Diferenças sexuais, hormônios sexuais e sistema cardiovascular

Tiago Januário da Costa, PhD

Disciplina de Farmacologia Cardiovascular
Ribeirão Preto – 1˚ semestre de 2020

Farmacologia Cardiovascular

Objetivo da aula

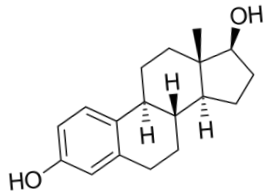
Compreender

Diferenças → **Vascular**

- **Fêmeas**
- **Machos**

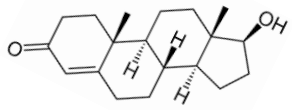
Diferenças

- Função
- Mecanismo de ação NO/ROS



Receptor Nuclear

- **Estrógeno**
  - **ERa**
- **Testosterona**
  - **AR**



Estrógeno aumenta lesão renal em fêmeas tratadas com vasopressina

1938

THE EFFECT OF ŒSTROGENIC AND OTHER SEX HORMONES ON THE RESPONSE OF THE RAT TO VASOPRESSIN

By F. B. Byrom, M.D., M.R.C.P. Lond.*

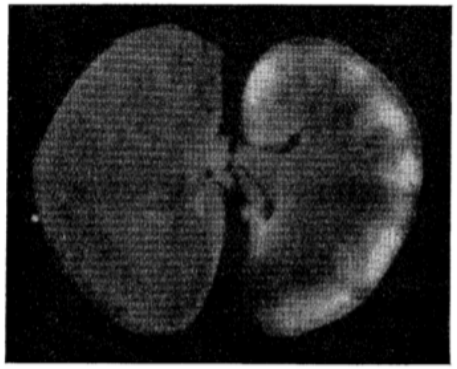
(*From the Bernhard Baron Institute of Pathology, the London Hospital*)

Showing the Degree of Sensitisation to Vasopressin Provoked by Œstrin Treatment

Rat	Preliminary treatment.	Dose of vasopressin (units). Per 100 g. body-weight.	Dose of vasopressin (units). Actual	Grade of renal damage (v. text).
410	Nil.	60	36	Gr. I, slight.
411	Nil.	30	20	Nil.
406	Œstrogenic hormone.	15 (1/2 & 1/4 of control)	8	Gr. II, severe.
407		10 (1/3 & 1/6 „)	6·2	„ II, mod.
408		6 (1/5 & 1/10 „)	3·2	„ I, mod.
409		4·3 (1/7 & 1/14 „)	2·1	„ I, slight.

mod. = moderate.

Rats 406–409 each received five daily doses of 0·15 mg. of œstradiol benzoate and a final injection of 50 units of aqueous theelin immediately before treatment with vasopressin. The *volume* of the vasopressin injection was the same in all experiments—i.e., 3 c.cm. per 100 g. body-weight.



Œstrin-sensitisation of the rat's kidney.—The kidney on the right is from an infant female rat treated with large doses of œstradiol benzoate for five days, followed by a subcutaneous injection of vasopressin (50 units per 100 g. body-weight). That on the left is from a litter-mate which was given the same dose of vasopressin, but no œstradiol. The former shows confluent infarction of the cortex. The latter appears normal.

Fêmeas normotensas respondem diferente as catecolaminas (microscopia intravital – Lembrar a aula da profa Luciana)

1972

SEX AS A FACTOR INFLUENCING THE RESPONSIVENESS OF ARTERIOLES TO CATECHOLAMINES *

Burton M. ALTURA **

Departments of Anesthesiology and Physiology, Albert Einstein College of Medicine of Yeshiva University, Bronx, N.Y. 10461, U.S.A.

Received 12 June 1972 Accepted 23 August 1972

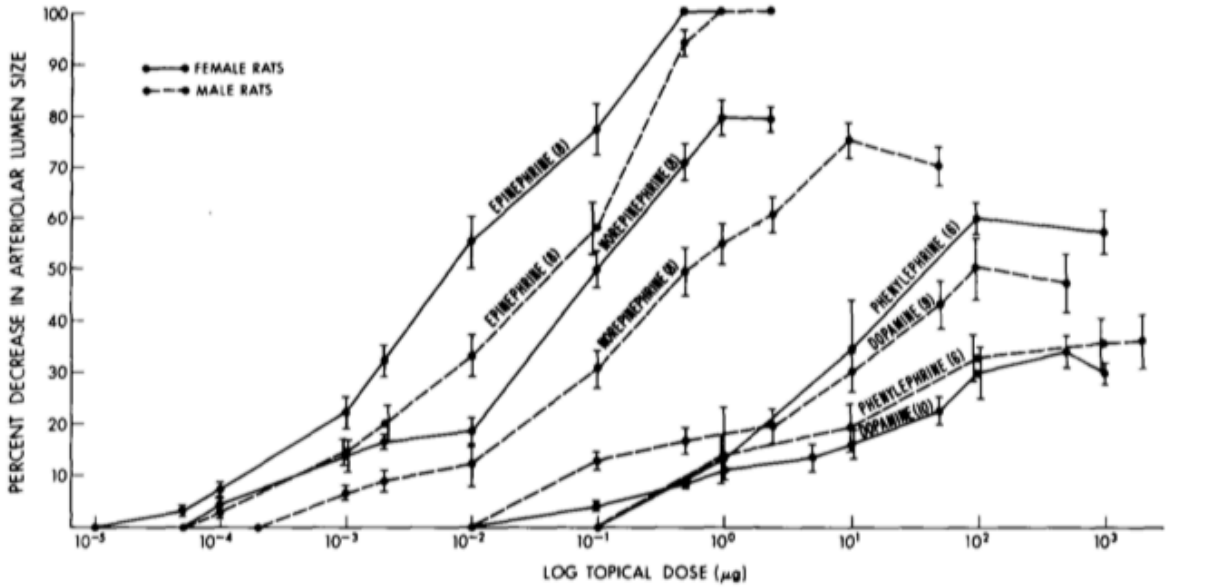


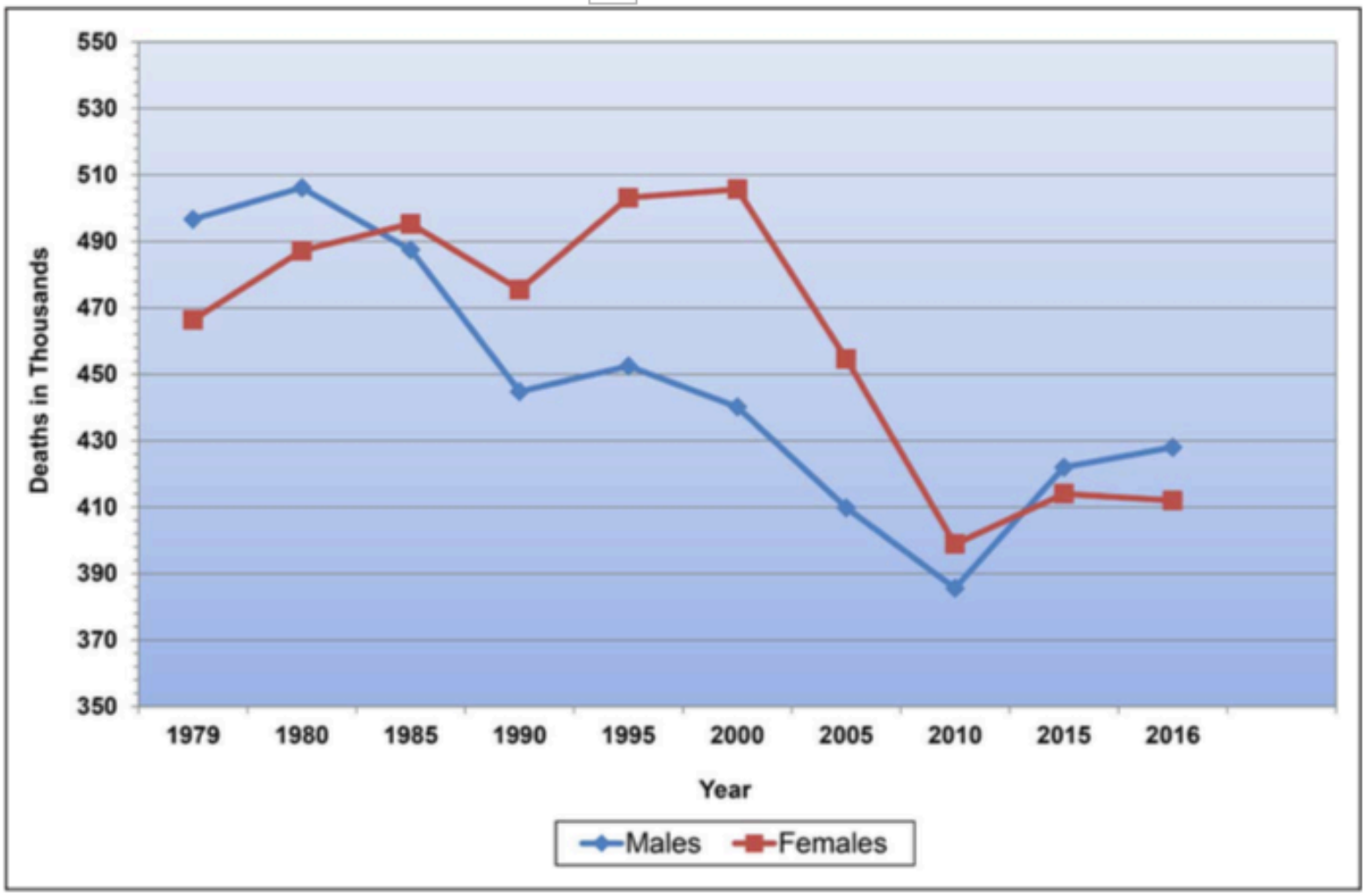
Fig. 1. Graded contractile responses of rat mesenteric arterioles to topically applied catecholamines, dopamine and phenylephrine in female vs. male rats. Each point represents the mean % change in lumen size obtained from measurements on vessels from different female (●——●) and male (●- - -●) rats (indicated by numbers in parentheses). Only one type of adrenergic drug was tested on each rat mesentery. The bars represent the S.E.M. The mean control lumen sizes for the arterioles in females were ($\mu \pm$ S.E.M.): epinephrine, 25.4 ± 1.7; norepinephrine, 29.4 ± 2.1; dopamine, 25.3 ± 1.8; and phenylephrine, 26.2 ± 2.2. The mean control lumen sizes for the arterioles in males were: epinephrine, 25.6 ± 1.9; norepinephrine, 28.0 ± 1.6; dopamine, 23.6 ± 1.0; and phenylephrine, 23.2 ± 3.9.

Pergunta que não quer calar:

Qual o índice de morte doenças cardiovasculares em mulheres ?

Não Sabemos!

Qual o índide de morte por doenças cardiovasculares em mulheres?



Circulation. 2019;139:e56–e528

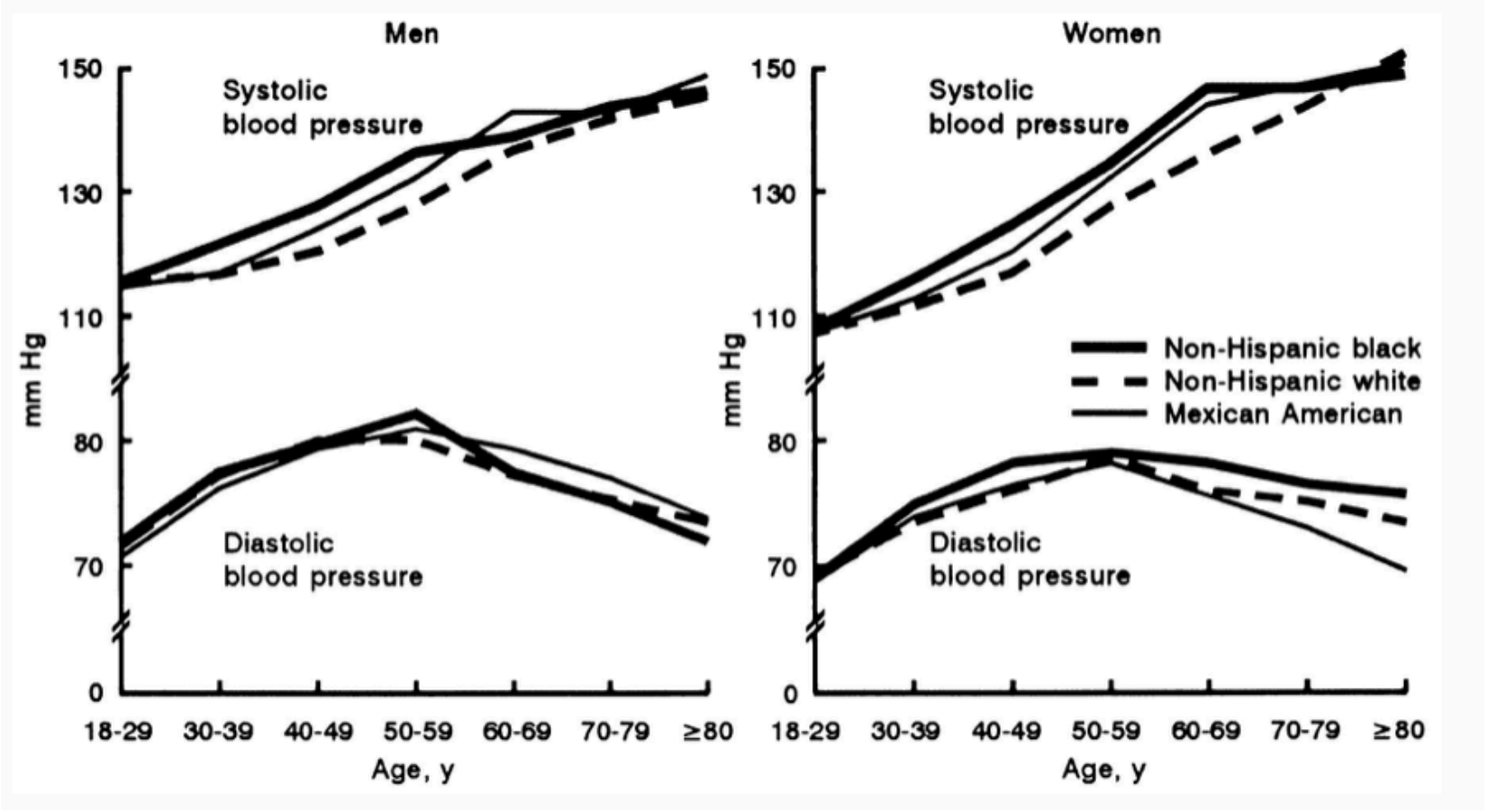
Os níveis pressóricos aumentam durante o envelhecimento, porém muito mais nas mulheres!

Prevalence of Hypertension in the US Adult Population

Results From the Third National Health and Nutrition Examination Survey, 1988-1991

Vicki L. Burt, Paul Whelton, Edward J. Roccella, Clarice Brown, Jeffrey A. Cutler, Millicent Higgins, Michael J. Horan, and Darwin Labarthe

Originally published 1 Mar 1995 | https://doi.org/10.1161/01.HYP.25.3.305 | Hypertension. 1995;25:305–313



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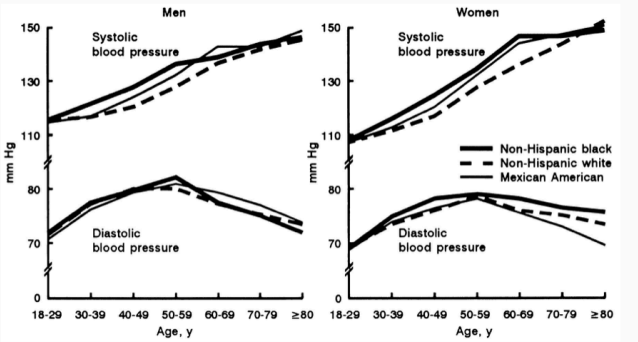


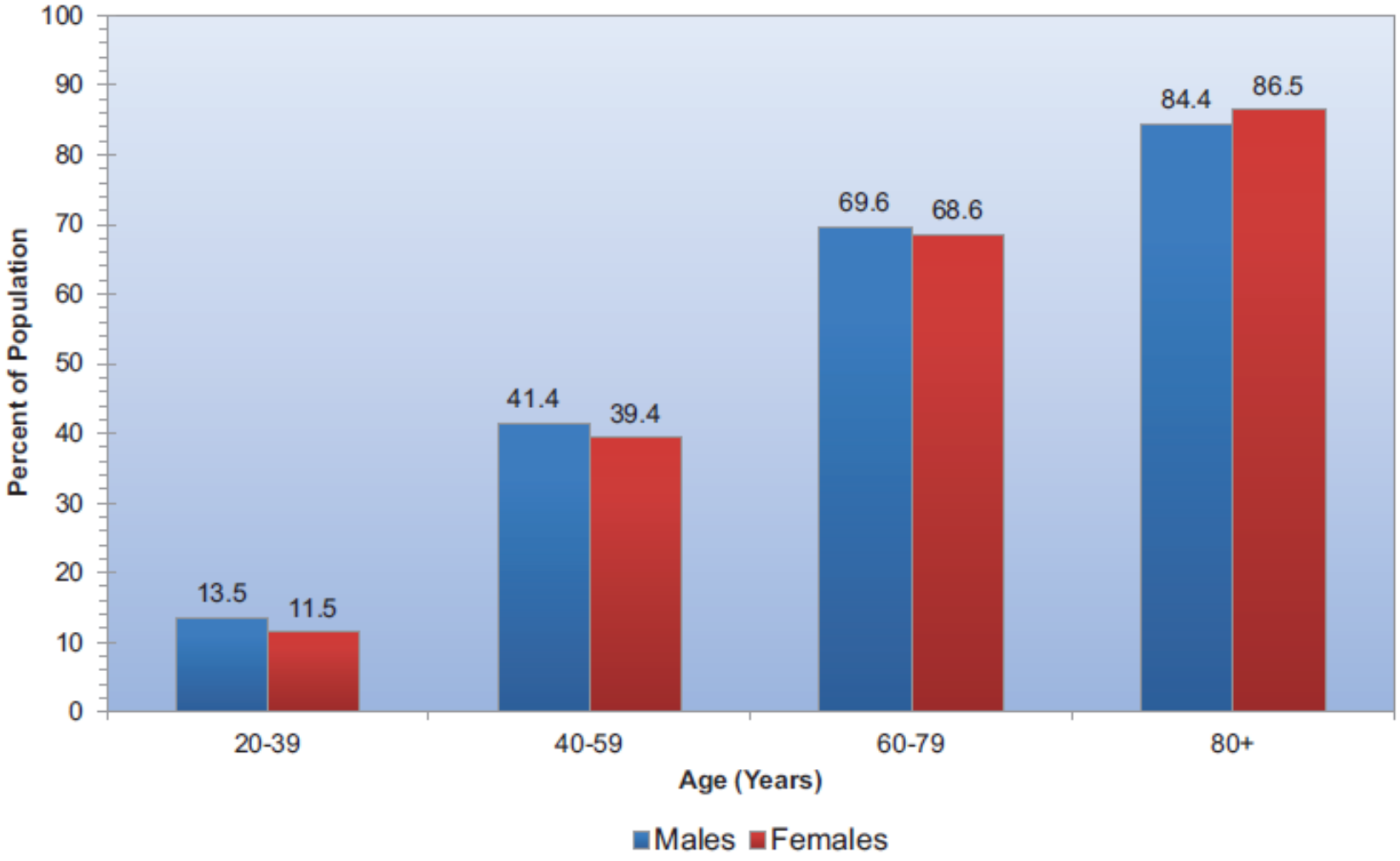
Hypertension. 1995; 25:305-313

SHR

* p<0.05, males compared with females.
‡ p<0.05, females compared to females.

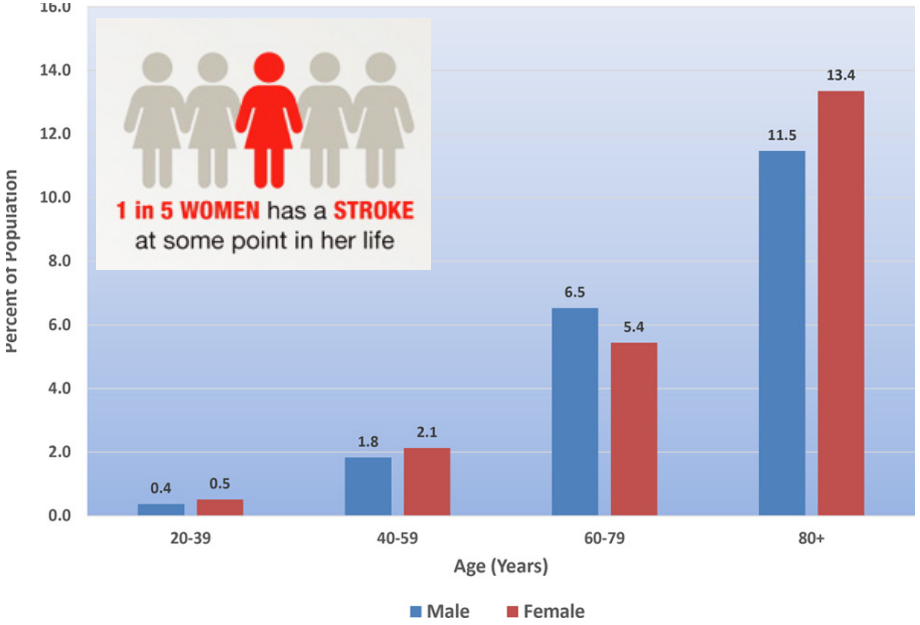
Hypertension. 2003;41:460–463.

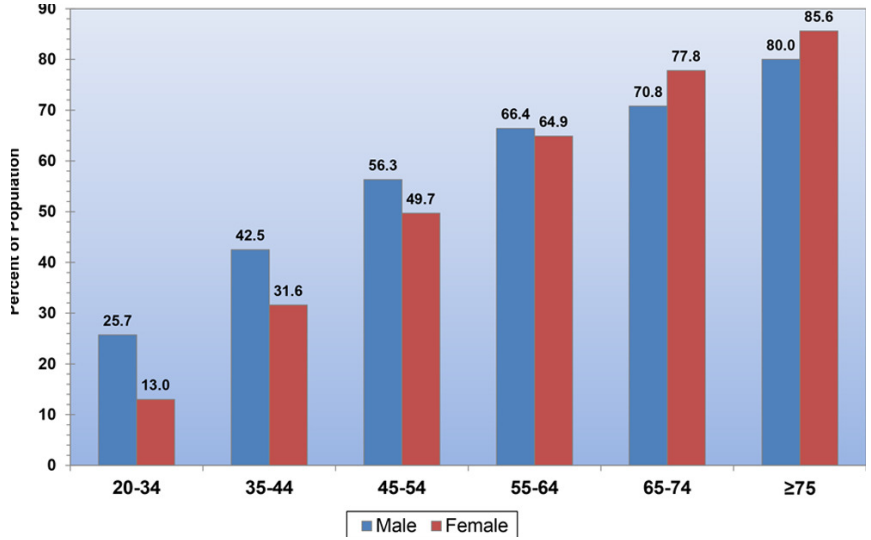
O índice de doenças cardiovasculares são menores em homens do que em mulheres até aproxidamente 50 anos.

