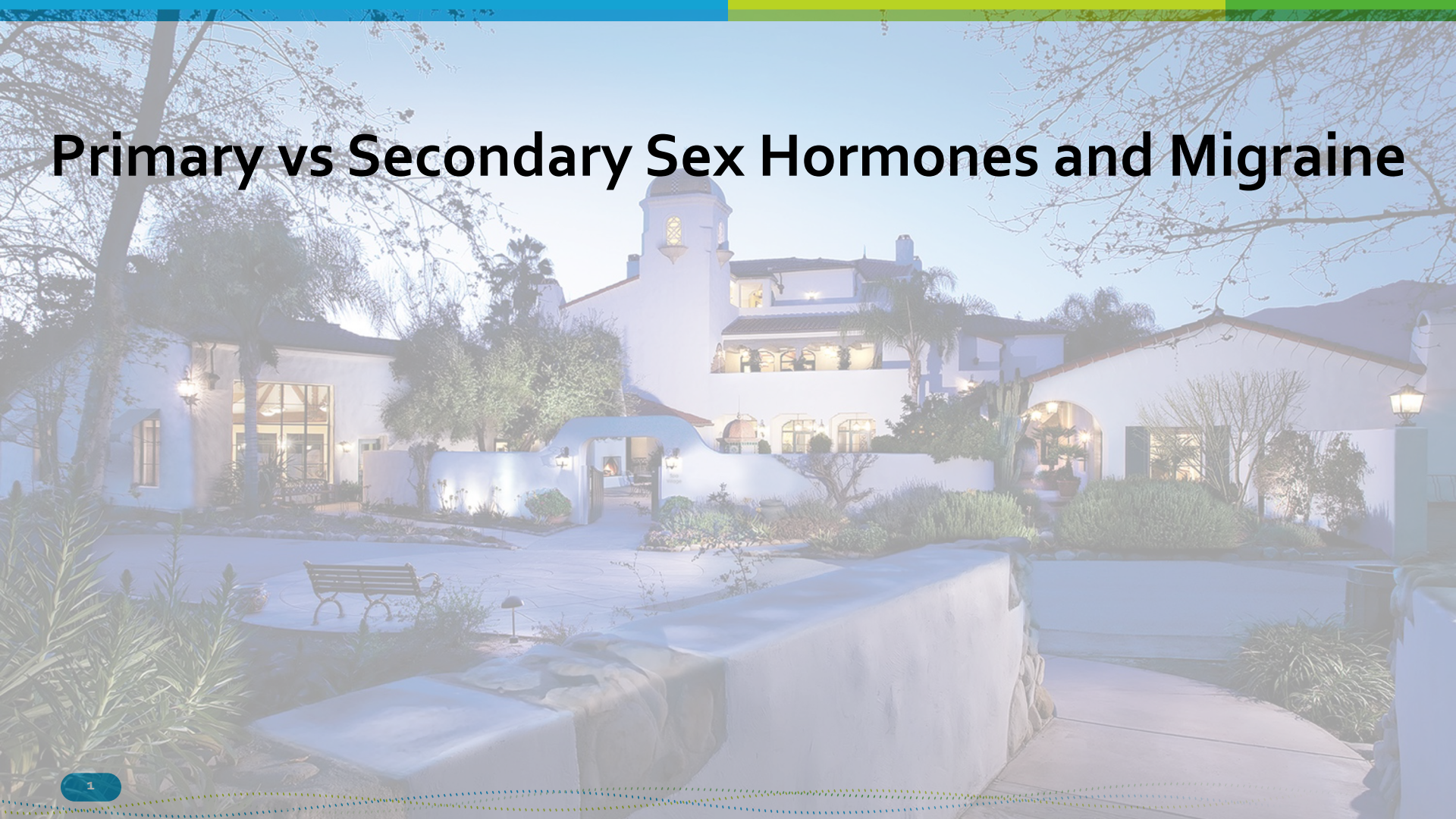
Primary vs Secondary Sex Hormones and Migraine



Disclosures

Professor David C Yeomans, Director of Pain Research, Stanford Medical School

- SiteOne Therapeutics – Founder
- NewBio – Founder
- Tonix Pharmaceuticals - Consultant
- Nalu Medical – SAB chair
- Cytonics – SAB chair
- Circuit Therapeutics – Consultant
- Endo Pharmaceuticals - Consultant

Sex Hormones

Sex hormones are critical regulators of sex-related characteristics and behaviors

Primary:

- Progesterone
- Estrogens
- Androgens

Secondary:

- Prolactin
- Oxytocin

Estrogens and Migraine

The “Estrogen withdrawal hypothesis”, developed by Somerville and colleagues in 1972, postulates that attacks of menstrual migraine are triggered by the decrease in estrogen levels preceding menstruation.

Hypothesized pathology:

- A drop in estrogen may cause an increased sensitivity to prostaglandins and a release of neuropeptides such as CGRP, substance P and neurokinins which could result in neurogenic inflammation.
- This physiological response provokes alterations in the microvasculature of the dura mater, changes in calcium and magnesium concentrations, and an imbalance in serotonin and dopamine concentrations

However, estrogens are generally ineffective in in migraine prevention RCTs

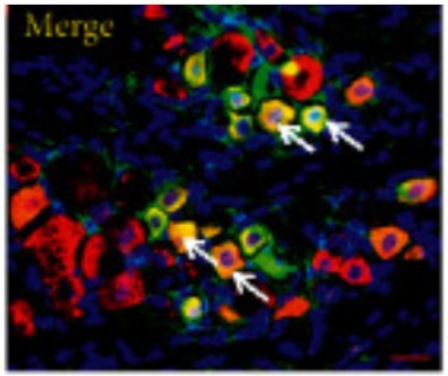
RCT (35 pts): Percutaneous Estradiol reduced migraine frequency by 22% compared to placebo but increased migraines as soon as drug stopped (MacGregor et al., 2006)

RCT (27 pts): Percutaneous Estradiol no significant effect vs. placebo (Almén-Christensson et al. 2011).

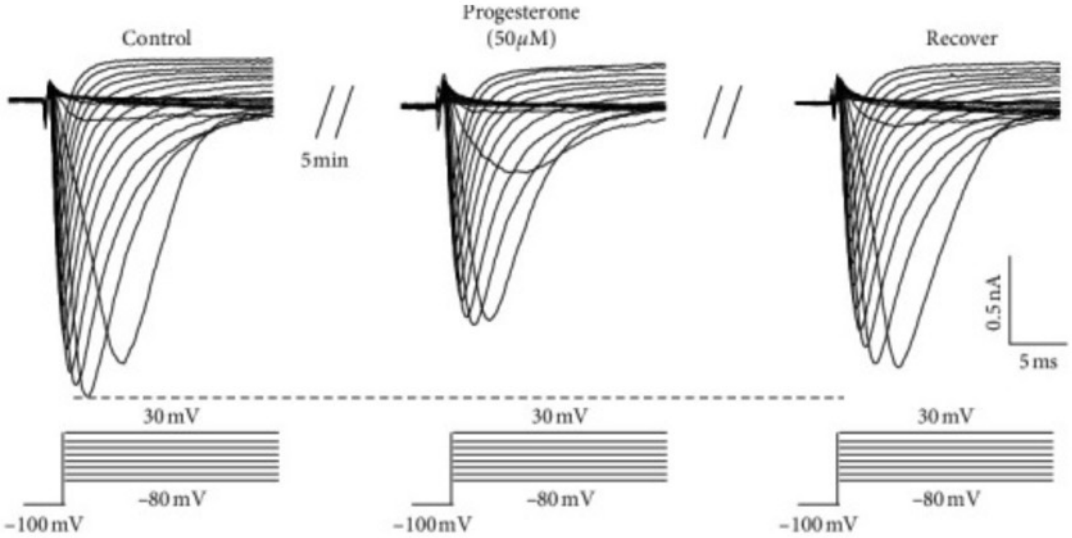
RCT (50 pts) Percutaneous Estradiol and progesterone or oral estradiol plus progesterone: significantly worsened migraine with aura (Nappi et al, 2001).

RCT (22 pts) Percutaneous estradiol significantly v placebo, reduced frequency of menstrual migraine (Dennerstein et al., 1988).

Progesterone is analgesic in the trigeminal system



Progesterone Receptors are co-Expressed with Nav1.7 in trigeminal ganglia neurons



Progesterone decreases sodium currents in mouse trigeminal ganglia neurons

Bi et al., 2020

However, Progesterone is minimally effective NO RCTs

Clinical implications

Warhurst et al., 2017

- The desogestrel 75 mcg/day POP is associated with modest reductions in migraine frequency and duration as well as reduced use of analgesics and triptans after 180 days' use in most women.
- Evidence is observational and future prospective, randomised trials will assist in determining the true clinical effects of the desogestrel POP and other progestin-only contraceptives in migraine treatment.
- The desogestrel POP should be considered in women with migraine, particularly those with common contra-indications to COC pill use such as migrainous aura and hypertension.

PROGESTERONE IN THE TREATMENT OF MIGRAINE

INDER SINGH
M.B. Rangoon, M.R.C.P.E., F.R.F.P.S.
LIEUT.-COLONEL I.M.S.

INDERJIT SINGH
M.B. Rangoon, Ph.D. Camb., M.R.C.S., F.A.Sc.
CAPTAIN I.M.S.

DEVINDER SINGH
L.S.M.F. Punjab

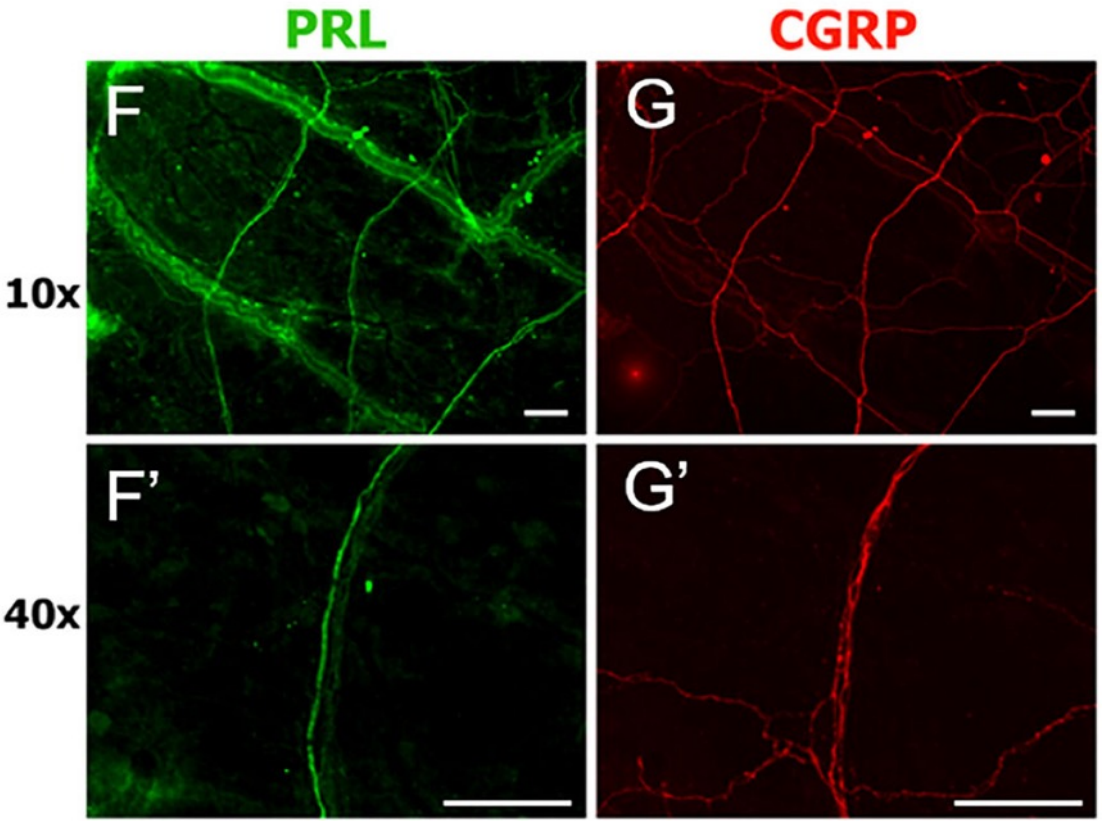
the amount of progesterone required to alleviate an induced attack of migraine was inversely proportional to the amount of œstradiol used to induce it. To prevent spontaneous attacks the amount of progesterone required was generally directly proportional to the severity of the symptoms of œstrogen hyperactivity.

