Environmental Estrogens in Female Cardiovascular Health

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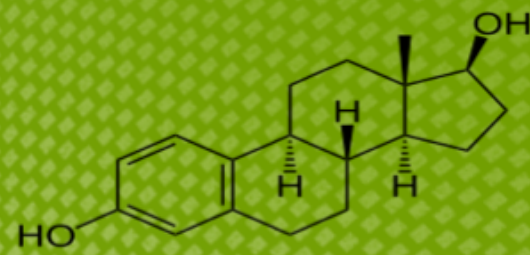
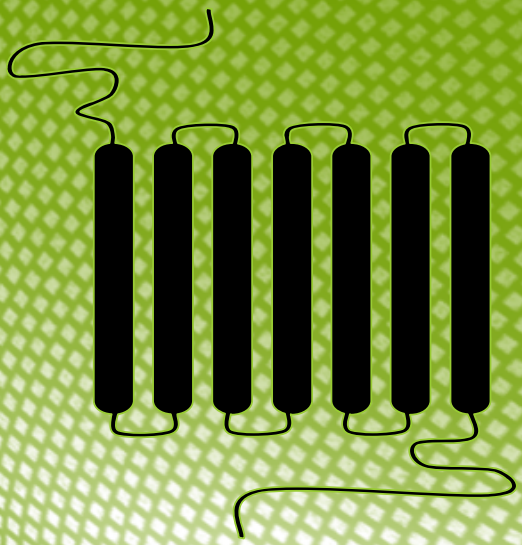
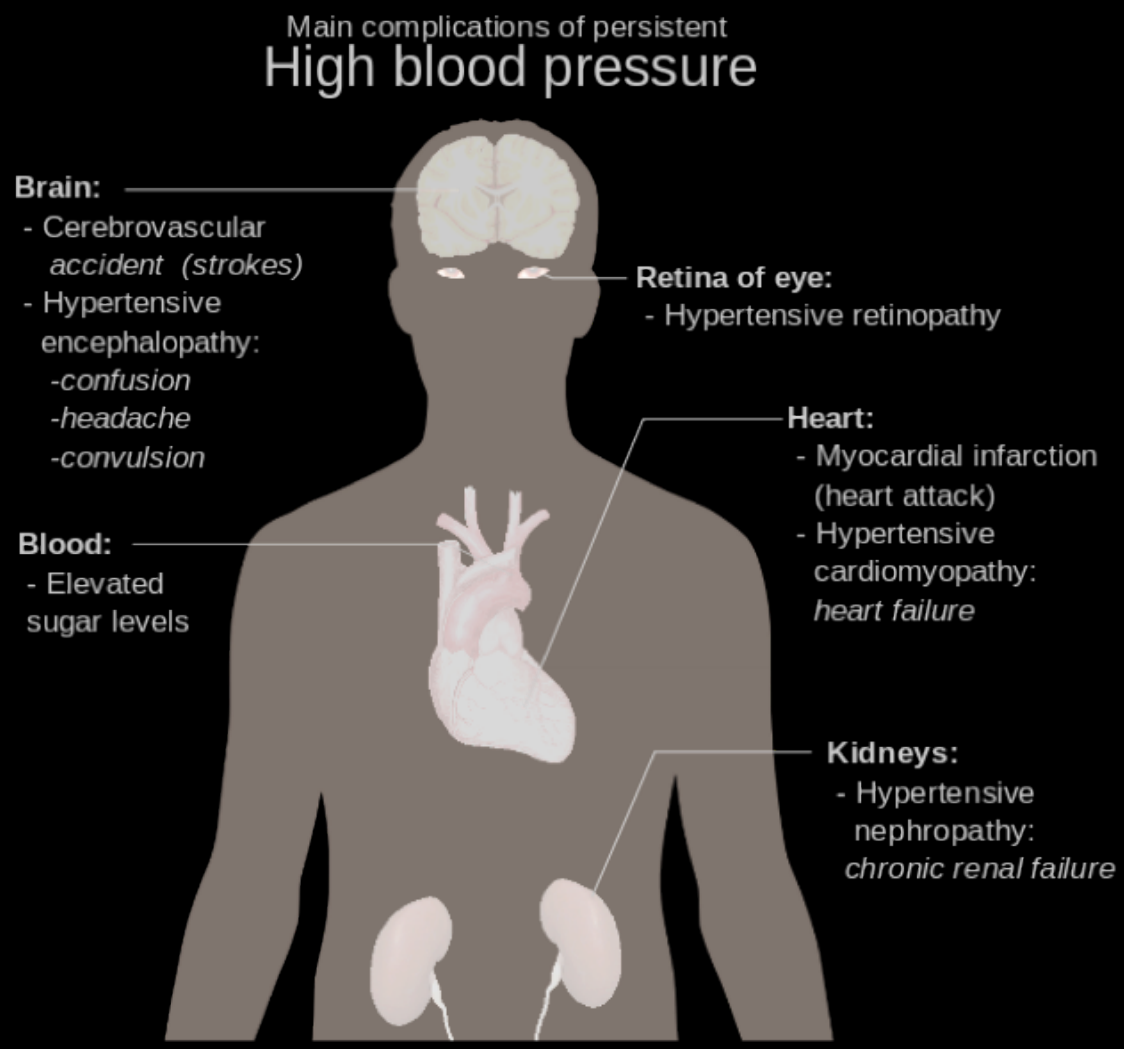


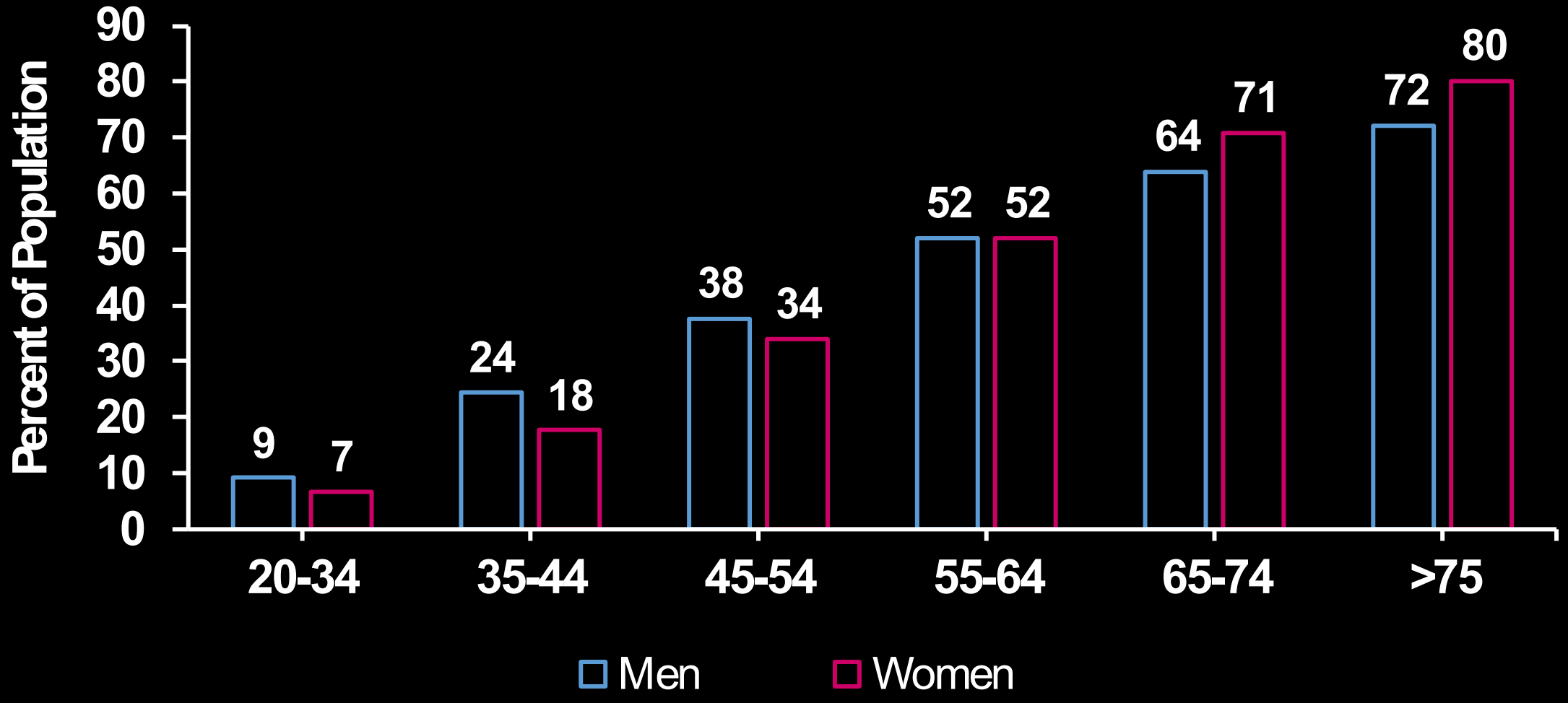


Hypertension induces end organ damage

- Increased force induces vascular stiffness > reduced ability to dampen pulsatility.
- Since high flow in the brain and kidneys is maintained by low capillary resistance, these organs are more susceptible to repetitive stress.
- In the heart, hypertension increases overload and reduces cardiac perfusion.

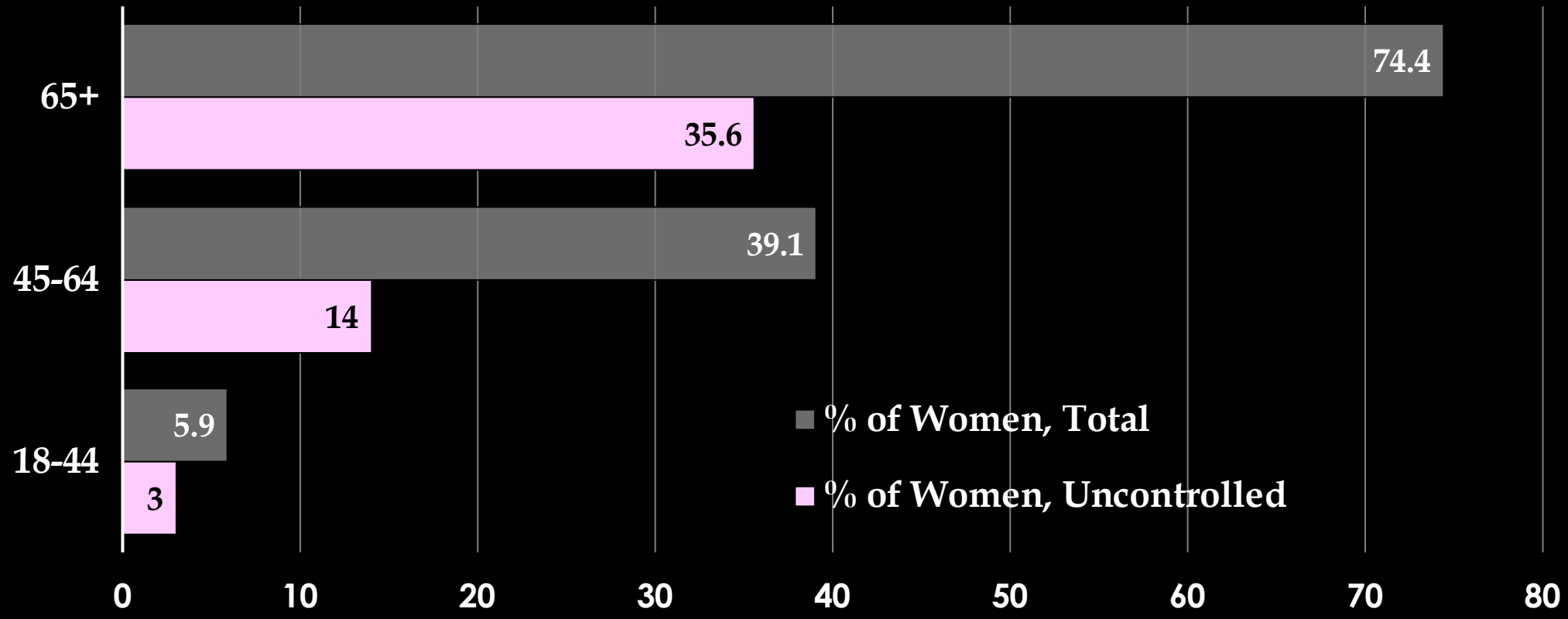


Women are protected from CVD until menopause



NHANES: 2007-2010. Go AS et al. (2013) Circulation.

Uncontrolled Hypertension in Aging Women



Source: CDC, NHANES 2009-10.

Observational studies

Meta-analysis

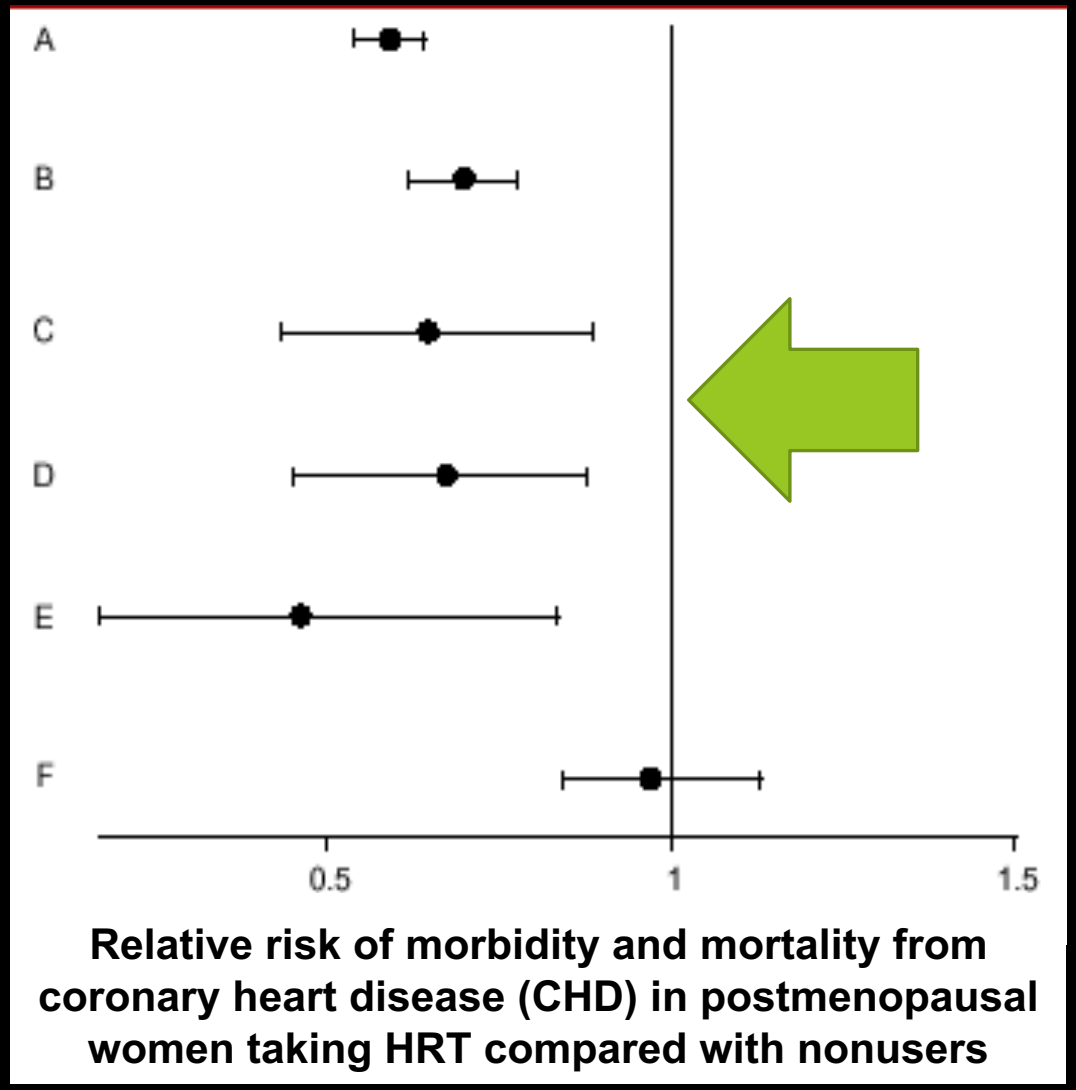
Meta-analysis

Nurses' Health Study

Nurses' Health Study

Nurses' Health Study

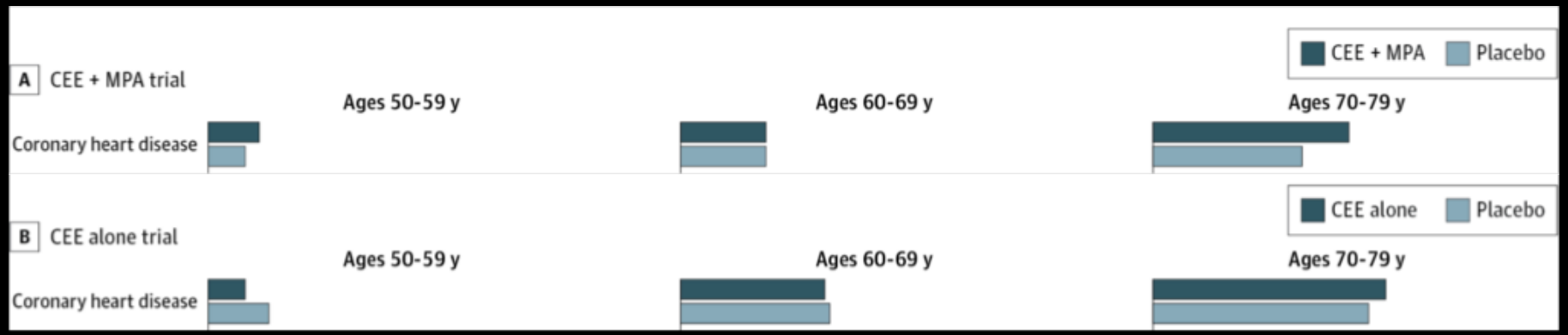
HERS = Heart and Estrogen/ Progestin Replacement Study



Relative risk of morbidity and mortality from coronary heart disease (CHD) in postmenopausal women taking HRT compared with nonusers

Contreras & Parra (2000) Am J Health Syst Pharm.

