

**THE NOVEL ORTHO-CHLORO DERIVATE PROPAFENONE INDUCED RELAXATION  
IN ISOLATED RAT AORTA**

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*The information on the inhibitory effect of propafenone in vascular smooth muscle is sparse. Propafenone acts through blockage of voltage-dependent cardiac Na<sup>+</sup> channels, L-type Ca<sup>2+</sup> channels, voltage-sensitive K<sup>+</sup> (K<sub>v</sub>) channels, as well as β-adrenergic receptors in the heart. The introduction of different chemical groups in the benzyl moiety of propafenone influences pharmacological properties of newly developed derivate of propafenone. Here we investigated the effect of new ortho-chloro derivate of propafenone (5OCl) on the vascular tone of precontracted rat aorta. 5OCl produced endothelium-independent relaxation of rat aorta. In order to test the involvement of different ion channels in 5OCl mechanism of action, antagonist of Na<sup>+</sup>, lidocaine, K<sub>v</sub> channels, 4-aminopyridine (4-AP) and L-type Ca<sup>2+</sup> channels, nifedipine were used. All tested antagonists of ion channels did not influence the relaxation of rat aorta induced by high a concentration of 5OCl (≥10 μM), but antagonized the relaxation induced by low concentrations of this propafenone derivate. Thus, 5OCl derivate has comparable potency and efficacy as propafenone. According to its interaction with lidocaine, 4-AP and nifedipine it seems that 5OCl partly shares the mechanism of action with propafenone. The mechanism of vasodilatation induced by high micromolar concentration of 5OCl is not defined and further investigations are necessary.*

*Key words: ion channels, ortho-chloro derivate of propafenone, rat aorta, relaxation*

**INTRODUCTION**

Propafenone is a class Ic antiarrhythmic drug used to maintain sinus rhythm in patients with supraventricular tachycardia, including atrial fibrillation (Goodman and Gilman, 2003). Propafenone acts through blockage of voltage-dependent

cardiac Na<sup>+</sup> channels (Malfatto *et al.*, 1988; Valenzuela *et al.*, 1988). However, may also inhibit the L-type Ca<sup>2+</sup> channels, K<sup>+</sup> channels, as well as β-adrenergic receptors in the heart (Malfatto *et al.*, 1988; Bryson *et al.*, 1993; Franqueza *et al.*, 1998). The information on the inhibitory effect of propafenone in vascular smooth muscle is sparse.

Perez-Vizcaino *et al.* (1994) have shown that propafenone inhibited contractions of rat aorta and porcine coronary artery which could be attributed to reduced Ca<sup>2+</sup> entry. A decrease in systemic vascular resistance may reduce ventricular afterload, while a decrease in coronary vascular resistance might increase coronary blood flow. Thus, it is possible that in some patients these vasodilator actions of propafenone may improve the cardiac performance, overriding its cardiodepressant effect. A possible role for Na<sup>+</sup> channel inhibition in the observed inhibitory effect of propafenone was excluded. Propafenone decreased the contraction of rat aorta induced by high KCl due to its L-type Ca<sup>2+</sup> channel blocking properties (Fernandez del Pozo *et al.*, 1996). In contrast to this, in the same blood vessel, propafenone inhibited the vasodilatation induced by K<sup>+</sup> channel opener, levcromakalim in a non-competitive manner. The concentration at which this effect was observed within the therapeutic range and similar to the one reported to inhibit ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels (Cogolludo *et al.*, 1998). Later, the same authors have shown that propafenone (10 μM) inhibited voltage-sensitive K<sup>+</sup> (K<sub>V</sub>), big calcium-sensitive K<sup>+</sup> (BK<sub>Ca</sub>) and K<sub>ATP</sub> channels in the isolated smooth muscle cell from rat portal veins (Cogolludo *et al.*, 2001). The inhibition of K<sup>+</sup> channels is expected to produce membrane depolarization, activation of L-type Ca<sup>2+</sup> channels and vasoconstriction (Nelson and Quayle, 1995). However, the intravenous administration of propafenone produced a transient and slight fall in systolic blood pressure (Feld *et al.*, 1987). It is possible that at certain concentrations the direct effect of propafenone on vascular K<sup>+</sup> channels may be counteracted by the blockage of L-type Ca<sup>2+</sup> channels (Cogolludo *et al.*, 2001).

