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Short communication

Synthesis and cardiovascular evaluation of N-substituted 1-aminomethyl-2-naphthols

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Abstract – A series of 1-alkylaminomethylnaphthols have been prepared. These compounds were readily prepared in good yields by addition of 2-naphthol to formalin and alkylamines. The hypotensive and bradycardiac effects of these compounds in normotensive rats as well as their in vitro inotropic and aortic contraction effects in isolated rat left atria and aorta have been evaluated. A higher depressor and bradycardiac activity was found for compounds substituted on nitrogen by naphthol with primary amines, i.e., ethylamine, propylamine, isopropylamine, or butylamine and with a cyclic secondary amine, i.e., pyrrolidinyl. These compounds produced biphasic changes in contractile force in isolated rat atria which was correlated to blood pressure and heart rate activity. 1-Isopropylaminomethyl-2-naphthol hydrochloride relaxed isolated rat aortic rings precontracted with high extracellular K^+ (80 mM) and Ca^{2+} (1.9 mM). The suppressive effects of the compounds may involve a direct inhibition of Ca^{2+} channels. The biological activity of these compounds can be explained in terms of substitution on nitrogen.

1-alkylaminomethyl-2-naphthol / blood pressure / heart rate / left atrial / aorta

1. Introduction

1-Pyrrolidinylmethyl-2-naphthol hydrochloride (TPY-β) has been shown to produce a reduction in blood pressure (BP) and heart rate (HR) in anaesthetized rats [1]. The ionic mechanism of the cardiovascular activity of TPY-β has also been examined. The results indicated that suppressive effects of TPY-β involve a direct depressant action on heart cells and vascular smooth cells [2]. The direct inhibition of voltage-dependent L-type Ca^{2+} channels is involved in the TPY-β mediated vasodilatory action. In addition, the inhibitory effect of TPY-β on cardiac contractibility through the blockade of L-type Ca^{2+} channels can be prevented by TPY-β mediated inhibition of the transient outward potassium current. Bril et al. [3] reported that a compound with a combination of potassium and calcium channel antagonistic properties might consititute a novel anti-arrhythmic agent with reduced proarrhythmic risk. Some of the drugs used to treat ventricular arrhythmias have been shown to also act on the transient outward current at therapeutic concentrations [4–6]. The actions of TPY-β on the cardiovascular system encouraged us to search for and synthesize novel derivatives of aminomethylnaphthol. This brought forth the modification of the pyrrolidinyl group in TPY-β with primary amines via the condensation of 2-naphthol with primary amines. The method exists for attaching carbon substituents to the 1-position of 2-naphthol, and many 2-naphthols bearing such substituents are known in the literature [7]. A selection of compounds possessing a variety of 1-substituents was desired in order to broadly define the structure activity relationship for this portion of the molecule. These compounds, shown in *table I*, either were known in the literature or were prepared according to well-established synthetic methods [7, 8]. The purpose of the present study was to evaluate the importance of the side substitution at the 1-position of the aminomethylnaphthols.

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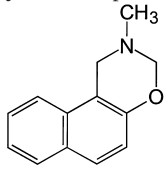
Table I. Hypotensive and bradycardic response following intravenous injection of aminomethylnaphthol derivatives (2.2 μmol/kg) in rats.



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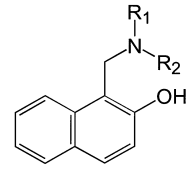

2–13

Compound	R_1	R_2	X	HR (beats/min)[a]		BP (mm Hg)[a]	
				maximum change	% maximum	maximum change	% maximum
N.S.				4 ± 2	1 ± 1	4 ± 3	3 ± 2
1				-8 ± 4	2 ± 1	-5 ± 4	6 ± 5
2	CH_3	H	HCl	-38 ± 15	11 ± 5	-10 ± 5	10 ± 5
3	C_2H_5	H	HCl	-240 ± 15*	62 ± 11*	-75 ± 19*	69 ± 16*
4	n-C_3H_7	H	HCl	-276 ± 31*	67 ± 13*	-94 ± 21*	81 ± 18*
5	i-C_3H_7	H	HCl	-268 ± 54*	65 ± 7*	-82 ± 11*	70 ± 20*
6	C_4H_9	H	HCl	-328 ± 43*	75 ± 21*	-103 ± 16*	85 ± 15*
7	CH_3	CH_3		-26 ± 3*	7 ± 2*	-16 ± 5*	15 ± 4*
8	C_2H_5	C_2H_5		-15 ± 4*	4 ± 2	-6 ± 4	5 ± 4
9	C_3H_7	C_3H_7		-13 ± 5*	3 ± 2	0	0
10	C_4H_9	C_4H_9		0	0	0	0
11	TPY-			-258 ± 33*	64 ± 15*	-81 ± 2*	77 ± 17*
12	-$(CH_2)_5$-			-137 ± 37*	32 ± 8*	-59 ± 13*	53 ± 11*
13	-$(CH_2)_2$-O-$(CH_2)_2$-			-121 ± 17*	28 ± 8*	-38 ± 8*	23 ± 9*