Women's Health Initiative



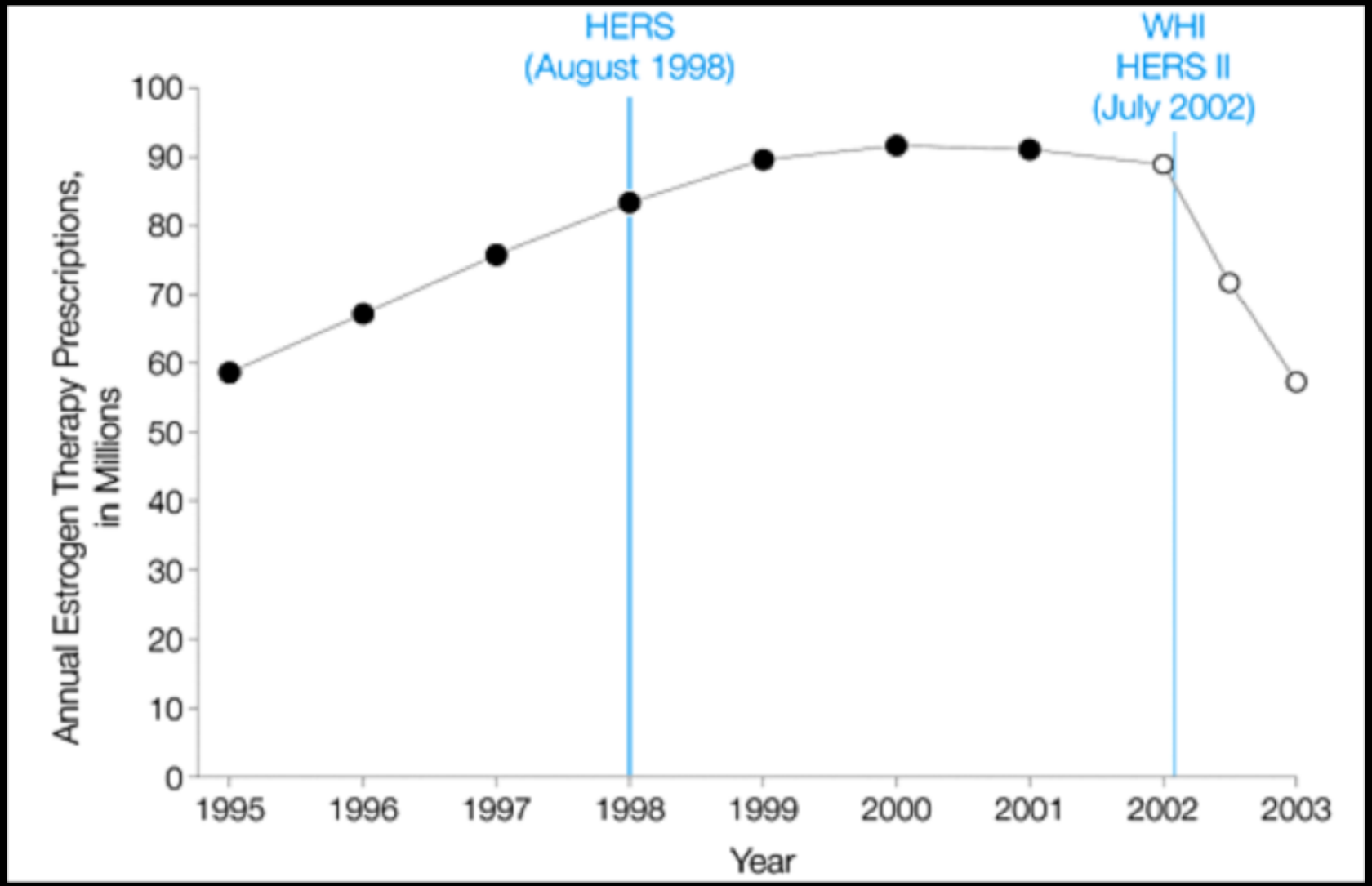
Rossouw et al. (2002) JAMA and Manson et al. (2013) JAMA.

Black Box Warning

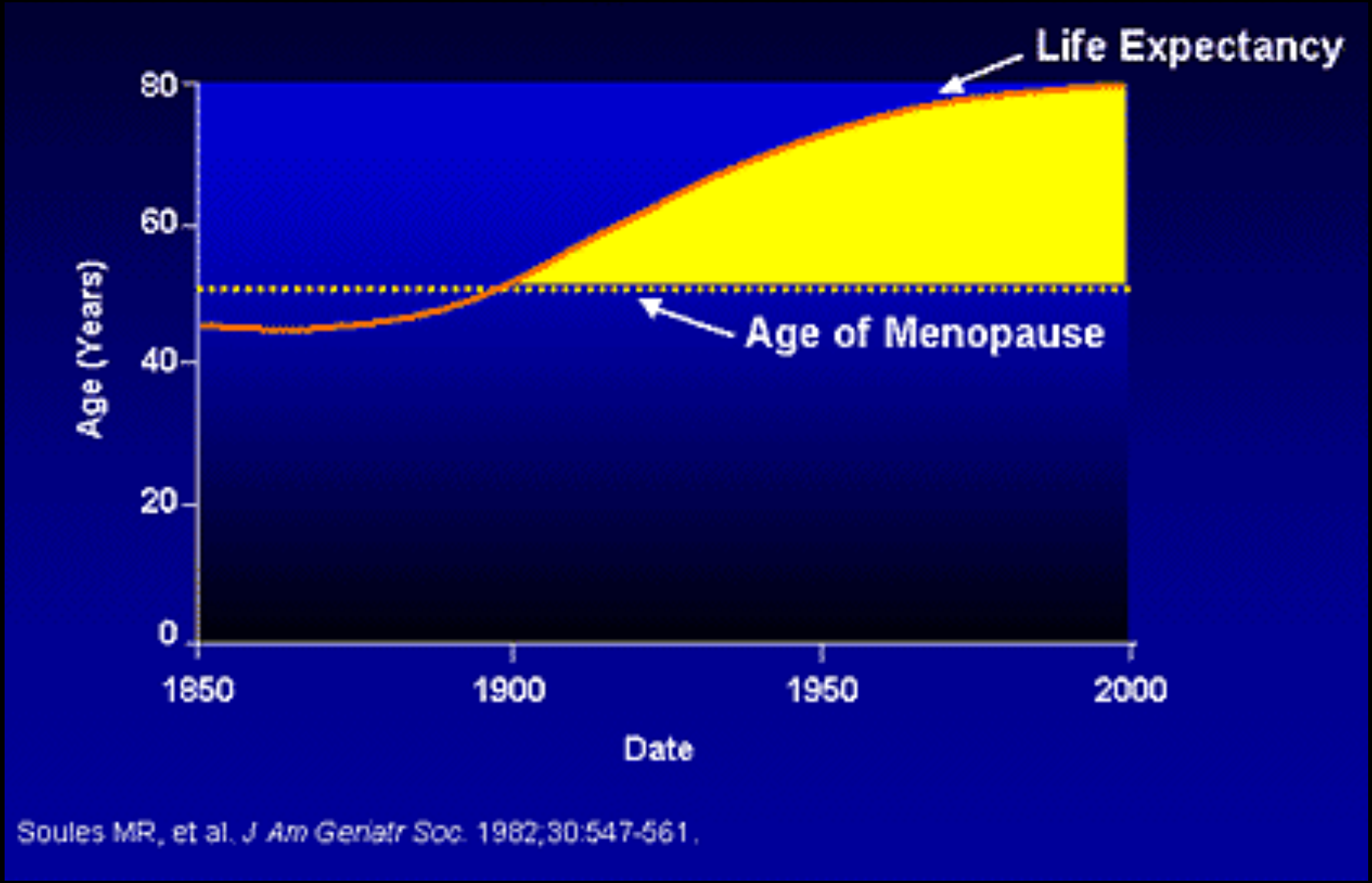
WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease.
- WHI reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50-79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens, relative to placebo.
- Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.
- Contraindicated in patients with:
  - Active or past history of confirmed venous thromboembolism.
  - Active or past history of stroke, myocardial infarction, coronary heart disease.

Impact of the WHI on hormone use

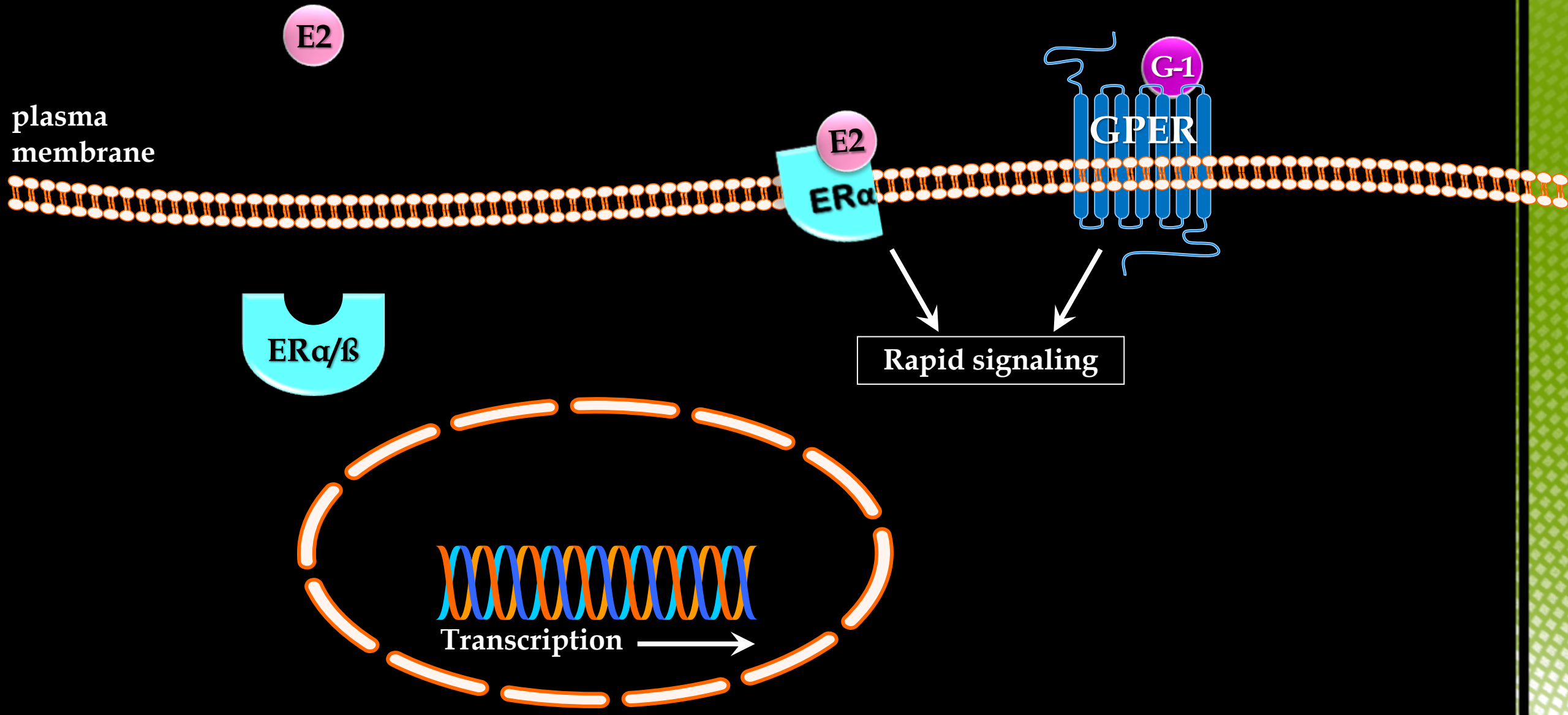


Gap widens between menopause and life expectancy



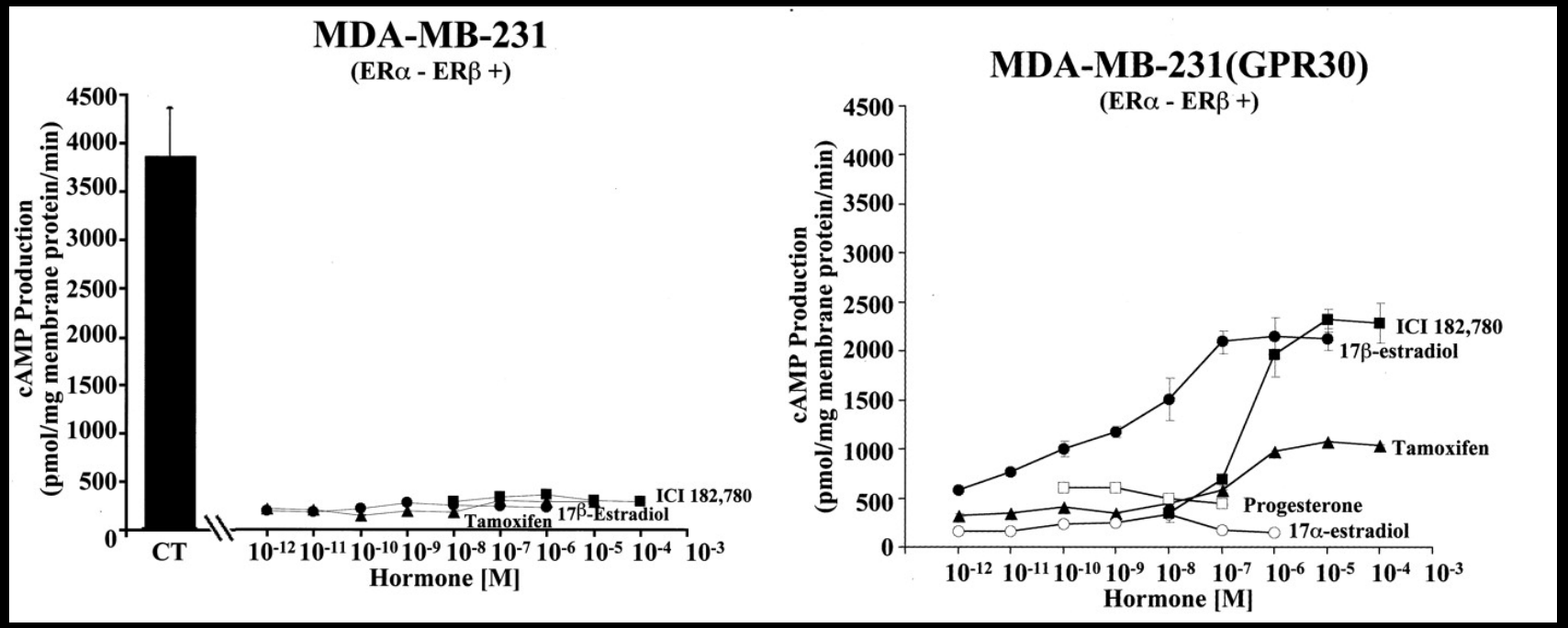
- What receptor mediates estrogen's vascular effects?
- How do aging and menopause alter these effects?
- Can we make hormone therapy more selective?