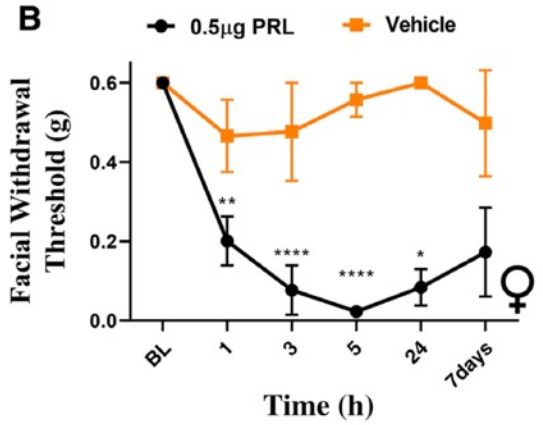
In no case did we inform the patient of the nature and action of the drugs used, and the relief from migraine was associated with disappearance of symptoms of œstrogen hyperactivity. Accordingly, it is unlikely that the success of treatment was due to suggestion

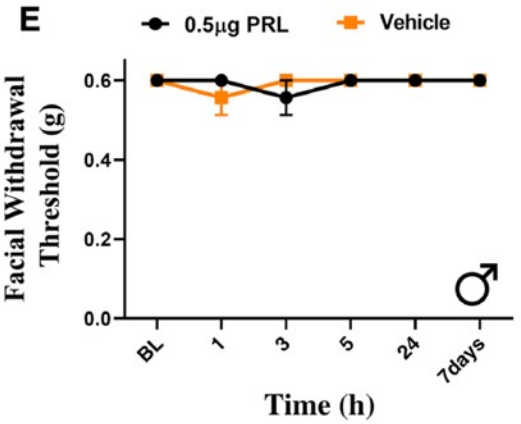
Testosterone

No RCT but pilot study showing strong effects of testosterone implant on 27 female migraineurs with symptoms of androgen insufficiency. Compared to pre-treatment, testosterone produced a significant decrease in migraine severity with 74% reporting severity scores of zero (Glaser et al., 2012).

Prolactin receptors on female, but not male mouse dural afferents

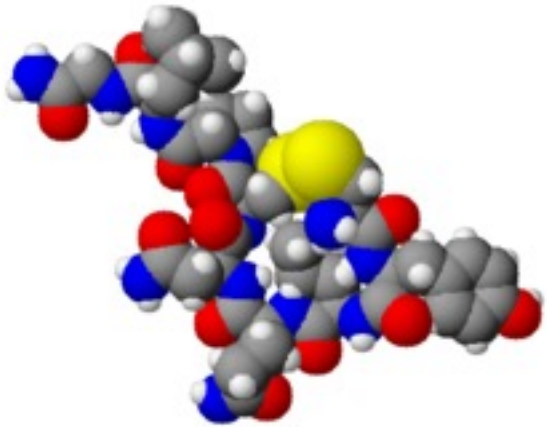


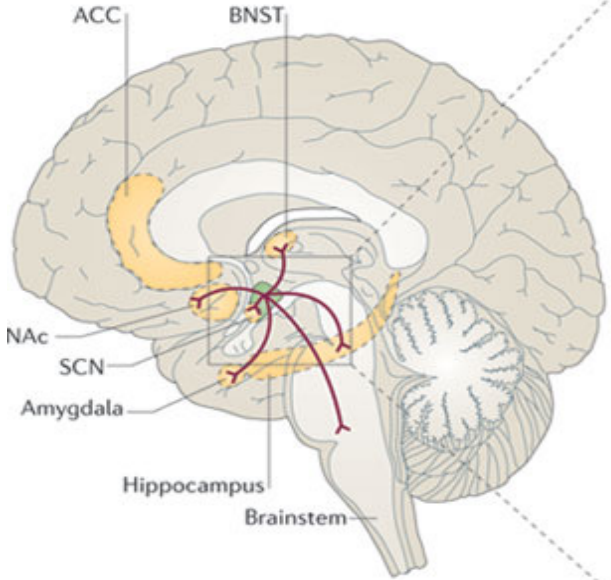


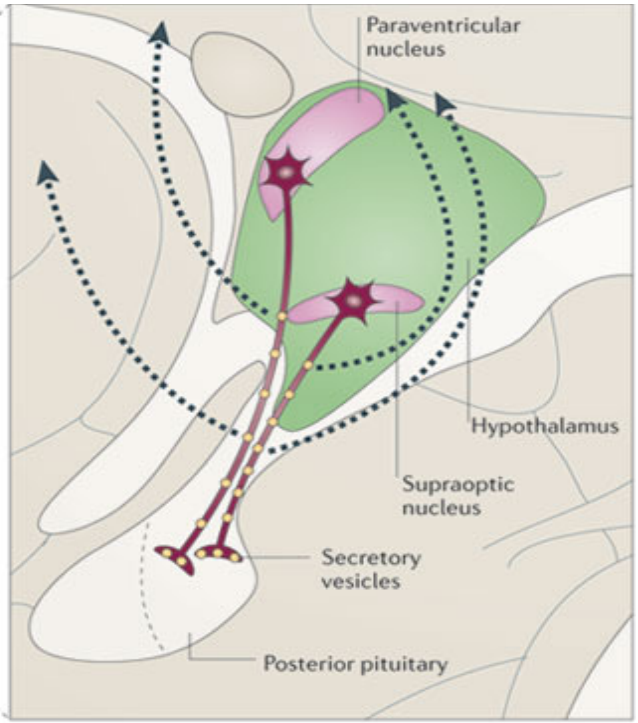


Avona et al., 202

Oxytocin is a 9 amino acid polypeptide hormone/neurotransmitter which is made in the hypothalamus and secreted both into the systemic circulation and into certain CNS sites