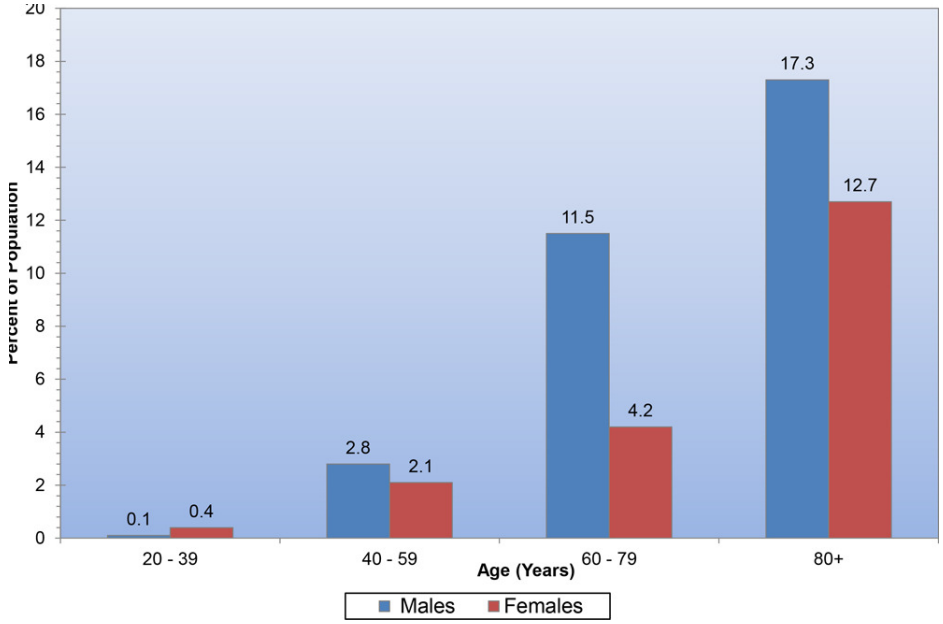


Circulation. 2019;139:e56–e528

National Stroke Association®







Reactivity of Aorta and Mesenteric Microvessels to Drugs in Spontaneously Hypertensive Rats: Role of the Endothelium

Maria Helena C. Carvalho, Regina Scivoletto, Zuleica B. Fortes, Dorothy Nigro and Sandra Cordellini

Journal of Hypertension 1987, **5**:377–382

The response to vasoactive agents of microvessels *in situ* and aortae *in vitro* was studied in normal and spontaneously hypertensive rats (SHR). Noradrenaline (NA) was equally effective in evoking a constrictor response of mesenteric microvessels in normal rats and SHR. The vasodilator response to acetylcholine (ACH), as endothelium-dependent relaxing agent, was lower in SHR microvessels whereas isoproterenol, papaverine, agents which are partially dependent on endothelium, and sodium nitroprusside, an endothelium-independent vasodilator, induced similar responses in control rats and SHR. Median effective concentrations and maximal responses to NA obtained in isolated SHR aortae, with or without endothelium, were similar to those obtained in their respective controls. NA-precontracted aortae with intact endothelium were less responsive to ACH in SHR than in controls. The relaxant response of the preparations was lost after endothelial cell removal in both groups. Sodium nitroprusside evoked similar relaxing effect in SHR and control NA-precontracted aortae. Isoproterenol-induced responses were potentiated in SHR-precontracted aortae, with or without endothelium. Removal of the endothelium diminished isoproterenol-induced relaxation, both in controls and SHR. With submaximal concentration of papaverine there was no difference between SHR aortae with or without endothelium and control aortae with endothelium. Control aortae without endothelium relaxed less than control aortae with endothelium and SHR aortae with or without endothelium. The rate of relaxation after papaverine was altered in aortae without endothelium isolated from SHR or control rats. These results indicate that the endothelium of SHR is altered. This could explain its decreased response to ACH. It is suggested that smooth muscle cells develop a compensatory mechanism that increases the response of agents that mobilize cAMP, such as papaverine and isoproterenol.

Materials and methods

Female 15–16-week-old, age-matched SHR and normotensive Wistar rats (NWR) were used. Systolic blood pressure (SBP) to characterize hypertension and normotension was determined using the tail cuff method in conscious animals. To induce oestrus, the rats received stilboestrol tetrasodium diphosphate (Honvan®) 20 μg/rat in oil solution s.c., 24 h before testing.

Reactivity of Aorta and Mesenteric Microvessels to Drugs in Spontaneously Hypertensive Rats: Role of the Endothelium

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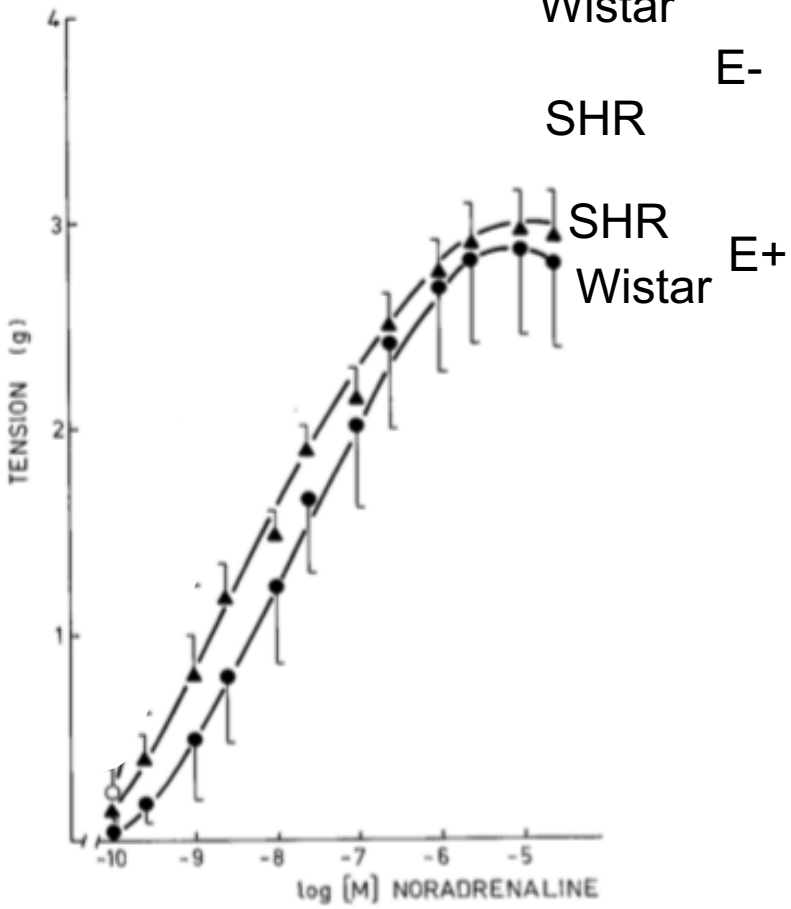
Wistar E-

SHR

SHR E+

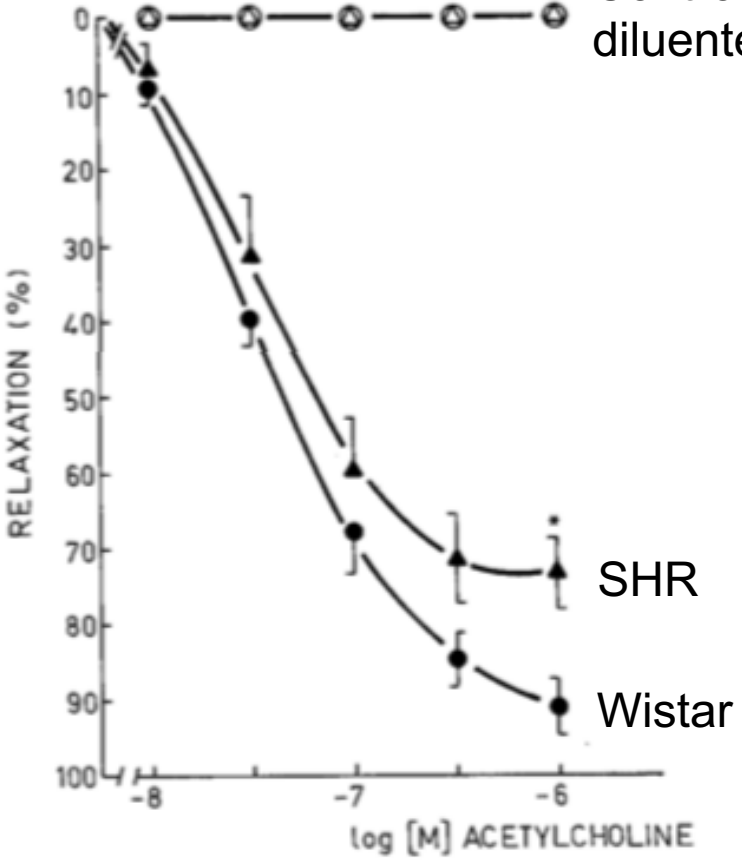
Wistar



Controle do diluente

SHR

Wistar



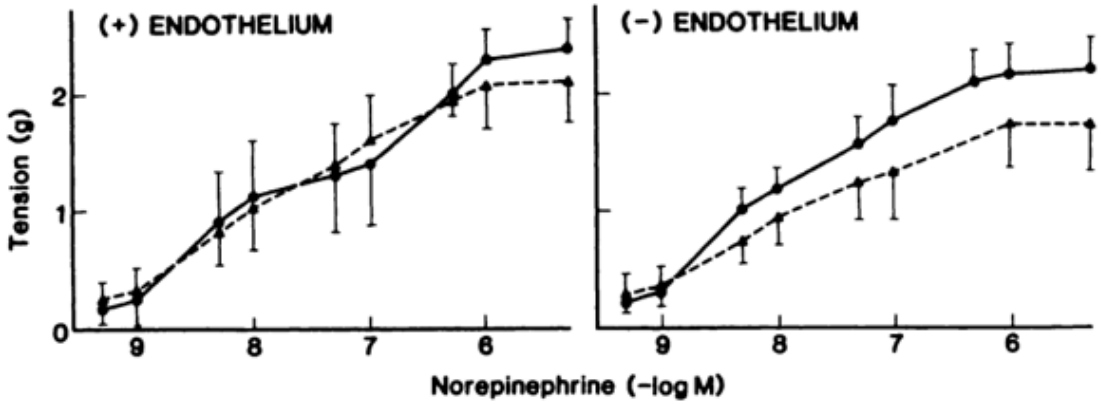
Endothelium-Dependent Gender Differences in the Response of the Rat Pulmonary Artery to the Thromboxane Mimic (U46619)[1]

CYNTHIA M. CUNARD, YVONNE T. MADDOX and PETER W. RAMWELL
Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, District of Columbia
Accepted for publication December 23, 1985

Endothelium-Dependent Gender Differences in the Response of the Rat Aorta[1]

YVONNE T. MADDOX, JOHN G. FALCON, MARK RIDINGER, CYNTHIA M. CUNARD and PETER W. RAMWELL
Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, District of Columbia
Accepted for publication October 20, 1986

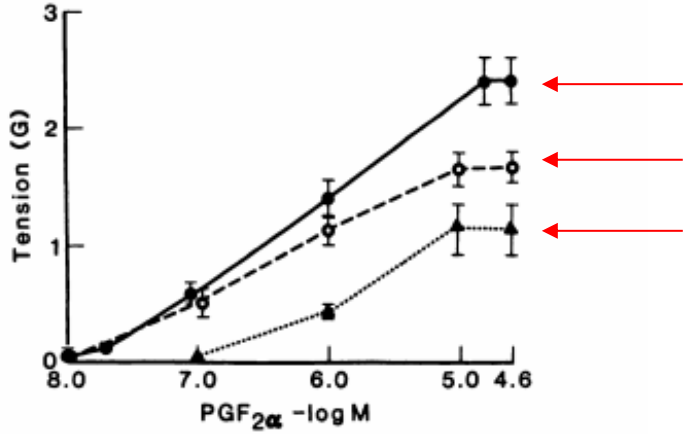
Artéria pulmonar – Sprangue-Dawley



Fêmeas

Fig. 2. Cumulative dose-response curves to norepinephrine in intact [(+)-Endothelium] and denuded [(−)-Endothelium] rat pulmonary artery segments dissected from females (●) and males (▲). Each point on the curve represents at least four observations.

Aorta Sprangue-Dawley



Fêmeas – tratadas com Testosterona

Machos intactos

Fêmeas intactas

Fig. 1. Cumulative dose-response curves to $PGF_{2\alpha}$ in intact segments of the aortic arch dissected from control female (▲), control male (○) and testosterone-treated female (●) rats.

Níveis pressóricos elevados

Machos X Fêmeas

Proteção Endotelial

Diferença na função

Hipertensão gera dano endotelial em ambos os sexos

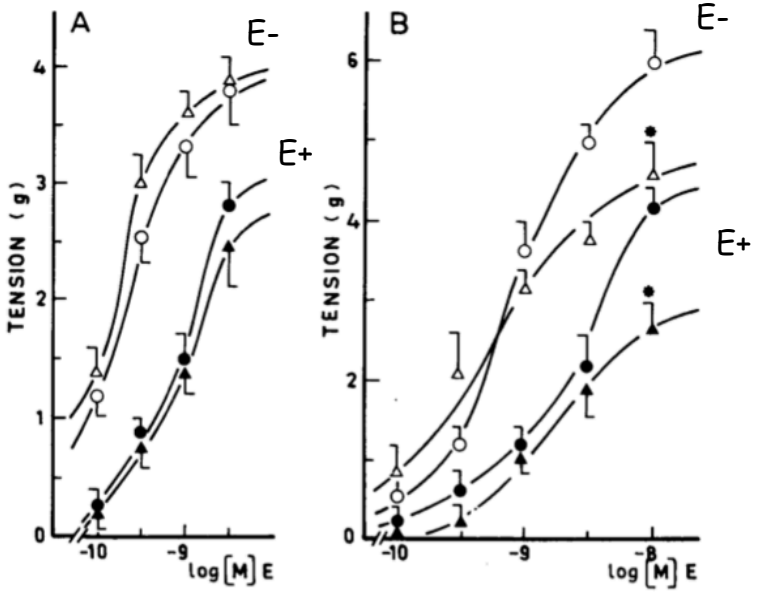
Pergunta de revisor de paper:
Quais os mecanismo envolvidos?

PA: uma variável a ser considerada ?

RESULTS

Blood pressures were elevated significantly in male and female SHR. Tail blood pressures of male rats at the time of the study were 165.5 ± 4.9 (mean ± SEM) and 112.5 ± 3.5 mmHg for 27 SHR and 31 controls respectively. Tail blood pressures of female rats were 166.5 ± 2.8 and 107.1 ± 3.2 mmHg for 22 SHR and 15 controls respectively.

Fêmeas Machos



MATERIAL AND METHODS

Animals

Male and female SHR (14-16 weeks old) and their respective normotensive Wistar controls were used. Tail blood pressures were measured by the tail cuff method in conscious rats. Oestrus was induced in all female rats by injecting subcutaneously stilboestrol tetrasodium acetate (Honvan^{R}) 20 ug/rat in oil solution 24 h before the experiments. Oestrus was determined by microscopic observation of vaginal smears.

Fortes ZB. Clin Exp Hypertens A. 1991;13(5):807-16

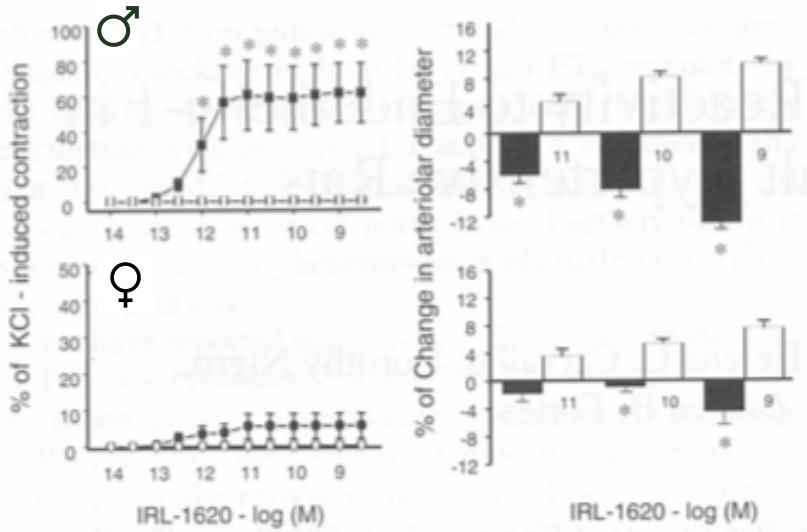
♂ ♀ DOCA-sal

acetato de desoxicorticosterona

NaCl a 1% 0.2% KCl na água de beber

RESULTS

After 4 weeks of DOCA treatment, SBP was: DOCA-salt, male = 203 ± 6 mmHg vs female = 168 ± 6 mmHg ($p < 0.05$); control, male = 123 ± 2 vs female = 119 ± 3 mmHg. Endothelium-intact aortas from male DOCA rats displayed increased sensitivity ($pD_2 = -\log EC_{50}$; $p < 0.05$) to NE (DOCA = 8.2 ± 0.1, control = 7.3 ± 0.1) and to 5-HT (DOCA = 7.3 ± 0.1, control =



Tostes RC. Cardiovasc Pharmacol. 2000 Nov;36:S99-101

Machos e fêmeas são diferentes em situações fisiológicas?

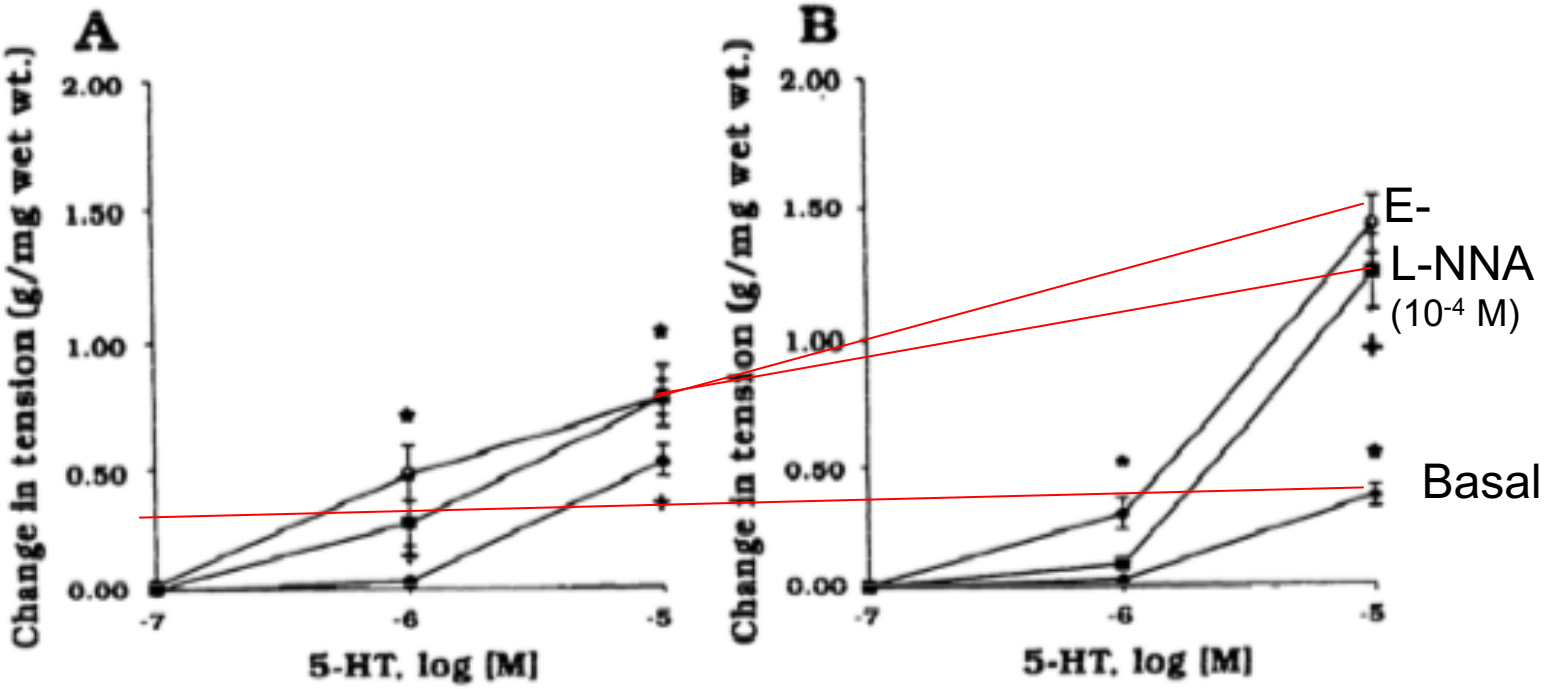
Diferença sexual em animais normotensos: NO ou Prostaciclina?

Gender difference in bioassayable endothelium-derived nitric oxide from isolated rat aortae

KATALIN KAUSER AND GABOR M. RUBANYI
Cardiovascular Department, Berlex Biosciences, Richmond, California 94804

Machos Wistar

Fêmeas Wistar



Kauser K. Am J Physiol. 1994 Dec;267(6 Pt 2):H2311-7.

Pergunta de revisor:

A diferença sexual em animais normotensos ocorre somente na resposta à 5-HT?

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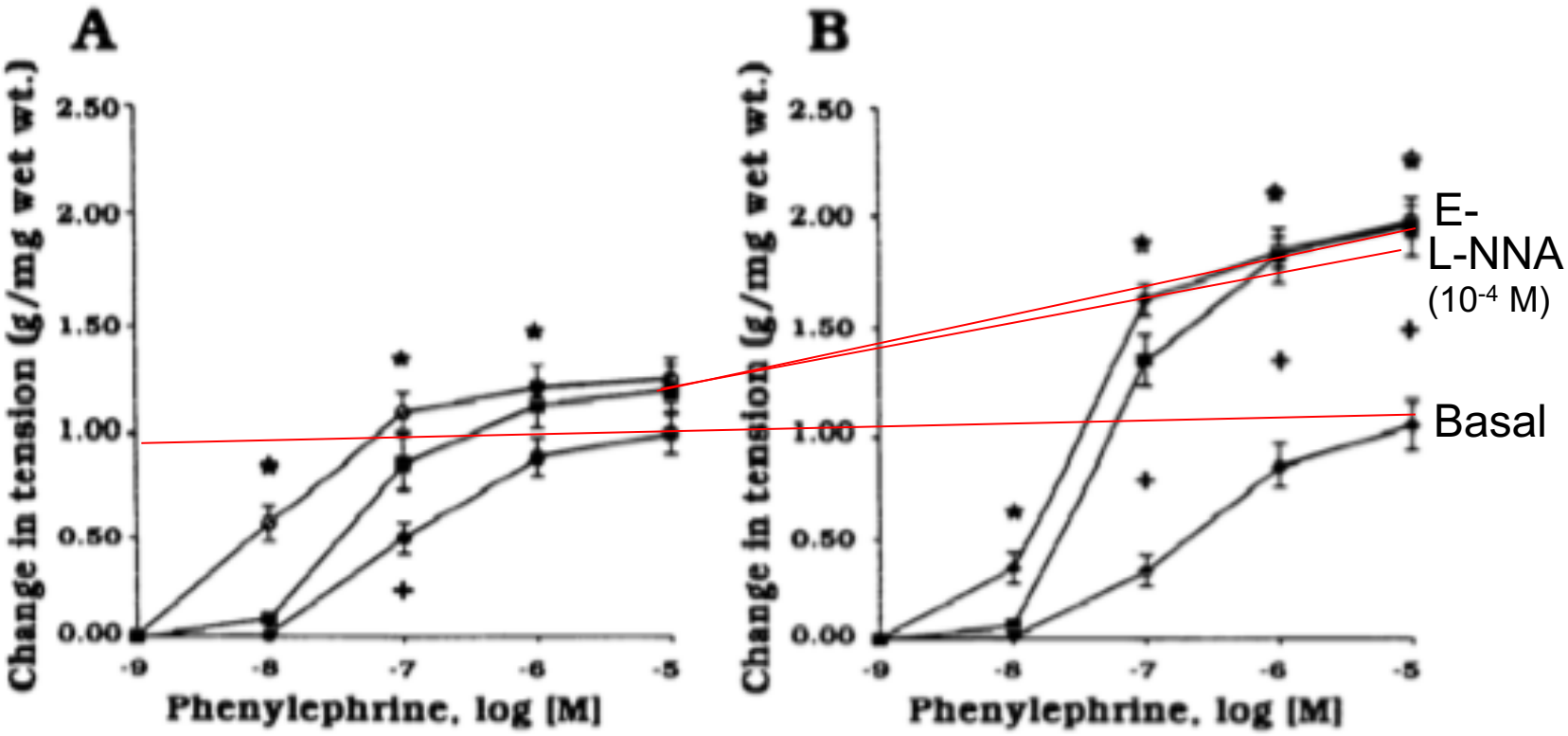
Cardiovascular Department, Berlex Biosciences, Richmond, California 94804

Machos Wistar

Fêmeas Wistar



Kauser K. Am J Physiol. 1994 Dec;267(6 Pt 2):H2311-7.

