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Short communication

Antiarrhythmic activity of new 2-methoxyphenylpiperazine xanthone derivatives after ischemia/reperfusion in rats

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ABSTRACT

Background: We have previously shown significant prophylactic and therapeutic antiarrhythmic activity in adrenaline-induced arrhythmia, as well as α_1-adrenolytic properties of new derivatives of xanthone. Herein, we investigated their antiarrhythmic activity in the model of ischemia/reperfusion in isolated hearts. Furthermore, we assessed antioxidant activity in biochemical studies.
Methods: Antiarrhythmic activity in the model of ischemia/reperfusion in isolated perfused hearts was performed according to the Langendorff technique. Antioxidant activity was measured by lipid peroxidation level in tissue homogenate and in the FRAP assay.
Results: All studied compounds (**MH-94**, **MH-99** and **MH-105**) showed significant antiarrhythmic activity in the model of ventricular arrhythmias associated with coronary artery occlusion and reperfusion. However, they did not demonstrate antioxidant effect, probably, because of the lack of free hydroxyl group(s) at a key position in the xanthone scaffold.
Conclusions: The present study provides evidences for antiarrhythmic activity of some 2-methoxyphenylpiperazine derivatives of xanthone.

Introduction

Ventricular tachycardia and ventricular fibrillation are the principal reasons of death in patients with myocardial infraction [1]. Since the prevalence of coronary heart disease increases worldwide, the possibility of sudden cardiac death (SCD) is more common. The occurrence of SCD in Europe and USA seems to be similar and there is approximately 1 incidence per 1000 per year [2,3]. On the one hand, ventricular arrhythmias are susceptible to many groups of antiarrhythmic drugs, such as sodium and calcium channel blockers, β-blockers, potassium current blockers. On the other hand, antiarrhythmic drug therapy is often limited by the adverse effects of these drugs, such as bradycardia, tiredness, dizziness or thyroid dysfunction, as well as the risk of causing new life-threatening arrhythmias (proarrhythmic effect). Therefore, the searching for new potential antiarrhythmics that can improve heart function with minimal side effects seems to be reasonable.

Extensive pharmacological studies in the group of xanthone derivatives indicated that they possess beneficial effects on several cardiovascular diseases [4–6]. In the pathogenesis of post-ischemic myocardial dysfunction the generation of oxygen free radicals and lipid peroxides seem to play a crucial role. Earlier studies have shown that xanthones were able to decrease ischemia/reperfusion induced arrhythmias and that this cardioprotective effect was related to the inhibition of lipid peroxides in myocardial tissues. It has been also reported that among oxygenated and prenylated xanthone derivatives new compounds with strong antioxidant activity were found [6,7]. On the other hand, in animal models of arrhythmia, α_1-adrenoceptor, as well as, α_1/α_2-adrenoceptor antagonists, like urapidil, prazosin and phentolamine protected against ischemia/reperfusion changes in isolated rat hearts [8,9]. Moreover, it has been recently reported that the 1,4-substituted piperazine derivatives with α_1-adrenolytic properties displayed significant antiarrhythmic activity in ischemia/reperfusion arrhythmias [10].

Our earlier work has demonstrated significant prophylactic and therapeutic activity in adrenaline-induced arrhythmias, as well as prominent hypotensive activity of several xanthone derivatives

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with 2-methoxyphenylpiperazine moiety [11,12]. Three of them: **MH-94**, **MH-99** and **MH-105** also revealed high affinity for α_1-adrenoceptors in radioligand binding assay. Moreover, we confirmed α_1-adrenolytic activity these agents in the *in vitro* (isolated rat aorta contracted by phenylephrine) and *in vivo* (influence on blood vasopressor response in rats) tests [11]. The obtained results suggest that the antiarrhythmic and hypotensive effects could be related to their α_1-adrenoceptors antagonistic properties.

In our present study we planned to investigate antiarrhythmic activity in the model of ischemia/reperfusion in isolated perfused rat hearts. In order to examine a possible antioxidant activity some *in vitro* biochemical studies were performed.

