17β-Estradiol attenuates vascular contraction through inhibition of RhoA/Rho kinase pathway

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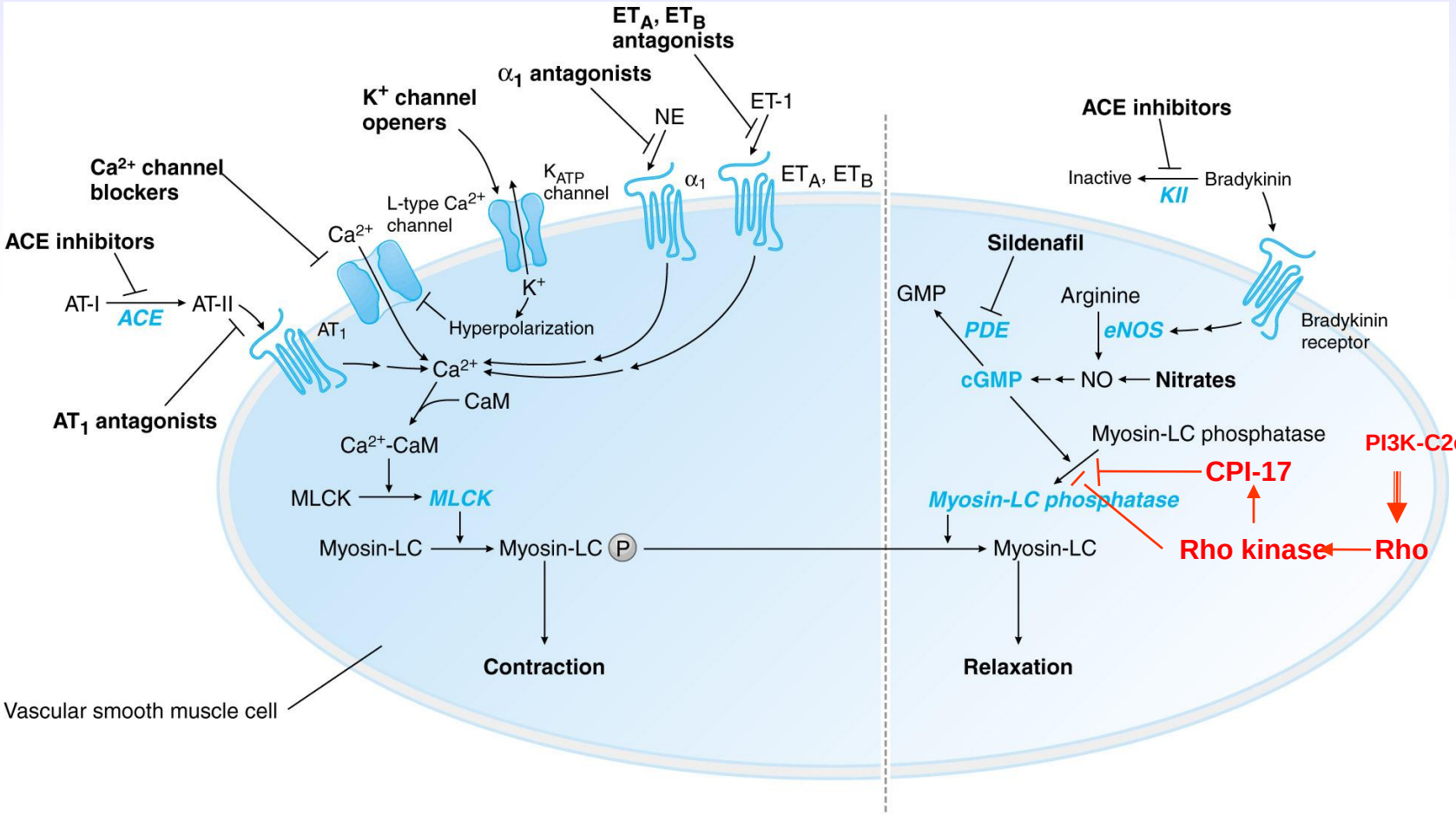
Department of Pharmacology,

Kyungpook National University School of Medicine

고혈압 치료제에 의한 혈관 수축 조절



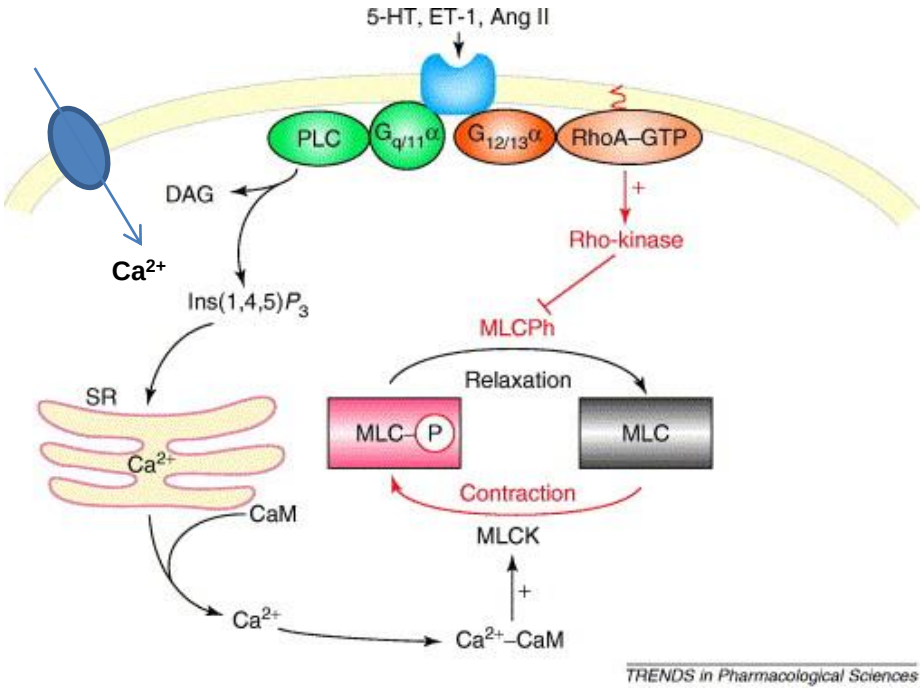
Golan DE et al.,
Principles of Pharmacology, 2007

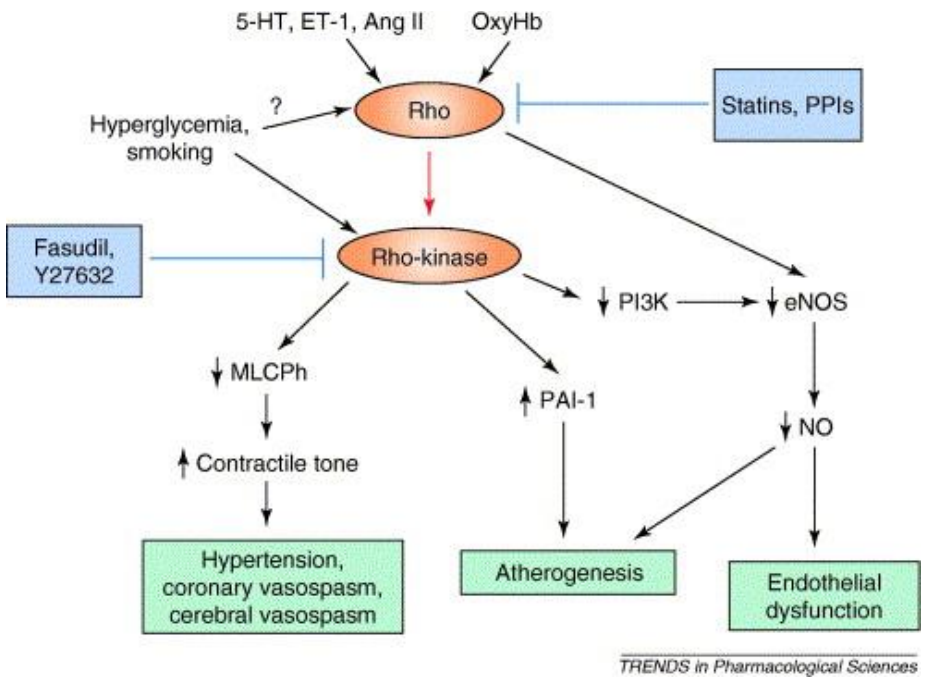
Review TRENDS in Pharmacological Sciences Vol.27 No.2 February 2006

Targeting Rho and Rho-kinase in the treatment of cardiovascular disease

Klaudia Budzyn, Philip D. Marley and Christopher G. Sobey

Department of Pharmacology, The University of Melbourne, Parkville, Victoria 3010, Australia





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Isoflavone attenuates vascular contraction through inhibition of RhoA/Rho-kinase signaling pathway

Young Mi Seok [1], Inji Baek [2], Yong-Hoon Kim [2], Yeon-Shin Jeong [2], In-Jung Lee [2], Dong Hyun Shin [2], Young Hyun Hwang [2], InKyeom Kim [1]*

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Abstract

Isoflavones decrease blood pressure, improve lipid profiles, and restore vascular function. We hypothesized that isoflavone attenuates vascular contraction by inhibiting RhoA/Rho-kinase signaling pathway. Rat aortic rings were denuded of endothelium, mounted in organ baths, and contracted with U46619, a thromboxane A2 analogue or KCl 30 min after the pretreatment with genistein, daidzein or vehicle. We determined the phosphorylation level of the myosin light chain (MLC_{20}), myosin phosphatase targeting subunit 1 (MYPT1) and protein kinase C (PKC) -potentiated inhibitory protein

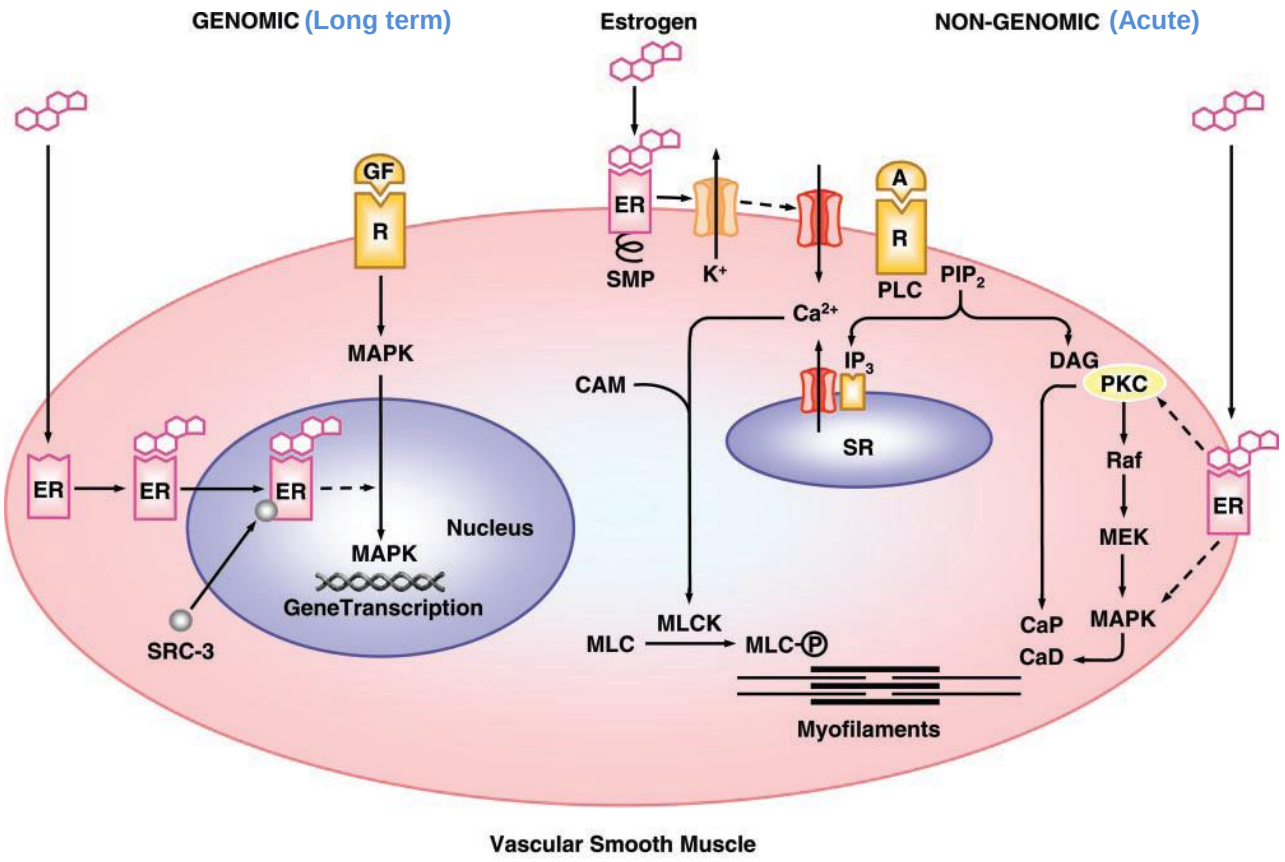
Am J Physiol Regul Integr Comp Physiol 286: R233–R249, 2004;
10.1152/ajpregu.00338.2003.