[a]Percent decrease in blood pressure and heart rate were calculated from the decrease in blood pressure and heart rate of the treatment group and the blood pressure (normally 105–120 mm Hg) and heart rate (normally 385–405 beats/min) of the control group; 2.2 μmol/kg usually amounts to 0.4–0.5 mg/kg; values are expressed as the mean ± SEM. Asterisks indicate significant difference (*t*-test, calculated on the changes) from the N.S. (normal saline). *$P < 0.05$.

2. Chemistry

In the present work, reaction of 2-naphthol with formaldehyde and methylamine in a molar ratio of 1:2:1, respectively, in a methanol solution at 60 °C was found to produce 2,3-dihydro-2-methyl-1H-naphth[1,2-e]-m-oxazine (**1**). Upon treating **1** with hot aqueous hydrochloric acid, formaldehyde was liberated and the hydrochloride of 1-methylaminomethyl-2-naphthol (**2**) was formed *(figure 1)* [7]. The condensation, run in the same manner except with ethylamine, propylamine, isopropylamine or butylamine, resulted in the formation of 1-alkylaminomethyl-2-naphthols directly instead of naphthoxazine products. Compounds **1**, **2**, **5**, and **6** were previously synthesized and reported [7]. The temperature and the particular amine seem to be the important factors in determining the course of the reaction of 2-naphthol with formaldehyde and primary amine as reported by Burke et al. [7].

The condensation of naphthols with formaldehyde and secondary amines has been studied previously [8]. Reaction of piperidine and formaldehyde with 1- and 2-naphthol has been shown to result in the introduction of a piperidinomethyl group into the 1-position of 2-naphthol and into the 2-position of 1-naphthol. This indicates that the substituent *ortho* to the naphthylene

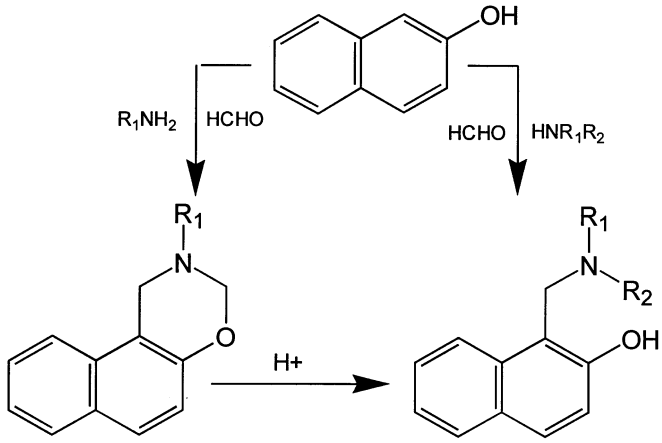

Figure 1. Synthetic routes for the 2,3-dihydro-2-methyl-1H-naphth[1,2-e]-m-oxazine (**1**) and aminomethylnaphthol derivatives (**2–13**).

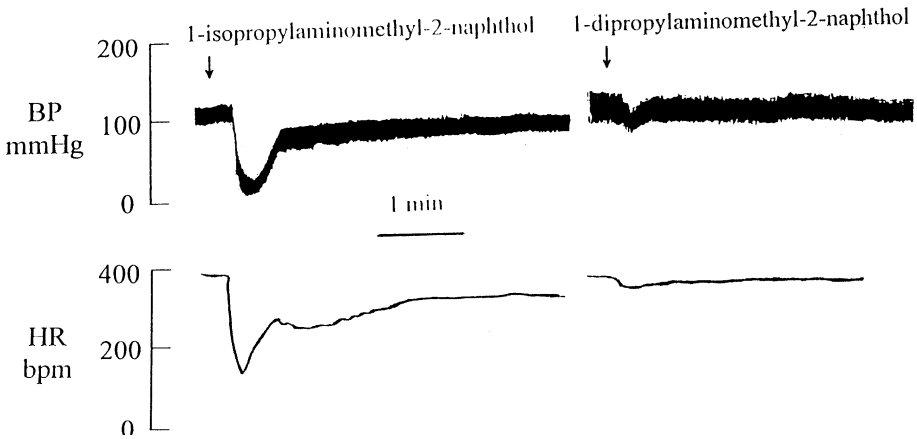

Figure 2. Effects of intravenous injection of 1-isopropylaminomethyl-2-naphthol (**5**) and dipropylaminomethyl-2-naphthol (**9**) on blood pressure and heart rate in one anaestherized normotensive rat. Compounds were administered at the time indicated by an arrow.

