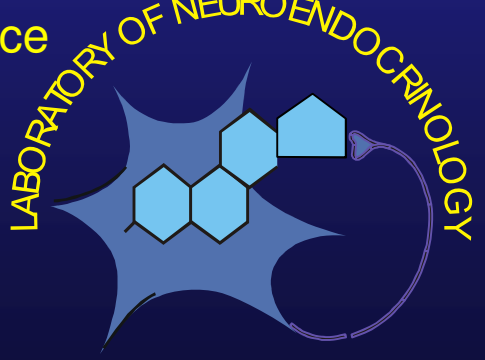
Hormonal Modulation of Pain : Estrogen Modulation of Visceral Nociception

Victor Chaban, Ph.D., MSCR

Department of Internal Medicine
Charles R. Drew University of Medicine and Science
Department of Medicine
David Geffen School of Medicine
University of California, Los Angeles



Background

The brain is one of the specific target tissues for sex steroid hormones. Estrogens, progestins and androgens are able to induce several effects in brain areas of the central and peripheral nervous system, through the binding with specific receptors. It has recently been demonstrated that the spinal cord is an active production center of neuroactive steroids including pregnenolone, dehydroepiandrosterone, progesterone, allopregnanolone and estrogen.

General Hypothesis:

Steroid hormones may be involved in the modulation of nociceptive mechanisms

Clinical Relevance:

Functional- disorders for which no pathophysiological cause can be identified?

Visceral pain-associated functional syndromes

- Irritable bowel syndrome (IBS)
- Interstitial cystitis (IC) a.k.a Painful Bladder Syndrome (IC/PBS)
- Chronic pelvic pain (CPP)

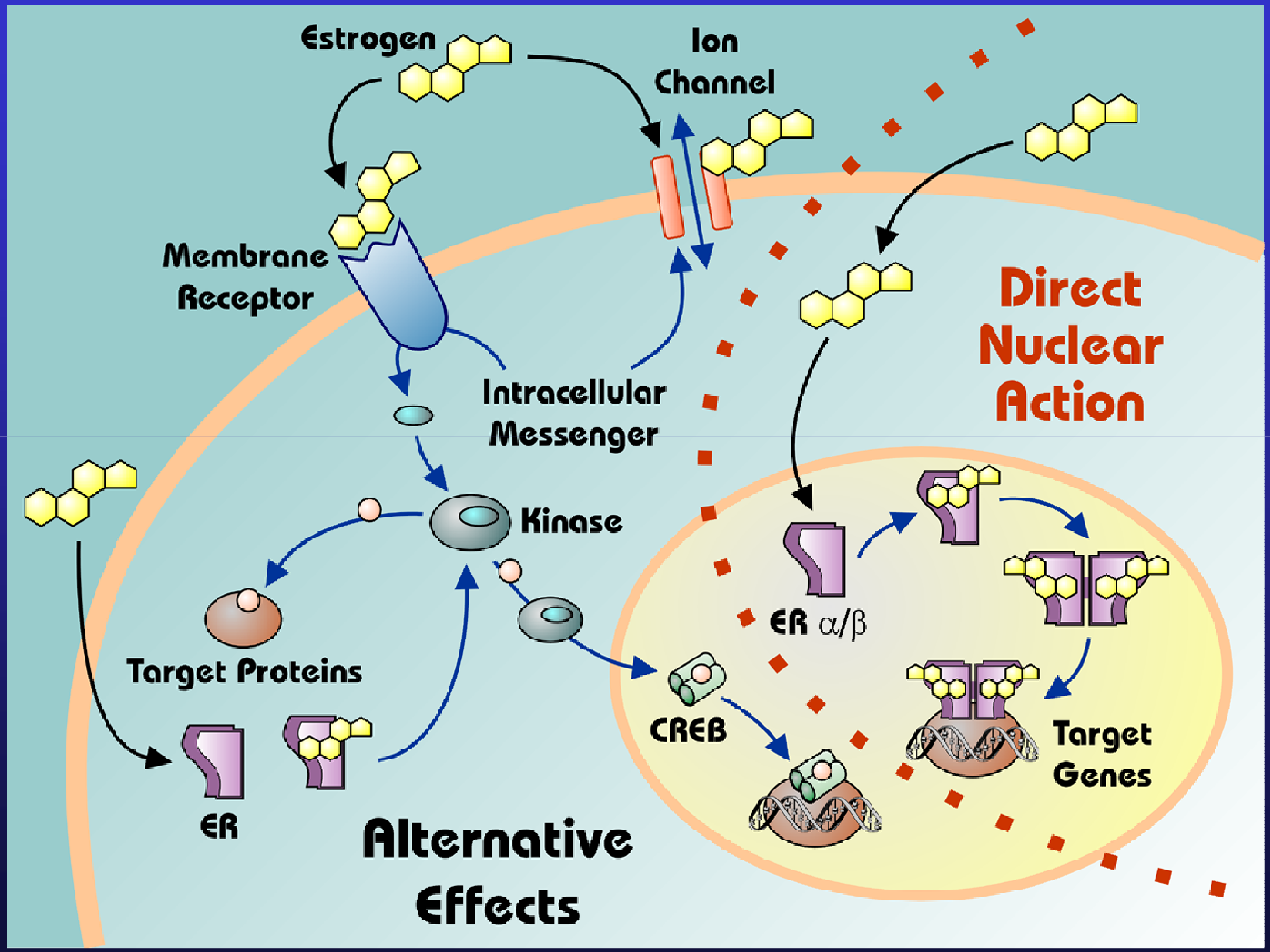
IBS estimated to affect 25% of the population in many countries and accounts for 40-50% of GI consultations worldwide. Symptoms description of IC/PBS (urgency, frequency, and bladder pain generally relieved by voiding) is parallel to the description of IBS-diarrhea predominance (urgency, frequency, and abdominal pain relieved by defecation)

Chronic pelvic pain (CPP) covers a wide range of reproductive disorders including dysmenorrhea, endometriosis, and pelvic congestion as well as bowel (IBS) and urinary tract problems (such as IC/PBS)

Incidence of episodic or persistent visceral pain associated with functional disorders is 2- 3x higher (IBS) or even more (IC/PBS) in women than men

Hypothesis I: *Estradiol modulates nociceptive signaling associated with pelvic pain*

The Estrogen Trinity: Membrane, Cytosolic, and Nuclear Effects



Alternative mechanisms of action of estrogens:

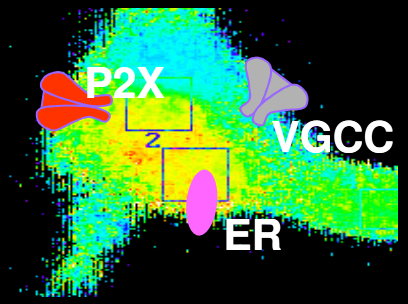
- The rapid time course of the primary effect is too fast to be compatible with RNA synthesis or protein translation (seconds to minutes)

- Dependence (or independence) on the presence of classic ERs (inhibition of the effect by ICI-182780)

- The extracellular membrane-delimited primary effect might be achieved by estrogen conjugated to membrane-impermeant molecules (E-6-BSA)

Activation and Sensitization of Primary Afferents

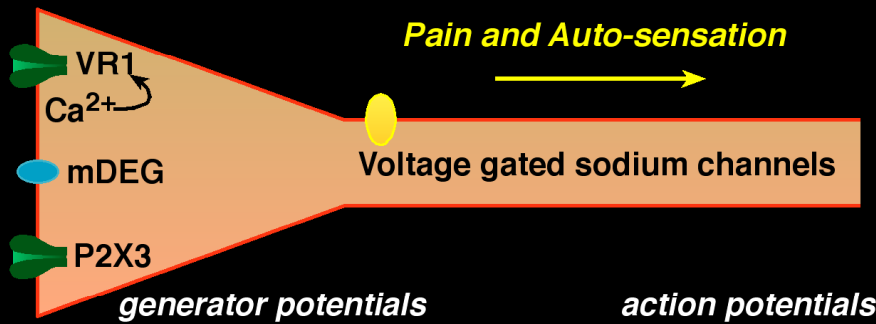
ACTIVATION

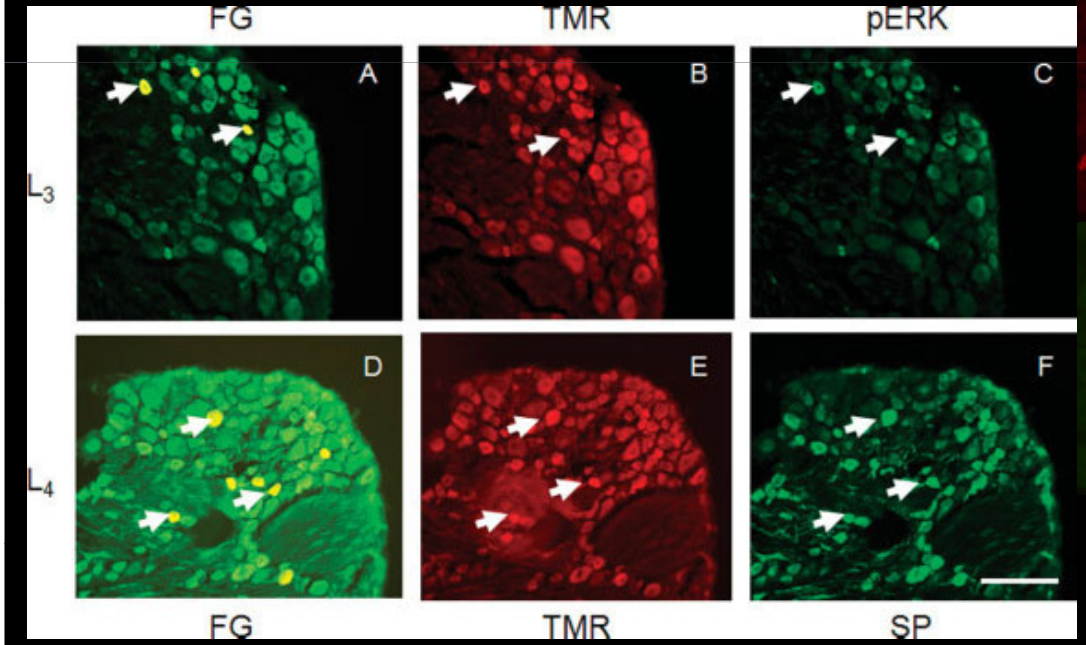


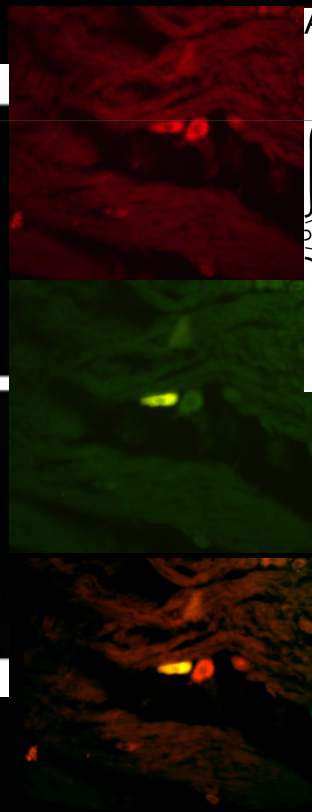
Acid

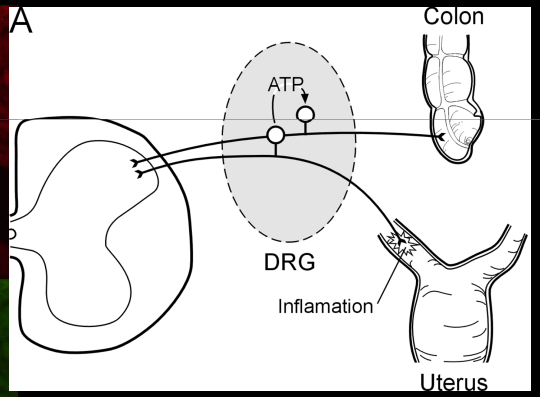
Mechanical

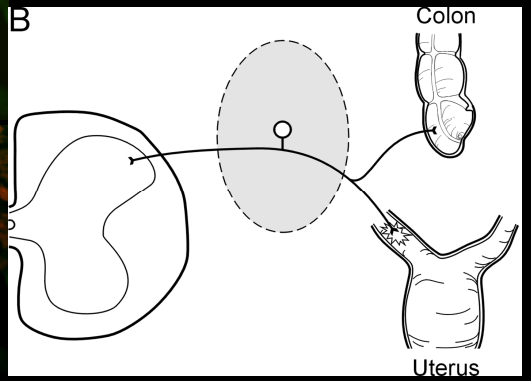
Chemical





