ± 10.0	241.8 ± 9.6	263.7 ± 11.8
	1×10^{-5}	101.0 ± 2.3	225.0 ± 12.6	254.0 ± 10.0	277.3 ± 15.6
	1×10^{-4}	110.3 ± 4.2	231.0 ± 14.0	262.0 ± 12.3	293.0 ± 16.0
	2.5×10^{-5}	127.0 ± 6.5	243.8 ± 13.6	273.0 ± 10.2*	302.0 ± 15.8
	5×10^{-4}	183.2 ± 8.6	259.7 ± 12.6*	300.5 ± 11.8**	327.5 ± 13.2**

The values are expressed as a mean ± SE of six preparations at each concentration; the stimulation rate 1 Hz; APD_{50}. APD_{90}, APD_{100}, the action potential duration at a level of 50%, 90% and 100% repolarization, respectively.

10.8%, the APD_{90} was less than 7% above baseline state. The more pronounced effect of the test compound either on the force of contraction or on AP duration at the higher concentrations (250.0 and 500.0 μmol/l) was seen. Thus, the isometric contraction increased by 27% and 83.2% and AP duration prolonged by 14% and 24.5%, respectively. The EC_{50} values (the negative logarithm of the concentration agent tested required for the 50% increase in the maximal force of contraction or AP duration) in both cases were the same – about 400 ± 80 μmol/l. By using that concentration as a single dose at the stimulation rate of 1.0 Hz the isometric contraction and APD_{50}, APD_{90}, AP_{100} increased by 56.0%, 13.2%, 16.5% and 17.2%, respectively.

Effect of $BaCl_2$

To assess the role of the inward rectifier potassium current, $I_{K1,}$ in the action of 5-bromisatin, we used barium chloride which is reported to selectively block I_{K1} (8, 9, 10). Our results obtained after a 20-min exposure of guinea pig papillary muscles to 3.1 μmol/l barium ions showed that $BaCl_2$ caused a slight lengthening (8.6%–7.5%) of APD measured at 50%, 90% and 100% repolarization level (Figure 2) and a decreased in contractile force.

Perfusion of the heart preparations with a solution containing Ba^{2+} and bromisatin extends the AP duration at all the afore-mentioned repolarization levels approximately by 20%. The isometric contraction of papillary muscles, which decreased under the impact of Ba^{2+} ions, was increased by bromisatin by about 25% over Ba^{2+} (83.4 ± 2.9% Ba^{2+} *vs*. 109.2 ± ± 12.7% Ba^{2+} + bromisatin), but it didn't reach the level of bromisatin alone (156.0 ± 9.6%).

Effect of glibenclamide

To evaluate whether the prolongation of APD does not occur under inhibition of K_{ATP} channels, the sulphonylurea compound glibenclamide that act as a specific blocker of ATP-sensitive K^+ channels was used (11).

Under our experimental conditions, glibenclamide (10 μmol/l) caused a slight prolongation of AP duration, more pronounced at a full repolarization

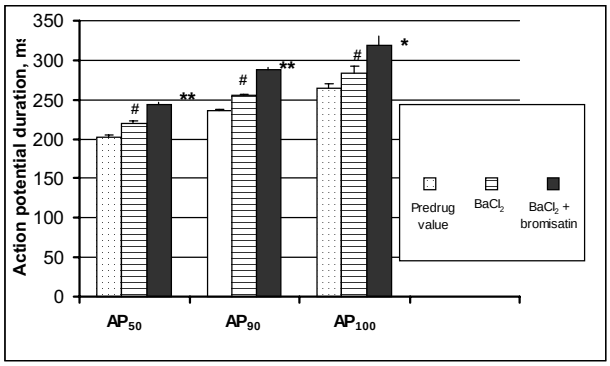

Fig. 2. Influence of bromisatin and $BaCl_2$ on the action potential duration in guinea pig papillary muscles. Data are expressed as a mean ±SE of five preparations; stimulation rate 1.0 Hz; $BaCl_2$ 3.1 μmol/l; bromisatin 400 μmol/l; #p < 0.01 *vs*. pre-drug value; *p < 0.05, **p < 0.001 *vs*. $BaCl_2$