hydroxyl group plays a role in determining the course of the reaction [7, 8].

3. Results and discussion

Aminonaphthols have been reported to exhibit antihypertensive, adrenoceptor blocking, and Ca^{2+} channel blocking activities [9–11]. As described in the experimental section, the hypotensive and bradycardiac activity of the analogue series was tested in normotensive rats at a dosage of 2.2 μmol/kg. *Figure 2* shows the chart recordings of blood pressure (top traces) and heart rate (bottom traces) of an anaesthetized rat. Intravenous injection of compound **5** (2.2 μmol/kg) induced a maximum reduction of mean arterial pressure from 120 mm Hg to 25 mm Hg within 30 s and the BP returned to the control value in 20 min. Along with the sudden decrease in BP, the heart rate was also reduced from 400 beats min^{-1} to a minimum value of 130 beats min^{-1}, and it took 40 min for full recovery to the control level. The acute hypotensive and bradycardiac responses induced by 2.2 μmol/kg of these compounds are summarized in *table I*. Substitution of the amine hydrogen atom by alkyl groups of increasing chain length altered the activity. In the dialkylaminomethyl-2-naphthol series, the straight chain derivatives (**7–10**) had less hypotensive and bradycardiac activity than the cyclic analogues (**11–13**). An increase in the size of the N-dialkyl group appeared to reduce hypotensive and bradycardiac activity. Despite the limited series from which to evaluate the structure-activity relationship, primary amine substitution (**3–6**) showed better potency than secondary amine derivatives except methyl side chain derivatives (**1–2**), which were not active even at a higher dosage (data not shown).

The present results *(table II)* in vitro show that the 1-alkylaminomethyl-2-naphthols (**3–6**) and the secondary amines with cyclic side chains (**11**–**13**), at 30 μM, produced a biphasic effect on the contractile force in isolated rat left atria, i.e., an initial decrease and a sustained increase. A representative inotropic response of an electrically driven left atrium to 1-isopropylaminomethyl-2-naphthol hydrochloride (**5**) is depicted in *figure 3*. However, the straight chain derivatives (**7–10**) show the negative inotropic effect. The 4-Aminopyridine-sensitive transient outward current (Ito) has been shown to be present in rabbit, rat, cat, dog and human cardiac myocytes, but not in guinea-pig cardiac myocytes [12–15]. It has been suggested that the compound **11** (TPY-β) mediated inhibition of Ito would reverse the rat myocardial depressant effect caused by its initial inhibition of L-type Ca^{2+} channels [3]. The similarity of the molecular structure suggests that 1-isopropylaminomethyl-2-naphthol hydrochloride (**5**) and other analogues work in the same manner as compound **11** (TPY-β). In addition, Ca^{2+} (1.9 mM) elicited a 100% contraction in rat aorta in the presence of high K^+ (80 mM), **5** was more potent in suppressing the tone induced by high K^+ and Ca^{2+} than **7** as shown in *table III*. High K^+ has been shown to evoke smooth muscle contraction by promoting Ca^{2+} influx through voltage-sensitive Ca^{2+} channels which are readily activated by membrane depolarization [16]. Therefore, extracellular Ca^{2+} entry is thought to be the main cause of the high K^+-induced contraction. The present studies indicate that the suppressive effects of

Table II. Characteristics of aminomethylnaphthols (30 μM) on the contractile force in rat left atria stimulated at 1.0 Hz.

