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MCI-154 on calcium sensitivity of contractile system and calcium 22s;L43;lilA;7iii iinsaponh nned myocar I'fI [1]

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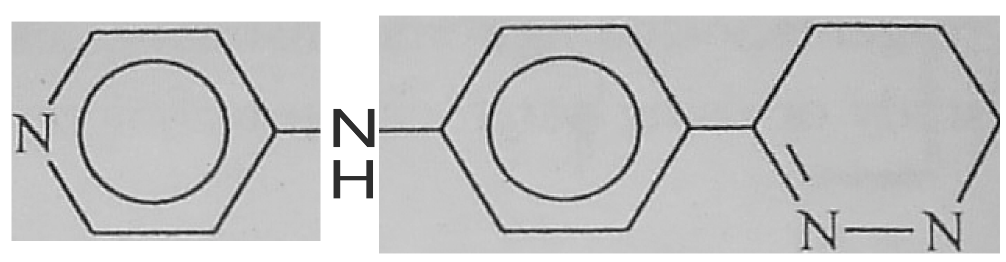
KEY WORDS' MCI-154; ωEdc agω mmdmωlcium; Ila miC reticublll1; papil!-1 m)ıαdial oontraction; caf:E

AIM: To explore the >SSible mechanisms underlying e itive inotropic effect of MCI-154. MEη10DS: Skinned fibers wi disrupted or pre ıv00 sarroplàstoic reticuhnn (SR) were ed by ponin 5 50 mg.L–[1]. The t sion-pCa relatioDsmɹ) d pCaso of saJ:nm (5(i)0 mg.L inned bers were taken as the indres øf Ca2+ sensitivity of ntractife pretei:lilS. TÀe amplitude of caffèine-indu d Intracture was an index of C a2+ release frotn SR in saponin (50 mg.L l)_S nned fibers. RE .JTS: 1) MCI-154 (0.1 mmol•L -1) showed a eaz+ seDSitizing effect on n actile proteins. The pCaso was increased to 5.84 (5.54 – 6.14) m ed with n 01 value 5.54 (5.30 – 5.79) (p < 0.01 n =8). Hill α)@{ficient n was d $@({by 0.29 (P < 0.01 n=8); 2) Noωntracture was produced by MCI-154 in preparations with PNServoo SR. Caffeme induced ntrac re beforemd after MCL154 treatm t were not changoo (p > 0.05 n = 4). CONCLUSωN: MCI-154 direcdy e ances e ea2+ nsitivity of n actile protein but has little effect on ea_2+ rel se from SRmmt skinned cardiac fi '8.

Enhancement Qf the sensiüMVityofmyøfilame1lts ω iωCdi and iTmmC11 ase Qf cytoplasmic Ca2+ Conc m hanisms of *positive* inQtropism. Ca2+ release rorn sarcoplasmic reticulum (SR)is tbmmincn of fq2+]i in cardiac celk MCLGhirmw POSItive Inotropic agent with vasodiiator acVO which exerts the cardiotonic effect witht m!olvemenl of adrenergic histarninergic muscar-ch1 r C ptωOrNa+ K"" -AτTP eωlυ An -increase [n 'Ca2+ sensitivity of the ωntractile proteins was probably involved in theμsitive inotropic action of MCI-154 in guinea pig and dog mylα:ardium [2,3].

In this paper we used rat papillary muscles skinned by high or low concen ation of saponin to explore whether or not MCI-154 would influence ea2''' sensi:tivity of cardiac co tractile proteins and Ca?-+ líelease from SR.



6-[4- -pyridyl) phenyl]-45-diby 3(2H) pwi one hyl chloride (Mα..154)

MATERIALS AND METHODS

Preparation of skinnωfibers Wistar rats weighing 100 – 150 g were d apitated. H rts weret ısfred to oxygenated Krebs-Henseleit solution. The papillary musdle (< 1 rnm m diameter) of right ventricle was tied to e perfusion chamb r and the other end attaehed by a silk 1 P to isometric force ısducer (Statham UGo USA). The muscles were x ed to skinning solution (below) at 20 CC for 30 rnin and washed by relaxing solution. The sarcolenuna b ame hyperp meable as the removal of h ATP from the relaxing solution brought the fibers into go:r state.