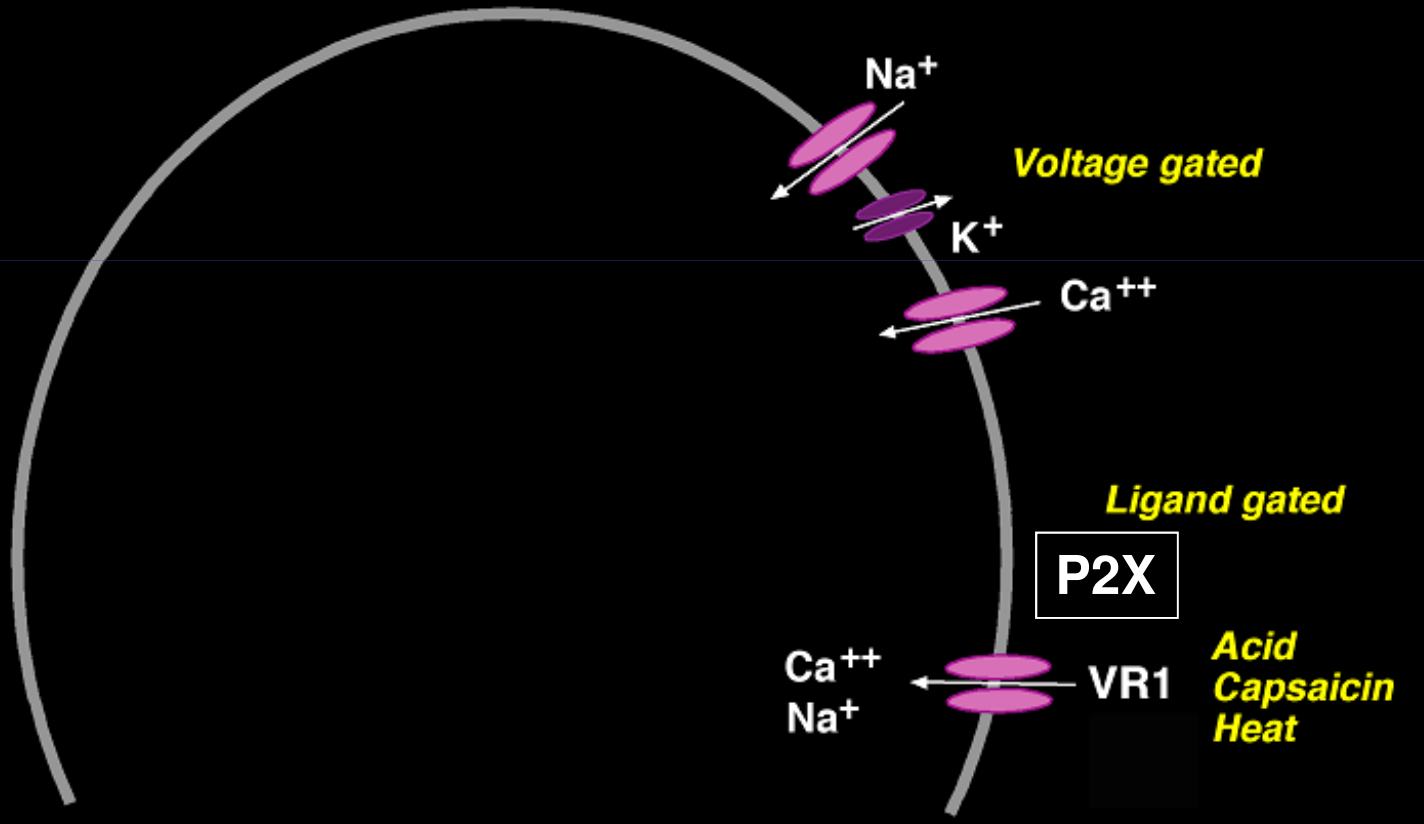




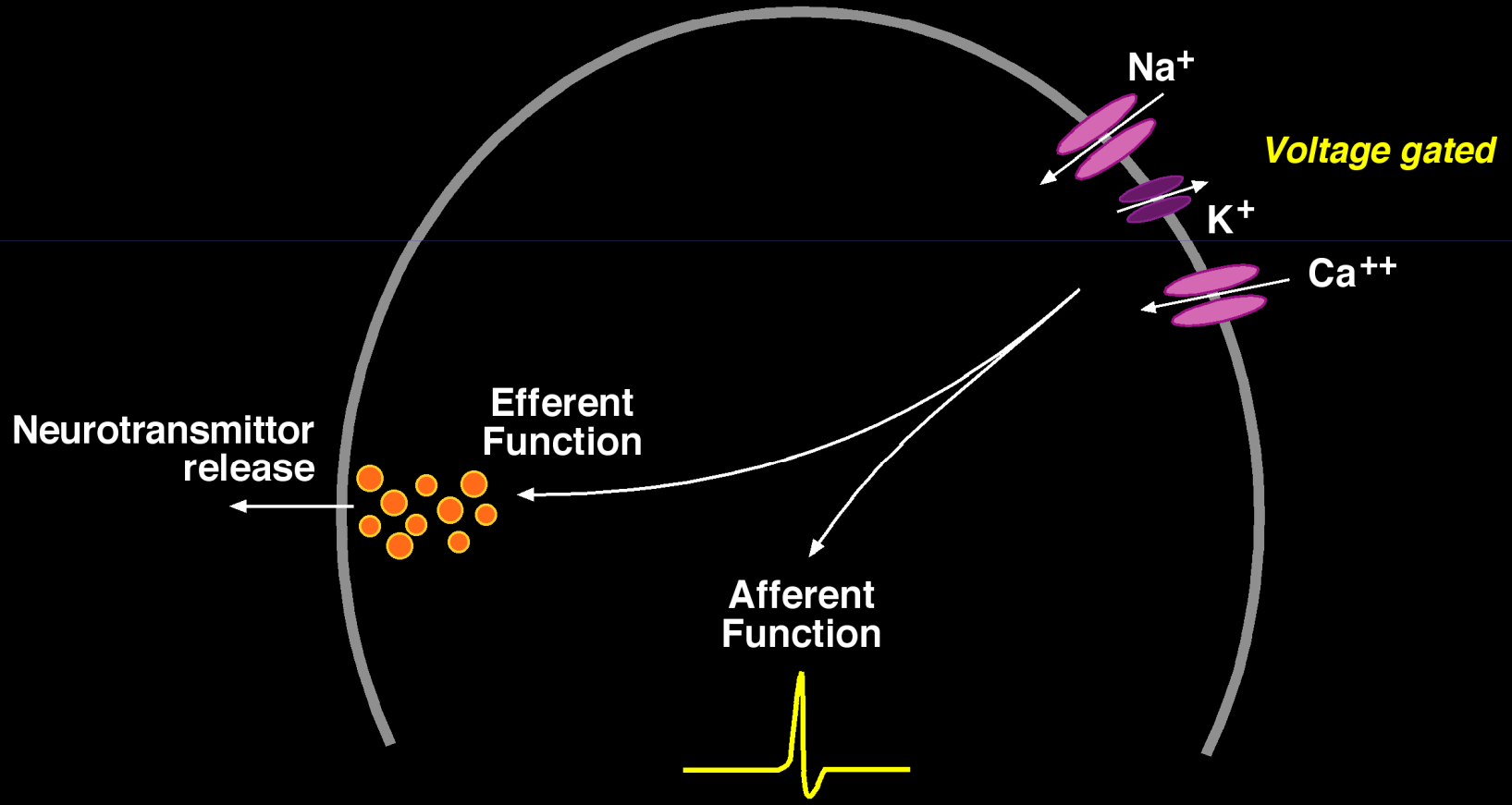


Chaban, J. Neurosci. Res. 2011

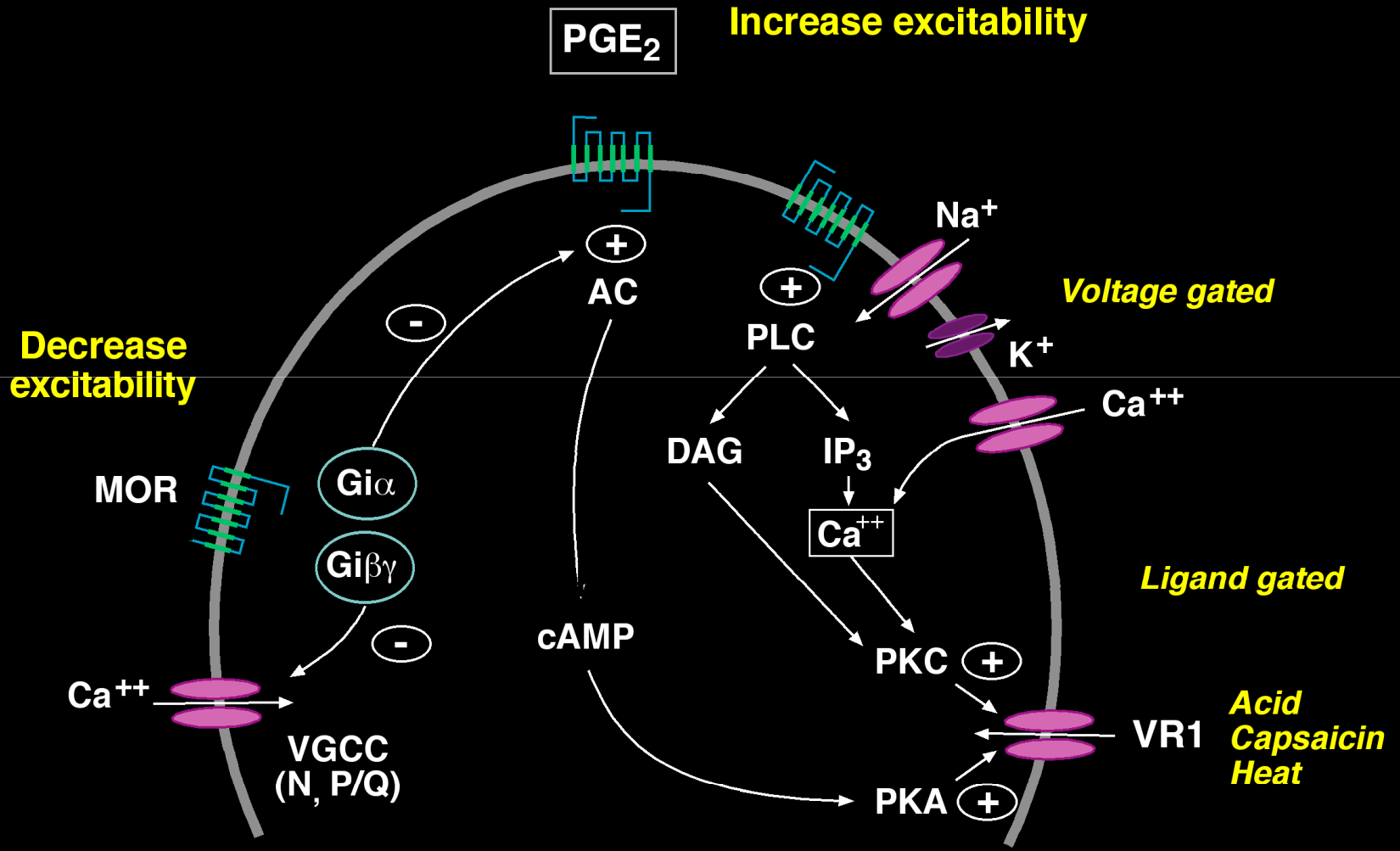
Ligand-gated Ion Channels



Voltage-gated Ion Channels



G-protein Coupled Receptors

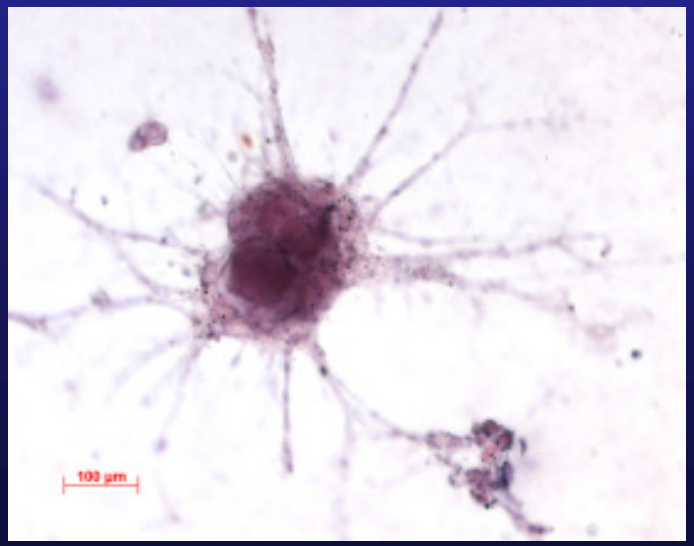


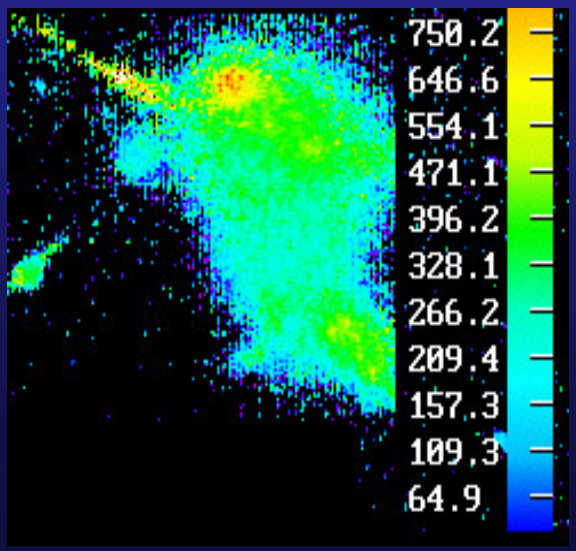
Previous findings:

17β-Estradiol inhibits ATP-induced $[Ca^{2+}]_i$ influx in DRG neurons

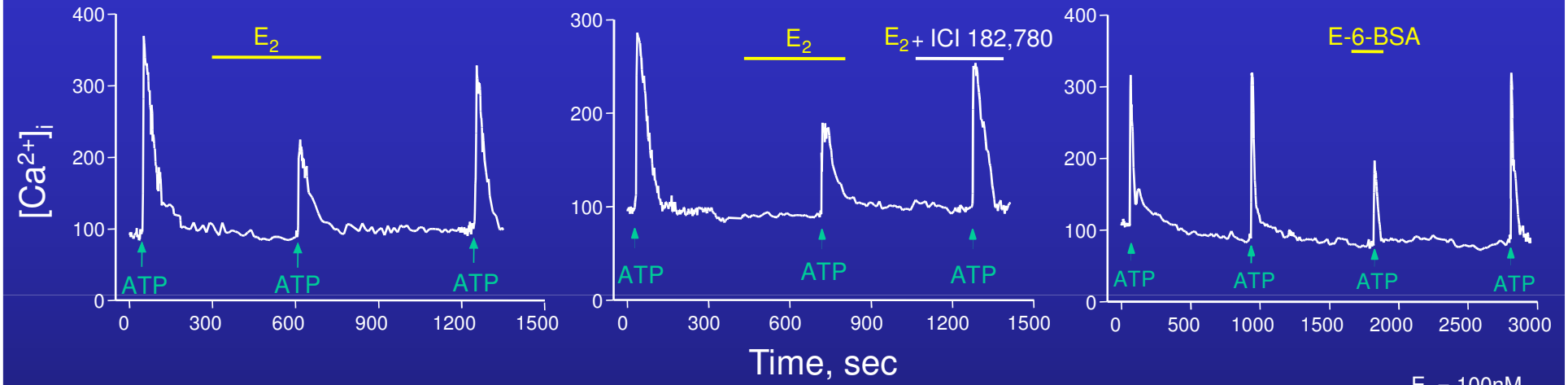
17β- Estradiol attenuates the ability of opioids to inhibit ATP-induced $[Ca^{2+}]_i$ response

17-β Estradiol attenuates the inhibition of PGE_2-induced $[cAMP]_i$ production in cultured DRG neurons mediated through MOP