Gender difference in bioassayable endothelium-derived nitric oxide from isolated rat aortae

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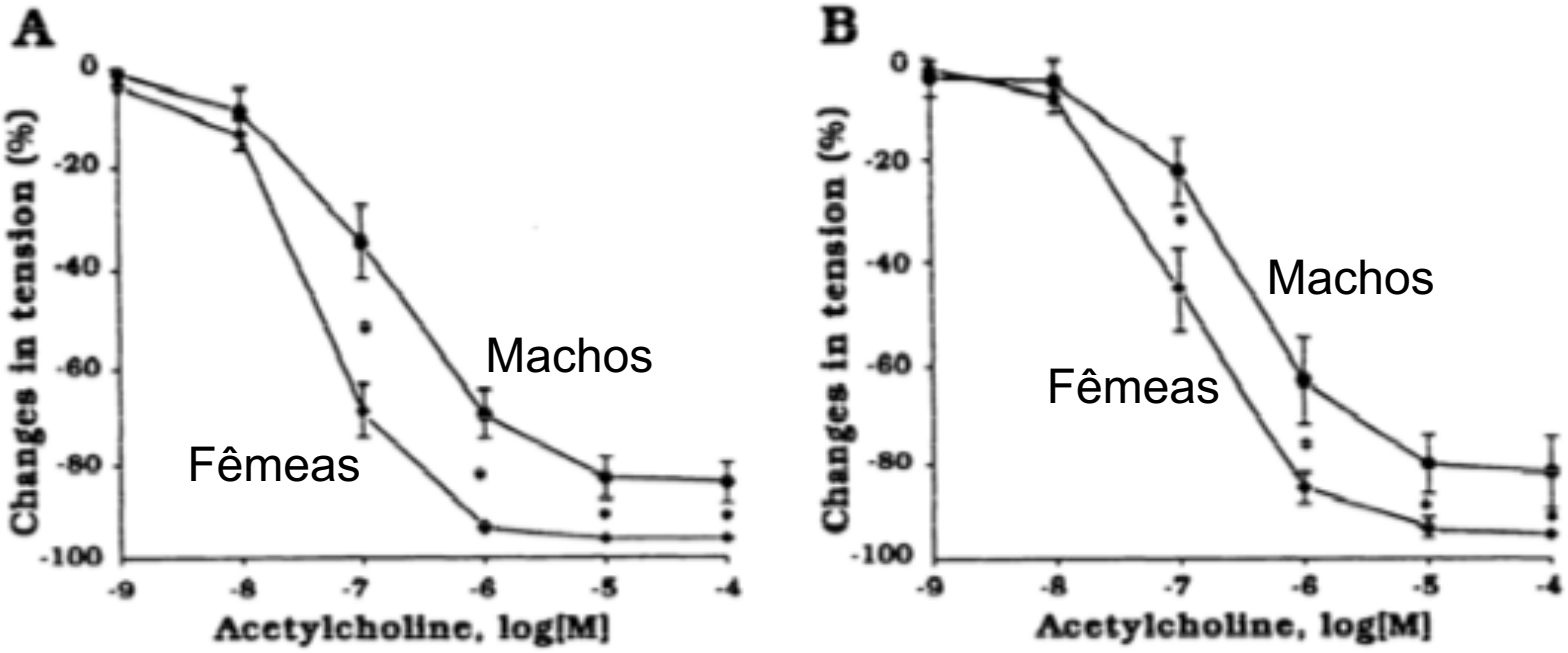
Cardiovascular Department, Berlex Biosciences, Richmond, California 94804

Basal

Com <u>indometacina</u> 10^{-5}M
<u>(inibidor não seletivo da COX)</u>



Kauser K. Am J Physiol. 1994 Dec;267(6 Pt 2):H2311-7.

Pergunta da Profa Rita:

Há alteração na produção de NO ou na maquinaria contrátil das CMLVs no macho vrs fêmea?

Superfusion biossay: NO proveniente de fêmeas induz relaxamento em artérias de machos!

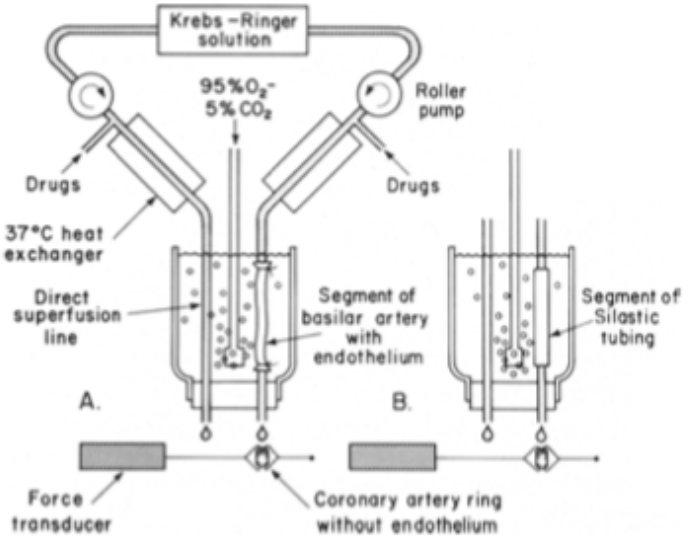


FIG. 1. Schematic illustration of the bioassay system for analysis of endothelium-derived relaxing factor released from the basilar artery. See text for the measuring procedure.

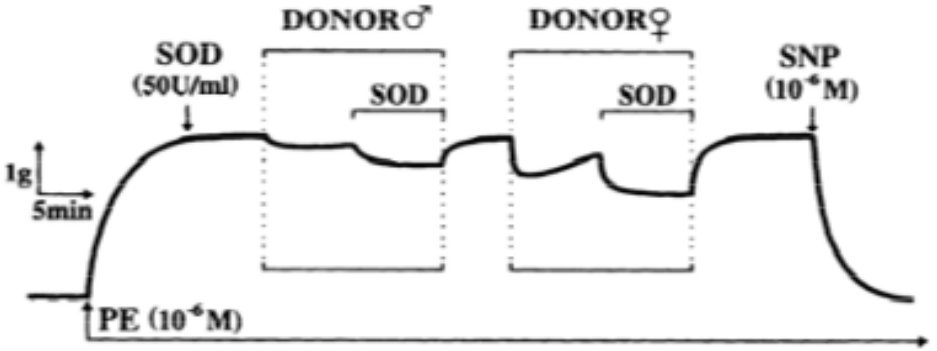


Fig. 7. Orig … wing relaxation of … e rat and contract … rived relaxing fac … with endothelium … d in parallel. Exp … nacin (10⁻⁵ M). SO …

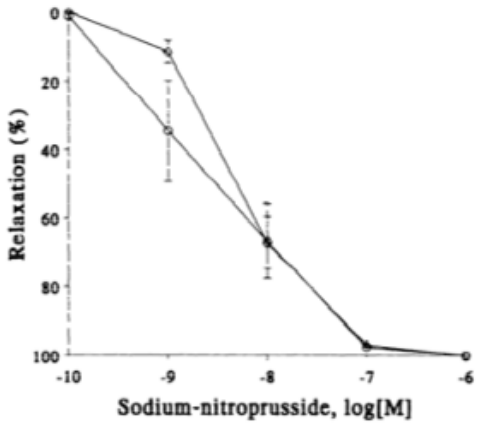


Fig. 6. Sodium nitroprusside (SNP)-induced relaxation (10^{-10}–10^{-6} M) in deendothelialized thoracic aortic rings isolated from male (○) and female (◇) rats. Values are means ± SE of 8 expts expressed as percent relaxation of contractions evoked by PE (10^{-7} M; 100% = 0.7 ± 0.1 and 1.1 ± 0.1 g/mg wet wt for males and females, respectively).

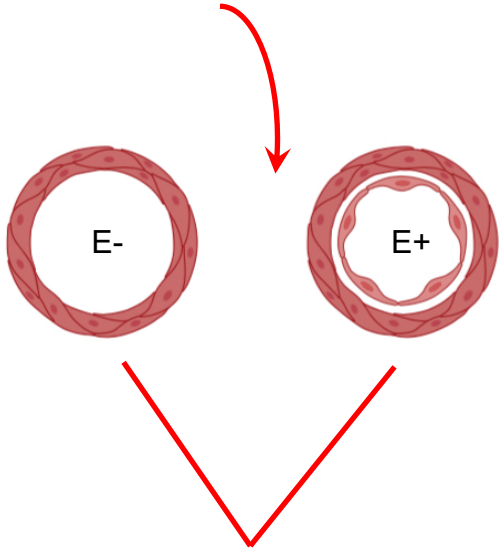
from male (hatched bars) and female rats (cross-hatched bars). Values are means ± SE (n = 8) of relaxation of assay rings in response to release of endothelium-derived NO from male and female donor segments in physiological salt solution (control) and after SOD infusion (+SOD) expressed as percent inhibition of initial contraction of assay rings (2.3 ± 0.2 g). *P < 0.05 compared with male; †P < 0.05 compared with control. L-NNA (10^{-4} M) perfusion of donor segments completely prevented relaxation of bioassay ring, indicating that the bioassayable endothelium-derived relaxing factor is probably NO (data not shown).

Kause K. Am J Physiol. 1994 Dec;267(6 Pt 2):H2311-7.

Diferença sexual na função vascular é mediada pelo NO

Fenilefrina (10^{-5} M)

α1-adrenérgico



Delta da vasconstrição

♀ ♂

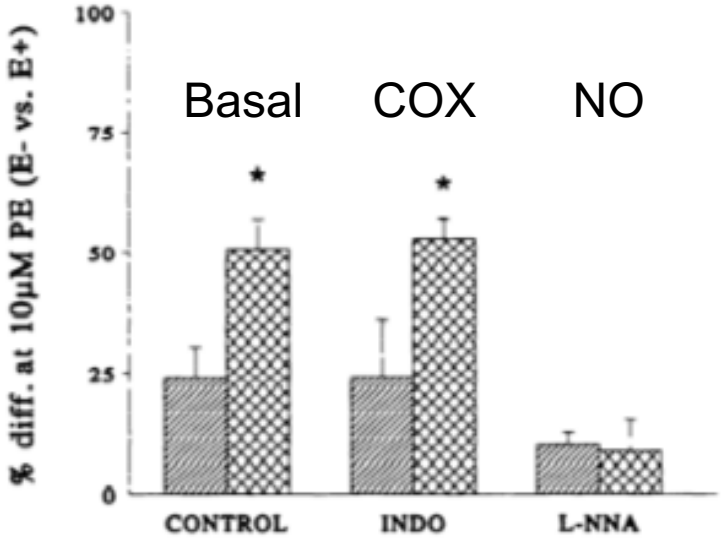
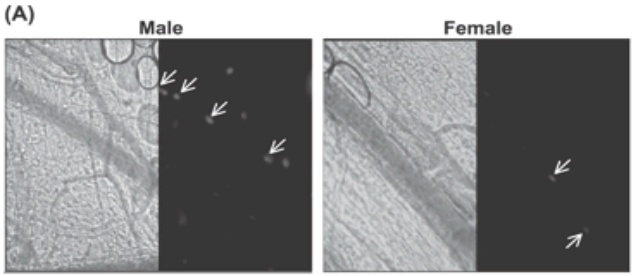
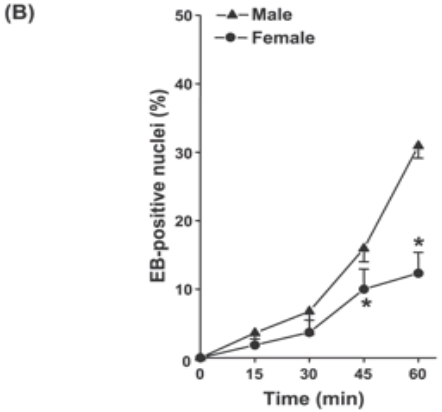
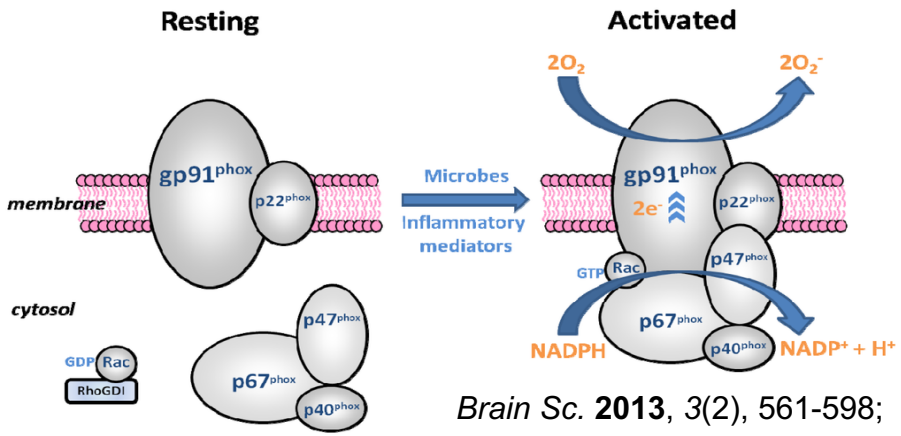


Fig. 4. Endothelium-derived NO effect in thoracic aortic rings isolated from male (hatched bars) and female (cross-hatched bars) rats. Values are means ± SE expressed as percent difference between contractions of intact and denuded segments evoked by PE (10^{-5} M). Control, control condition in physiological salt solution; INDO, after indomethacin (10^{-5} M) incubation; L-NNA, after L-NNA (10^{-4} M) treatment. Indomethacin had no effect, whereas L-NNA prevented endothelial suppression of contraction in intact male and female tissues. *Significantly greater sppression of PE contraction by endothelium in aortic rings isolated from female than from male rats ($P < 0.05$).

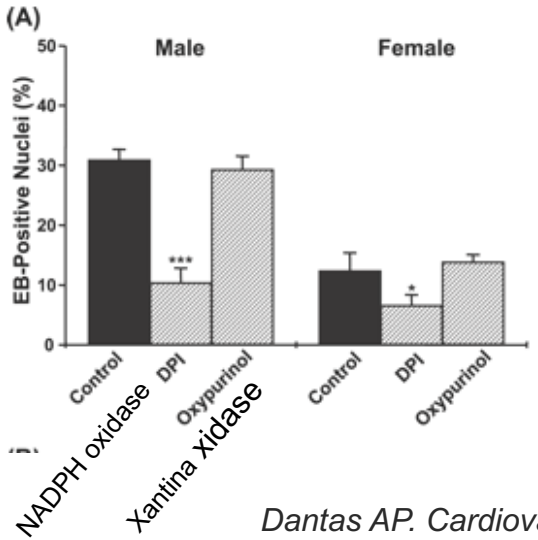
EROs e NO :machos vrs fêmeas





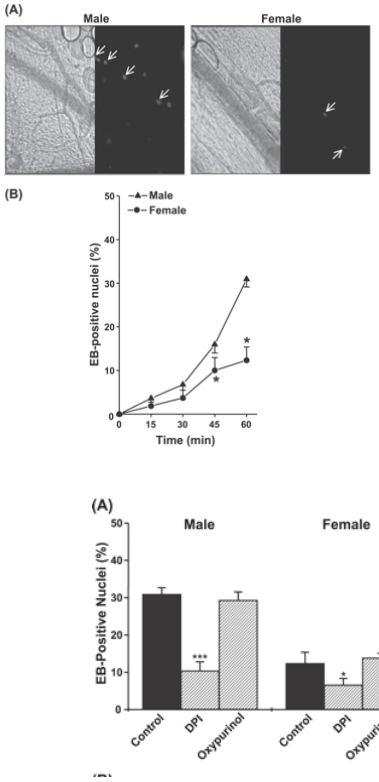


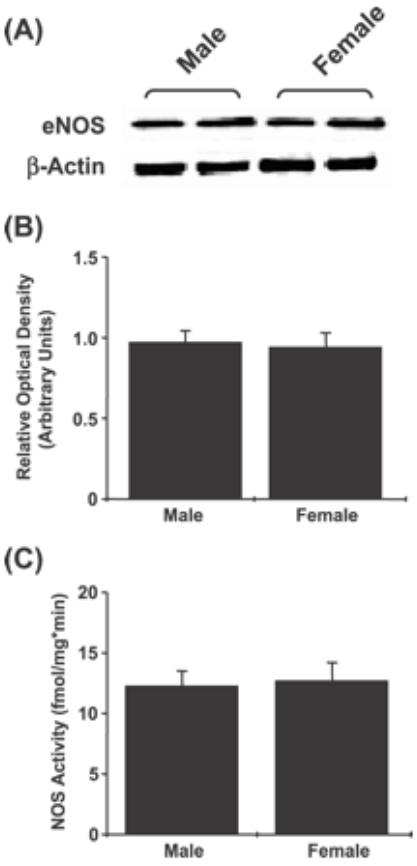
Brain Sc. **2013**, *3*(2), 561-598;

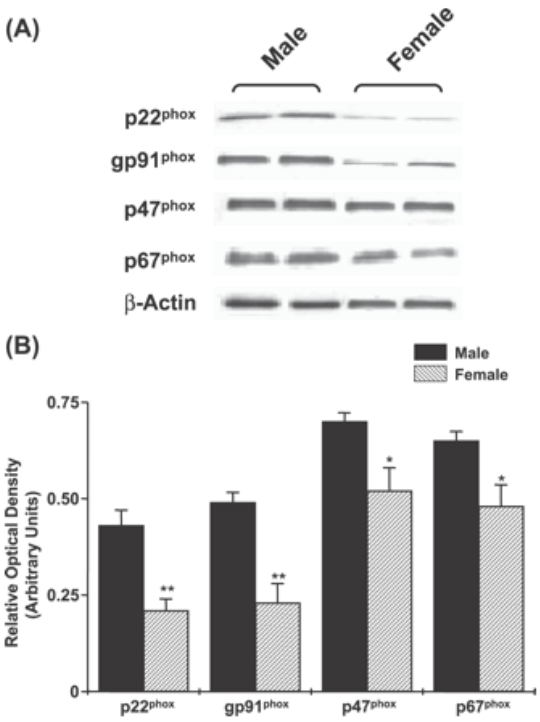


Dantas AP. Cardiovascular Research, Volume 61, Pages 22–29, 2004.

EROs e NO :machos vrs fêmeas







Dantas AP. Cardiovascular Research, Volume 61, Pages 22–29, 2004.

EROs e NO :machos vrs fêmeas

Aorta Rato Aorta Mouse Cerebral Mouse

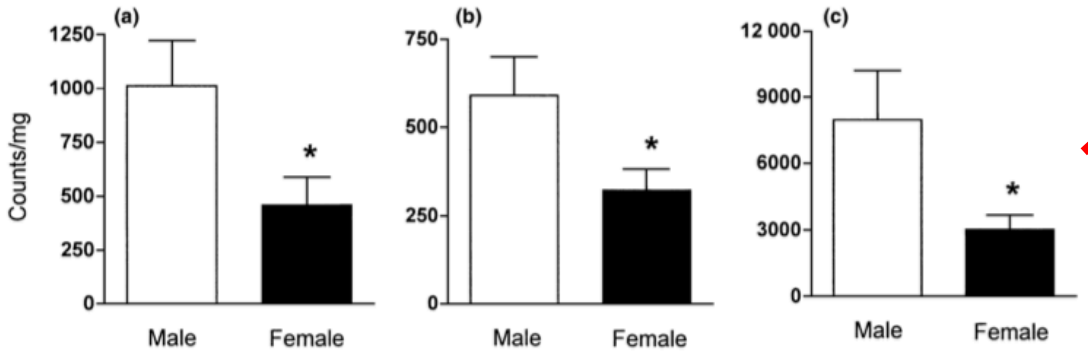
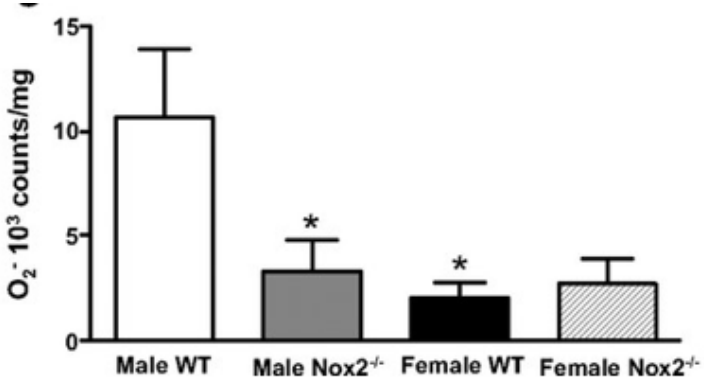
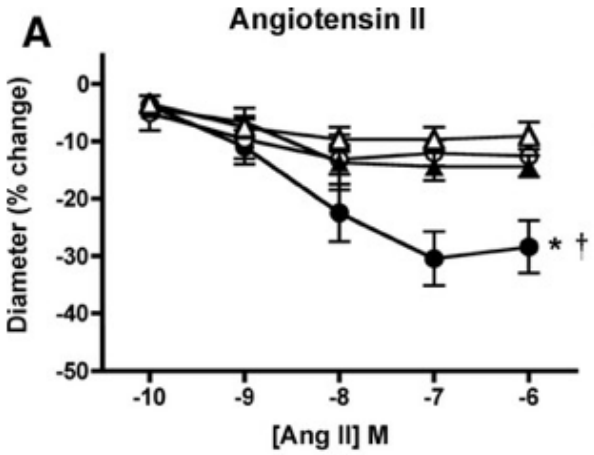
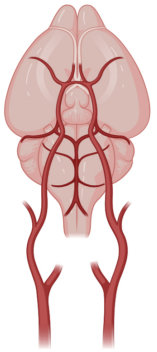


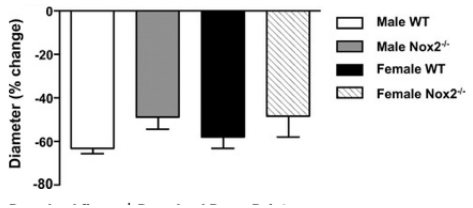
Fig. 2 Production of O_2^- by NADPH oxidases in systemic and cerebral arteries from male and female rats and mice, as measured by lucigenin-enhanced chemiluminescence. (a) Rat aorta; (b) mouse aorta; (c) mouse cerebral arteries. The NADPH (100 μmol/L)-stimulated O_2^- production is lower in aortas (a,b) and cerebral arteries (c) from female rats and mice than males. Values are expressed as the mean±SEM (counts/mg dry tissue; $n = 12$). $^*P < 0.05$ compared with males (unpaired *t*-test).







KCl

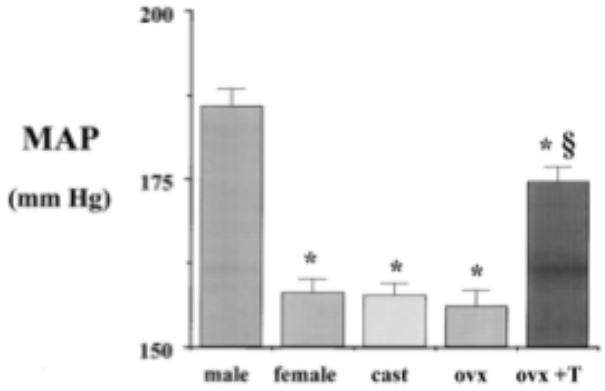


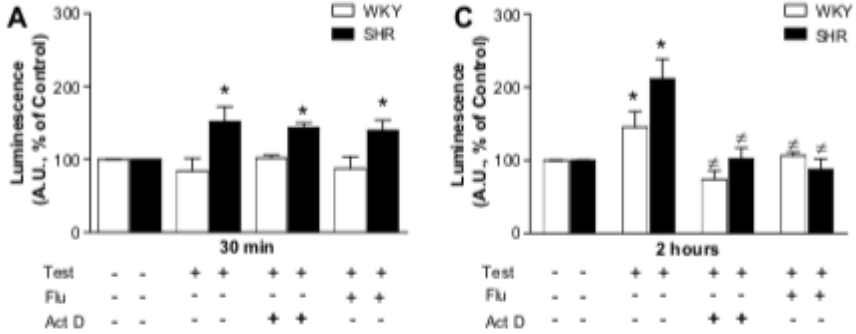
Miller AA. Stroke. 2009;40:1091–1097

Miller AA.Clinical and Experimental Pharmacology and Physiology (2007) **34**, 1037–1043

Pergunta de Jane Reckelhoff :
A testosterona está envolvida no processo de aumento de EROs?

Testosterona aumenta EROS em machos ! E nas fêmeas?





