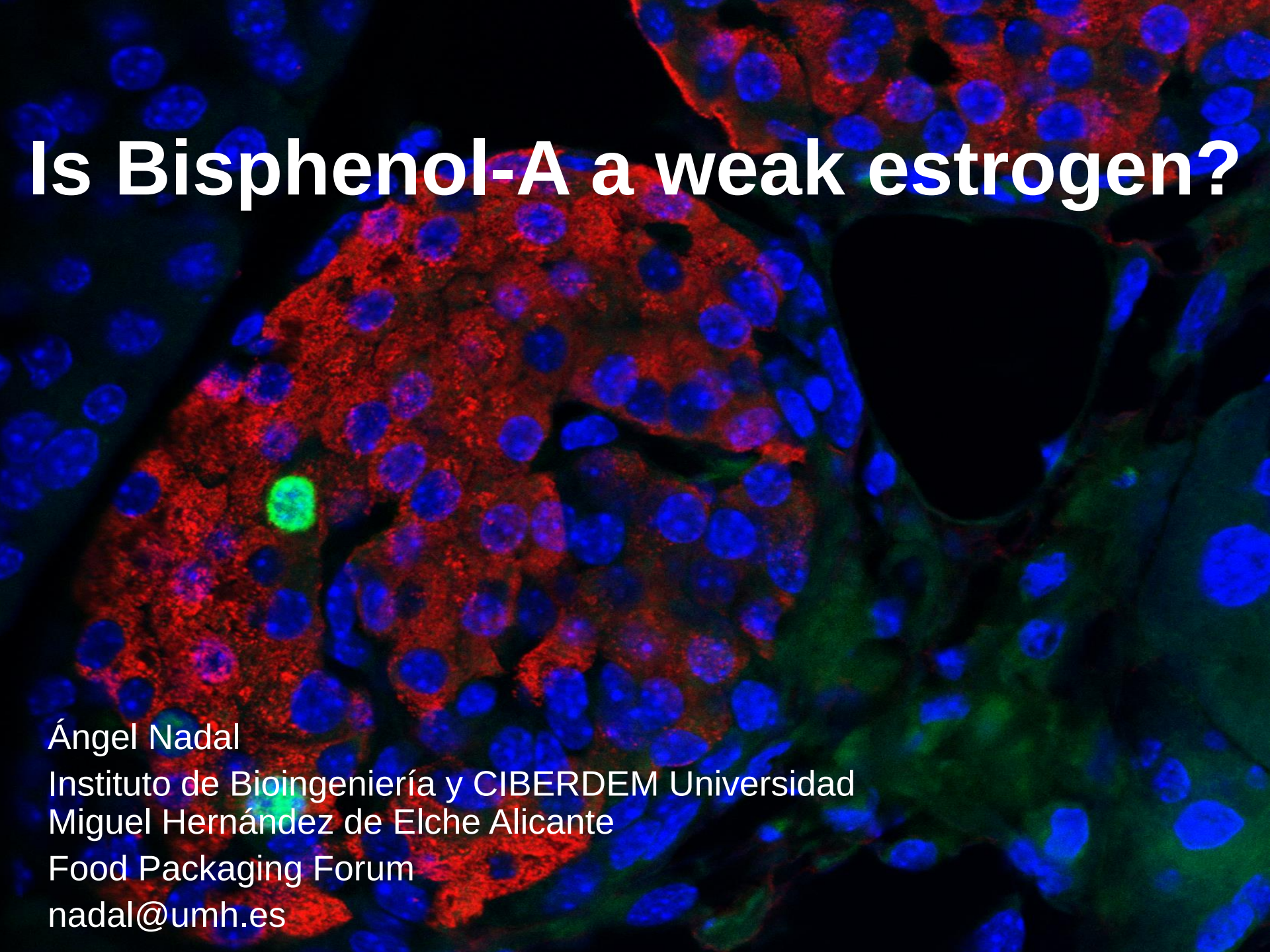
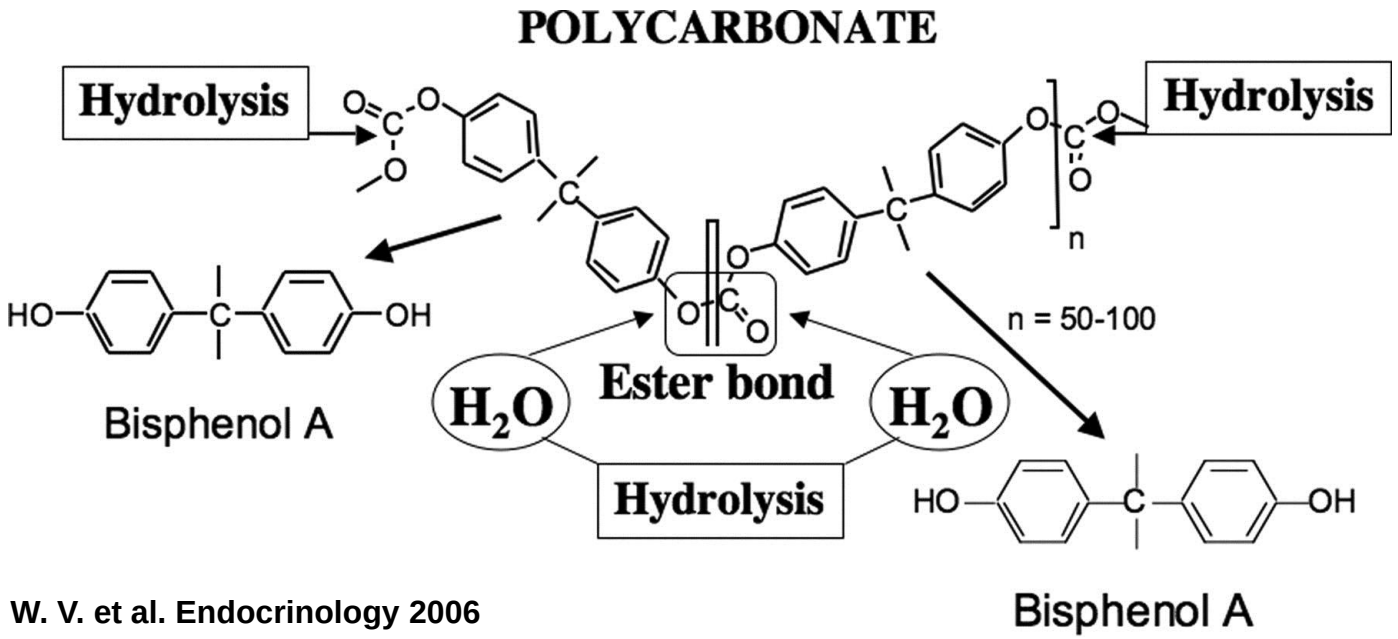
Is Bisphenol-A a weak estrogen?



Ángel Nadal
Instituto de Bioingeniería y CIBERDEM Universidad Miguel Hernández de Elche Alicante
Food Packaging Forum
nadal@umh.es



Welshons, W. V. et al. Endocrinology 2006

BISPHENOL-A is found in urine of 93% US citizens (Calafat et al, EHP 2008)

BISPHENOL-A CONCENTRATION IN HUMAN SERUM:

0.3-4 ng/ml (1.3-18 nM) unconjugated BPA in serum from adult men and women (Vandenberg et al, EHP 2010)

BISPHENOL-A EXPOSURE LEVELS OF HUMANS:

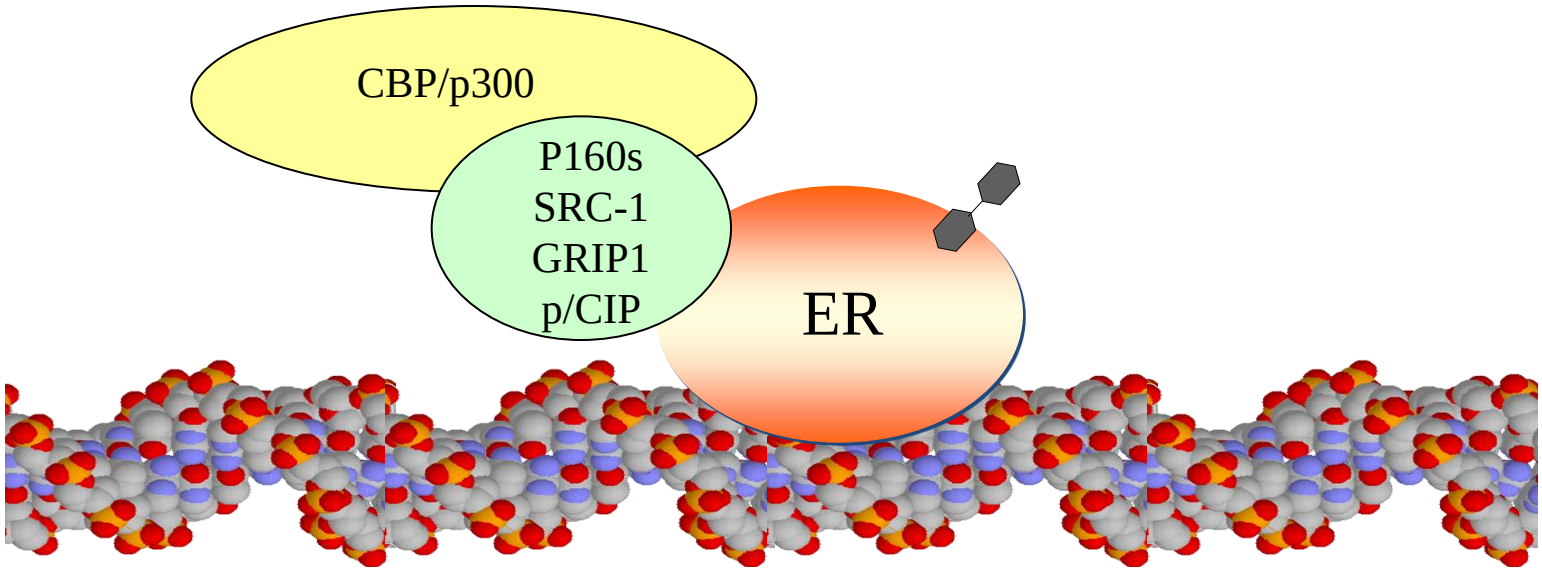
0.07-12 µg/kg bw/day
Joint Research Center. Institute for Health and Consumer Protection. European Commission.

500 µg/kg bw/day
Based in Pharmacokinetic experiments in monkeys (Taylor et al, EHP 2011).

Nonfood exposure (Stahlhut et al, EHP 2009; Zalco et al, Chemosphere 2011)

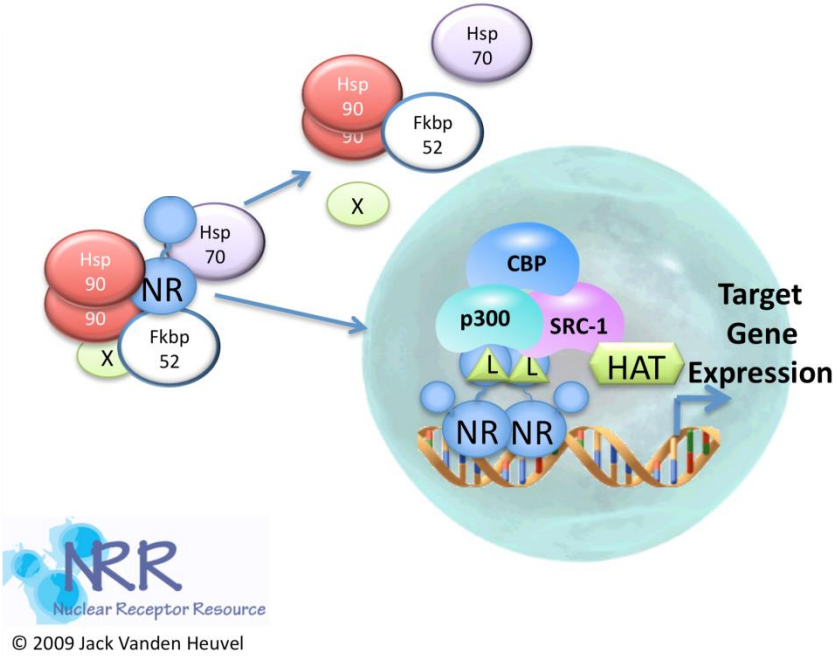
Environmental estrogens are endocrine disrupters that mimick 17β-estradiol actions

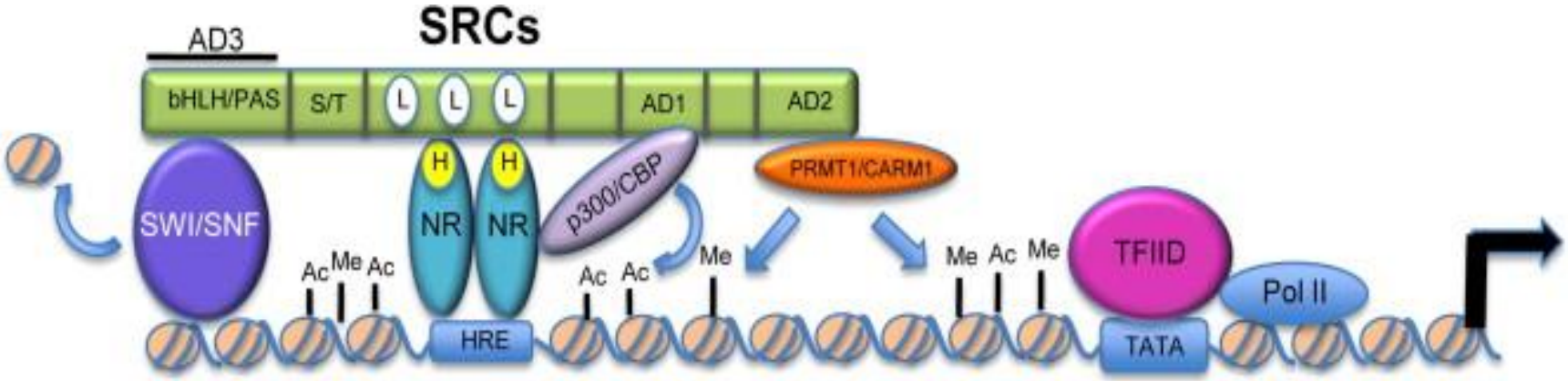
The concept of estrogenicity of an exogenous chemical is based on the property of these compounds to bind ERα and ERβ, and to act subsequently as transcription factors when binding to the ERE in the DNA



Matthews JB, Twomey K, Zacharewski TR. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chem Res Toxicol 2001;14(2):149-157.

A. Steroid hormone receptors
(AR, ER, GR, MR)





Amber B. Johnson , Bert W. O'Malley, Molecular and Cellular Endocrinology 348, 2012 430 - 439

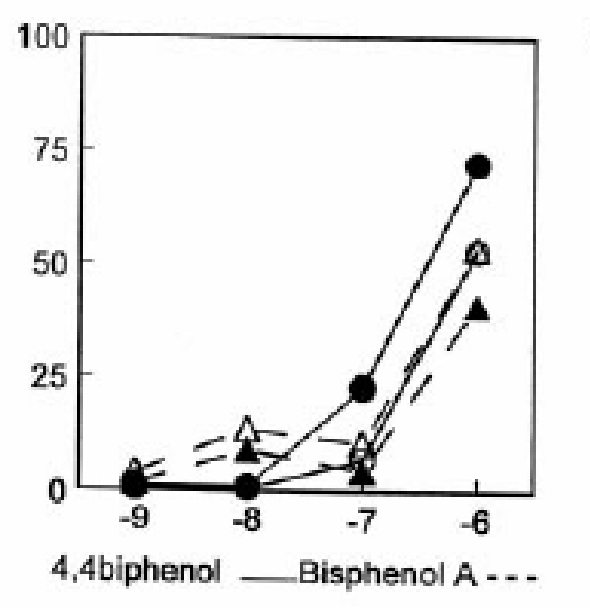


FIG. 4. Activation of transcription by various estrogenic chemicals and phytoestrogens. The experiment (two different experiments with each point in triplicate) were done as described in *Materials and Methods*. ERα = ○ or △ and ERβ = ● or ▲. Abscissa, log M of compound; ordinate, transcriptional activity as percentage of the maximal induction by E_2 for each ER subtype.

TABLE 1. RBA of suspected environmental endocrine disruptors for ERα and ERβ from solid-phase (Scintistrip) competition experiments

Compound	RBA[a]	
	ERα	ERβ
17β-estradiol	100	100
17α-estradiol	7	2
Diethylstilbestrol	236	221
4-*tert*-amylphenol	<0.01	<0.01
4-*tert*-octylphenol	0.01	0.03
4-octylphenol	0.02	0.07
Nonylphenol	0.05	0.09
Bisphenol A	0.01	0.01
Methoxychlor	<0.01	<0.01
Endosulfan	<0.01	<0.01
Chlordecone	0.06	0.1
4,4′-biphenol	<0.01	0.03

[a] RBA of each competitor was calculated as ratio of concentrations of E_2 or competitor required to reduce the specific radioligand binding by 50% (= ratio of IC_{50} values). RBA value for E_2 was arbitrarily set at 100.

"Bisphenol-A has an affinity 10,000-fold lower than that of E2 for both ER subtypes"

"The estrogenic potency of Bisphenol-A *in vitro* is 1000 to 5000 fold lower than that of E2…"

Kuiper et al, Endocrinology 1998

0013-7227/97/$03.00/0
Endocrinology

Vol. 138, No. 5
Printed in U.S.A.

The Environmental Estrogen Bisphenol A Stimulates Prolactin Release *in Vitro* and *in Vivo**

ROSEMARY STEINMETZ, NANCY G. BROWN, DONALD L. ALLEN, ROBERT M. BIGSBY, AND NIRA BEN-JONATHAN

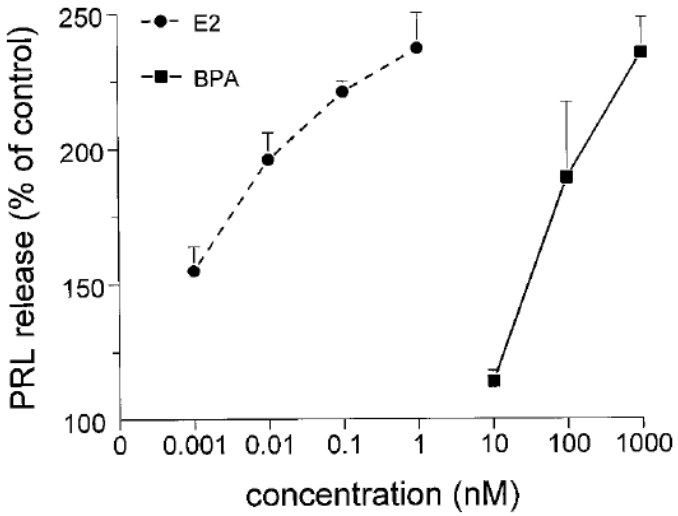


FIG. 2. Concentration-dependent stimulation of PRL release from primary anterior pituitary cells by E_2 and BPA. Cells were harvested from OVEX F344 rats and plated at 2.5×10^4 cells/well. After culturing in SFM for 4 days, the cells were incubated with BPA or E_2 for 3 days. Control cells were incubated with vehicle. Media aliquots were analyzed in duplicate for PRL by RIA. Each value is a mean ± SEM of five replicates. Data shown are representative of three experiments.

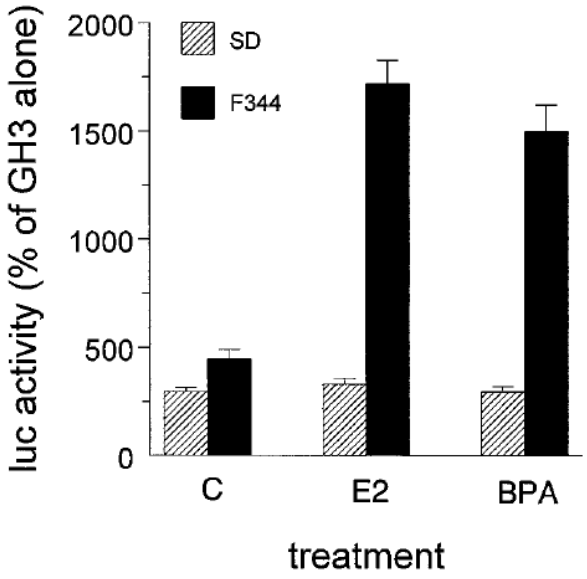
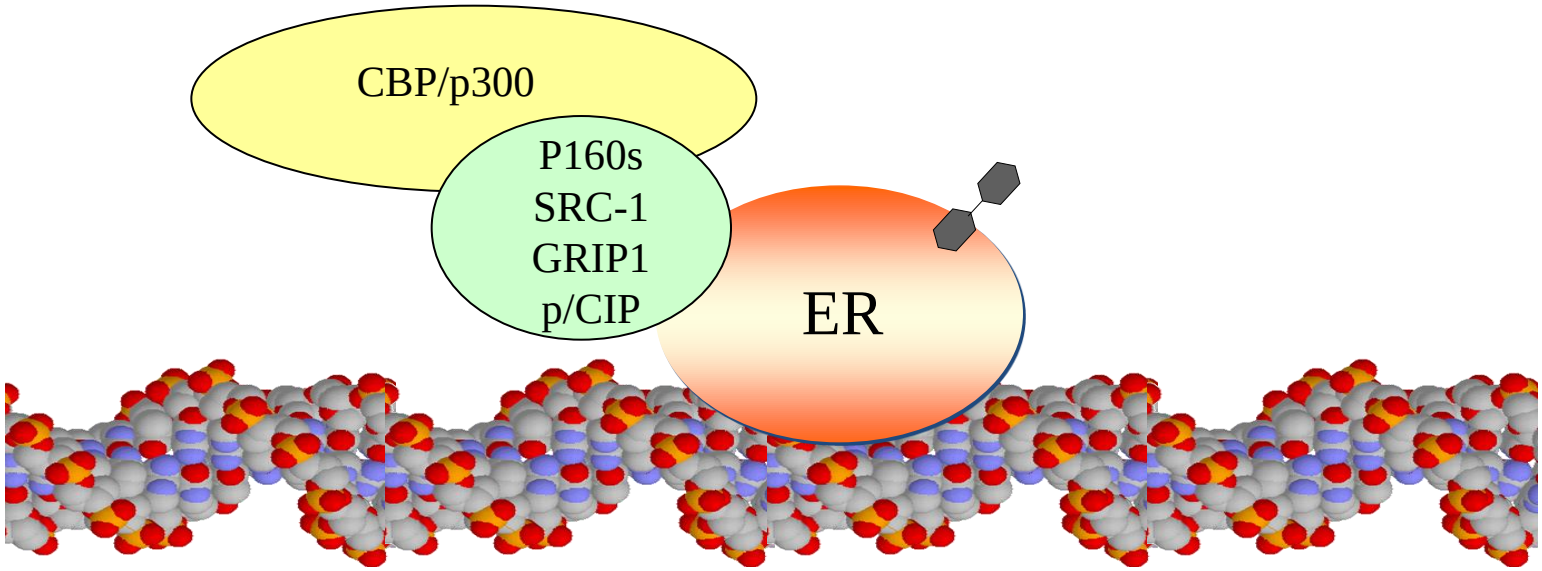


FIG. 7. Increased PRF activity in posterior pituitary cells from F344, but not SD rats, pretreated with E_2 or BPA for 3 days. Posterior pituitary cells, harvested from rats treated as in Fig. 5, were plated at 1×10^4 cells/well in SFM. After 4 days, the cells were cocultured for 24 h with GH3/*luc* cells (2×10^4 cells/well). Luciferase activity was determined in cell lysate and normalized for cell density, determined in parallel plates by MTT assay. Increased luciferase activity above GH_3 cells incubated alone indicates basal PRF activity. Each value is a mean ± SEM of 12 determinations from three separate experiments.

The concept of estrogenicity of an exogenous chemical is based on the property of these compounds to bind ERα and ERβ, and to act subsequently as transcription factors when binding to the ERE in the DNA



Matthews JB, Twomey K, Zacharewski TR. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chem Res Toxicol 2001;14(2):149-157.