Nuclear and Membrane Estrogen Receptors



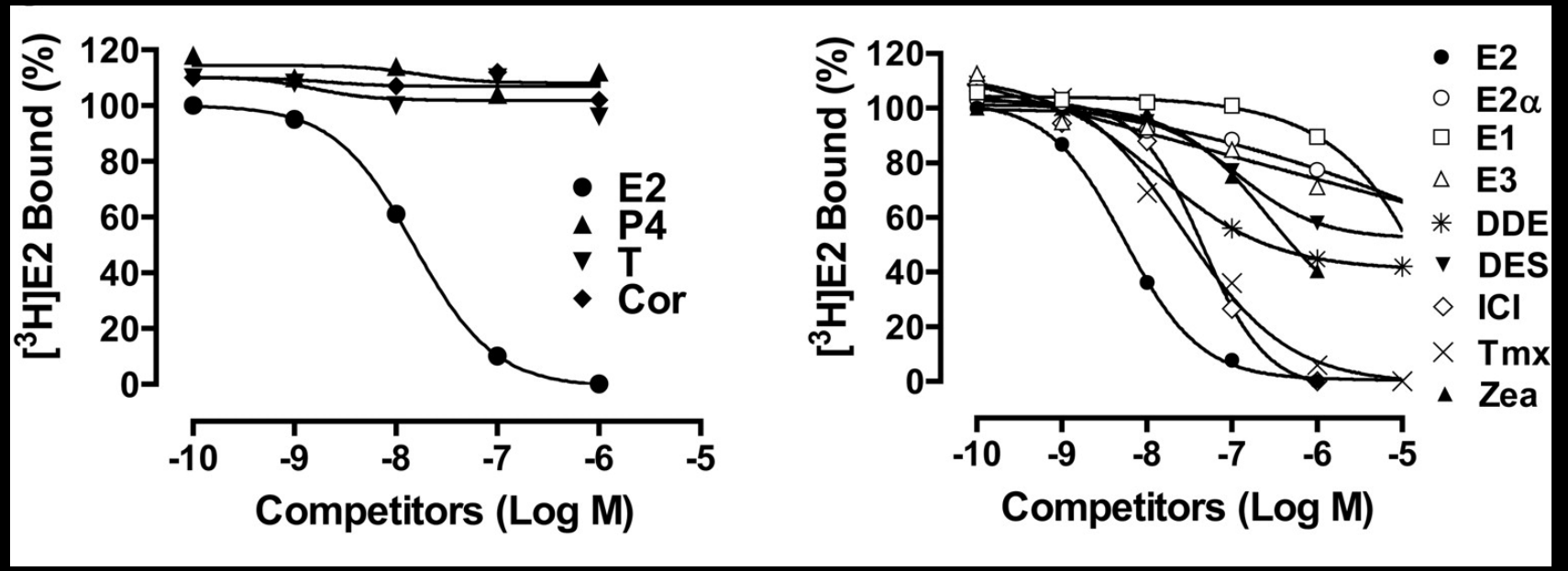
Discovery of GPER

- ER receptor has long been used as a diagnostic marker in breast cancer
- ER negative cancers are more aggressive and do not respond to endocrine therapy
- cDNA screen between an ER positive and an ER negative cell line



Filardo E J et al. Molecular Endocrinology 2002;16:70-84

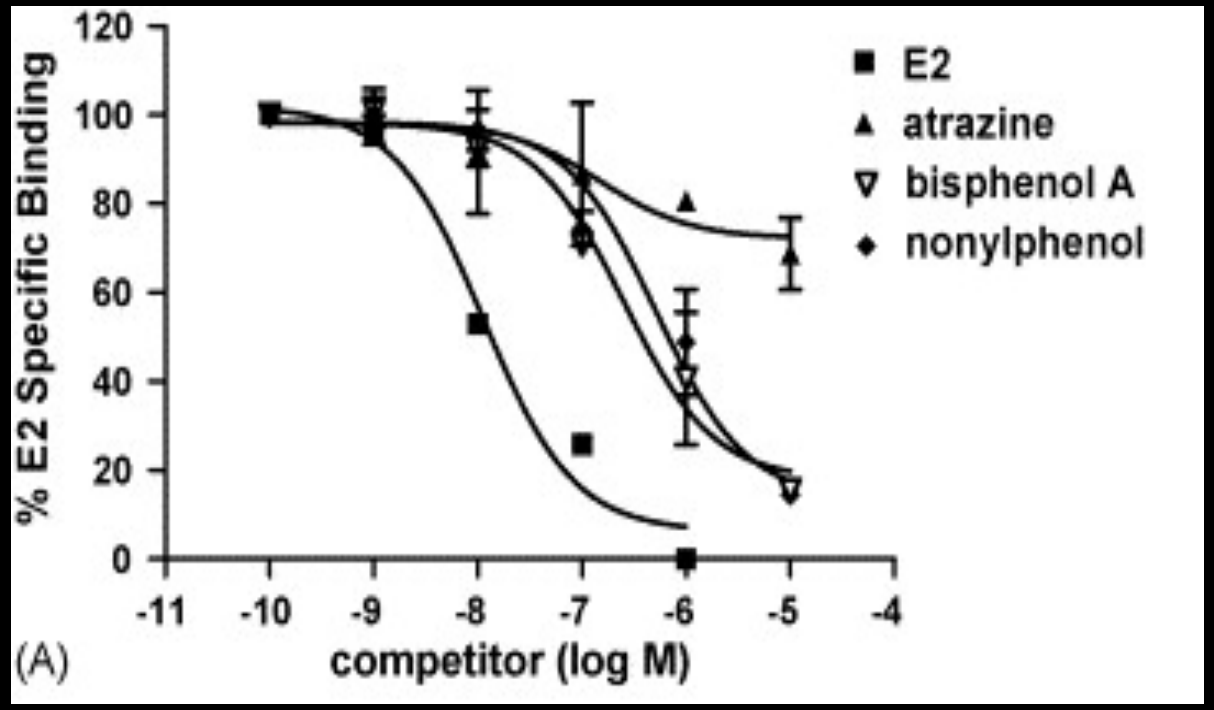
GPER binding characteristics



Plasma membranes from SKBR3 cells (ERa-, ERβ-, GPER+).

Thomas P et al. Endocrinology 2005;146:624-632

Environmental estrogens bind GPER



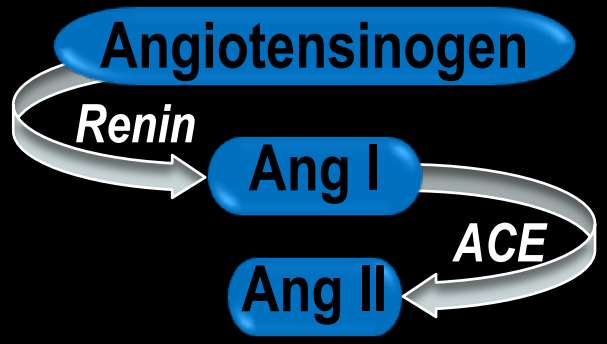
herbicide

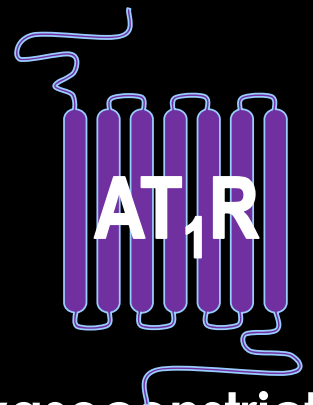
precursor to commercially important detergents

Competition curves of binding to plasma membranes of HEK293 cells (ERa-, ERβ-) stably transfected with GPR30. BPA competes with estradiol binding to GPR30.
IC50 = 7.8 nM (E2) vs. 630 nM (BPA)

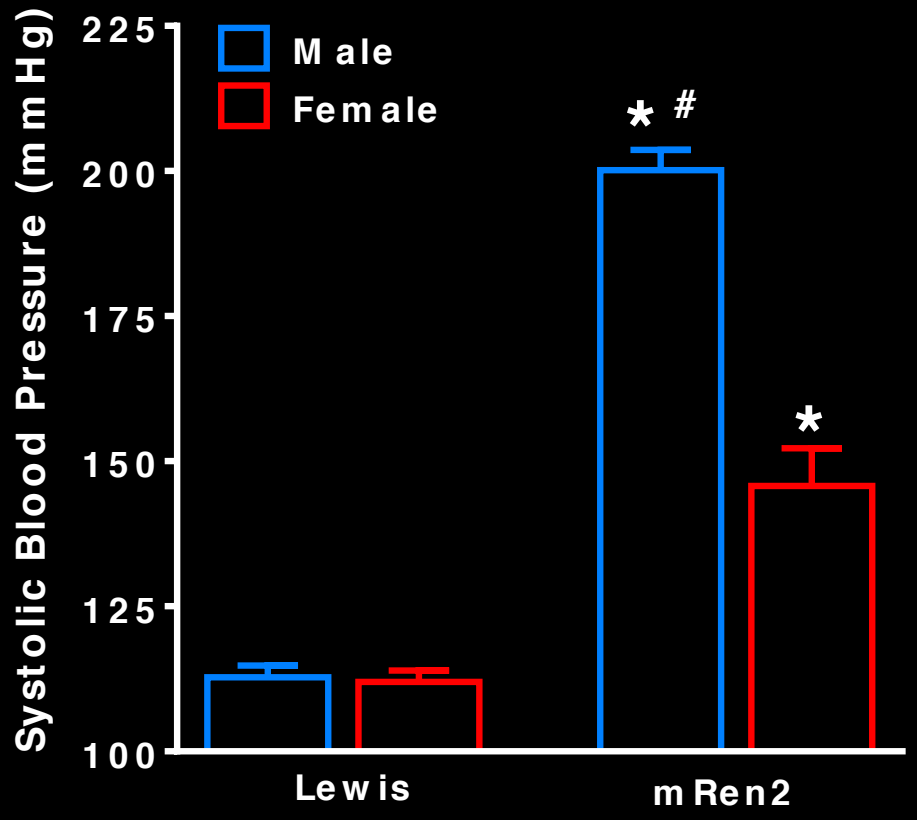
Thomas and Dong (2006) J Steroid Biochem Mol Biol.

mRen2 Hypertensive Rat Model





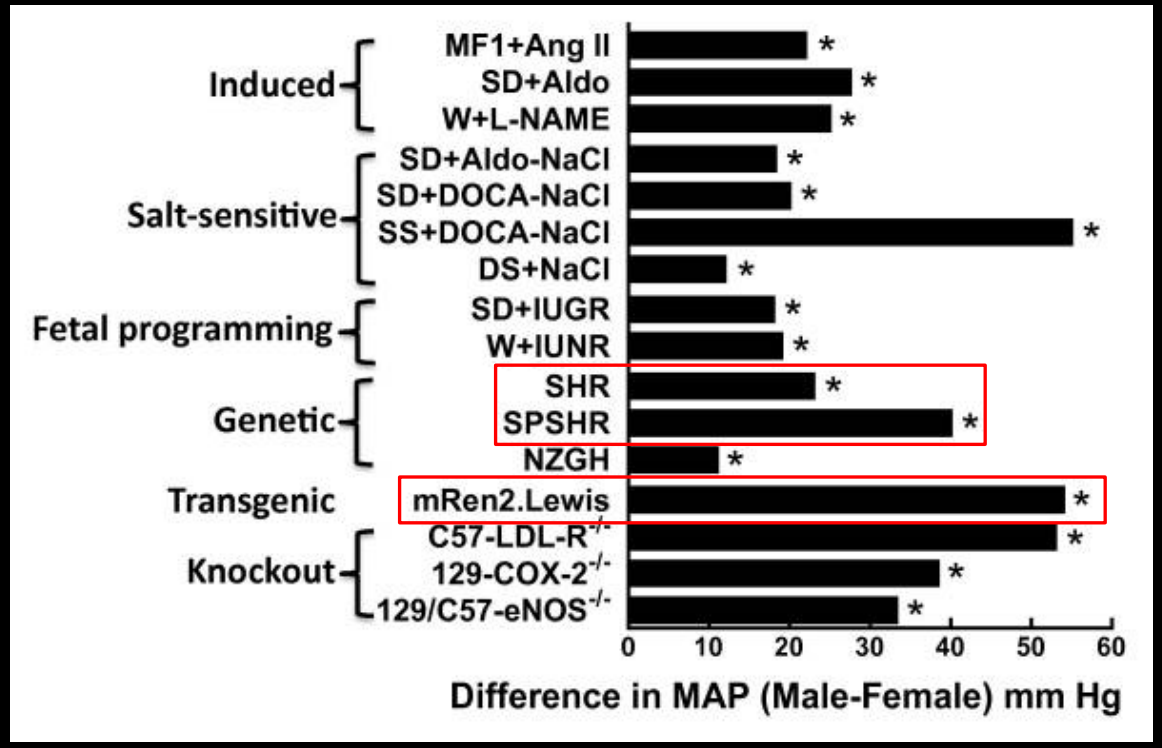
vasoconstriction, hypertrophy, sodium reuptake, fibrosis, sympathetic activation