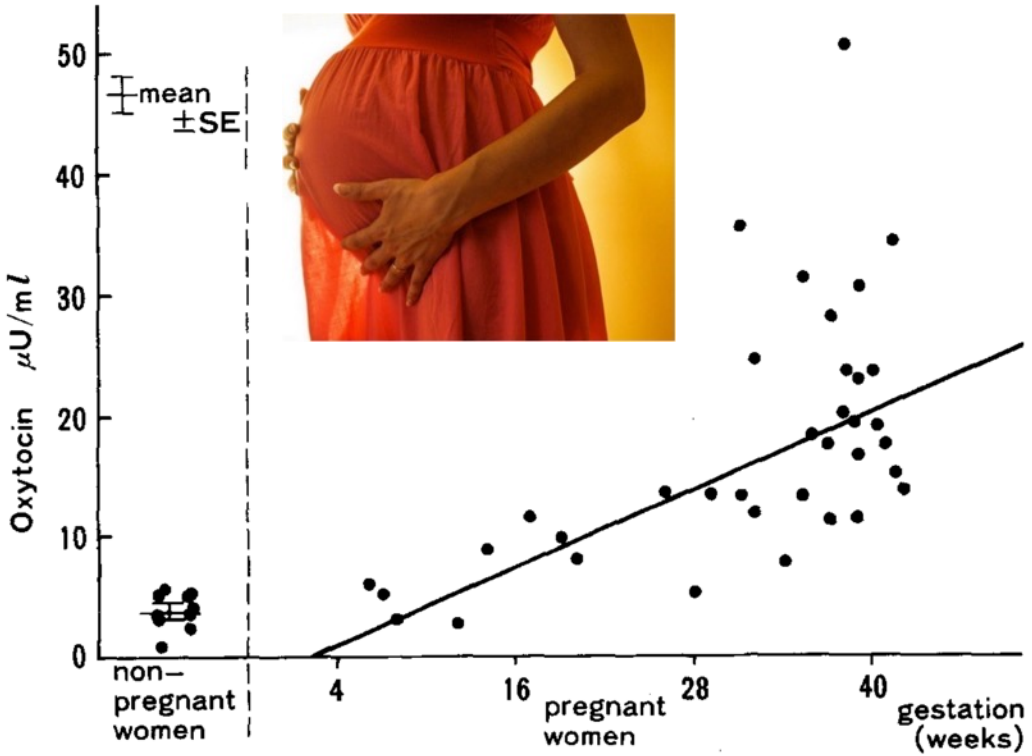




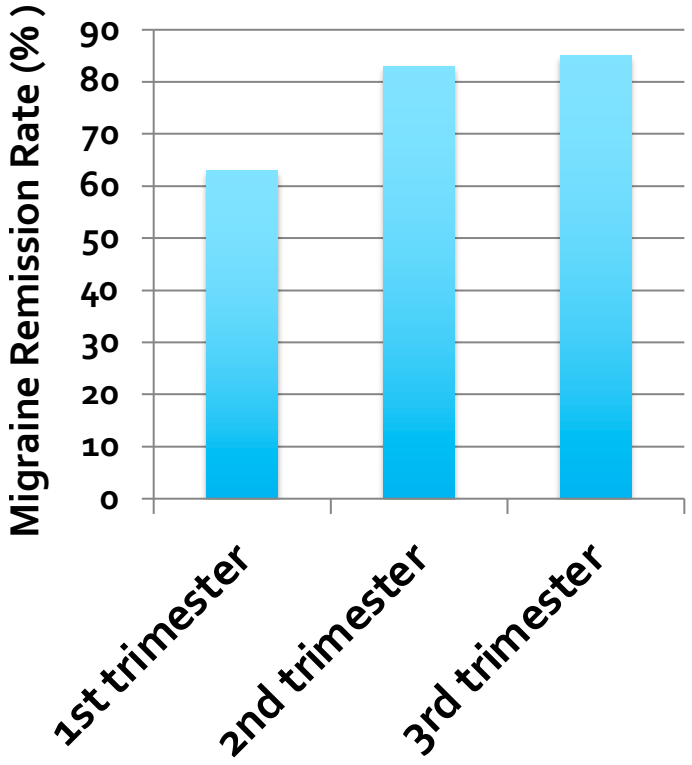


Nature Reviews | Neuroscience

Pregnancy increases oxytocin and decreases migraine frequency

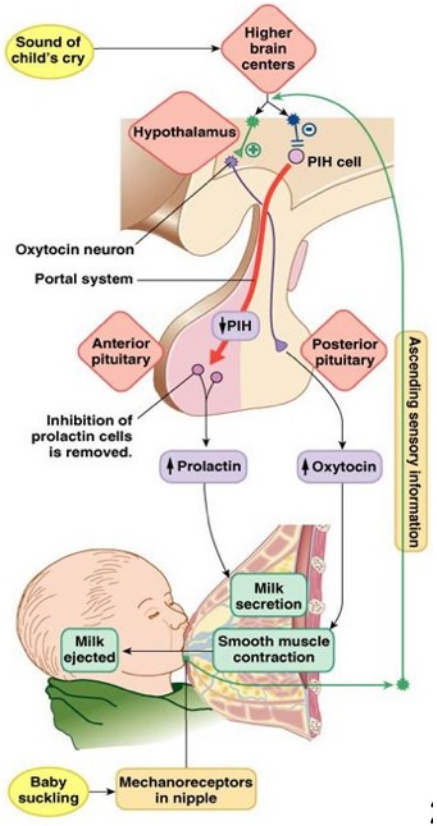


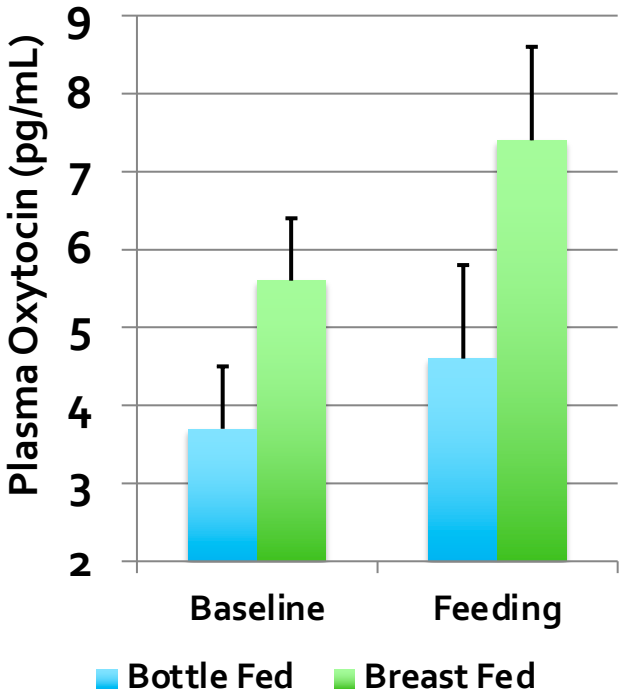
Kuwabara et al., 1987



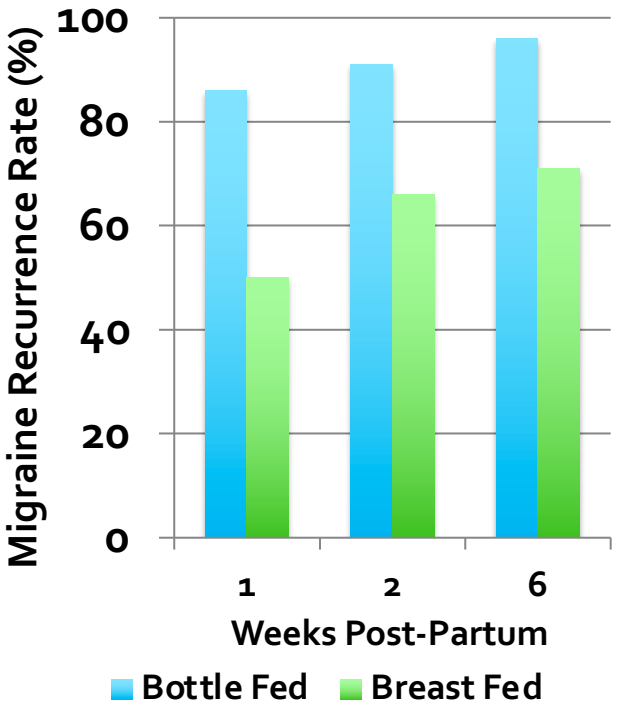
Adapted from Hoshiyama, 2012

Breast feeding releases oxytocin and prevents migraines



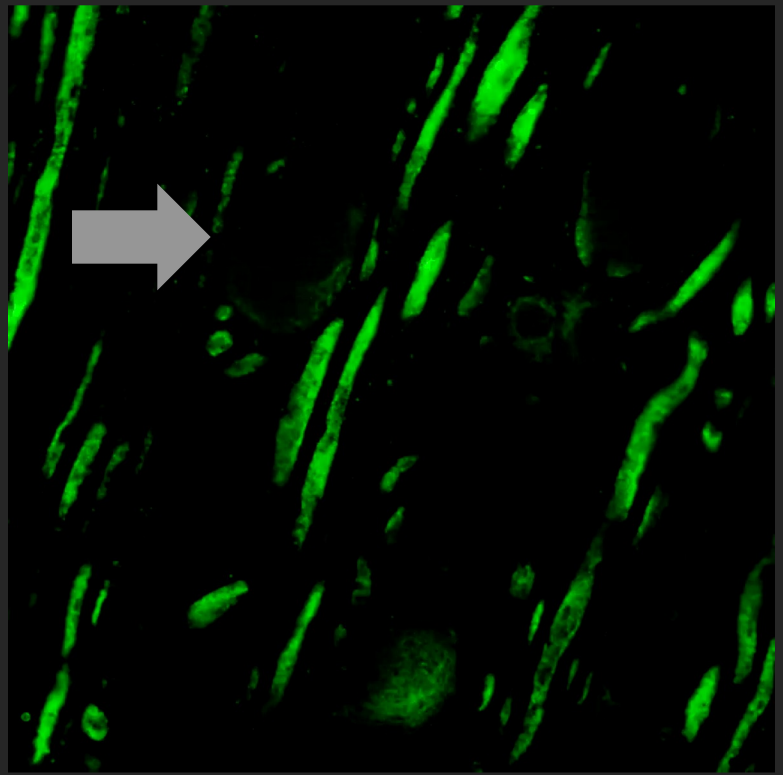


Grewen et al, 2010



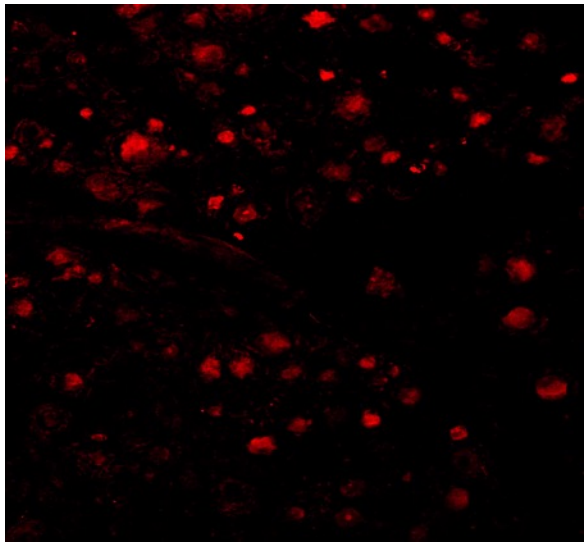
Hoshiyama, 2012

Oxytocin receptor expression on trigeminal ganglia neurons

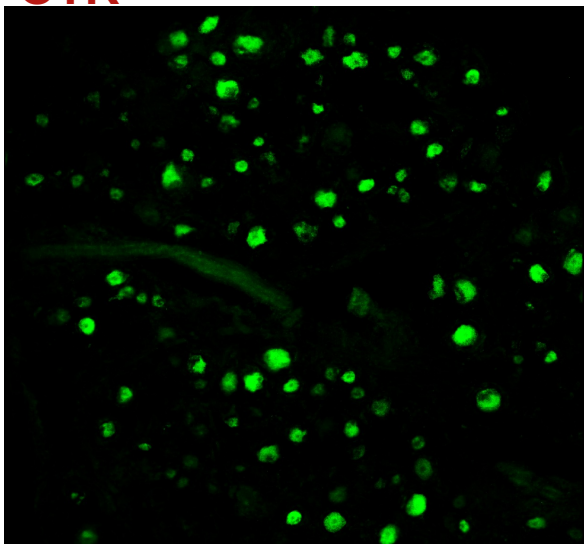


Oxytocin receptors co-express CGRP in human trigeminal ganglia neurons

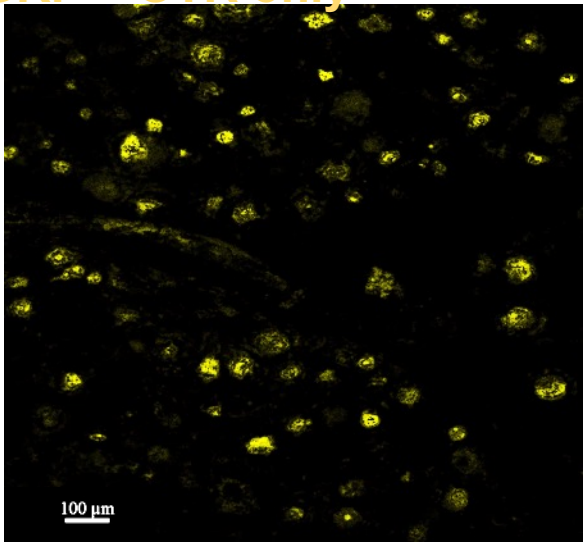
CGRP



OTR

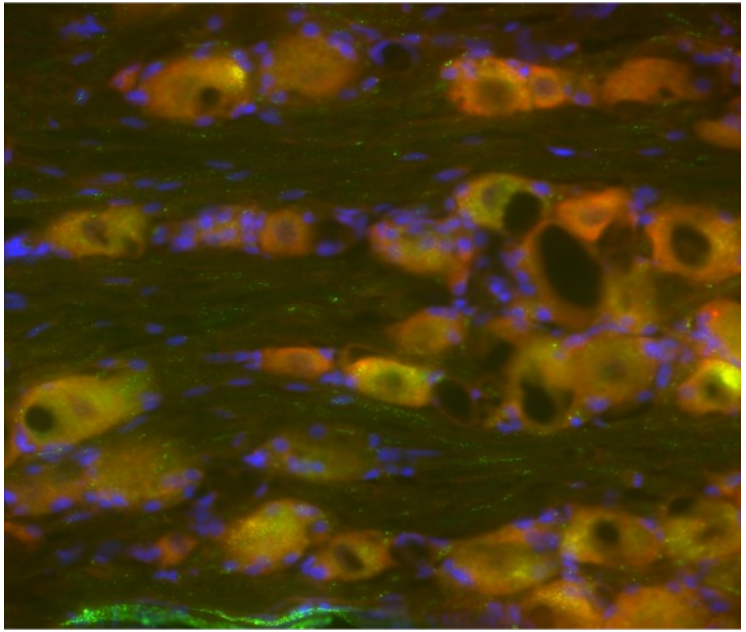


CGRP + OTR only



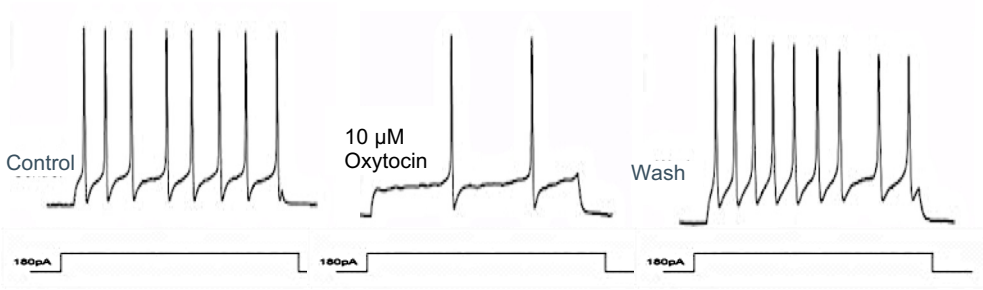
Oxytocin Inhibits Firing of Rat Trigeminal (TG) CGRP Neurons

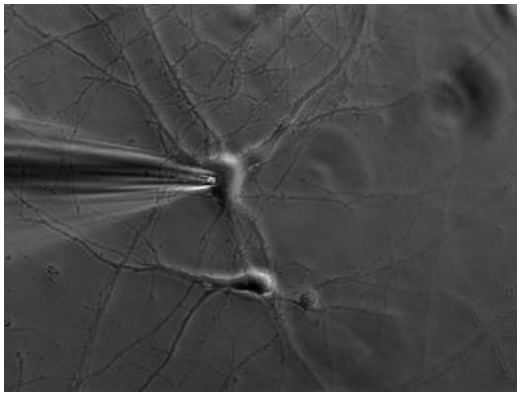
Oxytocin Receptors Co-Localize with CGRP in Trigeminal Ganglia Neurons