Membrane estrogen receptors identified by multiple antibody labeling and impeded-ligand binding

TODD C. PAPPAS,* BAHIRU GAMETCHU,† AND CHERYL S. WATSON*,1

*Department of Human Biological Chemistry and Genetics, University of Texas, Medical Branch, Galveston, Texas 77555-0645, USA; and †Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA

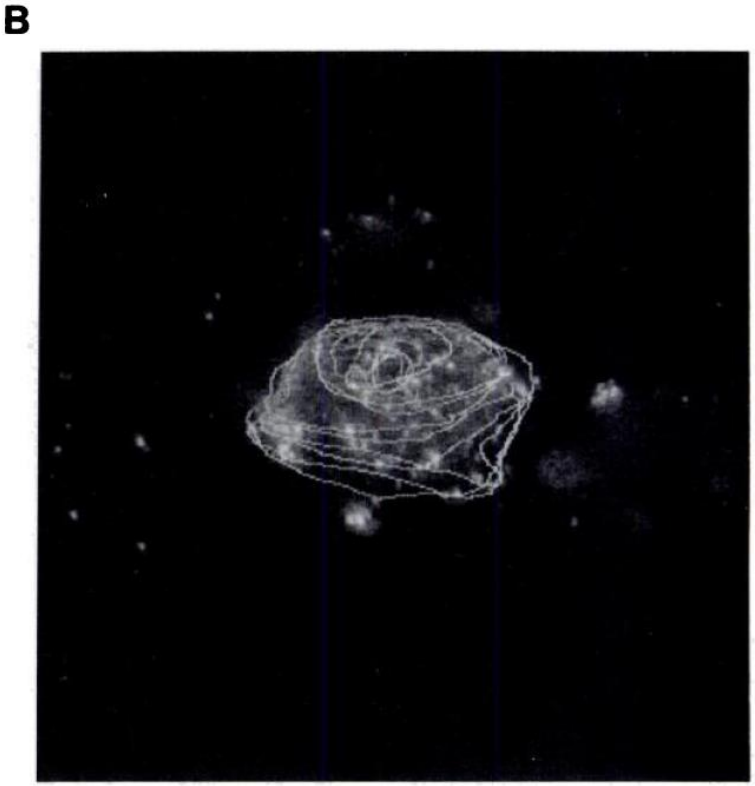


Figure 2. Serial sections show that anti-ER antibody (R3) localizes with the perimeter of the cell. A well-attached cell with punctate labeling and peripheral antigen localization is shown using five sections along the z axis (1–5) and with a reconstructed image (*B*) rotated 30° from horizontal.

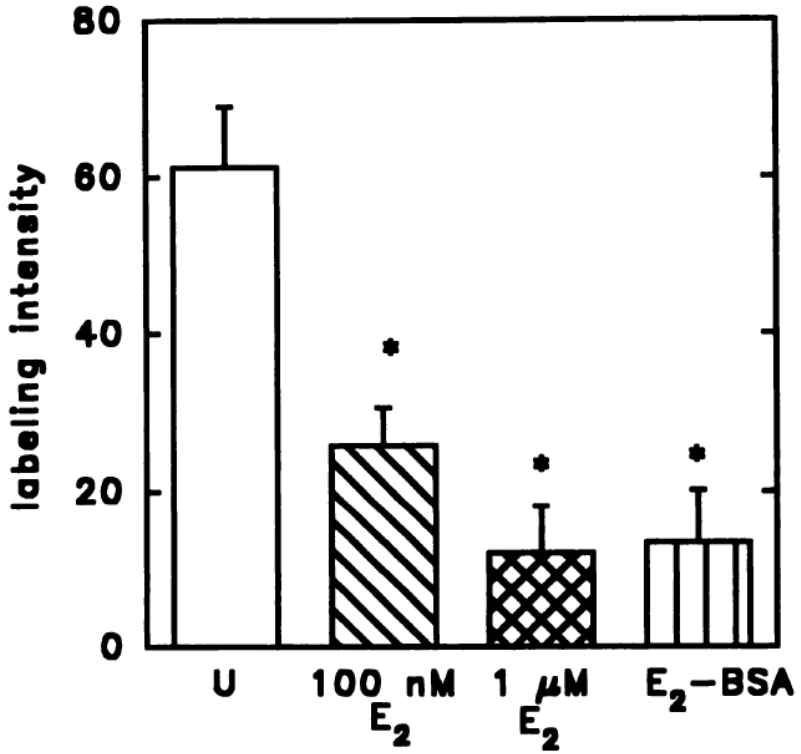
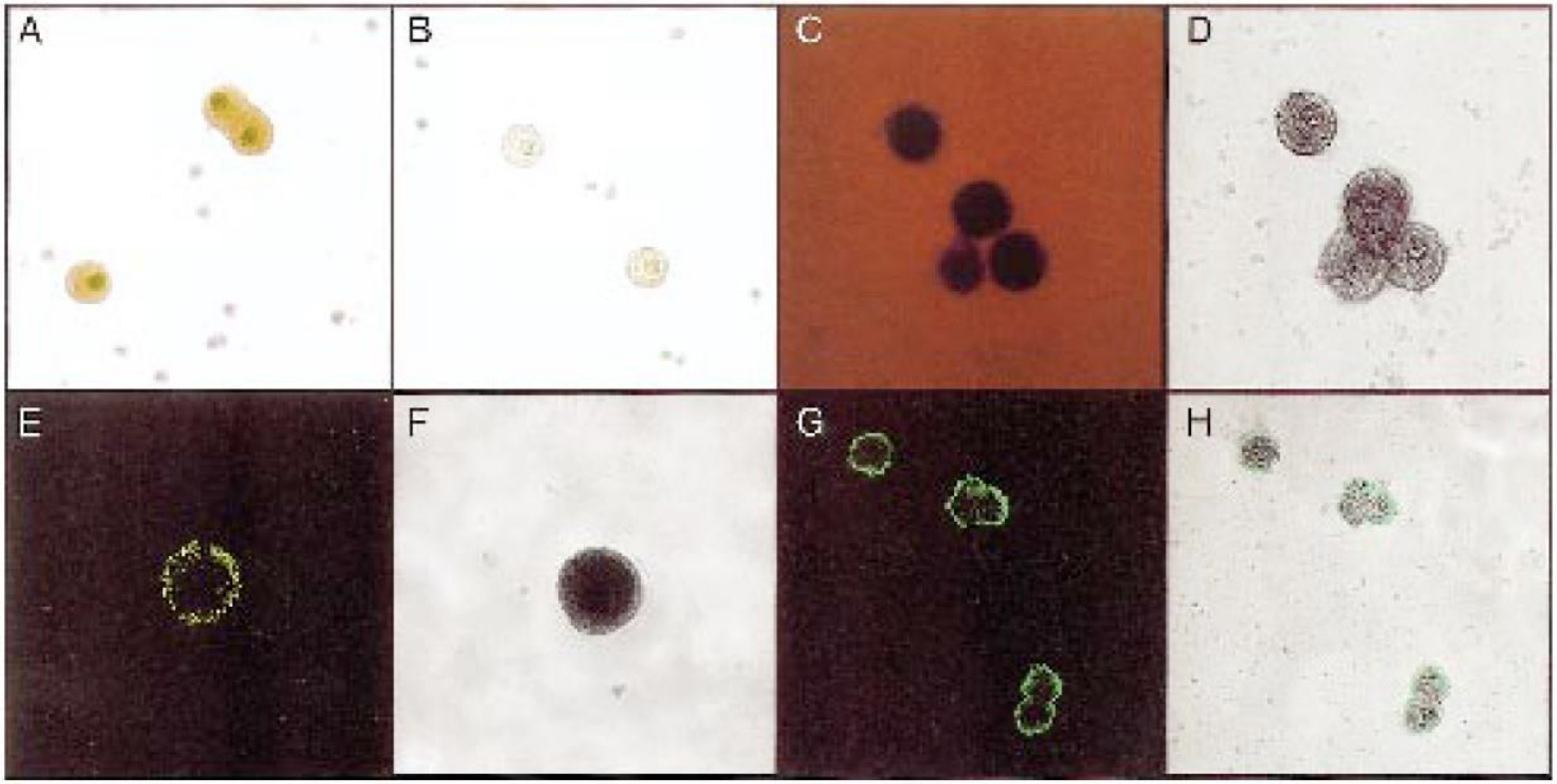


Figure 6. E_2-BSA-FITC binds to the surface of immuno-enriched GH_3/B6 cells in an estrogen-specific manner. Labels on the x-axis indicate amount of competitor added; U = uncompeted E_2-BSA-FITC; E_2BSA = 10-fold excess unlabeled E_2-BSA. Data are from four experiments; error bars are SEM.

Rapid insulinotropic effect of 17β-estradiol via a plasma membrane receptor

ANGEL NADAL,[1] JUAN M. ROVIRA, OUAHIBA LARIBI, TRINIDAD LEON-QUINTO, ETELVINA ANDREU, CRISTINA RIPOLL, AND BERNAT SORIA

Institute of Bioengineering and Department of Physiology, Miguel Hernández University, San Juan Campus, Alicante, Spain

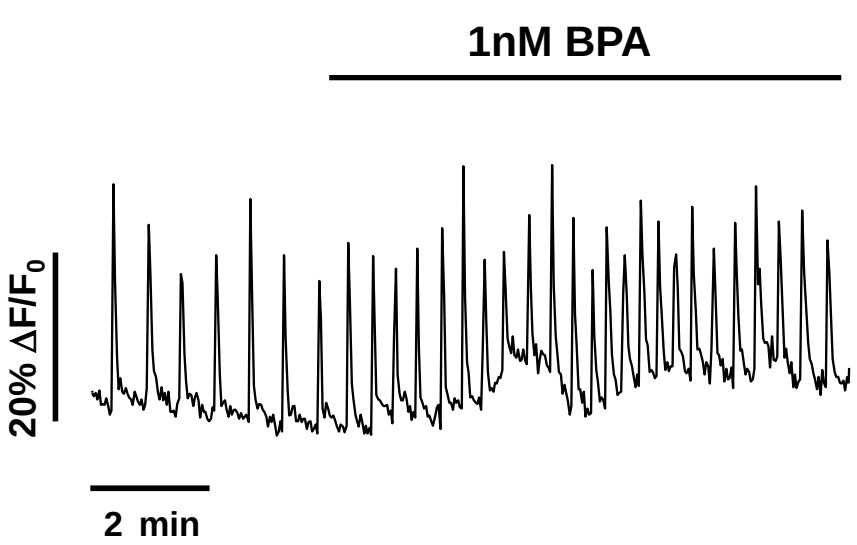


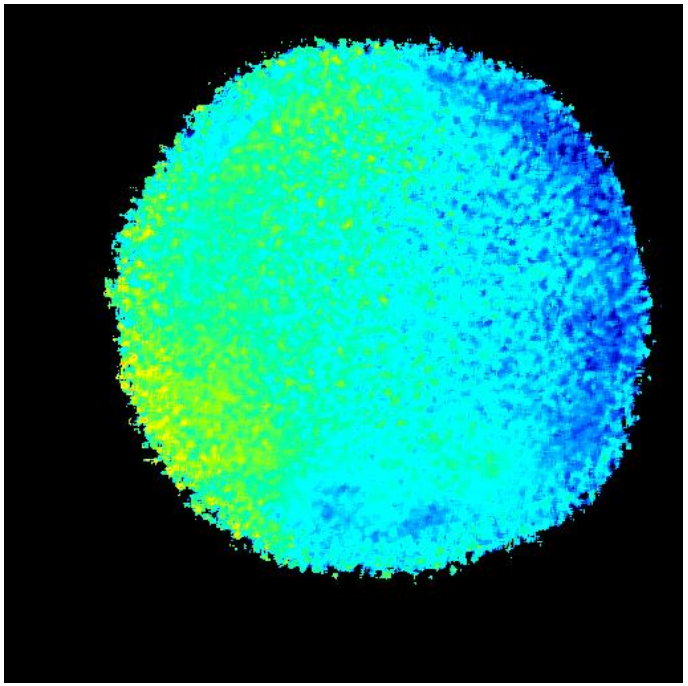
Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor α and estrogen receptor β

Angel Nadal*†, Ana B. Ropero*, Ouahiba Laribi*, Marjorie Maillet*, Esther Fuentes*‡, and Bernat Soria*

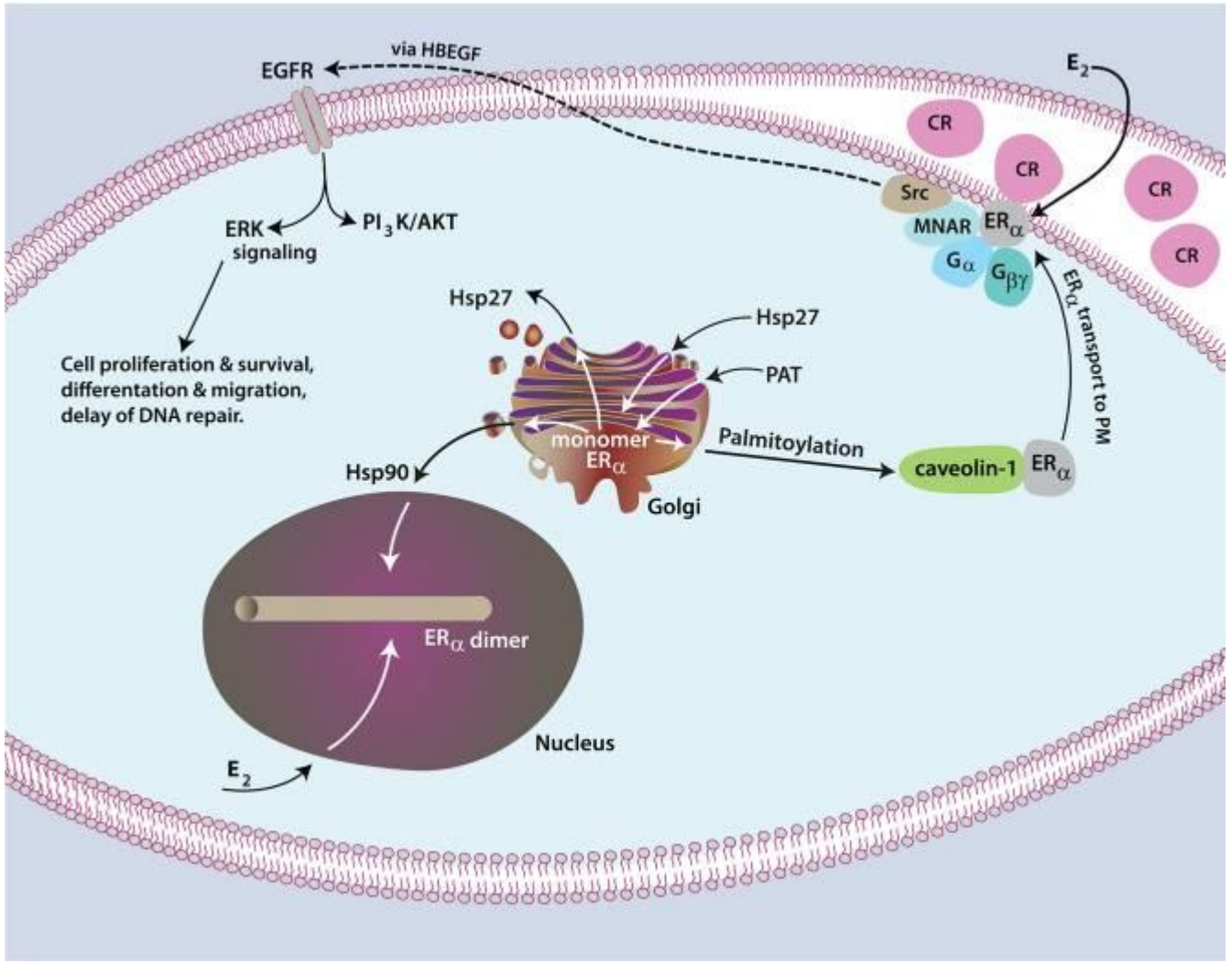
*Institute of Bioengineering, Department of Physiology, and ‡Department of Applied Biology, Miguel Hernández University, San Juan Campus, Alicante 03550, Spain

Edited by Ramon Latorre, Center for Scientific Studies of Santiago, Valdivia, Chile, and approved August 18, 2000 (received for review June 22, 2000)

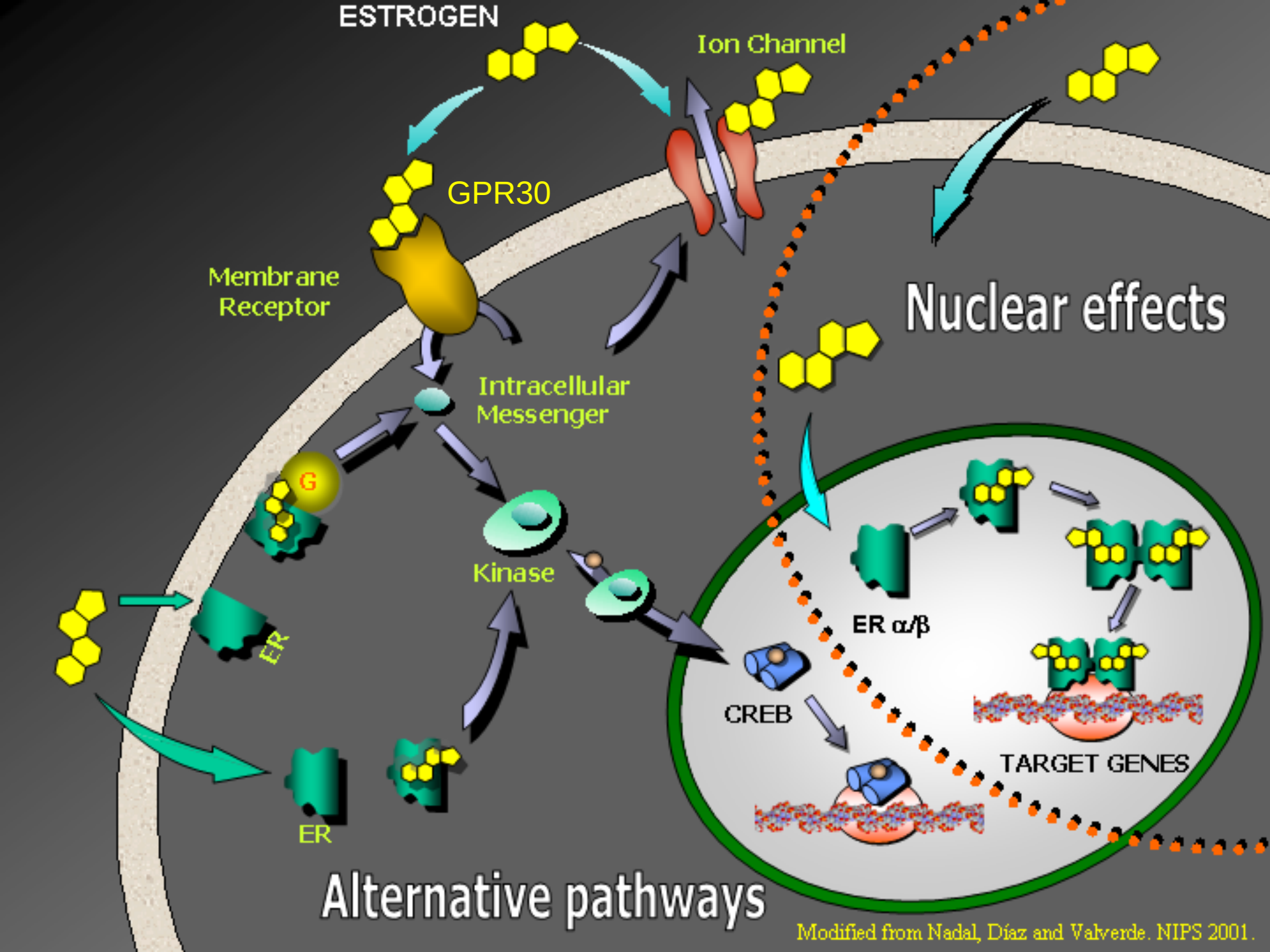




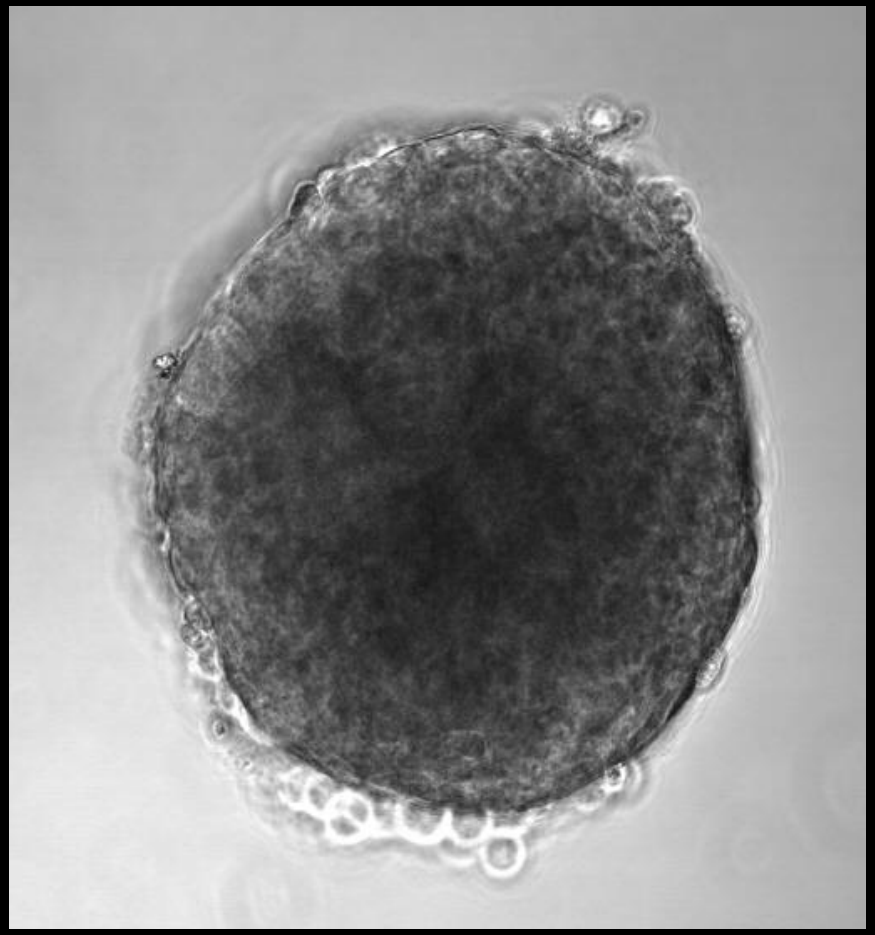
Model of ERα trafficking and signaling from the PM. In the Golgi, monomeric ERα is bound at cysteine 447 by Hsp27, promoting palmitoylation by an unknown palmitoylacyltransferase (PAT).

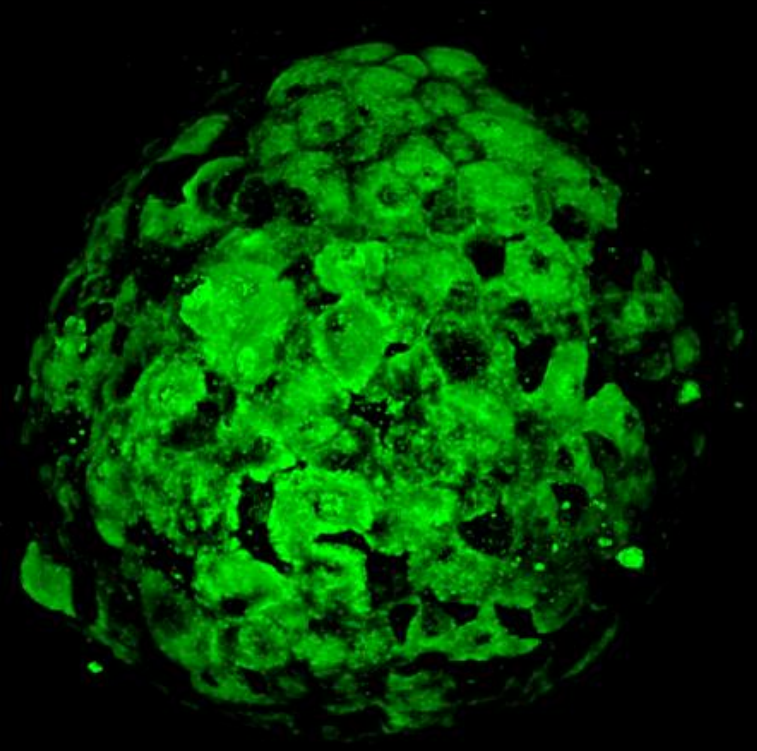


Levin ER, Mol Endocrinol 2011


ESTROGEN
Ion Channel
GPR30
Membrane Receptor
Nuclear effects
Intracellular Messenger
G
Kinase
ER
ER α/β
CREB
TARGET GENES
ER
Alternative pathways
Modified from Nadal, Díaz and Valverde. NIPS 2001.