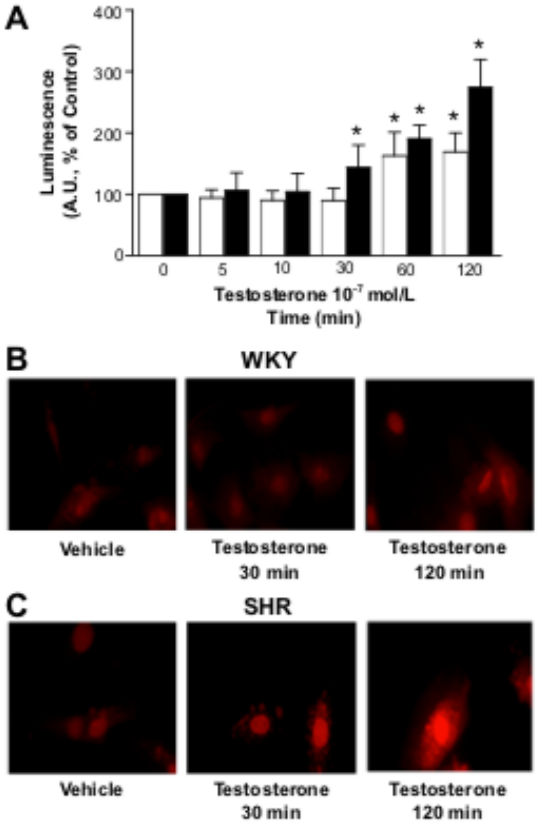
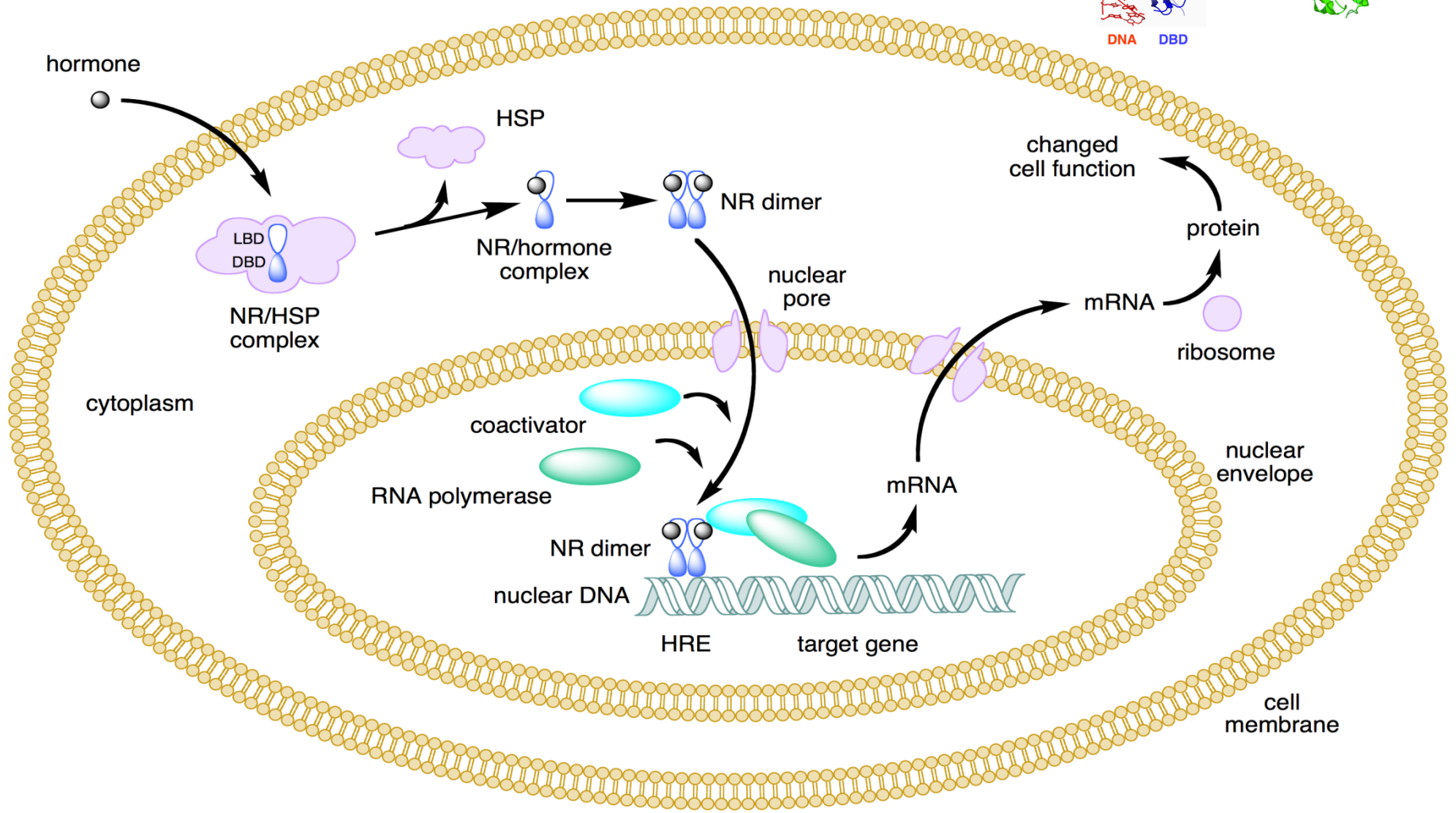


Figure 1. Differential time-course for testosterone-induced reactive oxygen species (ROS) production in vascular smooth muscle cells (VSMCs) from Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHRs). Time- course for ROS production assessed by lucigenin-enhanced chemiluminescence in WKY rat VSMCs and SHR VSMCs (**A**) stimulated with testosterone 10^{-7} mol/L. Data represent the mean±SEM of n=4 to 10 experiments; *P<0.05 vs control (vehicle). Representative images for ROS production, assessed by dihydroethidium microscopy fluorescence, in WKY rat VSMCs (**B**) and SHR VSMCs (**C**) stimulated with testosterone 10^{-7} mol/L.

Chinaglia AZ.Hypertension. 2012 Jun;59(6):1263-71


N-terminal domain
Hinge region
C-terminal domain
A/B
C
D
E
F
DNA binding domain (DBD)
Ligand binding doman (LDB)
LBD
Ligand
DNA
DBD
hormone
HSP
LBD
DBD
NR/HSP complex
NR/hormone complex
NR dimer
nuclear pore
changed cell function
protein
mRNA
ribosome
cytoplasm
coactivator
RNA polymerase
nuclear envelope
mRNA
NR dimer
nuclear DNA
HRE
target gene
cell membrane

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Am J Physiol Regul Integr Comp Physiol. 2016 Jan 1; 310(1): R1–R14.
Published online 2015 Nov 4. doi: 10.1152/ajpregu.00392.2014

PMCID: PMC4796634
PMID: 26538238

Reactive oxygen species: players in the cardiovascular effects of testosterone

Rita C. Tostes,[1] Fernando S. Carneiro,[1] Maria Helena C. Carvalho,[2] and Jane F. Reckelhoff[3]

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CLINICAL SCIENCE (LONDON, ENGLAND : 1979)
Portland Press Ltd

Clin Sci (Lond). 2017 Jul 1; 131(13): 1405–1418.
Published online 2017 Jun 23. doi: 10.1042/CS20170090

PMCID: PMC5736922
PMID: 28645930

Genomic and non-genomic effects of androgens in the cardiovascular system: clinical implications

Angela K. Lucas-Herald,[1,2] Rheure Alves-Lopes,[2] Augusto C. Montezano,[2] S. Faisal Ahmed,[1] and Rhian M. Touyz[2]

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Tratamento com testosterona em fêmeas promove disfunção vascular

♀

SHR

Função Vascular

2,85 mg/Kg/semana

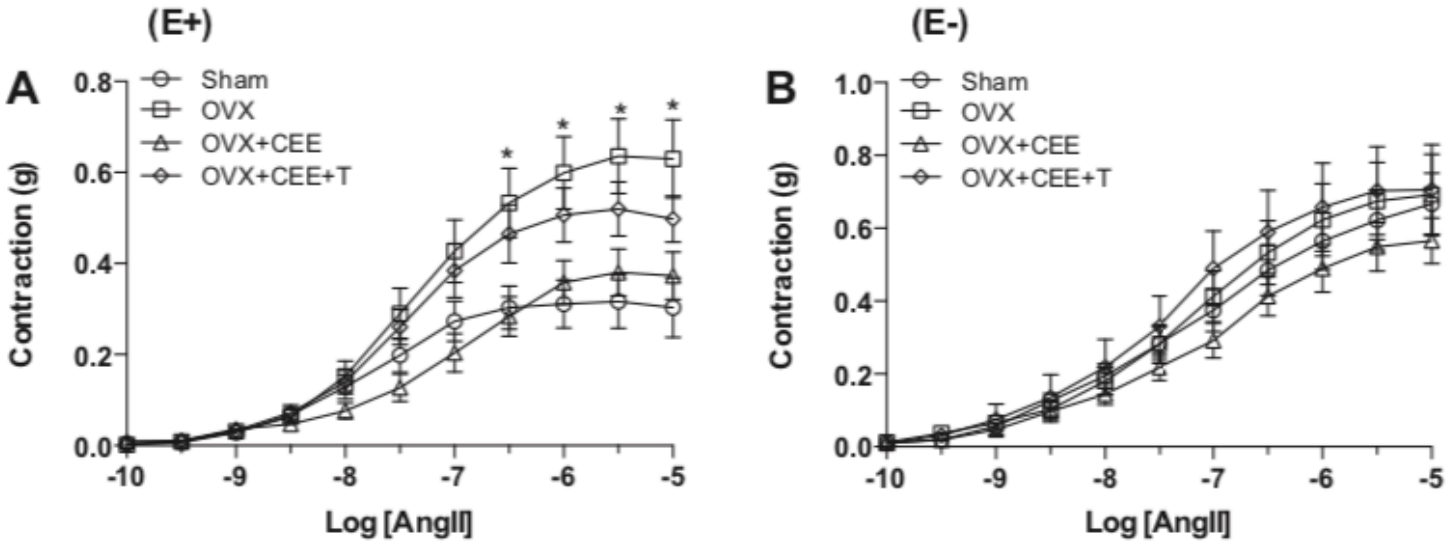
Costa TJ. Am J Physiol Heart Circ Physiol. 2015 Apr 1;308(7):H723-32

30% das mulheres na pós-menopausa tinham “redução do desejo sexual” (**Hypoactive** sexual desire **disorder)**

Testosterona = melhora no quadro

Shifren et al. N Engl J Med. 2000 Sep 7;343(10):682-8.

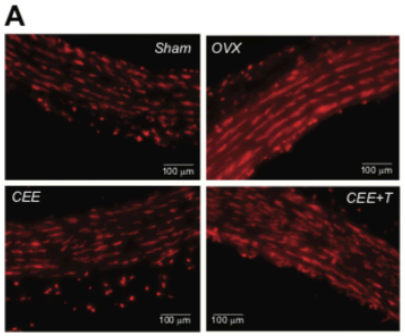
Tratamento com testosterona em fêmeas promove disfunção vascular

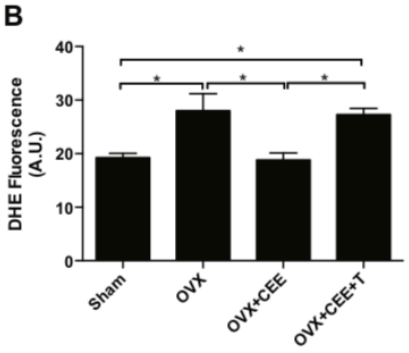


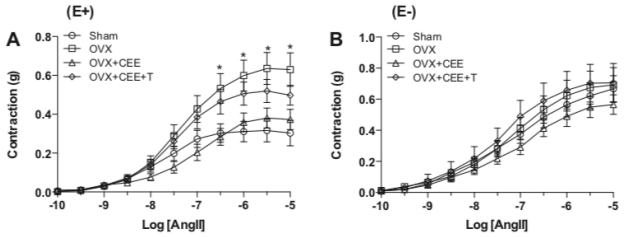
Costa TJ. Front Physiol. *2018; 9: 490.*

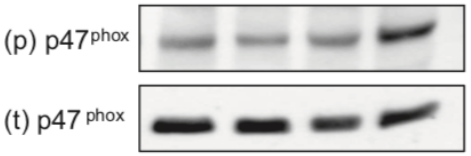
Costa TJ. Am J Physiol Heart Circ Physiol. 2015 Apr 1;308(7):H723-32

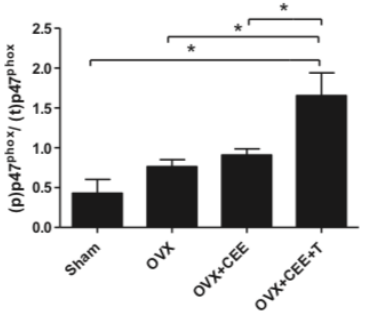
Tratamento com testosterona em fêmeas promove disfunção vascular

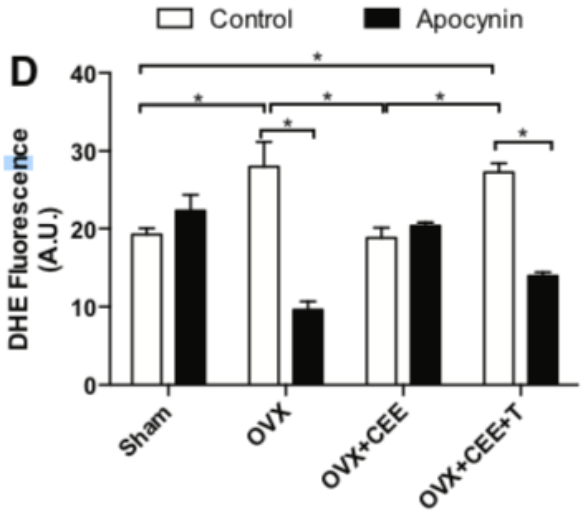


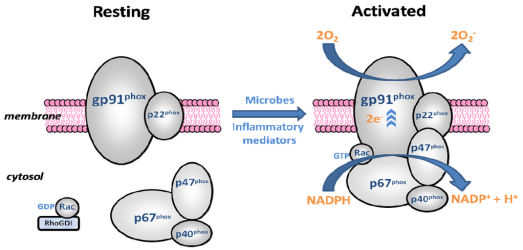












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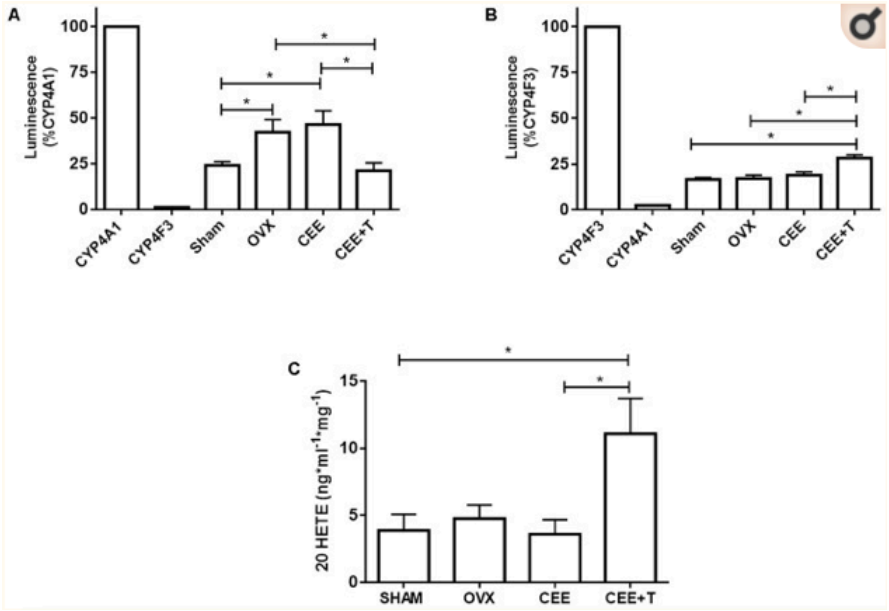
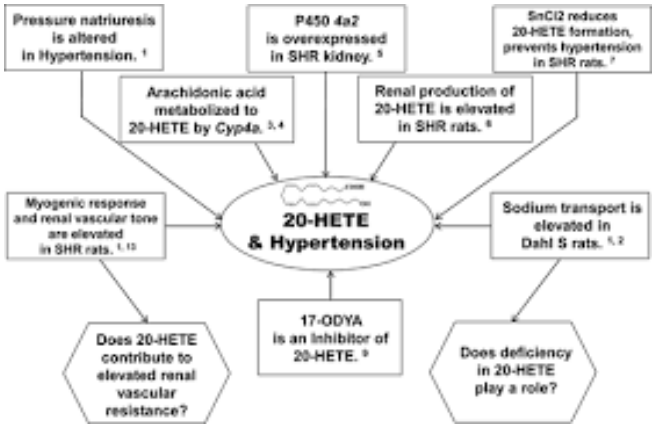
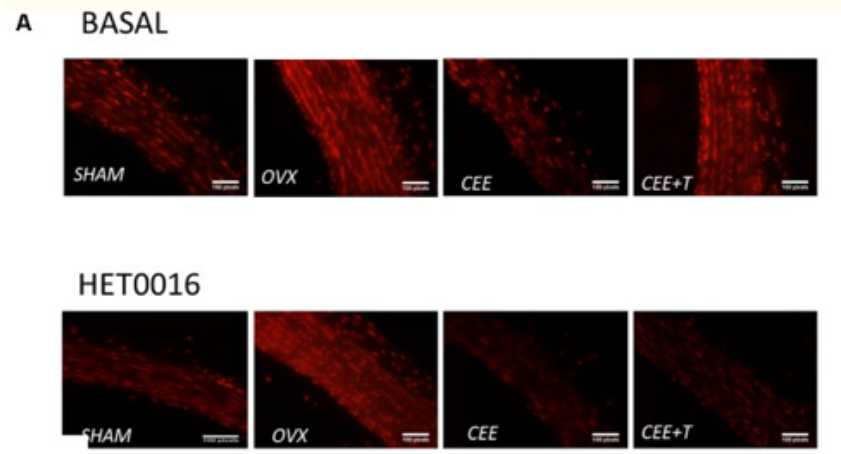
Costa TJ. Front Physiol. *2018; 9: 490.*

Costa TJ. Am J Physiol Heart Circ Physiol. 2015 Apr 1;308(7):H723-32

Tratamento com testosterona em fêmeas promove disfunção vascular - papel 20-HETE







Review > Pharmacol Ther. 2018 Dec;192:74-87. doi: 10.1016/j.pharmthera.2018.07.004. Epub 2018 Jul 23.

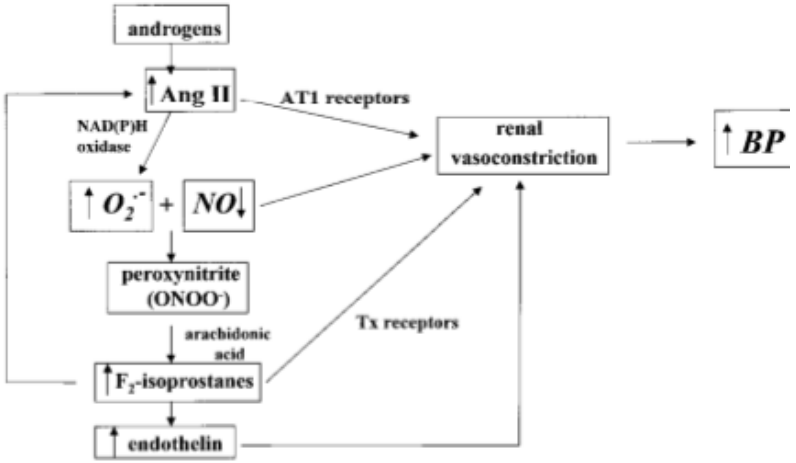
20-HETE in the Regulation of Vascular and Cardiac Function

Petra Rocic [1], Michal Laniado Schwartzman [2]

microvascular CYP4A2 expression and renal production of 20-HETE. Estrogen and growth hormone have also been shown to increase CYP4A/F expression primarily in non vascular tissues (Kalsotra, Anakk, Boehme, & Strobel, 2002; Y. Zhang & Klaassen, 2013). In ovariectomized SHR, a model of postmenopausal hypertension, treatment with estrogen alone increased aortic CYP4F3 expression but not 20-HETE production. Addition of testosterone to the estrogen treatment potentiated CYP4F3 expression and significantly increased 20-HETE production in the aorta (Costa et al., 2018).

Costa TJ. Front Physiol. *2018; 9: 490.*

Costa TJ. Am J Physiol Heart Circ Physiol. 2015 Apr 1;308(7):H723-32



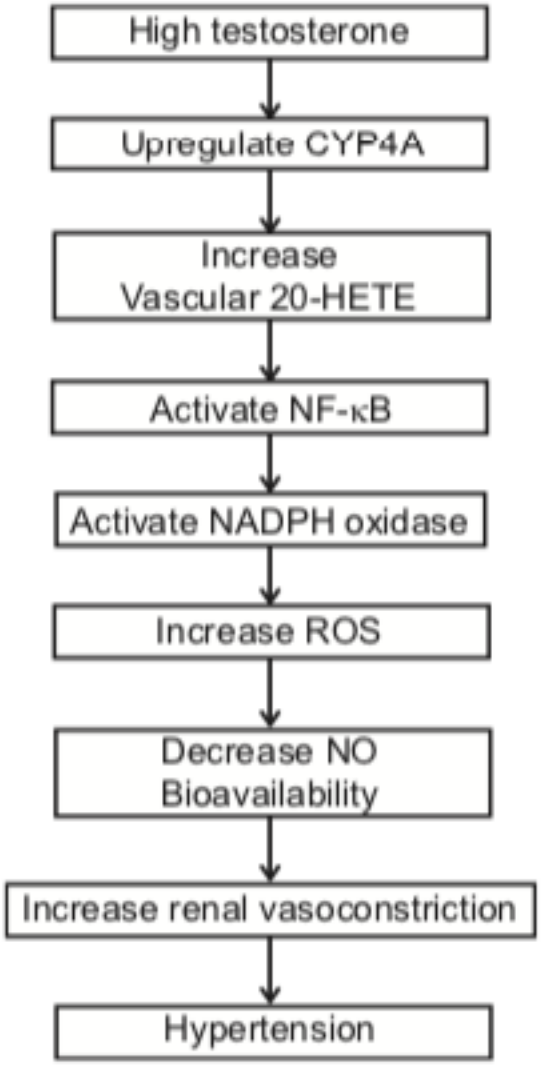
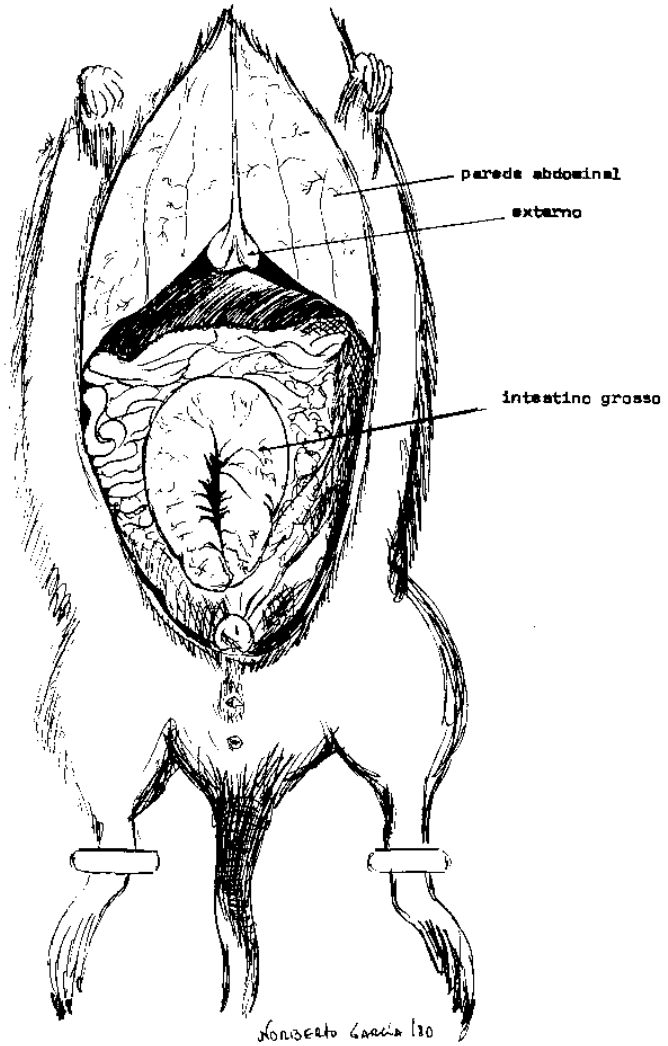
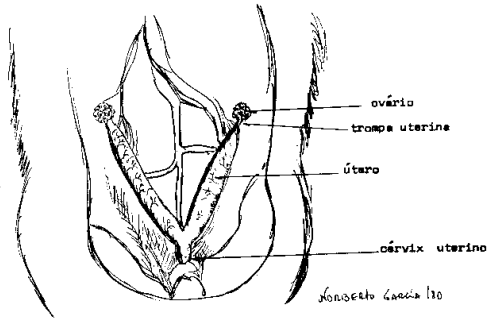


Figure. Potential mechanisms by which androgens could increase BP. Androgens could upregulate cytochrome P450 4A ω-hydroxylases, which would increase 20-HETE levels. 20-HETE would activate NF-κB, which would activate NADPH oxidase to increase production of reactive oxygen species (ROS) and decrease NO bioavailability. The reduction in NO would increase renal vasoconstriction, leading to hypertension.