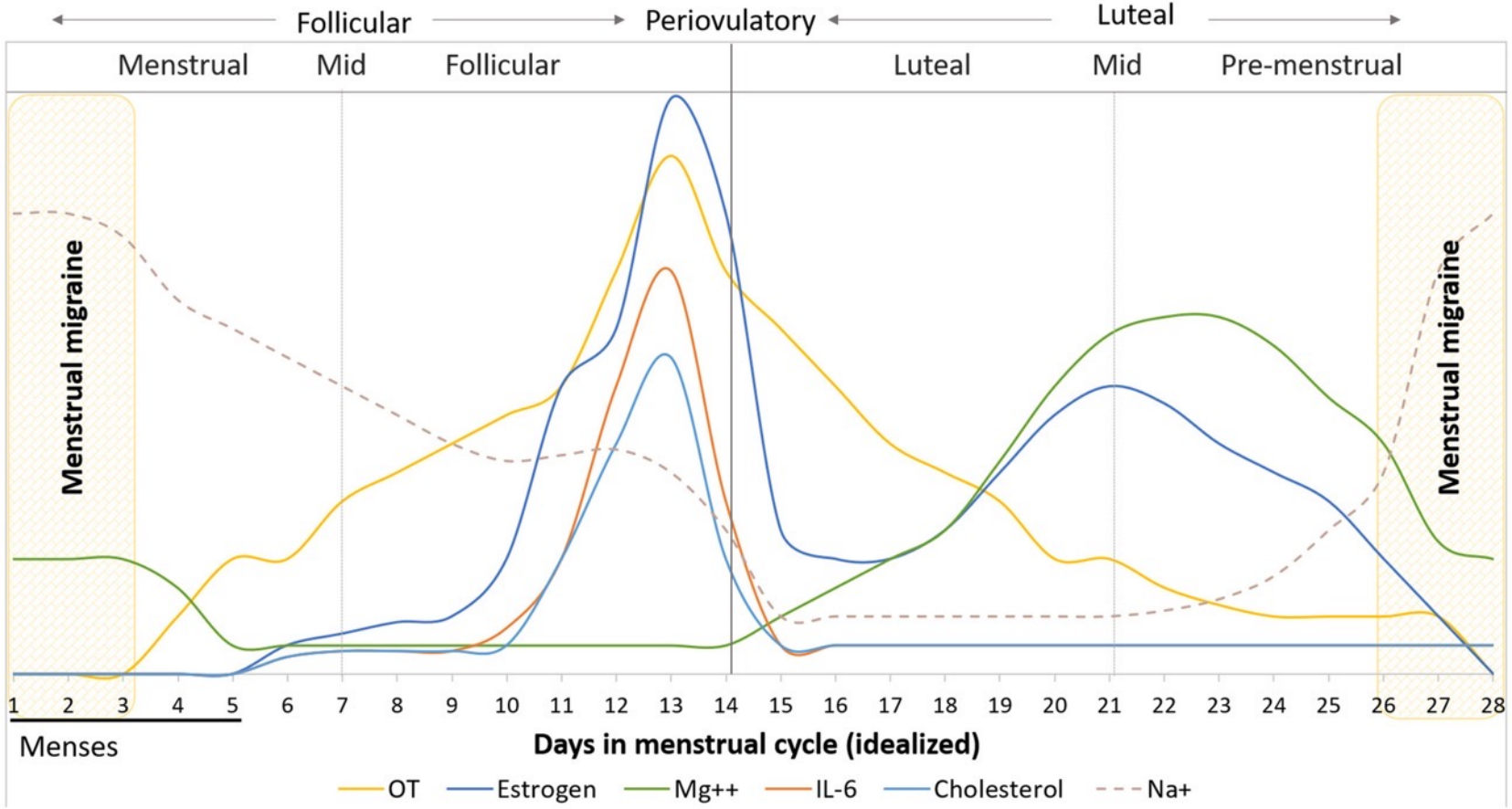
Oxytocin Receptors = red
CGRP = green

Oxytocin Inhibits Electrically Evoked Activity of Trigeminal Ganglia Neurons

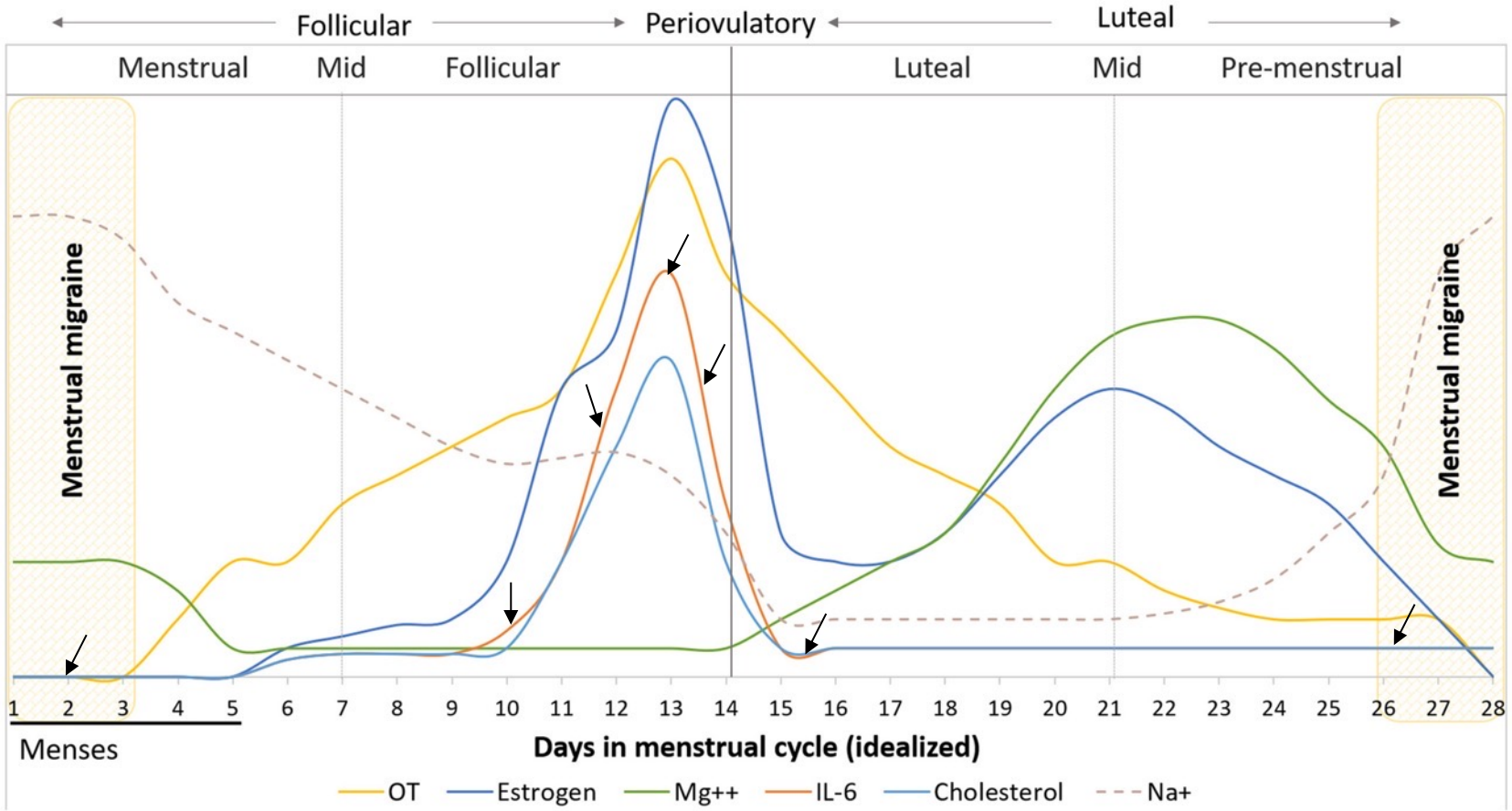




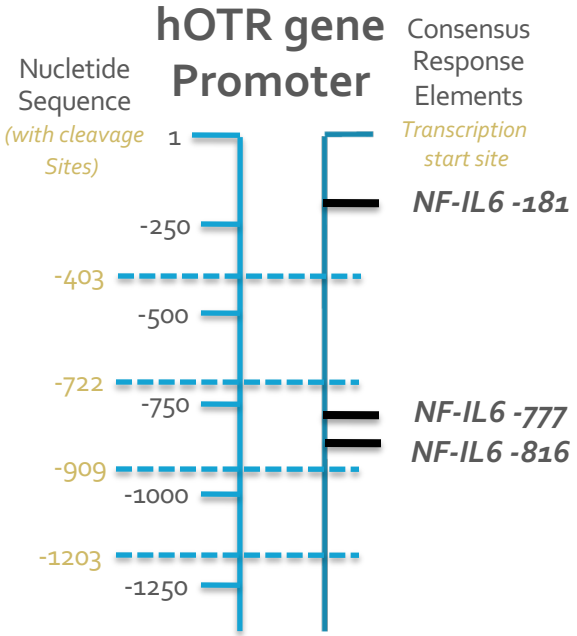
Multiple factors that vary over the menstrual cycle have been shown to control oxytocin activity



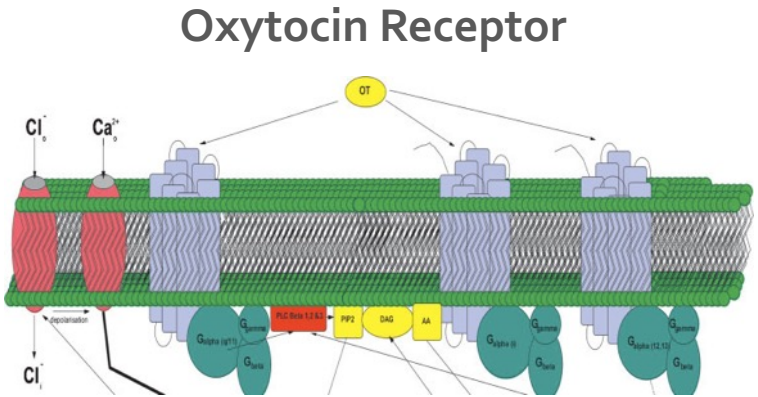
1. IL-6 is low during menstrual migraine



The OTR gene promoter has multiple response elements for the inflammatory cytokine IL-6



Schmid *et al.*, 2001



Gould and Zingg, 2003

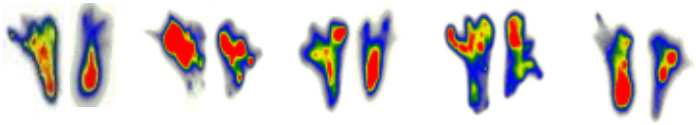
Oxytocin Is Preferentially Transported Throughout the Trigeminal System After Nasal Delivery (not systemically distributed)

Oxytocin tissue levels (nM) after intranasal administration*			
TRIGEMINAL NERVE	Ganglion	574	±191
	Maxillary branch	471	±117
	Mandibular branch	676	±235
	Ophthalmic branch	423	±143
OLFACTORY NERVE	Nucleus	34	±10
	Bulbs	33	±13
BRAIN	Cortex	29	±8
	Caudate	39	±12
	Thalamus	15	±6
	Midbrain	23	±12
	Cerebellum	20	±8
	Medulla	26	±10
SPINAL CORD	Cervical	34	±9
	Thoracic	5	±1
	Lumbar	5	±1
OTHER TISSUES	Muscle	16	±3
	Liver	16	±2
	Kidney	50	±5
	Lung	25	±4
	Heart	23	±4
BLOOD	Blood	63	±4

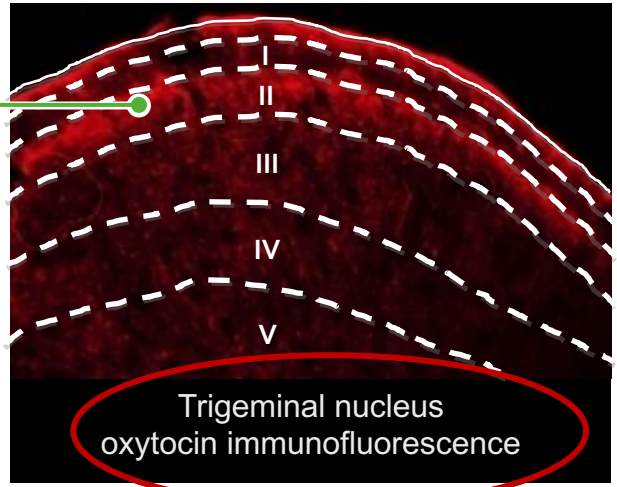
*Oxytocin applied to nose of rats, tissue levels assessed by gamma counts

Broad Distribution of ^{125}I-oxytocin in Trigeminal Ganglia After Nasal Application