Invited Review

Gender, sex hormones, and vascular tone

Endothelium - independent

Julia M. Orshal and Raouf A. Khalil
Research and Development, Department of Veterans Affairs Medical Center, West Roxbury; and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02132



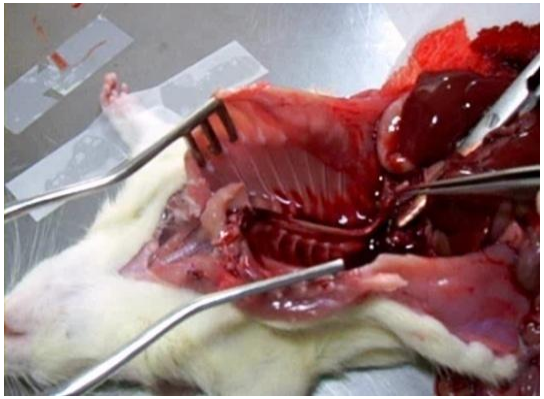
Hypothesis

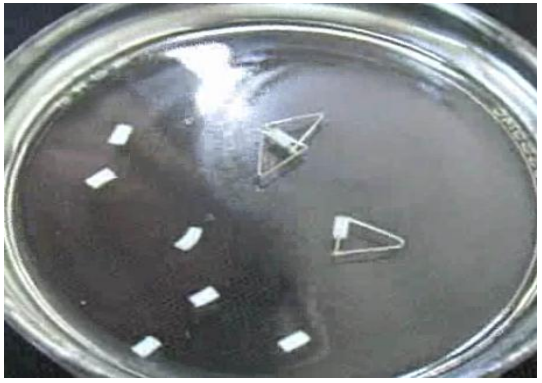
We hypothesized that 17β-estradiol attenuates vascular contraction by inhibiting RhoA/Rho kinase signaling pathway in rat aorta.

Materials and Methods

Tension measurements

- Organ bath (20ml)
- Animal : SD rat (10 week), Thoracic aorta (4mm in length)



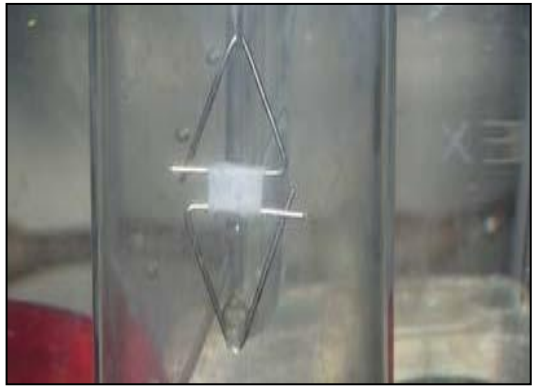
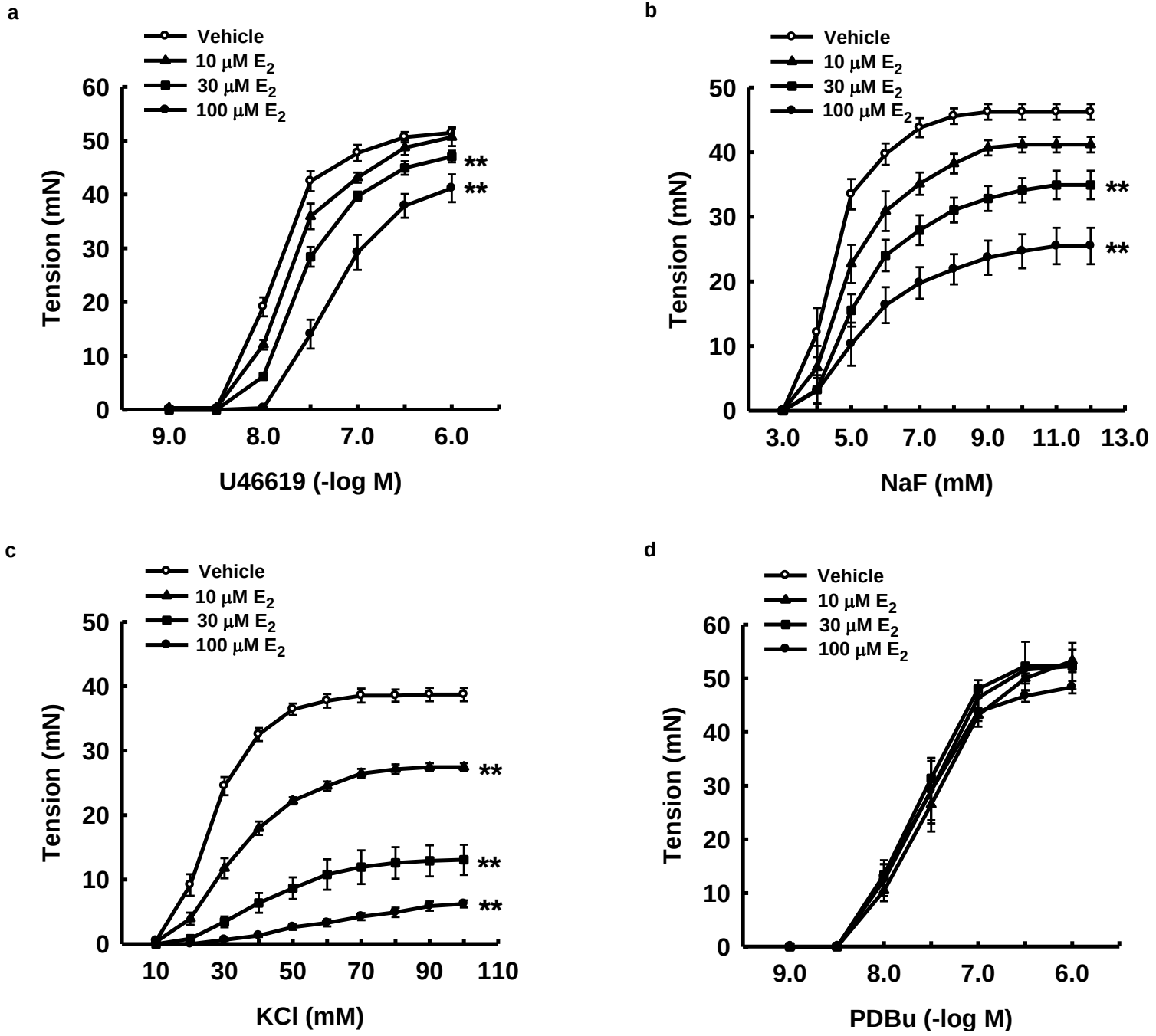
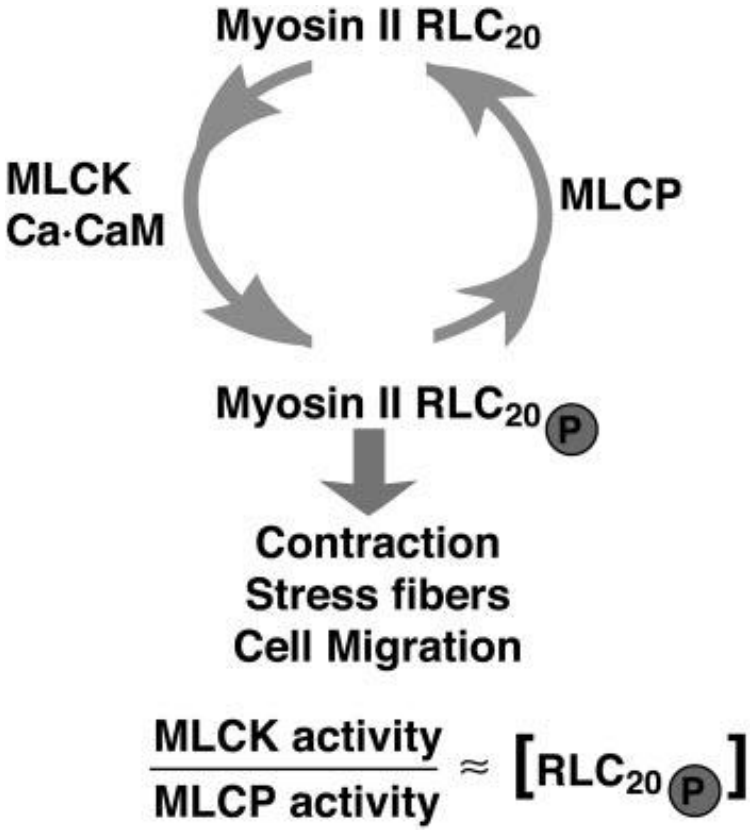


Fig. 1

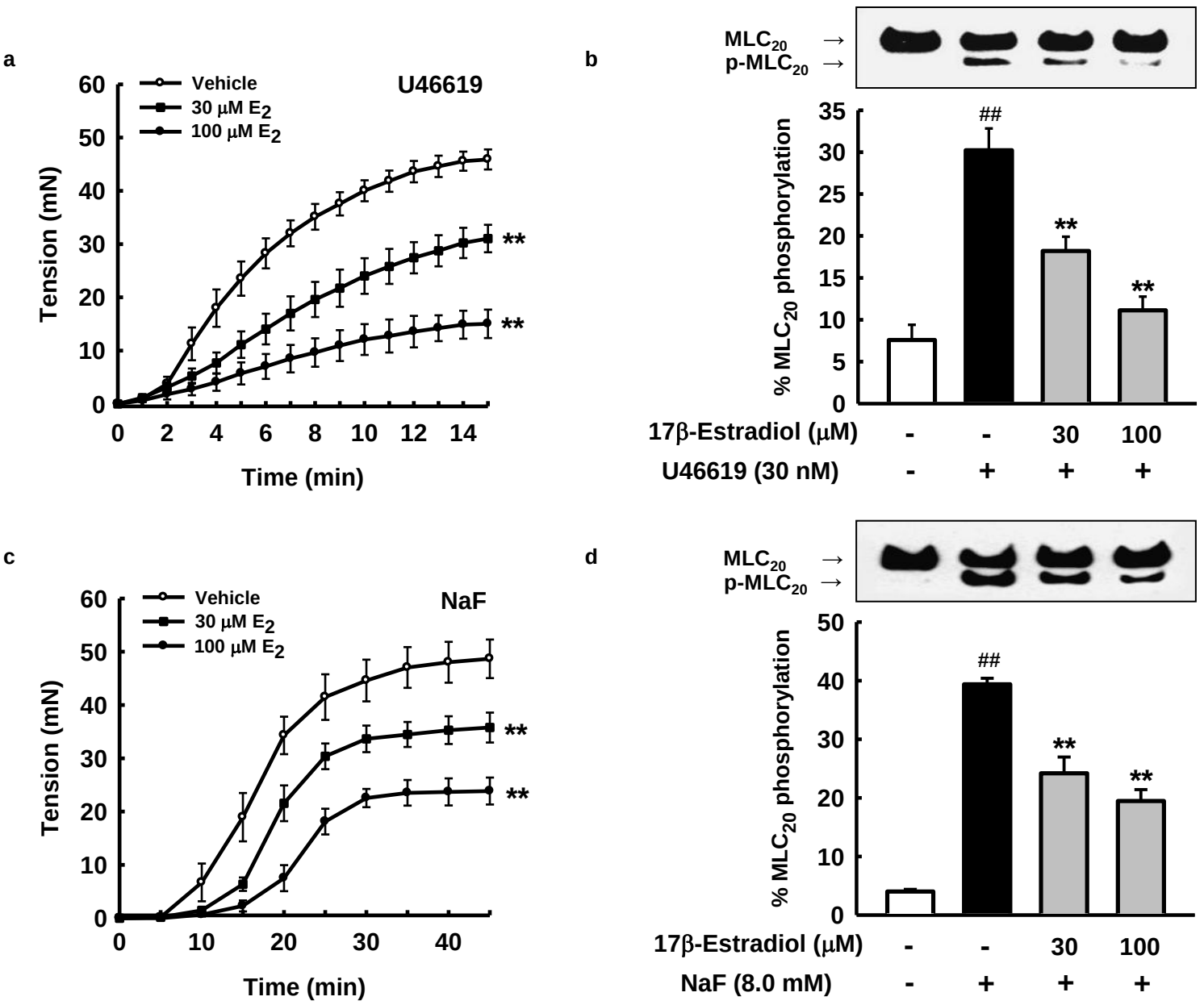

a
Vehicle
10 μM E2
30 μM E2
100 μM E2
Tension (mN)
U46619 (-log M)
**
**
b
Vehicle
10 μM E2
30 μM E2
100 μM E2
Tension (mN)
NaF (mM)
**
**
c
Vehicle
10 μM E2
30 μM E2
100 μM E2
Tension (mN)
KCl (mM)
**
**
**
d
Vehicle
10 μM E2
30 μM E2
100 μM E2
Tension (mN)
PDBu (-log M)