Compound	Maximal force of contraction (%)	
	phase 1	phase 2
1	100 ± 18 (3)	100 ± 16 (3)
2	100 ± 20 (3)	100 ± 19 (3)
3	90 ± 16* (5)	220 ± 36* (4)
4	85 ± 17* (5)	235 ± 42* (5)
5	82 ± 13* (6)	238 ± 29* (5)
6	83 ± 17* (5)	219 ± 23* (5)
7	78 ± 19* (4)	78 ± 19* (4)
8	80 ± 21* (4)	80 ± 21* (4)
9	88 ± 15* (4)	88 ± 15* (4)
10	97 ± 19* (4)	97 ± 19* (4)
11	77 ± 12* (5)	225 ± 49* (4)
12	90 ± 21* (5)	160 ± 23* (4)
13	89 ± 16* (6)	120 ± 25* (5)

Values are means ± SEM. Number of preparations (*n*) is given in parentheses.*$P < 0.05$ compared with the respective control by student *t* test.

these compounds could interfere with Ca^{2+} influx through the depolarized cell membrane to induce relaxation of rat aorta. The results observed are consistent with previous findings that **11** (TPY-β) or aminonaphthols effectively suppressed the voltage-gated Ca^{2+} current [2, 17, 18].

In conclusion, the biological activity of these compounds can be explained in terms of substitution on nitrogen. The development of N-substituted 1 aminomethyl-2-naphthols with dual effects would be of potential therapeutic advantage.

4. Experimental protocols

4.1. Chemistry

Melting points were determined on a Yanagimoto MP-3 micromelting apparatus and are uncorrected.

Table III. Effects of dimethylaminomethyl-2-naphthol (**7**) and 1-isopropylaminomethyl-2-naphthol hydrochloride (**5**) on the rat aortic contraction induced by KCl and Ca.

Compound	Contraction (% of Control) KCl (80 mM) + Ca (1.9 mM)
Control	100 ± 3.9
7 (45 μM)	79 ± 4.8
5 (45 μM)	50.4 ± 6.4
5 (150 μM)	15.3 ± 1.0

Percentages of the control contraction were calculated and presented as mean ± SEM ($n = 4$). *$P < 0.05$ as compared with the respective control.

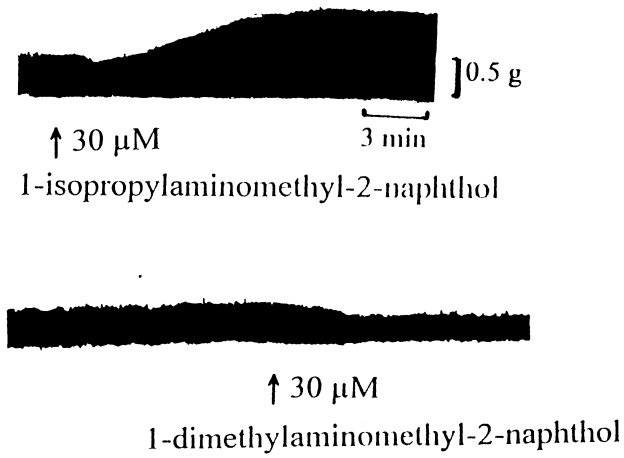

Figure 3. Effect of 1-isopropylaminomethyl-2-naphthol (**5**) and dimethylaminomethyl-2-naphthol (**7**) on the contractile force of isolated rat left atria. Stimuli were driven at 1 Hz with 2 times the threshold. The presence of compound **5** (30 μM) produced a biphasic response, while compound **7** (30 μM) produced only a negative intropic effect.

Analyses indicated by the symbols of the elements were within ± 0.4% of the theoretical values. Infrared spectra were obtained on a Shimadzu IR-408 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Gemini T-300 spectrometer at the National Sun Yat-Sen University, Kaohsiung, and are expressed in parts per million (δ) with tetramethylsilane used as an internal standard. Mass spectra recorded for the purposes of structure confirmation were obtained on a Jeol JMS-HX 110 mass spectrometer at the National Sun Yat-Sen University, Kaohsiung. Elemental analysis was performed on a CHN-O-Rapid Heraeus Elemental Analyzer at the National Cheng-Kung University, Tainan. Thin layer chromatography was carried out on precoated silica gel F_{254} chromatographic plates (20 × 20 cm; 0.2 mm). Methylamine, ethylamine, propylamine, isopropylamine and butylamine were all obtained from the Tokyo Chemical Industry Co. (TCI). 2-Naphthol was the product of the Sigma Co. All other reagents used in this study were EP grade products of E Merck.

Dialkylaminomethyl-2-naphthol derivatives were synthesized previously [8]. The synthesis and characterization of 1-alkylaminomethyl-2-naphthol will be reported here.