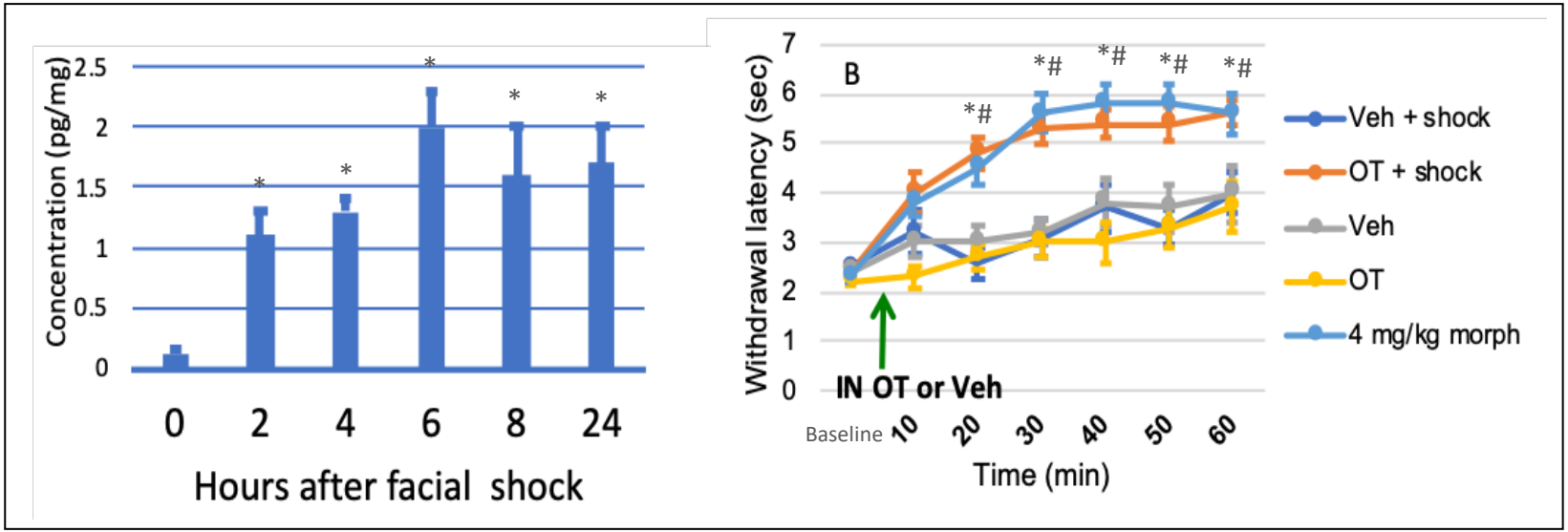
Autoradiograms of trigeminal ganglia



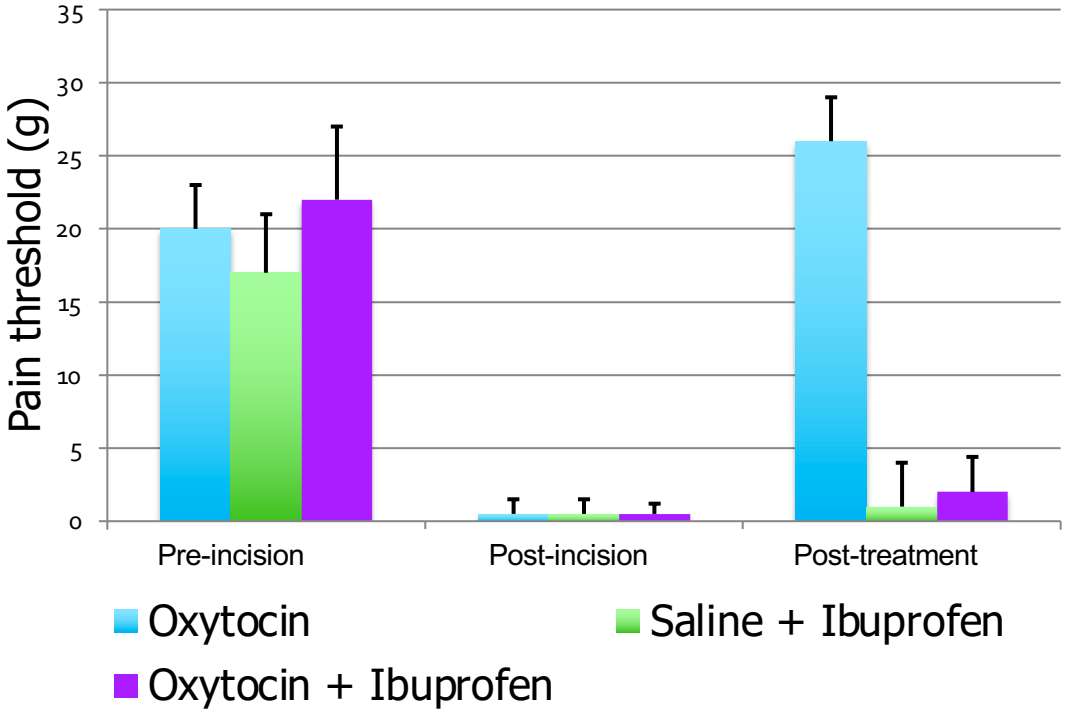
Band of Oxytocin Immunofluorescence in Lamina II – Where Trigeminal Pain Sensing Neurons Synapse



Inflammation increases trigeminal Oxytocin receptor expression

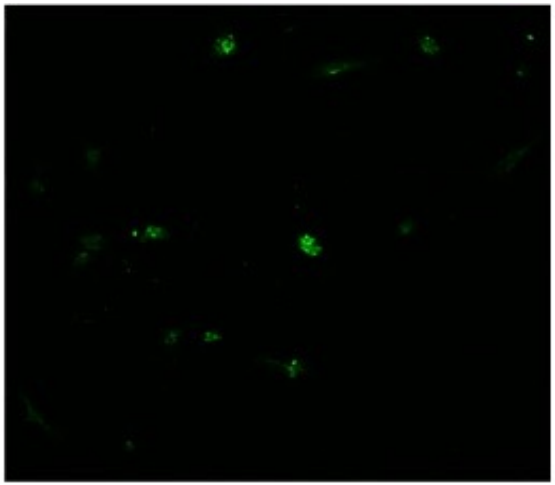


After incision, the analgesic efficacy of nasal oxytocin is blocked by ibuprofen – which blocks IL-6 production

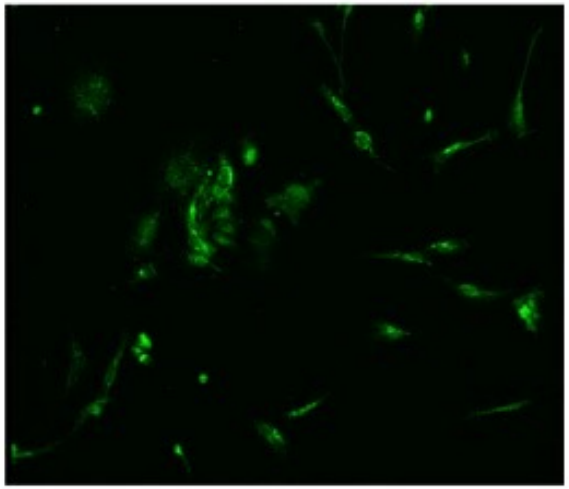


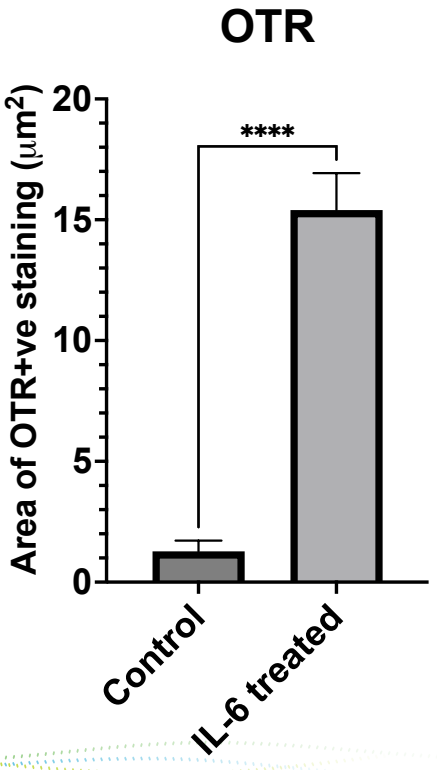
In vitro treatment of human ganglia with IL-6 induces upregulation of oxytocin receptors