It is well known that the presence of different chemical groups in drug's molecules influenced its potency, selectivity and mechanism of action. The computer-based analysis of substructures of various response modifiers suggested secondary amino groups, ethers, carbonyl groups and benzyl groups in the propafenone as possible pharmacophoric substructures (Chiba *et al.*, 1995). Thus, we have shown that propafenone and its derivatives which were synthesized by substitution in the benzyl moiety with -F, -CH<sub>3</sub> or CF<sub>3</sub> groups on the *ortho* or *para* position produced vasodilatation of rat aorta. Introduction of 5-*ortho*-CF<sub>3</sub> and 5-*para*-CH<sub>3</sub> group in the benzyl moiety of propafenone molecule changed its potency and K<sub>V</sub> and L-type Ca<sup>2+</sup> channels are involved in their mechanism of action. The introduction of other tested groups in the benzyl moiety did not influence pharmacological properties of derivatives of propafenone in relation to propafenone. Analogs of propafenone were synthesized with modifications in the benzyl moiety designed on the basis of the pre structure property relationship (SPR) and pharmacophoric studies (Ivković *et al.*, 2012).

Here we investigated the effect of new *ortho*-chloro derivate of propafenone (5OCl) on the vascular tone of rat aorta (Fig. 1). According to great efficacy of

propafenone in therapy of arrhythmia, the development of new structurally related propafenone derivatives with better clinical profile may be useful in future.

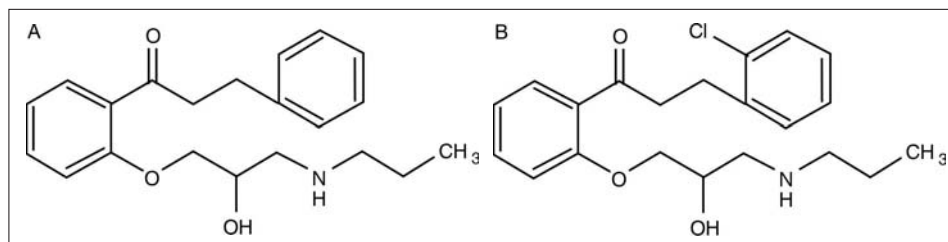


Figure 1. Chemical structures of (A) propafenone and (B) its *ortho* chloro derivate 5OCl

## MATERIAL AND METHODS

### *Assessment of vascular function*

Male Wistar rats obtained from the animal facilities of the University of Belgrade of Medicine faculty were used in all experimental procedures. The study was approved by the Ethical Committee of Faculty of Medicine, University of Belgrade. The studies reported in this work have been carried out in accordance with the Guide for the Care and Use of Laboratory Animals are adopted and promulgated by the United States National Institutes of Health.

Vascular rings were prepared from the aorta of male Wistar rats, body weight of 250 – 300 g. The aorta segments were dissected free from connective tissue. They were cut into rings (3 mm) and mounted between two stainless-steel triangles in an organ bath containing 10 mL Krebs-Ringer-bicarbonate solution (mmol/L: NaCl 120, KCl 5, CaCl<sub>2</sub> 2.5, MgSO<sub>4</sub> 1.2, NaHCO<sub>3</sub> 25, KH<sub>2</sub>PO<sub>4</sub> 1.2, glucose 11, T = 37°C, pH = 7.4), aerated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. One of the triangles has been attached to a displacement unit allowing fine adjustment of tension and the other was connected to an isometric transducer (K30; Hugo Sachs, Freiburg, Germany). The preparations were allowed to equilibrate for 30 min. We have examined the effects of 5OCl onto the rings with or without endothelium. After the equilibration period, the presence of functional endothelium was assessed. Rings were precontracted with phenylephrine (10 μM) and acetylcholine (20 μM) was added into the organ bath. In the some experiments endothelium was removed mechanically. The resting tension was 2 g. The vascular rings were allowed a further 30 min to equilibrate before being contracted with phenylephrine (10 μM).