Pergunta de orientador:
Você não irá estudar o estrógeno ?

OVX: modelo de pós-menopausa e/ou redução dos níveis plasmáticos de estrógeno





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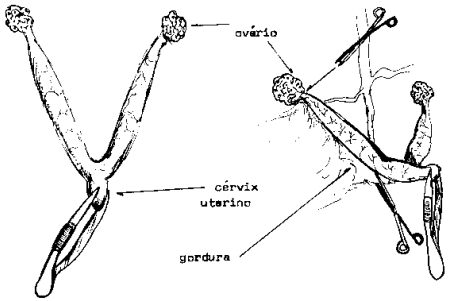
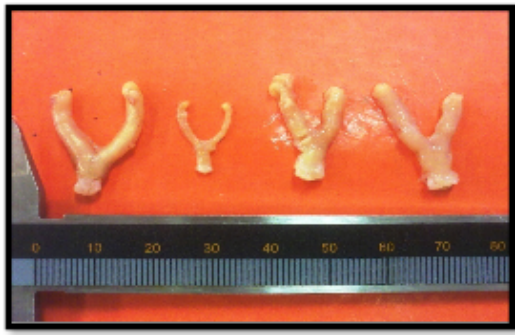




desenhos : Prof. Dr. Norberto G. Cairasco, FMRP, USP

Tratamento com estrógeno mellhora a função endotelial em fêmeas SHR

♀ SHR

Sham
Castradas (OVX)
OVX + E2
OVX +E2+P

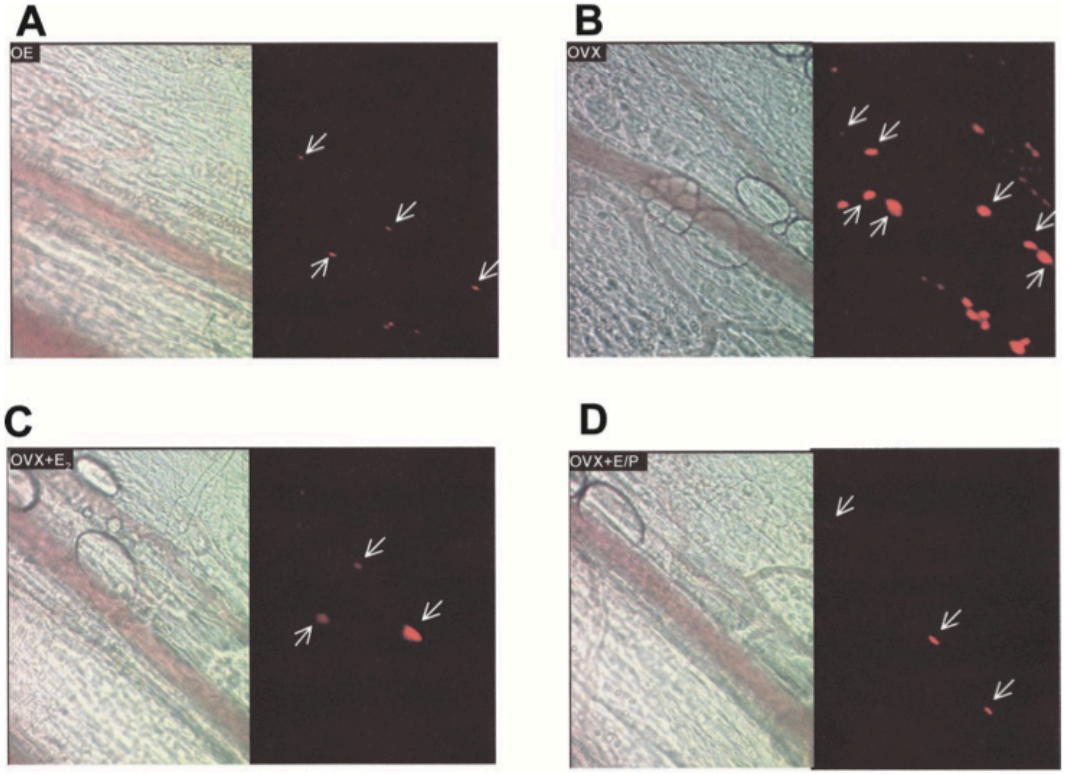


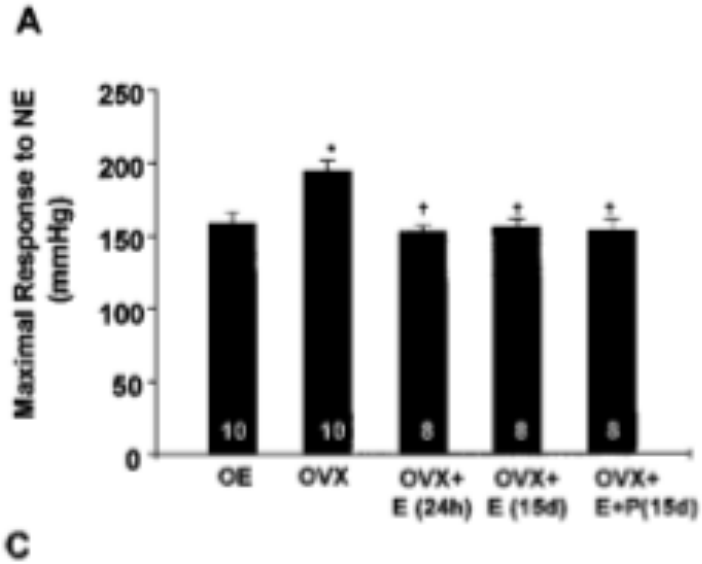
Figure 1. Representative images show on the left transillumination images of mesenteric arterioles and on the right ethidium bromide fluorographs 60 minutes after onset of hydroethidine superfusion. A, Arteriole of a female spontaneously hypertensive rat (SHR) in physiological estrous (OE); B, arteriole of a ovariectomized SHR (OVX); C, arteriole of a ovariectomized SHR treated with estrogen ($OVX+E_2$); or D, with estrogen + progesterone (OVX+E/P).

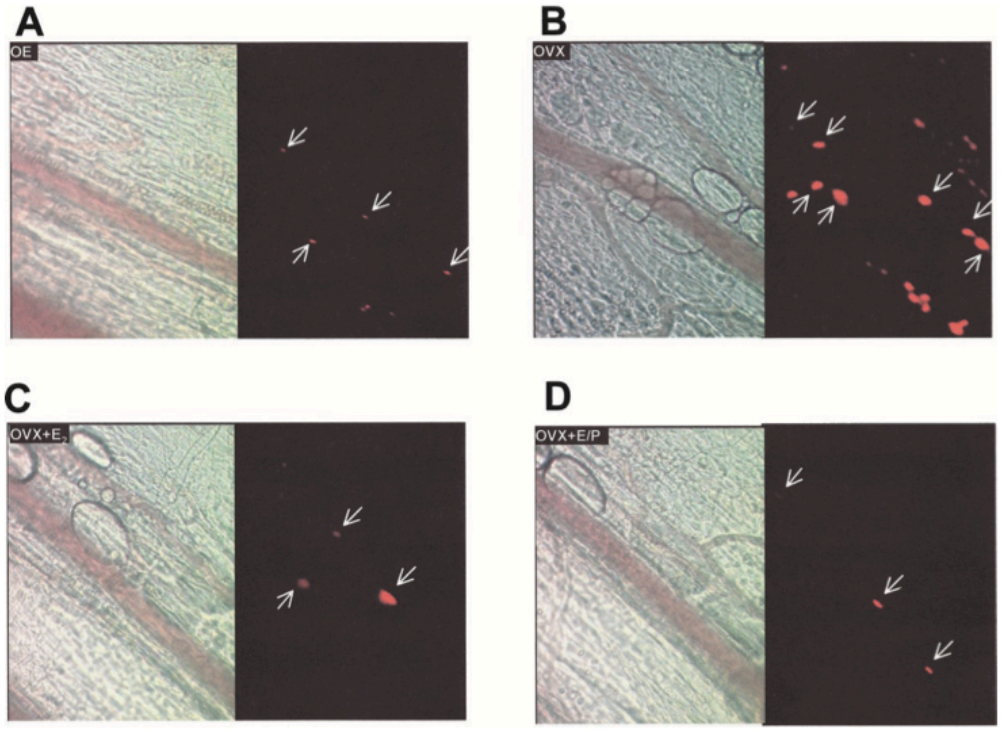
Dantas AP. Hypertension. 2002 Feb;39(2 Pt 2):405-11.

Tratamento com estrógeno mellhora a função endotelial em fêmeas SHR

♀ SHR

Sham
Castradas (OVX)
OVX + E2
OVX +E2+P





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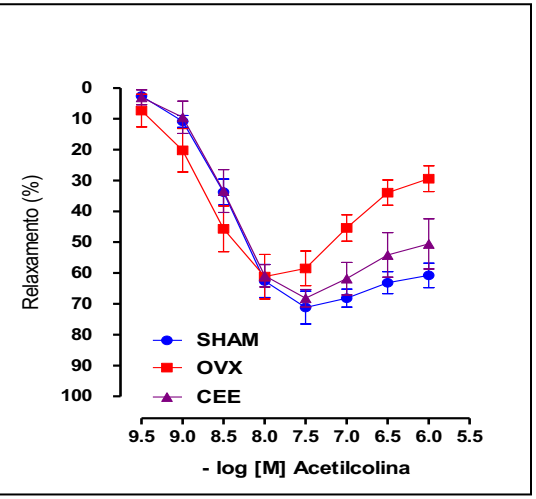
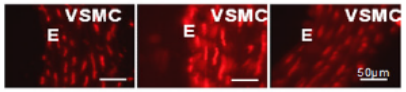
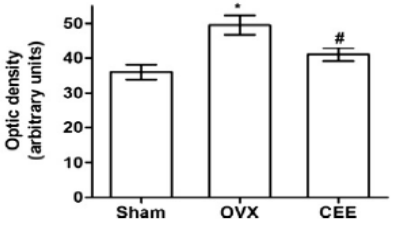
Dantas AP. Hypertension. 2002 Feb;39(2 Pt 2):405-11.

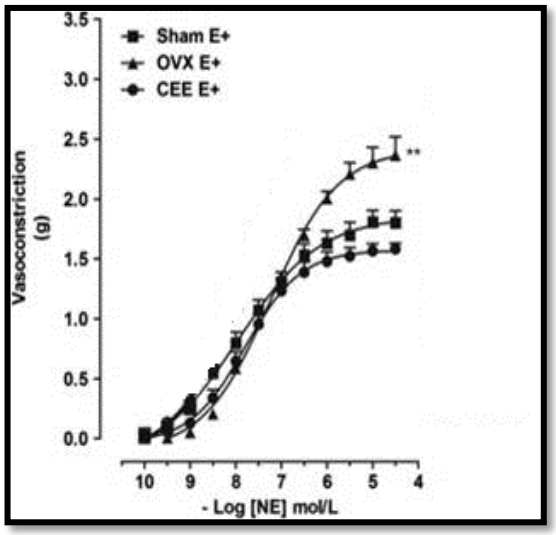
Ciência Básica – Mecanismo proteção do estrógeno

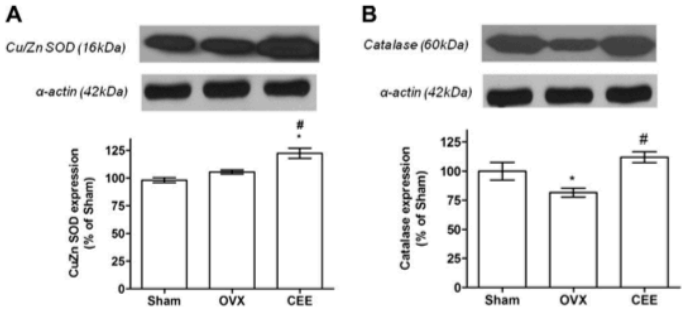
Estudo em aorta de ratas SHR ovariectomizadas (pós-menopausa precoce)











1999

2002

2013

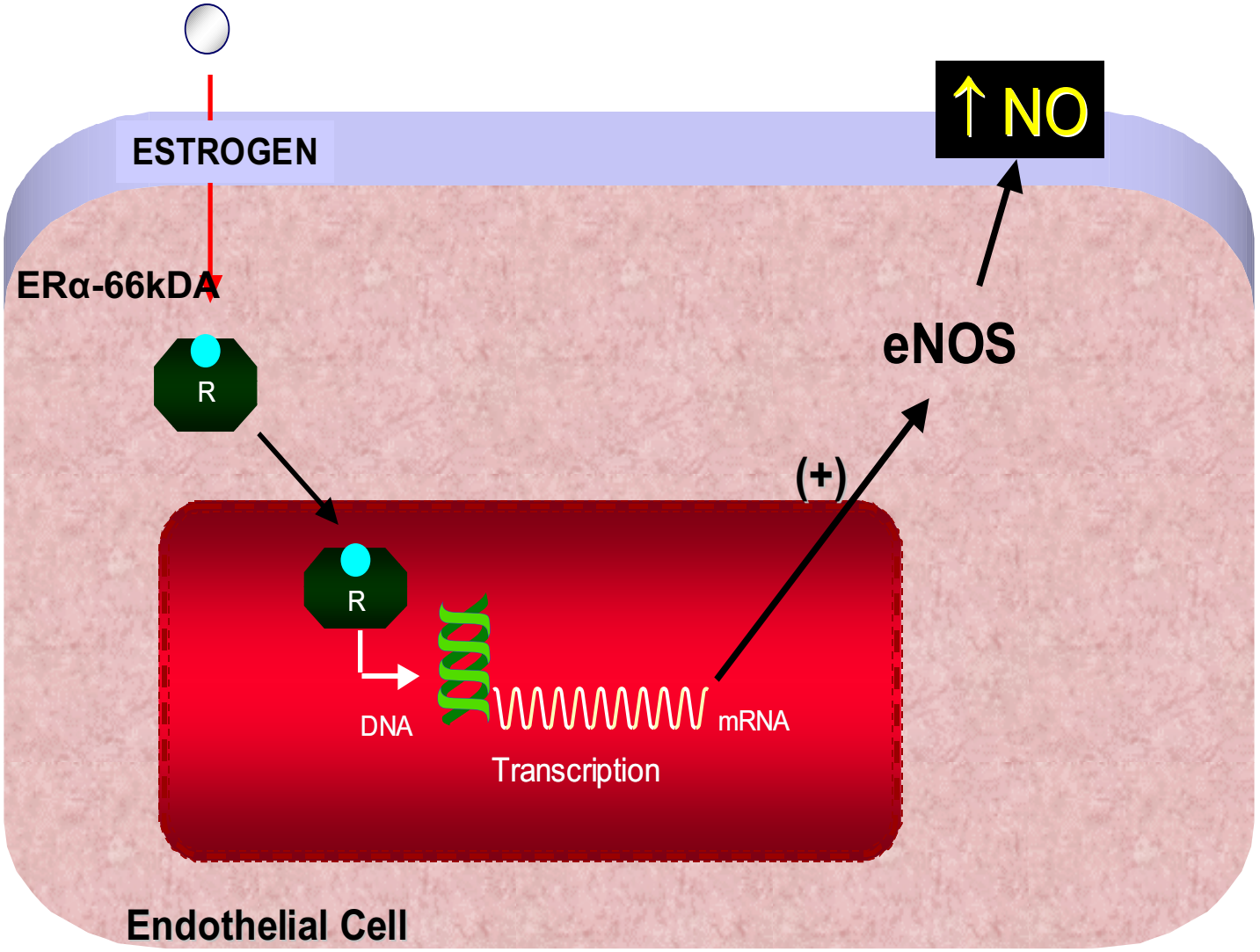
2015

2017

Hypertension. 1999 Oct;34(4 Pt 2):914-9; **Hypertension** 2002 39(2 Pt 2):405-11; **Steroids** 78; 341-346,2013; **Am J Physiol Heart Circ Physiol**. 2015 Apr 1;308(7):H723-32. **Front Physiol.** *2018; 9: 490.*

ERa clássico (ESR1 - 66kDa)

Mecanismos de ação vascular



Physiol Rev 97: 1045–1087, 2017
Published May 24, 2017; doi:10.1152/physrev.00024.2016

MEMBRANE AND NUCLEAR ESTROGEN RECEPTOR ALPHA ACTIONS: FROM TISSUE SPECIFICITY TO MEDICAL IMPLICATIONS

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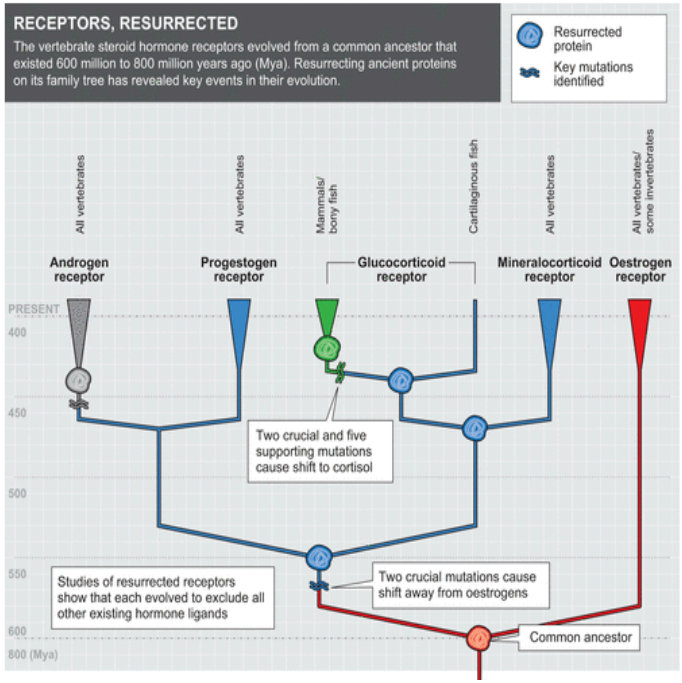
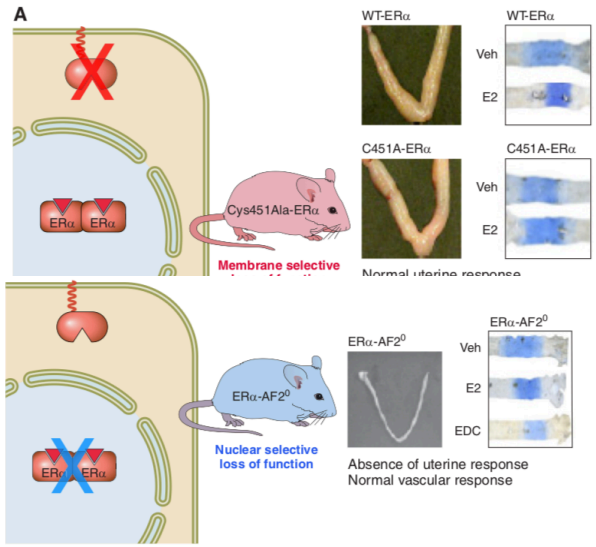
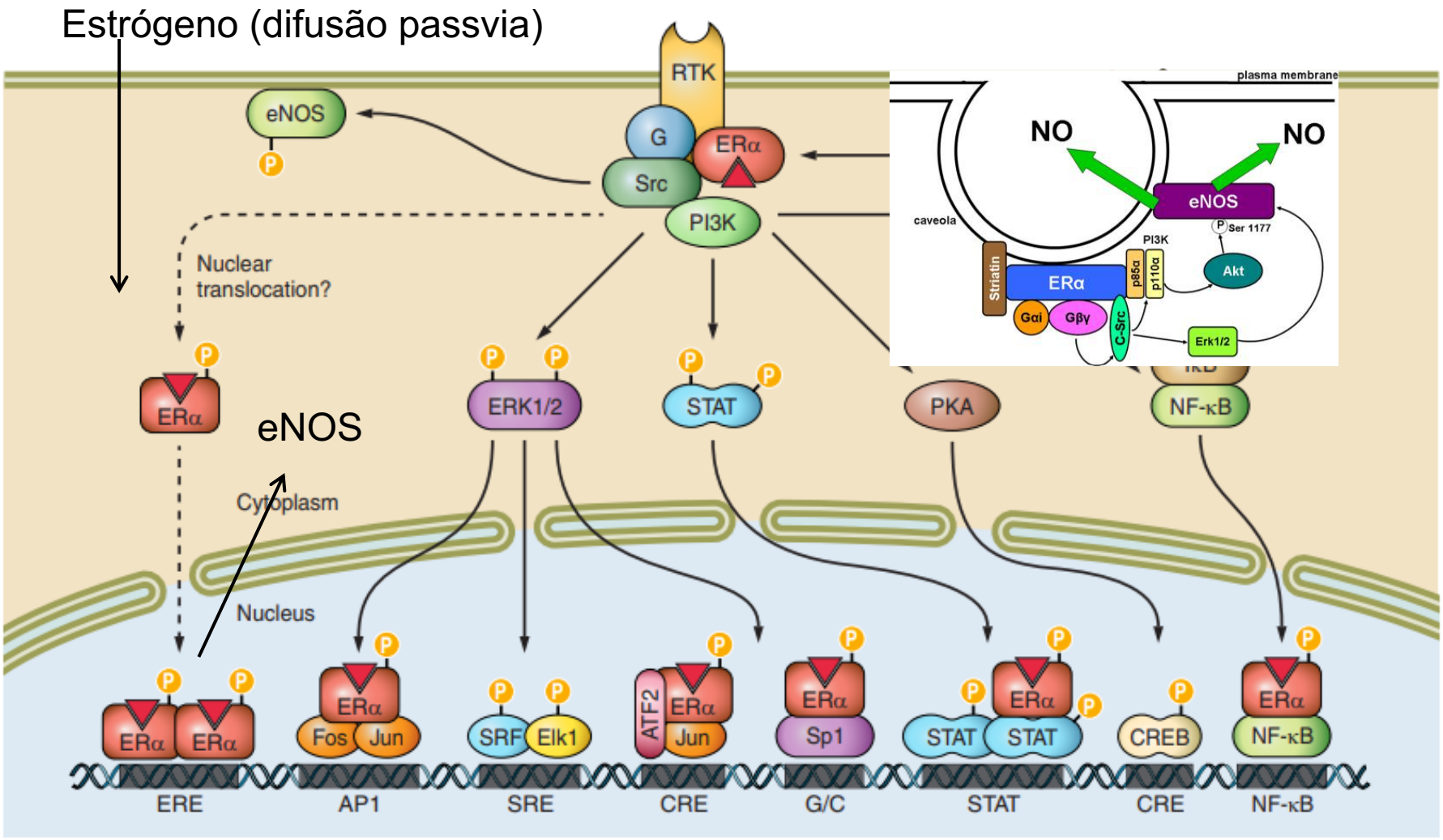
Aplysia californica





ERa (ESR1 - 66kDa)

