

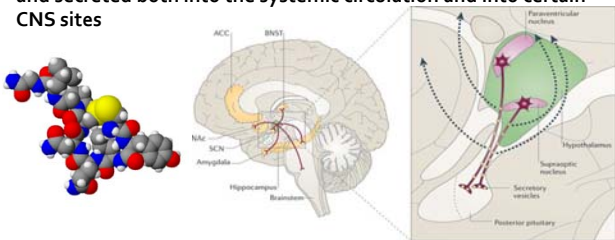


Disclosures

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

- Trigemina, Inc. – Founder
- SiteOne Therapeutics – Founder
- ADYNXX – SAB chair
- Nalu Medical – SAB chair
- Cytonics – SAB chair
- Circuit Therapeutics – Consultant
- Endo Pharmaceuticals – Consultant
- Orexigen Therapeutics – Consultant
- Rio Grande Neurosciences – Consultant

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

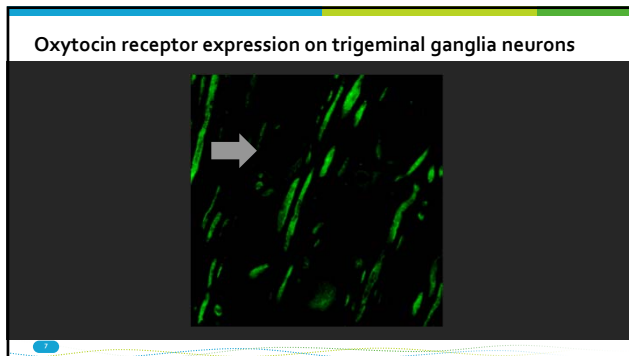


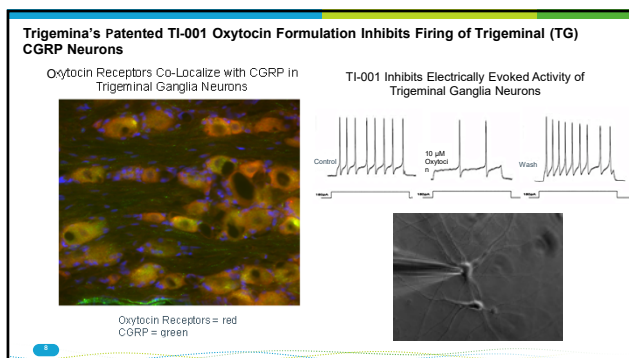
Hypothesis: Probability of a migraine attack is determined, in part, by oxytocin (OT) tone at trigeminal oxytocin receptors (OXTR)

Inhibition of Trigeminal Pain Signals by Oxytocin

The Trigeminal System





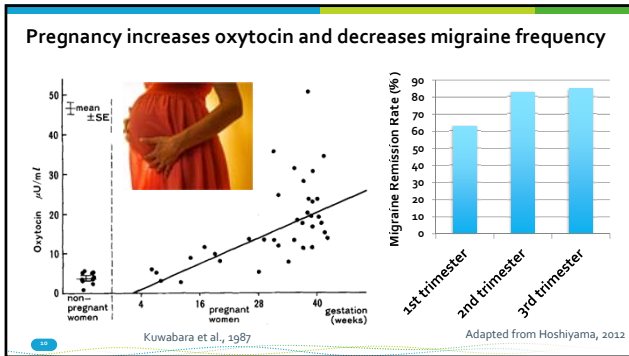


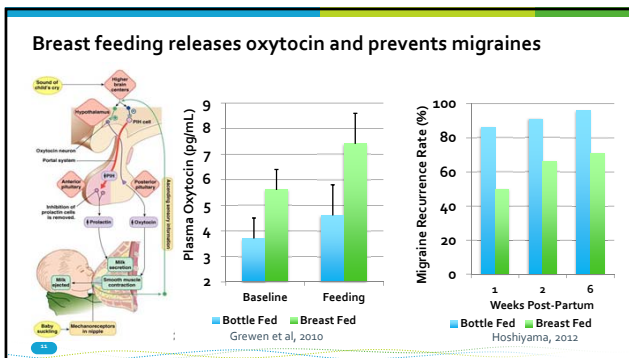
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OXTR tone is set by at least 3 factors:

- **OT concentration at the receptor**
- OXTR affinity for oxytocin (OT)
- Trigeminal OXTR expression levels