### *Contraction of the rat aorta evoked by phenylephrine*

Concentration-response curves were obtained by the cumulative addition of 5OCl to ring segments contracted to a stable plateau by adding phenylephrine. Increasing concentrations of 5OCl has been added only after the previous concentration had produced equilibrium response. Therefore, the following protocol was used: 1) contraction to phenylephrine and concentration - response

curve to 5OCl followed by three washes, addition of ion channel blockers (3 mM 4-aminopyridine or 1  $\mu$ M nifedipine or 3 mM lidocaine) and 20 min equilibration period; 2) contraction to phenylephrine and the concentration-response curve to 5OCl.

#### *Statistical analyses*

The results are expressed as the means  $\pm$  standard error (SEM); n refers to the number of experiments. The concentration of 5OCl producing 50% of its own maximum response ( $EC_{50}$ ) was determined for each curve by using a non-linear least square fitting procedure of the individual experimental data. The  $pD_2$  value was calculated from  $-\log EC_{50}$ . Responses are expressed as a percentage of the maximum possible relaxation, i.e., the return of tension to the pre-phenylephrine level ( $E_{max}$ ). All calculations were done by using the computer program Graph Pad Prism (Graph Pad Software Inc., San Diego, U.S.A.). Statistical difference between means was determined by Student's t-test and a p value  $<0.05$  was considered statistically significant.

#### *Drugs*

For chemical synthesis of 5OCl derivate the following compounds are used: 2-hydroxyacetophenone, 2-chlorobenzaldehyde, epichlorhydrine, propylamine, and hydrochloride acid (Sigma-Aldrich Inc., St. Louis, MO, USA).

In pharmacological experiments the following drugs were used: phenylephrine, acetylcholine, 4-aminopyridine (4-AP), nifedipine, lidocaine (Sigma-Aldrich Inc., St. Louis, MO, USA). 5OCl was dissolved in distilled water. Nifedipine was dissolved in 70% v/v ethanol with further dilution in distilled water before use. Working concentrations of ethanol in the bath were  $<0.01\%$  (v/v). Previous experiments showed that the solvents used had no effects on preparations at the applied concentrations. All drugs were added directly to the bath in a volume of 100  $\mu$ L and the concentrations given are the calculated final concentrations in the bath solution. The experiments with nifedipine were performed in a dark room.

## RESULTS

#### *Synthesis of phenylpropiophenone derivative*

Synthesis of the 5OCl compound was carried out according to the general method first reported by Ivković *et al.*, (2009) and its structure has been verified by NMR, MS and MS spectroscopy. The tested compound is derivative of phenylpropiophenone (as well as propafenone) with chloro substituent on the *ortho* position of the benzyl moiety (Fig. 1). Because of the high structural similarity between newly synthesized compound and propafenone, this compound may be considered derivatives of propafenone.

*Relaxant effects of 5OCl on the isolated rat aorta precontracted by phenylephrine*

5OCl (1 - 100  $\mu$ M) induced a concentration dependent relaxation of rings with endothelium and without endothelium with  $EC_{50}$  values of  $13.51 \pm 0.09 \mu$ M ( $E_{max} = 86.1 \pm 3.9\%$ ,  $n = 6$ ) and  $14.20 \pm 0.10 \mu$ M ( $E_{max} = 90.1 \pm 2.8\%$ ,  $n = 6$ )