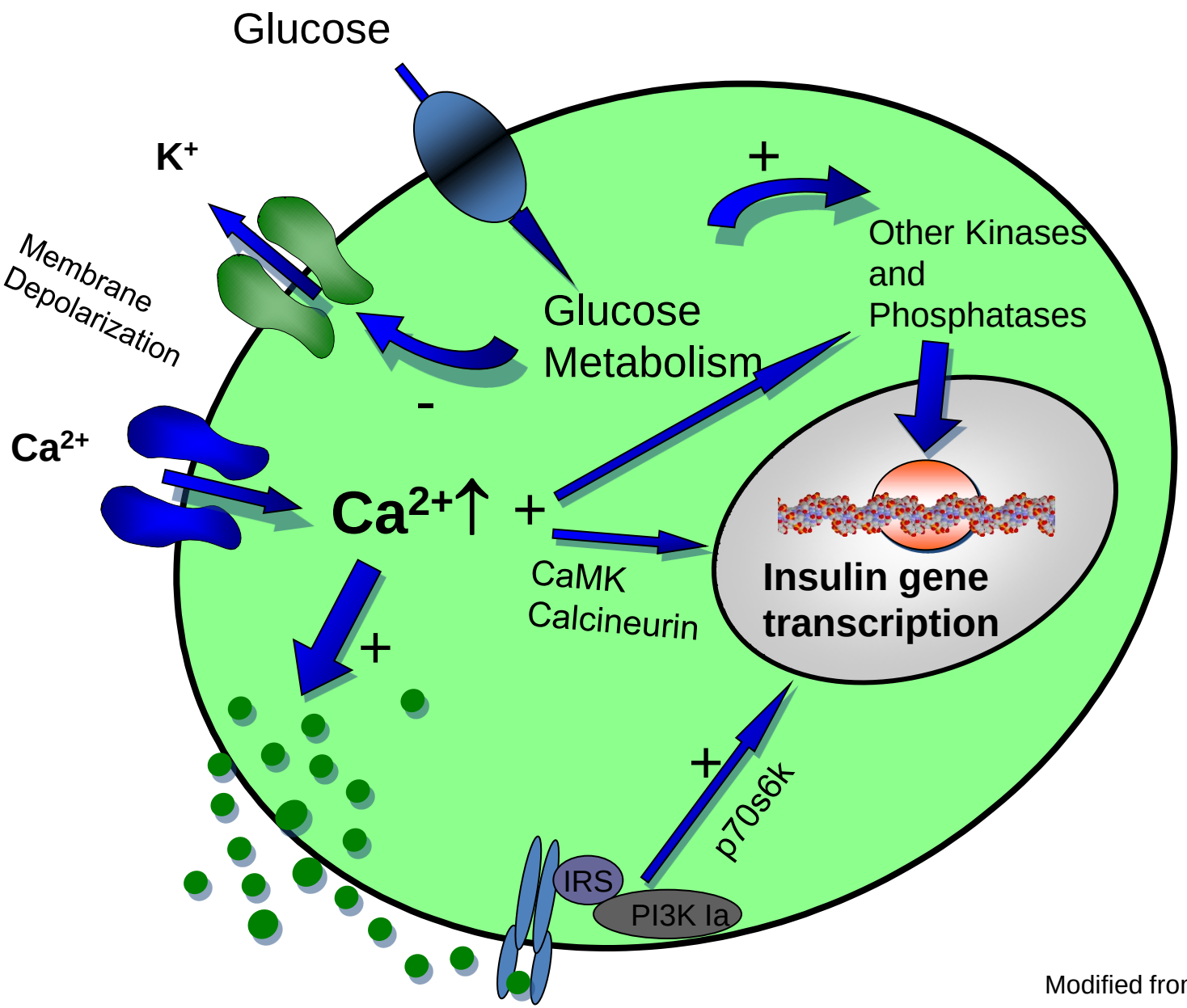
The Islet of Langerhans





insulin containing β-cells

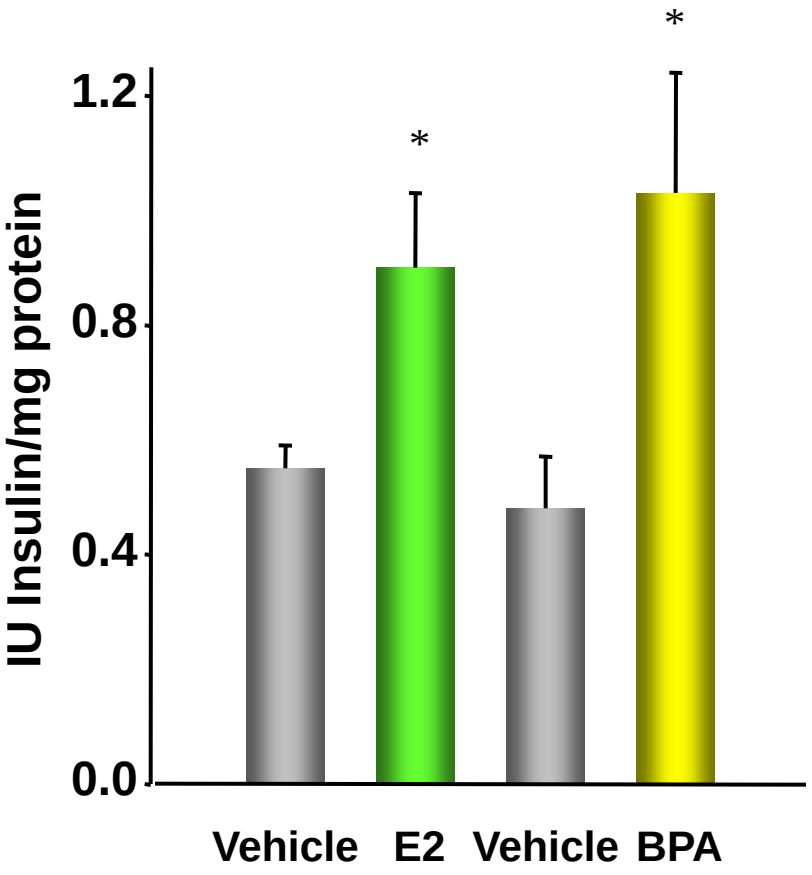
Insulin secretion/Insulin-Gene-Transcription coupling in β-cells



Modified from Leibiger et al 2002

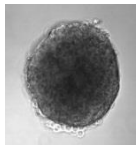
E2 or BPA 100µg/kg/day
4 days

Insulin content



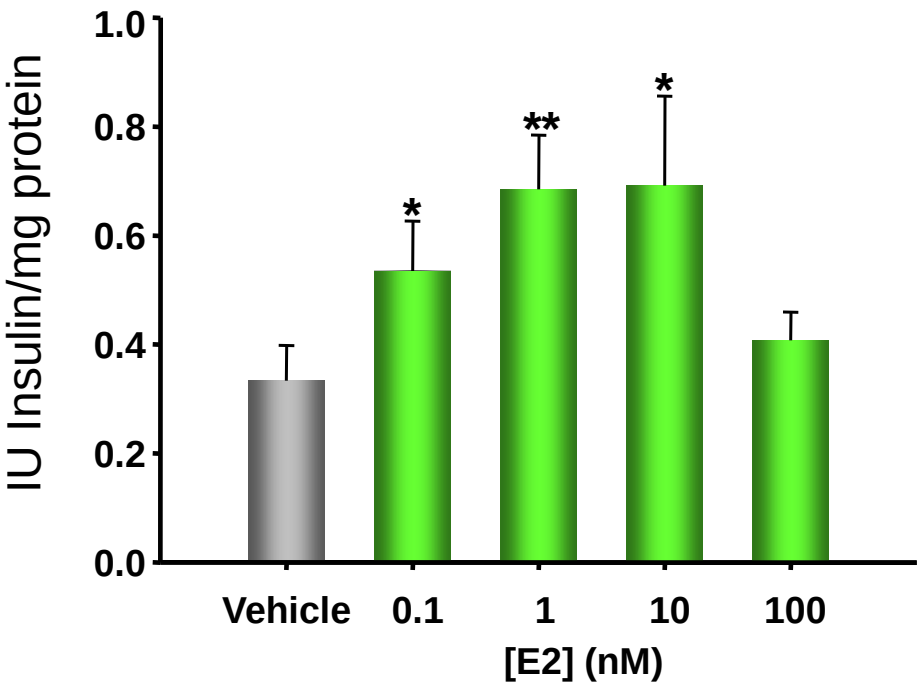
Alonso-Magdalena et al, Environ Health Perspect 2006

Ex vivo
48hrs cultured islets

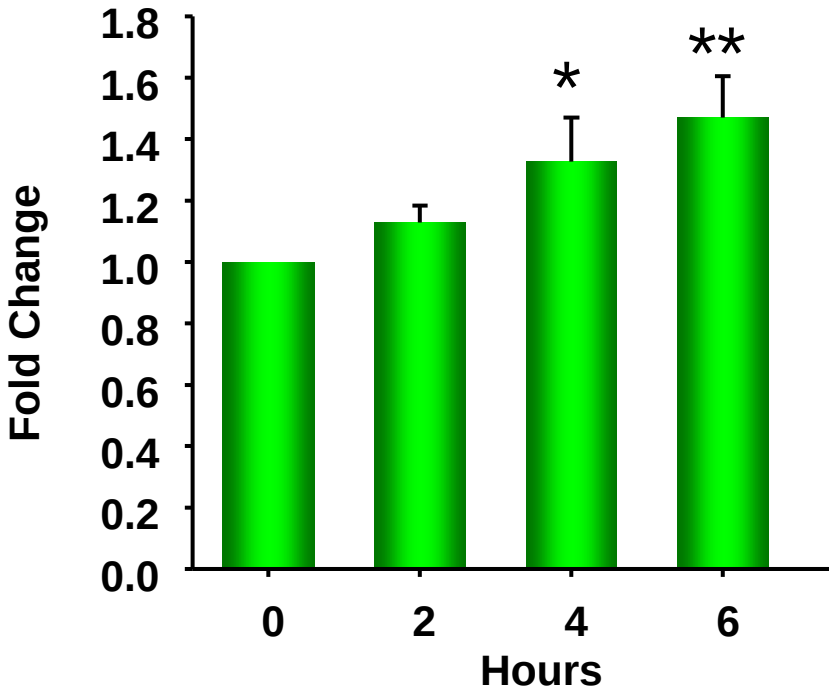


Vehicle
E2

Insulin content

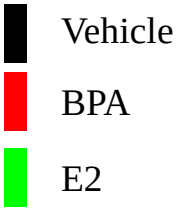


mRNA Real time PCR

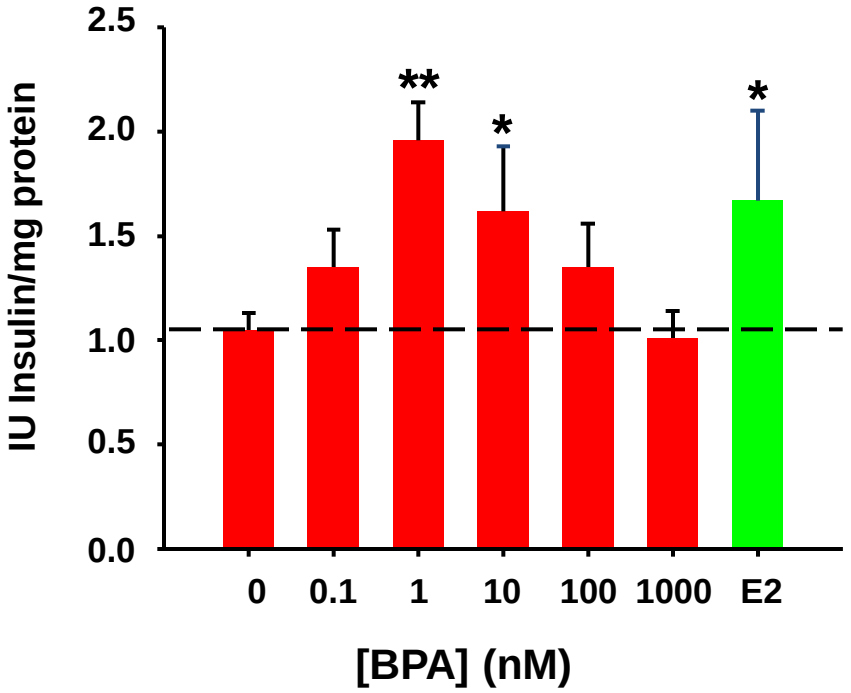


Alonso-Magdalena et al, PLoS ONE 2008

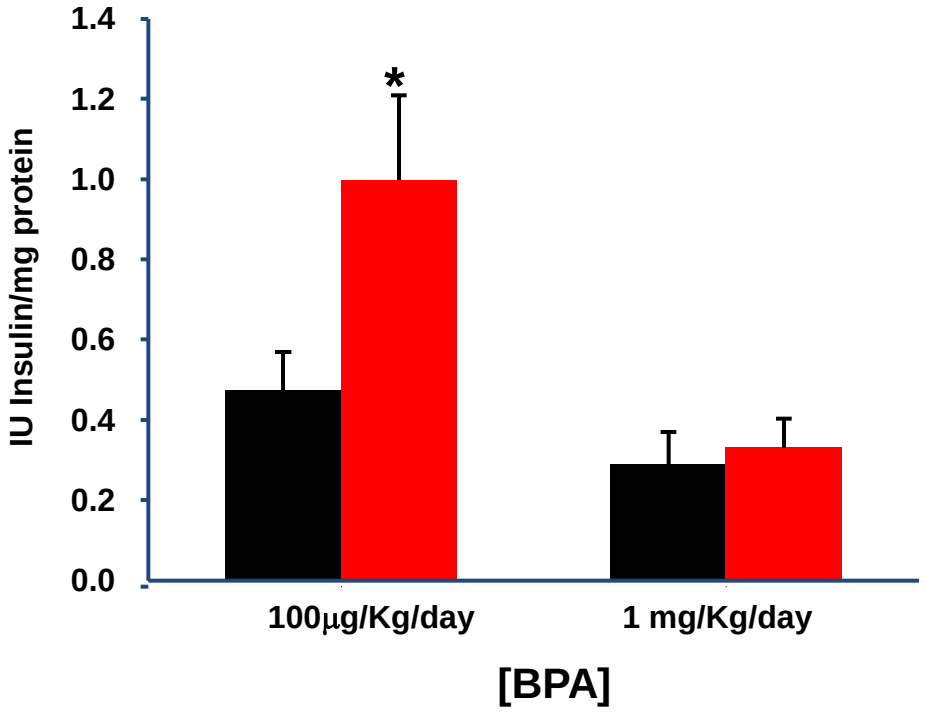
Insulin content



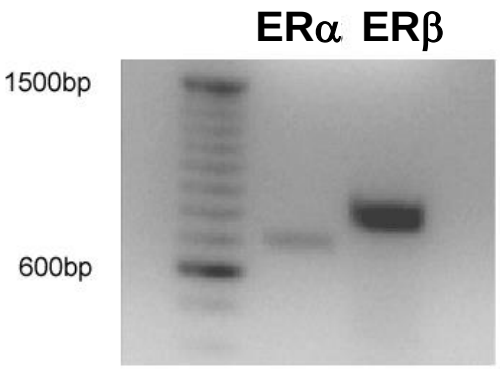
48hrs cultured islets

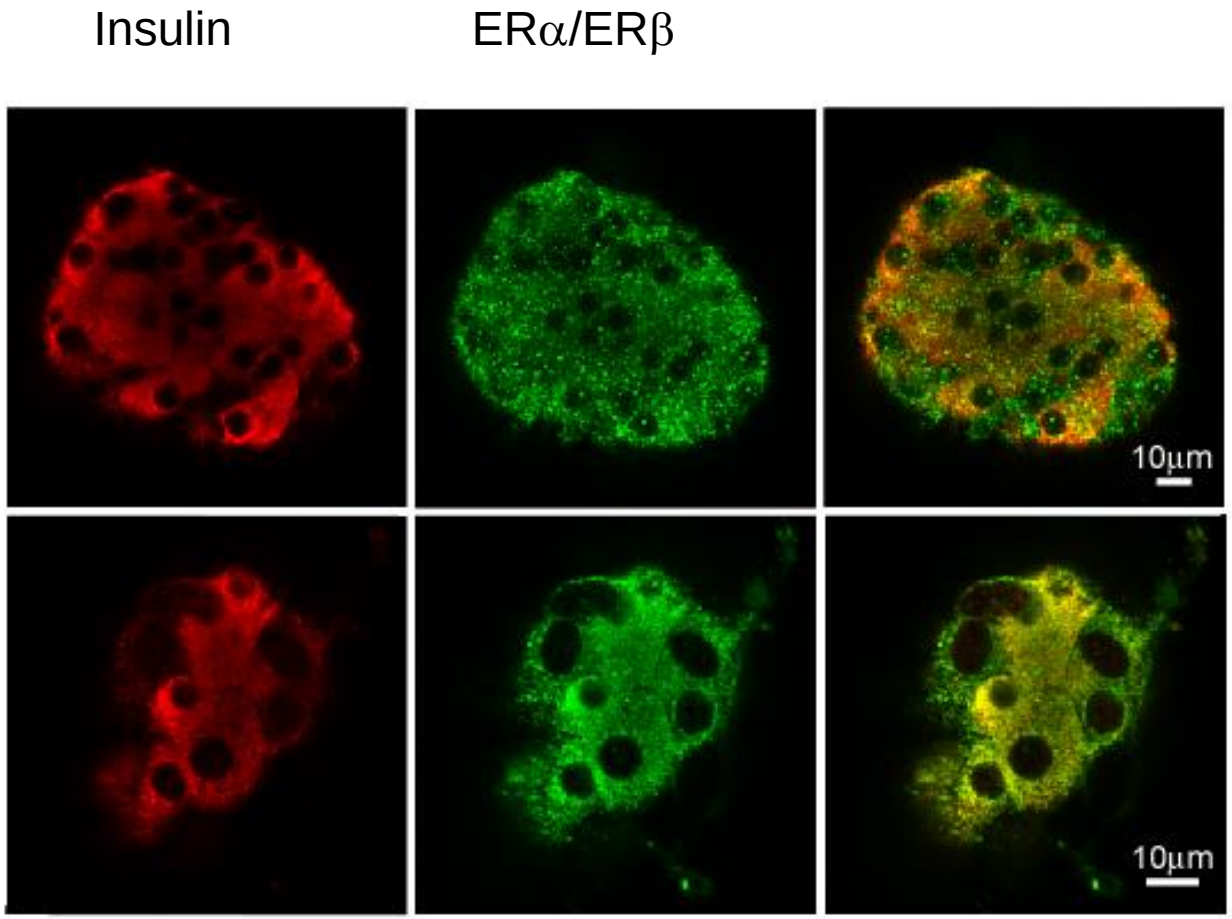


In vivo
4 days treatment



Alonso-Magdalena et al, Plos ONE 2008

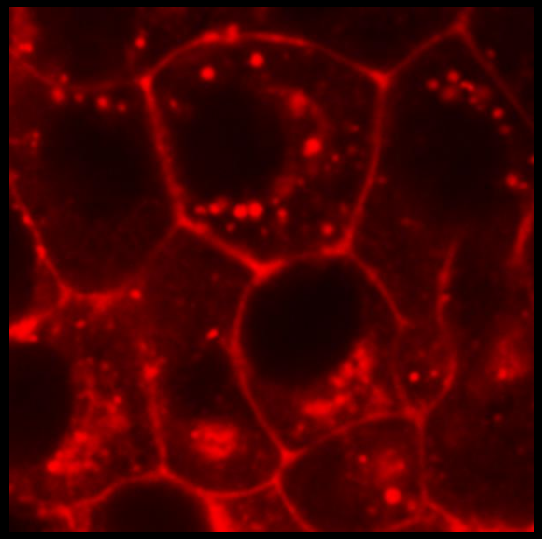


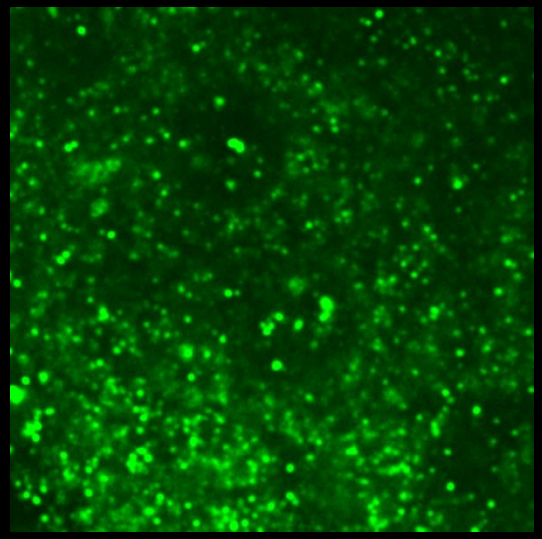


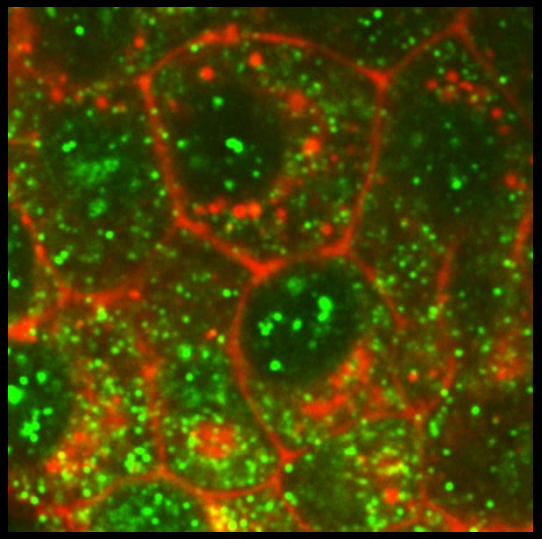
Nadal et al PNAS 2000; Alonso-Magdalena et al, PLoS ONE 2008