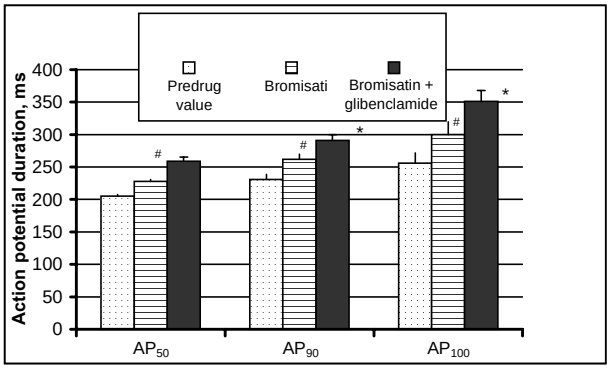

Fig. 3. Influence of bromisatin and glibenclamide on the action potential duration in guinea pig papillary muscles. Data are expressed as a mean ±SE of five preparations; stimulation rate 1.0 Hz; glibenclamide 10.0 μmol/l; bromisatin 400 μmol/l; #p < 0.01 *vs*. pre-drug value; *p < < 0.05 *vs*. bromisatin

level (11.3%, $p < 0.01$ *vs*. pre-drug value). Isometric contraction of the papillary muscles slightly (7%) reduced. Application of both agents together caused the further lengthening of AP duration by 24.2% (glibenclamide 1.6%), 25.5% (glibenclamide 3.5%) and 35.0% of baseline at APD_{50}, APD_{90}, and APD_{100}, respectively (Fig. 3). At the same time, the contraction force, which was decreased by 7% under the influence of glibenclamide, after adding bromisatin to the perfusion solution increased up to 20.0% of baseline, although it didn't reach the level of bromisatin alone (159.0 ± 11.3%).

Effect of dl-sotalol

Sotalol is a well-known blocker of the rapid (I_{Kr}) component of the delayed rectifier potassium current (12), *i.e*. under its influence the APD increases.

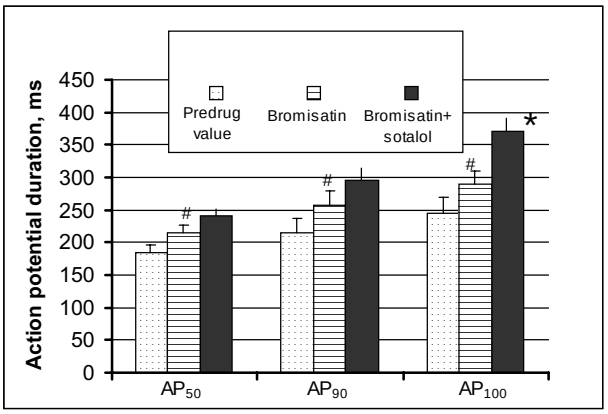

Fig. 4. Influence of bromisatin and dl-sotalol on the action potential duration in guinea pig papillary muscles. Data are expressed as a mean ±SE of five preparations; stimulation rate 1.0 Hz; dl-sotalol 10.0 μmol/l; bromisatin 400 μmol/l; #$p < 0.01$ *vs*. pre-drug value; *$p < 0.01$ *vs*. bromisatin

Our data, presented in Fig. 4, show that dl-sotalol (1 μmol/l) results in the minimal lengthening of AP duration in guinea pig papillary muscles, *i.e*. by 5.8%, 5.8% and 9.5% at 50%, 90% and full repolarization, respectively.

Bromisatin and sotalol caused the further lengthening of AP duration up to 36.6%, 37.9% and 48.5% at APD_{50}, APD_{90}, $APD_{100,}$ respectively. Data are statistically significant. At the some time, the isometric contraction of papillary muscles in a similar manner as in the case of glibenclamide has changed, *i.e*., bromisatin partially abolished the effects of sotalol on the force of contraction.