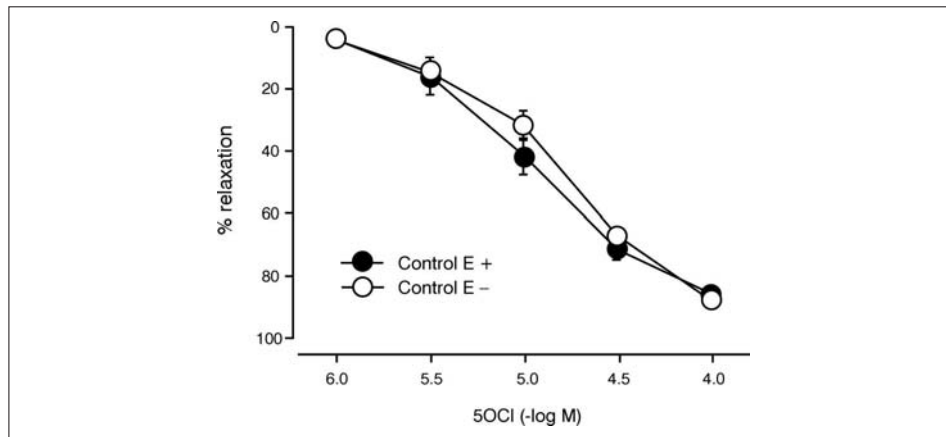


Figure 2. Cumulative concentration-response curves to 5OCl in the rat aorta with endothelium (black circle) and without endothelium (white circle) precontracted with phenylephrine (10  $\mu$ M). Responses are expressed as a percentage of the maximum possible relaxation (i.e., return to baseline tension). Each point represents the mean  $\pm$  S.E.M. ( $n = 12$ )

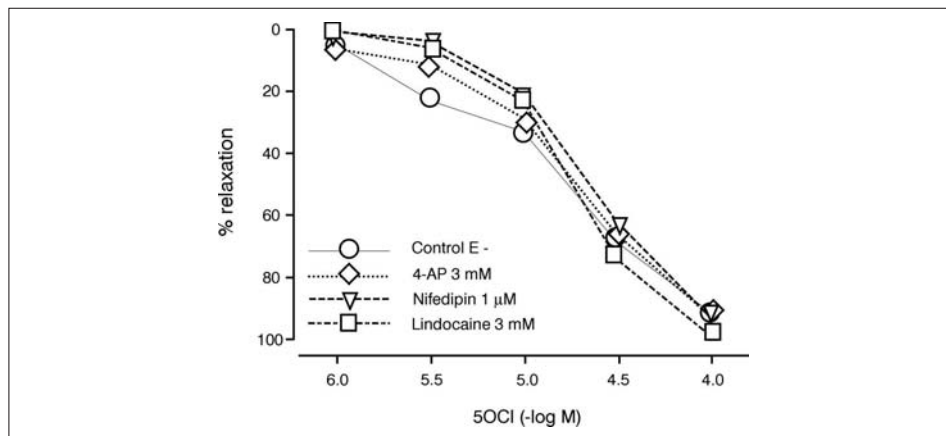


Figure 3. Antagonism of the relaxation effects of 5OCl by 4-AP, nifedipine and lidocaine on tension development in the rat aorta ring. Concentration-response curves for 5OCl in the absence (open circle) and presence of 4-AP (3 mM, open diamond), nifedipine (1  $\mu$ M, open triangle) and lidocaine (3 mM, open square). Each point represents the mean  $\pm$  S.E.M. ( $n = 4-7$ )

respectively ( $p > 0.05$ , Fig. 2). Regarded  $EC_{50}$  values, 4-AP (3 mM,  $n = 7$ ) did not modify the 5OCl induced-relaxation of the rat aorta ( $EC_{50} = 16.60 \pm 0.1 \mu\text{M}$ ,  $E_{\text{max}} = 91.1 \pm 3.5 \%$ ,  $p > 0.05$ ). Further, nifedipine (1  $\mu\text{M}$ ,  $n = 4$ ) did not modify the relaxation of the rat aorta induced by 5OCl ( $EC_{50} = 20.25 \pm 0.30 \mu\text{M}$ ,  $E_{\text{max}} = 92.0 \pm 4.5 \%$ ,  $p > 0.05$ ). Lidocaine (3 mM,  $n = 6$ ) did not modify the 5OCl induced relaxation of the aorta rings ( $EC_{50} = 13.92 \pm 0.11 \mu\text{M}$ ,  $E_{\text{max}} = 97.2 \pm 2.5 \%$ ,  $p < 0.05$ ). However, 4-AP, nifedipine and lidocaine significantly inhibited the relaxation elicited with concentration of 5OCl less than 10  $\mu\text{M}$  ( $EC_{25}$  without antagonist was  $5.34 \pm 0.11 \mu\text{M}$ ; in the presence of 4-AP, nifedipine and lidocaine  $EC_{25}$  were  $5.07 \pm 0.14 \mu\text{M}$ ,  $4.93 \pm 0.18 \mu\text{M}$  and  $4.99 \pm 0.09 \mu\text{M}$ , respectively,  $p < 0.05$ , Fig. 3)

4 - AP (3 mM), nifedipine (1  $\mu\text{M}$ ) and lidocaine (3 mM), did not affect the basal tension of aorta nor the contraction induced by phenylephrine (data not shown,  $n = 3 - 7$ ).