Regulation of Smooth Muscle Contraction

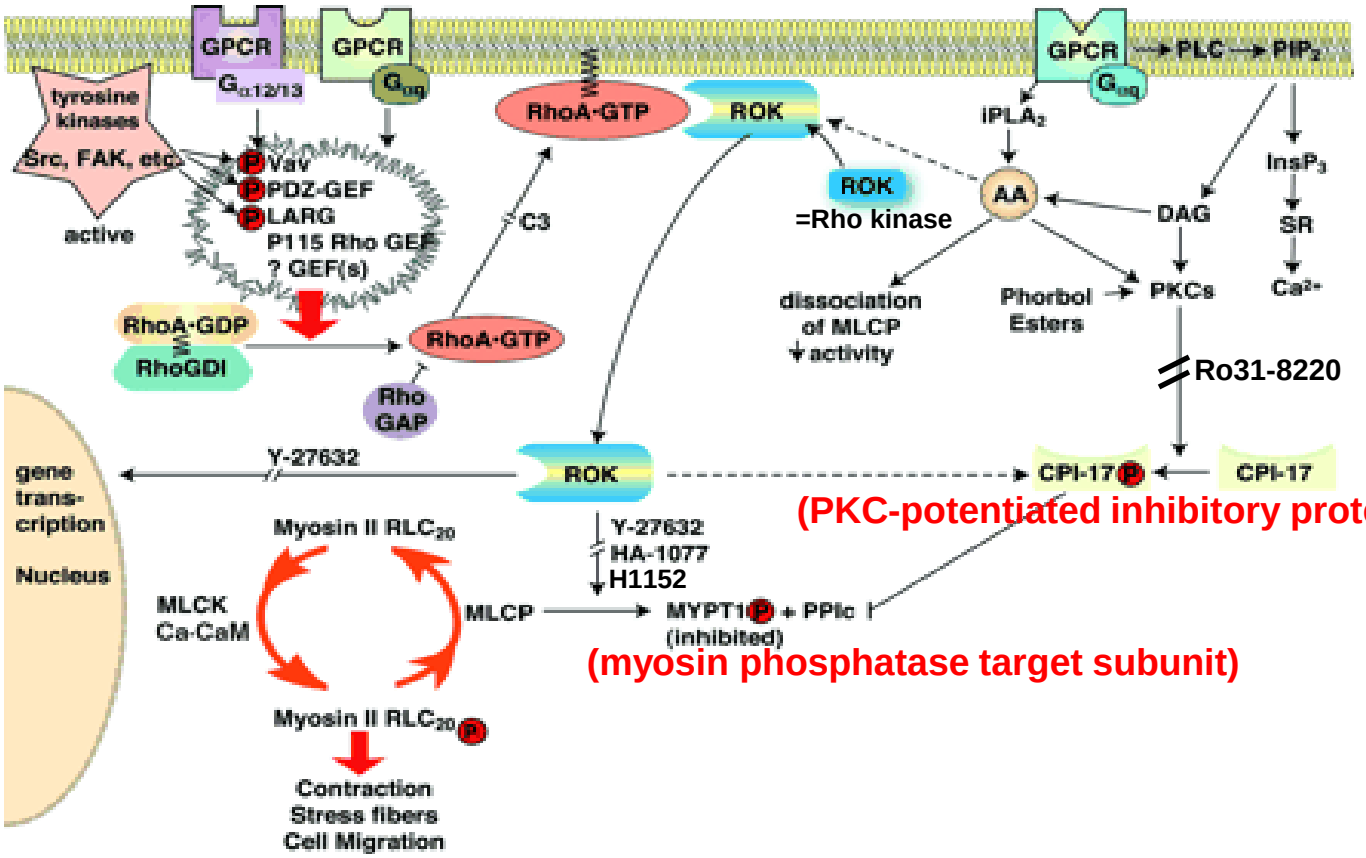


Physiol Rev 2003;83(4)

Fig. 2


a
Vehicle
30 μM E2
100 μM E2
U46619
Tension (mN)
Time (min)
**
**
b
MLC20 →
p-MLC20 →
% MLC20 phosphorylation
##
**
**
17β-Estradiol (μM) - - 30 100
U46619 (30 nM) - + + +
c
Vehicle
30 μM E2
100 μM E2
NaF
Tension (mN)
Time (min)
**
**
d
MLC20 →
p-MLC20 →
% MLC20 phosphorylation
##
**
**
17β-Estradiol (μM) - - 30 100
NaF (8.0 mM) - + + +

Regulation of smooth muscle contraction



Somlyo and Somlyo, Physiol Rev 2003:83:1325

Fig. 3

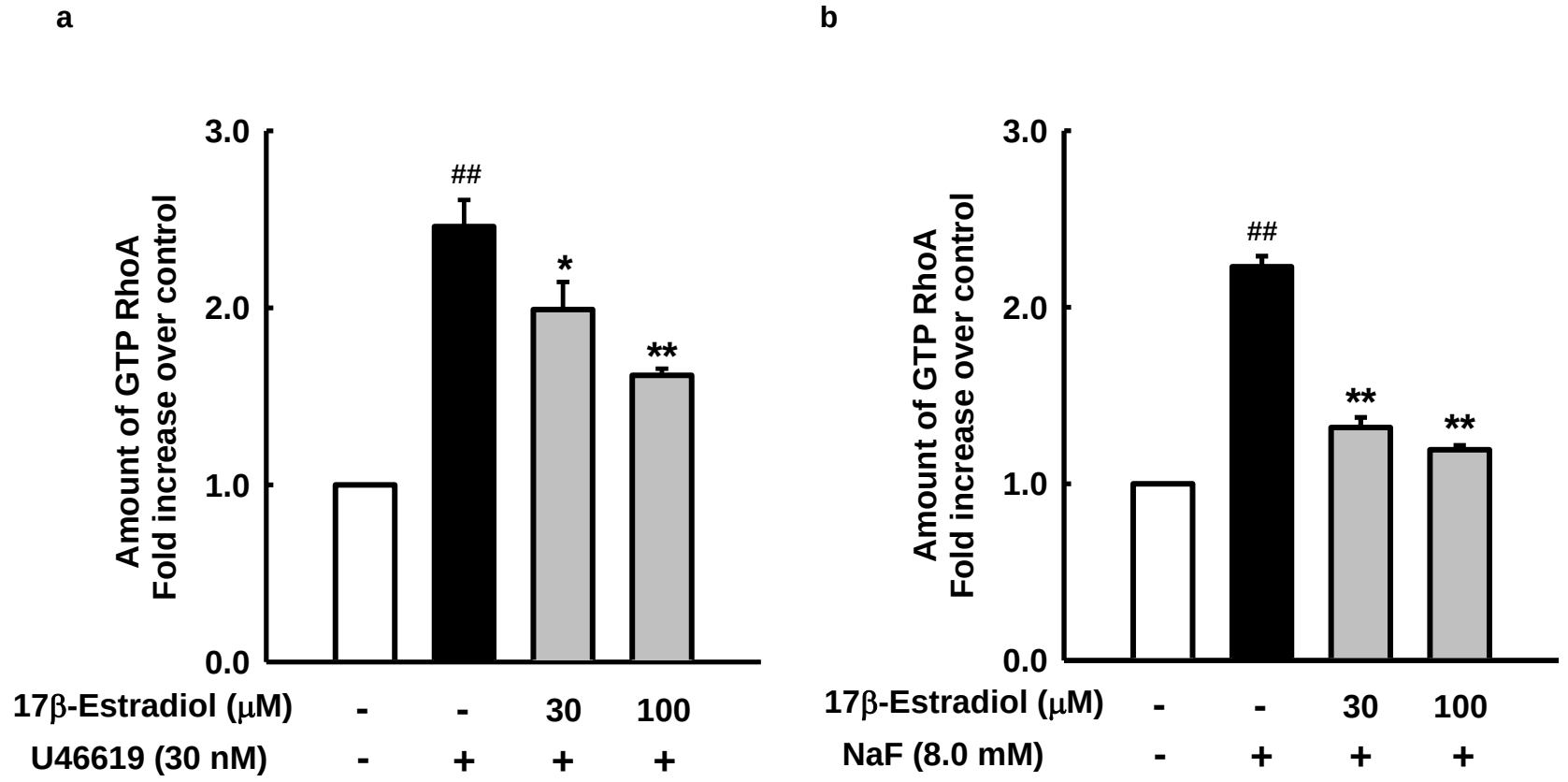

a
Amount of GTP RhoA
Fold increase over control
3.0
2.0
1.0
0.0
##
*
**
17β-Estradiol (μM)
-
-
30
100
U46619 (30 nM)
-
+
+
+
b
Amount of GTP RhoA
Fold increase over control
3.0
2.0
1.0
0.0
##
**
**
17β-Estradiol (μM)
-
-
30
100
NaF (8.0 mM)
-
+
+
+