Vascular effects



Physiol Rev 97:1045-1087, 2017

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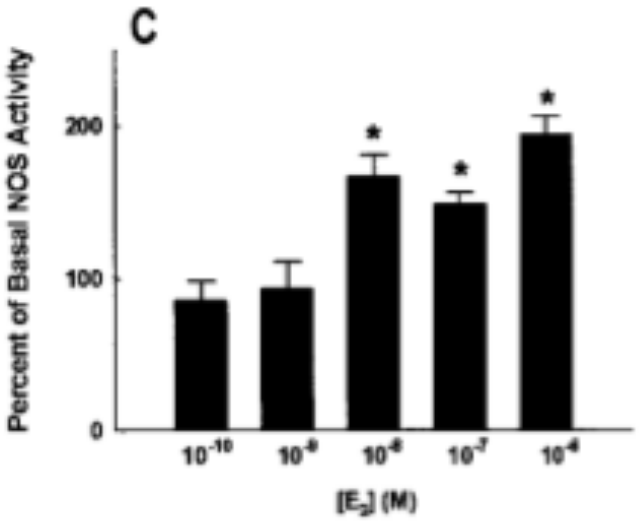
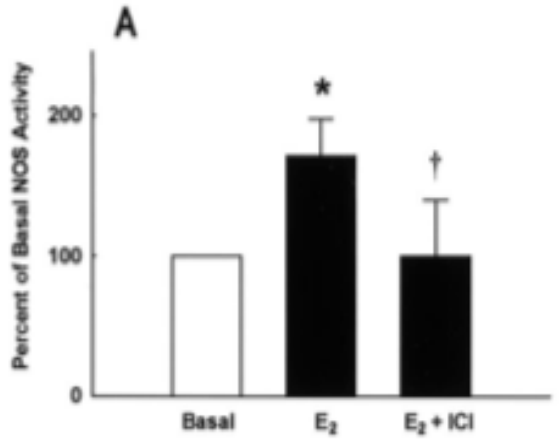
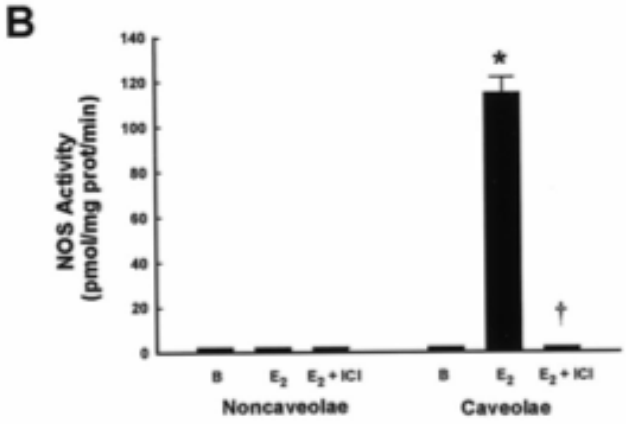
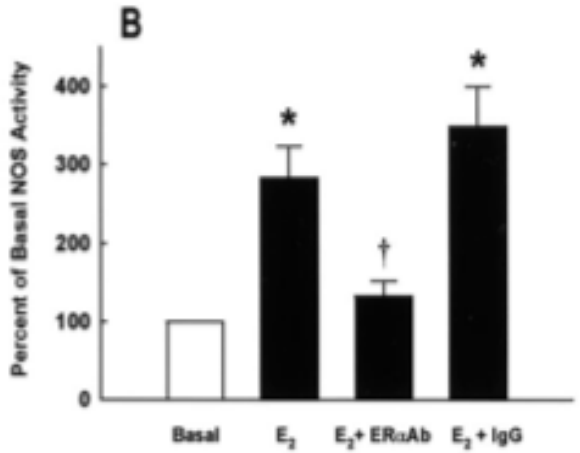
Estrogen Receptor α and Endothelial Nitric Oxide Synthase Are Organized Into a Functional Signaling Module in Caveolae

Ken L. Chambliss, Ivan S. Yuhanna, Chieko Mineo, Pingsheng Liu, Zohre German, Todd S. Sherman, Michael E. Mendelsohn, Richard G. W. Anderson, and Philip W. Shaul



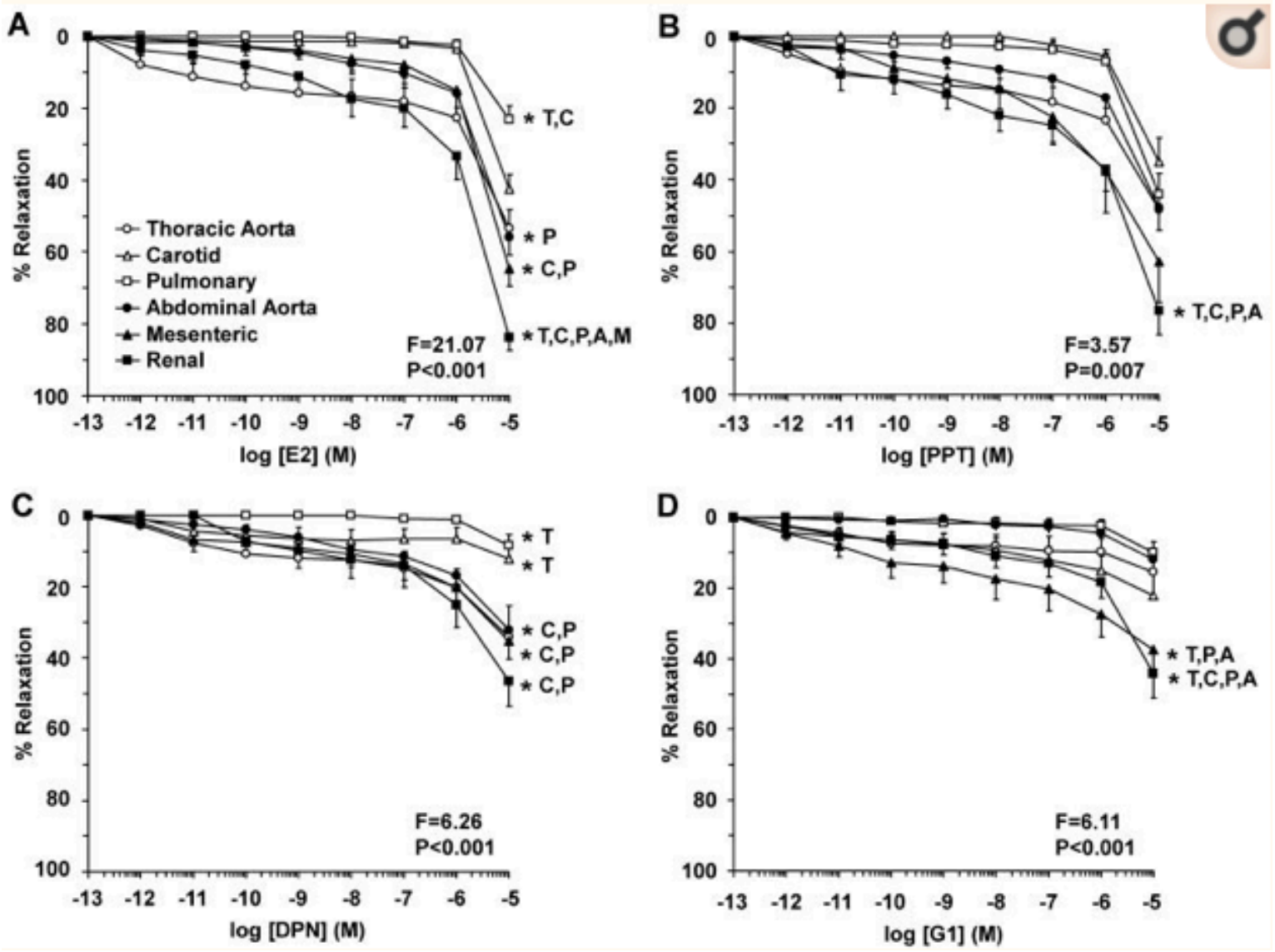




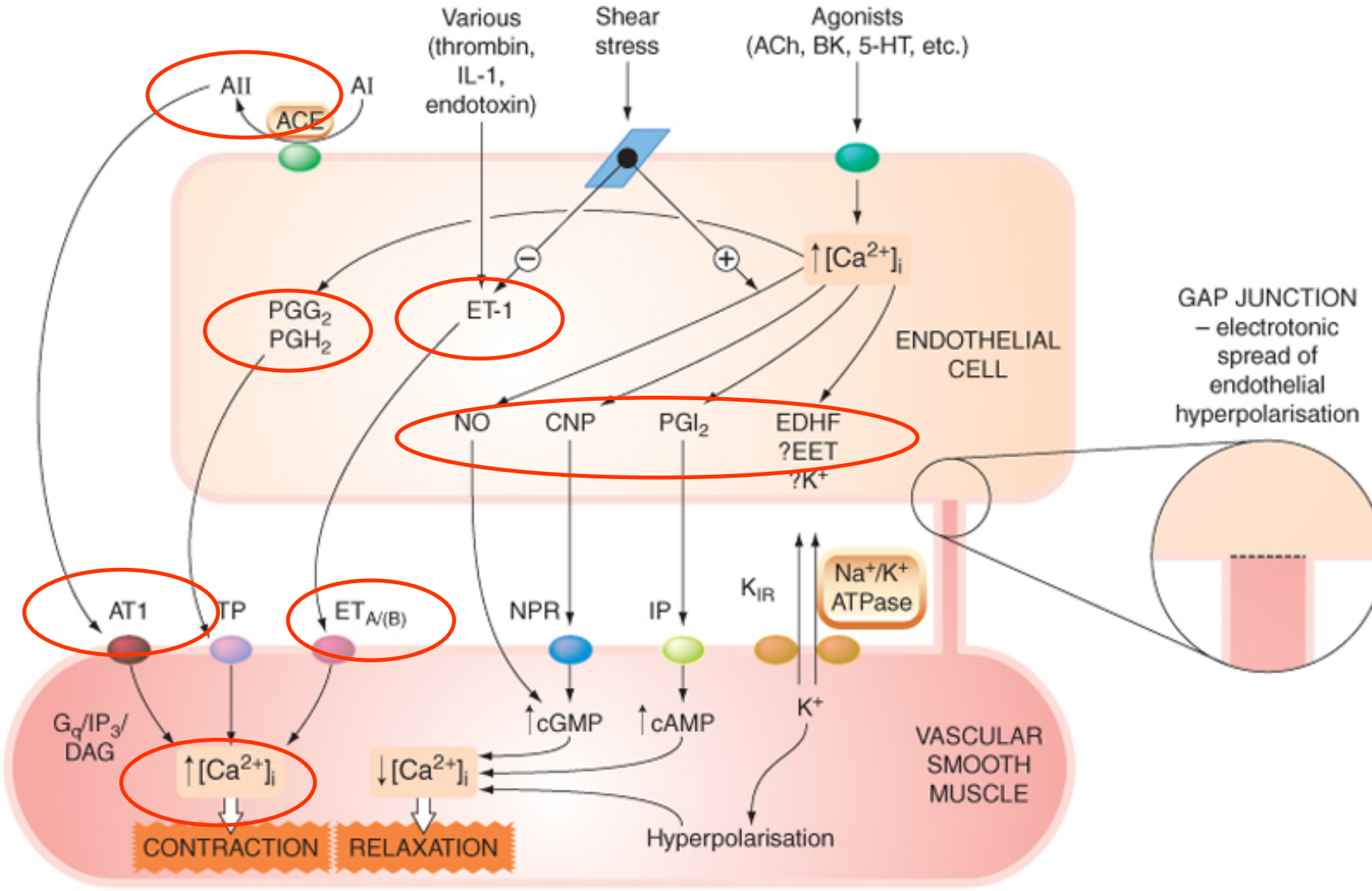


Chambliss. Circ Res.2000 Nov 24;87(11):E44-52.

Estrógeno atua via ERa na vasculatura e a resposta é leito-depedente.



Relan OM. Cardiovasc Pharmacol. 2013 Jul;62(1):26-40.



Sugestão de Leitura

Brazilian Journal of Medical and Biological Research
Print version ISSN 0100-879X*On-line version* ISSN 1414-431X

Braz J Med Biol Res vol.36 no.9 Ribeirão Preto Sept. 2003

https://doi.org/10.1590/S0100-879X2003000900002

Braz J Med Biol Res, September 2003, Volume 36(9) 1143-1158 (Review)

Effects of estrogen on the vascular system

R.C. Tostes, D. Nigro, Z.B. Fortes and M.H.C. Carvalho

Grupo de Pesquisa sobre Hipertensão Arterial, Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil

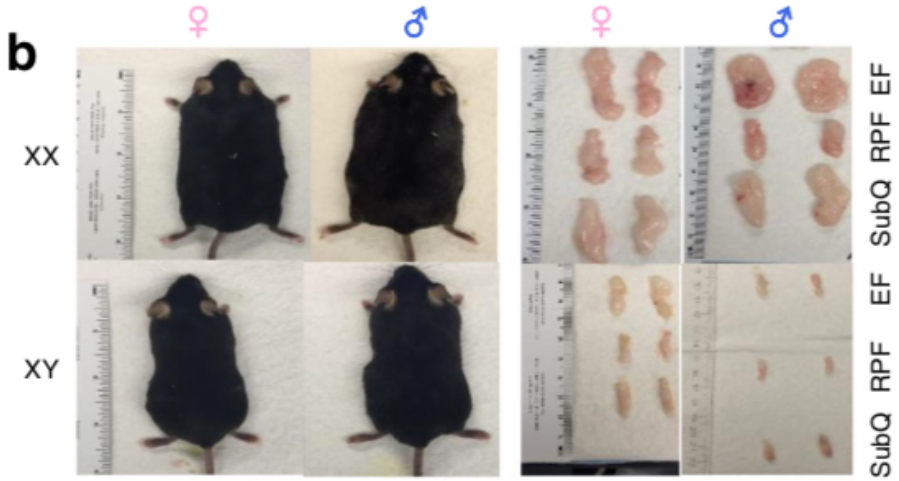
Pergunta de revisor que não estuda os hormônios.

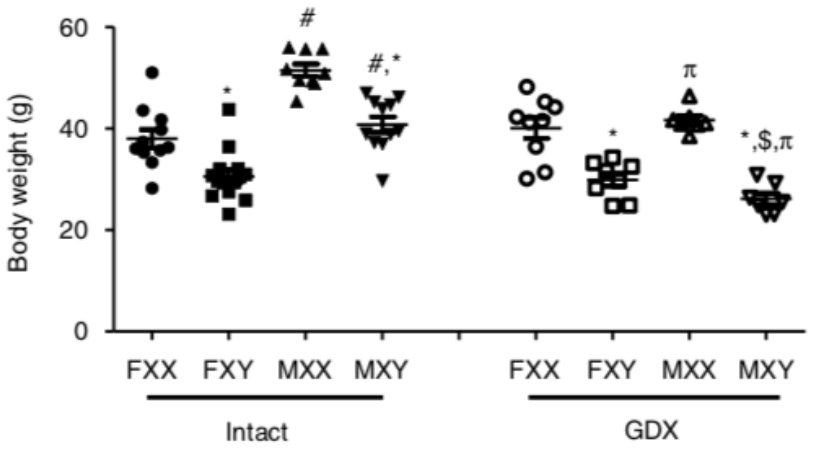
Os cromossomos sexuais podem interferir para a função cardiovascular em machos (XY) e fêmeas (XX)?

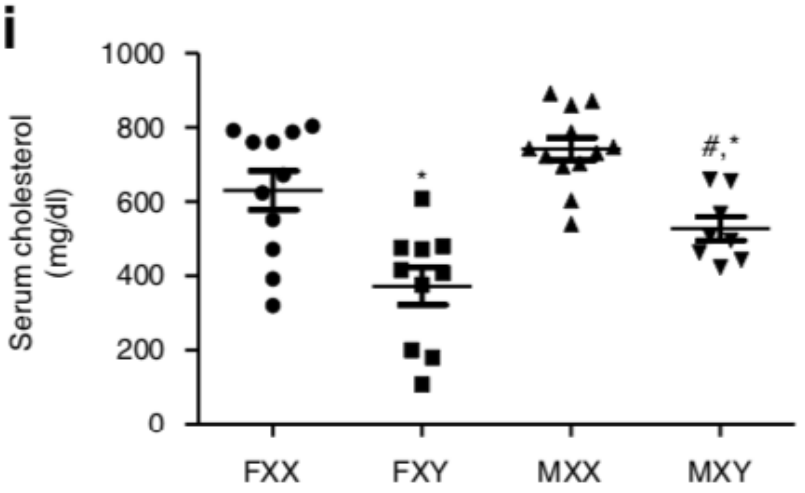
ARTICLE
https://doi.org/10.1038/s41467-019-10462-z OPEN

XX sex chromosome complement promotes atherosclerosis in mice

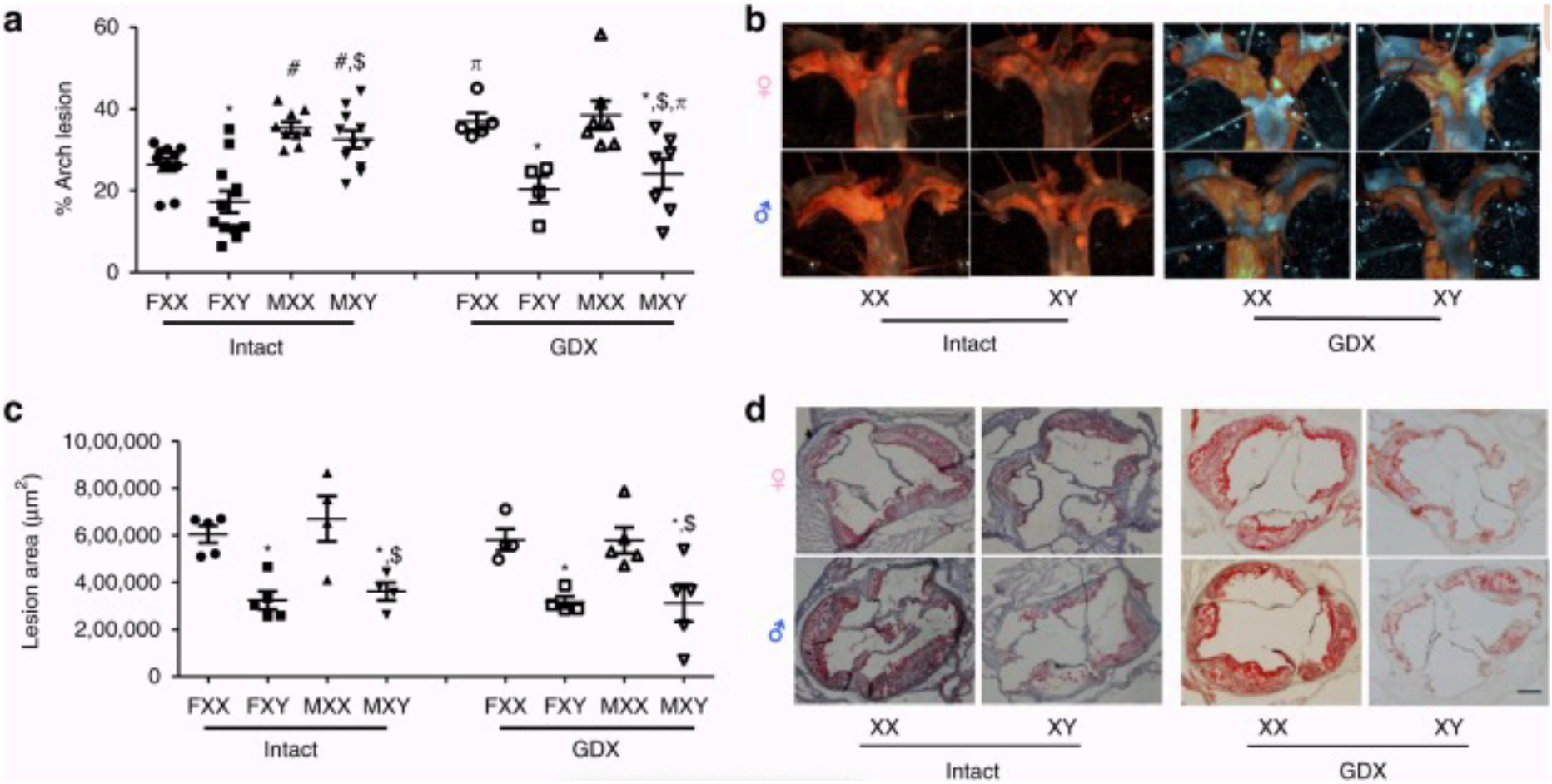
Yasir AlSiraj[1], Xuqi Chen[2], Sean E. Thatcher[1], Ryan E. Temel[3,4], Lei Cai[3,4], Eric Blalock[1], Wendy Katz[1], Heba M. Ali[1], Michael Petriello[5], Pan Deng[5], Andrew J. Morris[5], Xuping Wang[6,7,8], Aldons J. Lusis[6,7,8], Arthur P. Arnold[2], Karen Reue[8], Katherine Thompson[9], Patrick Tso[10] & Lisa A. Cassis[1]







Cromossomo XX aumenta o desenvolvimento de aterosclerose



MENOPAUSA

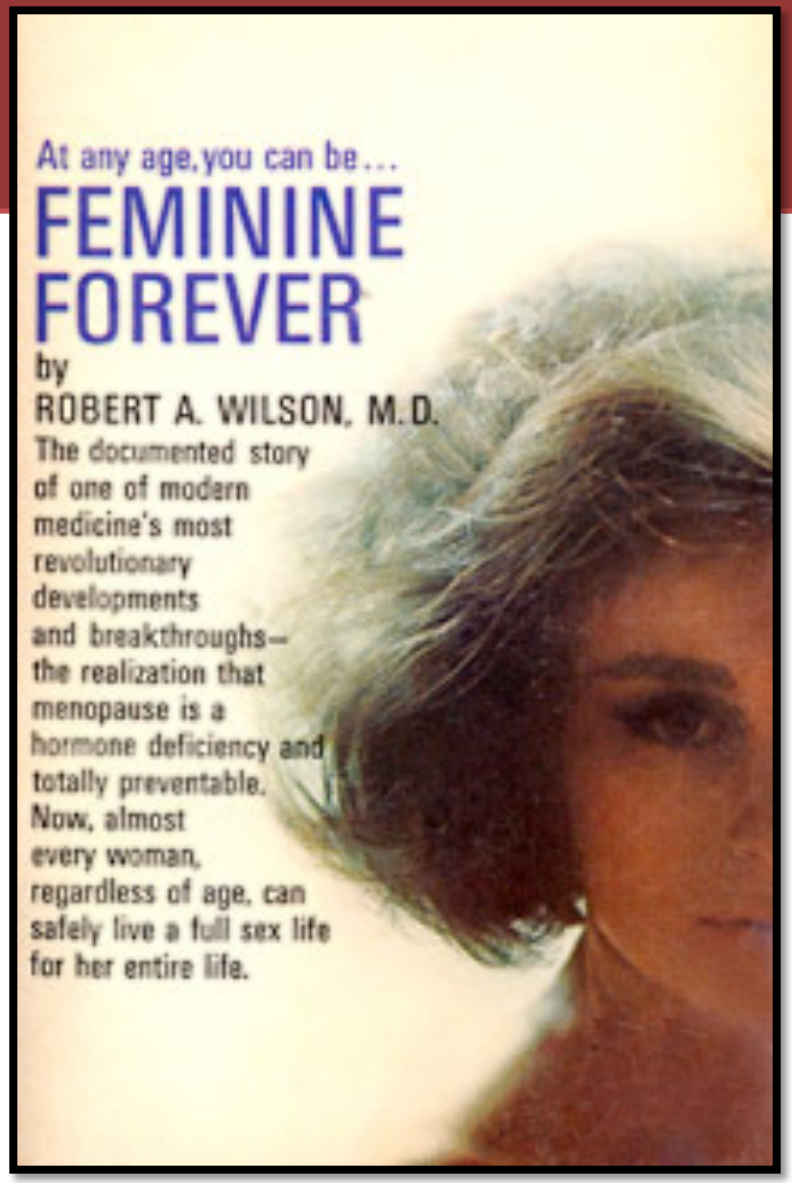
1986 Conceituada: decadência de vida:

Fase ruim para os aspectos físicos e psicológicos

Solução

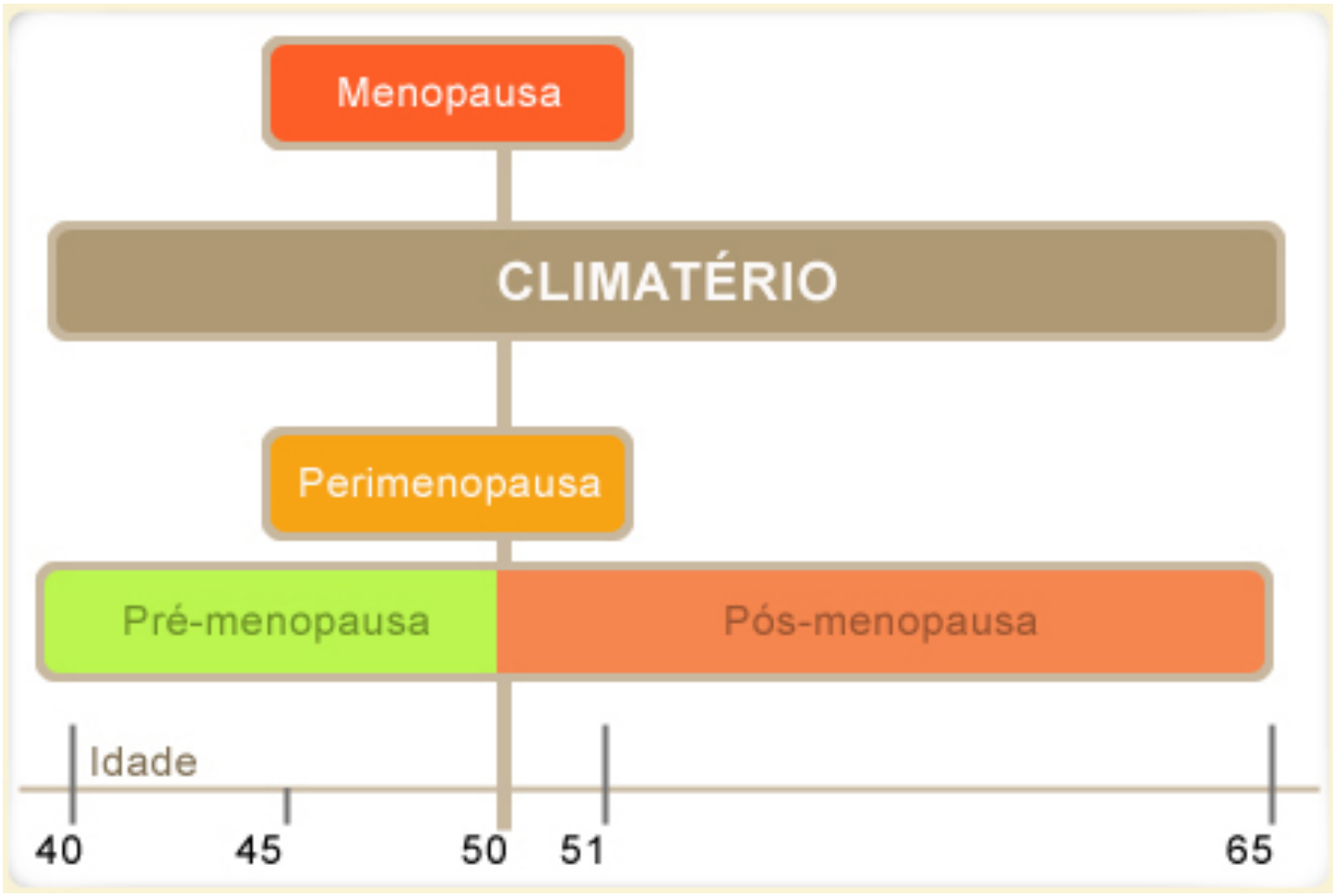
↓

Terapia Hormonal



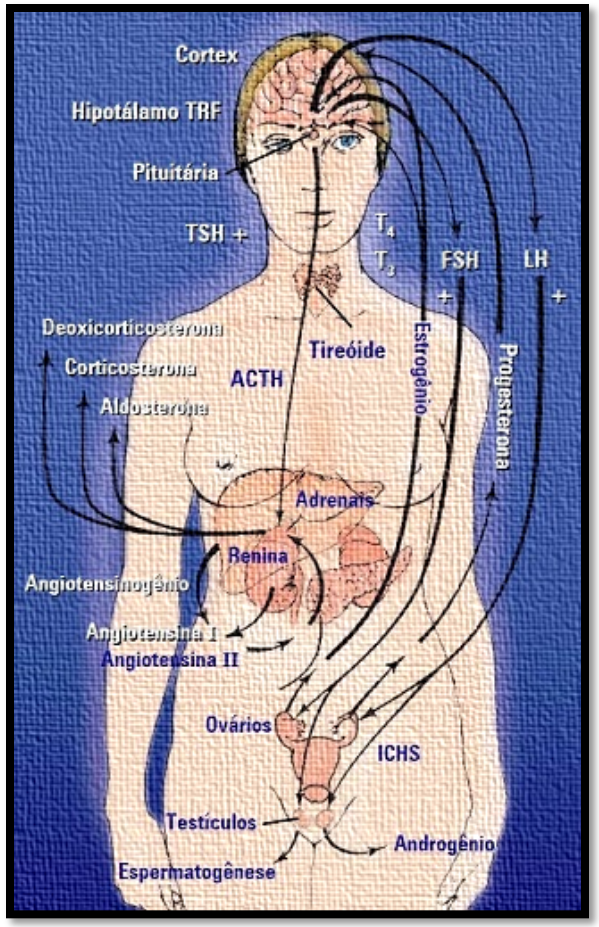
100 mil exemplares vendidos no 1º ano

Conceituando os termos



MENOPAUSA

2017: Processo fisiológico onde há redução da função folicular ovariana e redução dos níveis endógenos de estrógeno
Início: 49-52 anos



↓ Oócitos

↓ Inibina B (glicoproteína produzida células granulosas)

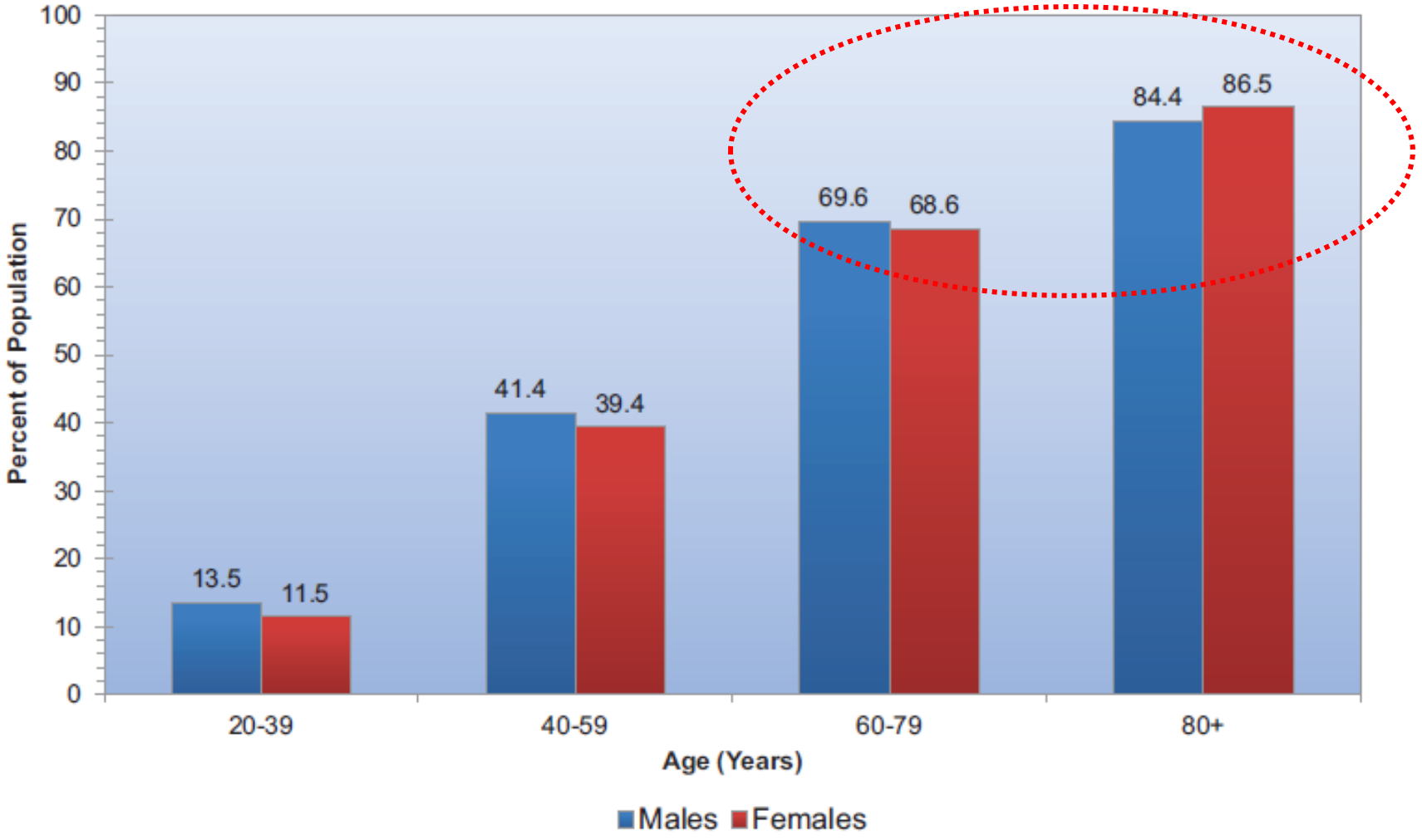
↓ Retroalimentação negativa (Feedback)

Eixo hipotalâmico-hipofisário-ovariano ↑ FSH

↓ E2

Medical Clinic of North America. 2015 99(3): 521-5340

O índice de doenças cardiovasculares são menores em homens do que em mulheres até aproxidamente 50 anos.



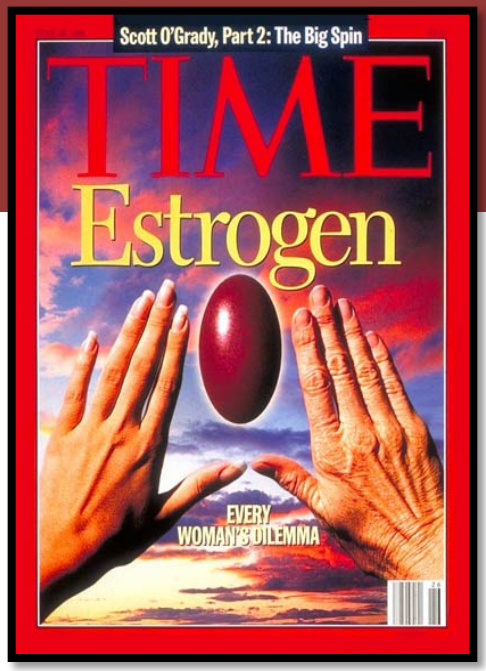
Circulation. 2019;139:e56–e528

Envelhecimento feminino = pós-menopausa

↓ estrógeno

↑ Doenças Cardiovasculares

Proteção cardiovascular



Terapia hormonal com estrógeno é a solução?

Estudo Clínico Observacinal - 1985

Nurses' Health Study

→ Mulheres 30-55 anos

→ Uso de estrógeno como terapia hormonal

↓

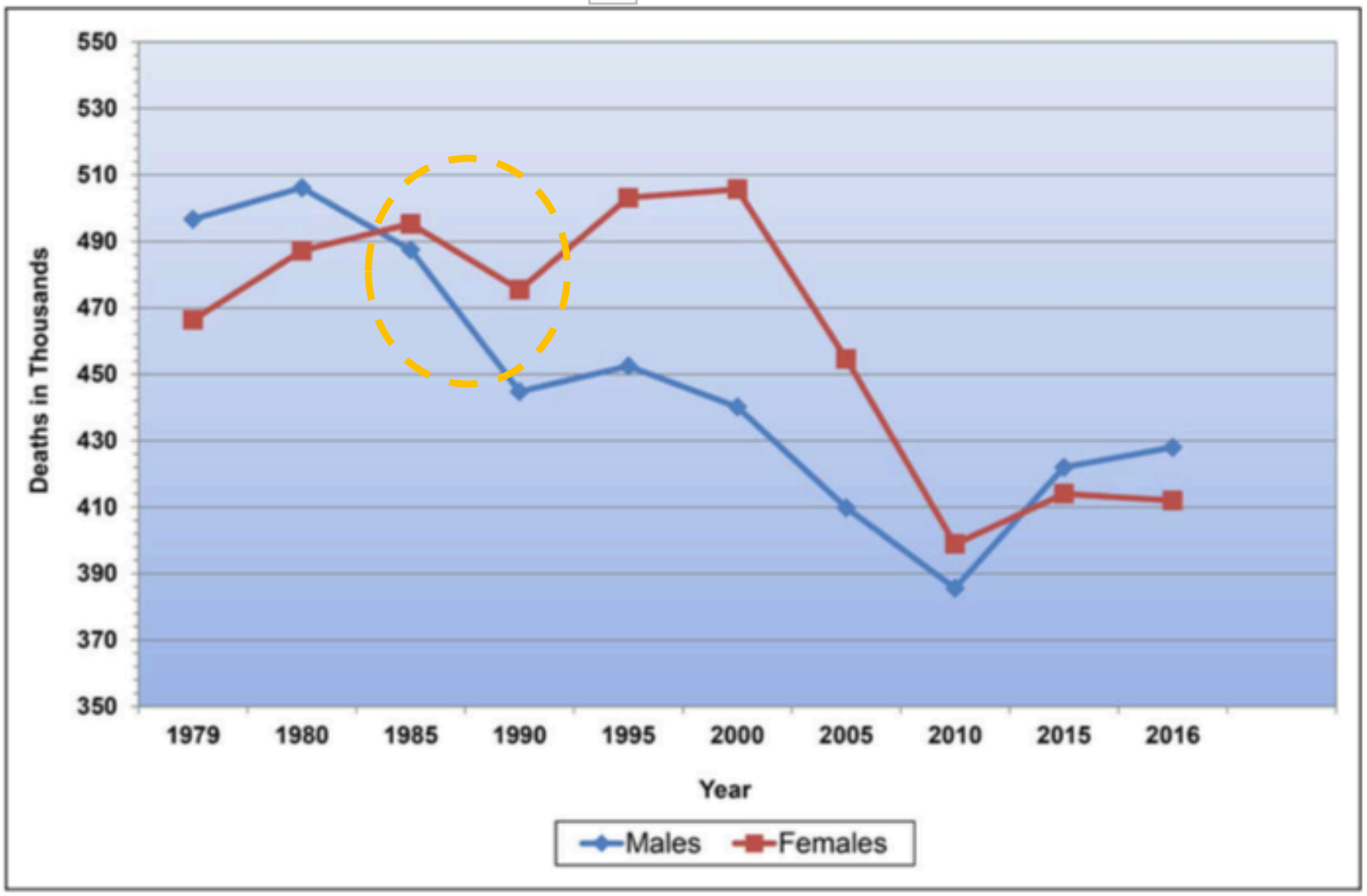
N Engl J Med. 1985 Oct 24;313(17):1044-9.

A prospective study of postmenopausal estrogen therapy and coronary heart disease.

Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH.

These data support the hypothesis that the postmenopausal use of estrogen reduces the risk of severe coronary heart disease.

Declínio do número de mortes por doenças cardiovasculares em 1985-1990.



Circulation. 2019;139:e56–e528

Novos Estudos clínicos – Resultados contraditórios

Estrógeno não é protetor para o sistema cardiovascular

Ideas and Opinions

The Discrepancy between Observational Studies and Randomized Trials of Menopausal Hormone Therapy: Did Expectations Shape Experience?

Nananda F. Col, MD, MPP, MPH; and Stephen G. Pauker, MD

Ann Intern Med. 2003;139(11):923-929. doi:10.7326/0003-4819-139-11-200312020- 00011

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 7, 2003 VOL. 349 NO. 6

Estrogen plus Progestin and the Risk of Coronary Heart Disease

JoAnn E. Manson, M.D., Dr.P.H., Judith Hsia, M.D., Karen C. Johnson, M.D., M.P.H., Jacques E. Rossouw, M.D., Annlouise R. Assaf, Ph.D., Norman L. Lasser, M.D., Ph.D., Maurizio Trevisan, M.D., Henry R. Black, M.D., Susan R. Heckbert, M.D., Ph.D., Robert Detrano, M.D., Ph.D., Ora L. Strickland, Ph.D., Nathan D. Wong, Ph.D., John R. Crouse, M.D., Evan Stein, M.D., and Mary Cushman, M.D., for the Women's Health Initiative Investigators*

Obstet Gynecol Surv. 2006 Oct;61(10):673-81.

Hormonal therapy: does it increase or decrease cardiovascular risk?

Schnatz PF[1].

WOMEN'S HEALTH INITIATIVE

Críticas:

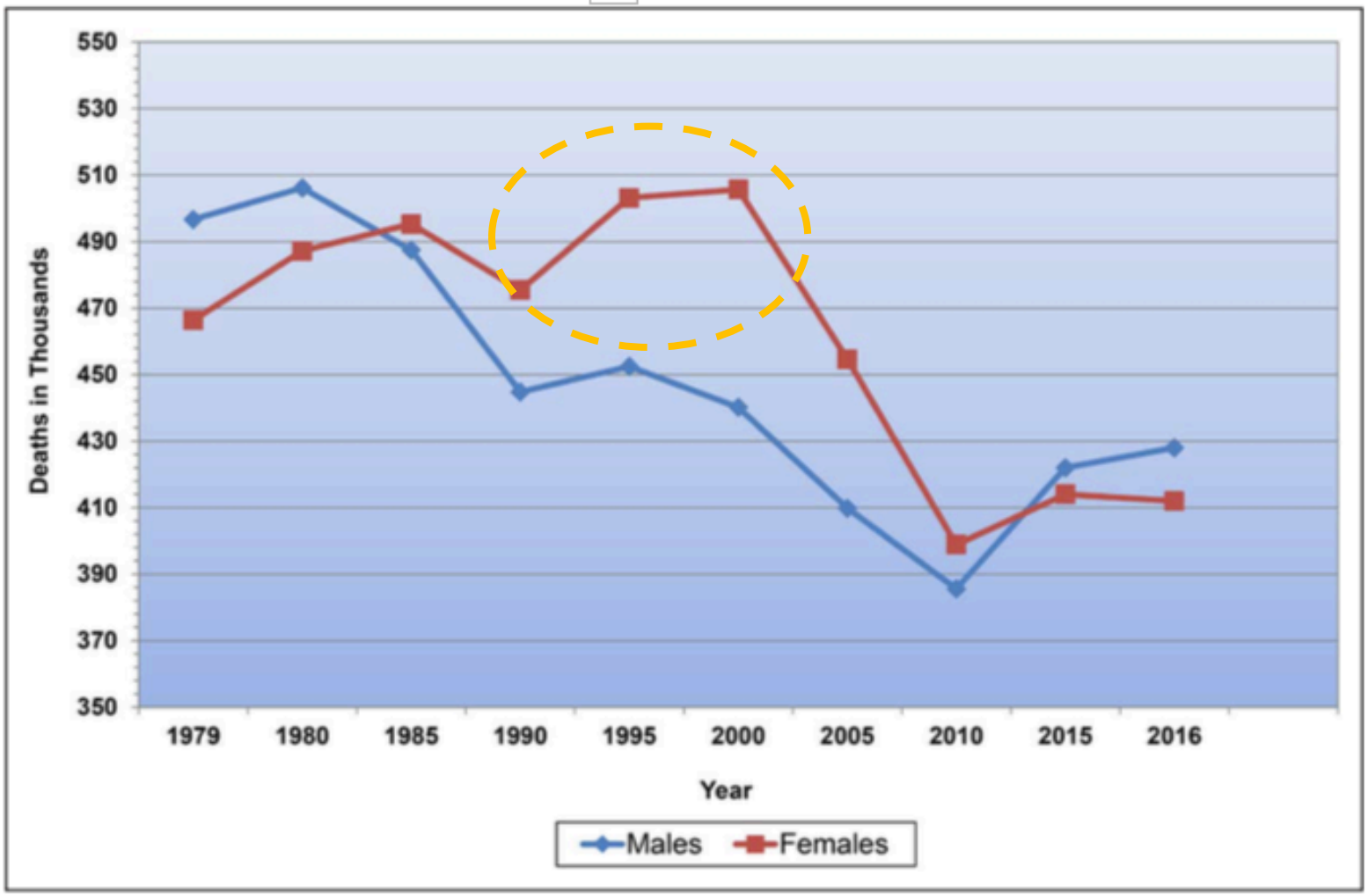
- doença cardiovascular pré-estabelecida;

HERS I e II

Heart **E**strogen/**P**rogestin **R**eplacement **T**herapy

- vias de administração do hormônio;

Diferenças sexuais em doenças cardiovasculares: E agora ?



Circulation. 2019;139:e56–e528

Novos Estudos clínicos – Resultados contraditório

Estrógeno não é protetor para o sistema cardiovascular

TH com estrógeno

50-59 = possível efeito protetor

60-69 = nenhum efeito favorável

70-79 = aumento do índice de DCVs

Grodstein et al., **Ann intern med**. Jul3;131(1):1-8,2001

mas

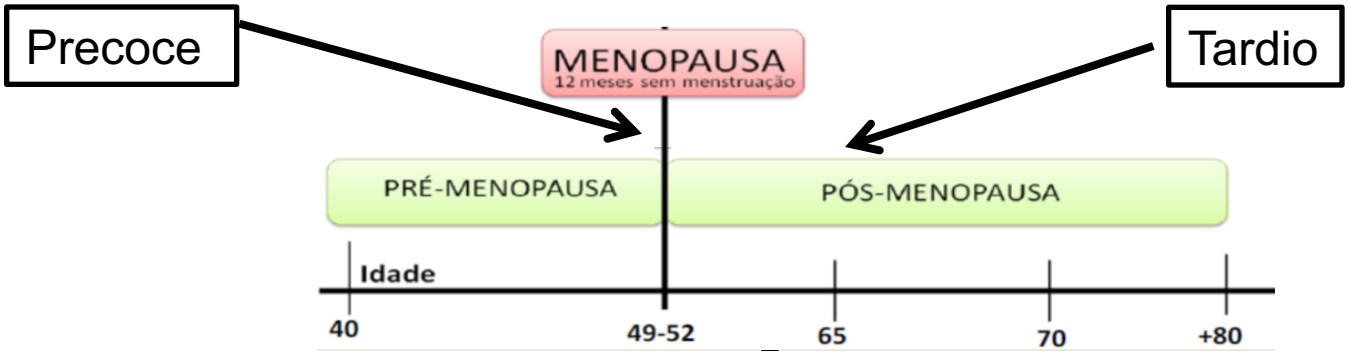
Envelhecimento

Estudos clínicos
Média de idade mulheres
(~ 63,2 anos)
(intervalo 50-79 anos)

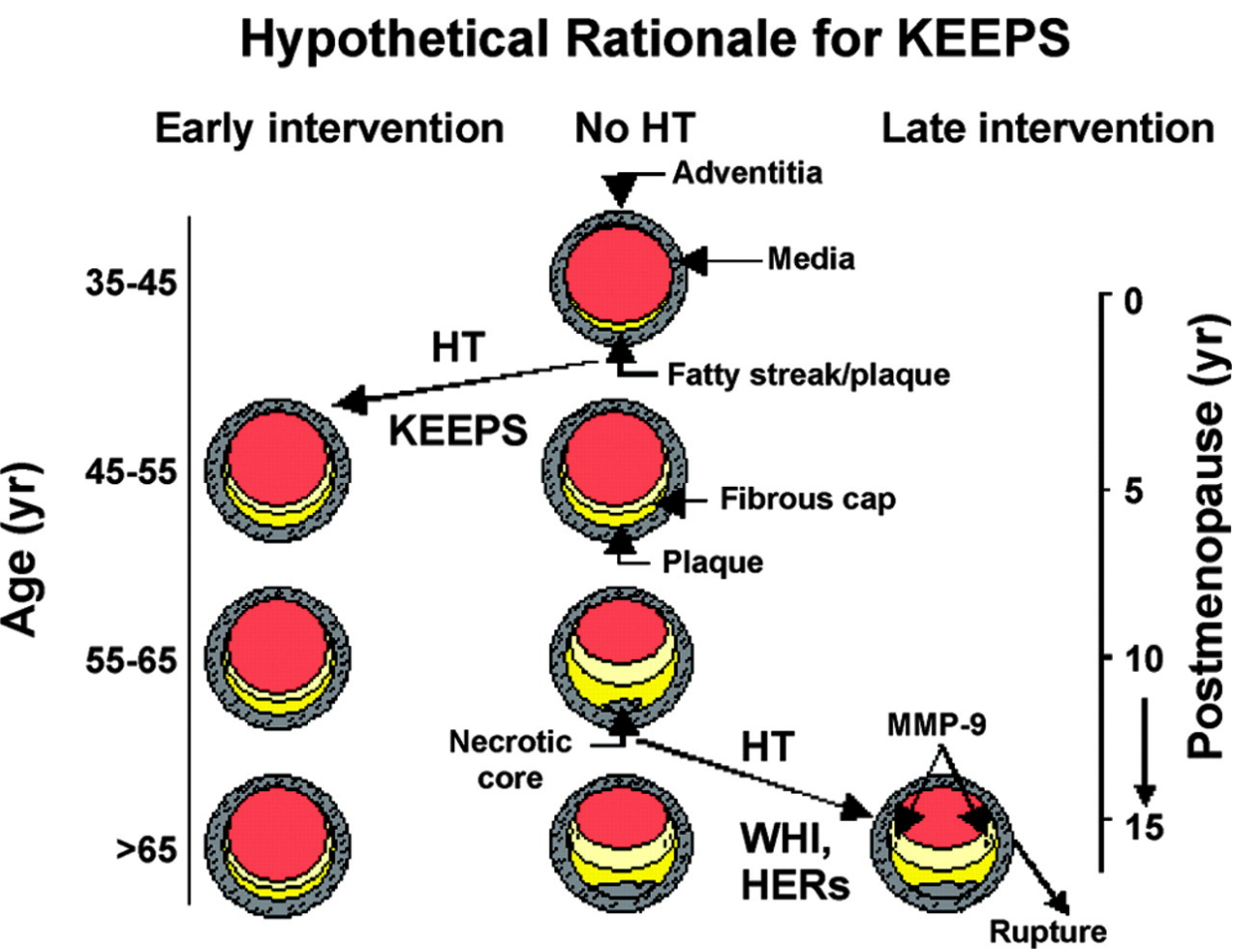
The timing hypothesis

"The 'timing hypothesis' theorizes that estrogen therapy has a more favorable effect in younger women closer to the onset of menopause than in older women, especially in terms of effects on heart disease".