4.1.1. 2,3-Dihydro-2-methyl-1H-naphth[1,2-e]-m-oxazine (**1**)

Following the procedure of Burke et al. [7], to a cooled solution of 12.4 g of 25% aqueous methylamine (0.1 mol)

in 60 mL of methanol was added 18.5 mL of 37% (0.2 mol) aqueous formaldehyde in 40 mL of methanol and 14.4 g of 2-naphthol (0.1 mol) in 50 mL of methanol. After 1.5 h of gentle refluxing at 60 °C, the reaction mixture was poured into 400 mL of cold water. The product (95% yield) was collected and recrystallized from methanol. M.p. 68–70 °C, IR (nuzol) cm^{-1}: 2 994 (aromatic C–H), 2 909 (CH_3), 1 427 (C–O), 1 214 (C–N). ^1H NMR (300 MHz, DMSO): δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.65 (m, 2H), 7.48 (m, 1H), 7.38 (m, 1H), 7.03 (d, *J* = 9.0 Hz, 1H), 4.82 (s, 2H), 4.22 (s, 2H), 2.53 (s, 3H). MS m/z (relative intensity): 128 M^+ (100), 144 (72), 156 (42). Anal. $C_{13}H_{13}NO$ (C, H, N).

4.1.2. 1-Methylaminomethyl-2-naphthol hydrochloride (**2**)

Following the procedure of Burke et al. [7], a solution of 0.013 mol of 2,3-dihydro-2-methyl-1H-naphth[1,2-e]-m-oxazine and 1.0 mL of concentrated aqueous hydrochloric acid in 60 mL of 85% aqueous propanol-1 was distilled for about 30 min. After the distillation was interrupted, 60 mL of acetone was added to the reaction mixture. Upon cooling and filtration the product was obtained (91% yield). M.p. 187–189 °C (dec.). IR (nuzol) cm^{-1}: 2 987 (aromatic C–H), 2 904 (CH_3), 1 443 (C–O). ^1H NMR (300 MHz, D_2O): δ 7.93 (m, 3H), 7.62 (dd, *J* = 8.7, 7.2 Hz, 1H), 7.45 (dd, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 9.6 Hz, 1H), 4.62 (s, 2H), 2.73 (s, 3H). MS m/z (relative intensity): 128 M^+ (100), 156 (42), 187 (26). Anal. $C_{12}H_{13}NO$ HCl (C, H, N).

4.1.3. 1-Ethylaminomethyl-2-naphthol hydrochloride (**3**)

To a solution of 3.6 g of 2-naphthol (0.025 mol) and 4.7 mL of 37% aqueous formaldehyde (0.06 mol) in 30 mL of methanol 1.6 g of 70% ethylamine (0.025 mol) in 10 mL methanol was added dropwise. After 1.5 h of gentle refluxing at 60 °C the oily residue was dissolved in absolute alcohol. The hydrochloride was obtained by treating a cold alcohol solution of the product with concentrated hydrochloric acid (yield 60%). M.p. 175–177 °C (dec.). IR (nuzol) cm^{-1}: 3 454 (broad, NH, OH), 3 010 (aromatic C–H), 2 909 (CH_3). ^1H NMR (300 MHz, D_2O): δ 7.88 (m, 3H), 7.59 (dd, *J* = 8.7, 7.2 Hz, 1H), 7.42 (dd, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 4.54 (s, 2H), 3.16 (q, *J* = 7.5 Hz, 2H). 1.29 (t, *J* = 7.5 Hz, 3H). MS m/z (relative intensity): 128 M^+ (100), 156 (57), 201 (47). Anal. $C_{12}H_{13}NO$ HCl (C, H, N).

4.1.4. 1-Propylaminomethyl-2-naphthol hydrochloride (**4**)

The product was prepared by a method similar to that described in the procedure for compound **3**. It was recrystallized from absolute alcohol (yield 65%). M.p. 188–190 °C (dec). IR (nuzol) cm^{-1}: 3 486 (NH), 3 442 (OH), 2 990 (aromatic C–H), 2 913 (CH_2, CH_3), 1 426 (C–O). ^1H NMR (300 MHz, D_2O): δ 7.89 (m, 3H), 7.5 (dd, *J* = 8.7, 7.2 Hz, 1H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 4.54 (s, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.70 (m, 2H). 0.92 (t, *J* = 7.5 Hz, 3H). MS m/z (relative intensity): 128 M^+ (42), 215(30). Anal. $C_{14}H_{17}NO$ HCl (C, H, N).