"lutiom The bmic relaxingm111tbn mtaind(mol ·L–1)': KOl 1140 1\Ol'2 5 tazic s0id 10 inùdazóle 2S ATP 5p th1W}hl0 g.L;S lmmlrlE Soluüb0nwas made byaddingsap0nin (50 cα 5 Omg. L-1 ω the b ic rd 19solu 0n & Adva utlon was made by adding CaCb to the basic relaxing solution The ncentration 01 free ea2+ wa... f'.XDr edas 11 ca (n 19of Ca2+ ncentra n)-zajmd egtazic acid were added so that each activatisolution 23 ω+ of pCa 7. 0 – 4.5ωmPuMomwge

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iondUdol b' oofffcdine 25 n ilfl • L- 1. 1he QU !Jfoi tm \-VQ$ eKan1 hed whOtl t wwld bv the SR. Af r smm lilUG1l't the 121T uentiaiiy ex 1ωActivalt g roltl tiO'S ..affmMmcmMimd GJ+ 'rlr cd4 dj ::1.onW ed the % of 1118Xinl 1 ension Mi?;k84.5.hpQ tension data were plot øbfalneu cl r Fgumft {α3 i(1(" + [α]") where T s % n/aA tenSion K κCa24ωkenmtionmq d for p. r ucing 50 % of maximal intl. TωωSimOn-κpa rela tiOωillship curve d elinea Cωa2+ JtW d mp0amlnml Jlih tald im ofCa2+ saMWofm e.sy: em_f[$)

Ca2+ rel ;e from SR $a.pønin 50' mg. L-} dishlp ed c 11I11 ane th t im $R membraJne abili y 1t@ uvtwndaremd rdmseQZ+. The preparaG was pOS00 -dmeEmol-fad ë ooIt:racture w o d 1 bathed inρ6.0 solution for :3 min to rell d the SR th Ca1+. The pre radon WBS Josed to MCI-154 (0.1 Il!Lllol L-1) ωmωgamed+relmsefromSR

S iαI anal is All cl.ata exdept aso were ented as x s. r>Ca sø ang 9Sc <onHdenoe 1t1rt8 were calculated wi BHssfFy thod- bmpmgoms f wm e ntrol and MCIIS4 t J is wi.5e' æa @ hy rt !St.

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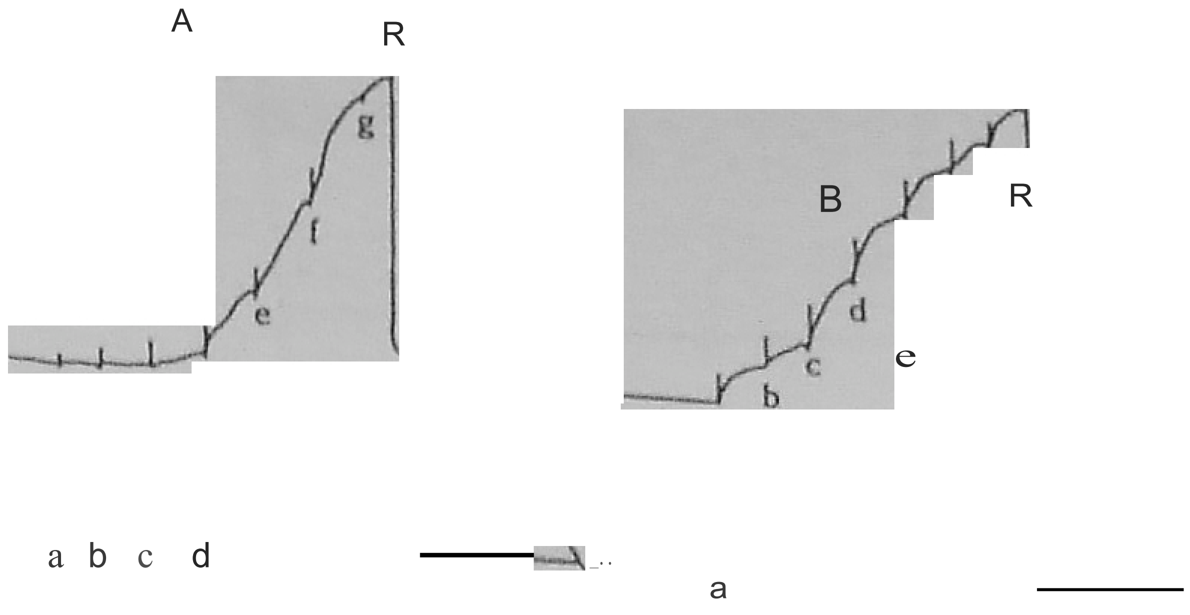