Agglutinin

ERα

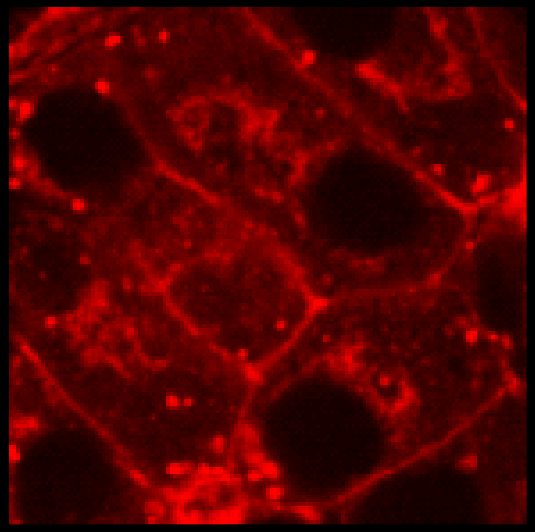


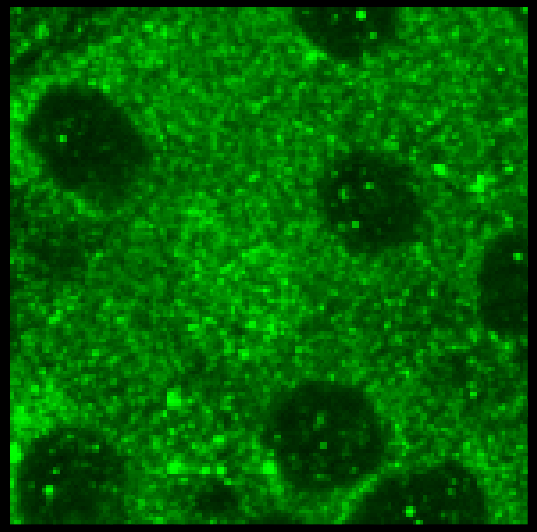


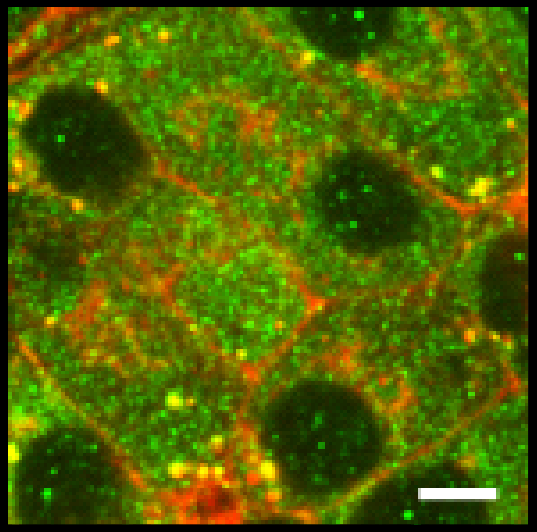


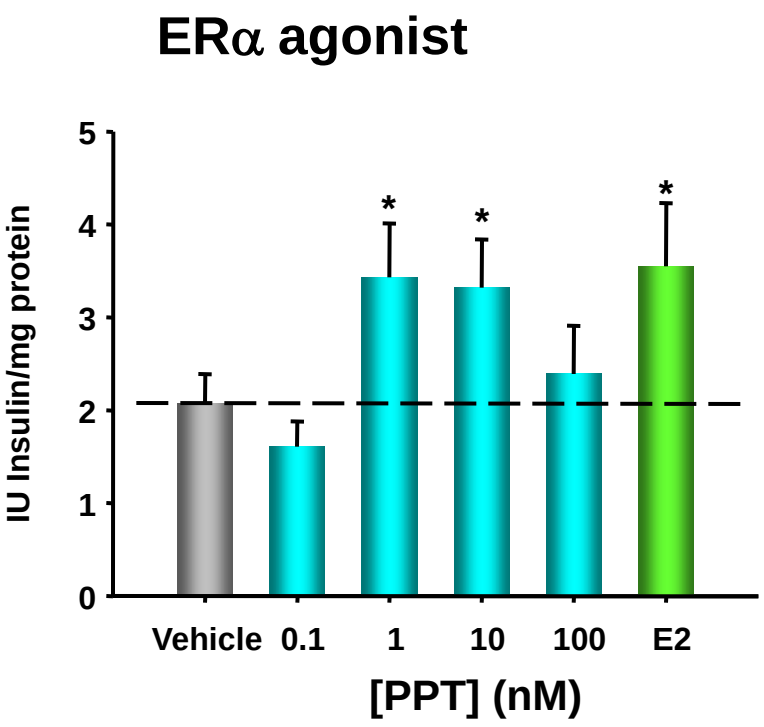
Agglutinin

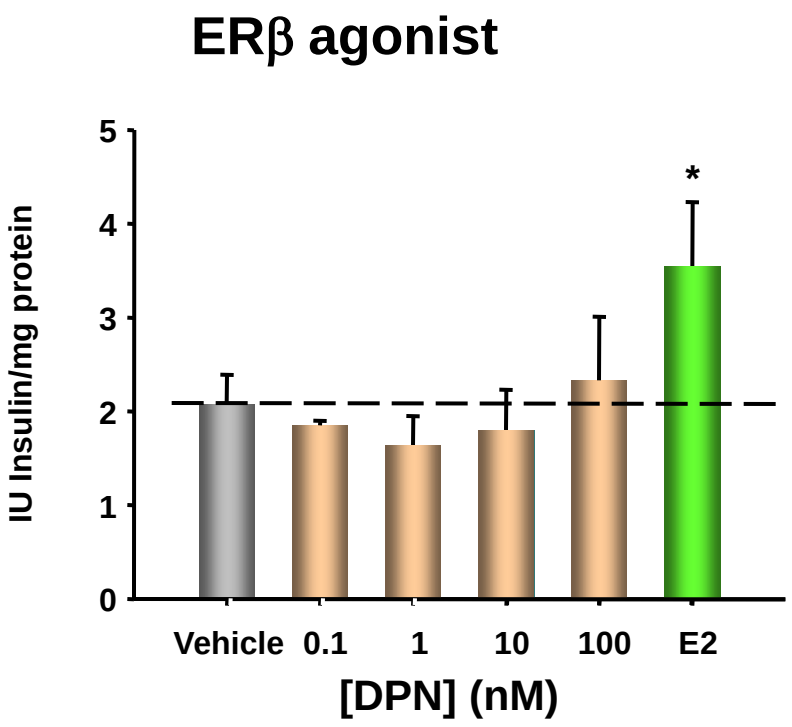
ERβ



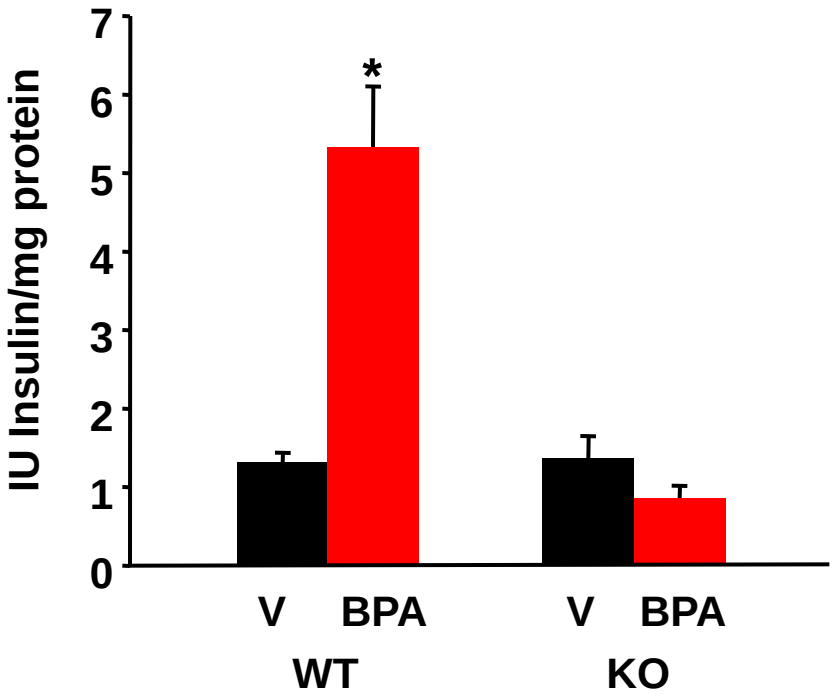




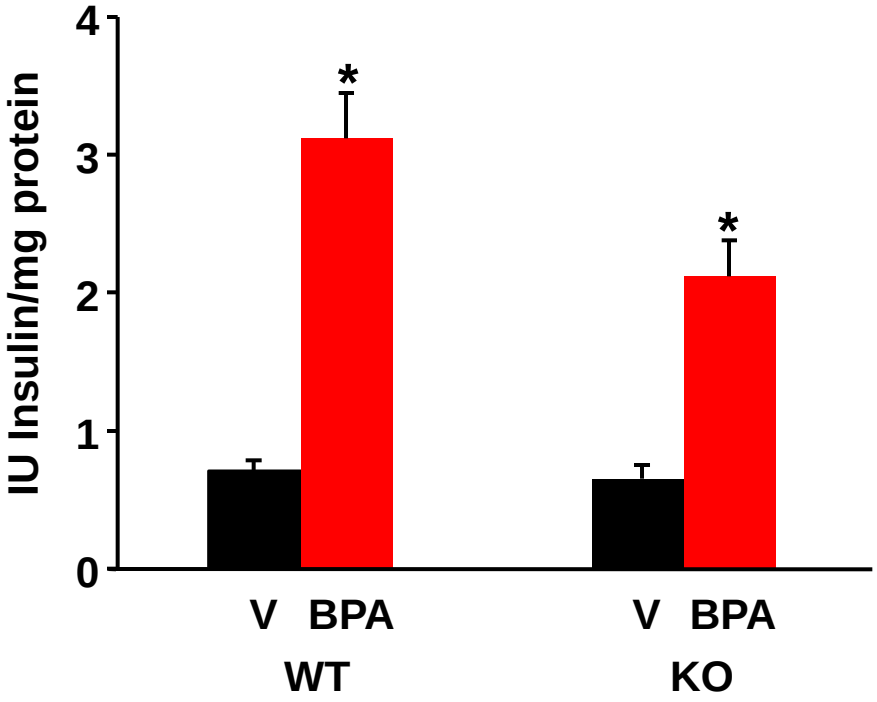

ERα agonist
IU Insulin/mg protein
5
4
3
2
1
0
*
*
*
Vehicle
0.1
1
10
100
E2
[PPT] (nM)

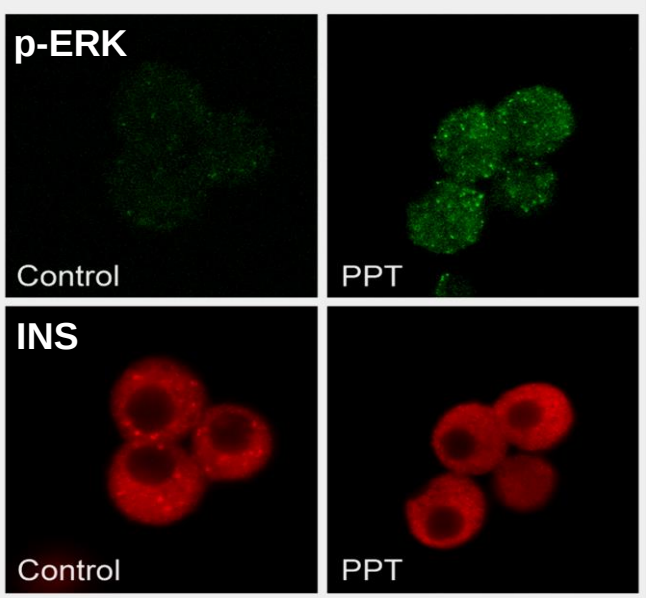

ERβ agonist
IU Insulin/mg protein
5
4
3
2
1
0
*
Vehicle
0.1
1
10
100
E2
[DPN] (nM)

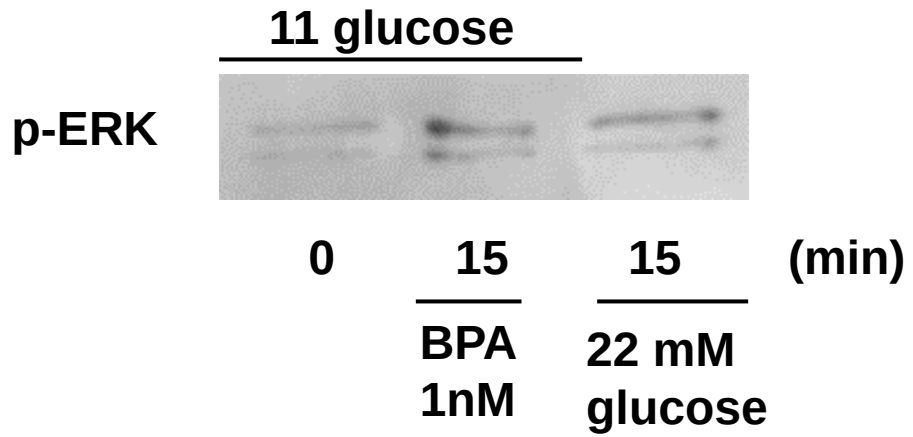
ERαKO

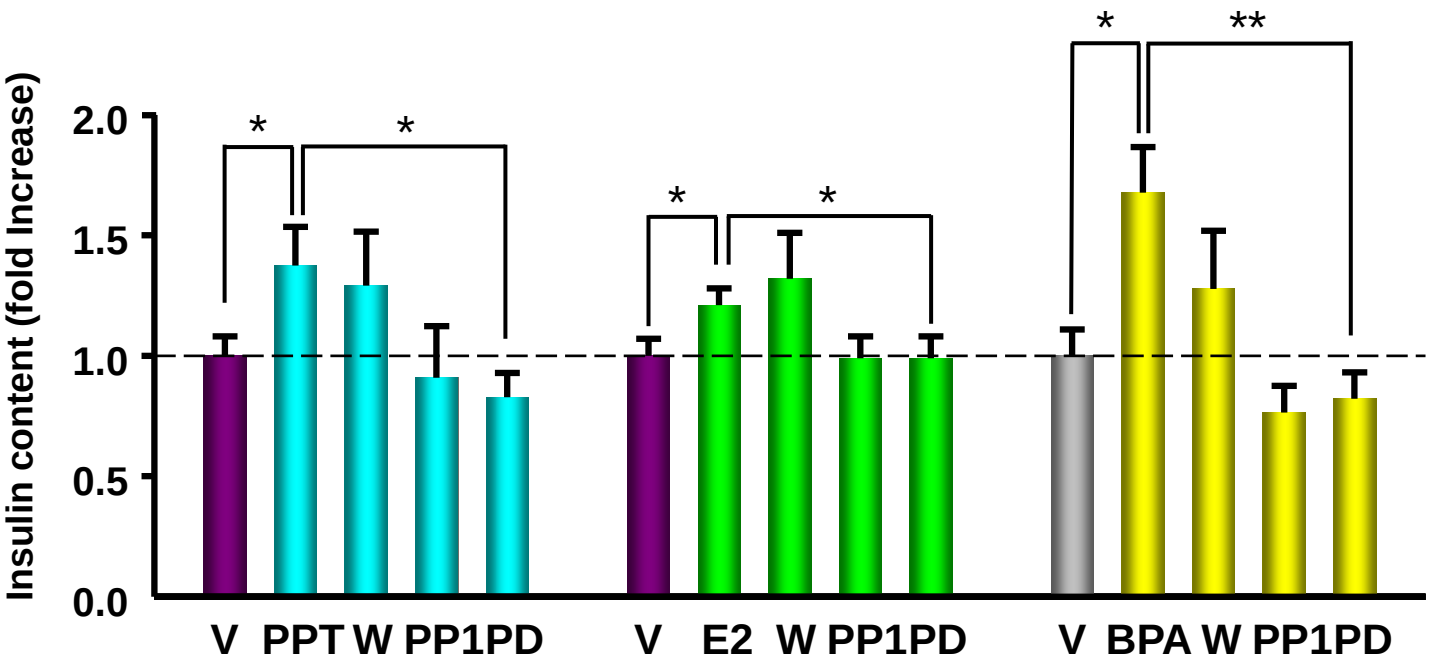

IU Insulin/mg protein
0
1
2
3
4
5
6
7
*
V
BPA
V
BPA
WT
KO

ERβKO


IU Insulin/mg protein
0
1
2
3
4
*
*
V
BPA
V
BPA
WT
KO

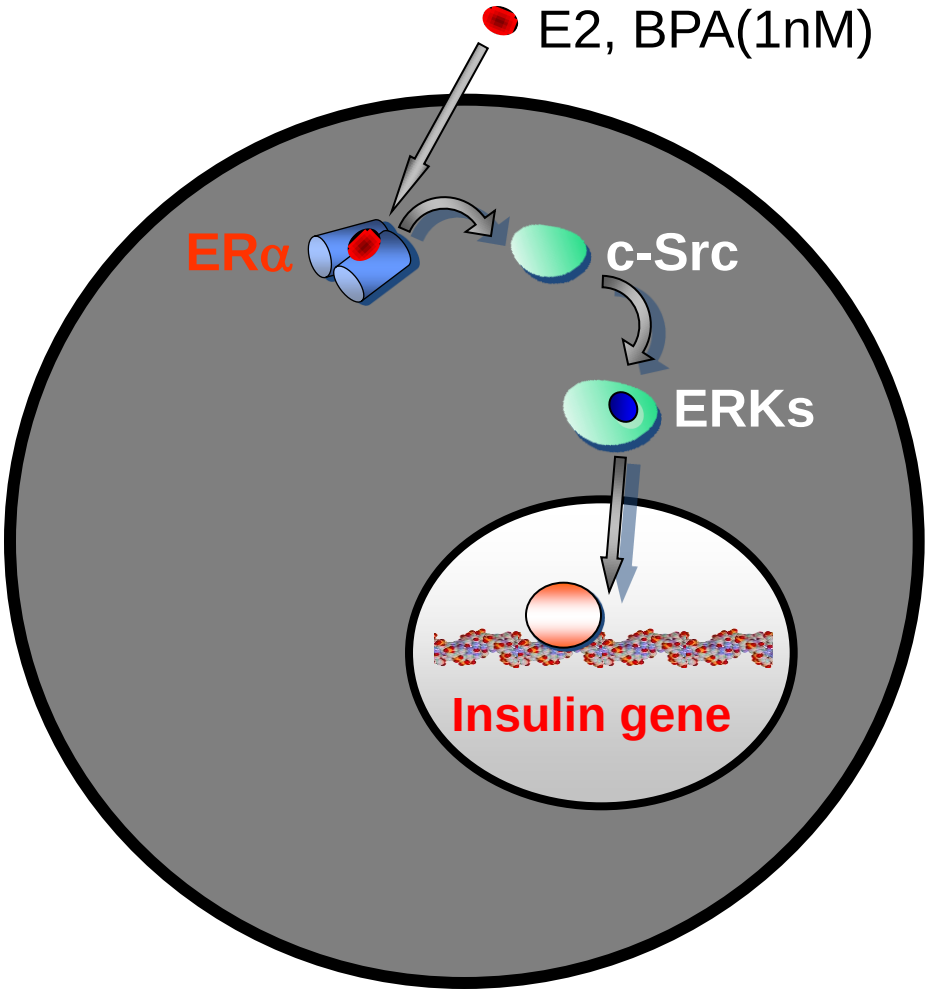

p-ERK
Control
PPT
INS
Control
PPT


11 glucose
p-ERK
0
15
15
(min)
BPA
1nM
22 mM
glucose


Insulin content (fold Increase)
2.0
1.5
1.0
0.5
0.0
*
*
*
*
*
**
V PPT W PP1PD
V E2 W PP1PD
V BPA W PP1PD