Rate-dependence effect

It is known that the agents whose effects depend on the rapid component of delayed rectifier potassium current, such a class III drugs, demonstrate a greater action transmembrane potential prolonging effect at slow heart rates than at higher frequencies (13). This "reverse use dependence" reduces the effectiveness of antiarrythmic agents during tachycardia and may cause proarrythmic effects during bradycardia. In order to illustrate this point, we recorded changes of guinea pig action potential duration at a slow (0.3 Hz) and a fast (1.5 Hz) stimulation rate. The results are produced in Table 2, which shows that in both groups (control and bromisatin) on increasing the stimulation rate the duration of transmembrane AP at all levels of repolarization shortened, but in the experimental group it was rather pronounced. For instance, at a frequency 1.5 Hz the lengthening of APD_{50} in bromisatin and control groups decreased to 44.7 ± 5.7% and 71.4 ± 2.6%, respectively, as compared to the baseline at a frequency 0.3 Hz.

Table 2. **Stimulation rate dependence of the millisecond increase in action potential duration and of the percentage change in isometric contraction induced by bromisatin on guinea pig heart pillary muscles**

	Stimulation rate, Hz	Contraction force, %	Action potential duration, ms		
			APD_{50}	APD_{90}	APD_{100}
Control	0.3	100.0 ± 1.2	238.0 ± 47.8	268.0 ± 6.9	288.0 ± 6.7
	0.5	144.8 8.2*	232.0 ± 11.9	264.0 ± 8.5	289.0 ± 8.2
	1.0	211.5 ± 15.6*	218.8 ± 6.0	247.0 ± 7.6	270.5 ± 7.9
	1.5	222.0 ± 23.0*	170.0 ± 8.0***	199.0 ± 8.5***	223.0 ± 9.4***
Bromisatin	0.3	152.0 ± 19.0	268.9 ± 14.9	298.5 ± 17.3	320.0 ± 15.2
	0.5	177.0 ± 19.0	250.3 ± 17.4	291.0 ± 16.8	326.0 ± 16.3
	1.0	163.6 ± 32.0	170.5 ± 12.7***	226.9 ± 11.9**	293.0 ± 15***
		150.7 ± 36.0	117.6 ± 8.6***	183.0 ± 6.7*	240.7 ± 14.7**

Data are expressed as a mean ± SE of six preparations at each frequency; bromisatin 400 μmol/l; **$p < 0.001$, ***$p < 0.001$ *vs*. 0.3 Hz.

Isometric contraction of papillary muscles in the control group progressively increased by augmentation in frequency, and at 1.5 Hz it reached 222.0 ± ± 23.0% over the baseline (100%) level. In bromisatin group we observed an insignificant alteration in contraction force as compared to the starting position.

DISCUSSION

The basic mode of action of the positive inotropic effect of the majority of cardiotonic agents is the increase of cAMP formation and consequently an augmentation in intracellular free calcium concentration. Our earlier experiments have shown that the positive inotropic effect of bromisatin result in an increased Ca^{2+} influx into the cardiomyocites via slow calcium channels in cAMP-independent way (7). The studies also have shown that the α_1-adrenergic receptors might play an important role in the positive inotropic action of bromisatin, and the depletion of endogenous catecholamines (noradrenaline) by reserpine attenuated the response of isometric contraction to the agent tested (14). It is established that by stimulating the α_1-receptors a lot of electrophysiology events occur in the cell, some of which are responsible for the mobilization of Ca^{2+} as well (15). Besides, the activation of slow Ca-channels might be indirect and defined by inhibition of K^+-channels and consequently by lengthening of action potential duration (16).

The inward rectifier potassium current in the cardiac muscle cells, I_{K1}, has been suggested to play a central role in the maintenance and stabilization of membrane resting potential as well as in repolarization of the later phase of AP (8, 10, 17). In the present study we found that in response to a concerted influence of bromisatin and $BaCI_2$, a specific blocker of potassium current I_{K1}, on the changes of action potential duration the additive effect of these agents was seen. It seems that this finding suggests the lack of involvement of the I_{K1}-dependent mechanisms in the action of 5-bromisatin on the cardiac membrane potential. A convincing explanation for the decrease in isometric contraction by the action of Ba^{2+} could be that Ba^{2+} blocks the entrance of Ca^{2+} via slow calcium channels into myocardium, while bromisatin abolishes it due to the prolonged repolarization state.