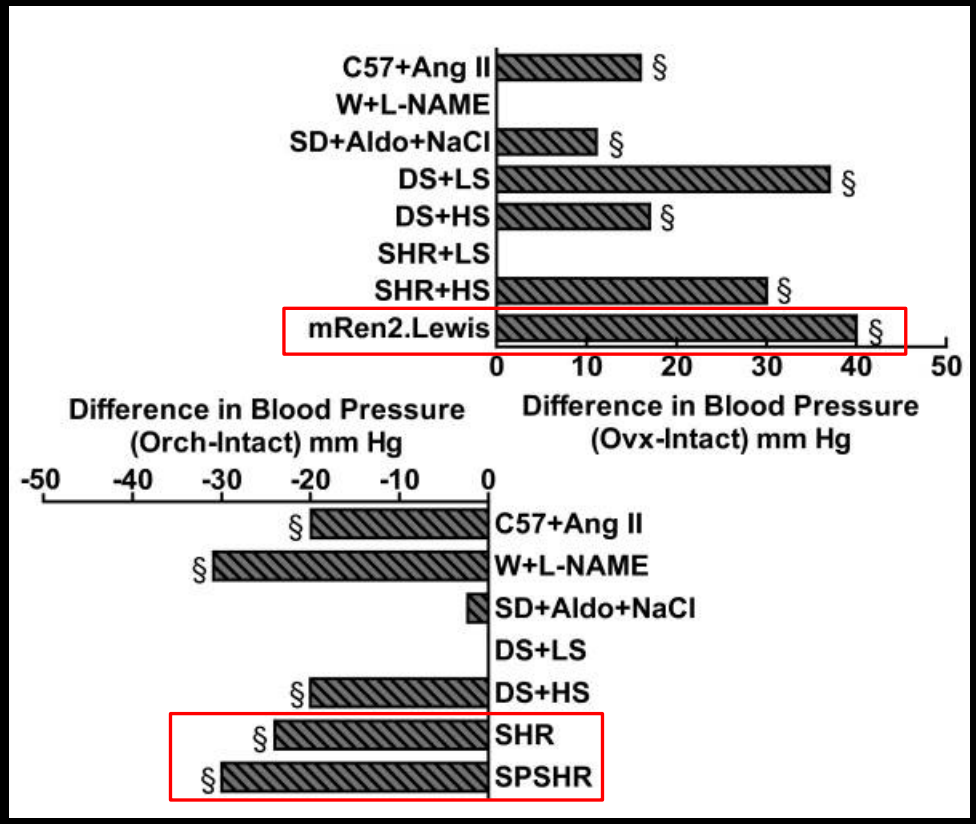


** P < 0.01 vs strain*
\# P < 0.01 vs gender

Pendergrass et al. (2008) AJP-Heart

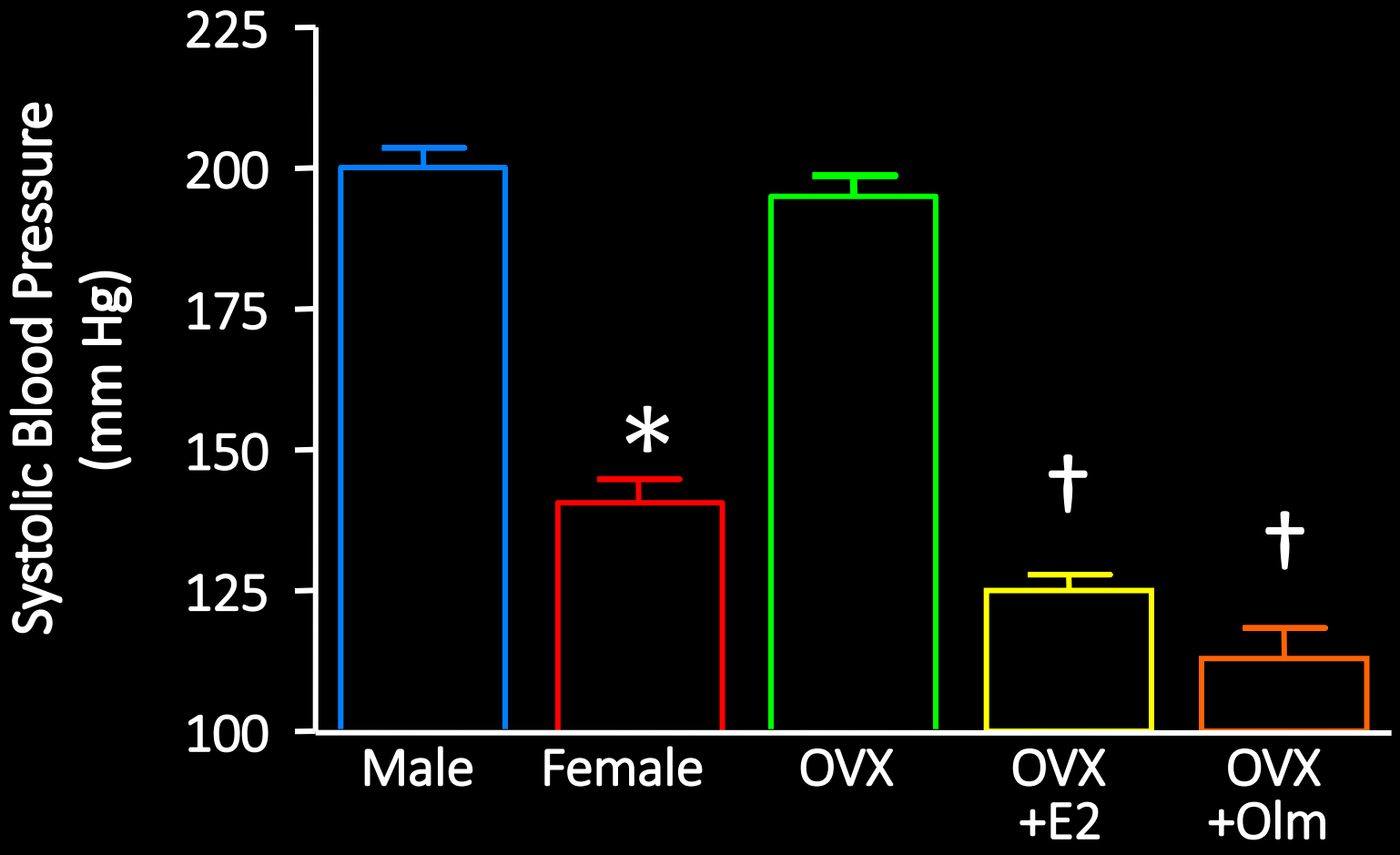
Sex differences in hypertensive models





Sandberg and Ji (2012) Biol Sex Differ

Estrogen & Ang II dependence

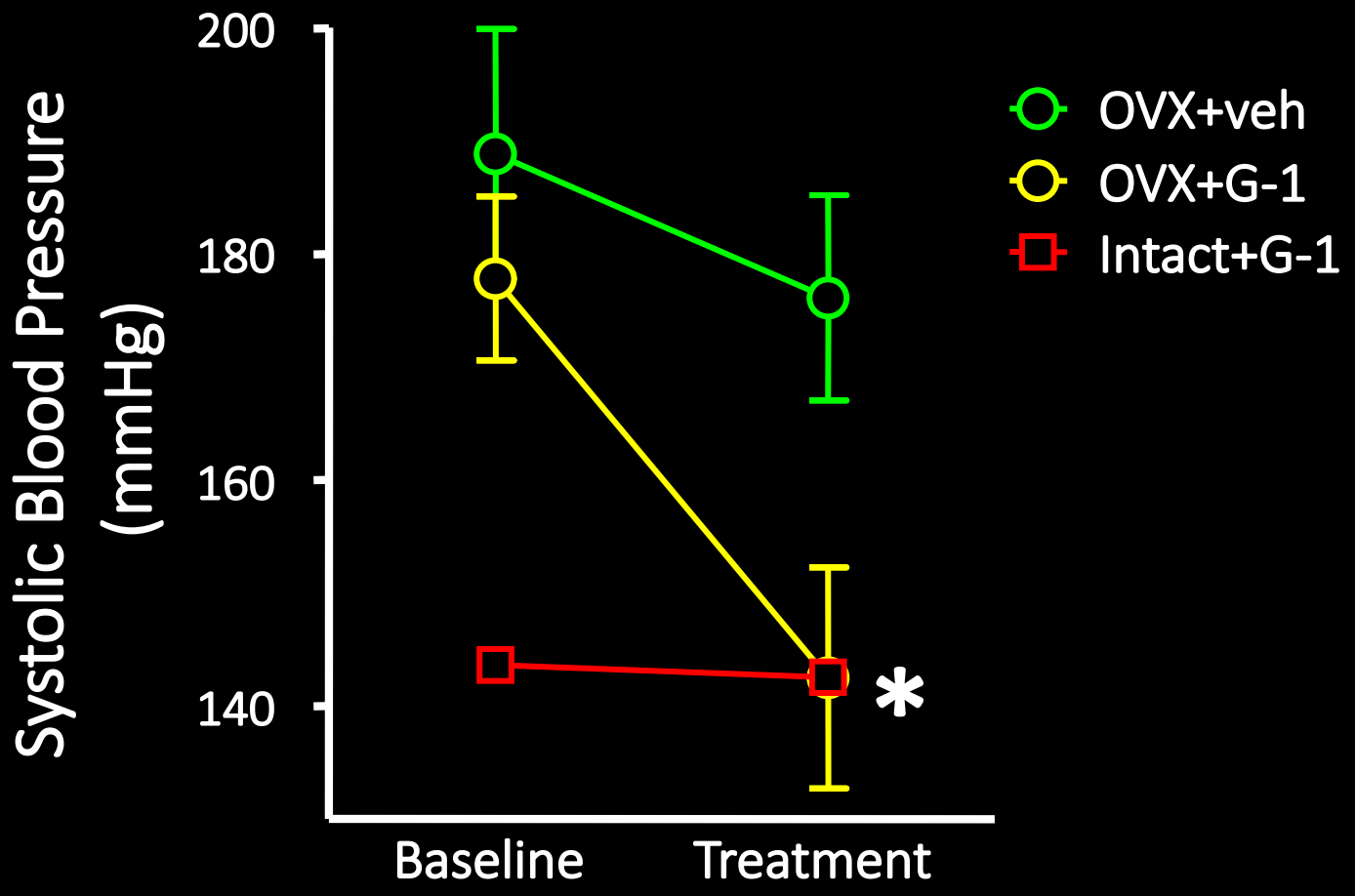


* P < 0.001 vs. Males

† P < 0.001 vs. OVX

Chappell et al. (2003) Hypertension

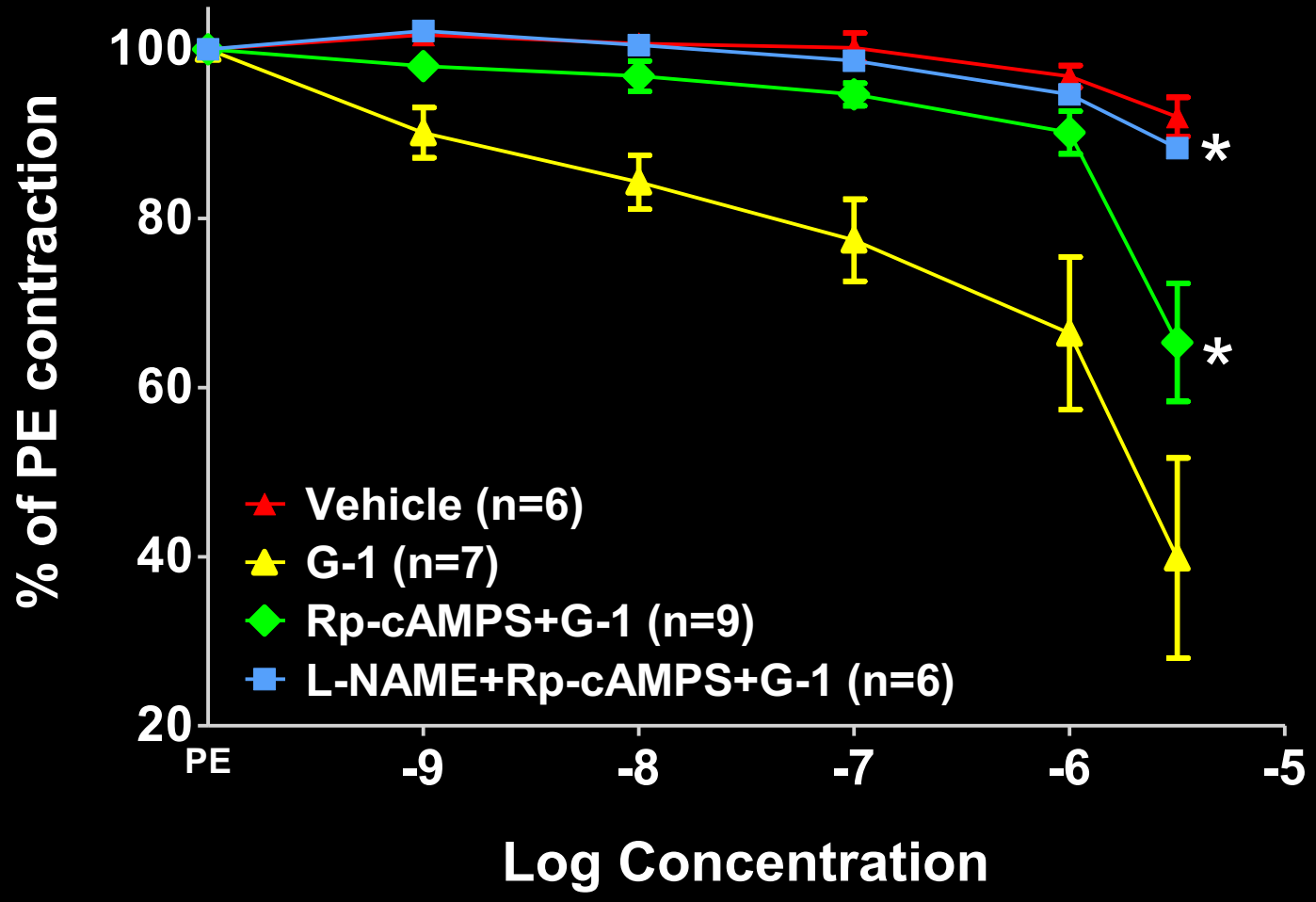
G-1 attenuates blood pressure



* *P* < 0.001 vs. Baseline

Lindsey et al. (2009) Endocrinology

GPR30 relaxes arteries via NO and cAMP

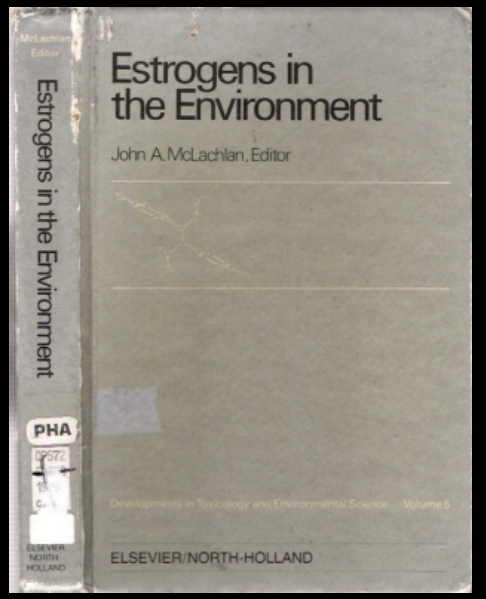


Lindsey et al. (2013) Steroids

Endocrine Disruptors

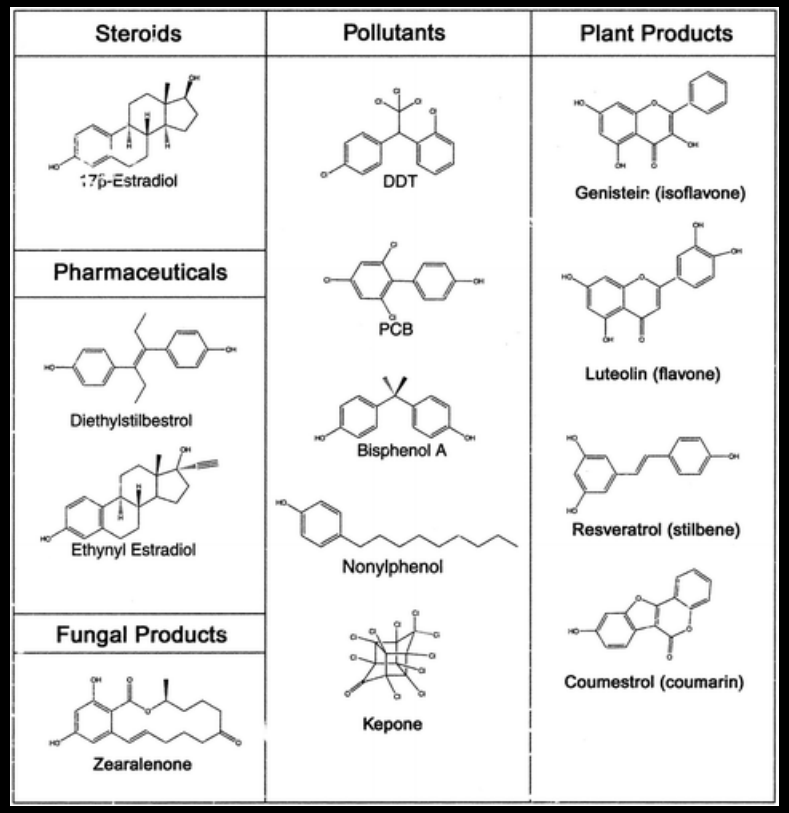
- Endocrine-disrupting chemicals influence biological pathways associated with a variety of hormones, predominantly estrogens.

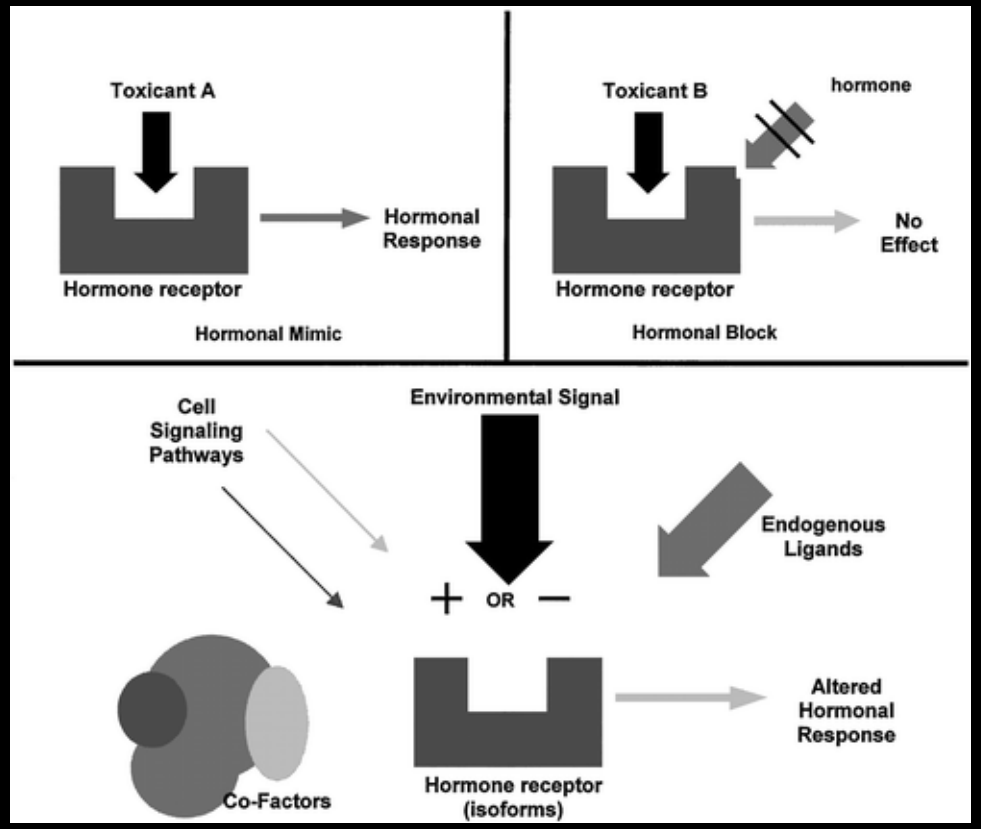
Dr. John McLachlan
Prof, Pharmacology



- Leader in the field of environmental endocrine disruption research (e.hormone.tulane.edu)

Environmental Signaling





McLachlan JA. (2001) Endocr Rev.

Bisphenol A

- One of the most ubiquitous endocrine disruptors is bisphenol A (BPA), a plasticizing agent found in most manufactured plastic products and the lining of canned goods.