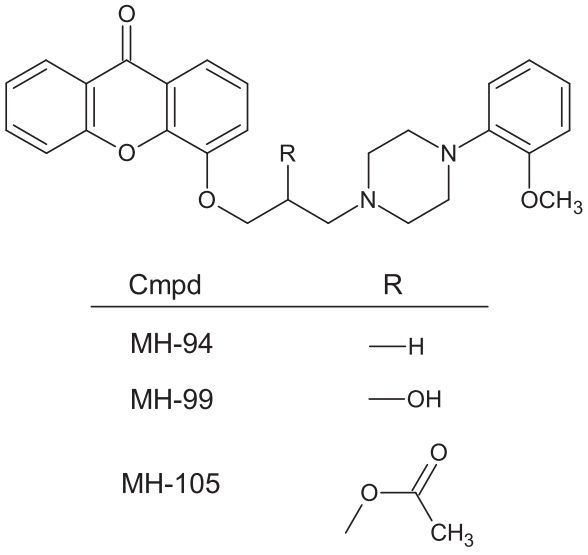
Materials and methods

Animals and experimental conditions

The studies were carried out on normotensive male Wistar rats weighing 180–200 g (KRF: WI (WU)). The animals were kept in plastic cages at room temperature of 20 ± 4 °C, under a 12/12 h light/dark cycle (light on from 7 a.m. to 7 p.m.). Standard food (standard laboratory pellets) and tap water were freely available before experiments. The control and study groups consisted of 6–8 animals each. The study was performed according to the Animal Care and Use Committee guidelines and was approved by the Local Ethics Committee of the Jagiellonian University in Kraków.

Drugs

The examined compounds: **MH-94** (4-(3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9*H*-xanthen-9-one hydrochloride), **MH-99** ((*R*,*S*)-4-(2-hydroxy-3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9*H*-xanthen-9-one hydrochloride) and **MH-105** ((*R*,*S*)-4-(2-acetoxy-3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9*H*-xanthen-9-one hydrochloride) were synthesized at the Department of Bioorganic Chemistry, Jagiellonian University Medical College (Scheme 1). The synthesis and preliminary pharmacological studies of these compounds were described earlier [12]. The following drugs were used: quinidine, urapidil (Sigma–Aldrich, Germany), heparin sodium (Polfa, Poland), thiopental sodium (Biochemie Gmbh, Austria). Other chemicals used were purchased from Polskie Odczynniki Chemiczne (Poland).



Scheme 1. Schematic structure of the studied 2-methoxyphenylpiperazine derivatives of xanthone.

Ischemia/reperfusion

Antiarrhythmic activity in the model of ischemia/reperfusion in isolated perfused hearts was performed according to the modified Langendorff technique as we precisely described previously [8,13]. After a 20 min stabilization period, a clip was placed on the left coronary artery for 15 min to induce acute myocardial ischemia. Then the clip was removed and the occurrence of ventricular premature beats (VBs), ventricular tachycardia (VT) and ventricular fibrillation (VF) during reperfusion period were monitored for 30 min. The arrhythmia severity index was calculated in order to quantify the arrhythmias [14]. The tested compounds were put into the perfusion solution 15 min before coronary artery ligation and the concentration was sustained for the rest of the perfusion period. The following grades were attributed: the occurrence of up to 10 ventricular extrasystoles during 30 min of reperfusion – 1, more than 10 – 2, ventricular tachycardia – 3, ventricular fibrillation – 4.

In separate series of experiments the effect of the tested compounds, at the concentrations of 10^{-7}–10^{-5} M on electrocardiogram (ECG), was assessed after 20 min of initial equilibration period.

Antioxidant activity

The ferric reducing antioxidant power (FRAP) assay

Antioxidant activity was examined using the FRAP assay as described previously [13]. This method is based on the reduction of ferric tripyridyltriazine (Fe^{3+}-TPTZ) complex to the ferrous (Fe^{2+}-TPTZ) form at low pH by antioxidant agents. The reduced ferrous forms, which have an intense blue color, with absorption maximum at 593 nm were measured [15]. The results were obtained as the increase in absorbance of the test sample compared to the sample containing the solvent alone. Trolox (synthetic vitamin E analog) at the concentrations range from 10^{-5} to 3×10^{-4} M was used as a reference compound. The tested compounds were added at the concentration of 10^{-4} M.

Influence on lipid peroxidation

Lipid peroxidation level was determined in rat brain homogenate as we precisely described previously [8,10]. The membrane lipid peroxide content was quantified by the formation of thiobarbituric acid reactive substances (TBARS). The absorbance of the supernatant was measured at 532 nm. The amount of TBARS was determined using a standard curve of malonaldehyde bis (dimethyl acetal).

Data analysis

All results, presented in the tables as mean ± SEM. Statistically significant differences between groups were calculated using one-way analysis of variance (ANOVA), followed by Dunnett's *post hoc* test or repeated measures ANOVA. Values of $p < 0.05$ were considered to be statistically significant.