An analysis of the results obtained with glibenclamide, a blocker of sarcolemmal K_{ATP} channels, shows that this compound intensifies the effects of bromisatin on the repolarization process, since the common action of both agents caused the further lengthening of AP duration. Even if these data do not permit to answer the question whether bromisatin acts in a similar manner as glibenclamide with respect to sarcolemmal K_{ATP} channels, it is well known that the main effect of sulphonylurea derivatives (also of glibenclamide) is the improvement of metabolism and decrease of blood glucose level both by pancreatic and extrapancreatic mechanisms (18–21). Our earlier experimental studies carried out with rabbits and rats have shown that undr the effect of some isatin-2,3-dione derivatives, bromisatin included, the utilization of carbohydrates improved and simultaneously the content of glycogen in liver increased. So, these indirect findings suggest that the sarcolemmal ATP-sensitive K^+ current could be involved in the bromisatin's effects in respect to repolarazation process of cardiac potentials. The glibenclamide-induced decrease of isometric contraction may be associated with its inhibitory effect on Ca^{2+} ion influx via slow calcium channels (22).

The delayed rectifier potassium current ($I_{K)}$ is a major outward current responsible for ventricular action potential repolarization (12). In most species, also in guinea pig, I_K can be separated into rapid (I_{Kr}) and slow (I_{Ks}) components by both kinetic and pharmacological differences, *i.e.* they differ from one another in terms of their sensitivity to drugs (23). Experimental studies have demonstrated that the most selective inhibitor of the rapidly activating component I_{Kr} is sotalol, a representative of class III antiarrhythmic agent (13, 24). Our results indicated that dl-sotalol (1 μmol/l), which did not substantially prolonged APD, strengthened the effects of the test agent bromisatin, since the application of both compounds in equivalent concentrations significantly lengthened action potential duration in guinea pig papillary muscles as compared to bromisatin alone. This effect suggests that bromisatin may prolong the repolarization of guinea pig cardiac muscle by blocking the rapid component of the delayed rectifier potassium current. Besides, compounds that predominantly block the rapid component I_{Kr} demonstrate a reverse use dependency, *i.e.* they prolong the action potential duration with slower stimulation rates (13, 24, 25). In our study, the influence of bromisatin on AP duration by increasing the stimulation rates from 0.3 Hz (interval 3 s) to 1.5 Hz (interval 0.75 s) appeared as a sharp decrease in APD, more significant than in control papillary muscles. The latter effect may be related to the release of endogenous catecholamines (noradrenaline), which occurs under the action of the test compound (14), because it is hypothesized that at rapid rates or during sympathetic stimulation the contribution of the rapid component in APD is reduced, and then the slow component of the delayed rectifier potassium current becomes more prominent (23, 26). The isometric contraction in the control

group increased in a rate-dependent manner and in the experimental group it did not change substantially during the whole stimulation period. It is well known that by gradually increasing the stimulation rate a higher amount of Ca^{2+} accumulates in the intracellular stores (sarcoplasmic reticulum) from where they are released and participate in the contraction process (27, 28). Our earlier studies have shown that bromisatin in a dose-dependent manner significantly prolonged the time to 50% of relaxation in isometric contraction of guinea pig papillary muscle. The computed relaxation-onset index, which is related to relaxation processes, decreased as well (29). These findings seem to be related to a decreased absorption of Ca^{2+} and their accumulation in the sarcoplasmic reticulum; in turn, a less content of Ca^{2+} participates in contraction processes. The shorter AP duration also decreases the entering of Ca^{2+} ions through slow calcium channels.

CONCLUSIONS

We found that 5-bromisatin prolonged the transmembrane action potential as well as increased isometric contraction in guinea pig papillary muscles in a dose-dependent manner with an EC_{50} value of 400 ± 80 μmol. The efficacy in APD lengthening appeared to be frequency-dependent, *i.e*. the bromisatin's effect decreased with faster stimulation rates. Inhibition of K_{ATP} channel with glibenclamide (10.0 μmol) or inhibition of the rapid component of the delayed rectifier potassium current (I_{Kr}) with dl--sotalol (1.0 μmol) further increased the duration of 50%, 90% and 100% repolarization of cardiac action potentials. The selective blockade of the inward rectifier potassium channel (I_{K1}) by barium (3.1 μmol) showed no substantial influence on bromisatin's effects. Bromisatin partially abolished the negative inotropic effects of $BaCI_2$, glibenclamide or sotalol. These findings support the hypothesis that the inhibition of the ATP-sensitive potassium channel (K_{ATP}) or the delayed rectifier potassium current (I_K) contribute to the mechanism of action of the 5-bromindolin-2,3-dione and therefore may be beneficial for the prognosis of patients with advanced heart failure. Further studies are necessary to clarify the precise mechanisms of inotropic or potential duration of bromisatin as well as of other indolin-2, 3-dione derivatives.