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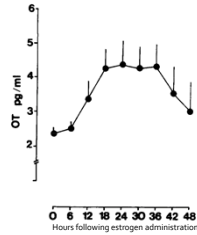






Plasma OT level is modulated by exogenous estrogen

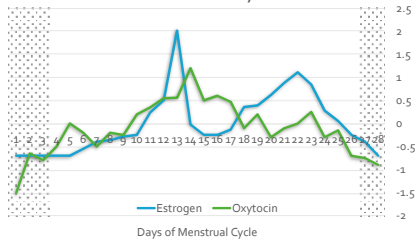
Plasma oxytocin levels following oral estrogen (1 mg)



Chiodera et al., 1991

Menstrual Migraine is associated with lowered oxytocin levels

Relative Estrogen and Oxytocin Plasma Levels over the Menstrual Cycle

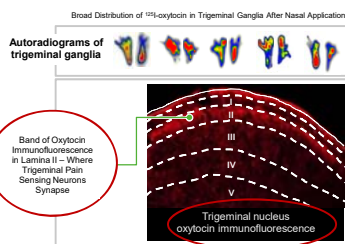


Days of Menstrual Cycle

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 ±135
	Distal trigeminal ganglion	423 ±142
OLFACTORY NERVE	Nucleus	34 ±10
	Substantia	33 ±13
	Cortex	28 ±8
	Caudate	39 ±12
BRAIN	Thalamus	15 ±6
	Midbrain	23 ±12
	Cerebellum	20 ±8
	Medulla	26 ±10
SPINAL CORD	Cervical	34 ±9
	Thoracic	5 ±1
	Lumbar	5 ±1
	Sacral	16 ±3
OTHER TISSUES	Liver	16 ±2
	Kidney	35 ±5
	Lung	25 ±4
	Heart	23 ±4
BLOOD	Blood	63 ±4

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



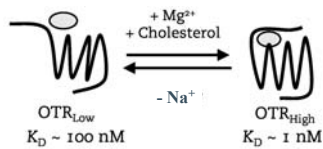
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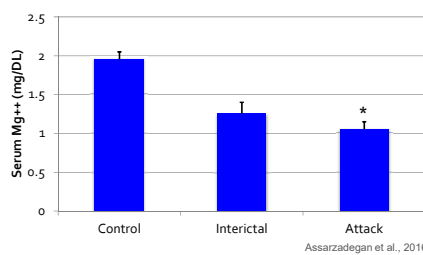
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Mg⁺⁺ and cholesterol positively, and Na⁺ negatively allosterically modulate the oxytocin receptor

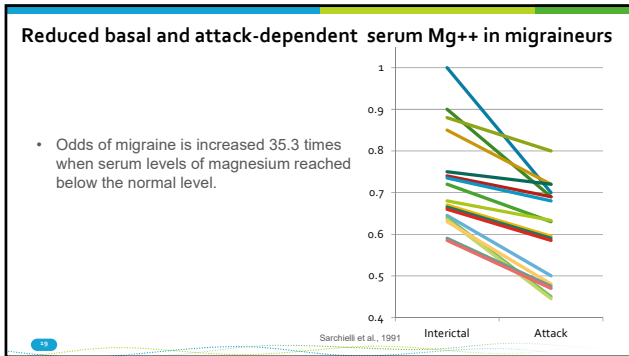


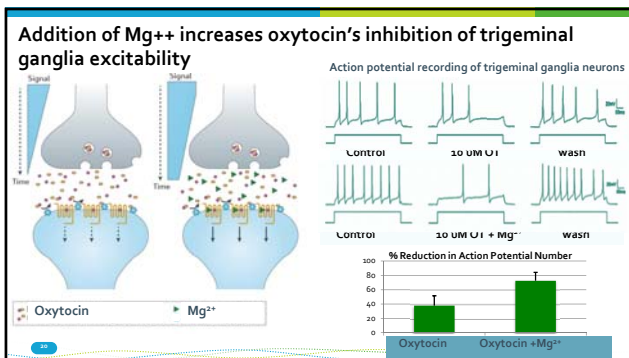
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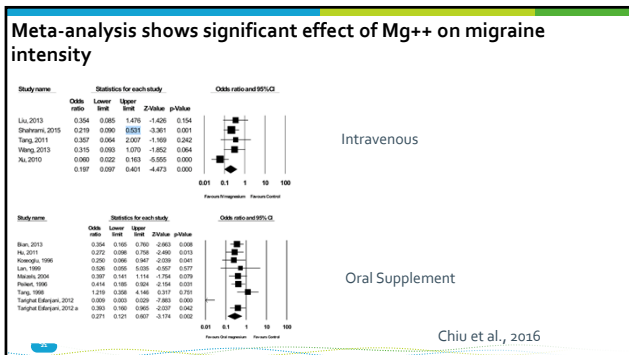
Serum Mg⁺⁺ is lower in migraineurs suggesting positive allosteric modulation of OXTR