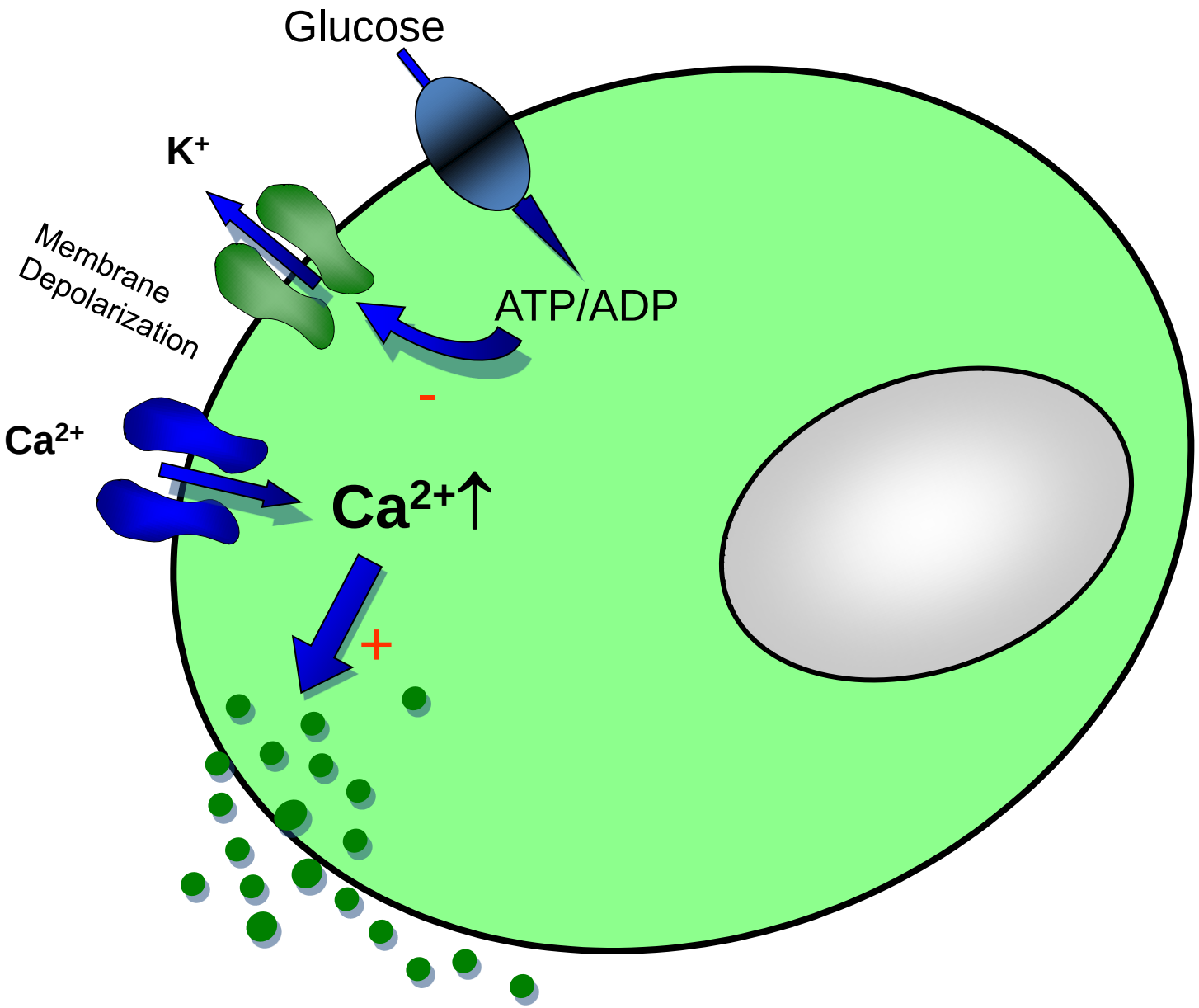
Insulin biosynthesis

β-Cells

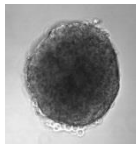


Alonso-Magdalena et al, Plos One 2008

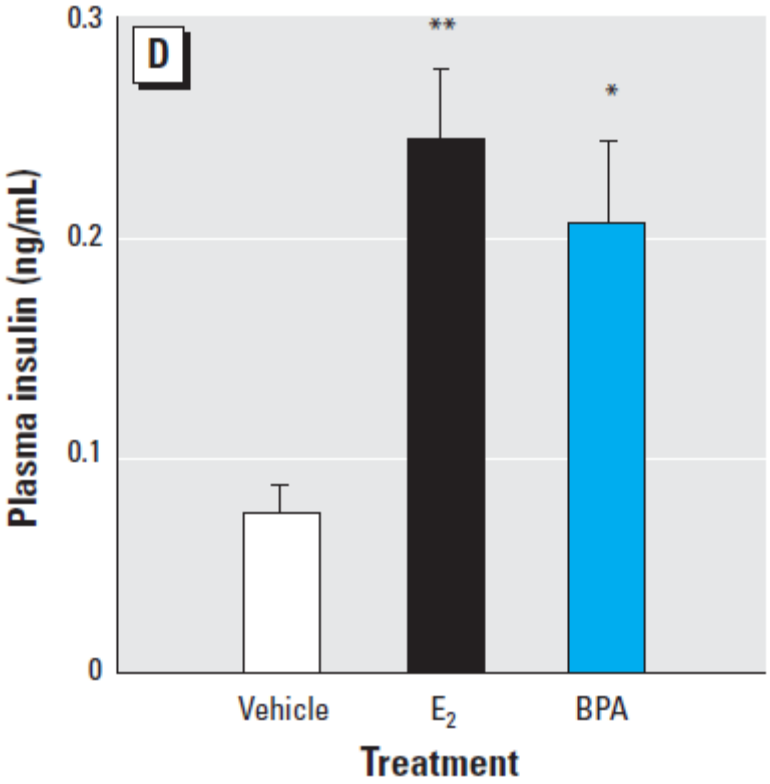
Stimulus-secretion coupling in β-cells

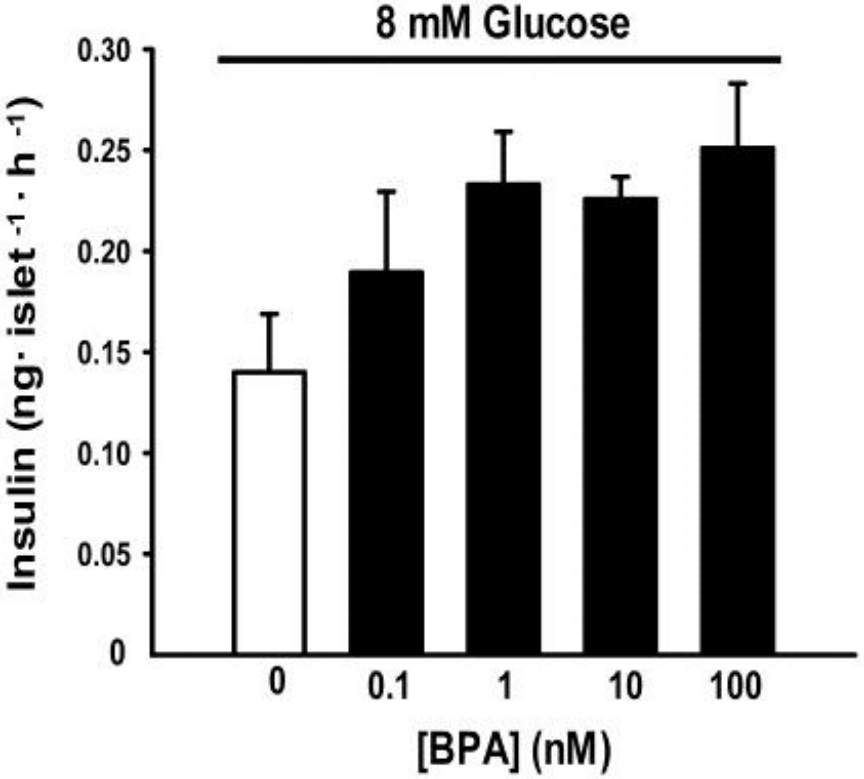


E2 or BPA 10µg/kg/ml



Ex vivo

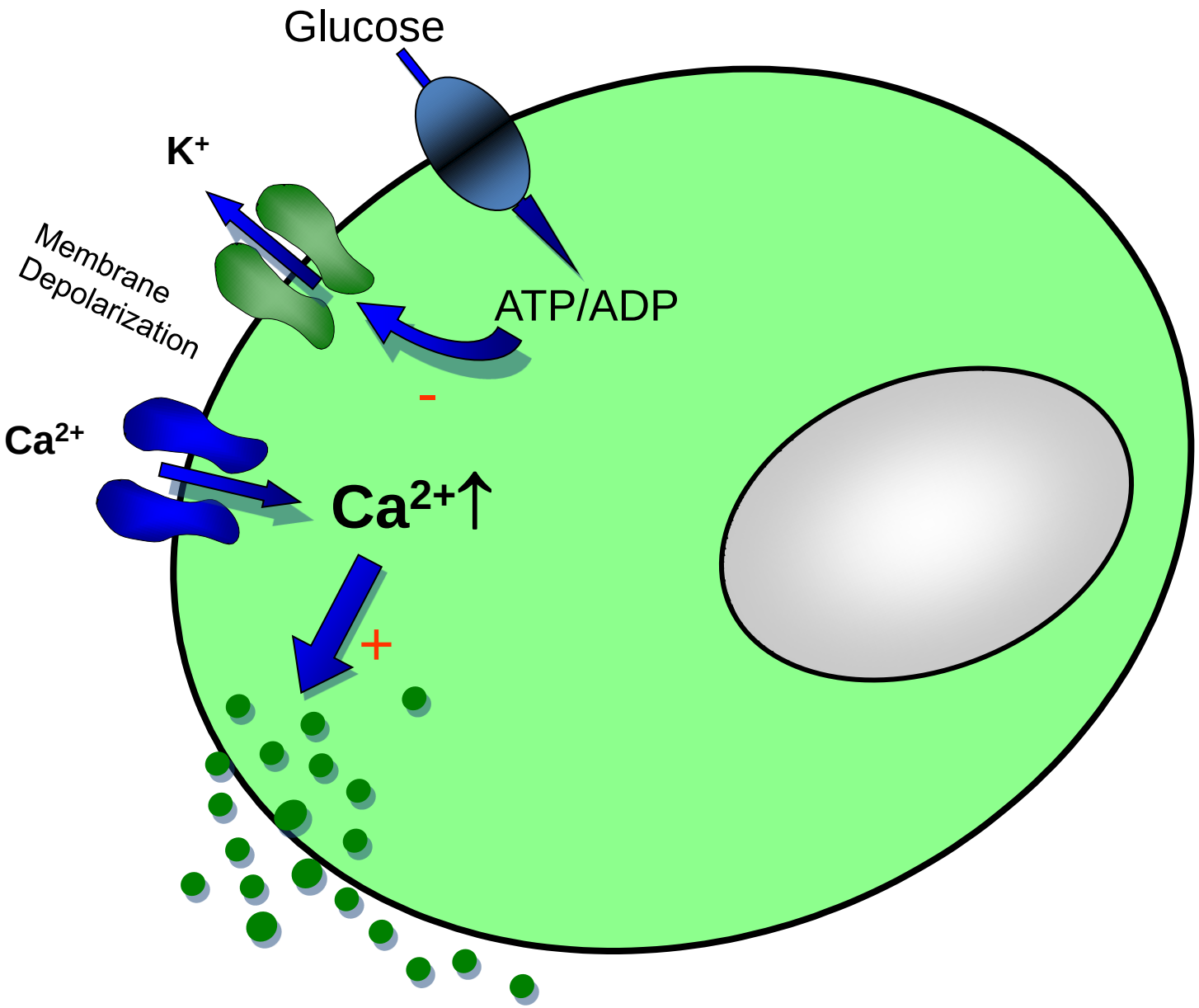


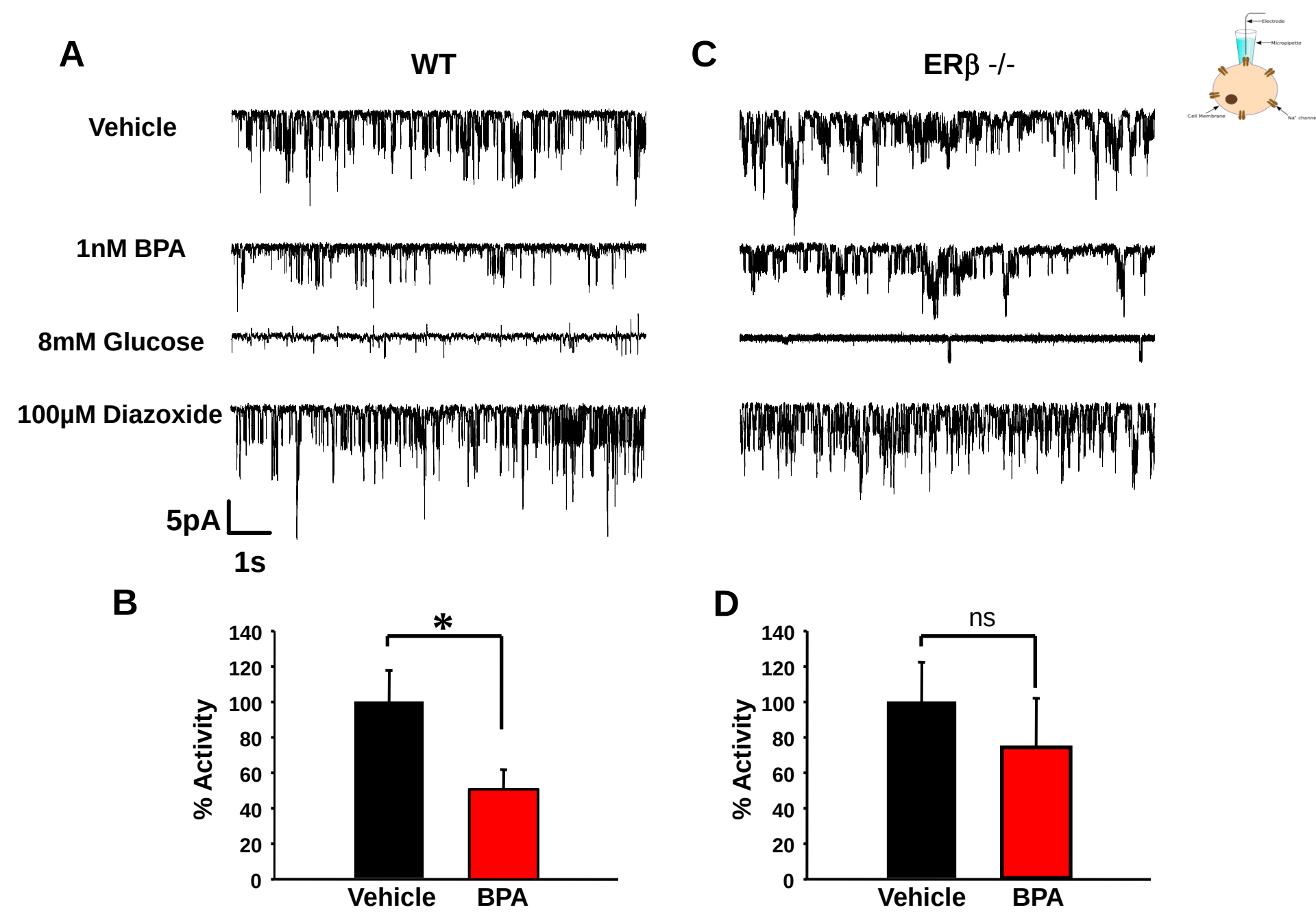


Alonso-Magdalena et al, EHP 2006

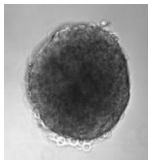
Soriano et al, Plos One 2012

Stimulus-secretion coupling in β-cells





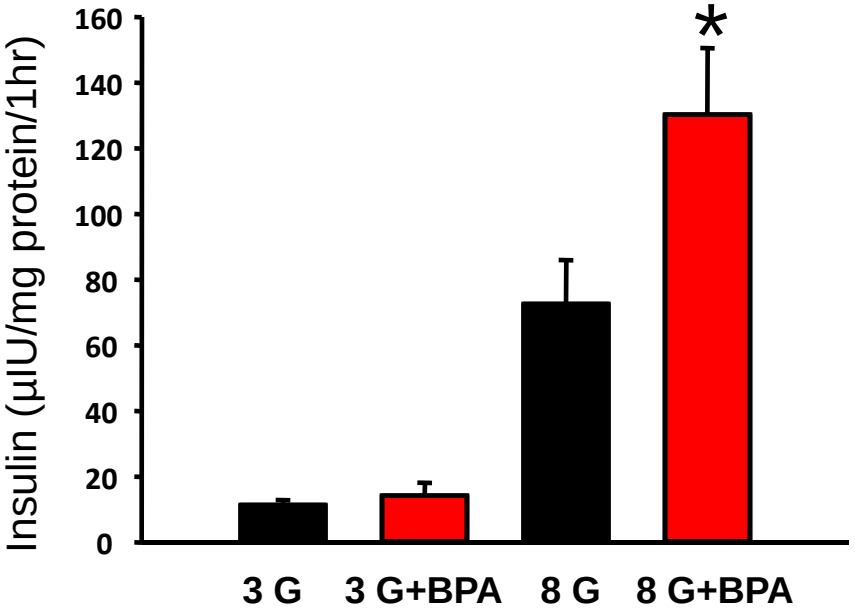
Soriano et al, Plos One 2012



1nM BPA increases Glucose-Stimulated Insulin Secretion in mice in an Estrogen Receptor β dependent manner