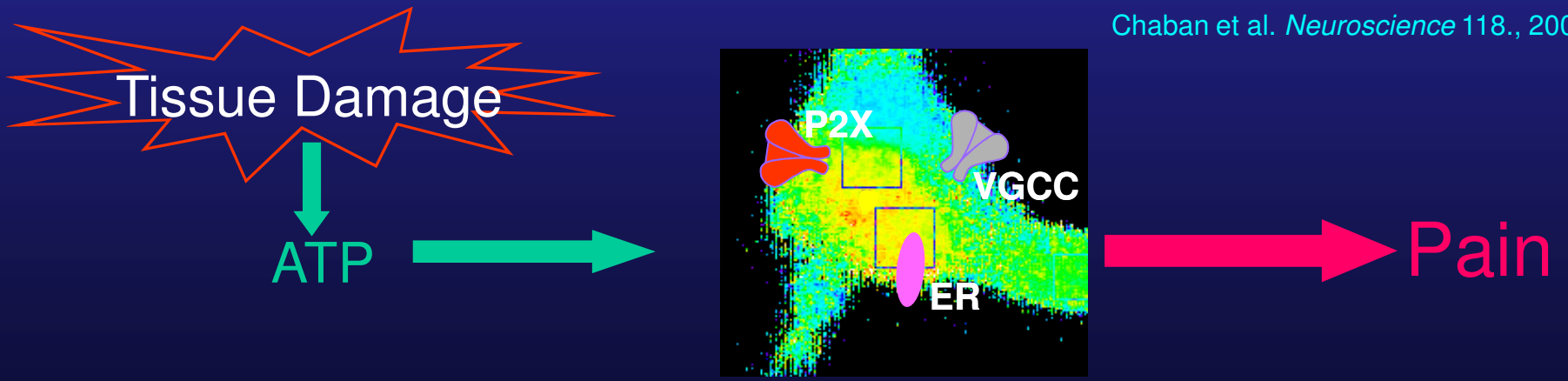


ESTRADIOL INHIBITS ATP-INCREASED $[Ca^{2+}]_i$ IN DRG NEURONS



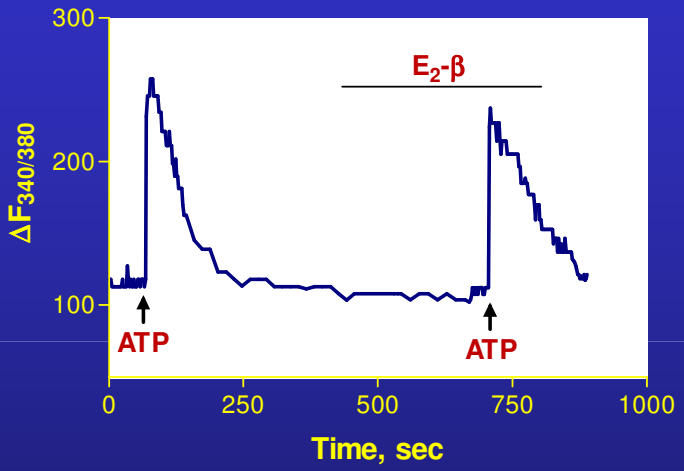
E_2 = 100nM
ATP= 10μM

Chaban et al. *Neuroscience* 118., 2003

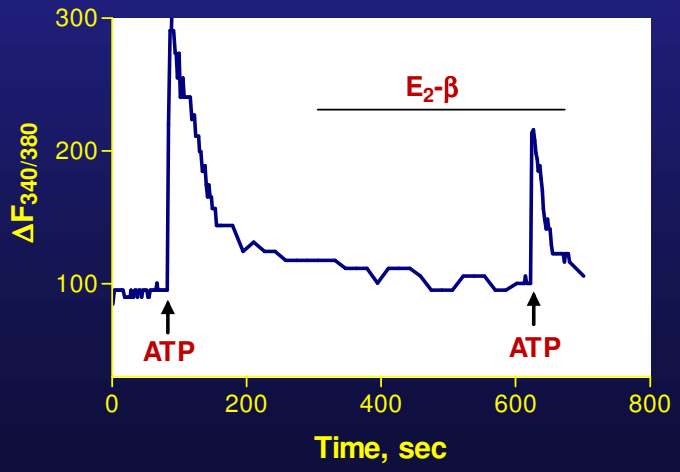


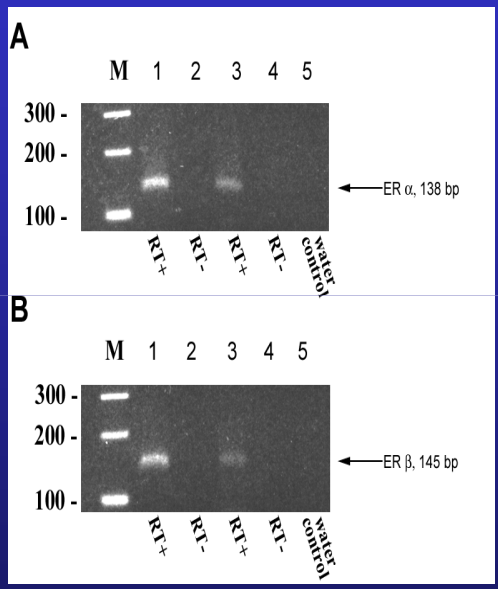
Estradiol do not inhibit ATP-induced $[Ca^{2+}]_i$ in ERαKO mice

Wild type



ERαKO

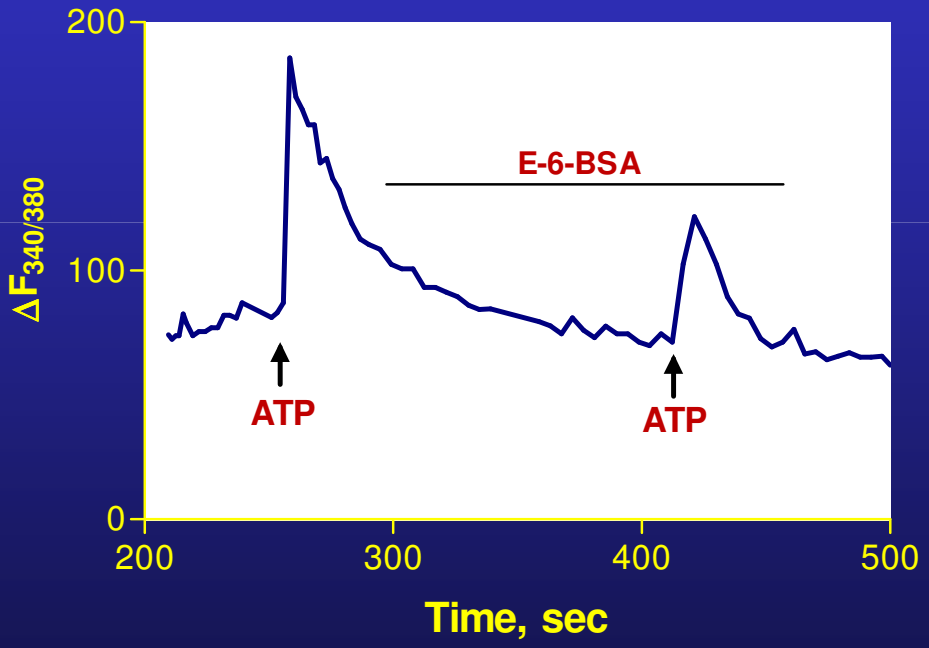


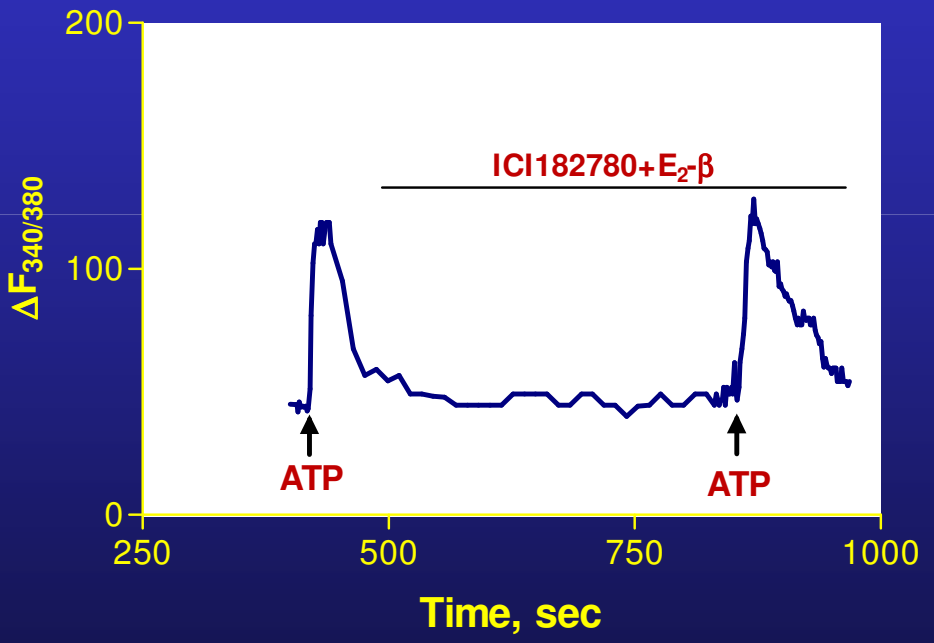


RT-PCR analysis of estrogen receptor (ER)α & ERβ gene expression. Samples without reverse transcriptase (RT-) have no amplicon. Lane M: DNA size-marker.