Photo by Dr. Ricardo Mostany

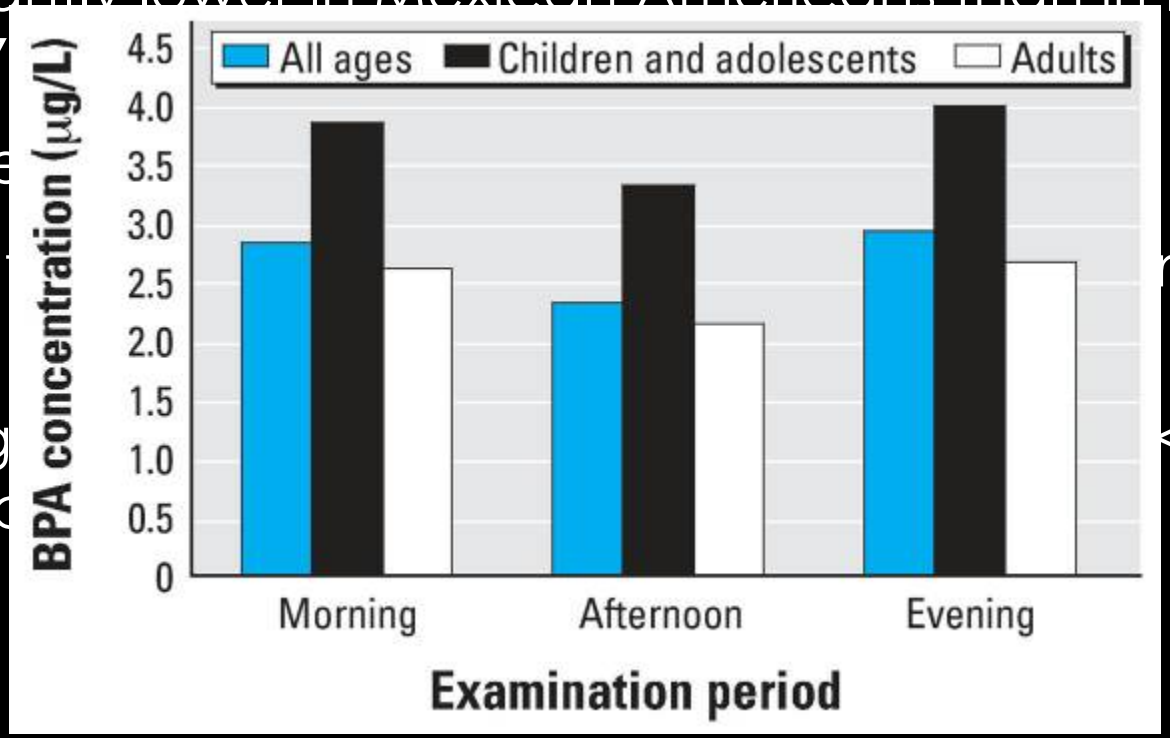
History of BPA production

- 1991-A production volume of **16 million pounds** was reported for bisphenol A
- 2003-United States bisphenol A consumption was reported at **~1.9 billion pounds**
  - **~1.4 billion pounds** in polycarbonate resins
  - **~406 million pounds** in epoxy resins
  - **~117 million pounds** in other applications
- 2004-U.S. bisphenol A production volume was reported at **~2.3 billion pounds**

Volume 83, Issue 3,
http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20147/full#fig1

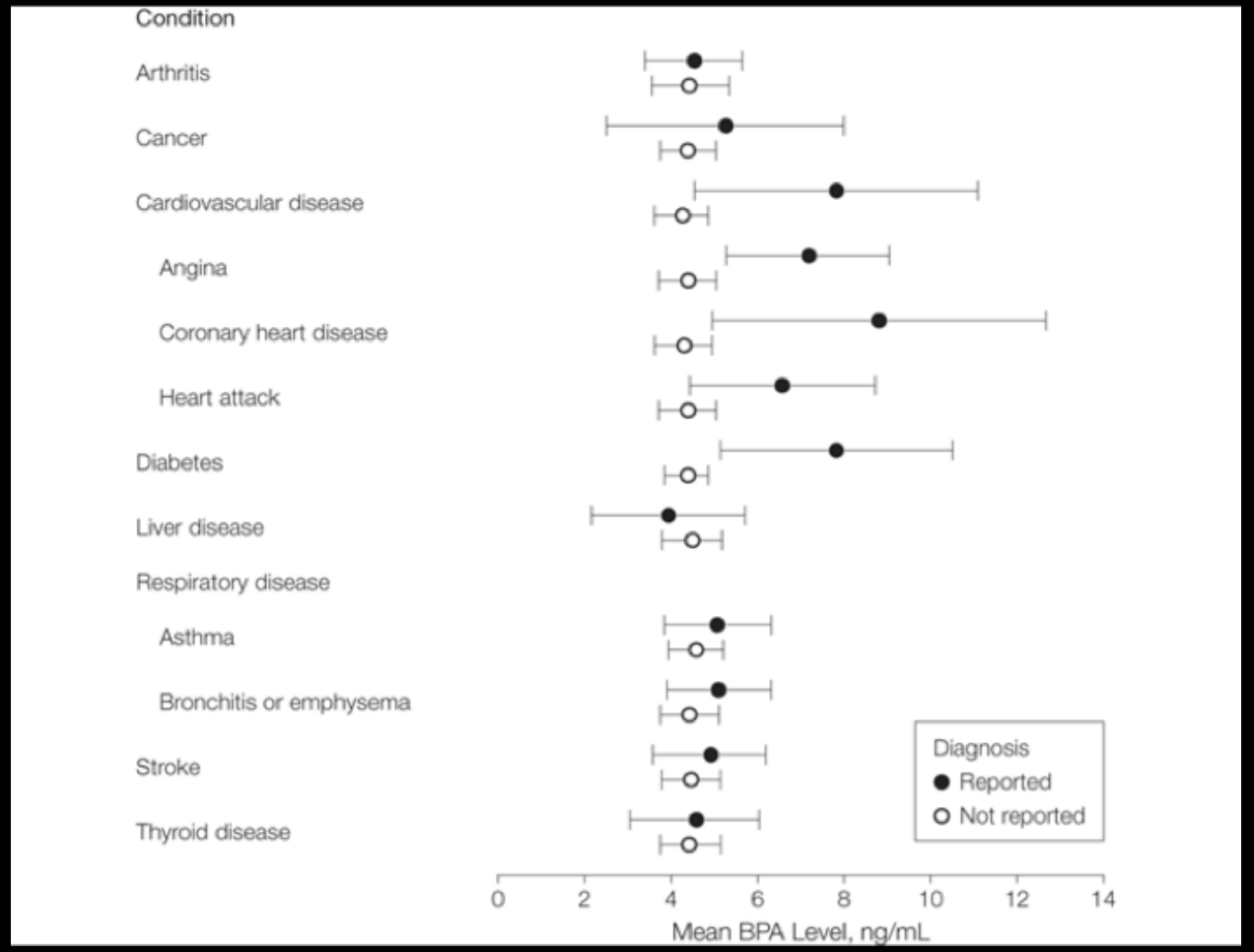
BPA Exposure

- Urinary BPA was detected in 92.6% of NHANES participants (2003-2004).
- BPA was significantly lower in Mexican Americans than in blacks and whites (p = 0.007
- No difference be
- Females had sta males (p = 0.043).
- Children had hig < 0.001), who in turn had higher c



Calafat et al. (2008) Environ Health Perspect. 2008.

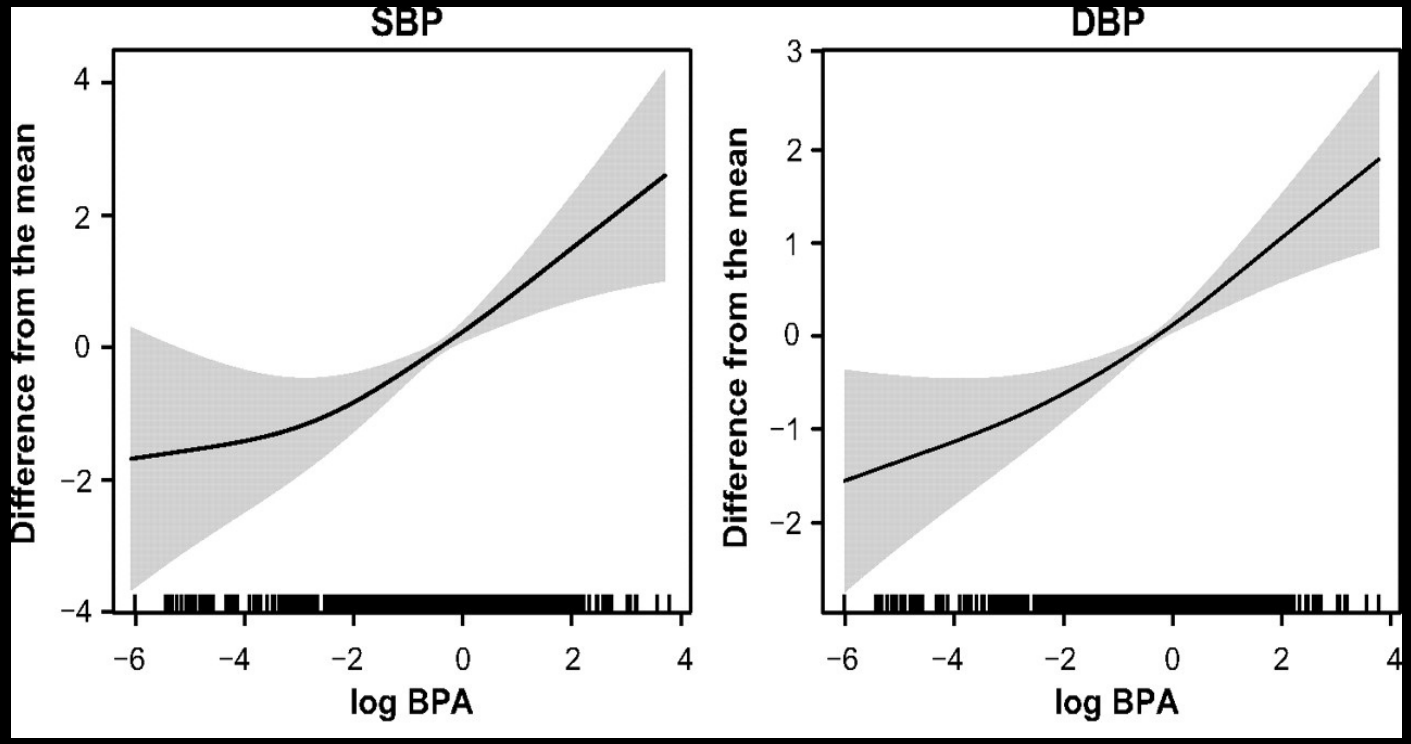
Clinical association of urinary BPA with CVD



Data from the National Health and Nutrition Examination Survey 2003-2004Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

Lang et al. (2008) JAMA

Clinical association of BPA with BP



Nonparametrical association of concentration of urinary BPA with blood pressure. Data were adjusted for sex, age, date of examination, height, weight, mean fast blood glucose, smoking status, current consumption of alcohol, and previous history of hypertension.

Bae et al. (2012) Hypertension

Exposure to bisphenol a from drinking canned beverages increases blood pressure: randomized crossover trial.

Variables	GG, n=60		CG, n=60		CC, n=60	
	Mean±SD	P	Mean±SD	P	Mean±SD	P
Urinary BPA, μg/L	1.13±1.76	Ref	7.93±6.01	<0.0001	16.91±12.55	<0.0001
Urinary BPA, μg/g Cre	1.25±2.26	Ref	9.43±5.01	<0.0001	20.65±8.61	<0.0001
SBP_{before}, mm Hg	134.9±18.2	Ref	135.8±18.4	0.5495	131.9±14.4	0.0846
SBP_{after}, mm Hg	127.0±14.0	Ref	128.2±16.0	0.4078	129.0±14.8	0.1889
ΔSBP, mm Hg	−7.9±14.3	Ref	−7.6±11.0	0.8484	−2.9±10.6	0.0160

•Compared using the paired *t* test. ΔDBP indicates DBP_{after}–DBP_{before}; ΔSBP, SBP_{after}–SBP_{before}; BP, blood pressure; BPA, bisphenol A; CC, 2 canned beverages; CG, 1 canned and 1 glass bottled beverages; GG, 2 glass bottled beverage; HRV, heart rate variability; RMSSD, root mean square of successive differences; SBP_{after} and DBP_{after}, systolic BP and diastolic BP measured 2 hours after consumption of the beverage; SBP_{before} and DBP_{before}, systolic BP and diastolic BP measured before consumption of the beverage; and SDNN, SD of normal-to-normal intervals.

Sanghyuk Bae, and Yun-Chul Hong Hypertension. 2015;65:313-319

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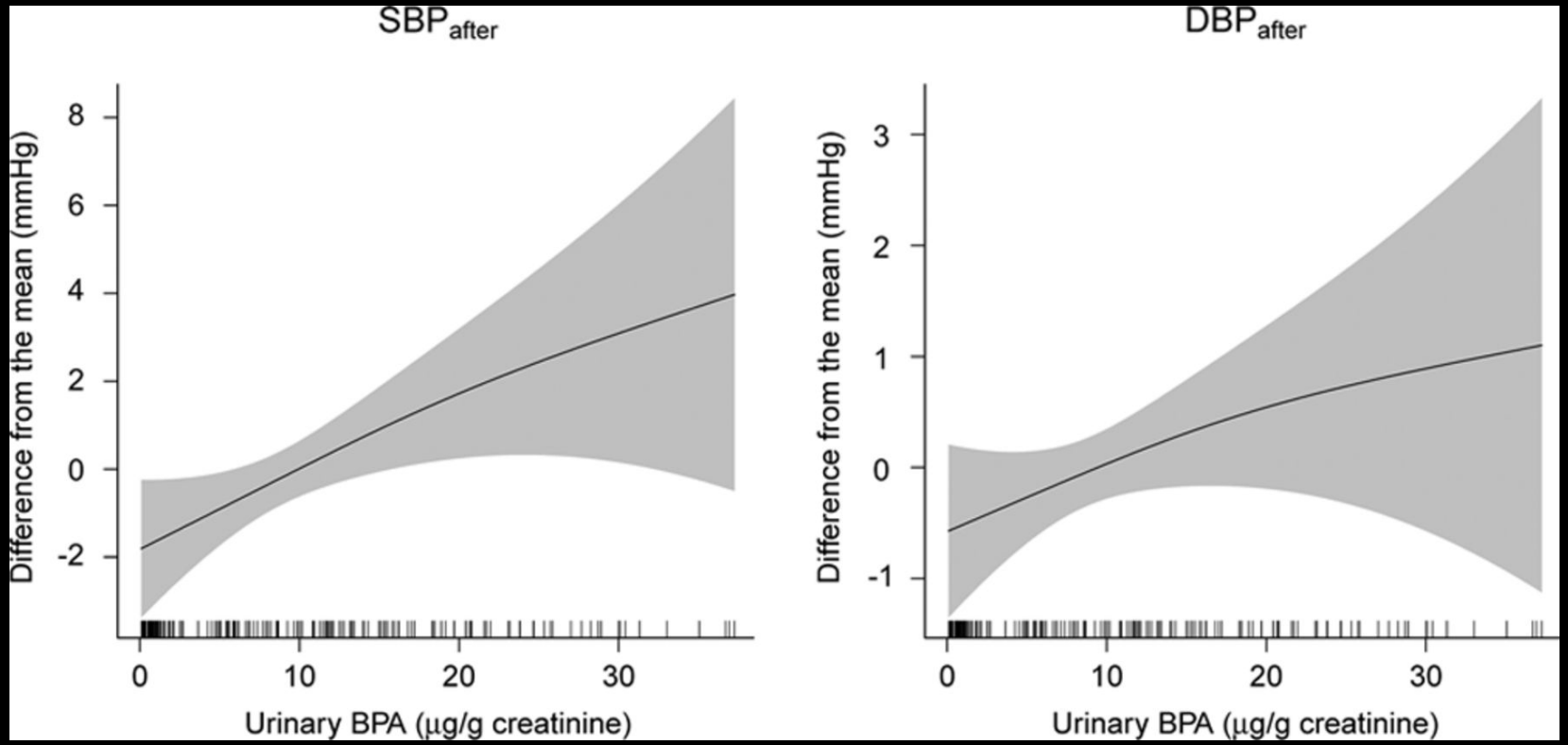
Nonparametric associations of urinary bisphenol A (BPA) concentration with systolic blood pressure (SBPafter) and diastolic blood pressure (DBPafter) in all observations.



Sanghyuk Bae, and Yun-Chul Hong Hypertension. 2015;65:313-319

American Heart Association.

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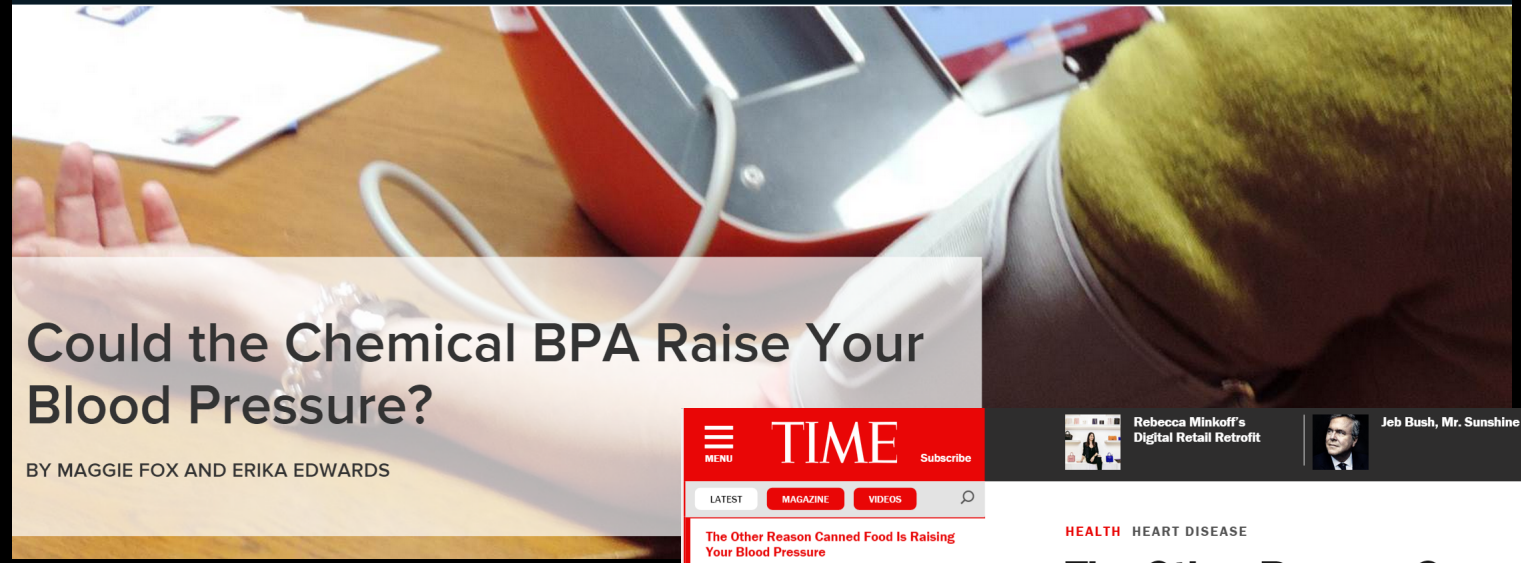

Could the Chemical BPA Raise Your Blood Pressure?