Fig. 4

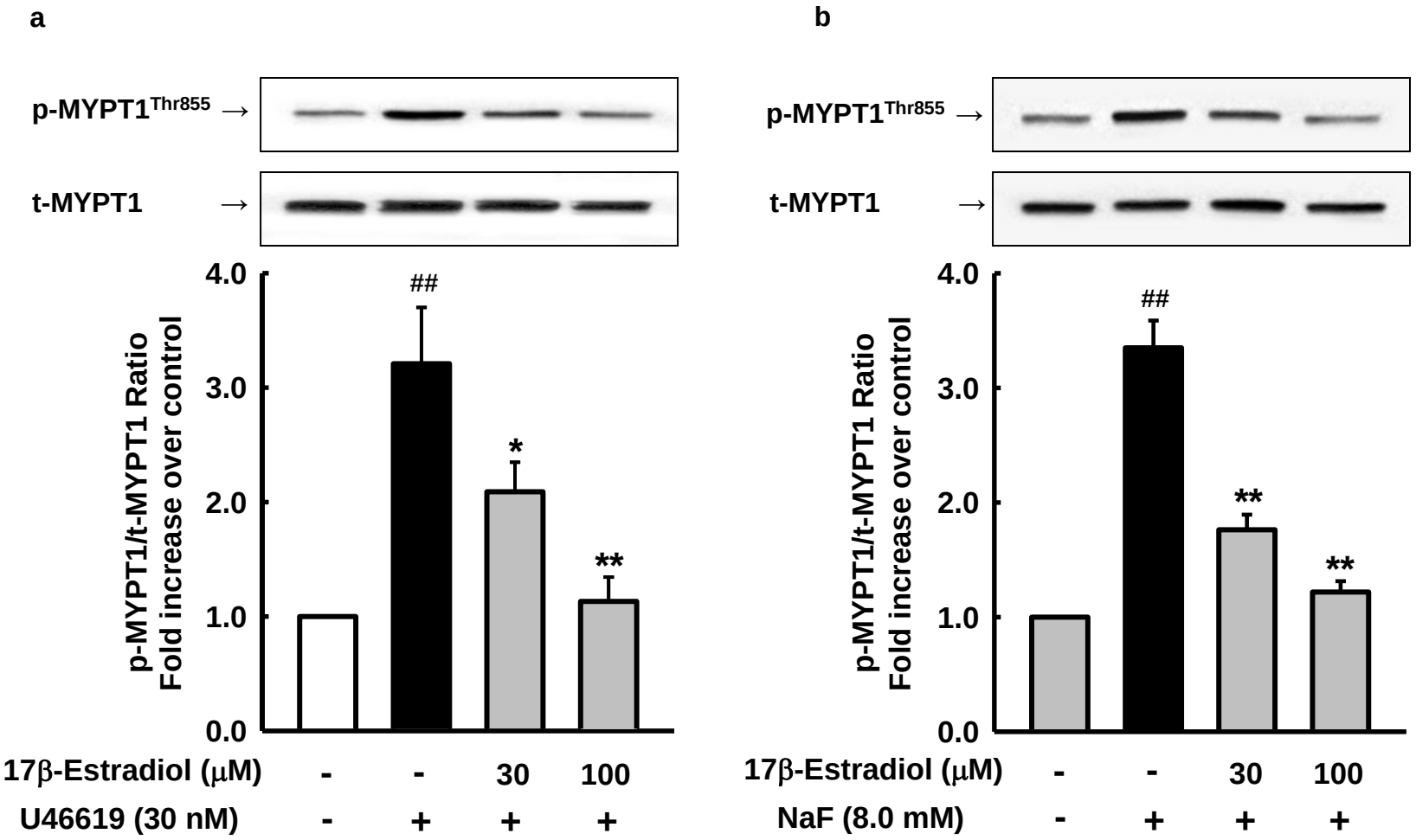
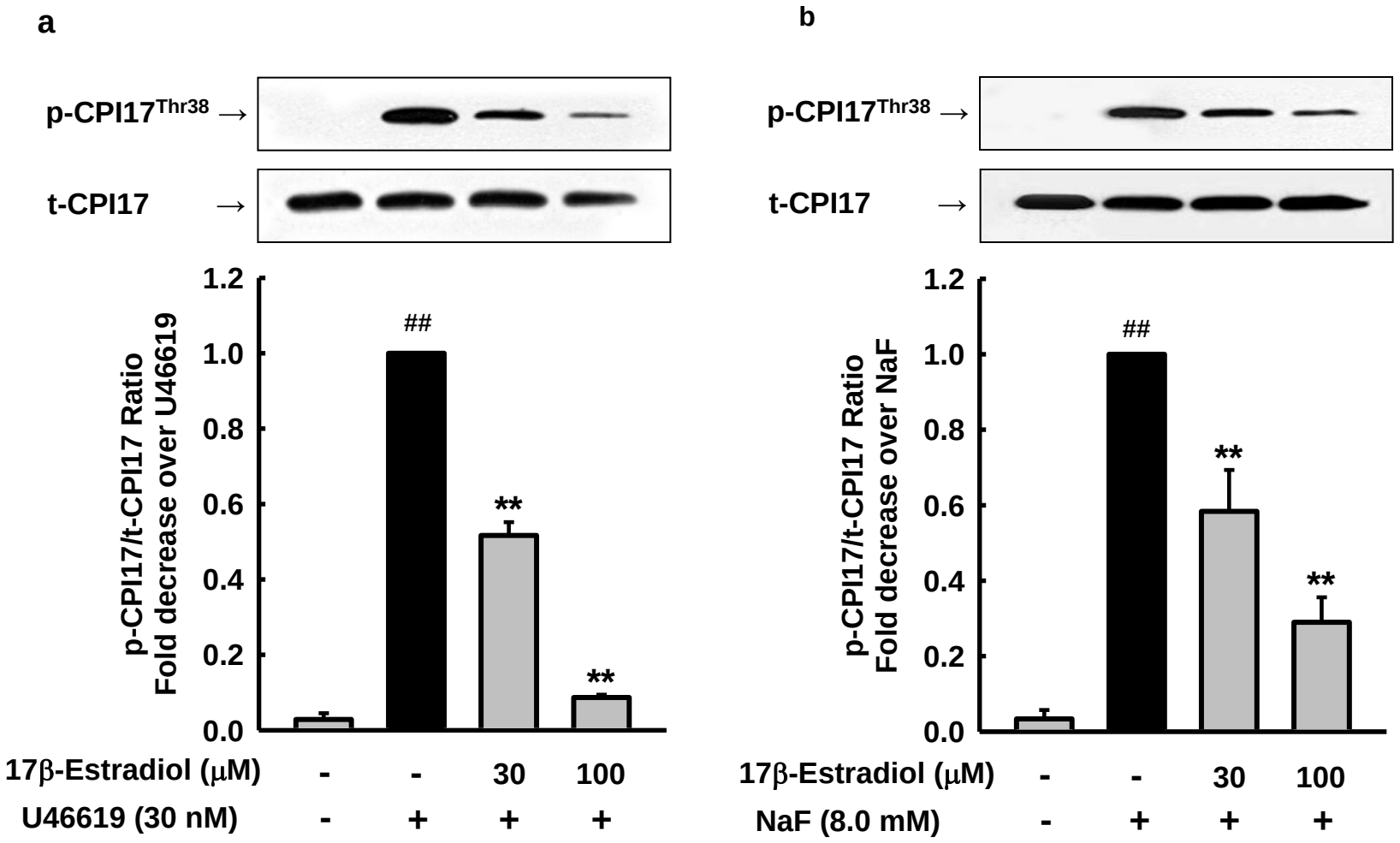
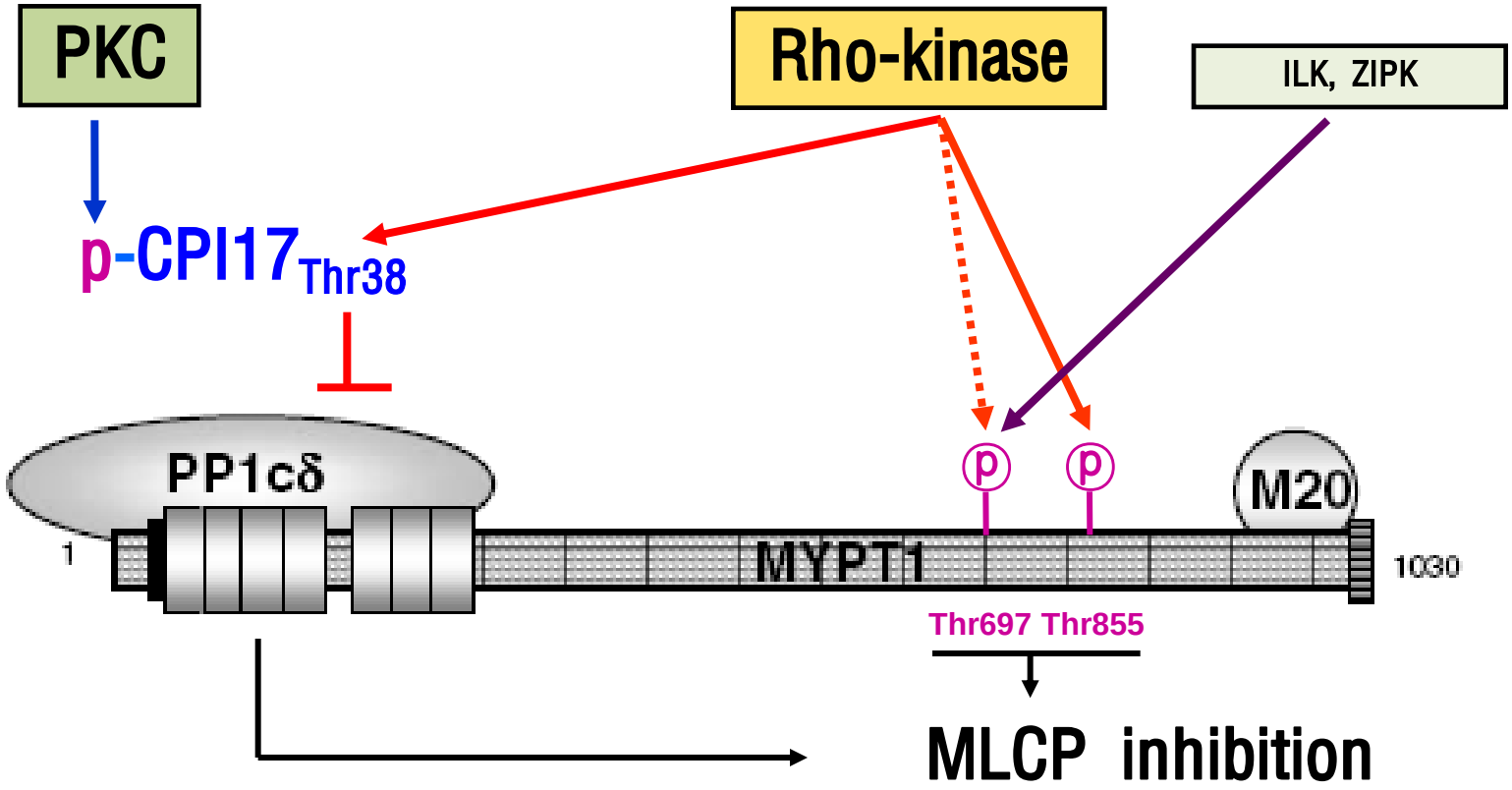

a
p-MYPT1Thr855 →
t-MYPT1 →
p-MYPT1/t-MYPT1 Ratio
Fold increase over control
4.0
3.0
2.0
1.0
0.0
##
*
**
17β-Estradiol (μM) - - 30 100
U46619 (30 nM) - + + +
b
p-MYPT1Thr855 →
t-MYPT1 →
p-MYPT1/t-MYPT1 Ratio
Fold increase over control
4.0
3.0
2.0
1.0
0.0
##
**
**
17β-Estradiol (μM) - - 30 100
NaF (8.0 mM) - + + +

Fig. 5

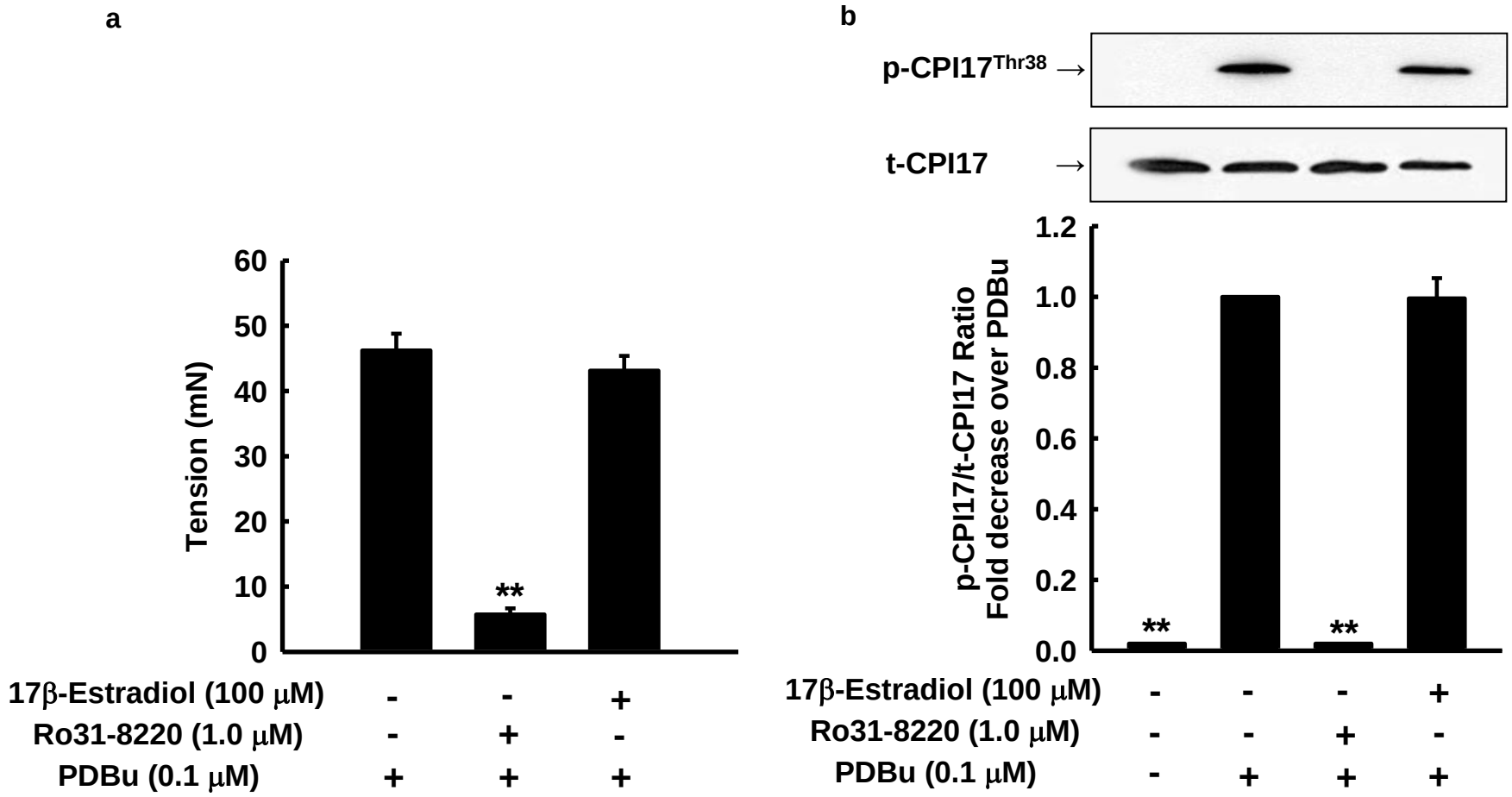

a
p-CPI17Thr38 →
t-CPI17 →
p-CPI17/t-CPI17 Ratio
Fold decrease over U46619
1.2
1.0
0.8
0.6
0.4
0.2
0.0
##
**
**
17β-Estradiol (μM) - - 30 100
U46619 (30 nM) - + + +
b
p-CPI17Thr38 →
t-CPI17 →
p-CPI17/t-CPI17 Ratio
Fold decrease over NaF
1.2
1.0
0.8
0.6
0.4
0.2
0.0
##
**
**
17β-Estradiol (μM) - - 30 100
NaF (8.0 mM) - + + +