Manson JE. **Womens Health (Lond Engl.)** 2015 Jul;11(4):437-40.



Atualmente



Hipótese confirmada em 727 mulheres

< 6 anos pós-menopausa – Estrógeno cardioprotetor

> 10 anos pós-menopausa – Estrógeno não exerce proteção

N Engl J Med. 2016;374(13):1221-31.

Efeito do estrógeno no processo de envelhecimento

SAMR1

8 Meses

- OVX
- OVX + E2 precoce
- OVX + E2 tardio

SAMP8

8 Meses

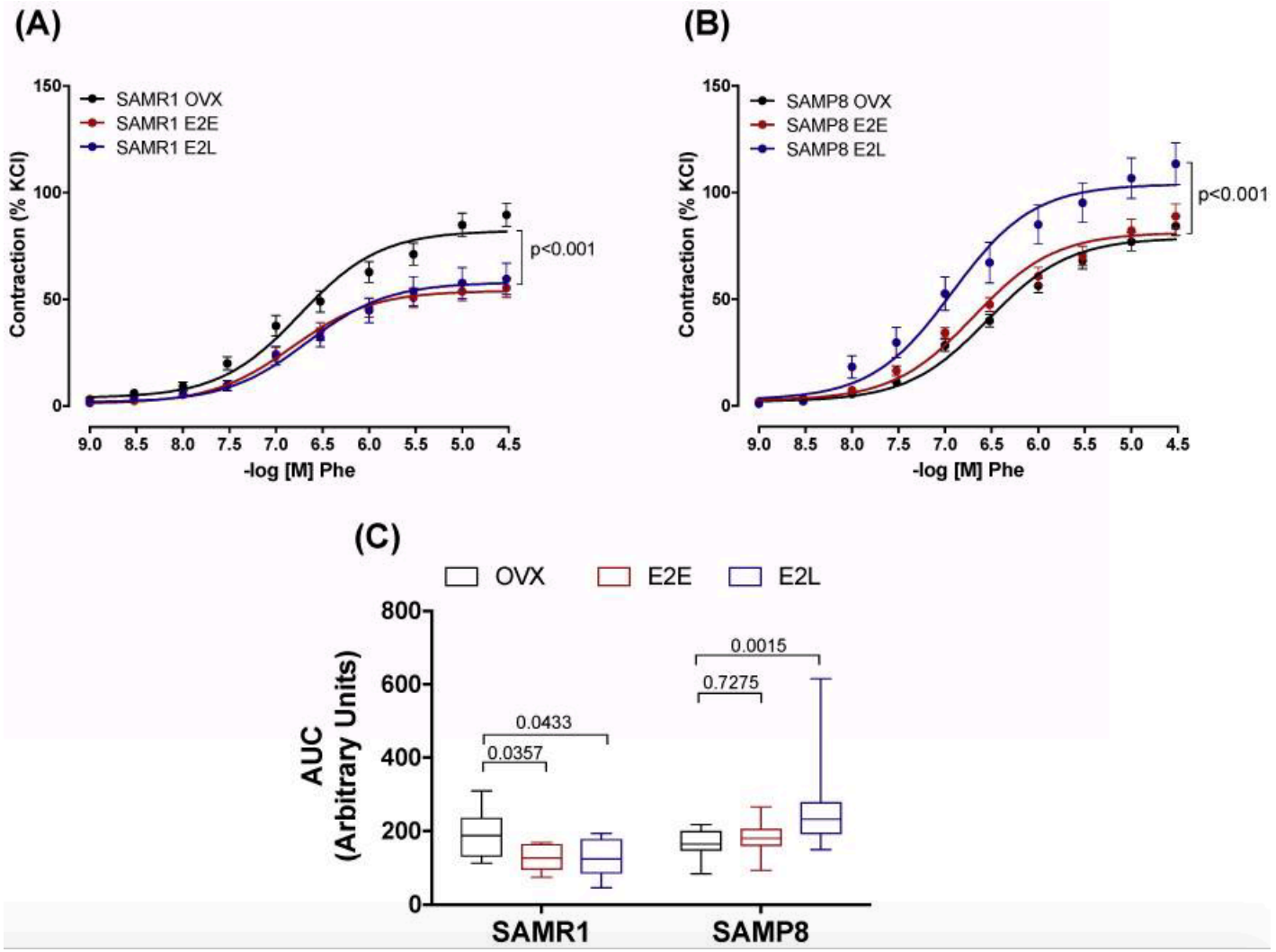
- OVX
- OVX + E2 precoce
- OVX + E2 tardio

Costa TJ.Cells. 2019 Oct 8;8(10):1217

Nova proposta: estrógeno e envelhecimento

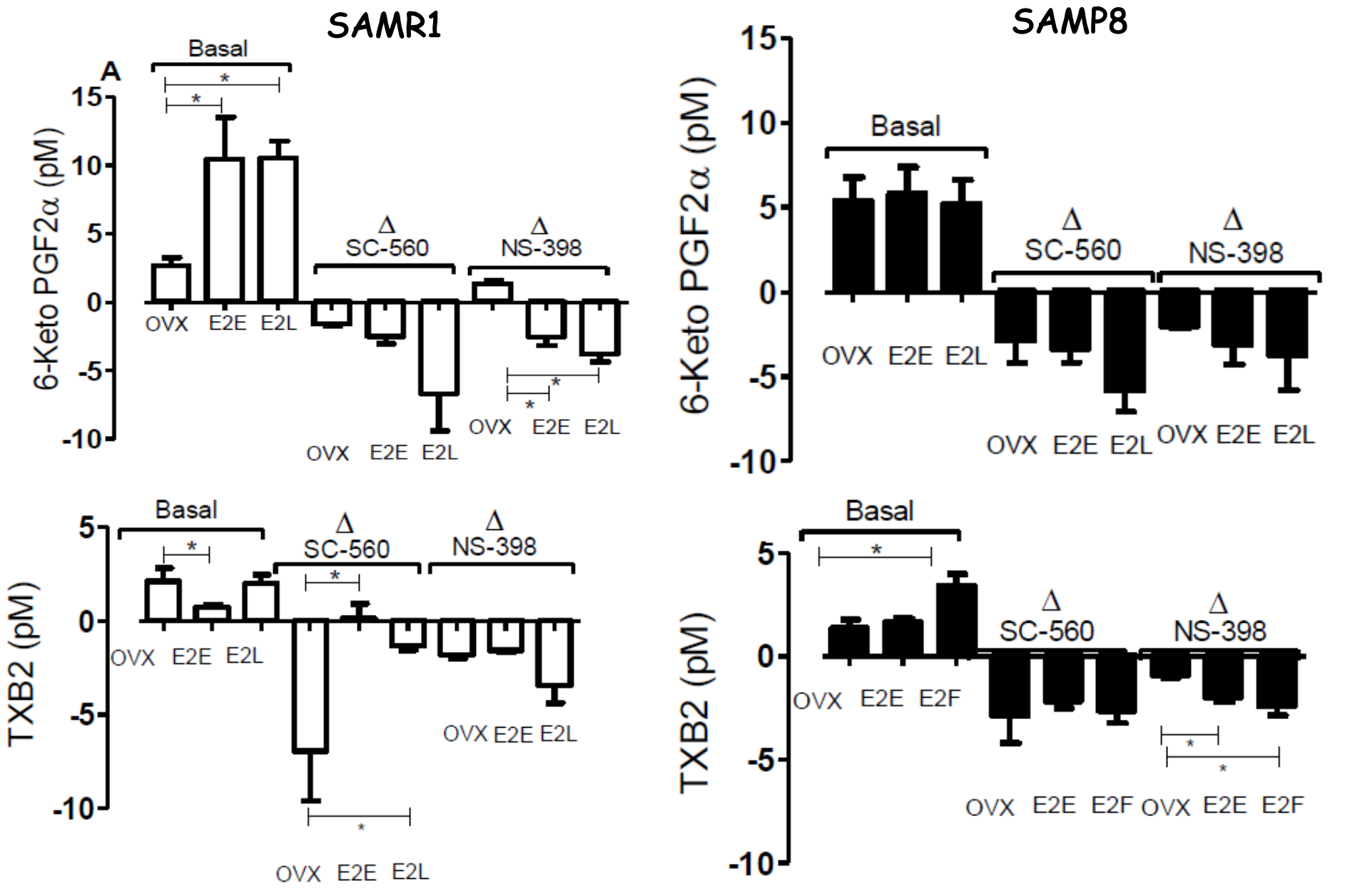
Não-senescentes

Senescentes



Costa TJ.Cells. 2019 Oct 8;8(10):1217

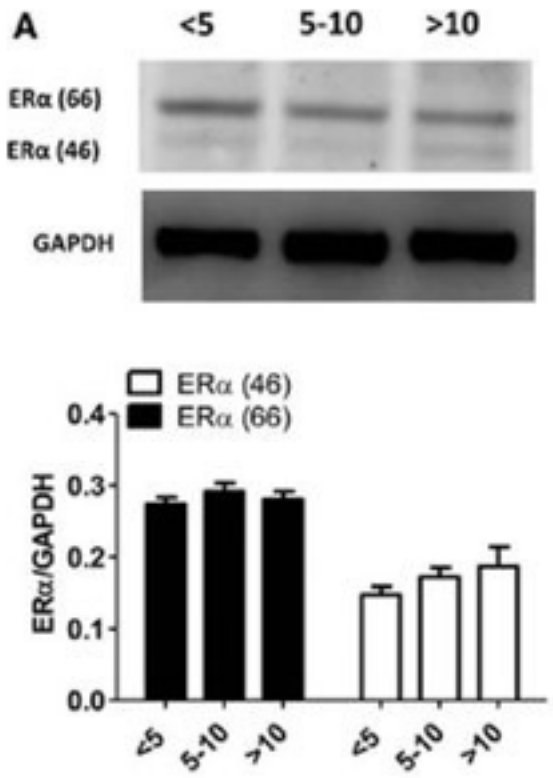
Participação dos prostanóides derivados das COXs no proceso de envelhecimento



Por que o estrógeno atua de forma distinta na vasculatura de fêmeas jovens/velhas?

Splicing alternativos do receptor de estrógeno

Artérias uterinas de mulheres na pós menopausa



Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 32, Issue 8, August 2012, Pages 2035-2042
https://doi.org/10.1161/ATVBAHA.112.250308

American Heart Association.

CLINICAL AND POPULATION STUDIES

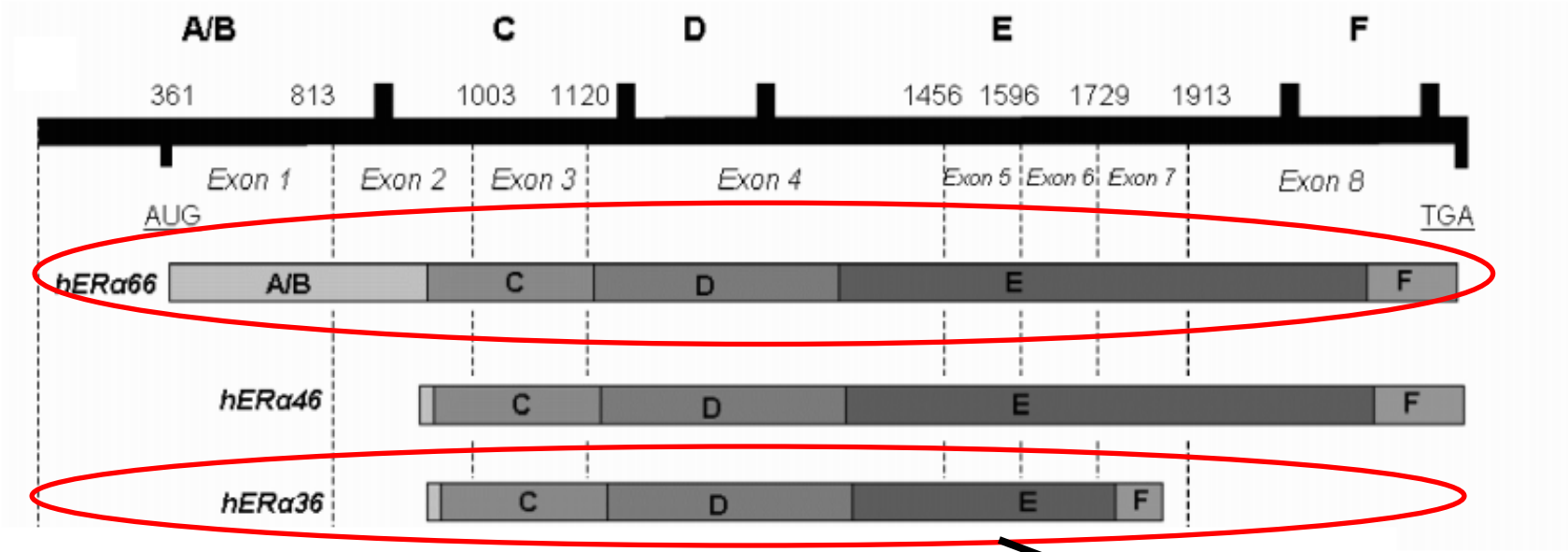
Effects of Estrogen on Vascular Inflammation

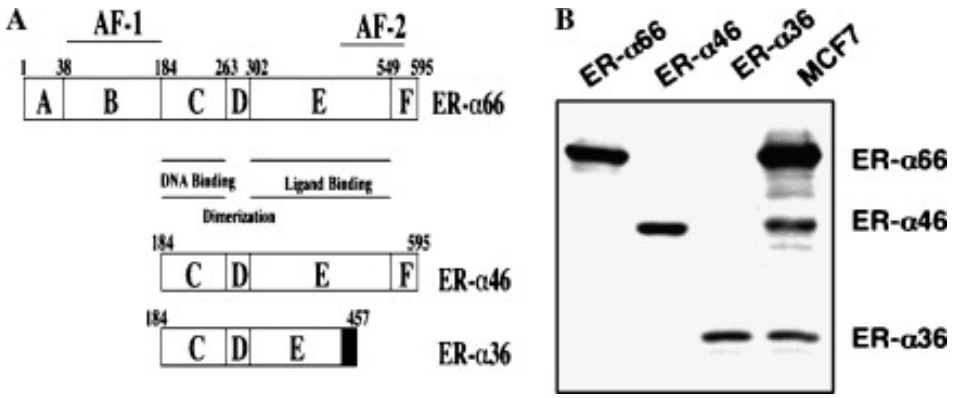
A Matter of Timing

Susana Novella, Magda Heras, Carlos Hermenegildo, and Ana Paula Dantas

ERα "Splicing" alternativo – novo vilão das doenças cardiovasculares?

Câncer de mama estrógeno positivo:
2002: 30% não respondia ao Tamoxifeno
2010: 50% não respondia ao Tamoxifeno





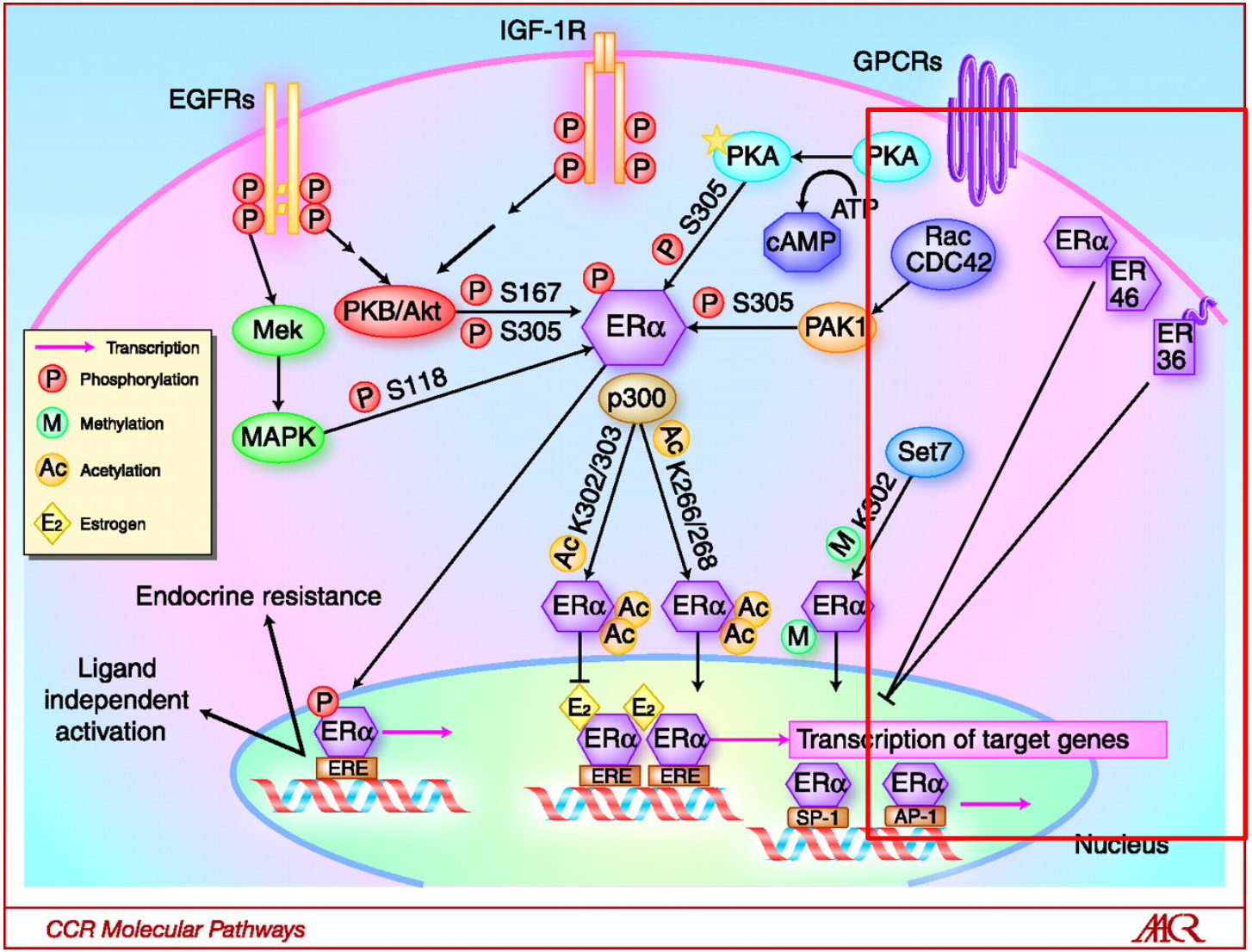
Células MCF7

Proliferação celular

Wang et al. **Biochemical and Biophysical Research Communication**. V:336 (1): 2005. Pages 1023-1027.

ERα (ESR1 - 36kDa)

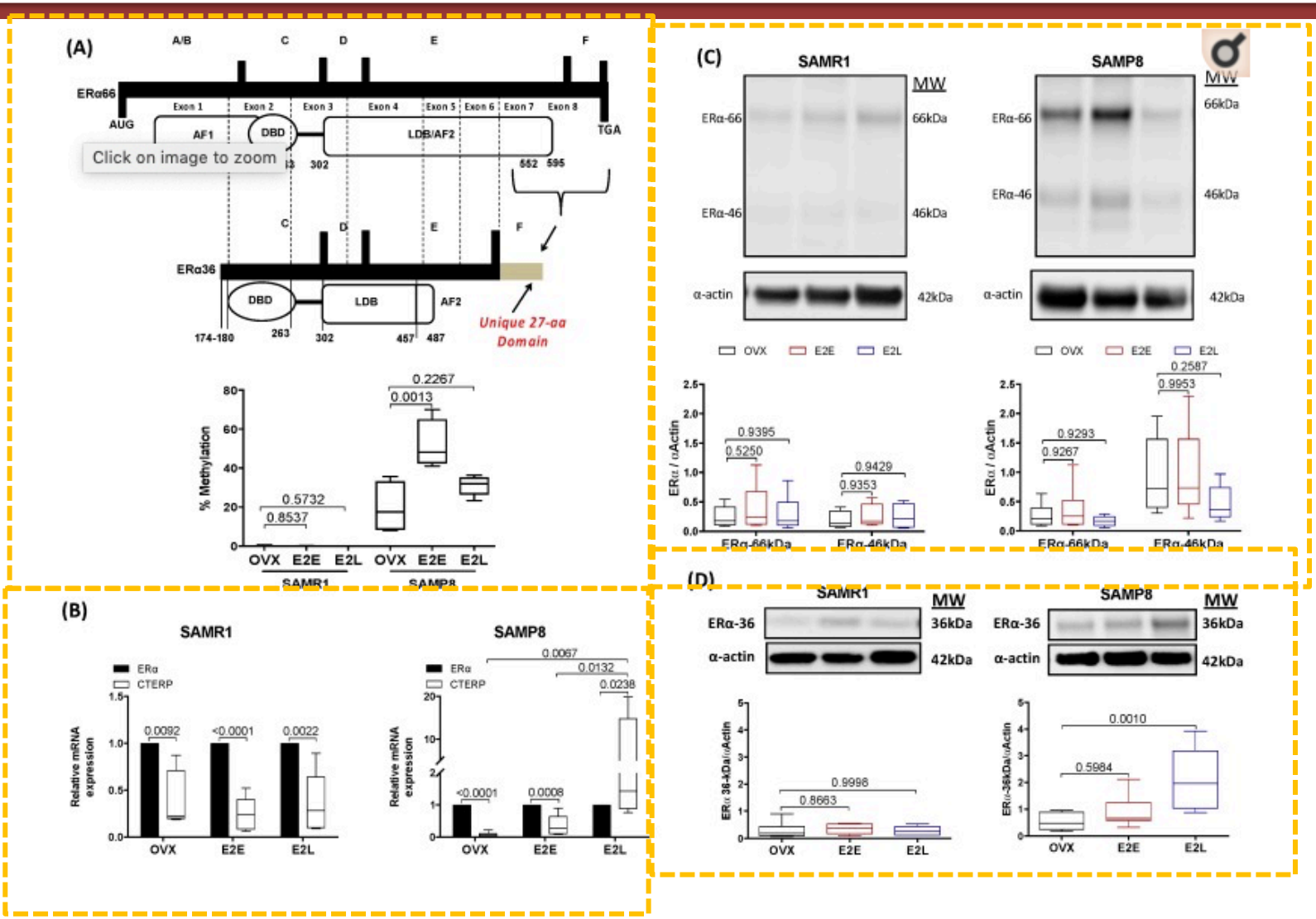
Splicing variant



Clinical Cancer Research Volume 16, Issue 10,2010

ERα (ESR1 - 36kDa)

Splicing variant



Costa TJ.Cells. 2019 Oct 8;8(10):1217

Diferenças sexuais na função dos vasos sanguíneos

Fêmeas: vasculoprotetor

NO/ROS

Estrógeno

Machos

Testosterone

Terapia hormonal no século XXI: Janela de oportunidade Terapêutica

Obrigado!

tjcosta@usp.br

Tiago Januário da Costa

Tiago J. Costa