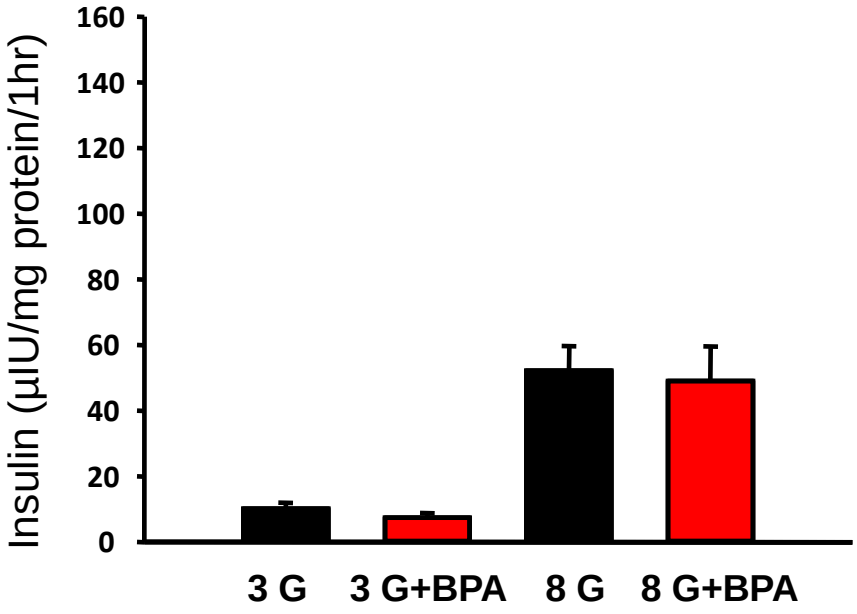
A

WT MICE



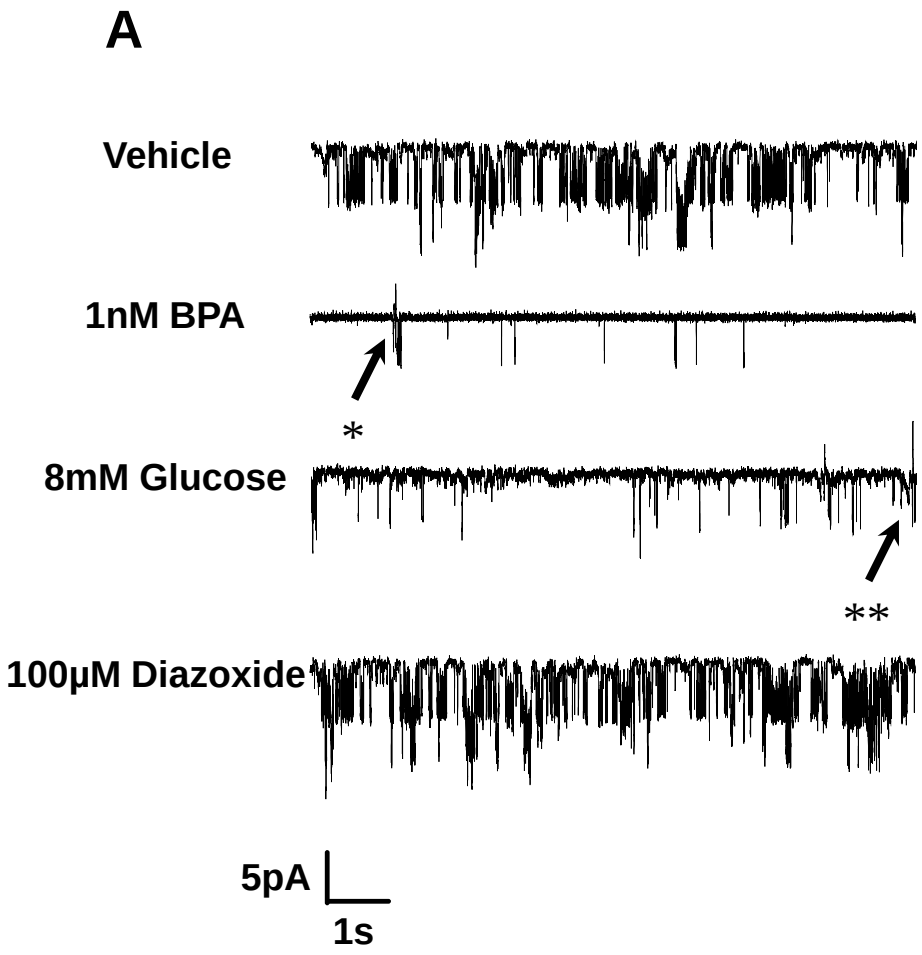
B

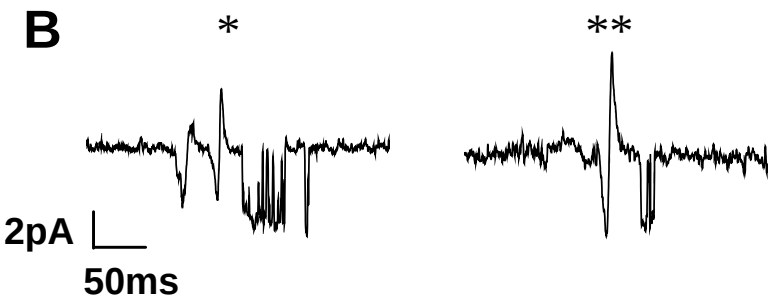
ERβ-/- MICE

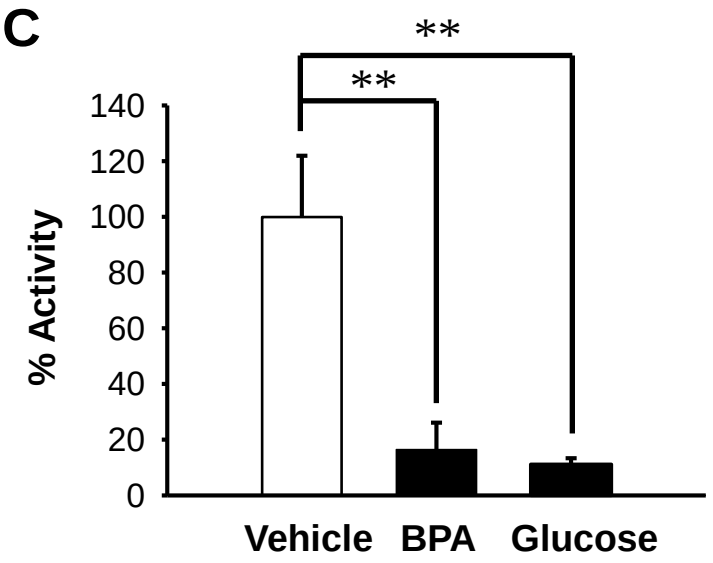


Soriano et al, Plos ONE 2012

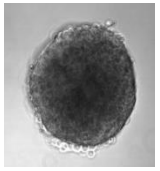
HUMAN BETA CELLS



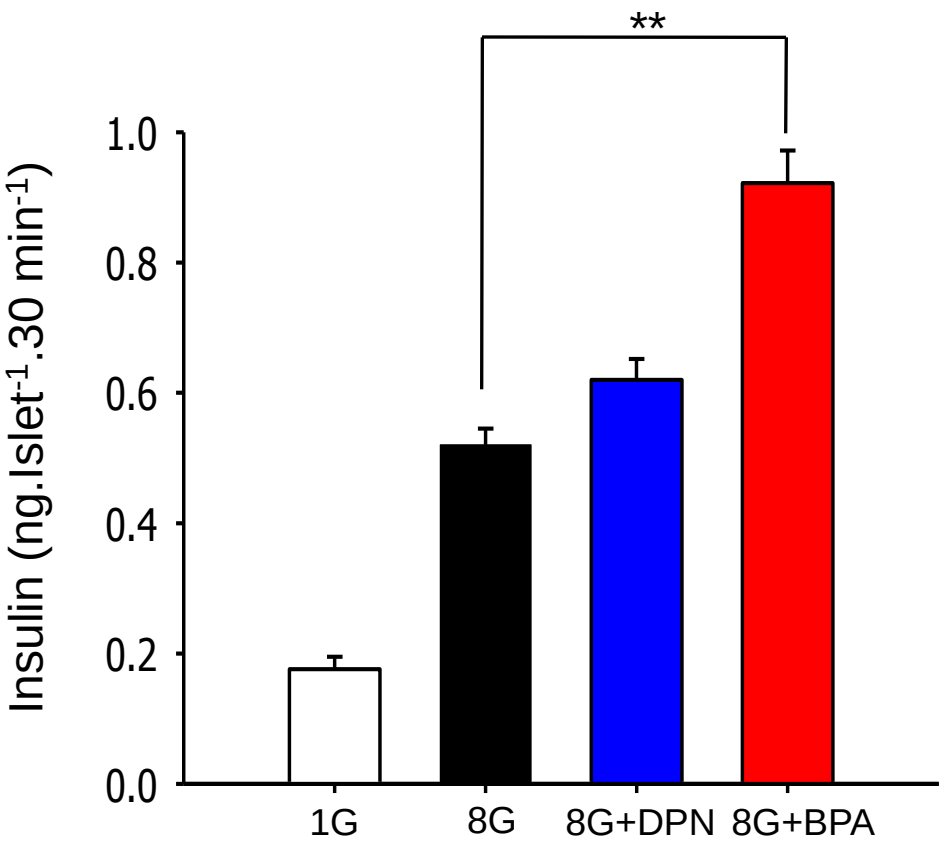




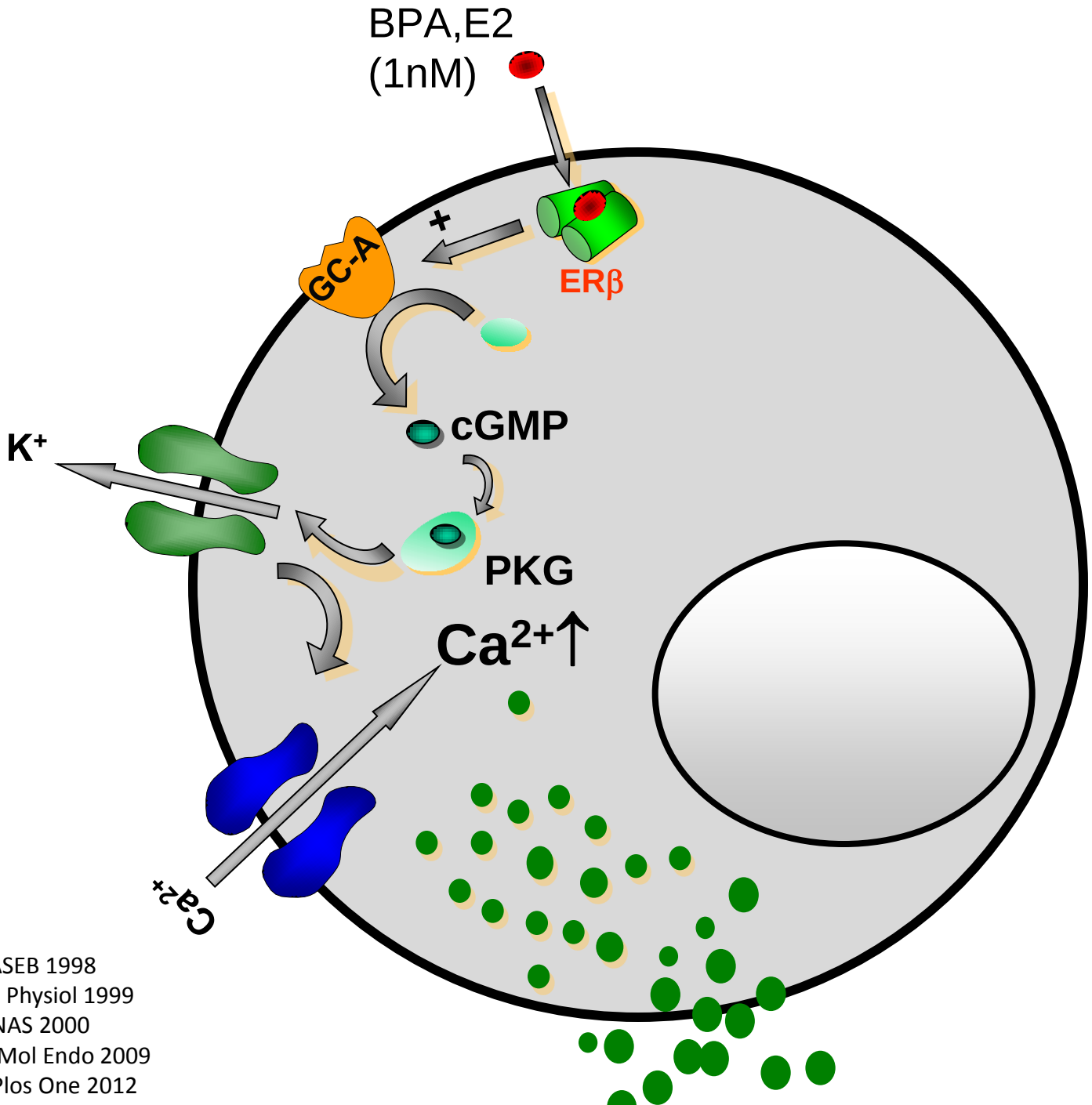
Soriano et al, Plos ONE 2012



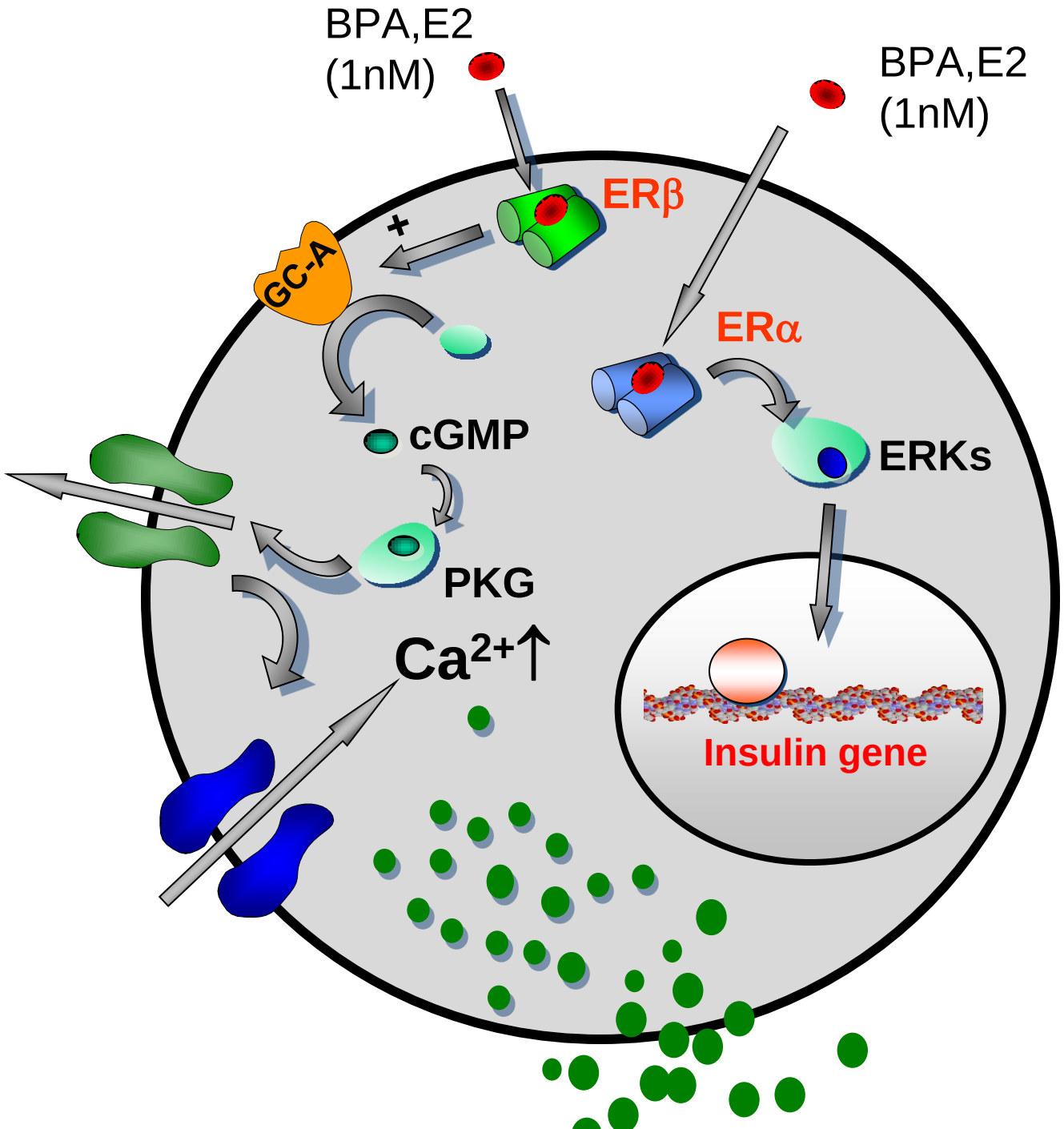
HUMAN ISLET OF LANGERHANS
1nM BPA increases Glucose-Stimulated Insulin Secretion



Soriano et al, Plos ONE 2012



Nadal et al, FASEB 1998
Ropero et al, J Physiol 1999
Nadal et al, PNAS 2000
Soriano et al, Mol Endo 2009
Soriano et al,Plos One 2012


BPA,E2
(1nM)
BPA,E2
(1nM)
ERβ
GC-A
+
ERα
cGMP
ERKs
PKG
Ca2+↑
Insulin gene

Instituto de Bioingeniería
Universidad Miguel Hernández de Elche

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Marta García-Arévalo
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Sabrina Villar
Cristina Ripoll
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Sarheed J. Muhammed and Albert Salehi, University of Lund, Sweden
Anna Novials, IDIBAPS, Barcelona, Spain
Christopher Cederroth and Serge Nef, University of Geneva, Switzerland
Thiago Batista and Everardo M. Carneiro, Institute of Biology, State University of Campinas, Brazil

Grant support:
MINECO, Generalitat Valenciana and ISCarlos III

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Journal of Steroid Biochemistry & Molecular Biology 102 (2006) 175–179

Molecular Biology

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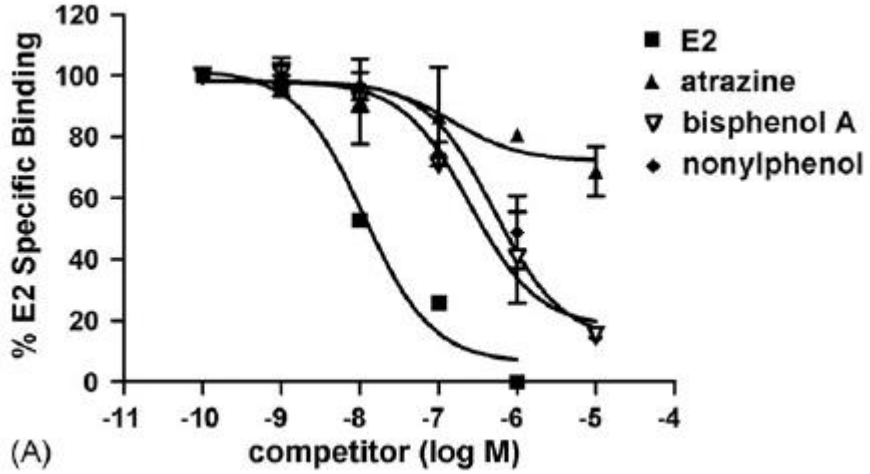
Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption☆

Peter Thomas*, Jing Dong

Marine Science Institute, University of Texas at Austin, 750 Channel View Drive, Port Aransas, TX 78373, USA



(A)

Table 1
Rank order of binding affinities of environmental estrogens to plasma membranes prepared from HEK293 cells transfected with GPR30[a]

Compound	IC_{50} nM	RBA
Estradiol-17β	17.8	100.00
Genistein	133	13.41
Bisphenol A	630	2.83
Zearalenone[b]	763	2.34
Nonylphenol	828	2.15
Kepone	1350	1.32
p,p′-DDT	2719	0.66
2,2′,5′ PCB-4-OH	3763	0.47
o,p′-DDE[b]	7144	0.25
Atrazine	ND	ND
Methoxychlor	ND	ND
o,p′-DDT	ND	ND
p,p′-DDE	ND	ND

[a] Each value is the mean of three separate competitive binding assays. IC_{50} is the competitor concentration that causes 50% displacement of [^{3}H]estradiol-17β. RBA is the relative binding affinity (%) compared to that of estradiol-17β. ND, not determined; displacement <50% at 10^{-5} M.

[b] Calculated from competitive binding assays with SKBR3 cells (24).

Low Concentrations of Bisphenol A Induce Mouse Spermatogonial Cell Proliferation by G Protein–Coupled Receptor 30 and Estrogen Receptor-α

Zhi-Guo Sheng[1] and Ben-Zhan Zhu[1,2]

[1]State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Science, Chinese Academy of Sciences, Beijing, People's Republic of China; [2]Linus Pauling Institute, Oregon State University, Corvallis, Oregon, USA

Environmental Health Perspectives • VOLUME 119 | NUMBER 12 | December 2011

Bisphenol A induces a rapid activation of Erk1/2 through GPR30 in human breast cancer cells

S. Dong [a,b], S. Terasaka [a], R. Kiyama [a,*]

[a] *Biomedical Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8566, Japan*
[b] *Institute of Urban Environment, Chinese Academy of Sciences, Xiamen, China*

We showed here that the mechanism by which BPA induces the activation of Erk1/2 is distinguishable from the mechanism of ERα-mediated signaling in human breast cancer cells.

Environmental Pollution 159 (2011) 212–218

In vitro molecular mechanisms of bisphenol A action☆

Yelena B. Wetherill[a,b], Benson T. Akingbemi[c], Jun Kanno[d], John A. McLachlan[e], Angel Nadal[f], Carlos Sonnenschein[g], Cheryl S. Watson[h], R. Thomas Zoeller[i], Scott M. Belcher[j,*]

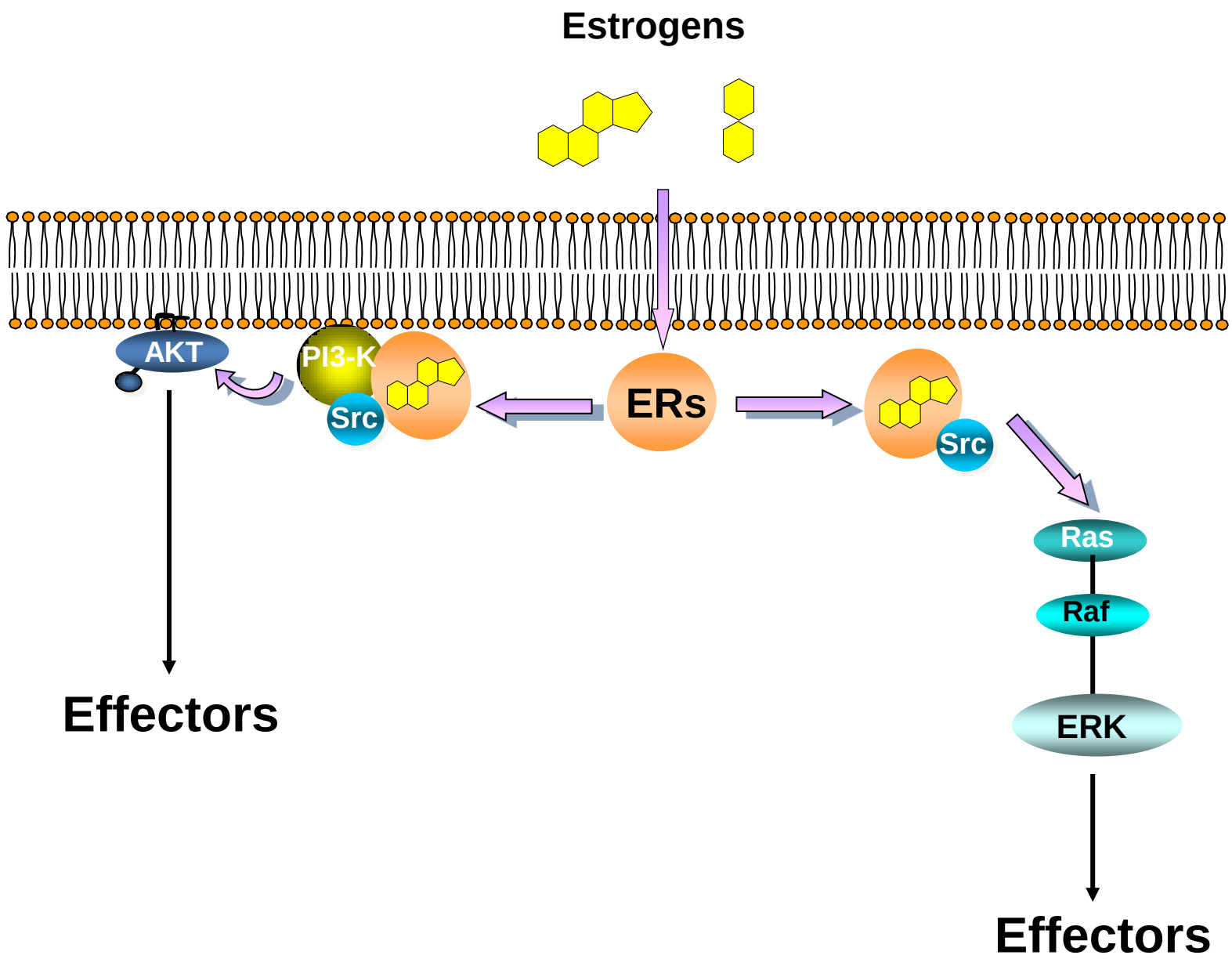
Reproductive Toxicology 24 (2007) 178–198

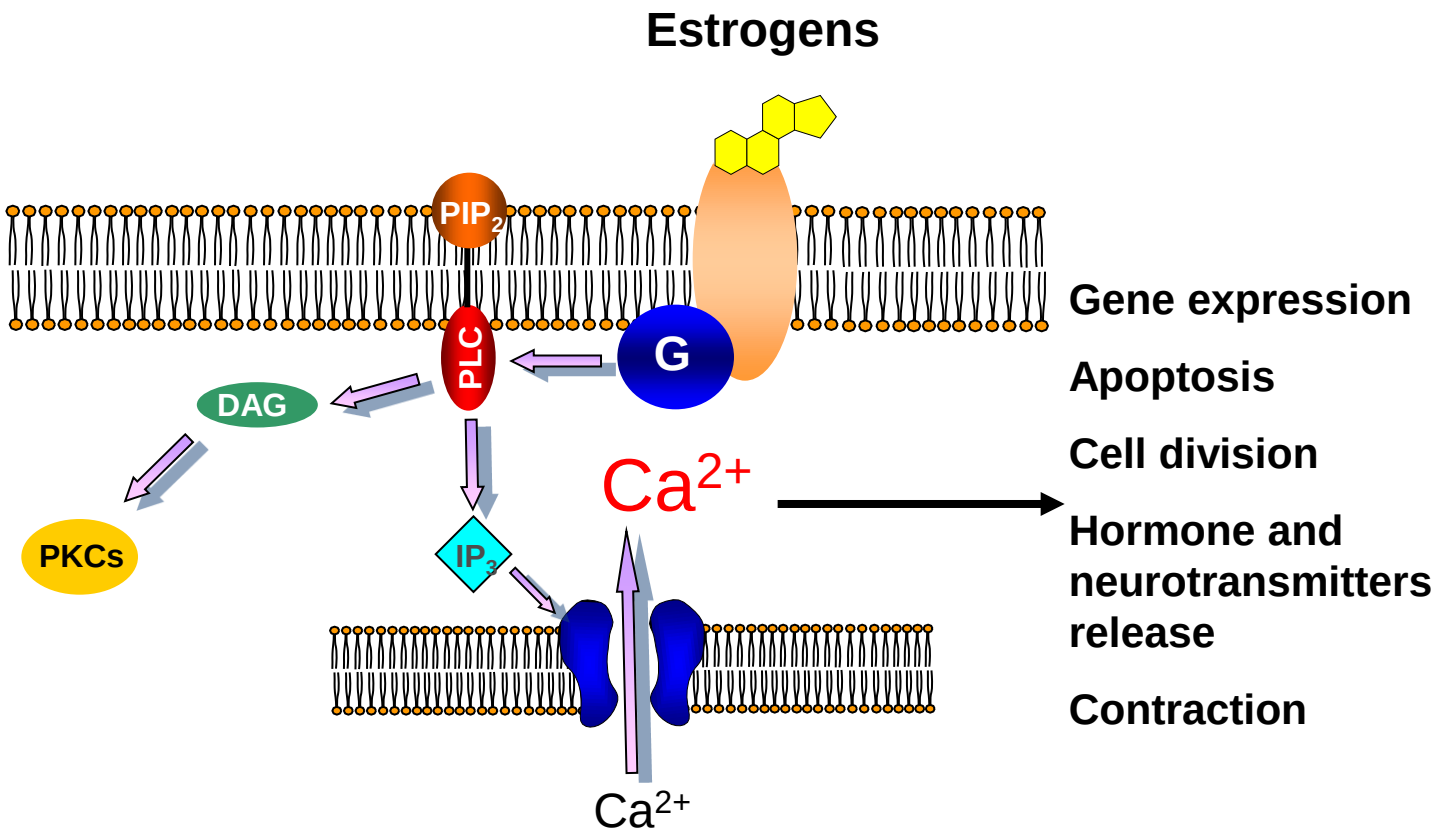
16. Conclusions and levels of confidence from the results of mechanistic *in vitro* studies

16.1. Based on existing evidence, we are confident of the following

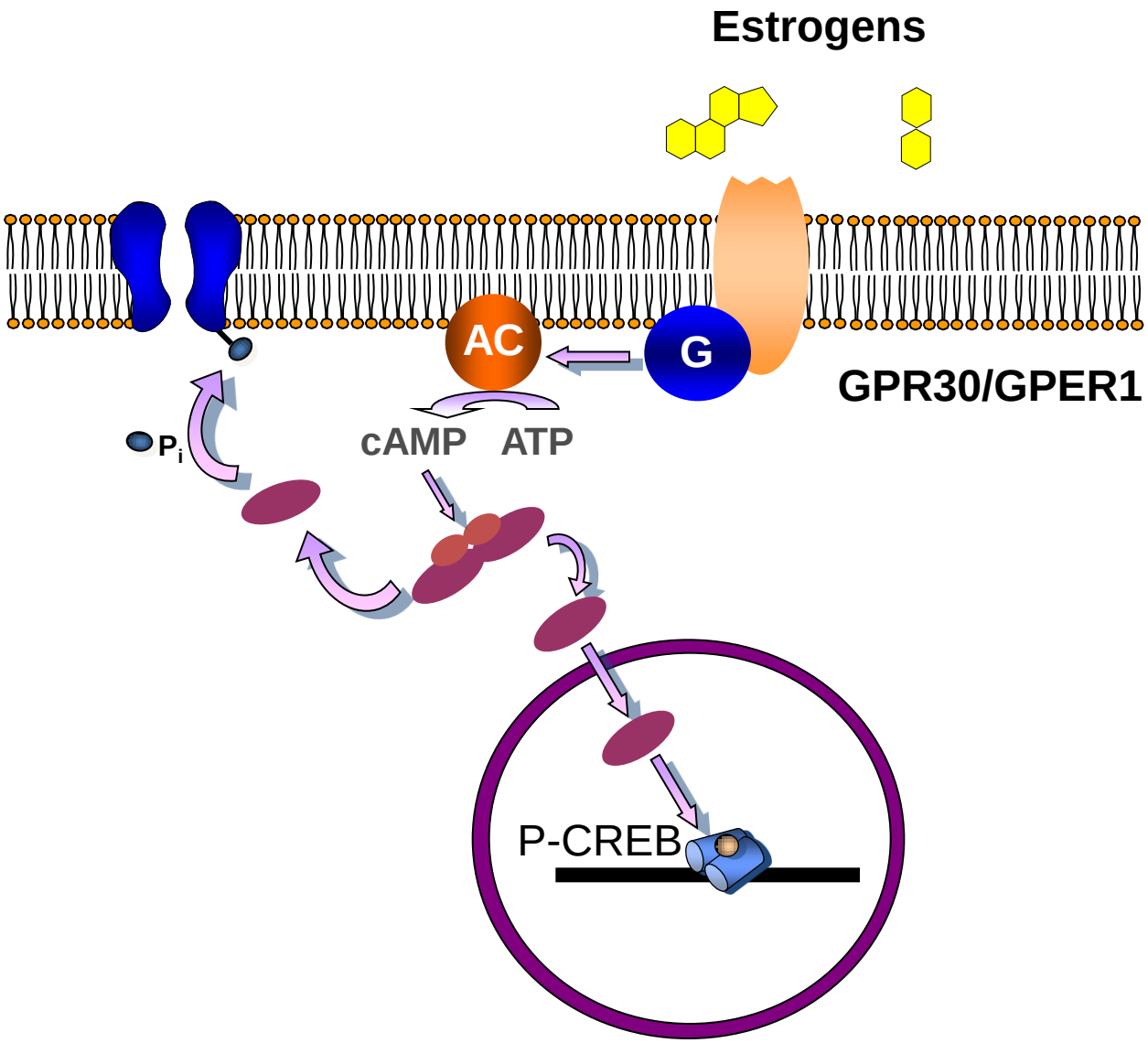
The criterion for achieving this confidence level is that multiple independent studies had been conducted that showed the same or similar outcome.

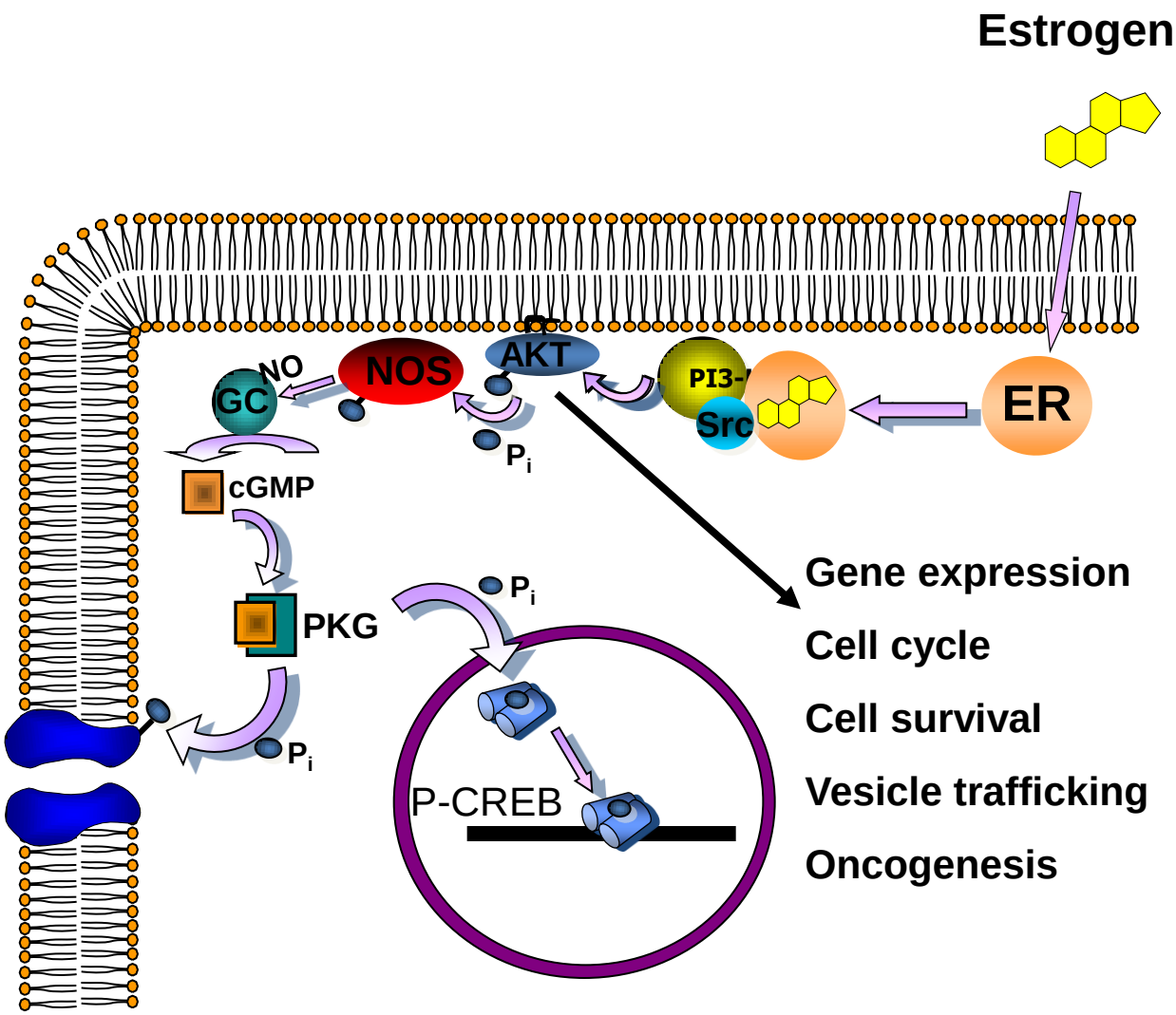
a. BPA can act as an estrogen. Its effects are, however, cell type specific.
b. Timing (developmental stage) of exposure and exposure dose/concentration are critical.
c. When BPA binds to classic nuclear estrogen receptors and induce specific ERE binding, BPA is usually less potent than estradiol.
d. When BPA action is mediated by estrogen receptors outside the nucleus, its potency is as high as that of estradiol, ranging within the pico- and nano-molar concentrations.