#### DISCUSSION

5OCl induced endothelium-independent relaxation of rat aorta. This result is consistent with previous findings for propafenone-induced dilatation of rat aorta and portal vein (Carron *et al.*, 1991; Cogolludo *et al.*, 1998). Also, we have shown previously that five newly developed phenylpropiofenone derivate produced endothelium-independent relaxation of rat aorta (Ivkovic *et al.*, 2012), as well. The potency of 5OCl (4.85) calculated from the  $pD_2$  value from the concentration-response curves was significantly lower than the potency of propafenone (5.03) and its derivatives, ortho- $\text{CF}_3$  (5.12) and ortho- $\text{CH}_3$  (4.96) (Ivkovic *et al.*, 2012). It is obvious that the presence of different chemical groups in the molecule of propafenone influences its potency.

In order to test the involvement of different ion channels in 5OCl mechanism of action, antagonist of  $\text{Na}^+$ ,  $\text{K}_v$  and L-type  $\text{Ca}^{2+}$  channels were used.

To analyze the contribution of  $\text{Na}^+$  channels to the 5OCl-induced relaxation of the rat aorta, lidocaine was used. Lidocaine is the local anesthetic that blocks  $\text{Na}_v1.5$  channels and has been used therapeutically to manage cardiac arrhythmias (Glaaser and Clancy, 2006). Our data suggest the involvement of lidocaine-sensitive channels in the relaxation of the rat aorta by 5OCl (if it is used in concentration lower than 10  $\mu\text{M}$ ). The rank order of concentration ratio (CR) value in presence of lidocaine was 0.98. Lidocaine produced a stronger inhibition of the propafenone effect in the same experimental model (CR = 1.37; Ivkovic *et al.*, 2012). Lidocaine did not block the effect of higher concentrations of 5OCl ( $\geq 10 \mu\text{M}$ ). It seems that 5OCl has a complex mechanism of action.

To analyze the contribution of  $\text{K}^+$  channels to the 5OCl-induced relaxation of the precontracted aorta's ring, we used 4-AP, a blocker of  $\text{K}^+$  channels (Wulff and Zhorov, 2008). Used in low milimolar concentratons, 4-AP achieved some selectivity for  $\text{K}_v$  channels (O'Rourke, 1996). In this study the CR values of 5OCl and 4-AP (1.17) was comparable with CR values obtained for ortho- $\text{CH}_3$  (1.17) derivate of propafenone and 4-AP (Ivkovic *et al.*, 2012). In contrast to the results



presented here, it has been shown that propafenone blocks the open state of K<sup>+</sup> channel (Delpón *et al.*, 1995, Duan *et al.*, 1993, Arias *et al.*, 2003). The effect of propafenone depends on whether the membrane is in a resting potential or in a state of depolarization (Lemennas - Gruber *et al.*, 1997). Our finding supports a relevant participation of Kv channels in the relaxation of the aorta ring produced by 5OCl if it is used in concentrations ≤10 μM. As propafenone, 5OCl in concentrations >10 μM acts through Kv channel-independent mechanism of action (Arias *et al.*, 2003; Ivkovic *et al.*, 2012).

In order to analyze the contribution of the L-type Ca<sup>2+</sup> channels to the 5OCl-induced relaxation of the rat aorta, we used nifedipine. Nifedipine (1 μM) caused significant antagonism of the effect of = 10 μM 5OCl suggesting the involvement of the nifedipine-sensitive Ca<sup>2+</sup> channels. In rat isolated aortic strips and portal veins nifedipine inhibited the propafenone effect with similar potency (Carrón *et al.*, 1991; Perez-Vizcaino *et al.*, 1994; Ivkovic *et al.*, 2012). However, we have shown that nifedipine inhibited more potently the effect of other propafenone derivate, i.e. *ortho*-CF<sub>3</sub> (Ivkovic *et al.*, 2012). As propafenone, high micromolar concentrations of 5OCl have ion a channel-independent mechanism of action (Ivkovic *et al.*, 2012). It has been shown previously that propafenone inhibited Ca<sup>2+</sup> release from intracellular stores in the rat aorta (Carrón *et al.*, 1991).