Chaban & Micevych, 2005

Pharmacological profile of estradiol-modulated ATP-induced $[Ca^{2+}]_i$ increase in Wt mice





Chaban & Micevych, 2005

17β-estradiol inhibits ATP-induced $[Ca^{2+}]_i$ response in small DRG neurons from Wt and ERβKO mice

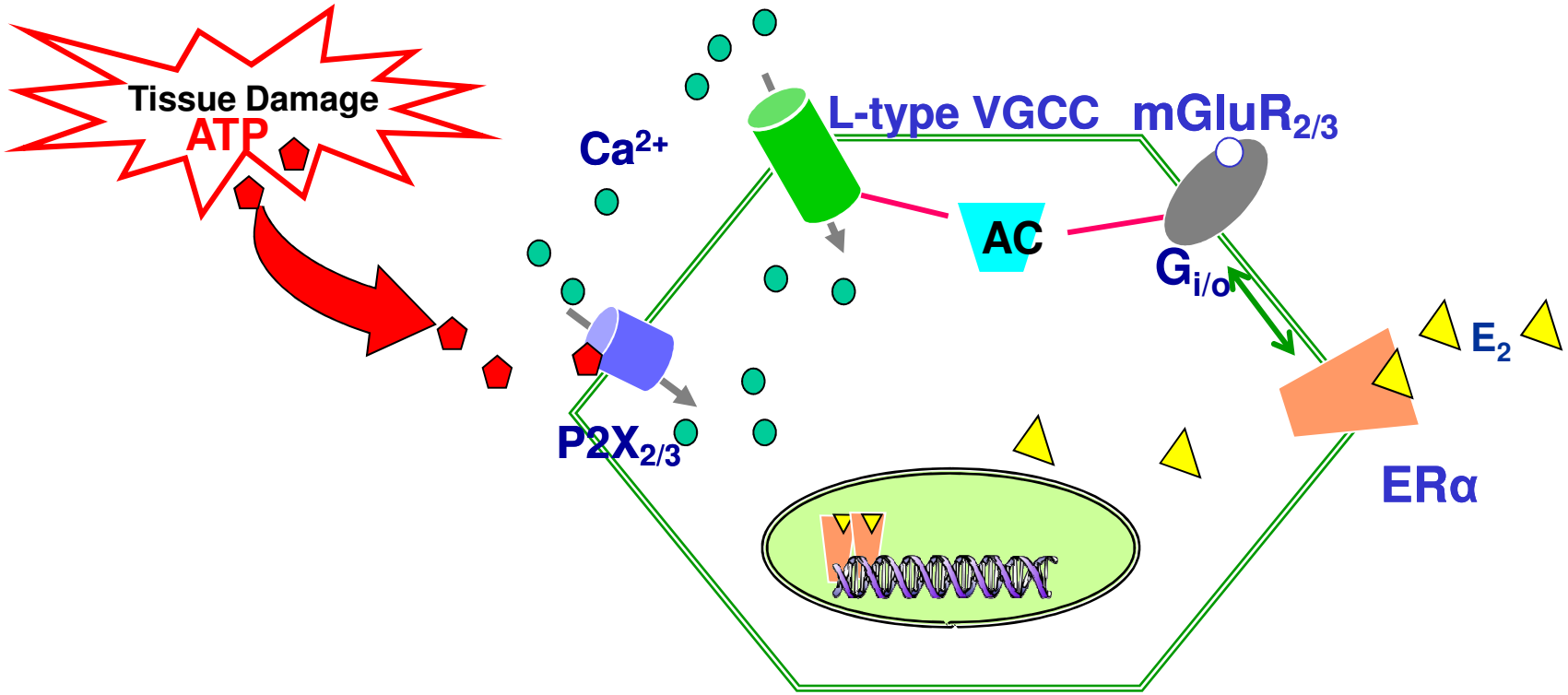
The effect on the pharmacology of an ER:

- E_2 effect is stereo-specific since 17α-estradiol had no effect
- E_2 effect is steroid-specific- blocked by ICI 182780.

Mediated via membrane-associated ERα

- E-6-BSA mimics the effect of E_2 in Wt mice
- E_2 did not attenuate ATP-induced $[Ca^{2+}]_i$ flux in DRG neurons from ERαKO mouse

Proposed mechanisms of visceral nociception modulation



ATP released by tissue damage acts on P2X3 that activate VGCC - signaling nociception. 17-E_2 modulates L-type VGCC in DRG neurons via the direct interaction of a membrane ERα with the $mGluR_{2/3}$ inhibiting adenylyl cyclase (AC) activation of L-type VGCC

(Chaban et al. *American Journal of Translational Research*, 2013)

Hypothesis II:

Primary afferent neurons as site of convergence for different pelvic organs (*In vivo studies*):

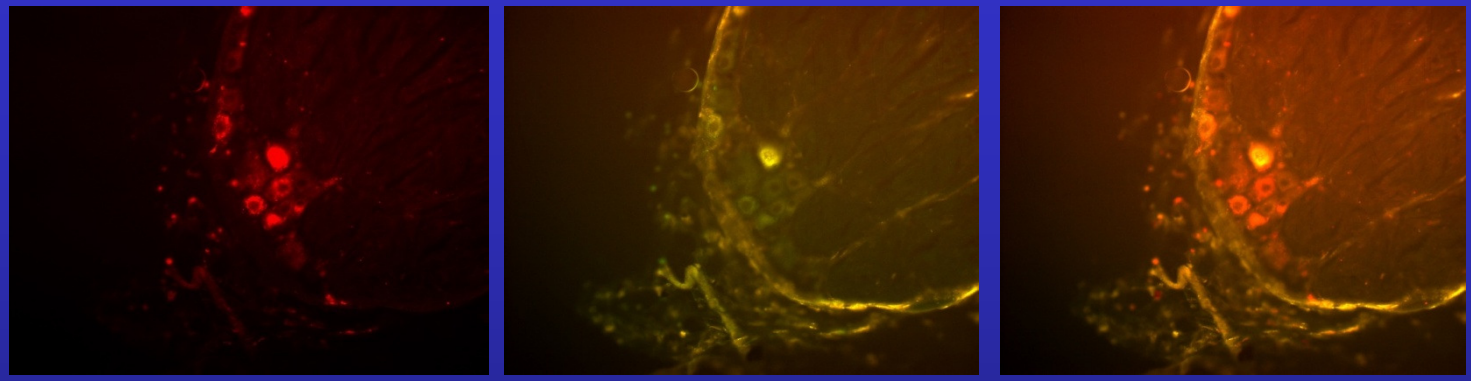
Communication between somatic and visceral organ systems has been demonstrated. Unclear where systems converge