Control

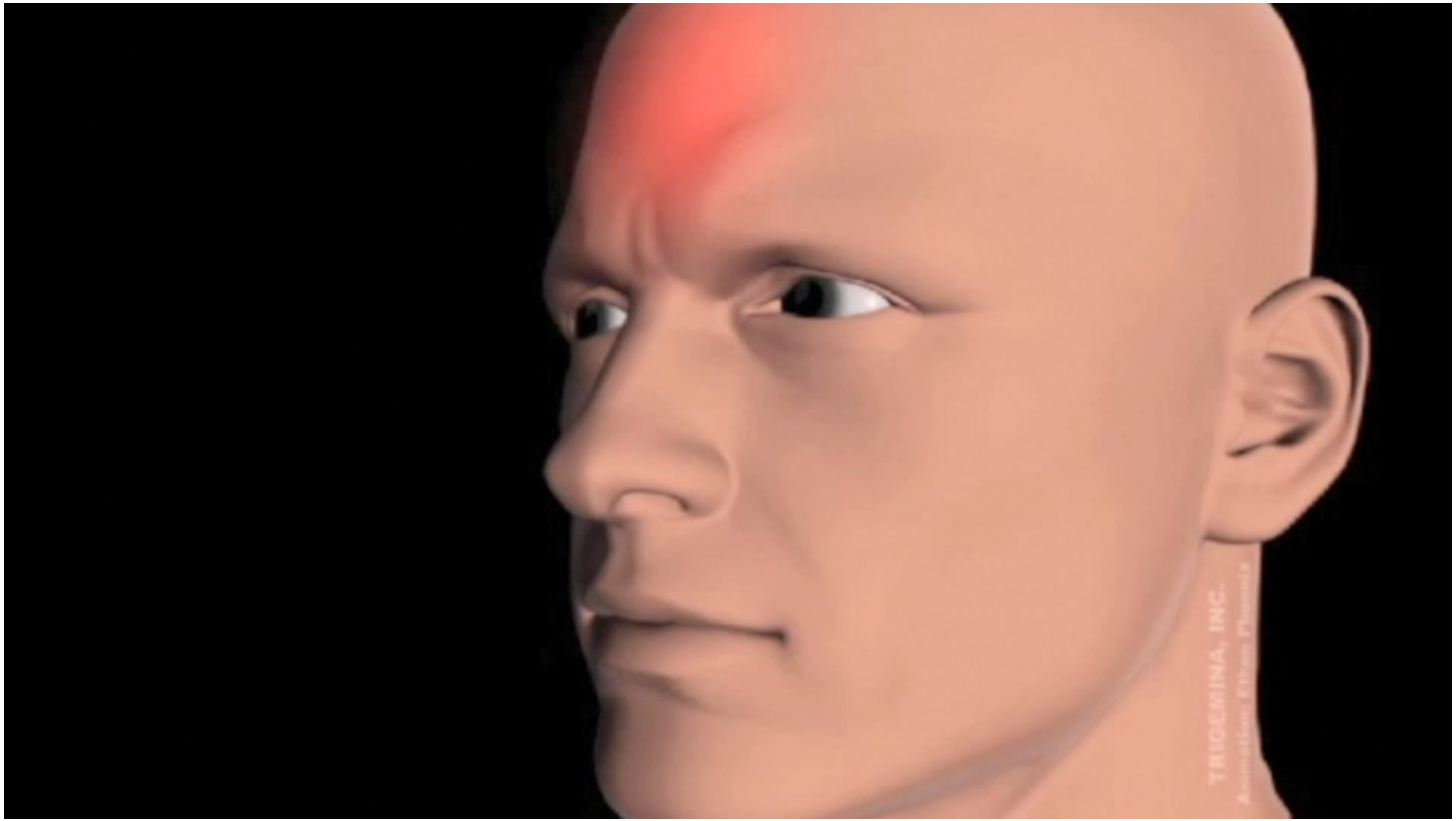


IL-6 treated

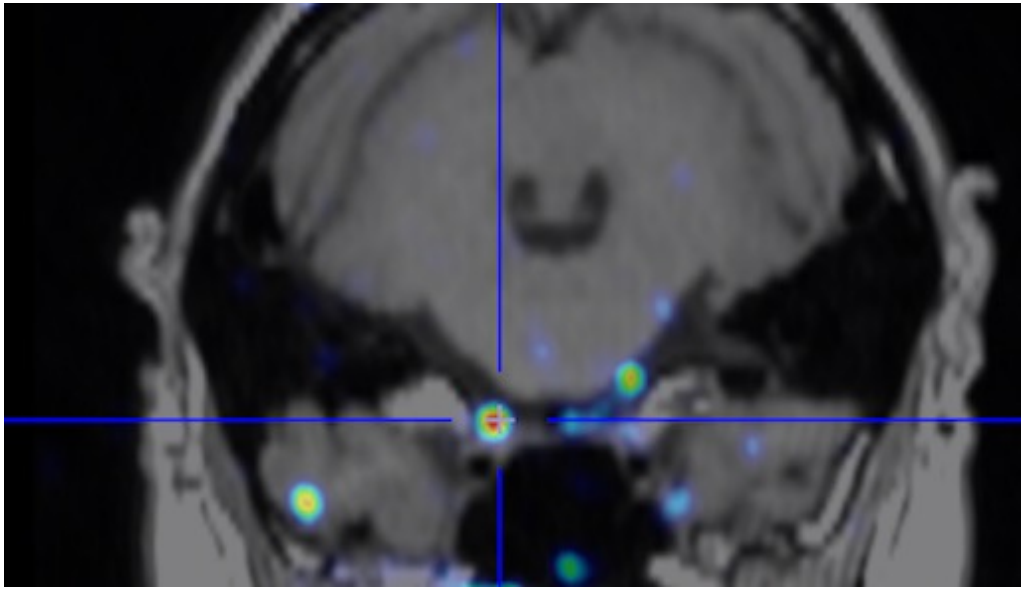




Nasal delivery of oxytocin to the trigeminal system of humans

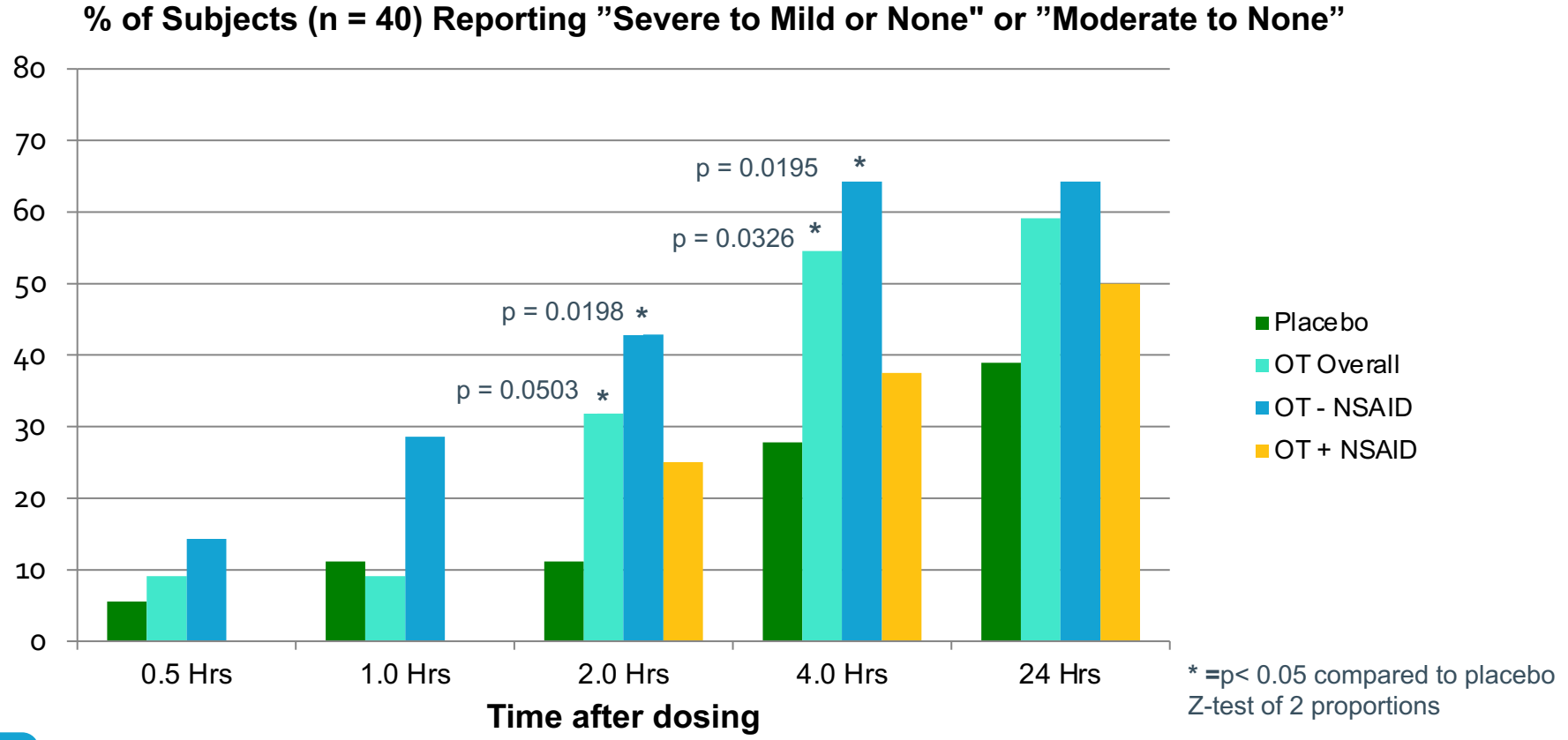


^{13}N-Oxytocin in human TG after nasal application



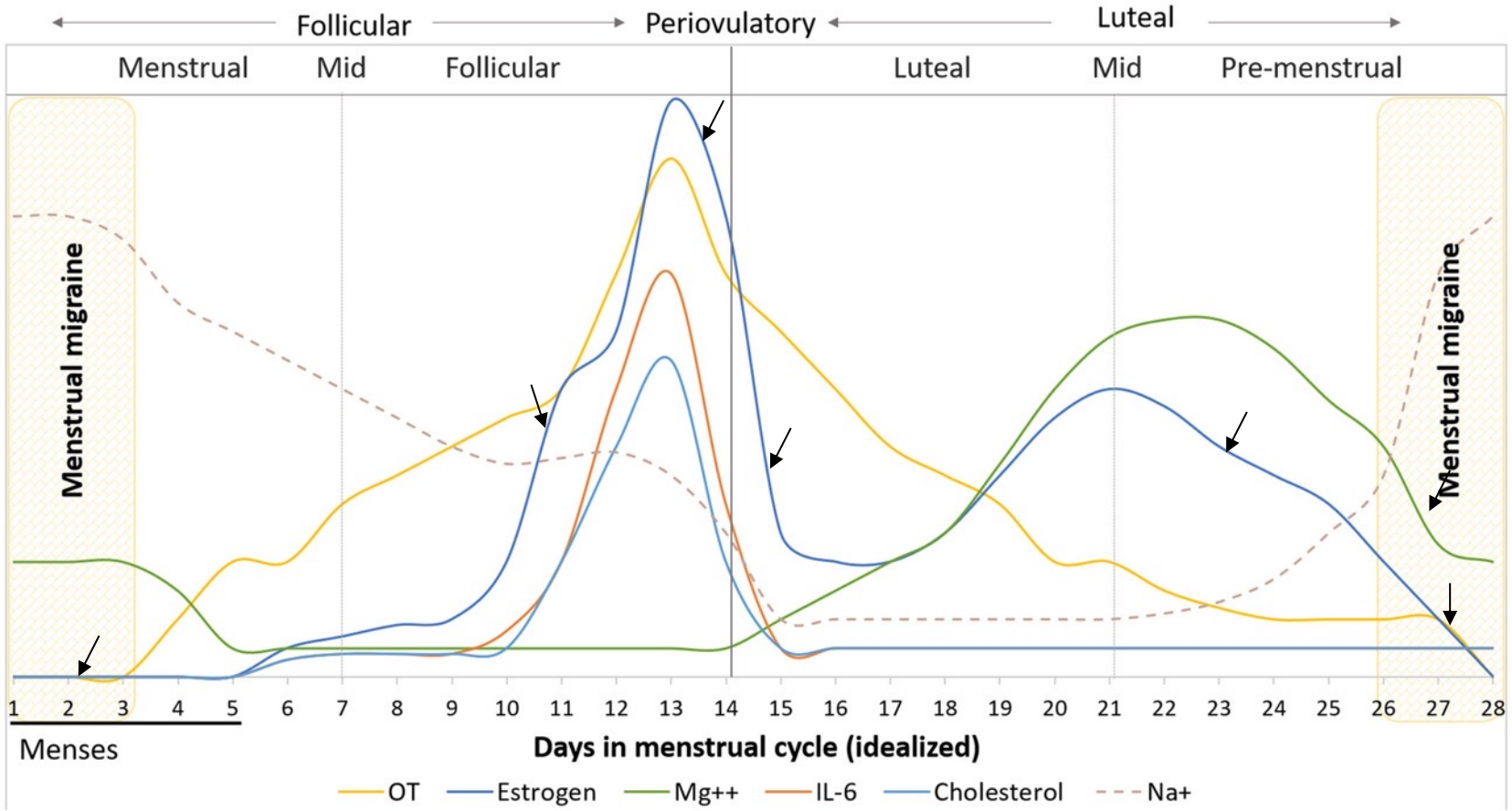
Pilot Clinical Study: Nasal Oxytocin Reduces Pain In Chronic Migraineurs

Excluding patients who took NSAIDs within 24 hours increases efficacy



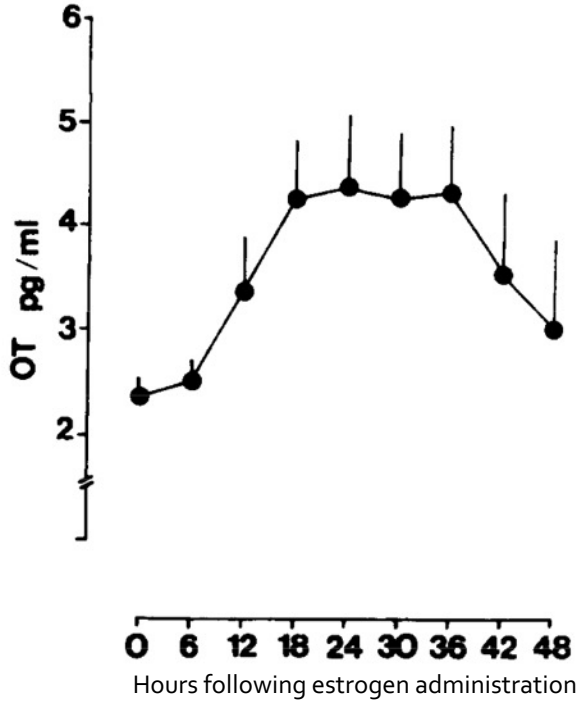
* =p< 0.05 compared to placebo
Z-test of 2 proportions

2. Estrogen is low during menstrual migraine



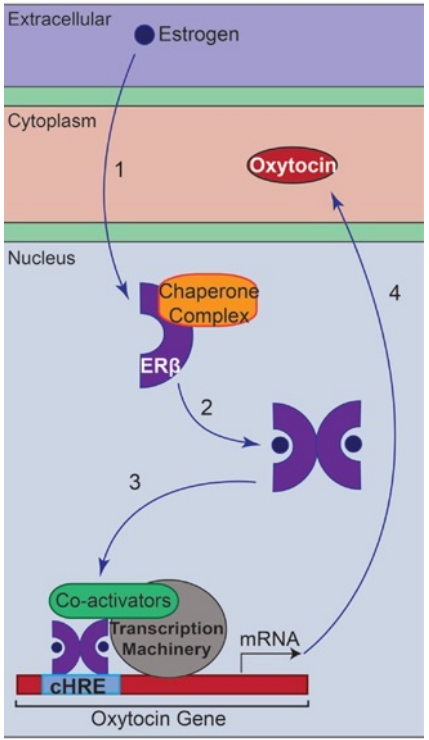
Plasma OT level is modulated by exogenous estrogen

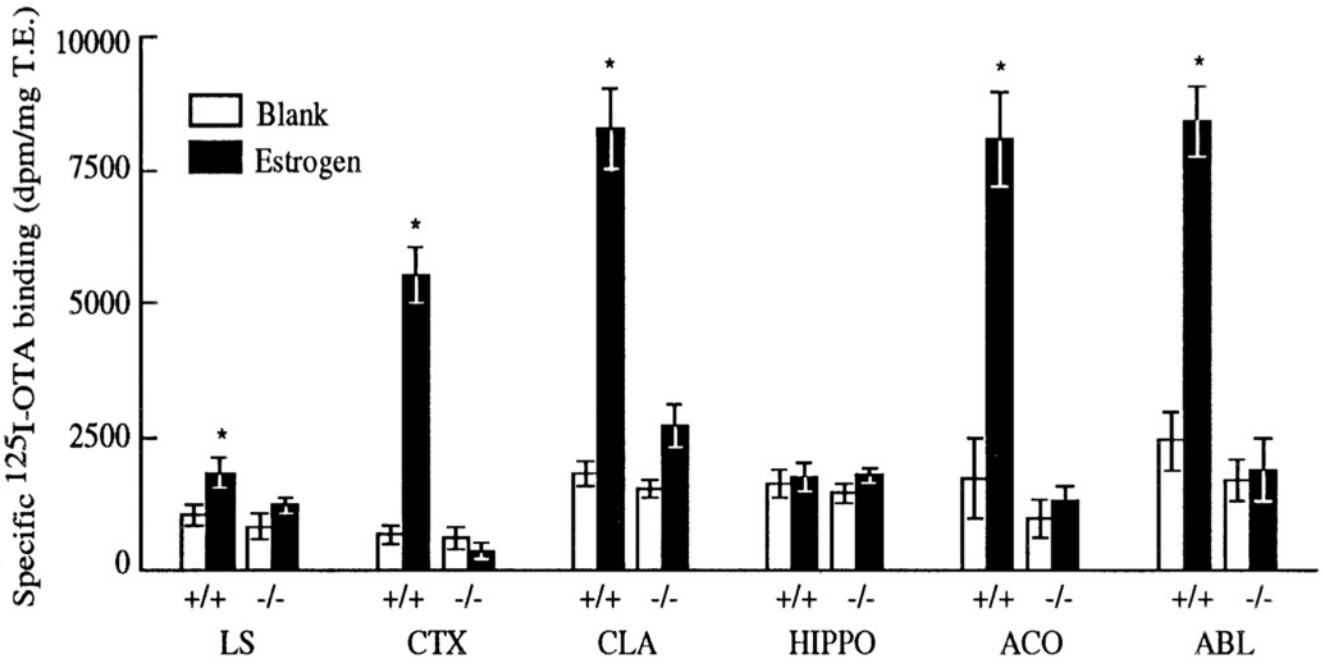
Plasma oxytocin levels following oral estrogen (1 mg)