4.1.5. 1-Isopropylaminomethyl-2-naphthol hydrochloride (**5**)

The product was prepared by a method similar to that described in the procedure for compound **3**. It was recrystallized from absolute alcohol (yield 70%). M.p. 183–185 °C (dec.). IR (nuzol) cm^{-1}: 2 990 (aromatic C–H), 2 989 (C–C–C), 1 440 (C–O). ^1H NMR (300 MHz, DMSO): δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 6.6 Hz, 1H), 7.55 (dd, *J* = 7.2, 7.5 Hz, 1H), 7.37 (m, 2H), 4.09 (bs, 2H), 3.45 (m, 1H), 1.37 (s, 3H). 1.34 (s, 3H). MS m/z (relative intensity): 128 M^+ (42), 215(12). Anal. $C_{14}H_{17}NO$ HCl (C, H, N, O).

4.1.6. 1-butylaminomethyl-2-naphthol hydrochloride (**6**)

The product was prepared by a method similar to that described in the procedure for compound **3**. It was recrystallized from absolute alcohol. M.p. 150–153 °C (dec.). IR (nuzol) cm^{-1}: 3 473 (broad, OH, NH), 3 006 (aromatic C–H), 2 916 (CH_3), 1 436 (C–O), 1 299 (C–N). ^1H NMR (300 MHz, D_2O): δ 7.86 (m, 3H), 7.59 (dd, *J* = 8.1, 6.9 Hz, 1H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 4.43 (s, 2H), 3.31 (m, 1H), 1.84 (m, 1H), 1.62 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). MS m/z (relative intensity): 128 M^+ (100), 156 (52), 229 (17). Anal. $C_{15}H_{19}NO$ HCl (C, H, N).

4.2. Measurement of BP and HR by intravenous injection

The in vivo experiments have been described previously [2]. In brief, Wistar rats (250–300 g) of either sex were used in these studies. The animals were housed in an animal room with a light/dark cycle of 12 h/12 h and were fed rat chow and tap water ad libitum. The animals were anaesthetized with urethane (Aldrich, 1.0 g/kg IP, supplemented with 300 mg/kg i.v. if necessary). The trachea was intubated to keep the airway patent. Femoral arterial blood pressure was measured through a PE 50 tubing filled with heparin solution (25 units/mL) (Sigma) connected to a polygraph (Lectromed, U.K.) via a transducer (PDCR 75, Lectromed, UK). The femoral vein was cannulated for drug administration. The HR was derived by means of a cardiotachometer that was triggered by the arterial pressure pulse. The BP and HR were monitored

continuously. Rectal temperature was monitored and maintained between 37 and 38 °C.

4.3. Measurement of contractile force in isolated rat left atria

Experiments were performed following the methods described previously [2]. In brief, the hearts were quickly removed and rinsed in ice-cold Tyrode's solution. Then, left atria were dissected and mounted at 0.5 g resting tension on stainless steel hooks in a 50 mL organ bath, and bathed at 37 °C in physiological saline solution containing (mM): NaCl 118, KCl 4.8, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 24, glucose 11. The bath was aerated with 95% O_2 and 5% CO_2 mixture. One end of the preparation was fixed to the bottom of the bath and the other end was connected by a hook to the level of a force-displacement transducer (Ugo Basile, Comero, Italy). Stimuli were delivered as rectangular pulses of 5 ms duration at 2 times the threshold via two platinum electrodes placed on either side of the muscle. The tissues were always allowed to equilibrate for 90 min before the experiments were begun [2, 19].

4.4. Measurement of contractile force in isolated rat aorta

Experiments were performed following the methods described previously [20]. In brief, the thoracic aorta was isolated and excess fat and connective tissue were removed. Aortic rings (5 mm) were mounted in organ baths containing 5 mL and bathed at 37 °C in physiological saline solution containing (mM): NaCl 118.4, KCl 4.7, $CaCl_2$ 1.9, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.7. The bath was aerated with a 95% O_2 and 5% CO_2 mixture. Two stainless steel hooks were inserted into the aortic lumen, one was fixed while the other was connected to the transducer. The contractile effects of calcium were studied in rings stabilized in high-K^+ solution without Ca^{2+}. Calcium was then added to obtain the desired concentrations. The high K^+ solution was prepared by substituting NaCl with KCl (80 mM) in an equimolar amount. Contractions were recorded isometrically via a force-displacement transducer connected to a Gould polygraph (Model 2400).

4.5. Statistical analysis

Values are expressed as means ± standard error of the mean (SEM). Statistical analysis was performed with a paired *t* test, and a *P* value smaller than 0.05 was regarded as statistically significant.

Acknowledgements

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