The introduction of Cl group on the *ortho* position in the bezyl moiety of propafenone changed its effect on the precontracted rat aorta. 5OCl derivate has comparable potency and efficacy as propafenone. According to its interaction with lidocaine, 4-AP and nifedipine it seems that 5OCl partly shares the mechanism of action with propafenone. The mechanism of vasodilatation induced by high micromolar concentration of 5OCl is not defined and further investigations are necessary. But we must be cautious in extrapolating their results to *in vivo* conditions.

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#### REFERENCES

1. Arias C, González T, Moreno I, Caballero R, Delpón E, Tamargo J *et al.*, 2003, Effects of propafenone and its main metabolite, 5-hydroxypropafenone, on HERG channels, *Cardiovasc Res*, 57, 660-9.
2. Bryson HM, Palmer KJ, Langtry HD, Fitton A, 1993, Propafenone, A reappraisal of its pharmacology, pharmacokinetics and therapeutic use in cardiac arrhythmias, *Drugs*, 45, 85-130.
3. Carrón R, Pérez-Vizcaino F, Delpón E, Tamargo J, 1991, Effects of propafenone on 45Ca movements and contractile responses in vascular smooth muscle, *Br J Pharmacol*, 103, 1453-7.
4. Chiba P, Burghofer S, Richter E, Tell B, Moser A, Ecker G, 1995, Synthesis, Pharmacologic Activity and Structure-Activity Relationships of a Series of Propafenone-Related Modulators of Multidrug Resistance, *J Med Chem*, 38, 2789-93.

5. Cogolludo AL, Pérez-Vizcaino F, López-López G, Ibarra M, Zaragoza-Arnáez F, Tamargo J, 2001, Propafenone modulates potassium channel activities of vascular smooth muscle from rat portal veins, *J Pharmacol Exp Ther*, 299, 801-10.
6. Cogolludo AL, Perez-Vizcaino F, Tamargo J, 1998, Antagonism by class I antiarrhythmic drugs of levromakalim-induced relaxation in isolated rat aorta, *J Pharmacol Exp Ther*, 287, 81-6.
7. Delpón E, Valenzuela C, Pérez O, Casis O, Tamargo J, 1995, Propafenone preferentially blocks the rapidly activating component of delayed rectifier K<sup>+</sup> current in guinea pig ventricular myocytes. Voltage-independent and time-dependent block of the slowly activating component, *Circ Res*, 76, 223-35.
8. Duan D, Fermi B, Nattel S, 1993, Potassium channel blocking properties of propafenone in rabbit atrial myocytes, *J Pharmacol Exp Ther*, 264, 1113-23.
9. Feld GK, Nademanee K, Singh BN, Kirsten E, 1987, Hemodynamic and electrophysiologic effects of combined infusion of lidocaine and propafenone in humans, *J Clin Pharmacol*, 27, 52-9.
10. Fernández del Pozo B, Pérez-Vizcaino F, Fernández C, Zaragoza F, Tamargo J, 1997, Effects of several class I antiarrhythmic drugs on isolated rat aortic vascular smooth muscle, *Gen Pharmacol*, 29, 539-43.
11. Franqueza L, Valenzuela C, Delpón E, Longobardo M, Caballero R, Tamargo J, 1998, Effects of propafenone and 5-hydroxy-propafenone on hKv1.5 channels, *Br J Pharmacol*, 125, 969-78.
12. Glaaser IW, Clancy CE, 2006, Cardiac Na<sup>+</sup> channels as therapeutic targets for antiarrhythmic agents, *Handbook Exp Pharmacol*, 171, 99-121.
13. Goodman and Gilman's Manual of pharmacology and therapeutics. EDS. LL Brunton and KLP Parker. McGraw Hill, 2008, Arias, 2003.
14. Ivkovic B, Sokovic M, Markovic B, Vladimirov S, Synthesis and evaluation of derivatives of propylpropylphenone as potential antibacterial and antifungal agents, in Mátyus P, Wöfling J, eds. Hungarian-Austrian-Czech-German-Greek-Italian-Polish-Slovak-Slovenian Joint Meeting on Medicinal Chemistry: 2009 June 24-27 Budapest, Hungary. Bologna: MEDIMOND, 2009, 61-4.
15. Ivković B, Vladimirov S, Novaković R, Cupić V, Heinle H, Gojković-Bukarica L, 2012, The novel propylpropylphenone derivatives induced relaxation of isolated rat aorta, *Arzneimittelforschung*, 62, 345-50.
16. Lemmens-Gruber R, Marei H, Heistracher P, 1997, Electrophysiological properties of the propafenone-analogue GE 68 (1-[3-(phenylethyl)-2-benzofuryl]-2-(propylamino)-ethanol) in isolated preparations and ventricular myocytes of guinea-pig hearts, *Naunyn Schmiedeberg's Arch Pharmacol*, 355, 230-8.
17. Malfatto G, Zaza A, Forster M, Sadowick B, Danilo P Jr, Rosen MR, 1988, Electrophysiologic, inotropic and antiarrhythmic effects of propafenone, 5-hydroxypropafenone and N-depropylpropafenone, *J Pharmacol Exp Ther*, 246, 419-26.
18. Nelson MT, Quayle JM, 1995, Physiological roles and properties of potassium channels in arterial smooth muscle, *Am J Physiol*, 268, C799-822.
19. O'Rourke ST, 1996, Effects of potassium channel blockers on resting tone in isolated coronary arteries, *J Cardiovasc Pharmacol*, 27, 636-42.
20. Pérez-Vizcaino F, Fernández del Pozo B, Zaragoza F, Tamargo J, 1994, Voltage- and time-dependent inhibitory effects on rat aortic and porcine coronary artery contraction induced by propafenone and quinidine, *Br J Pharmacol*, 113, 1281-8.
21. Valenzuela C, Delpón E, Tamargo J, 1988, Tonic and phasic V<sub>max</sub> block induced by 5-hydroxypropafenone in guinea pig ventricular muscles, *J Cardiovasc Pharmacol*, 12, 423-31.
22. Wulff H, Zhorov BS, 2008, K<sup>+</sup> channel modulators for the treatment of neurological disorders and autoimmune diseases, *Chem Rev*, 108, 1744-73.