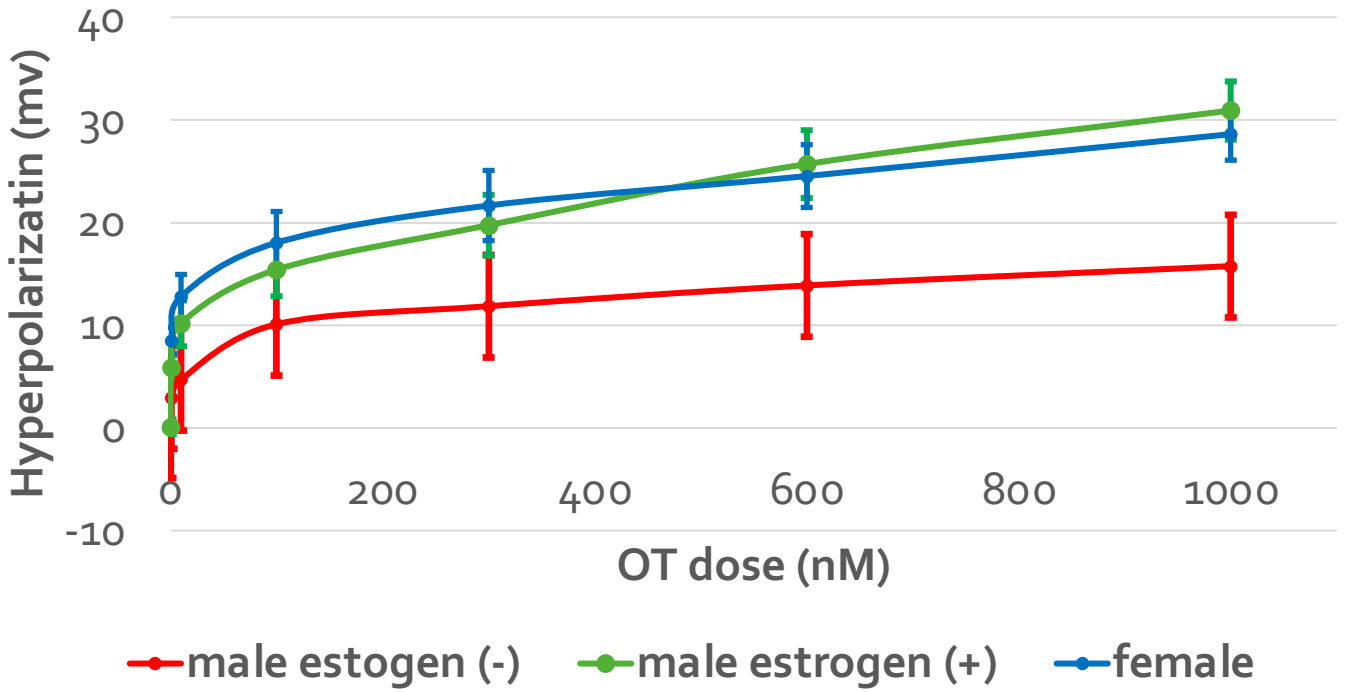
Chiodera et al., 1991

Increase in brain OXTR induced by estrogen

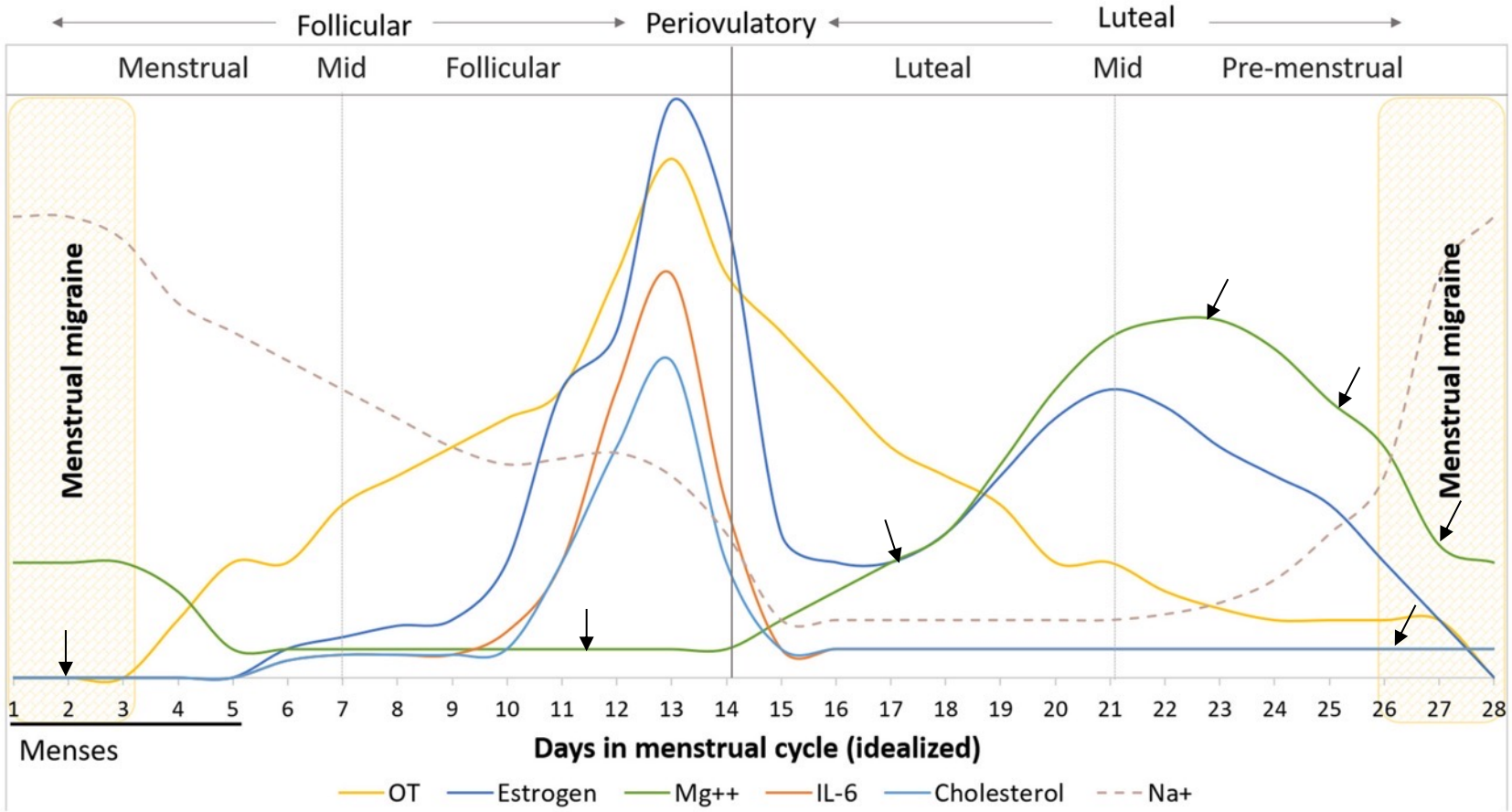




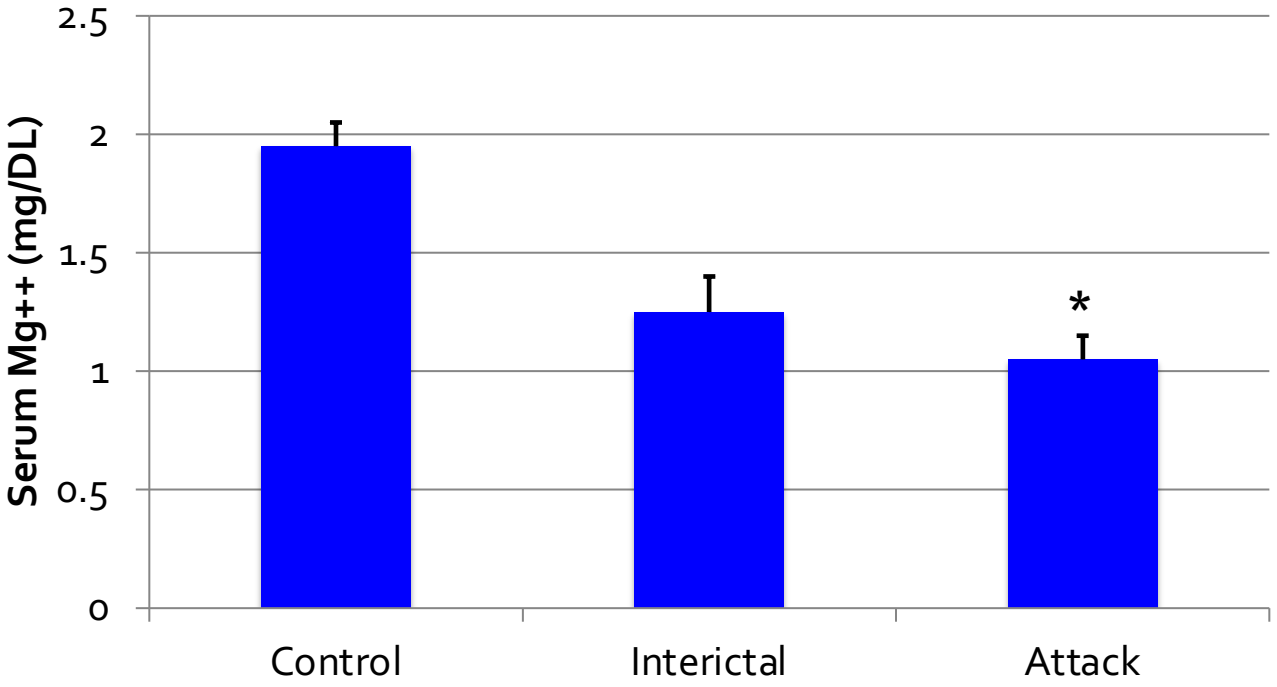
OT is more potent in inhibiting TG excitability in females, but with estrogen pretreatment, male potency is similar to female



3. Magnesium ion plasma level is low during menstrual migraine



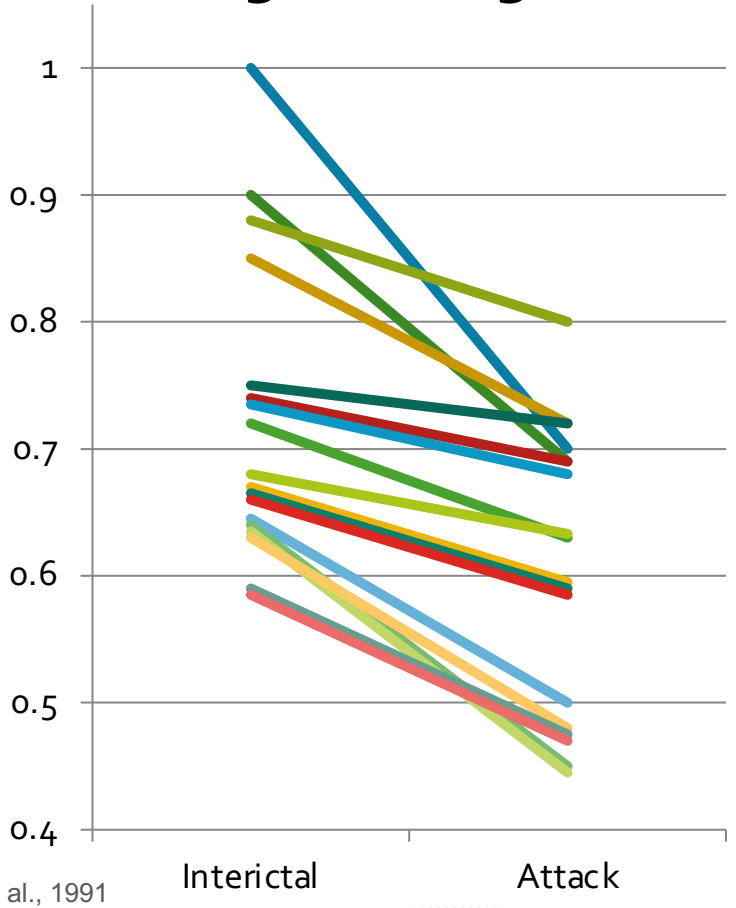
Serum Mg++ is lower in migraineurs



Assarzadegan et al., 2016

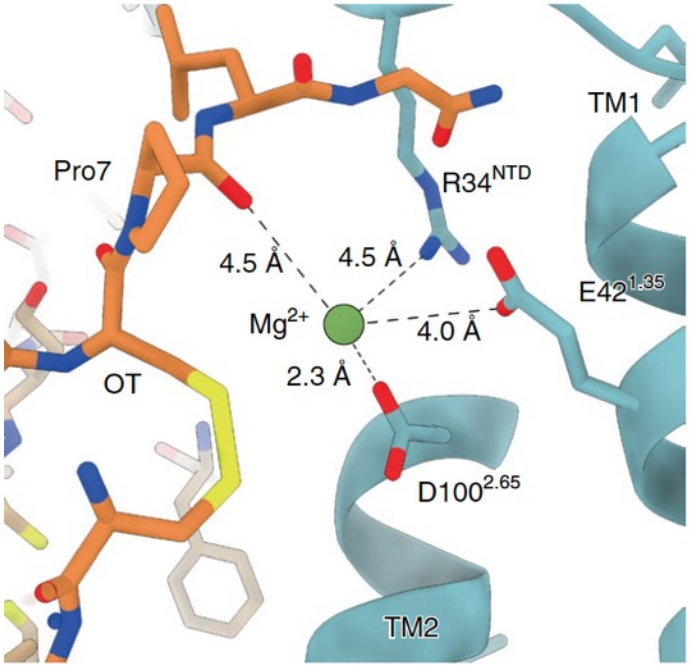
Reduced basal and attack-dependent serum Mg++ in migraineurs

- Odds of migraine is increased 35.3 times when serum levels of magnesium reached below the normal level.