Regulation of smooth muscle myosin phosphatase



Modified from Molecular & Cellular Biochemistry 259:197-209, 2004

Fig. 8


a
Tension (mN)
60
50
40
30
20
10
0
**
17β-Estradiol (100 μM) - - +
Ro31-8220 (1.0 μM) - + -
PDBu (0.1 μM) + + +
b
p-CPI17Thr38 →
t-CPI17 →
p-CPI17/t-CPI17 Ratio
Fold decrease over PDBu
1.2
1.0
0.8
0.6
0.4
0.2
0.0
** **
17β-Estradiol (100 μM) - - - +
Ro31-8220 (1.0 μM) - - + -
PDBu (0.1 μM) - + + +

Summary

- **17β-Estradiol attenuated vascular tension induced by U46619, NaF or KCl, but not PDBu.**
- **17β-Estradiol decreased not only the activation of RhoA, but also MLC_{20} phosphorylation induced by U46619 or NaF.**
- **17β-Estradiol also decreased the level of phosphorylation of MYPT1 and CPI17 induced by U46619 or NaF.**
- **17β-Estradiol did not affect vasocontraction and CPI17 phosphorylation induced by PDBu.**

Conclusion

17β-Estradiol attenuates vascular contraction through inhibition of RhoA/Rho kinase pathway.


Thank you for your attention!

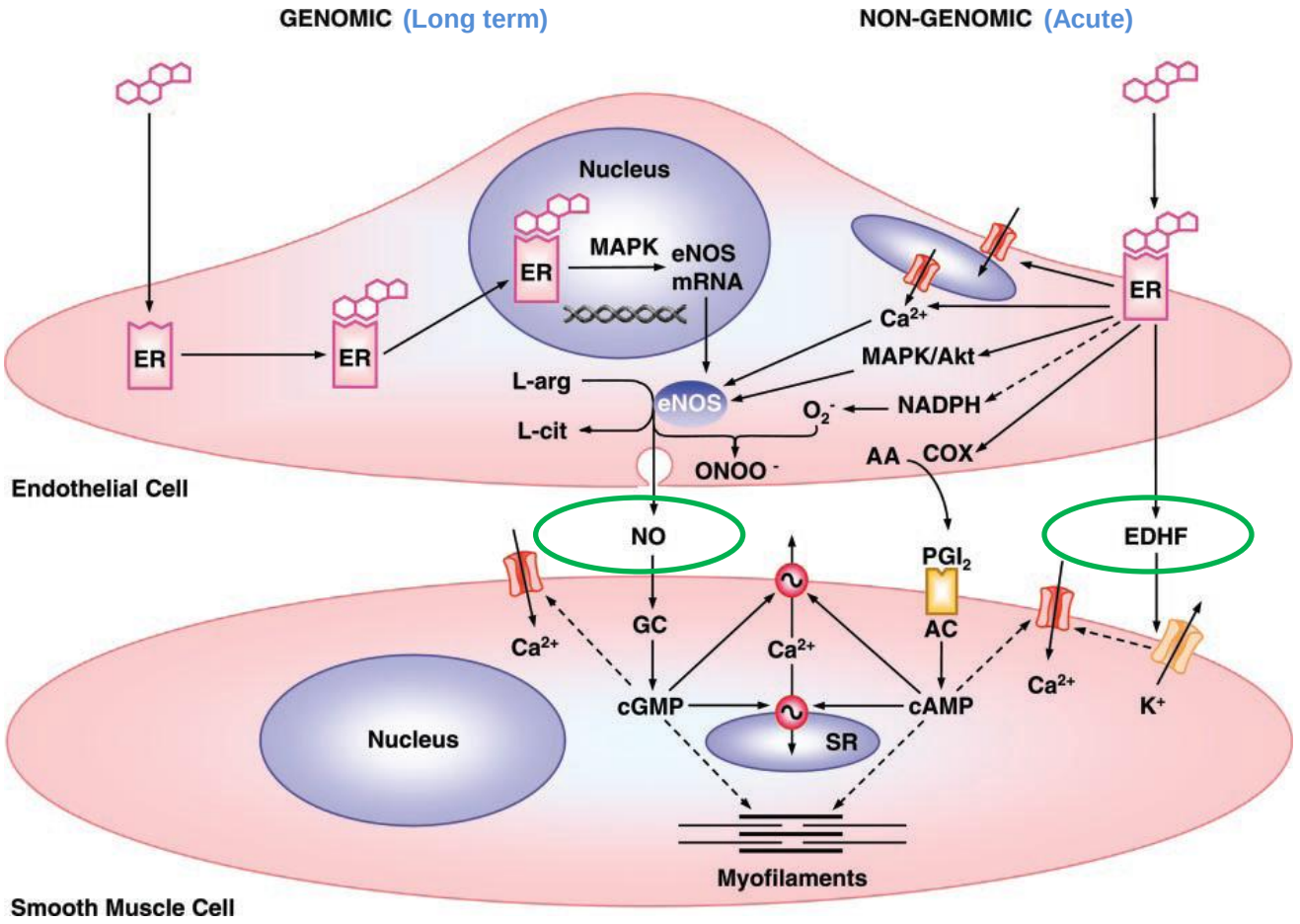
Am J Physiol Regul Integr Comp Physiol 286: R233–R249, 2004;
10.1152/ajpregu.00338.2003.

Invited Review

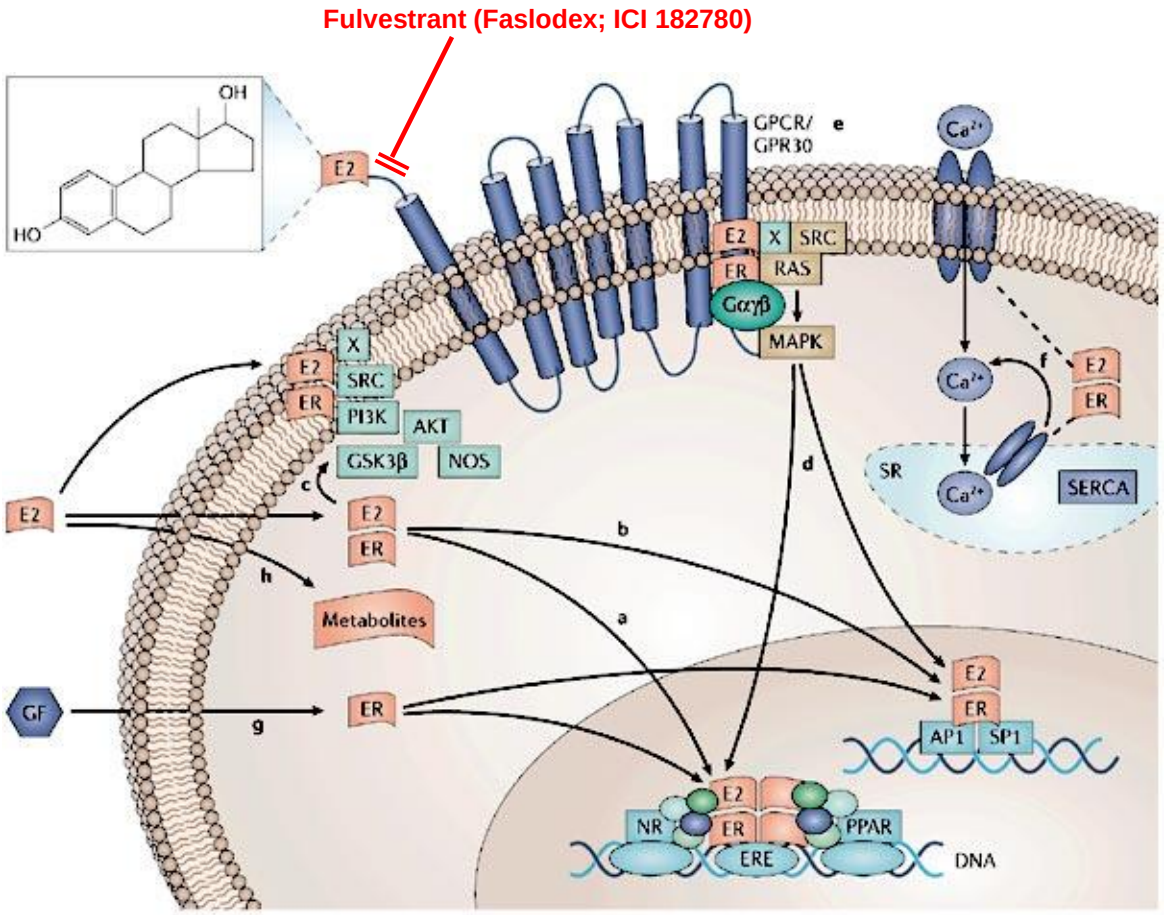
Gender, sex hormones, and vascular tone

Endothelium - dependent

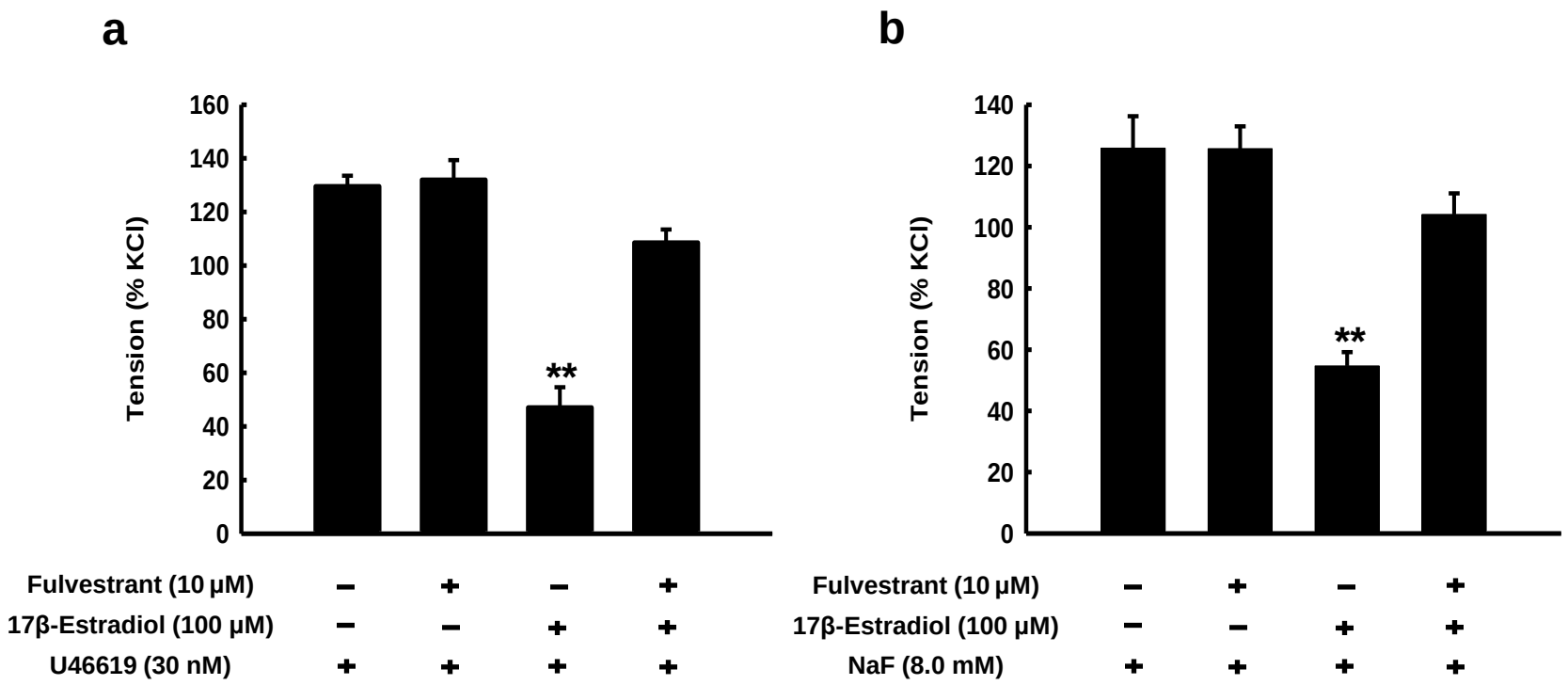
Julia M. Orshal and Raouf A. Khalil
Research and Development, Department of Veterans Affairs Medical Center, West Roxbury; and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02132



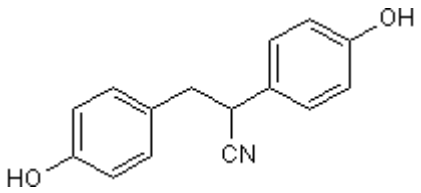
Multiple signaling pathways of estrogen in cardiovascular cells



Reverse effect of estrogen receptor antagonist ICI 182,780 on the 17β-estradiol induced vasorelaxation in rat aorta.