Estrogens
AKT
PI3-K
Src
ERs
Src
Ras
Raf
ERK
Effectors
Effectors



Nadal et al, Pfluegers Arch 2004


Estrogens
AC
G
GPR30/GPER1
cAMP
ATP
Pi
P-CREB



Nadal et al, Pfluegers Arch 2004

The EMBO Journal (2009) 28, 523–532 | © 2009 European Molecular Biology Organization | All Rights Reserved 0261-4189/09
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THE EMBO JOURNAL

Estrogenic GPR30 signalling induces proliferation and migration of breast cancer cells through CTGF

Deo Prakash Pandey[1,3], Rosamaria Lappano[2,3], Lidia Albanito[2], Antonio Madeo[2], Marcello Maggiolini[2,4] and Didier Picard[1,4,*]

[1]Département de Biologie Cellulaire, Sciences III, Université de Genève, Genève, Switzerland and [2]Department of Pharmaco-Biology, University of Calabria, Rende, Italy

bound transcription factors. ERs have been extensively studied at the molecular, cellular, physiological and pathological levels (reviewed by Dahlman-Wright *et al*, 2006; Deroo and Korach, 2006; Heldring *et al*, 2007). Tamoxifen and its hydroxylated active form hydroxytamoxifen (OHT) are synthetic ER ligands that compete with the physiological oestrogen 17β-estradiol (E2) for binding. Depending on promoter, cell and signalling context, OHT functions either as a partial

0888-8809/06/$15.00/0
Printed in U.S.A.

Molecular Endocrinology 20(3):631–646

doi: 10.1210/me.2005-0280

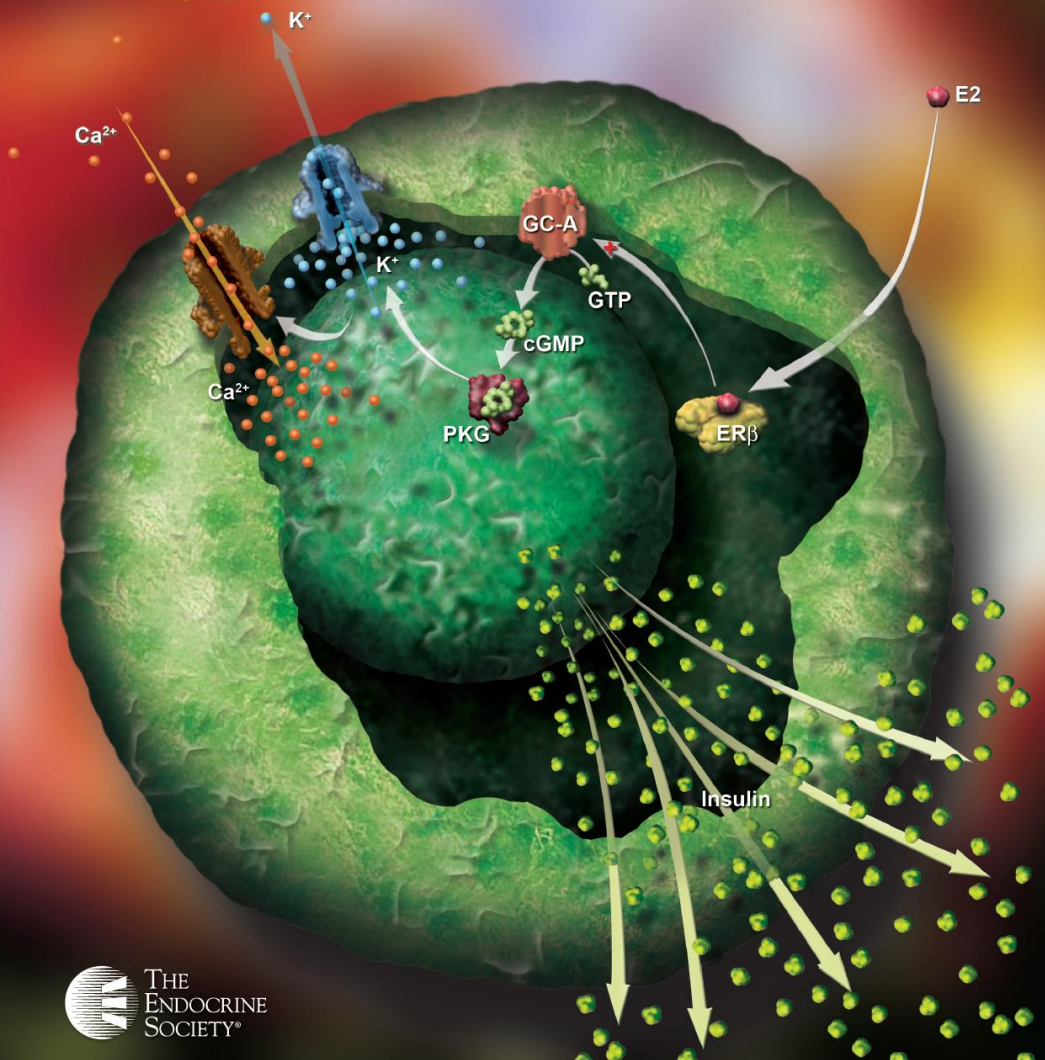
The G Protein-Coupled Receptor GPR30 Mediates the Proliferative Effects Induced by 17β-Estradiol and Hydroxytamoxifen in Endometrial Cancer Cells

Adele Vivacqua,* Daniela Bonofiglio,* Anna Grazia Recchia, Anna Maria Musti, Didier Picard, Sebastiano Andò, and Marcello Maggiolini

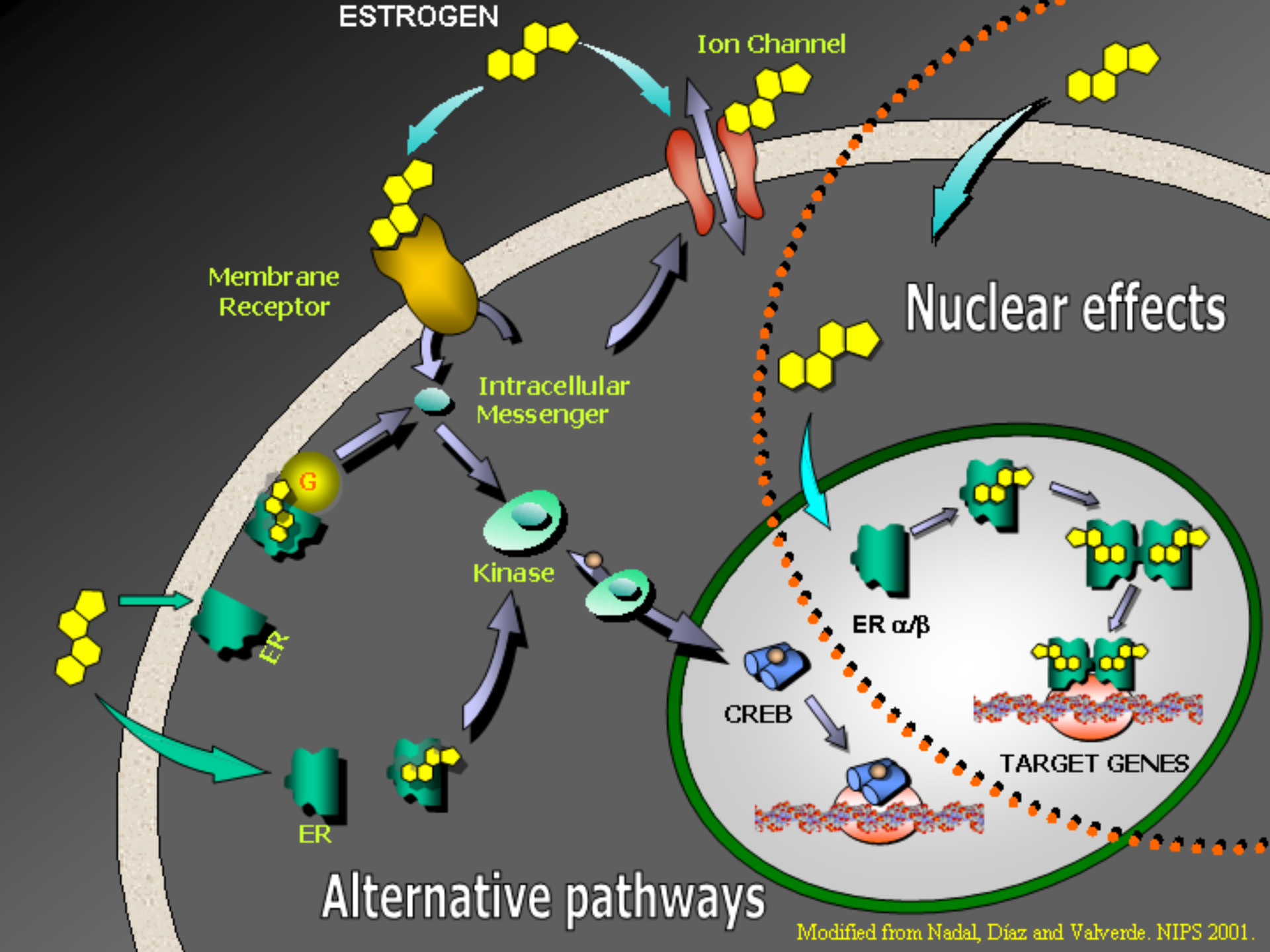
Departments of Pharmaco-Biology (A.V., D.B., A.G.R., A.M.M., M.M.) and Cellular Biology (S.A.), University of Calabria, 87030 Rende (Cosenza), Italy; and Department of Cellular Biology (D.P.), University of Geneva, 1211 Geneva, Switzerland

December 2009
Volume 23 • Number 12

MOLECULAR ENDOCRINOLOGY



The Endocrine Society®


ESTROGEN
Ion Channel
Membrane Receptor
Nuclear effects
Intracellular Messenger
G
Kinase
ER
ER α/β
CREB
TARGET GENES
ER
Alternative pathways
Modified from Nadal, Díaz and Valverde. NIPS 2001.

0013-7227/05/$15.00/0
Printed in U.S.A.

Endocrinology 146(2):624–632

doi: 10.1210/en.2004-1064

Identity of an Estrogen Membrane Receptor Coupled to a G Protein in Human Breast Cancer Cells

P. Thomas, Y. Pang, E. J. Filardo, and J. Dong

Marine Science Institute (P.T., Y.P., J.D.), University of Texas at Austin, Port Aransas, Texas 78373; and Department of Medicine (E.J.F.), Brown University School of Medicine, Providence, Rhode Island 02903

mapped the TβRI-interacting region of OCLN to extracellular loop 2 (L2) (Fig. 4C). TβRI is localized to tight junctions in polarized NMuMG cells (*25*). To determine whether OCLN might contribute to regulating TβRI localization, we used OCLN(ΔL2) as a dominant negative. Confocal microscopy in polarized NMuMG cells revealed that the WT, as well as the extracellular loop 1 (ΔL1) and ΔL2 mutants of OCLN, localized with ZO-1 on the apical aspect of the cell in tight junctions (Fig. 4D). Localization of Myc-tagged TβRI in tight junctions was unaffected by WT OCLN or OCLN(ΔL1), both of which interacted with TβRI. In contrast, OCLN(ΔL2) caused mislocalization of TβRI across the surface of the cell (Fig. 4D). Moreover, when we examined the epithelial-to-mesenchymal transition (EMT) in these cells, 40% of OCLN(ΔL2)-expressing cells exhibited retained tight junctions after TGFβ treatment, compared with only 10% of control cells (Fig. 4E) (*11*). In contrast, none of the OCLN mutants affected TGFβ-dependent induction of a Smad-responsive reporter gene (fig. S8). Thus, OCLN regulates TβRI localization to tight junctions, and this is important for efficient TGFβ-dependent dissolution of tight junctions during EMT. This suggests that targets of the receptor complex localized to tight

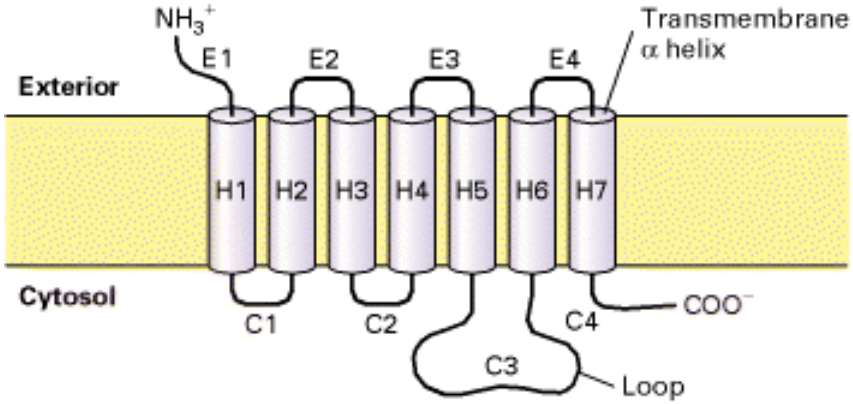
A Transmembrane Intracellular Estrogen Receptor Mediates Rapid Cell Signaling

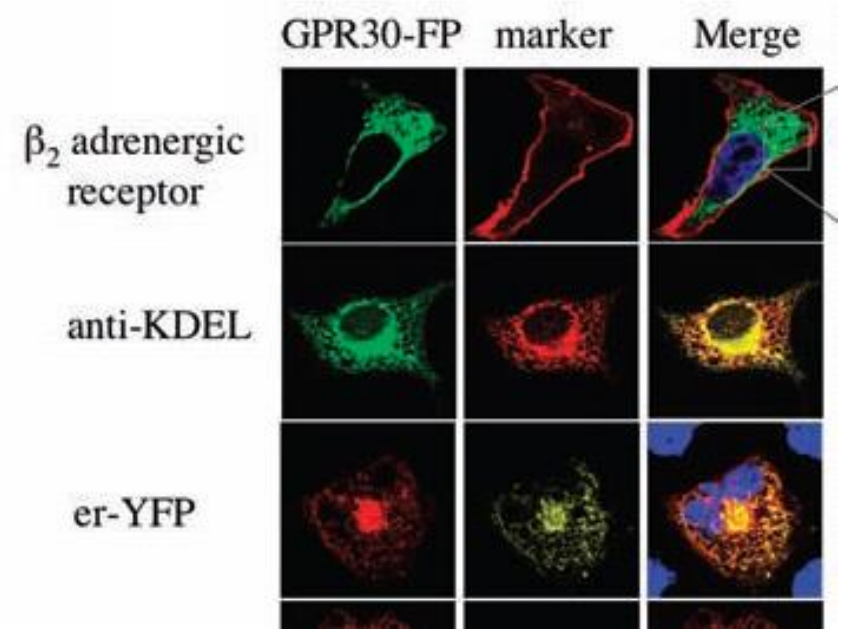
Chetana M. Revankar,[1,2] Daniel F. Cimino,[1,2] Larry A. Sklar,[2,3] Jeffrey B. Arterburn,[4] Eric R. Prossnitz[1,2]*

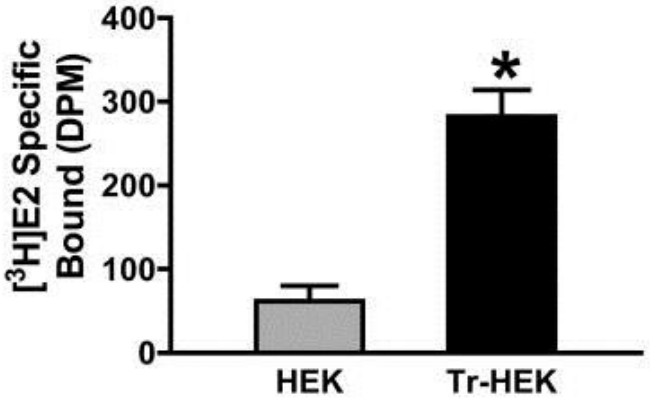
The steroid hormone estrogen regulates many functionally unrelated processes in numerous tissues. Although it is traditionally thought to control transcriptional activation through the classical nuclear estrogen receptors, it also initiates many rapid nongenomic signaling events. We found that of all G protein–coupled receptors characterized to date, GPR30 is uniquely localized to the endoplasmic reticulum, where it specifically binds estrogen and fluorescent estrogen derivatives. Activating GPR30 by estrogen resulted in intracellular calcium mobilization and synthesis of phosphatidylinositol 3,4,5-trisphosphate in the nucleus. Thus, GPR30 represents an intracellular transmembrane estrogen receptor that may contribute to normal estrogen physiology as well as pathophysiology.

Estrogen (17β-estradiol, E2) represents one of a family of steroid hormones that act through soluble intracellular receptors. Once activated, these receptors translocate to the nucleus, where they function as ligand-dependent transcription factors (*1*, *2*). This mode of action of two such estrogen-binding receptors, ERα and ERβ, is reasonably well understood (*3*, *4*). However, the existence of functional ERs associated with the plasma membrane has been debated (*5*). It has been suggested that such membrane receptors me-

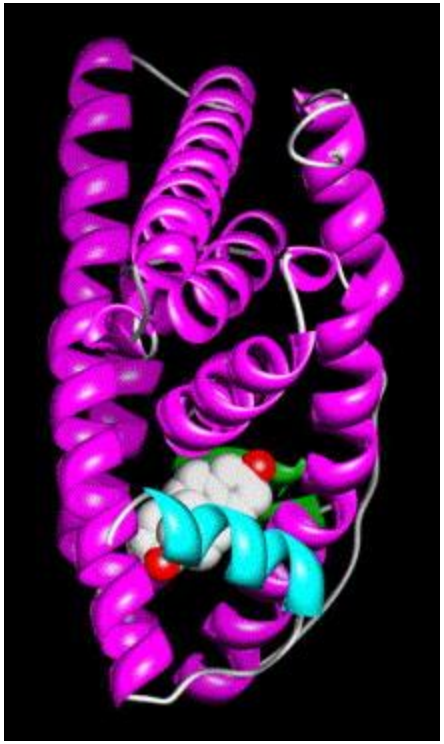
GPR30/GPER1



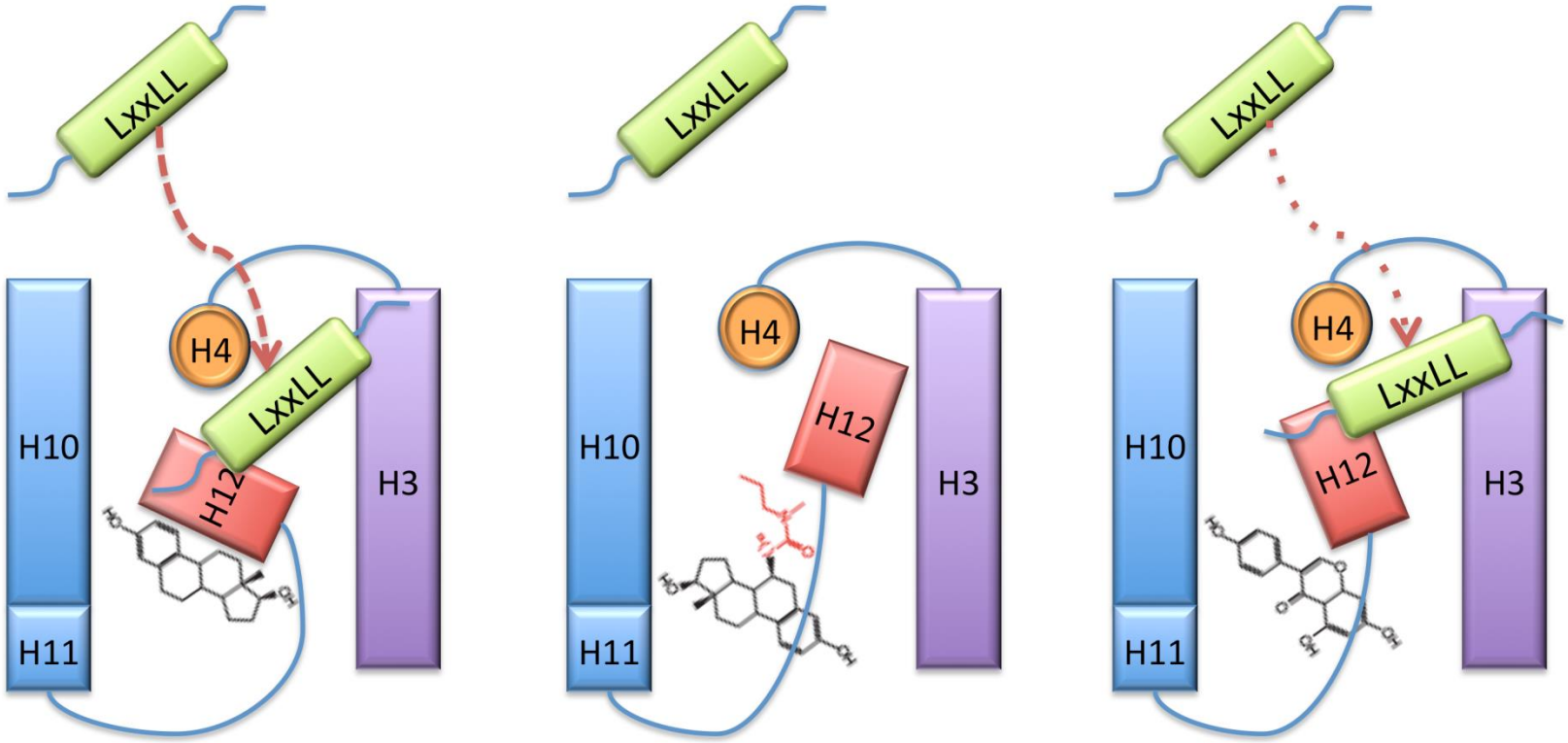




Thomas et al. Endocrinology 2005; Revankar et al. Science 2005; Prossnitz et al. Ann. Rev. Physiol. 2008; Prossnitz et al. TIPS 2008



Three-dimensional structure of the human ERα LBD-E2 complex (1ERE) (Brzozowski et al., 1997). The α-helices are drawn in magenta, the β-strand in green, and the H12 α-helix in cyan. E2 is shown in space-filling form and colored according to atom type. The picture has been generated with UCSF Chimera (Pettersen et al., 2004).



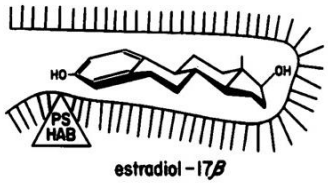
Agonist
Estradiol

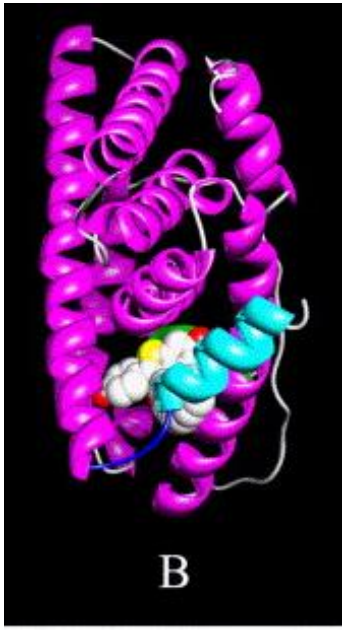
Antagonist
ICI164384

Partial Agonist
Genistein

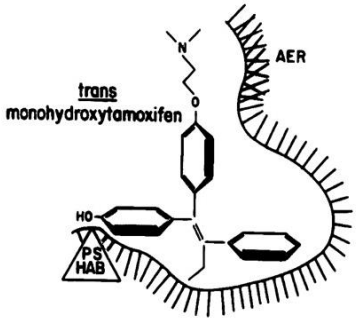
NRR
Nuclear Receptor Resource

Human ERα **LBD in complex with E2 and SRC-2 NR-box3 peptide (1GWR)** (Wärnmark et al., 2002).