BY MAGGIE FOX AND ERIKA EDWARDS

http://www.wxyz.com/newsy/bpa-now-linked-to-increased-blood-pressure

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HEALTH HEART DISEASE

The Other Reason Canned Food Is Raising Your Blood Pressure

Alice Park @aliceparkny | Dec. 8, 2014

Forget sodium—BPA might be the real canned food villain

If your food or drink comes out of a can, chances are it's not the healthiest choice for your blood pressure (thanks to all that salt preserving your beans, for example.) But the latest research suggests there may be another reason to avoid canned goods. In a study published in *Hypertension*, researchers from South Korea found that drinking from cans, many of which have linings that contain the chemical bisphenol A (BPA), can raise blood pressure by 16 times compared to drinking from glass bottles.

The data isn't the first to implicate BPA as a potential health hazard. Previous studies have connected the chemical, which can be found in plastics, the linings of cans and coating some

Basic Characteristics of the Participants

Variables	Parameter
n	60
Age, y, mean±SD	73.1±4.2
Sex, female, n, %	56 (93.3)
Weight, kg, mean±SD	57.9±7.6
Hypertension, n, %	
Yes, with treatment	26 (43.3)
Yes, without treatment	1 (1.7)
No	33 (55.0)

Sanghyuk Bae, and Yun-Chul Hong Hypertension. 2015;65:313-319

American Heart Association.

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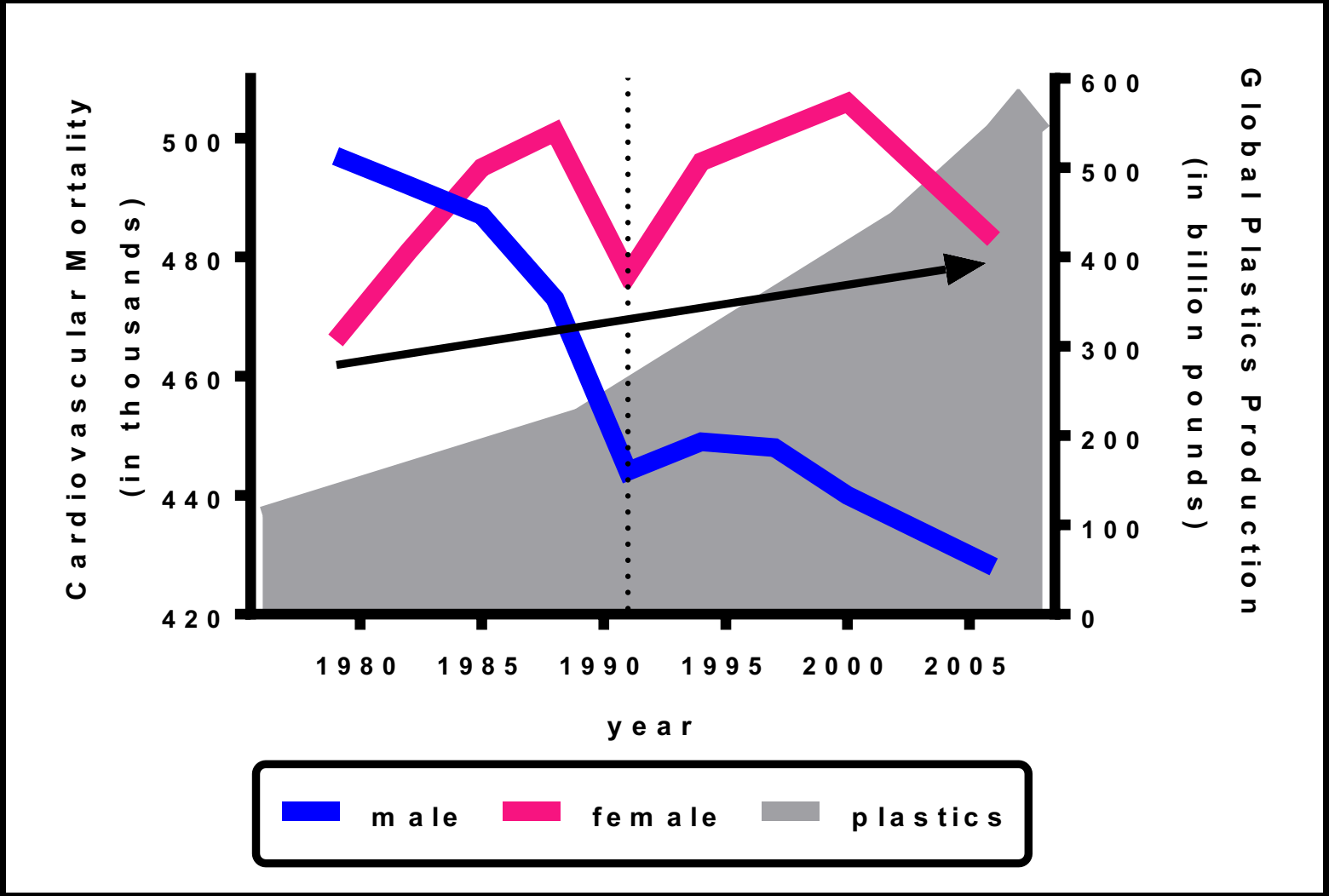
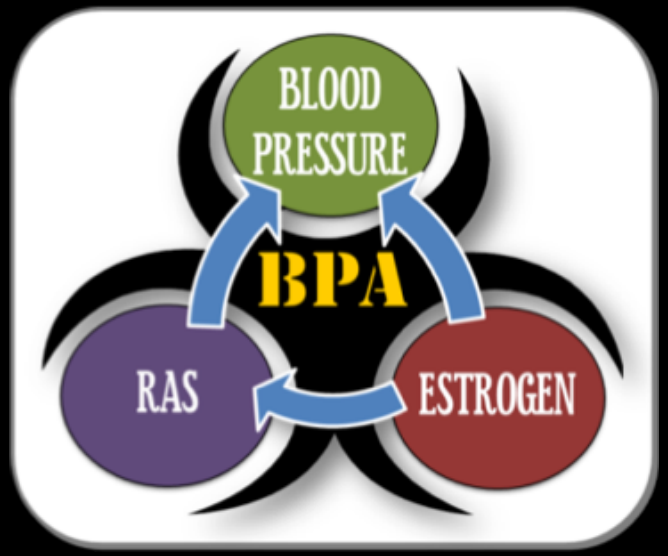
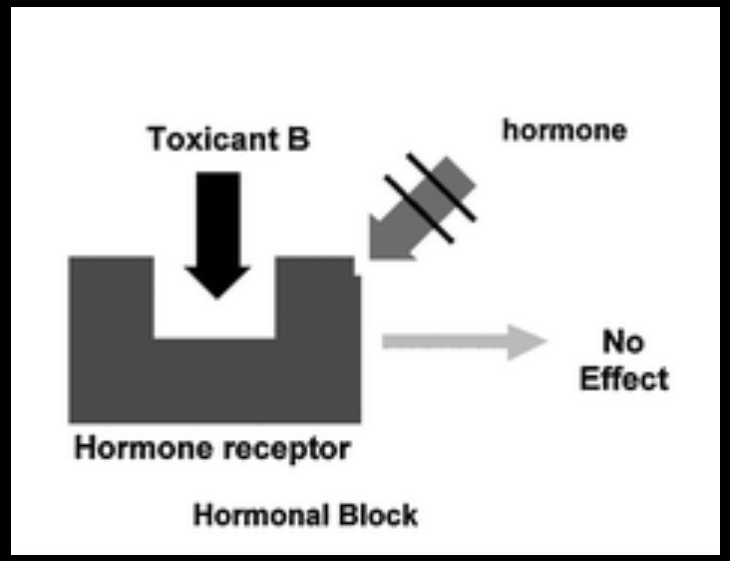
Treating male vs female CV disease



Hypothesis

- Our overall hypothesis is that BPA increases blood pressure in females by inhibiting GPER's beneficial effects on vascular function and the RAS.



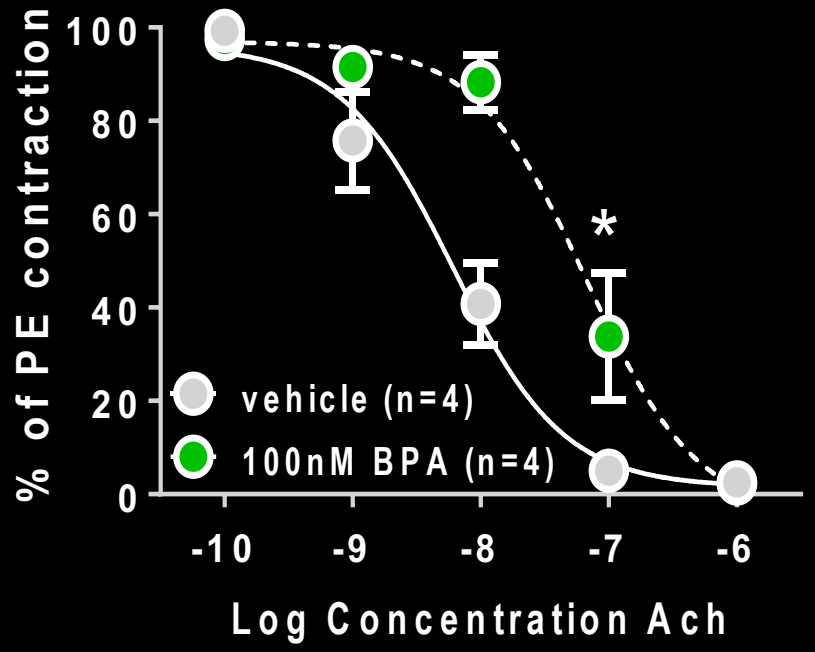


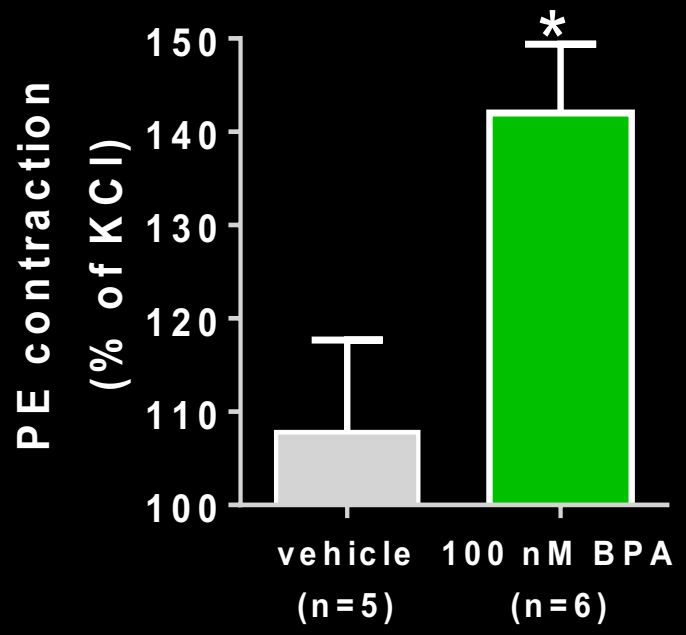
AHA Grant-in-Aid

The goal of this application is to elucidate how BPA impacts two key endocrine pathways involved in the regulation of blood pressure.

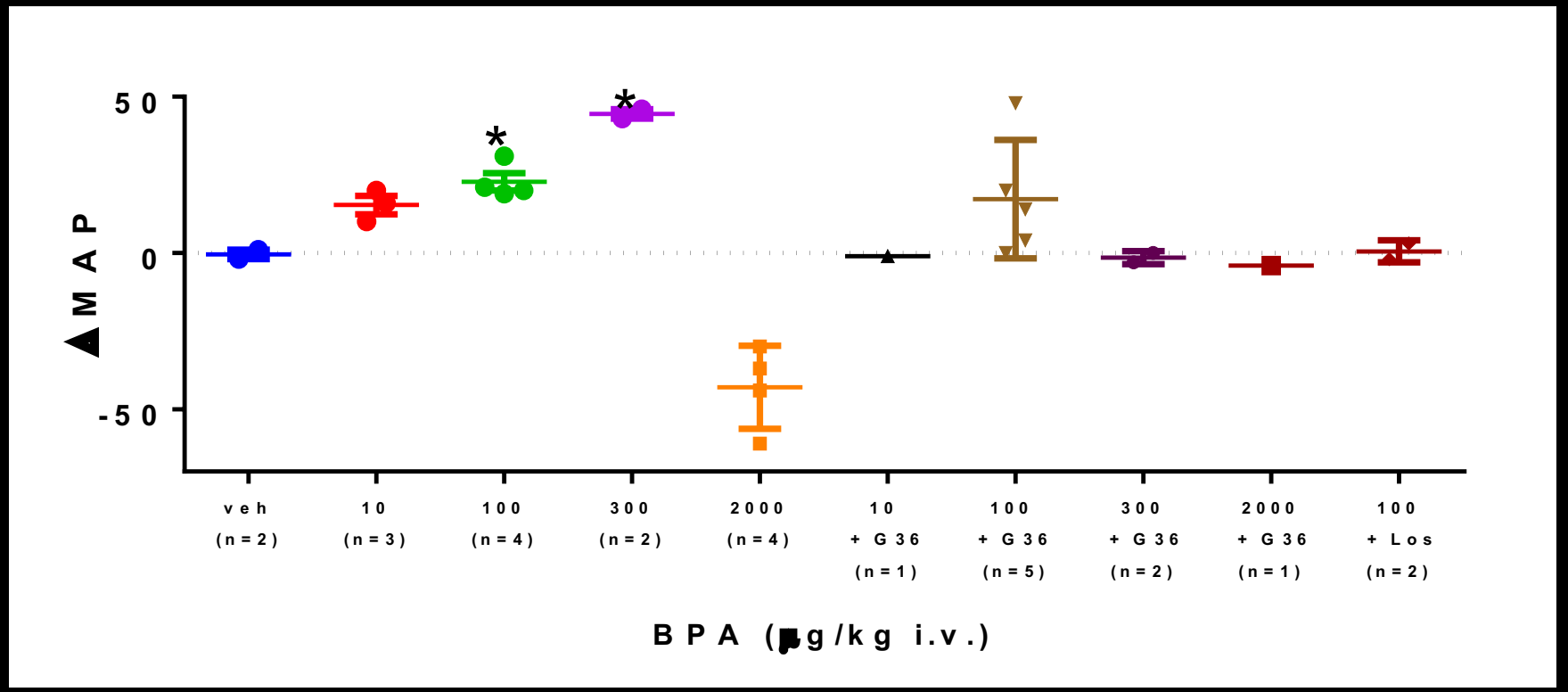
- Aim 1. Determine the vascular, hemodynamic, and RAS effects of BPA in females.
- Aim 2. Ascertain the role of GPER in these effects.