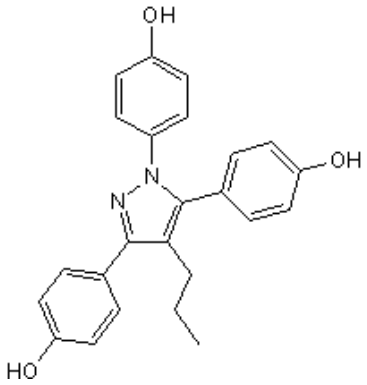
Selective Estrogen Receptor agonist



DPN

(4,40,400-(4-propyl-[1H]-pyrazole-1,3,5-triyl) tris-phenol)

ERα agonist



PPT

(2,3-bis(4-hydroxyphenyl)-propionitrile

ERβ agonist

Inhibitory effects of 17β-estradiol, PPT and DPN on U46619-induced vasocontraction in rat aorta

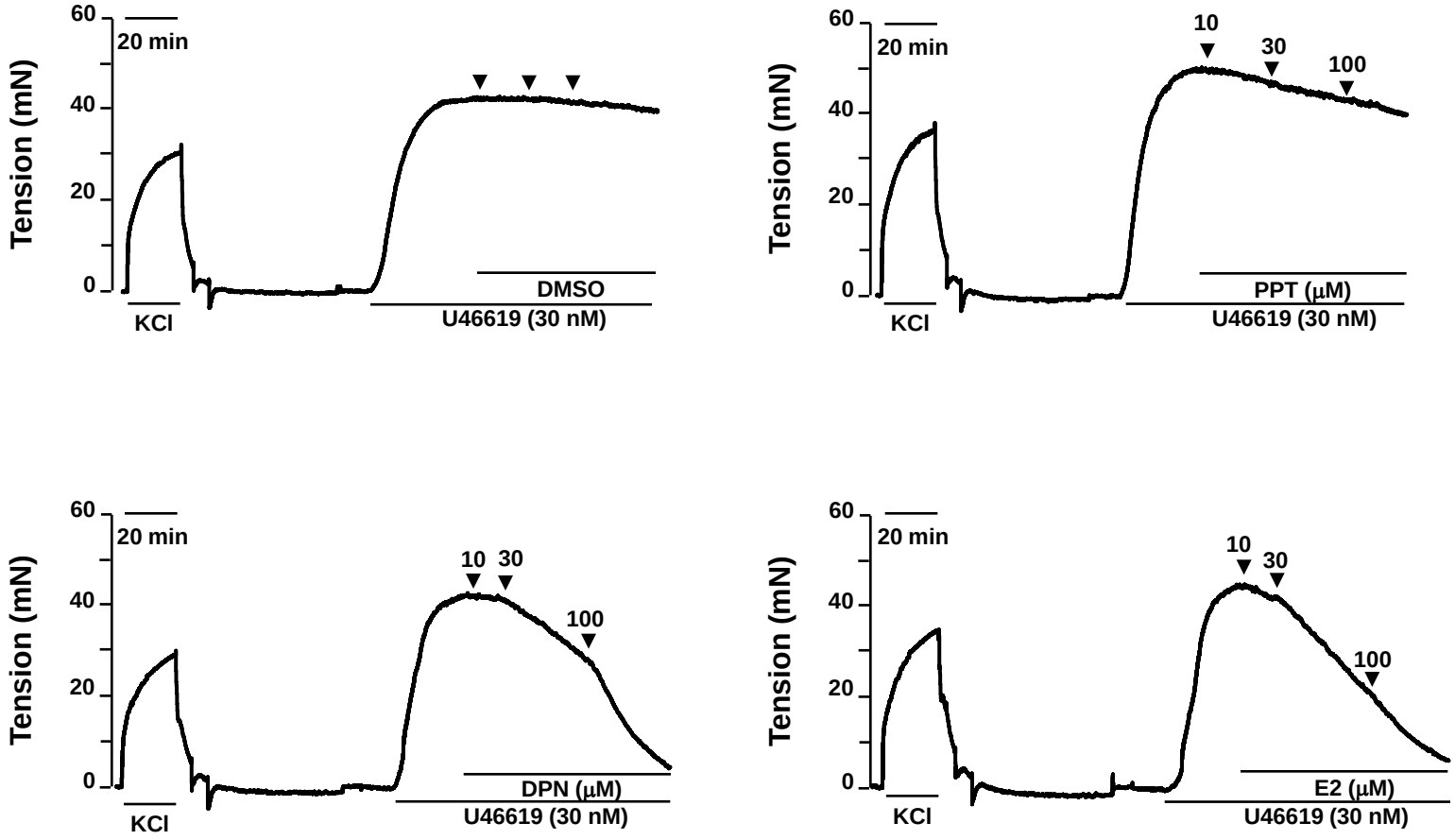


Fig. 6

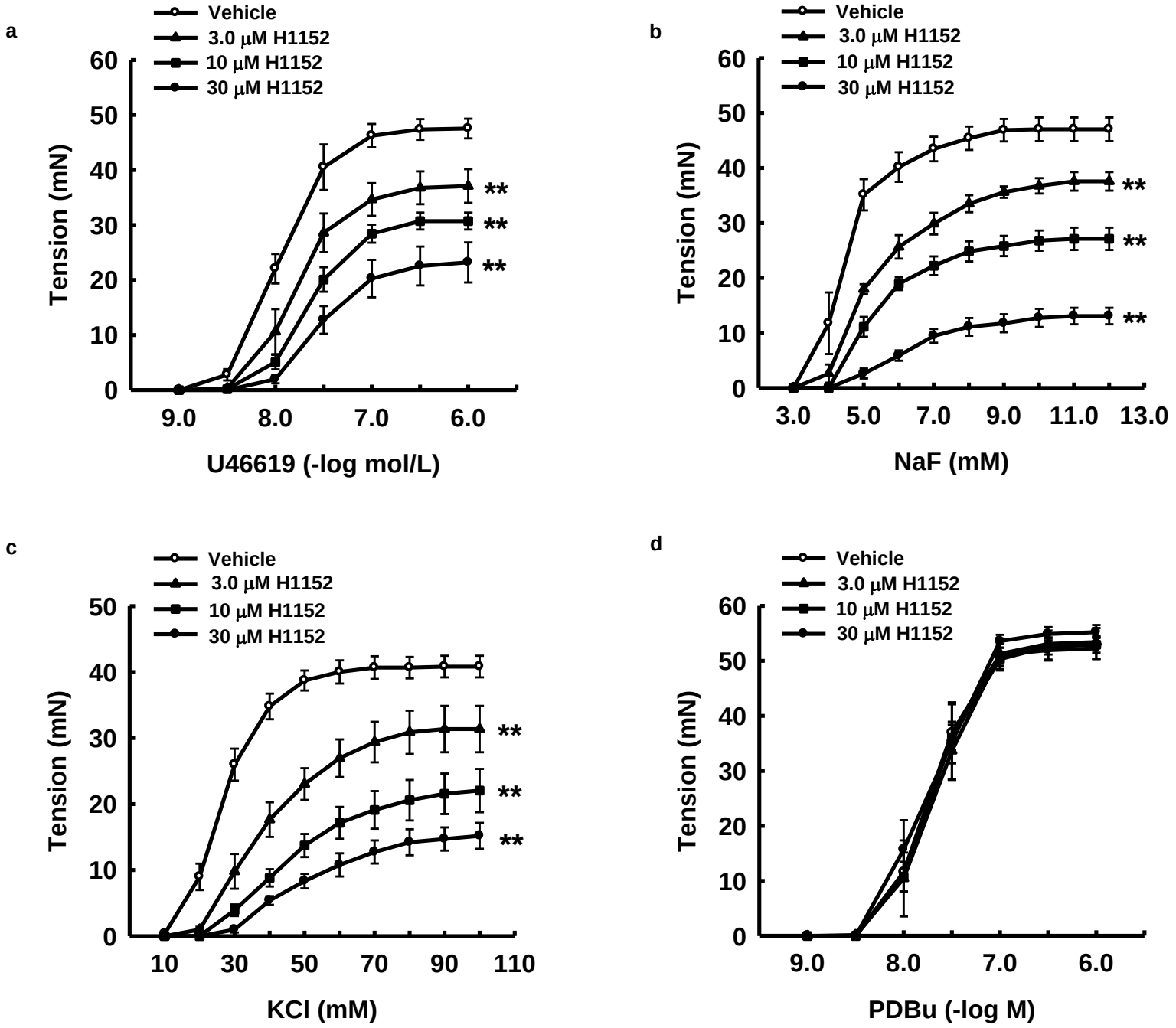
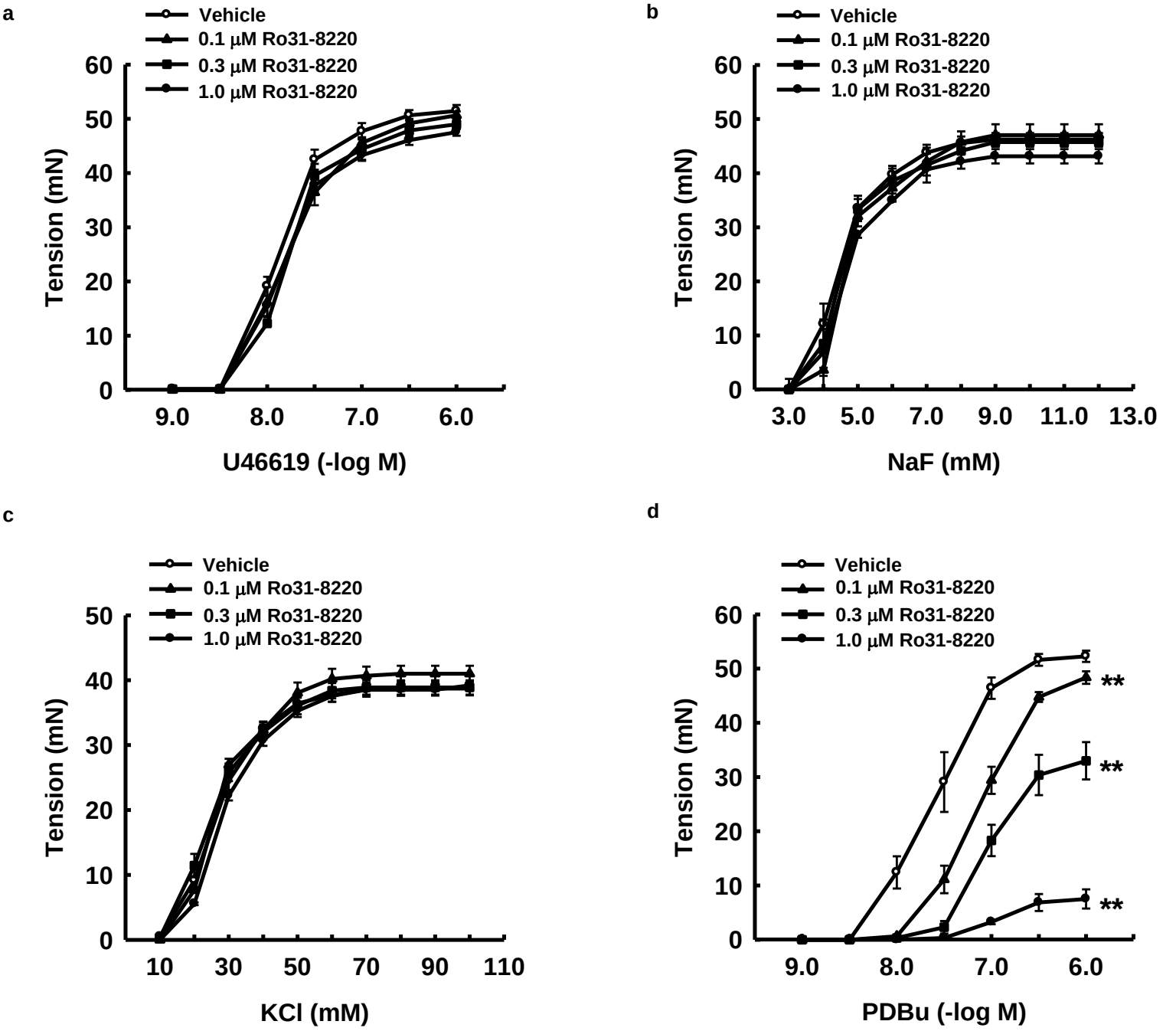

a
Vehicle
3.0 μM H1152
10 μM H1152
30 μM H1152
Tension (mN)
U46619 (-log mol/L)
**
b
NaF (mM)
c
KCl (mM)
d
PDBu (-log M)