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V. Garalienė, E. Povilonis, A. Navalinskas

5-BROM-2,3-INDOLINDIONO POVEIKIS JŪRŲ KIAULYČIŲ PAPILIARINIŲ RAUMENŲ IZOMETRINIAM SUSITRAUKIMUI IR TRANSMEMBRANINIO VEIKIMO POTENCIALO TRUKMEI

S a n t r a u k a

Eksperimentais nustatyta, kad izatino darinys 5-brom-2,3-indolindionas (bromizatinas) pasižymi teigiamomis inotropinėmis savybėmis ir jo veikimo efektai siejasi su $alfa_1$-adrenerginiais receptoriais bei vidinėmis katecholaminų atsargomis. Be to, preliminarūs tyrimai parodė, kad veikiant bromizatinui, ilgėja širdies ląstelių veikimo potencialo (VP) trukmė. Šio darbo tikslas – išsiaiškinti, ar bromizatino poveikis VP trukmei priklauso nuo širdies ląstelių kai kurių ($I_{K1,}$ K_{ATP} ir I_K) kalio jonų kanalų. Tam panaudotos vienkartinės $BaCI_2$, dl-sotalolo ir glibenklamido dozės, atitinkamai blokuojančios įeinamąją išlyginamąją kalio jonų srovę (I_{K1}), nuo ATP priklausomus kalio jonų kanalus (K_{ATP}) ir greitąją (I_{Kr}) komponentę užlaikytosios išlyginamosios kalio jonų srovės (I_K).

Tyrimai atlikti su jūrų kiaulyčių papiliariniais raumenimis, perfuzuojant juos deguonimi prisotintu Tyrode fiziologiniu tirpalu, esant 36–37°C temperatūrai. Papiliariniai raumenys, prijungti prie judesių daviklio, buvo stimuliuoti angliniais elektrodais 0,3–1,5 Hz dažniu 5 ms trukmės stačiakampio formos elektriniu impulsu. Transmembraninis veikimo potencialas užregistruotas standartine mikroelektrodine technika.

Rezultatai parodė, kad vien bromizatinas, priklausomai nuo panaudotos dozės, patikimai padidina papiliarinių raumenų susitraukimo jėgą ir prailgina VP trukmę. EC_{50} reikšmė, apskaičiuota pagal dozės efekto kreives, abiem atvejais buvo lygi 400 ± 80 μmol. Glibenklamidas (10 μmol/l) ir dl-sotalolas (1 μmol/l) stiprino bromizatino poveikį VP trukmei, t. y., veikiant minėtiems blokatoriams kartu su tiriamu preparatu (400 μmol/l), VP trukmė, esant 50%, 90% ir 100% repoliarizacijai, toliau statistiškai patikimai ilgėjo. Taikant selektyvią I_{K1} blokadą bario jonais (3,1 μmol/l), bromizatino poveikis VP trukmei nepakito. Bromizatinas iš dalies naikino neigiamą dl sotalolo, glibenklamido bei bario jonų inotropinį poveikį. Didėjant stimuliacijos dažniui, bromizatino poveikis VP trukmei staiga mažėjo, o izometrinė susitraukimo jėga beveik nekito. Gauti rezultatai leidžia daryti išvadą, kad 5-brom-2,3-indolindiono poveikio mechanizmai siejasi su kai kuriais (K_{ATP}, I_K) kalio jonų kanalais, dalyvaujančiais širdies ląstelių repoliarizacijos procesuose.

Raktažodžiai: 5-brom-2,3-indolindionas, izometrinis susitraukimas, veikimo potencialo trukmė, bario chloridas, glibenklamidas, dl-sotalolas, jūrų kiaulyčių papiliariniai raumenys