Results

Antiarrhythmic activity in the model of ischemia/reperfusion in isolated perfused rat heart

In the control group the incidence of ventricular premature beats and ventricular tachycardia was 100%, whereas ventricular fibrillation occurred in 16.7% hearts. Table 1 shows that all tested

Table 1
Effect of the tested and referenced compounds on reperfusion-induced arrhythmia.

Compound	Concentration (M)	VBs incidences	VT incidences	VF incidences	Arrhythmia severity index
Control	–	6/6	6/6	1/6	4.83 ± 0.17
MH-94	10^{-7}	4/6	3/6	0/6	$2.33 \pm 0.67^{**}$
	10^{-6}	3/6	1/6	0/6	$1.50 \pm 0.43^{***}$
	10^{-5}	4/6	0/6	0/6	$0.67 \pm 0.21^{***}$
MH-99	10^{-7}	2/6	2/6	0/6	$1.50 \pm 0.72^{***}$
	10^{-6}	5/6	0/6	0/6	$1.17 \pm 0.31^{***}$
	10^{-5}	5/6	0/6	0/6	$1.00 \pm 0.26^{***}$
MH-105	10^{-7}	3/6	2/6	0/6	$1.67 \pm 0.67^{***}$
	10^{-6}	4/6	0/6	0/6	$1.00 \pm 0.36^{***}$
	10^{-5}	2/6	0/6	0/6	$0.33 \pm 0.21^{***}$
Urapidil	10^{-7}	8/8	6/8	2/8	4.5 ± 0.4
	10^{-6}	7/8	2/8	1/8	$3.6 \pm 0.2^{*}$
	10^{-5}	8/8	4/8	3/8	4.9 ± 0.3
Quinidine	10^{-6}	5/6	3/6	0/6	$2.3 \pm 0.8^{*}$
	5×10^{-6}	1/6	2/6	0/6	$1.2 \pm 0.6^{***}$

The data indicate: number of hearts affected/number of hearts per group. The arrhythmia severity indices are the means of 6–8 experiments ± SEM. Statistical analysis were performed using one-way analysis of variance (ANOVA), followed by Dunnett's *post hoc* test; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

compounds significantly diminished the incidence of arrhythmia in comparison with the control hearts ($F[3,20] = 18.52$, $p < 0.0001$, **MH-94**; $F[3,20] = 18.73$, $p < 0.0001$, **MH-99**; $F[3,20] = 24.43$, $p < 0.0001$, **MH-105**; one-way ANOVA, Dunnett's *post hoc* test). Compound **MH-99** was the most active at the concentration of 10^{-7} M and significantly reduced the incidence of ventricular premature beats (by 66.7%), ventricular tachycardia (by 66.7%) and there was no incidence of ventricular fibrillation. The arrhythmia severity index was much lower – 1.50 as compared with the index of control hearts, which was 4.83 ($n = 6$, $p < 0.001$). Similarly, compound **MH-105** at this concentration showed high antiarrhythmic activity and significantly reduced the incidence of ventricular premature beats (by 50%), ventricular tachycardia (by 66.7%), and there was no incidence of ventricular fibrillation. The arrhythmia severity index for compound **MH-105** at the concentration of 10^{-7} M was 1.67 ($n = 6$, $p < 0.001$). Compound **MH-94** at the concentration of 10^{-7} showed weaker activity, with the arrhythmia severity index 2.33 ($n = 6$, $p < 0.01$). However, at higher concentrations (10^{-6} and 10^{-5} M) was more active. Urapidil significantly reduced the incidence of ventricular arrhythmia at the concentration of 10^{-6} M, with the arrhythmia severity index 3.6 ($n = 4$, $p < 0.05$), whereas quinidine was active at the concentrations of 10^{-6}–5×10^{-6} M.

Table 2 presents the influence of the tested compounds on the heart rate and electrocardiogram parameters. The tested compounds at the concentrations of 10^{-7}–10^{-5} M revealed weak and statistically insignificant influence on ECG parameters (PR, QRS, QT intervals). At the concentration of 10^{-5} M the tested compounds decreased the number of cardiac beats per minute (**MH-94** by 25%; **MH-99** by 17%; **MH-105** by 14%). It is worth noting that the tested compounds, did not influence the QT_c interval. Urapidil only at the concentration of 10^{-5} M significantly prolonged PR interval by 31%. Moreover, at concentrations of 10^{-6}–10^{-5} M it decreased significantly the number of cardiac beats per minute by 12–19%. Only quinidine significantly influenced PR, QRS, QT_c intervals. At the concentration of 10^{-5} M it significantly prolonged PR interval by 36%, QRS complex by 74%, QT_c interval by 23% and decreased the number of cardiac beats per minute by 33%.