Fig. 7


a
Vehicle
0.1 μM Ro31-8220
0.3 μM Ro31-8220
1.0 μM Ro31-8220
Tension (mN)
U46619 (-log M)
b
NaF (mM)
c
KCl (mM)
d
PDBu (-log M)
**

Stroke
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American Stroke Association
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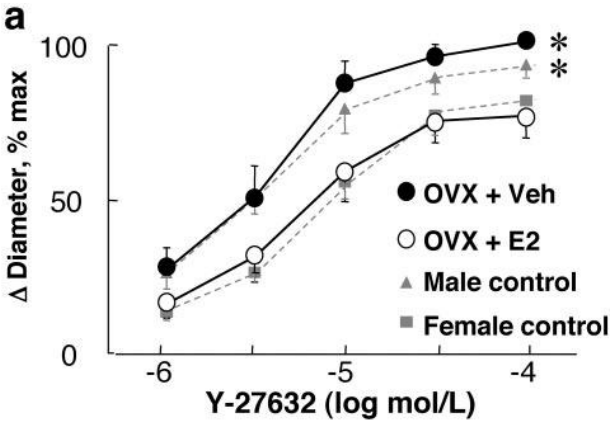
Evidence That Estrogen Suppresses Rho-Kinase Function in the Cerebral Circulation In Vivo

Sophocles Chrissobolis, Klaudia Budzyn, Philip D. Marley and Christopher G. Sobey

Stroke 2004;35;2200-2205; originally published online Jul 15, 2004;



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Biochemical and Biophysical Research Communications 326 (2005) 154–159

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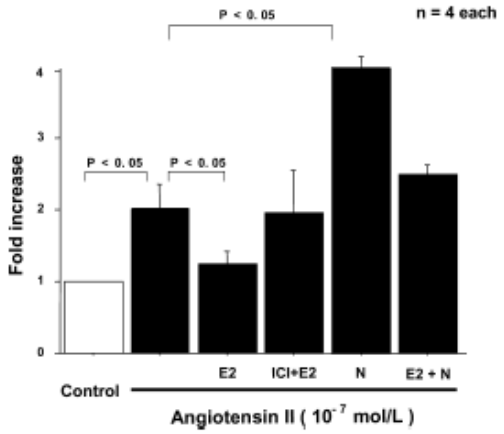
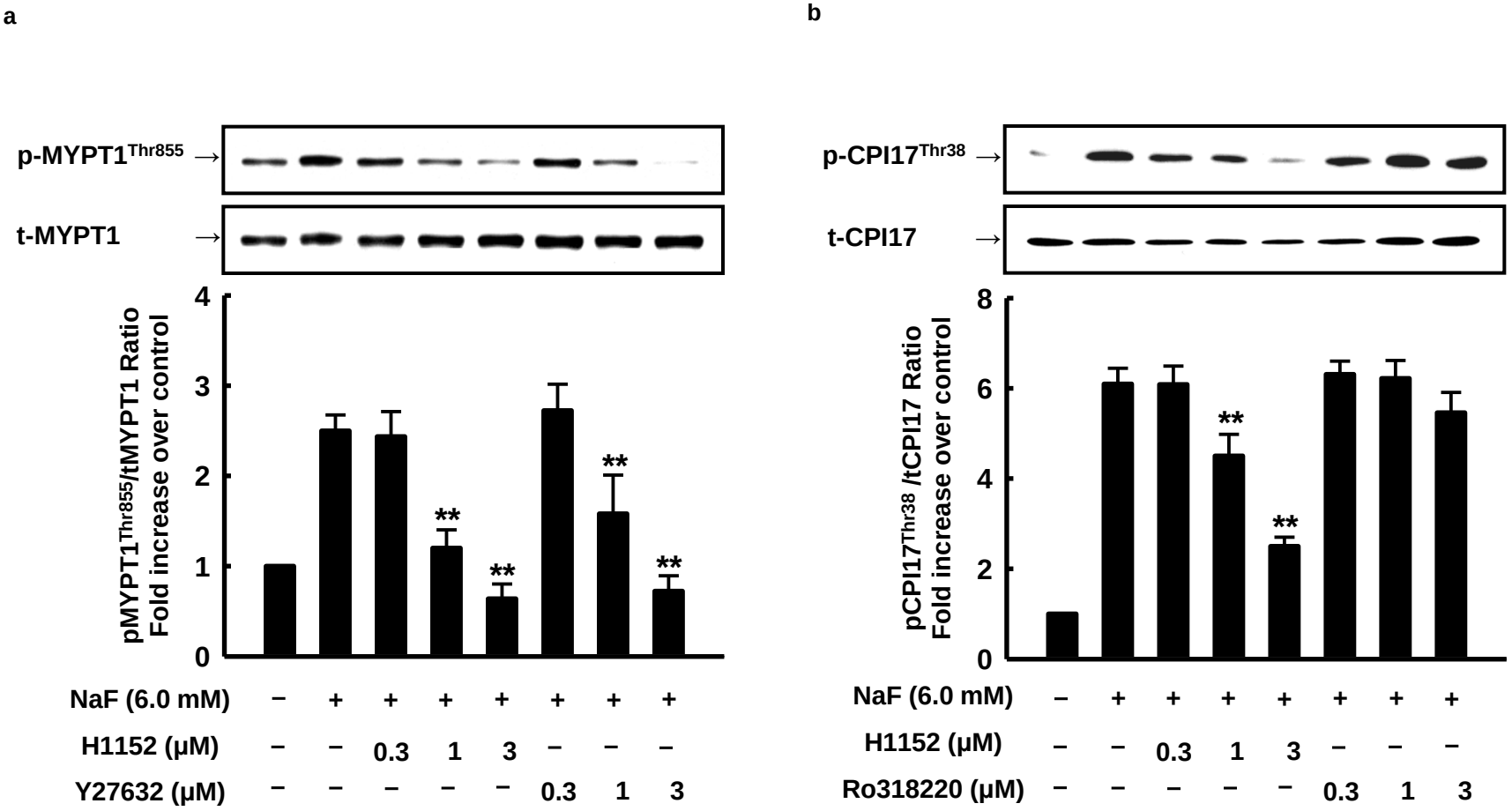
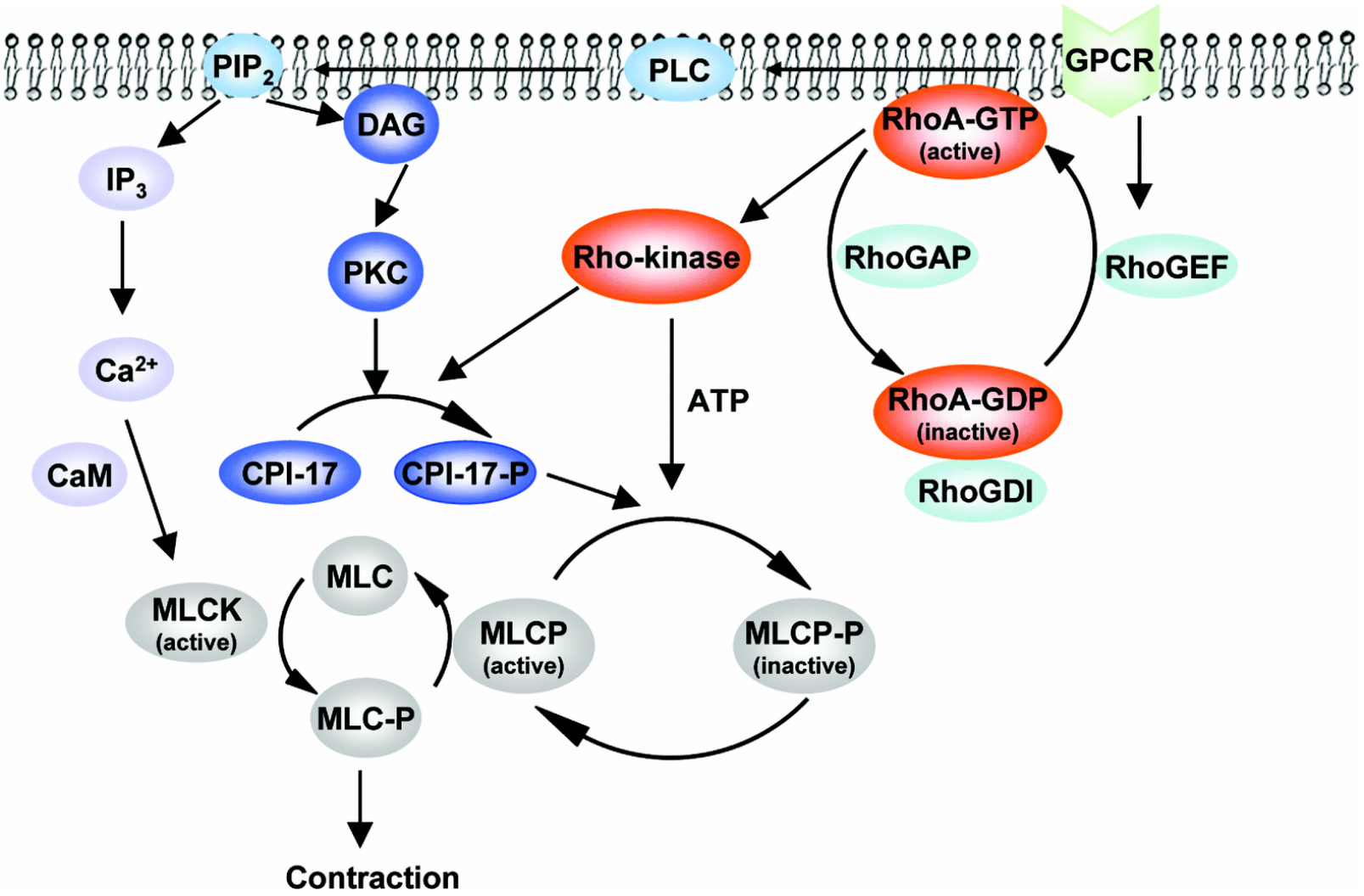
Divergent effects of estrogen and nicotine on Rho-kinase expression in human coronary vascular smooth muscle cells




a
p-MYPT1Thr855
t-MYPT1
pMYPT1Thr855/tMYPT1 Ratio
Fold increase over control
0
1
2
3
4
**
**
**
NaF (6.0 mM) − + + + + + + +
H1152 (μM) − − 0.3 1 3 − − −
Y27632 (μM) − − − − − 0.3 1 3
b
p-CPI17Thr38
t-CPI17
pCPI17Thr38 /tCPI17 Ratio
Fold increase over control
0
2
4
6
8
**
**
NaF (6.0 mM) − + + + + + + +
H1152 (μM) − − 0.3 1 3 − − −
Ro318220 (μM) − − − − − 0.3 1 3

Regulation of smooth muscle contraction



Clinical Science www.clinsci.org Clin. Sci. (2006) 110, 153-165

Hypertension 2009;54;11-18; originally published online May 26, 2009;