DRG may be a site for viscero-visceral cross-sensitization

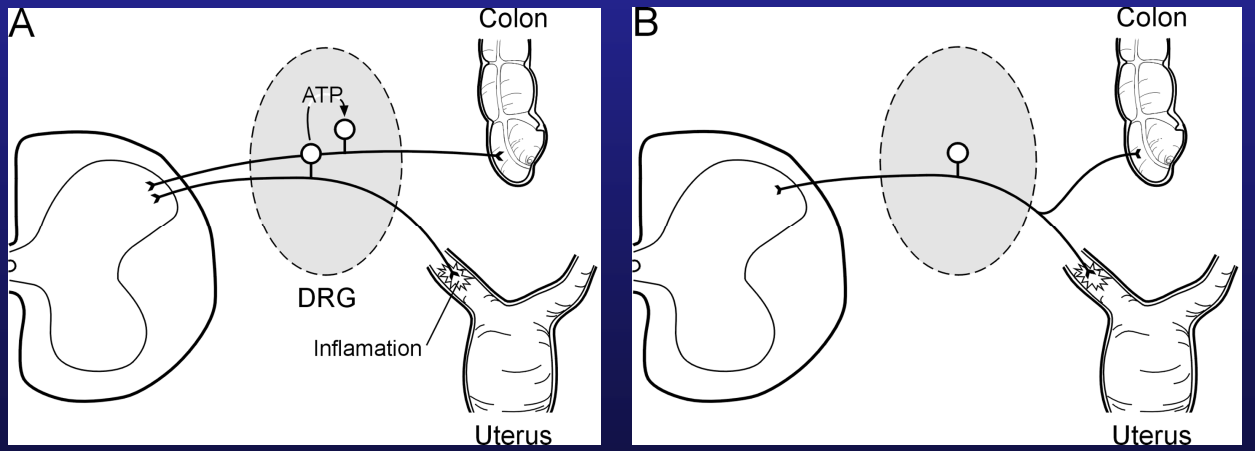
Methods:

Retrograde labeling of DRG neurons innervating uterus /colon or hind paw by retrograde tracers determined modulation of intracellular calcium influx induced by ATP (P2XR- agonist) or α,β- me ATP (P2X3R agonist) in visceral and cutaneous primary sensory neurons .

A subset of DRG neurons innervate both visceral organs: uterus and colon

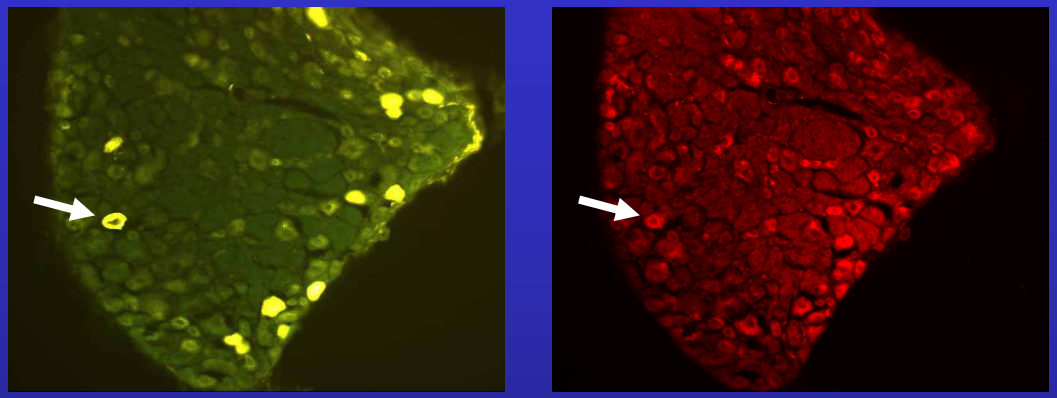


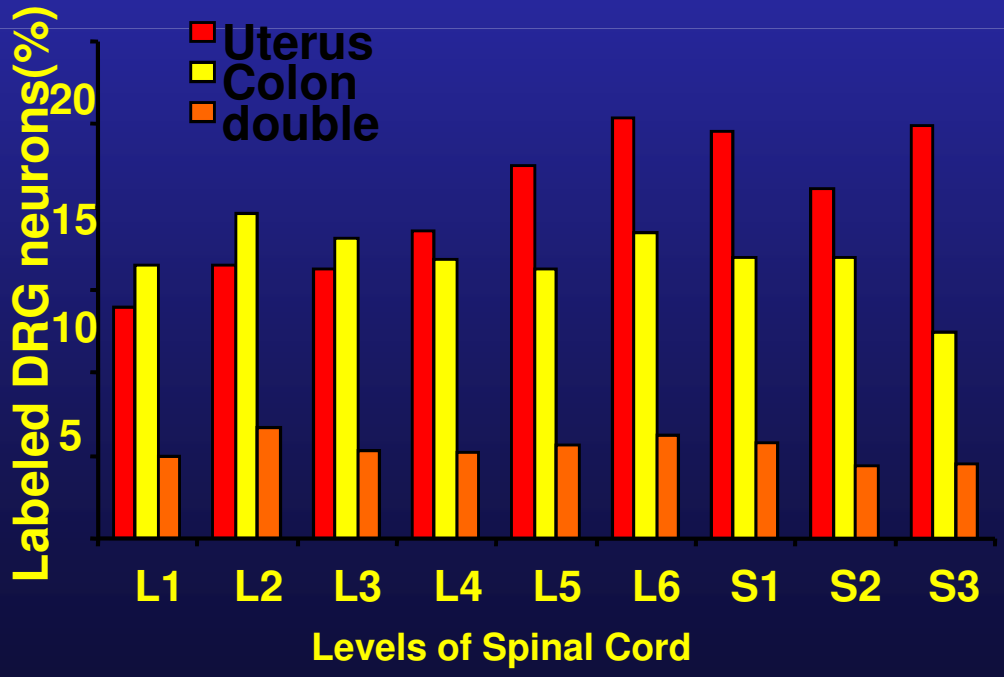
Chaban et al, *Neuroreport*, 2007



Chaban V. In: "Neuroactive Steroids in Brain Function, and Mental Health: New Perspectives for Research and Treatment", Springer 2008

Labeled DRG Neurons





Conclusions

Estrogen down-regulates intracellular signaling associated with *nociception* and decreases *anti-nociceptive* opioid signaling in primary afferent sensory neurons. Thus, depending on the presence or absence of opioid receptor agonists, estrogen can be either *anti-nociceptive or pro-nociceptive* (Chaban et al., 2004- 2014)

Estrogen *differently* acts on visceral and cutaneous sensory neurons

Gonadal hormones are necessary for reproduction, but it appears that no body region, no neuronal circuit, and virtually no cell is unaffected by them. Thus, increased attention toward these hormones appears to be *obligatory*

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