Antioxidant activity

In the FRAP assay all examined xanthone derivatives at the concentration of 10^{-4} M exerted weak antioxidant activity – compared with trolox (reference compound), it was only 4–8% of its activity. Similarly, the tested compounds did not significantly decrease lipid peroxidation, measured as thiobarbituric acid reactive substances in rat brain homogenate (data not shown).

Discussion

In the described experiment, we examined the antiarrhythmic activity of three most interesting 2-methoxyphenylpiperazine xanthone derivatives, selected from the previous studies, in the model of ischemia/reperfusion [11,12]. *In vitro* pharmacological profile of the tested compounds revealed their high affinity for α_1-adrenoceptors. Already presented functional surveys displayed their non-selective α_1-adrenolytic properties [16]. Earlier research by many groups indicated that some agents with α_1-adrenoceptor antagonistic properties revealed prominent antiarrhythmic activity in animal models [9,10,17]. Also in our studies, we demonstrated that prazosin, as well urapidil significantly reduced the incidence of ventricular tachycardia and ventricular fibrillation in the isolated rat heart [8]. It is well known, that α_1-adrenoceptors play a major role in the regulation of blood pressure, lipid metabolism and prostatic function. However, these receptors appear to be essential also in heart, especially under pathological conditions, when they maintain cardiac contractile responses in the failing heart.

It is worth to note, that the effects mediated through α_1-adrenoceptors are species dependent. The α_{1A}-adrenoceptor subtypes prevail in human heart, whereas the α_{1B}-adrenoceptor subtypes predominate in rat heart. Moreover, the density of these receptors in rodent heart is about five times greater than in the human heart [18]. Previous studies have shown that in rat heart, the period of ischemia causes the formation of large amounts of inositol 1,4,5-triphosphate (IP_3), which seems to provoke arrhythmias in the reperfusion period. Consequently, α_1-adrenoceptor blockade, resulting in the reduction in the amount of IP_3, contributes to the reduction of cardiac arrhythmia [19]. In rodent models of ischemia/reperfusion arrhythmia α_1-adrenoceptor antagonists seem to be very effective. However, it is worth to note, that none of them is used as antiarrhythmic agent nowadays.

It has been reported by many groups that xanthone derivatives revealed antiarrhythmic activity in the model of ischemia/reperfusion arrhythmia associated with coronary artery occlusion and reperfusion in rats hearts [4–6]. This model of arrhythmia seems to be useful in searching for new antiarrhythmic agents

Table 2
The influence of the tested and referenced compounds on ECG intervals and heart rate.

Compound	Parameters	Concentration (M)			
		Control	10^{-7}	10^{-6}	10^{-5}
MH-94	PR (ms)	59.0 ± 1.0	60.0 ± 0.8	61.0 ± 0.6	62.5 ± 1.0
	QRS (ms)	28.5 ± 1.5	29.5 ± 1.3	29.5 ± 0.5	30.0 ± 0.4
	QT_c (ms)	200.6 ± 10.0	190.5 ± 11.5	186.4 ± 9.6	181.2 ± 10.0
	HR per min	131.6 ± 10.9	115.3 ± 10.0	109.0 ± 10.0*	98.7 ± 8.2**
MH-99	PR (ms)	59.0 ± 1.0	59.5 ± 0.5	60.0 ± 0.8	60.5 ± 1.3
	QRS (ms)	23.0 ± 0.6	23.0 ± 0.6	23.0 ± 0.6	23.0 ± 0.6
	QT_c (ms)	212.1 ± 16.3	204.5 ± 25.2	198.6 ± 25.0	207.2 ± 16.3
	HR per min	140.0 ± 9.3	139.8 ± 13.2	122.4 ± 9.3	116.6 ± 6.0*
MH-105	PR (ms)	61.0 ± 0.6	61.0 ± 0.6	60.5 ± 0.5	61.0 ± 0.6
	QRS (ms)	29.0 ± 1.3	28.5 ± 1.0	28.5 ± 1.0	28.5 ± 1.0
	QT_c (ms)	212.1 ± 16.3	205.9 ± 14.3	205.9 ± 14.3	200.0 ± 11.5
	HR per min	139.9 ± 4.2	126.0 ± 6.3	122.3 ± 9.2	121.0 ± 8.9*
Urapidil	PR (ms)	51.6 ± 2.4	59.4 ± 6.4	64.1 ± 5.1	67.6 ± 8.4*
	QRS (ms)	20.1 ± 1.2	21.1 ± 2.2	21.1 ± 2.2	23.4 ± 2.9
	QT_c (ms)	247.1 ± 18.1	251.3 ± 23.1	247.7 ± 15.1	250.9 ± 13.6
	HR per min	150.1 ± 10.7	140.5 ± 8.1	132.2 ± 5.2*	121.4 ± 10.2**
Quinidine	PR (ms)	53.0 ± 3.0	58.0 ± 3.0	61.0 ± 2.0	72.0 ± 2.0**
	QRS (ms)	23.0 ± 2.0	31.0 ± 2.0*	36.0 ± 3.0***	40.0 ± 3.0***
	QT_c (ms)	256.0 ± 18.0	268.0 ± 12.0	301.0 ± 16.0**	315.0 ± 25.0***
	HR per min	159.0 ± 11.0	132.0 ± 10.0	120.0 ± 10.0*	106.0 ± 13.0**