Acute vascular effects of BPA





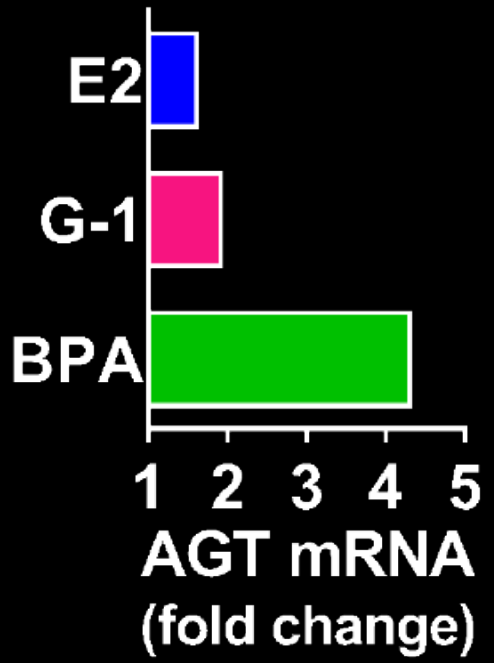
Hemodynamic changes in response to BPA

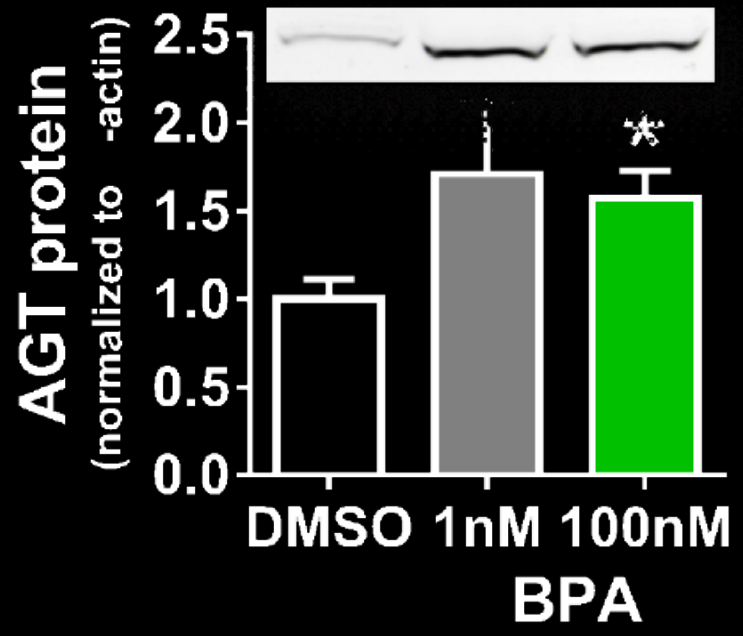


Emma Trimmer

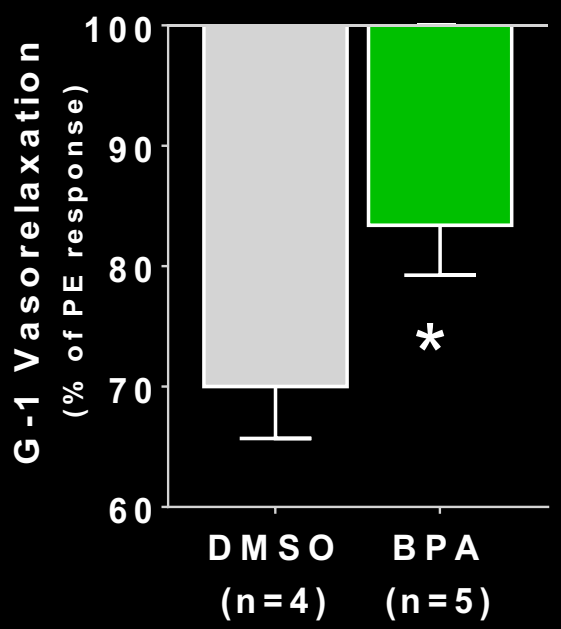
Phil Kadowitz

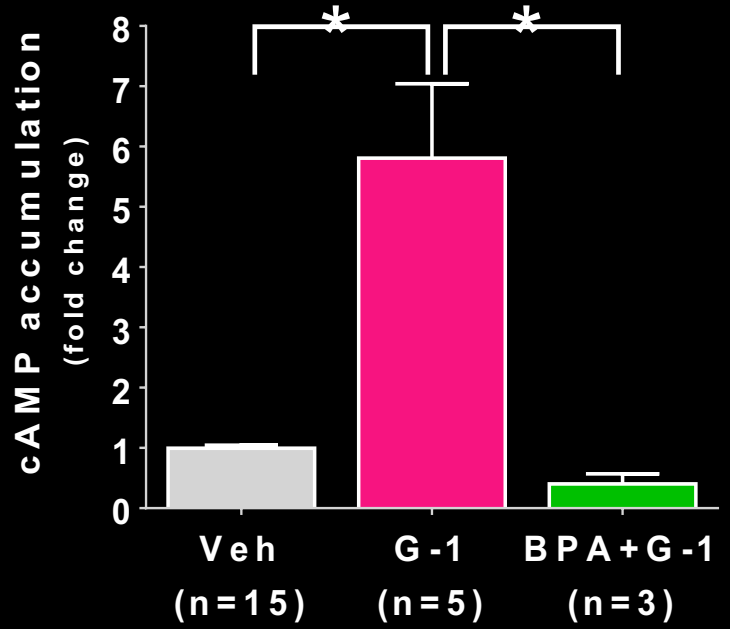
BPA regulates the vascular renin-angiotensin system



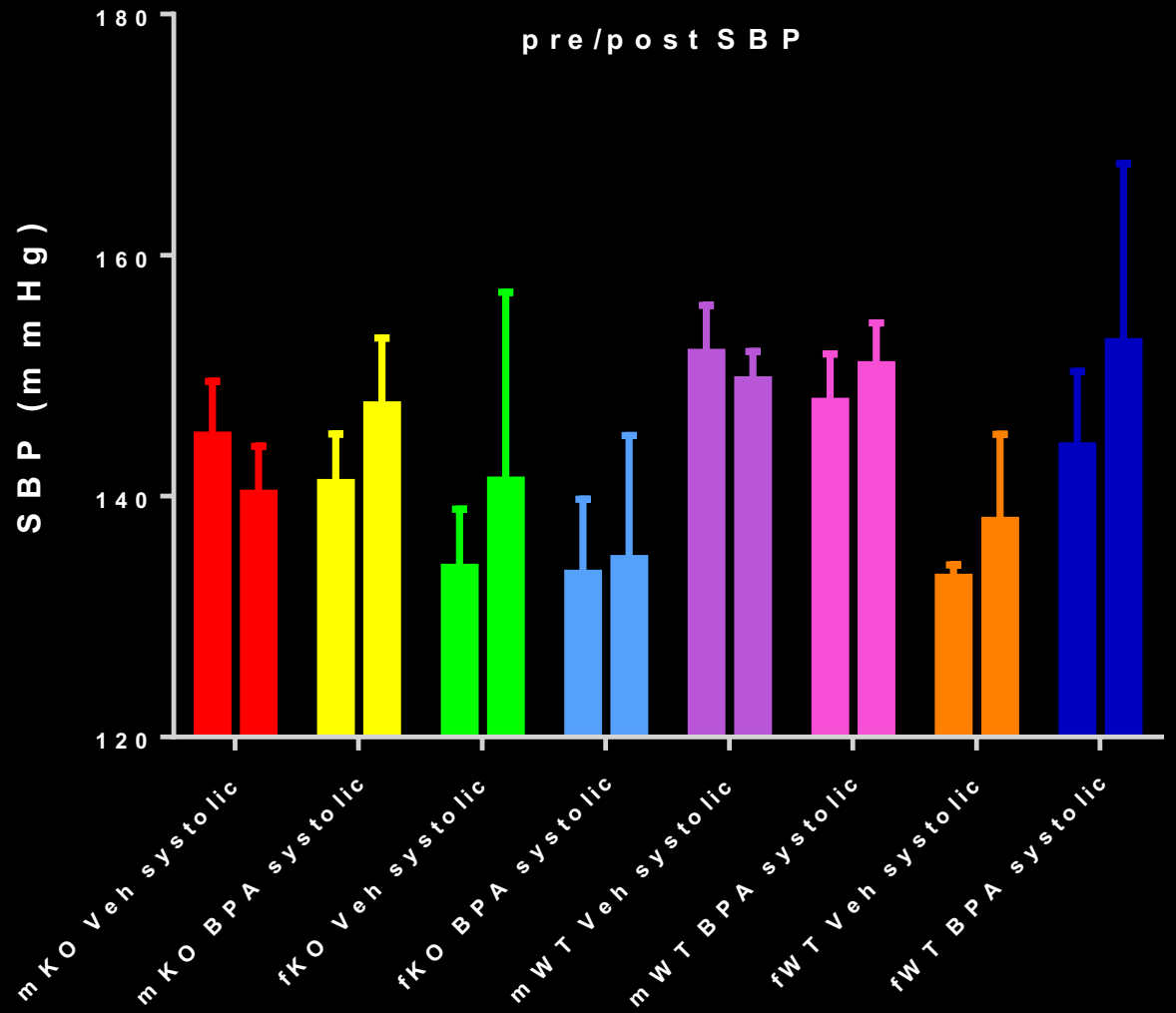


BPA attenuates GPER signaling



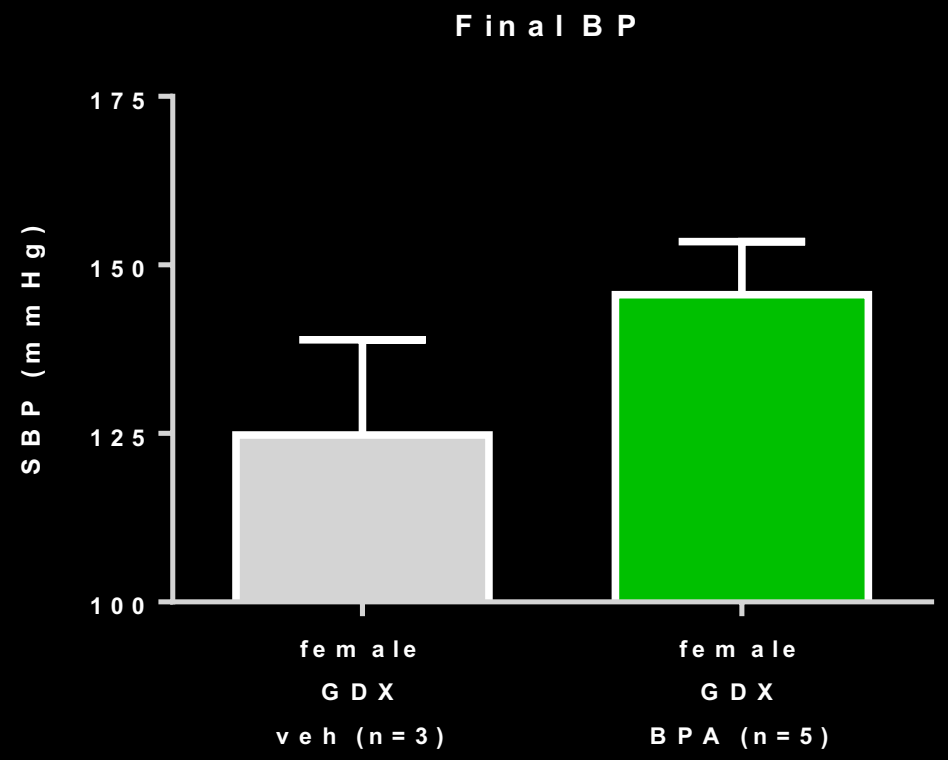


In vivo results show no increase in mouse BP

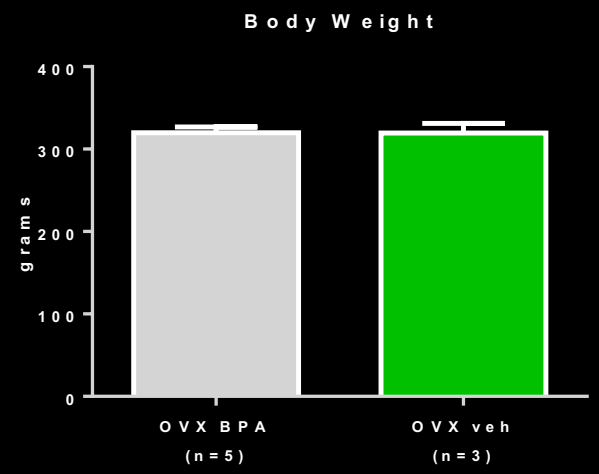


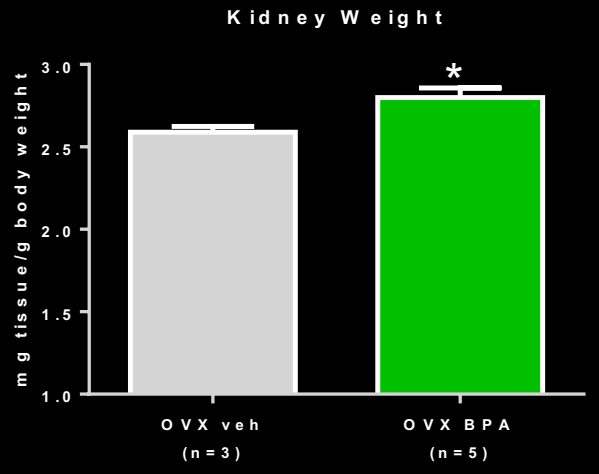
- OVX the animals?
- Different dose?
- Different environmental estrogen?

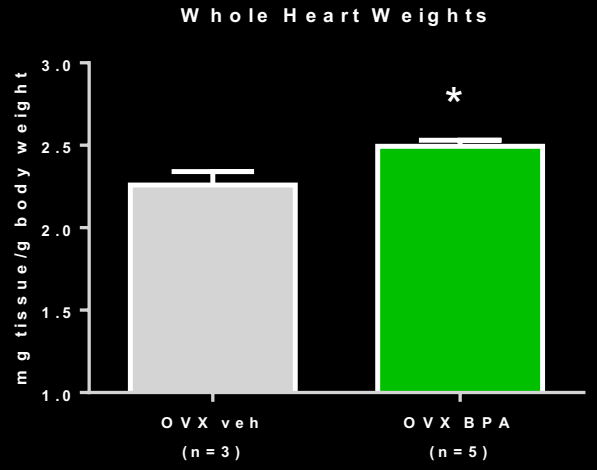
BPA does not increase BP in gonadectomized mRen2 females

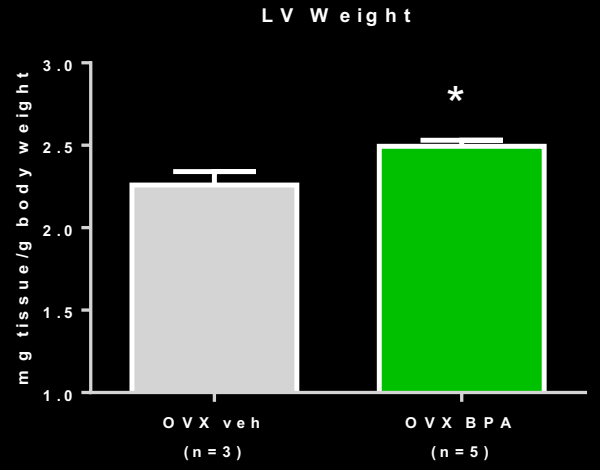


BPA increases tissue hypertrophy









Conclusions

- GPER may mediate some of the beneficial cardiovascular actions of estrogen.
- Environmental estrogens such as Bisphenol A may act as a "hormonal block" of GPER.
- Increasing amounts of environmental estrogens may promote cardiovascular problems, especially in aging postmenopausal women.