Fig 19 ea+-acl a d for<!e of " sldnn rat ri2ht pa rIlary m e in ahsen (A) or prese f MU-154(0·1Emmol-Iu-1)-caZ+concmtauon (a): a=7.0 b=6·5p c=6·0.dz5·6 ez5·2 f=5.0. g=45R:Cah fm

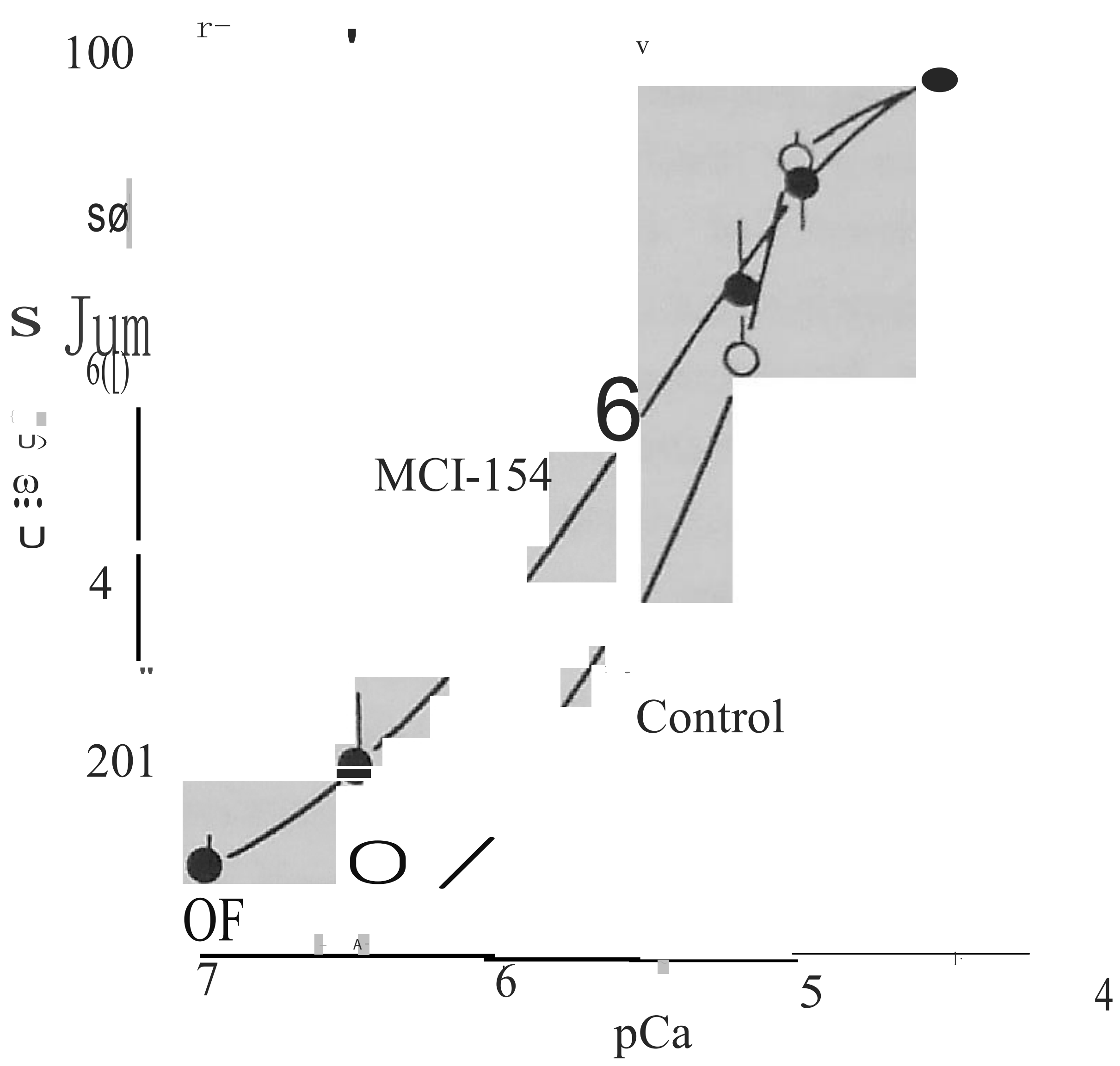

Fig 2. Effect of MCI-lS4 oJ1 tensiOB-pCa relationship of saponin(500 mg.L-1) skinned rat rt ventri.oar papillary cles ($n = 8$).

Thls was considered to be caused by caffeine-induced ea2 4- release from SR. After reloading SR with pCa 6..0 solution noωm.tracture was induced by L CI-1$4 {@'.i ßm ldl L J. The caffeine-induced t'ontractmes were 14339mg(n= after MCI-154 ueatment (Fig 3).

D CUSSION

AQ'ents that are able to enhance the sensitivity of m filamentsωcalcium have been called " iClum .sensitizers 6 . The pr oot study has deθionstra ed quarnt tke sensiMV i*y @f ωlgtnte il e $yst '1] ûlfr in. i1 ßed f sfmm ht ventricula:r

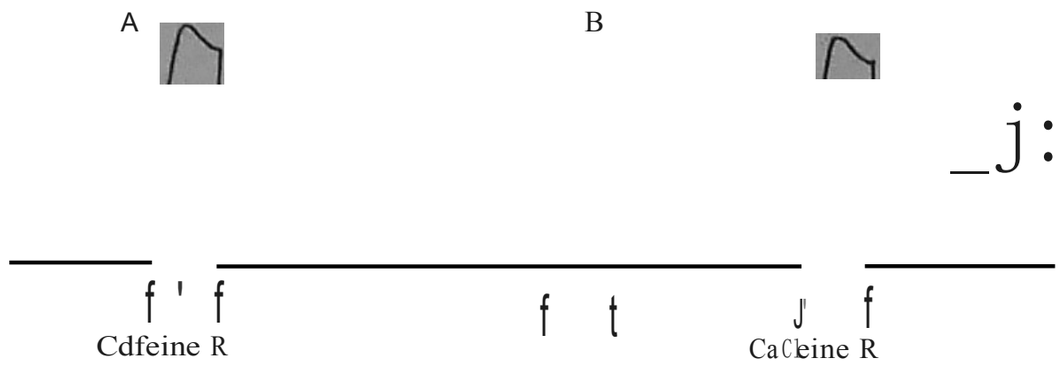

Fig 3. Effects of Mα-154 on caffeine-induced contractm E Msa n (50 L-1) -skinned rat right ventricular pill31γm es (R: relaxi solution)•

papillary n1uscles. Mecnanisms underlying the sensitizing effect of MCI-154 e uncl r. A direct action on regulatory protein troponin and it8 subunits (eg enhancement of troponin C ea^{2+} binding) may be involved(2 78). In our study the Hill efficient of tenslon-pCa relatl000hip w81s reduced significantly which suggested that the α)()peration between actin and myosin had been changed by the treatment of MCI-154(9). Further experimmts are neceg y to fully explore the molecular mechanism hy which MCl-154 increa8es the Ca^{2+} sensitivity.

The present study was also taken to analyze the possible efloct of MCI-154 on SR functions. The results indicated that MCI-154 itself could not induce Ca^{2+} release from SR and it had no effect on caffeine-induced Ca^{2+} release in the preparations skinned by saponin (50 mg.L-1). Whether or not MCI-154 affects the $[Ca^{2+}]_i$ of myocardial cells through CA1VIP system is stiU a matter of contro ersy(3 10). From the present studty we can infer at least that enhancement of SR Ca^{2+} release is not included in the mechanisms underlying the positive inotropic effect of MCI-154.