The values are expressed as the means ± SEM of 5–6 experiments.
Statistical analysis: repeated measures ANOVA, *post hoc* Dunnett's test. Significant difference compared to the initial values: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

[8]. In our experiment, the highest antiarrhythmic activity had compounds **MH-99** and **MH-105**, which revealed similar activity at the concentrations of 10^{-7}–10^{-6} M. At the concentration of 10^{-5} M compound **MH-105** was the most active, with the arrhythmia severity index 0.33, whereas compound **MH-94** revealed the weakest antiarrhythmic effect, with the arrhythmia severity index 2.33. Taking into account the chemical structure of three tested xanthones, compound **MH-99** contains typical β-blocker linker with hydroxyl group: 3-amine-2-hydroxypropan-1-yloxy, which is acetylated in compound **MH-105**, whereas compound **MH-94** is devoided of hydroxyl group and contains 3-amine-2-propan-1-yloxy linker. Nevertheless, at all concentrations the studied compounds were more active than urapidil. Moreover, at the concentration of 10^{-6} M the arrhythmia severity indices of three tested compounds were lower from that of quinidine. This is in agreement with the results obtained by several authors that inhibitors of the fast inward current (class I), as well as α-blocking agents (urapidil, phentolamine, prazosin) seem to be notably effective antiarrhythmics against myocardial ischemia-reperfusion injury in rats [8,9]. We conclude that the effectiveness of the tested xanthone derivatives in this experiment could depend on their α_1-adrenolytic properties.

The ECG study showed that at higher concentrations the studied compounds insignificantly prolonged PR interval and QRS complex. In case of quinidine, a well-known Na^+ channel blocker, these parameters were significantly changed. None of the tested compounds influence the QT_c interval, which means that they did not reveal proarrhythmic potential in rats.

Post-ischemic recovery of function has also been found to be enhanced by xanthone derivatives without complex substituents in their structure, but with the presence of numerous hydroxyl groups in their chemical scaffolds [20]. The mechanism of cardioprotection of these xanthone derivatives is probably connected with their strong antioxidant properties. Also natural xanthones, like mangostin and manigiferin exert a powerful radical-scavenging activity. α-Mangostin was found to reveal strong protective effect against lipid peroxidation, whereas mangiferin enhanced the glutathione level. Moreover, mangiferin, the first xanthone examined for pharmacological purposes, showede anti-inflammatory, as well as immonomodulatory properties [7,20]. Three tested xanthone dervatives: **MH-94**, **MH-99** and **MH-105** exerted weak antioxidant activity in the FRAP assay, and did not inhibit lipid peroxidation in rat brain homogenate. These data support the hypothesis that antioxidant properties of xanthone derivatives are connected with the presence of free hydroxyl groups in their scaffolds.

In summary, the potential antiarrhythmic activity of three new 2-methoxyphenylpiperazine derivatives of xanthone in the model of ischemia/reperfusion arrhythmia associated with coronary artery occlusion and reperfusion was investigated. At all concentrations the studied compounds (**MH-94**, **MH-99**, **MH-105**) prevented or decreased the incidences of arrhythmia. The obtained arrhythmia severity indices are better than those obtained for urapidil. All tested compounds showed weak antioxidant properties. Based on the previous and present studies, we may conclude that the considerable effectiveness of the tested xanthone derivatives in ischemia/reperfusion arrhythmia depends on their α_1-adrenolytic properties.

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Conflict of interest

There is no conflict of interests.

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