## RELAKSACIJA AORTE PACOVA INDUKOVANA NOVOSINTETISANIM ORTO-HLORNIM DERIVATOM PROPAFENONA

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### SADRŽAJ

Informacije o efektima propafenona na vaskularne glatke mišiće su oskudne. Propafenon blokira voltažno-zavisne Na<sup>+</sup> kanale, Ca<sup>2+</sup> kanale L-tipa, voltažno-senzitivne K<sup>+</sup> (Kv) kanale i β-adrenergičke receptore u srcu. Uvođenje različitih hemijskih grupa u benzilni deo molekula propafenona utiče na promenu njegovih farmakoloških osobina. U ovoj studiji je ispitivan uticaj novog orto-hloro derivata (5OCl) propafenona na vaskularni tonus prekontrahovane aorte pacova. Orto hlorni derivat (5OCl) je izazvao endotel-nezavisnu relaksaciju aortnih prstenova. Da bi se ispitala uloga različitih jonskih kanala u ovoj relaksaciji, korišćeni su lidokain, (antagonist Na<sup>+</sup> kanala), 4-aminopiridin (antagonist Kv kanala) i nifedipin (antagonist Ca<sup>2+</sup> kanala L-tipa). Testirani antagonisti jonskih kanala nisu uticali na relaksaciju aorte pacova izazvanu visokom koncentracijom 5OCl (≥10 μM), ali su zato antagonizovali relaksaciju aorte koncentracijama 5OCl koje su bile manje od 10 μM. Prema tome, 5OCl derivat ima sličnu jačinu i efikasnost kao propafenon. Prema njegovoj interakciji sa lidokainom, 4-AP i nifedipinom može se reći da je mehanizam dejstva 5OCl sličan propafenonu. Mehanizam vazodilatacije 5OCl derivata u koncentracijama većim od 10 μM nije definisan i za to su potrebna dalja istraživanja.