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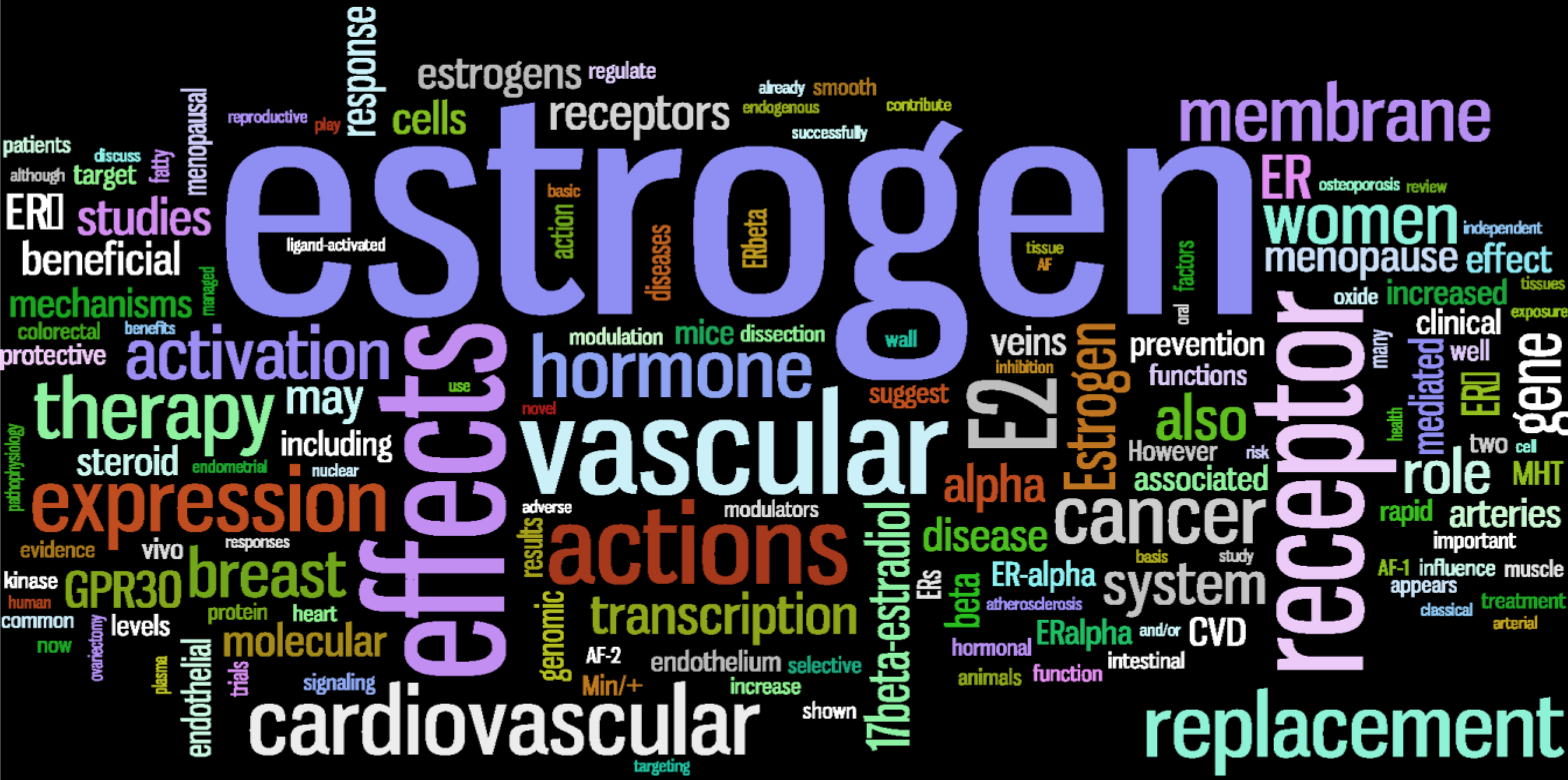
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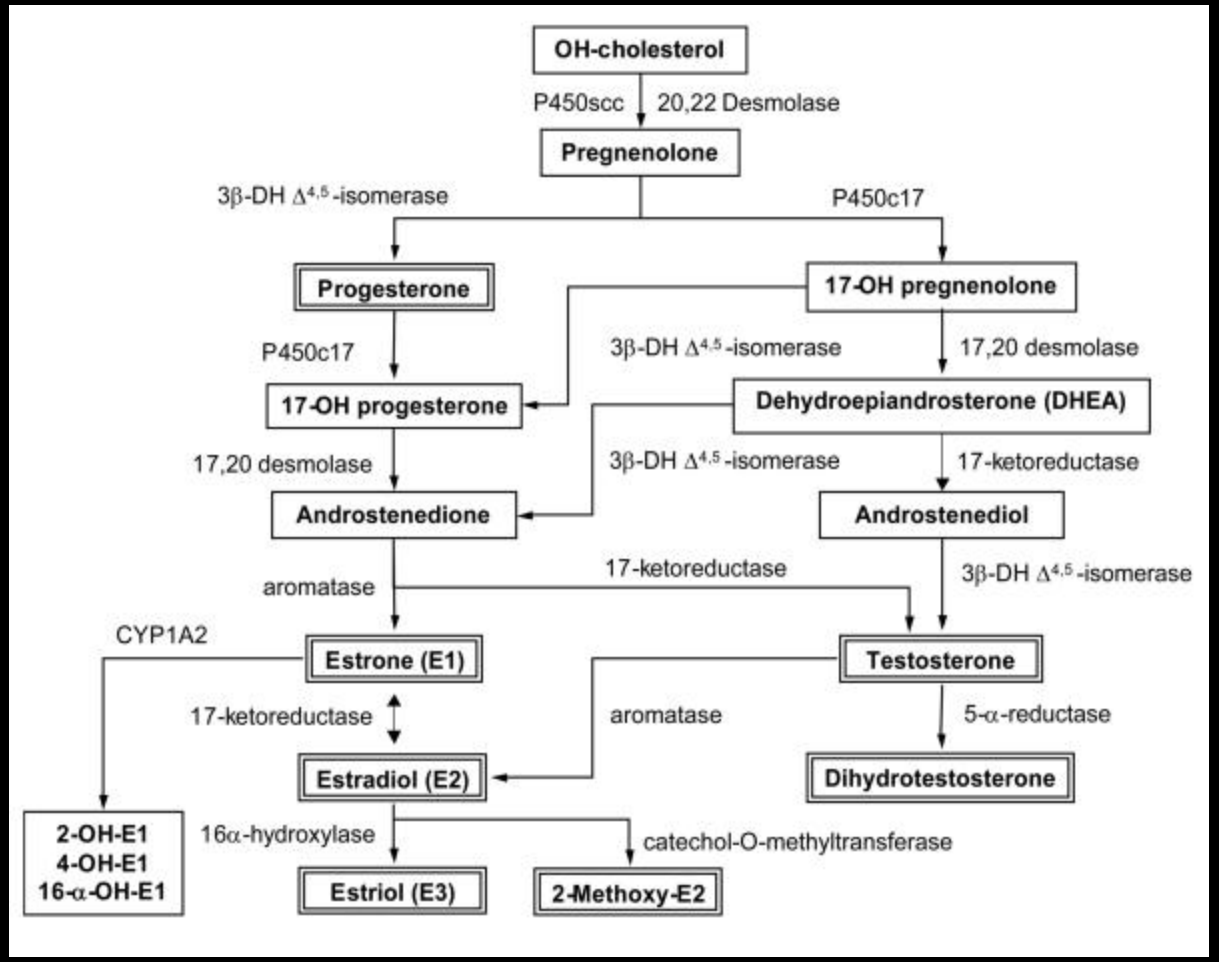
Thank you!

Sex Steroid Biosynthesis



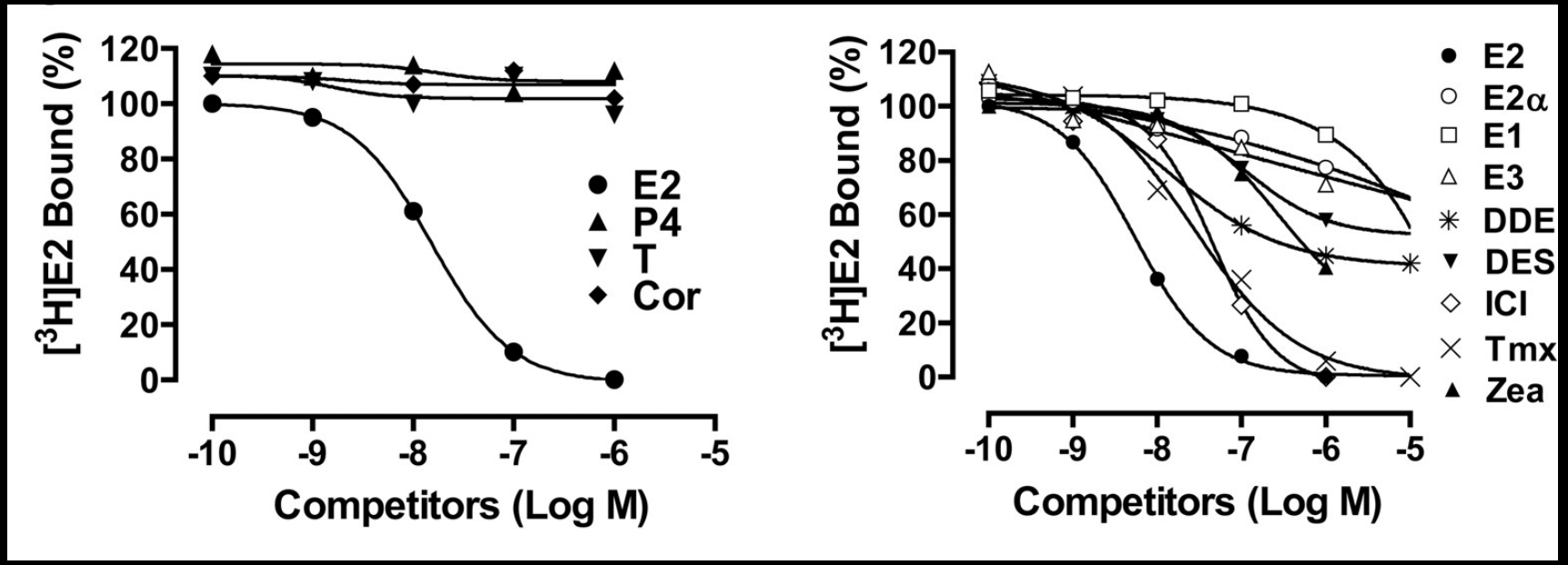
The JAMA Network

Table 1. Sample Characteristics Including Mean Bisphenol A Concentrations (N = 1455)

Characteristic	Unweighted, No.	Weighted	
		Percentage of Sample[a]	Mean BPA Concentration (95% CI), ng/mL
Sex			
Men	694	48.2	4.53 (3.98 to 5.08)
Women	761	51.8	4.66 (3.67 to 5.65)
Age group, y			
18-29	449	23.5	5.69 (4.74 to 6.64)
30-39	244	20.4	4.38 (3.20 to 5.57)
40-49	252	22.8	4.17 (3.18 to 5.16)
50-59	182	17.7	4.98 (3.85 to 6.12)
60-74	328	15.7	3.41 (2.41 to 4.41)
Race/ethnicity			
Mexican American	324	8.5	4.45 (3.48 to 5.41)
Other Hispanic	57	4.3	4.74 (2.86 to 6.62)
Non-Hispanic white	690	69.2	4.45 (3.73 to 5.17)
Non-Hispanic black	313	11.6	6.50 (5.45 to 7.55)
Other (including multiracial)	71	6.4	2.83 (2.03 to 3.63)
Level of education			
Less than high school diploma	430	18.1	5.00 (3.99 to 6.00)
High school diploma (including GED)	356	25.9	4.91 (4.02 to 5.80)
Some college education	669	56.1	4.32 (3.57 to 5.07)
Household annual income			
<$25 000	457	21.8	5.38 (4.19 to 6.58)
$25 000-$55 000	457	32.2	5.25 (4.38 to 6.11)
>$55 000	449	41.0	3.72 (3.08 to 4.37)
Unknown	92	5.0	4.11 (2.51 to 5.71)
BMI[b]			
Low weight (<18.5)	31	2.1	3.81 (2.86 to 4.77)
Recommended weight (18.5-24.9)	469	33.6	3.91 (3.34 to 4.48)
Overweight (25.0-29.9)	448	30.4	4.18 (3.43 to 4.92)
Obese I (30.0-34.9)	283	20.0	5.10 (3.97 to 6.24)
Obese II (≥35)	199	12.2	6.93 (4.39 to 9.47)
Unknown	25	1.6	3.89 (1.86 to 5.92)
Cigarette smoking			
Never smoked[c]	640	48.8	4.37 (3.52 to 5.22)
Former smoker	311	22.6	4.53 (3.82 to 5.24)
Some days	63	4.4	3.72 (3.00 to 4.44)
Every day	264	20.5	5.00 (3.88 to 6.12)
Unknown	177	3.8	6.69 (5.59 to 7.79)

Abbreviations: BMI, body mass index; BPA, bisphenol A; CI, confidence interval; GED, General EducationalDevelopment.
[a] Percentages may not sum to 100 because of rounding.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Included those who had ever smoked <100 cigarettes.

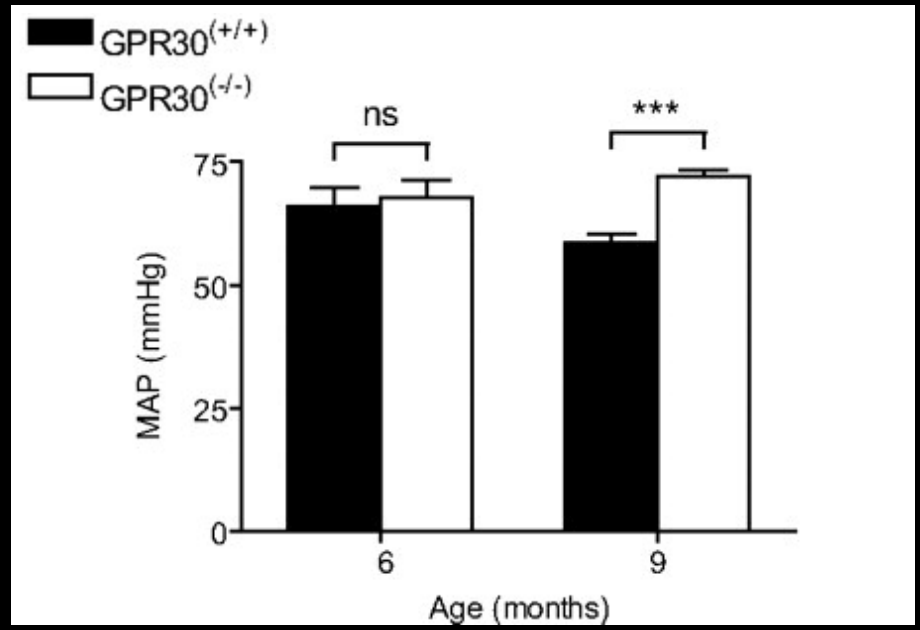
Estrogen binding characteristics of plasma membranes from SKBR3 cells (ERα-, ERβ-, GPR30+).



Thomas et al. (2005) Endocrinology

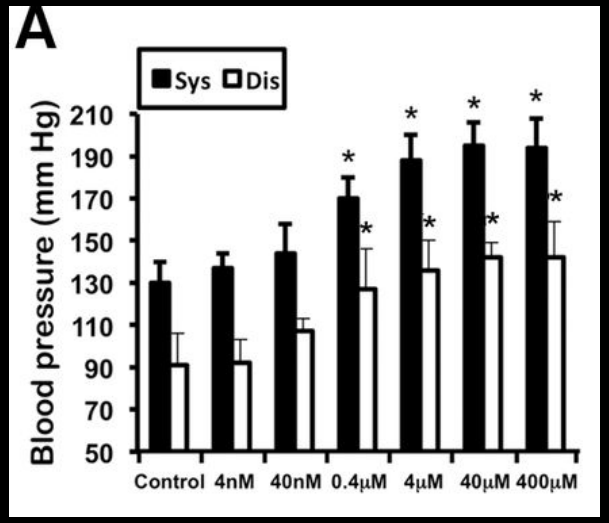
GPER knockout mice

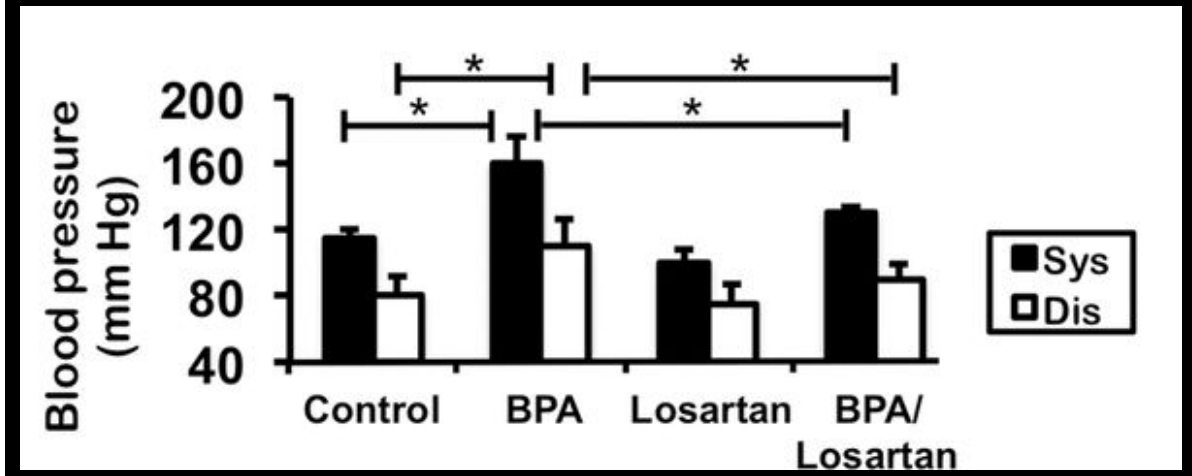
- Four models of GPR30 deficiency
- No reproductive abnormalities
- Reduced skeletal growth
- Increased visceral fat
- Thymic biology, decreased T cells
- Increased vascular tone
- Decreased glucose tolerance and insulin release

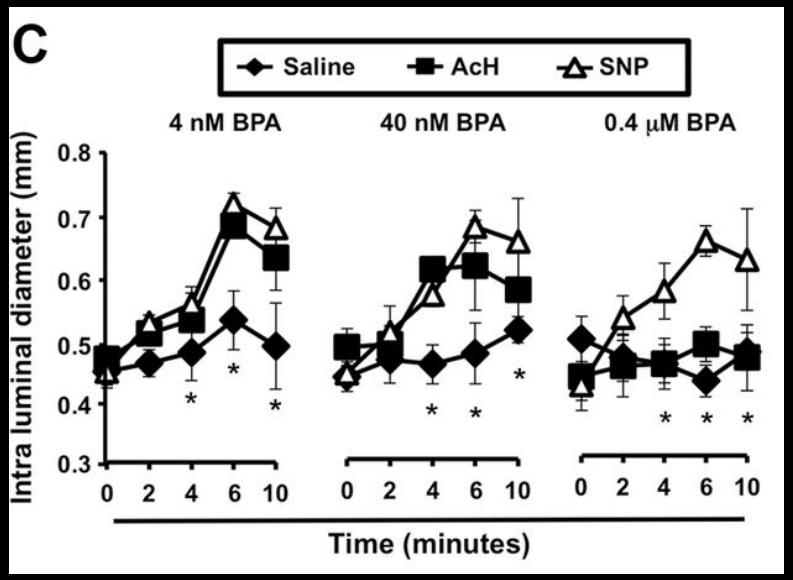


Mårtensson et al. (2009) Endocrinology

Oral administration of bisphenol A induces high blood pressure through angiotensin II/CaMKII-dependent uncoupling of eNOS.







- BPA induces the expression of eNOS and inhibits the production of NO.
- BPA induces eNOS-dependent production of superoxide and peroxynitrite.

Saura M et al. FASEB J 2014;28:4719-4728 The FASEB Journal