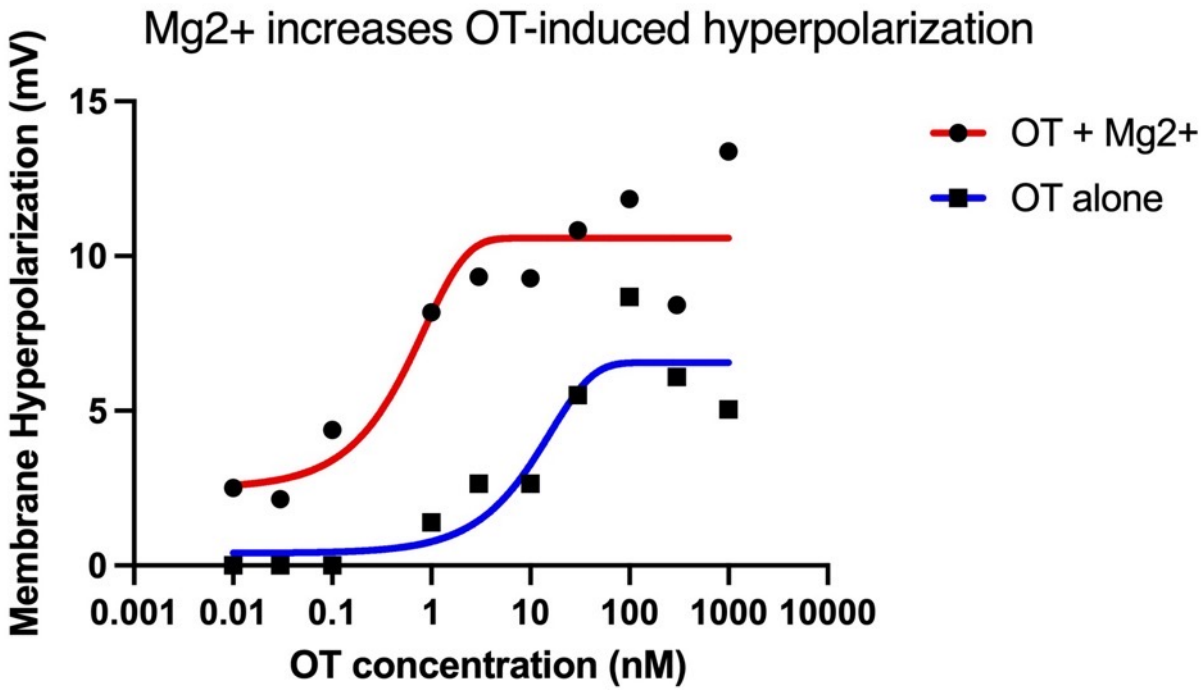


Sarchielli et al., 1991

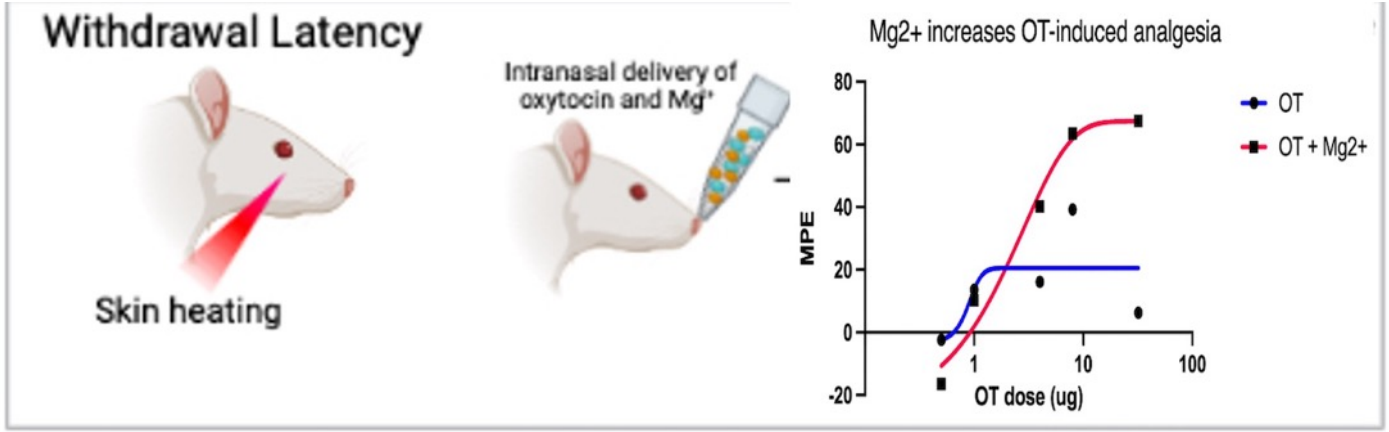
Binding site for Mg^{2+} between OT and OTR



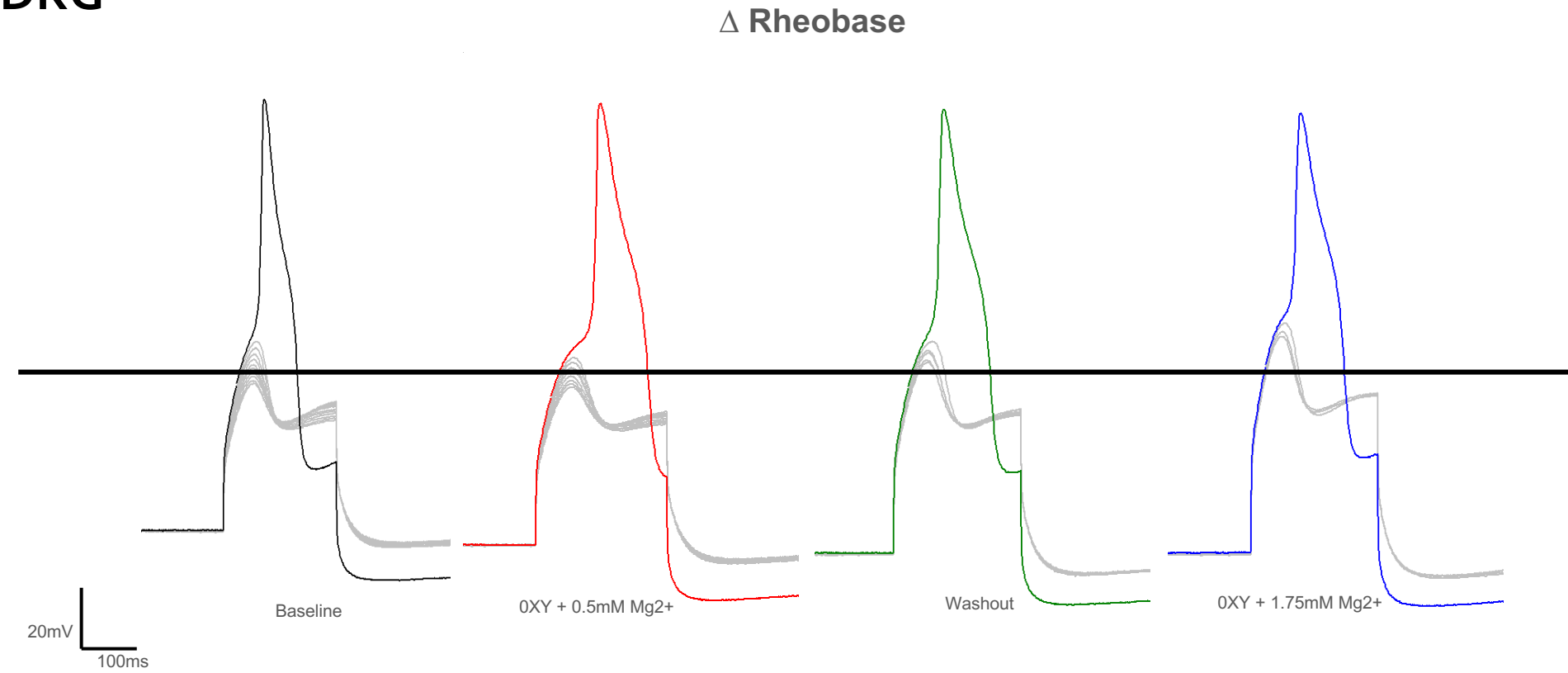
Addition of Mg^{2+} enhanced OT-driven desensitization of rat TG



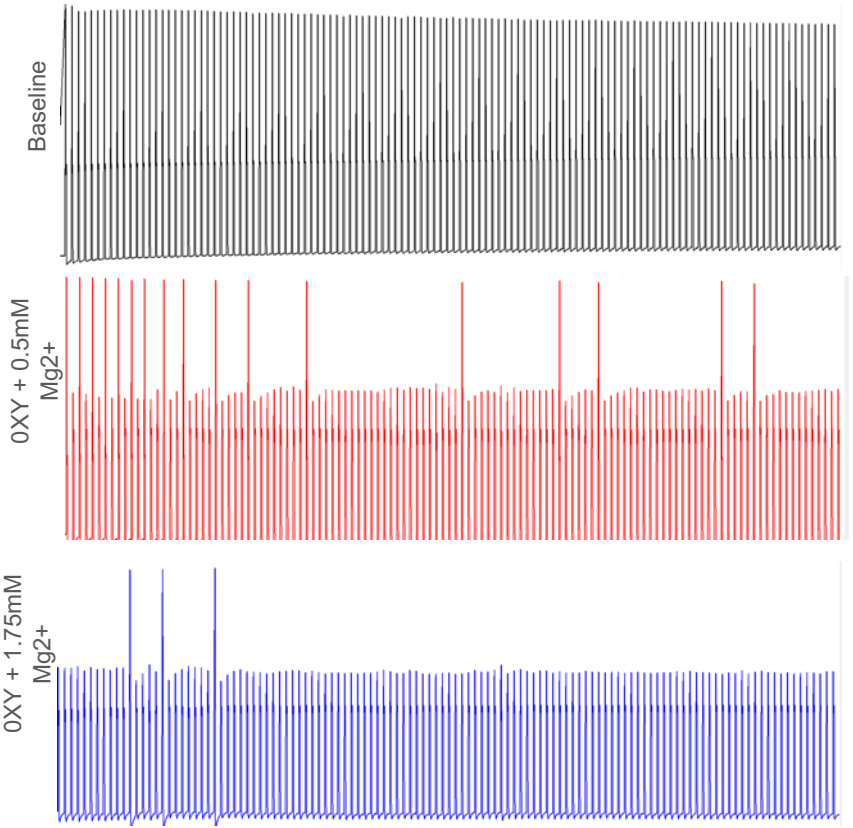
Addition of Mg^{2+} enhanced OT-driven craniofacial analgesia



Addition of Mg^{2+} enhanced OT-driven increase of rheobase of human DRG



Addition of Mg^{2+} enhanced OT-driven decrease in AP following in human DRG

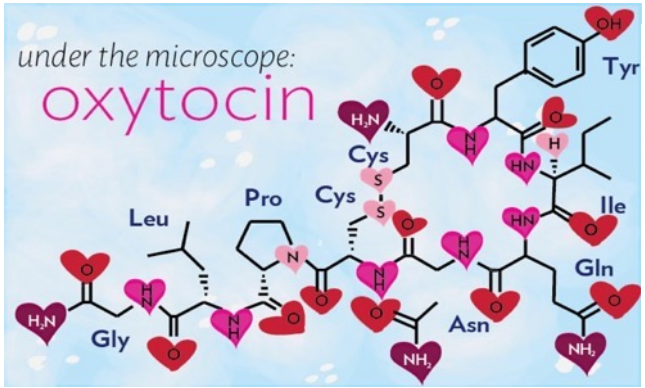


Summary: Sex hormone modulation of migraine

- Evidence for Direct modulation of TG excitability by primary sex hormones in not strong
- Evidence for extended sex hormones (Prolactin, oxytocin) robust
- Oxytocin effects are modulated by several endogenous factors that vary over the menstrual cycle
- IL-6 levels drive OT receptor expression and increases OT analgesic efficacy
- Estrogen drives OT and OT receptor expression and likely enables OT analgesia
- Mg^{2+} is decreased during menstruation and during migraine attacks
- There is a binding site for Mg^{2+} between OT and its receptor
- Mg^{2+} dramatically increases the analgesic efficacy of OT in animal models and human sensory neurons

A Mg^{2+} containing nasal formulation of OT is being used in an ongoing multi-site US study of chronic migraine prophylaxis

Alternatively, hugging, massage, sex, looking at your dog could help prevent migraines



Thank you!