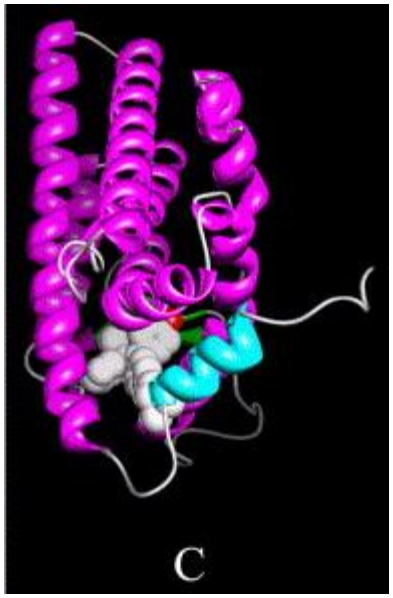


Human ERα **LBD-raloxifene** complex (1ERR) (Brzozowski et al., 1997).



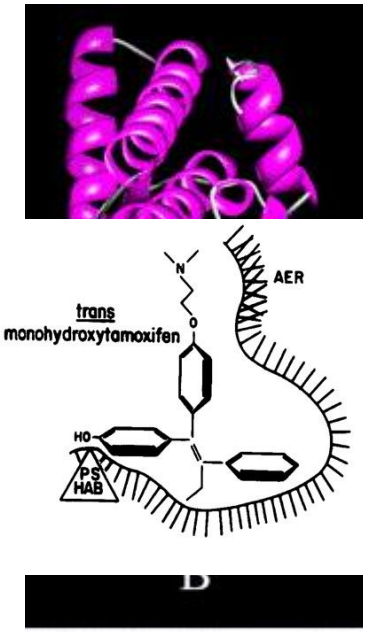
Partial antagonist
Selective estrogen receptor modulator (SERM)

Read also Jensen E V , Jordan V C Clin Cancer Res 2003;9:1980-1989

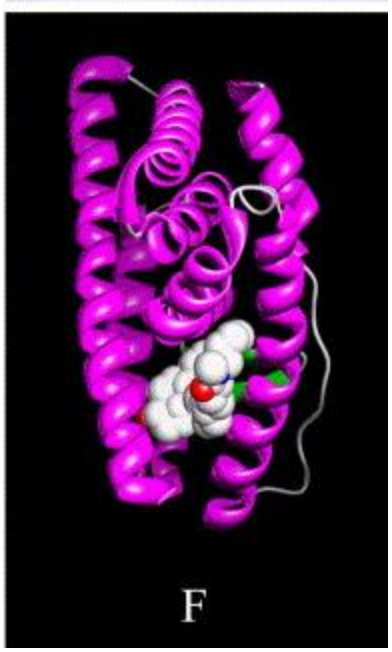


Human ERα LBD-4-hydroxytamoxifen complex (3ERT) (Shiau et al., 1998).

(SERMs)



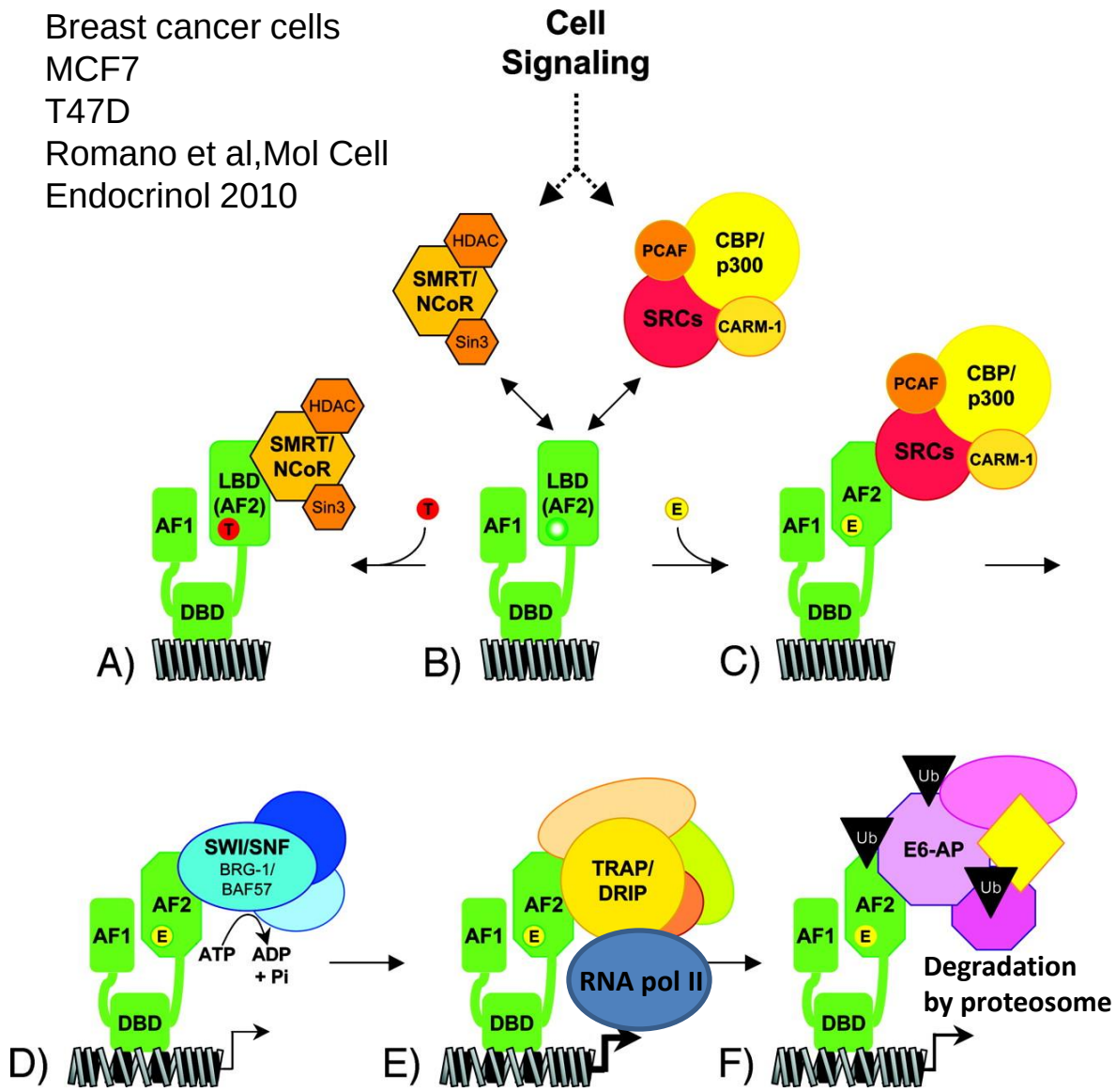
Raloxifeno



Rat ERβ LBD-ICI 164,384 (1HJ1) (Pike et al., 2001). The binding of ICI 164,384 to rat ERβ LBD abolishes the association between the H12 α-helix and the rest of the LBD. The H12 α-helix is not shown because it is completely invisible in the experimental electron density maps (Pike et al., 2001).

Pure antagonist

Breast cancer cells
MCF7
T47D
Romano et al,Mol Cell Endocrinol 2010



Smith, C. L. et al. Endocr Rev 2004;25:45-71

Model of nuclear receptor-dependent gene expression. This represents a hypothetical schematic of the exchange of coregulators involved in activation of a gene by a steroid hormone receptor, such as ER. Coactivators and corepressors exist in complexes in the cell and do not appear to bind to receptor as monomers.

CBP/p300 histone acetylases

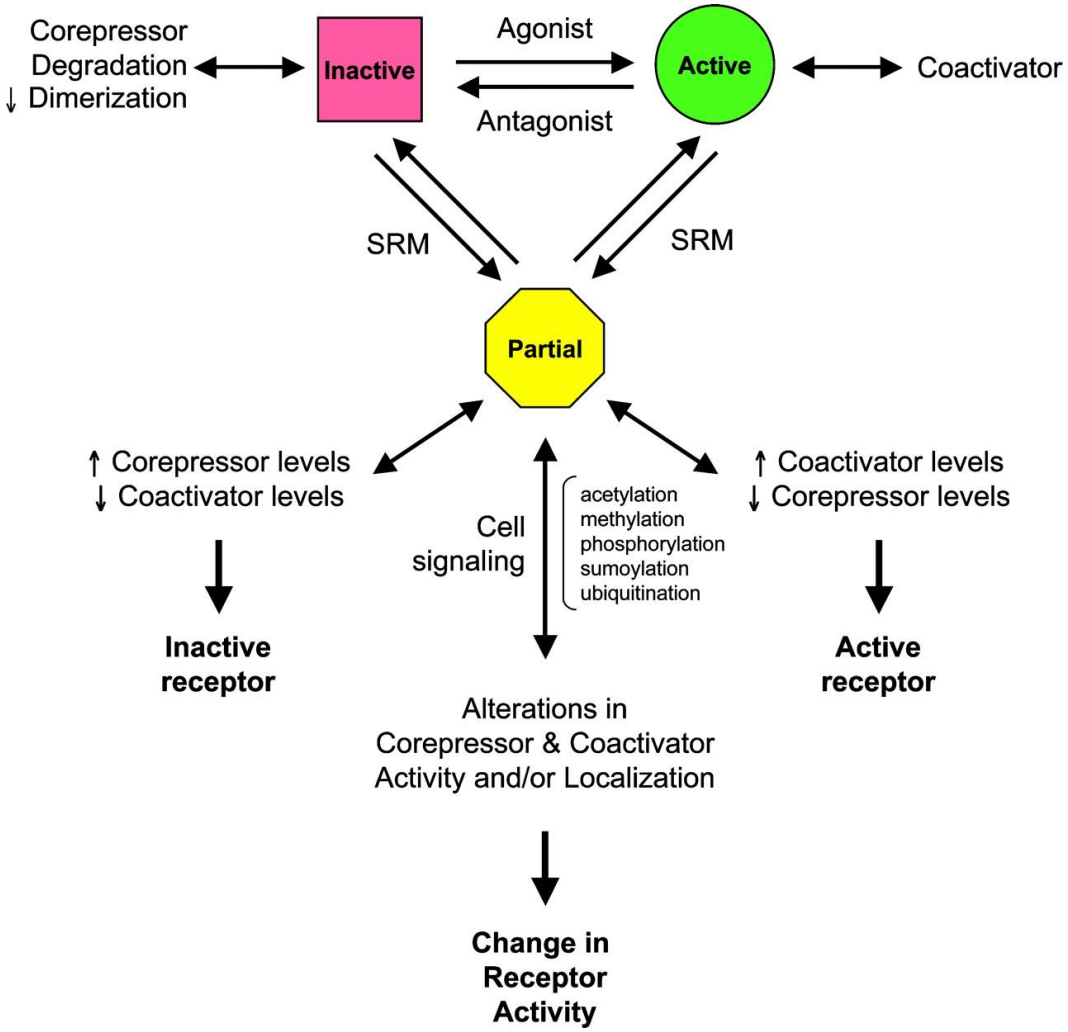
CARM1 Co activator-associated arginine methyltransferase
pCAF CBP/p300-associated factor

TRAP/DRIP Thyroid hormone receptor associated protein/Vitamin D receptor-integrating protein

SNF sucrose non-fermenting factor complex, an ATP coupled chromatin-remodeling

E6-AP ubiquitin ligases

Model of the contribution of coactivators and corepressors to relative SRM agonist/antagonist activity

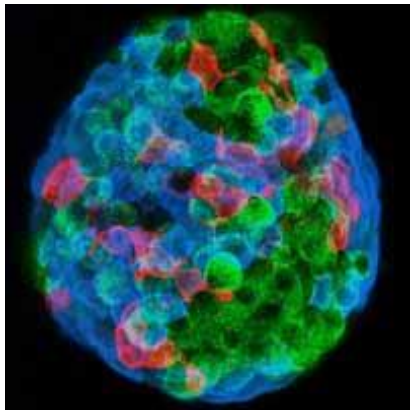


Smith, C. L. et al. Endocr Rev 2004;25:45-71

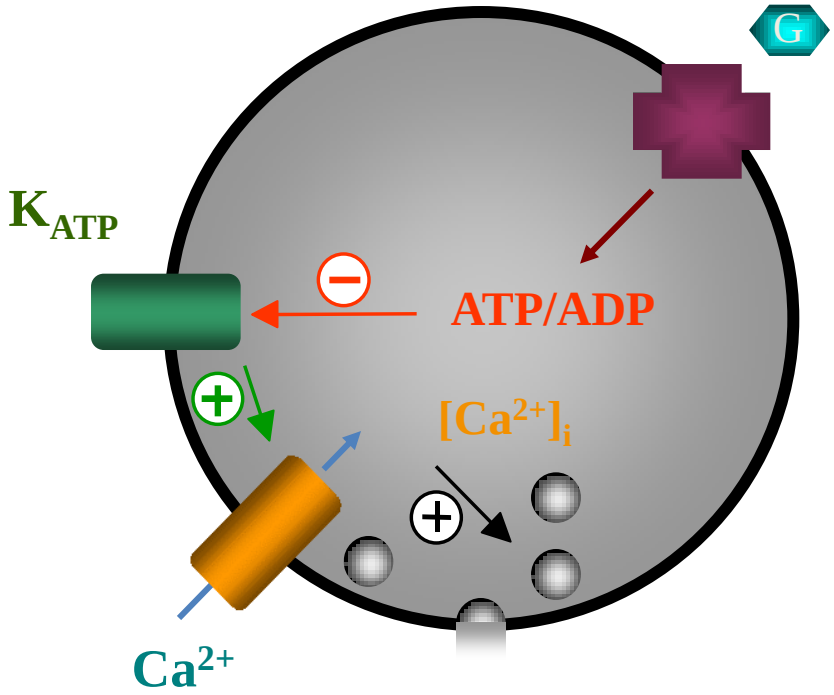
ENDOCRINE REVIEWS

Efecto insulinotrópico en la célula β del islote de Langerhans

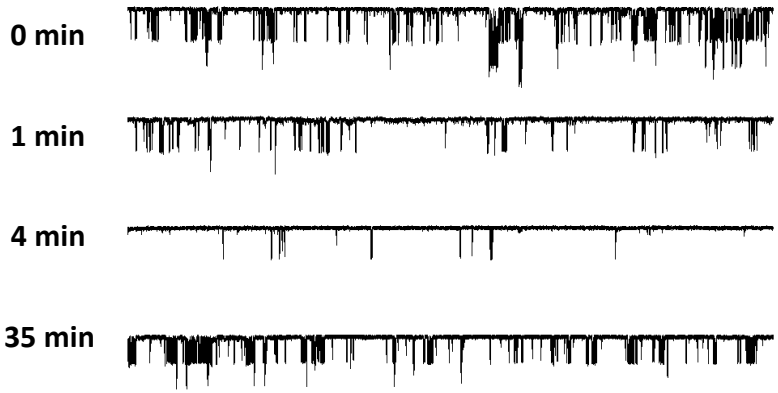
Efecto rápido



R.L Sorenson y T.C. Brelje

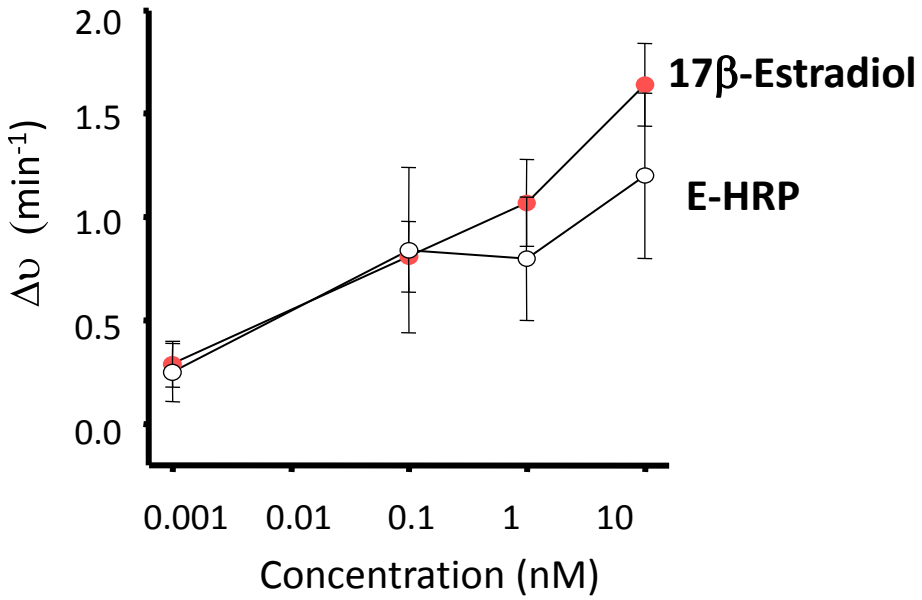


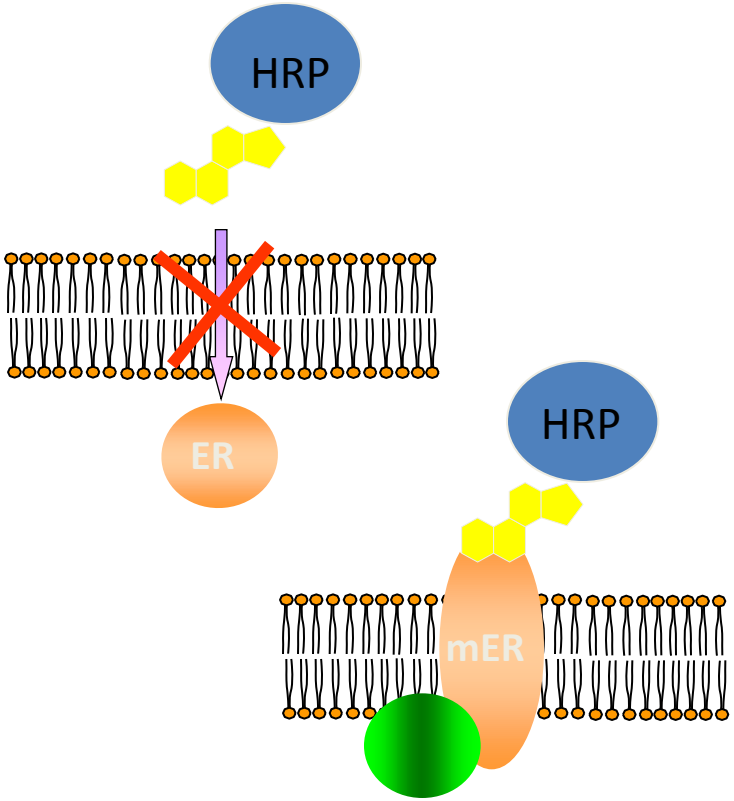
1nM 17β-Estradiol **K_{ATP}**

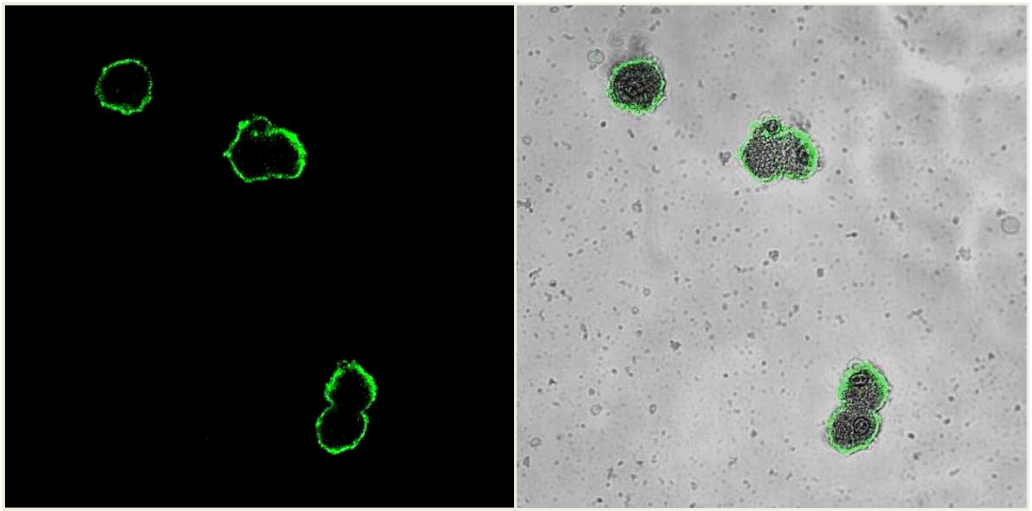


Nadal et al, FASEB J 1998

Efectos sobre la membrana plasmática

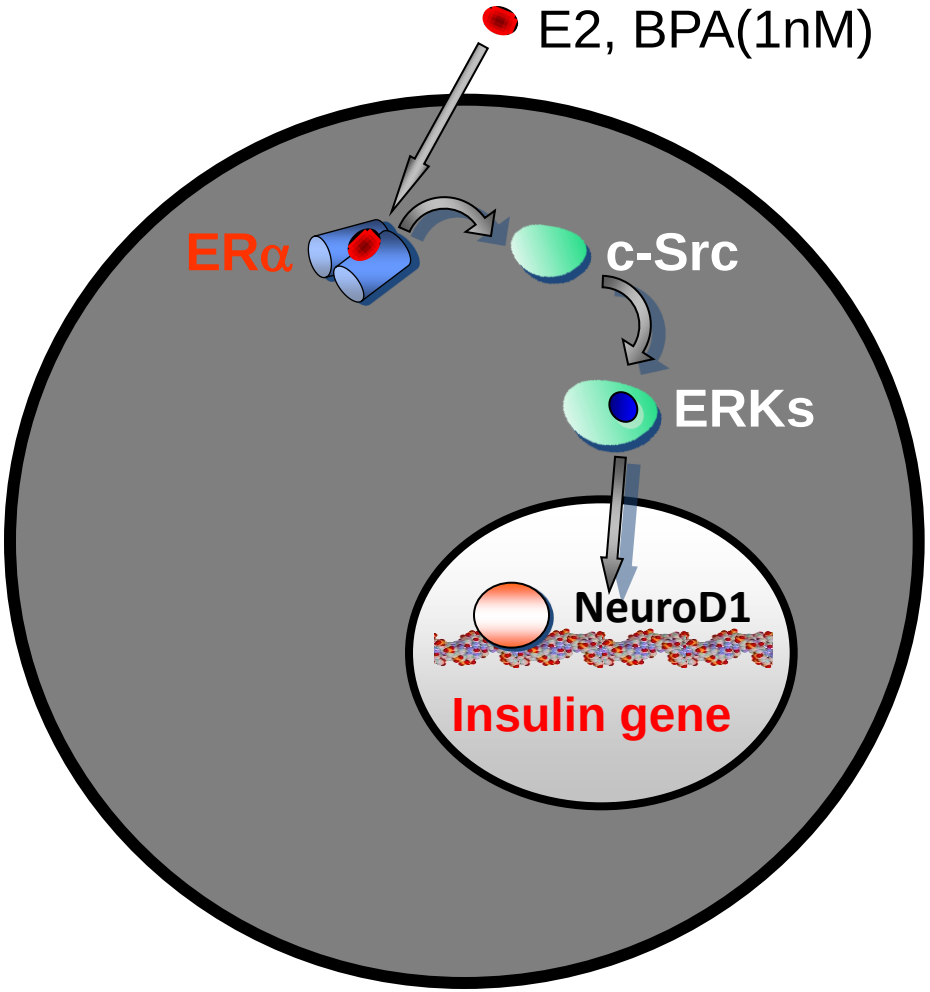






Insulin biosynthesis

β-Cells



Alonso-Magdalena et al, Plos One 2008
Alonso-Magdalena et al, EHP2006

Wong et al, PNAS 2010