In conclusion MCl-154 is a kind of new αlci n sensitizer it increases the sensitivity of ntractile system to ea^{2+} without influence Ca^{2+} release from SR in skinned cardiac fibers of rat.

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MCI-lS4

Ca^{2+} ea^{2+}

(410078)

MCI...154; ; ; ; ; ; ;

: MCI-154 - :

500 50 mg.L -1 (SR)

- 500 mg.L-1

PCa ea^{2+}

50 eaz^{+} ; 50 .L–1 蜕膜

SR ea^{2+} -

: 1) ea^{2+} MCI-154 (0.1 mmol.L-1) (

Ca^{2+}

5.54 (5.30 – 5.79) $.84 (5.54 – 6.14)

0 nz8 ; Hn .29 (P< (P< 0.01, "ZLz2 SR MCI- (P>O.05). : MCI-

154 不能引起 SR 内 Ca^{2+} 释放，并对咖啡因引起 154Q ea^{2+}

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Altered α_1-adrenoceptor subtypes mediated cardiac function after treatment of prowanoIolto rats

LI waflZHANG YWANG Xiao-Liang (Deμrtment of Pharmacology Institute of Mateγia Medicα Chinese -aLatimzyofMdicaf Sdmω and Pek

KEY WORDS pap a. ry mu es; heart a: um; myocardial ntractiOR; h t J' e; alp 2 adrenergic ptors; propranolol; phenyle me; clonidine — ; apidil; caroochol

AIM To study otrol c C únotropic effects mediated by α1A- and B eptors ter 5-d propranolol ( ) eatInent METHODS: the positive imuo c and chroño' Opiè e ts mdiated by A and CX1B subtypes w dete. "Jnired on isdl a: left ωlar pa; !ary rø S mzd ghtm mm Pro- aod Naα mted Eats-RESUL :ZEe Mite contractility of - pill 1- muscl induredl Jgy phenylephrine (Phe) w 90 18 xng in Pli treated rats and 53 :t 17 mg in ntr0l group (P<0.ØS)· The inmmmt on 'æ of ntracti was 20 :t 12 mg iñ Pro-pretreated rats(1d 5:t 5 mg in NaCl treated mω(p<0.05). AJter preinωbated chloroethylclonidine.e increment on forre of contraction was educed in Pro-treated fa: Þ1 !t was not much 'ed in 00n / gfO - Pbe m presence of 5-methylurapi il indnωd SttVe inotropic effl with 13 5 mg in Pro- eated group, but oot in NaJα.-treated rats. Under the normal and the inhil i carruac statee maximal increment in beat rate mediated by a1B showed no difference between the pro-tr d and NaCl-treated rats. α USION! After CbrωiC 'eaønent of Pro, αr loceptor-lnedi ω c effect iII rat heut was m oved! whioo was mBitJJy il d by im tion of Q1S when ß adrenocep s were odked-

Myocardial α1- and ¯adrenoceptors were e exlstent in hearts of variOU$ species includ.ing ratl[1J]. 130th adrenoceptors mediate positive iftQtropic and chronotropie effeëts. Since the aårénoceptQI&m. ediated responses are ""dominant " al2kenöc pllors biockad@ ßnhanω e significance 0> 0.1-â etloc ;p>ltor-mediated. effecls.α1-Adr no- t>@lf denSIDJEf 1reaS@S ln rat heart after chronic oprandot treatment 213?. We demonstrated that 1tA rece])tOlr cdensity tnCI s-ed rnore pronounced thanr ulB-adreRoceptor aftett chronic eatment of pJJropralløIot (Pro) <. The present mhent was t oIbserve the fU!1ctional alterations of sitiv notrooicand. chronωlotropic effects mediated by α1A- d α~i e ! σ ;rats-

MAEERMLS AND WETHOBS

Wistali rats 230 – 260 g were treated with Pro (50 mg ip bid) 9%Mdutionb5d FOrceoiconmction papillgy mmd isolated from the left ven icles of Pr and NaC1- eated rats were attachedωa zrzg:ztj; ZZTJf lt;l wmi gluωe 114:.1 CaG 2.5 mmol.L 8!I1d dJ :tcωaG : L% recorder (XWT-204 TYPE)- was maximal- 1 1The

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