Hypertension

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Postmenopausal Hypertension Mechanisms and Therapy

Matthias Barton, Matthias R. Meyer

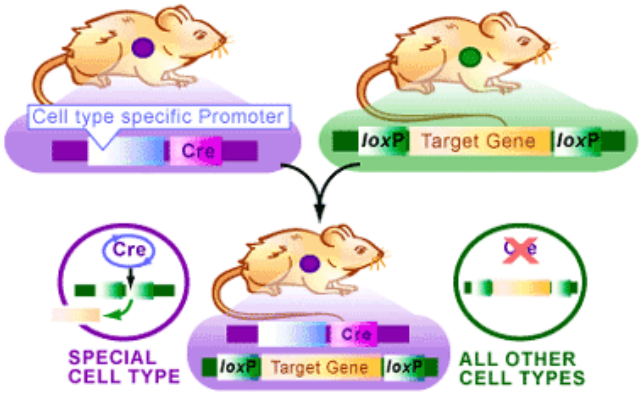
Table. Effects of Postmenopausal HT on Blood Pressure and Atherosclerotic Vascular Disease

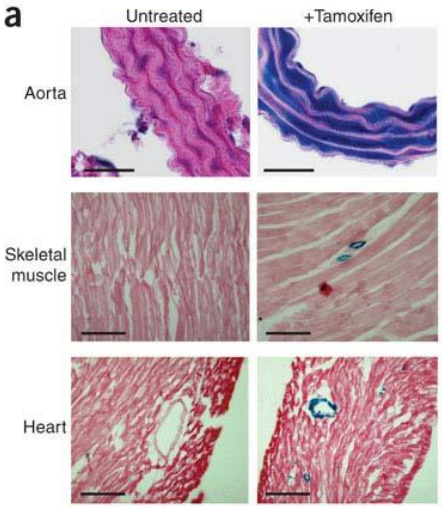
Potentially Beneficial	Potentially Negative
HT using 17β-estradiol	HT using animal estrogens (CEEs)
Transdermal administration of HT	Oral administration of HT
Begin of HT early after menopause	Begin of HT late after menopause
Low dosage of HT	High dosage of HT
Cyclic administration of HT	Progestins with adverse effects (MPA)

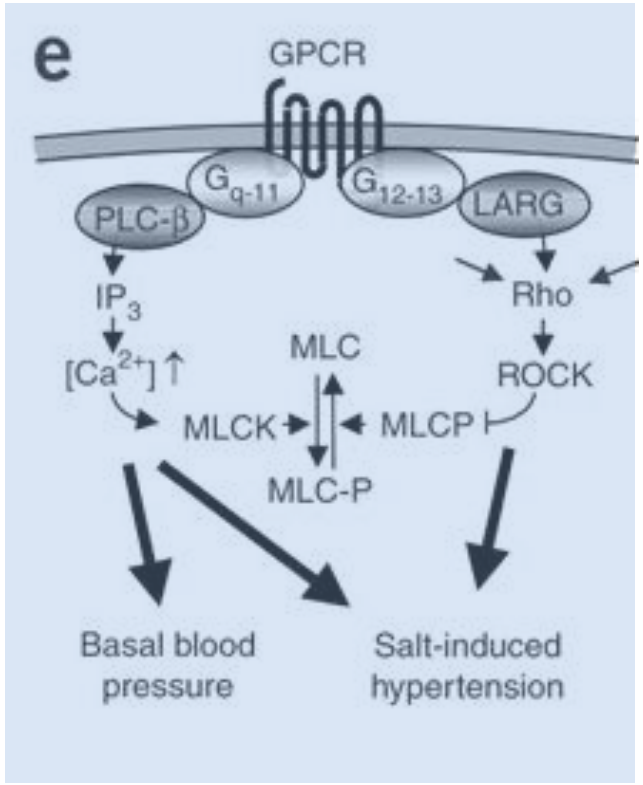
nature medicine

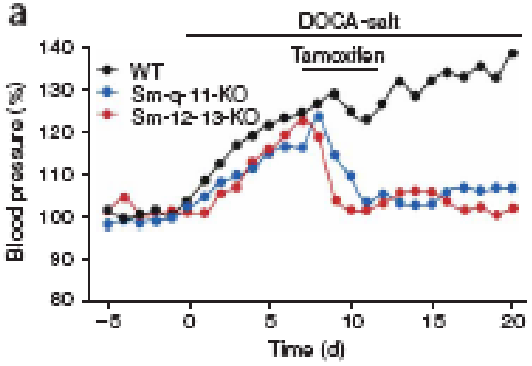
G_{12}-G_{13}–LARG–mediated signaling in vascular smooth muscle is required for salt-induced hypertension

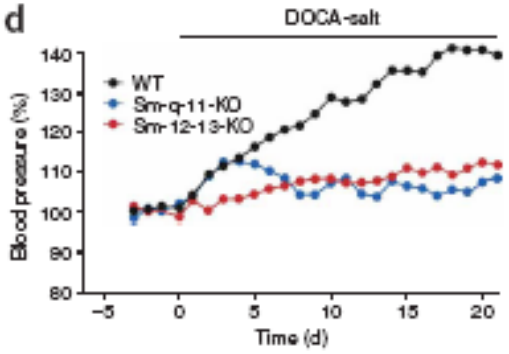
Angela Wirth[1], Zoltán Benyó[1,2,7], Martina Lukasova[1,7], Barbara Leutgeb[1,6], Nina Wettschureck[1], Stefan Gorbey[3], Petra Őrsy[1], Béla Horváth[1], Christiane Maser-Gluth[1], Erich Greiner[4,6], Björn Lemmer[3], Günther Schütz[4], J Silvio Gutkind[5] & Stefan Offermanns[1]







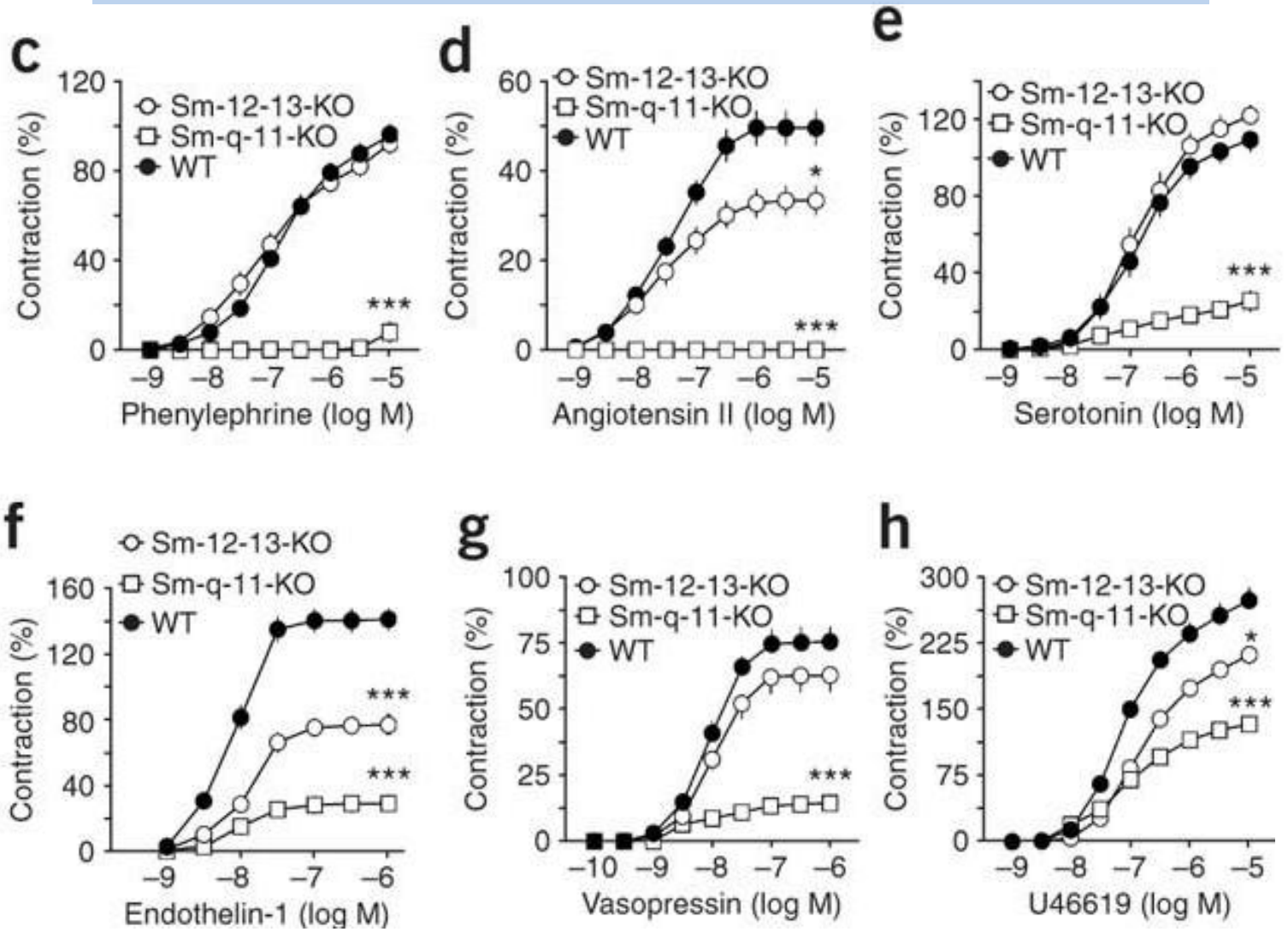


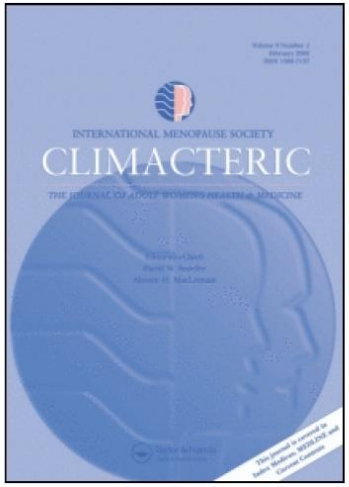


G_{12}-G_{13}–LARG–mediated signaling in vascular smooth muscle is required for salt-induced hypertension

Angela Wirth[1], Zoltán Benyó[1,2,7], Martina Lukasova[1,7], Barbara Leutgeb[1,6], Nina Wettschureck[1], Stefan Gorbey[3], Petra Őrsy[1], Béla Horváth[1], Christiane Maser-Gluth[1], Erich Greiner[4,6], Björn Lemmer[3], Günther Schütz[4], J Silvio Gutkind[5] & Stefan Offermanns[1]

nature medicine





Climacteric
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Menopause and cardiovascular disease: the evidence

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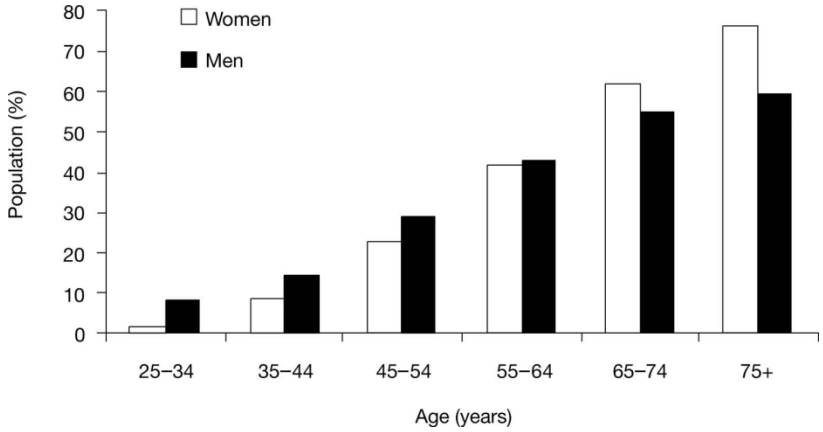

Estrogen should reduce development of hypertension through peripheral actions such as up-regulation of endothelium-derived vasodilator factors with simultaneous down-regulation of vasoconstrictor factors, such as endothelin-1 (Barber et al., 1996; Barber and Miller, 1998; Best et al., 1998; Dubey et al., 2001), inhibition of the renin-angiotensin system by reducing transcription of angiotensin-converting enzyme in endothelial cells (Brosnihan et al., 1994; Gallagher et al., 1999), and down-regulation of angiotensin 1 receptors (Nickenig et

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Vascular Actions of Estrogens: Functional Implications

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