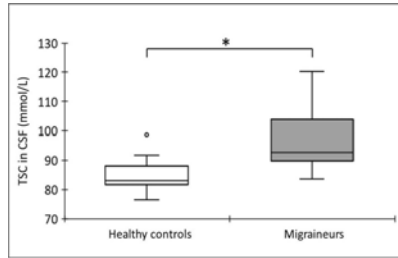
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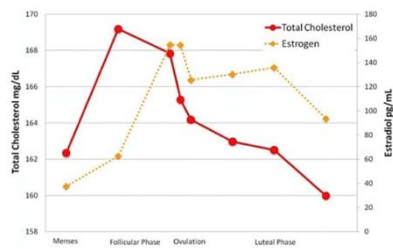


Total sodium concentration is higher in migraineurs, suggesting negative allosteric modulation of OXTR



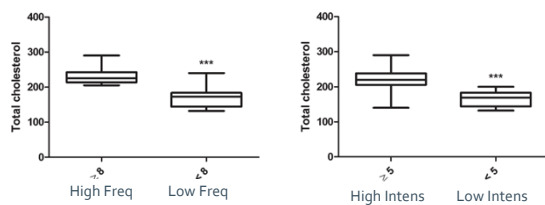
Meyer et al., 2019

Cholesterol drops with estrogen over menstrual cycle, suggesting negative modulation of OXTR affinity



Mumford et al., 2011

Higher total cholesterol is associated with more frequent and stronger migraine attacks



Tana et al., 2014

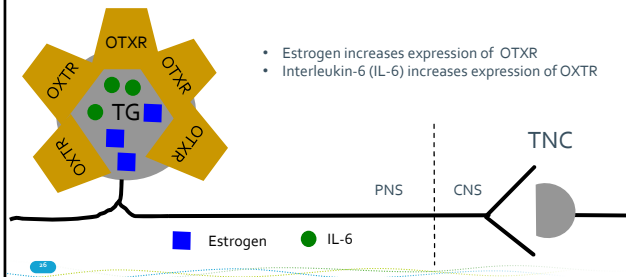
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- **Trigeminal OXTR expression levels**

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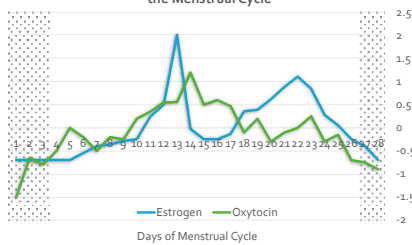
Influences on trigeminal OXTR expression



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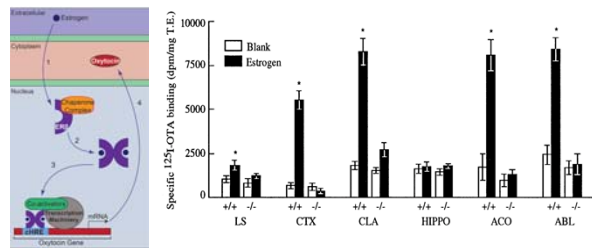
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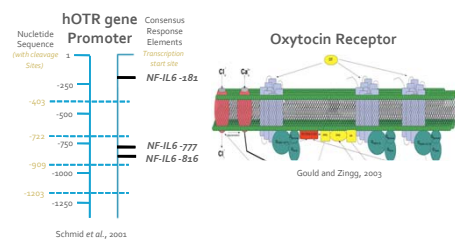


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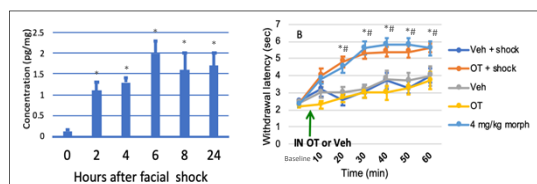
Increase in brain OXTR induced by estrogen



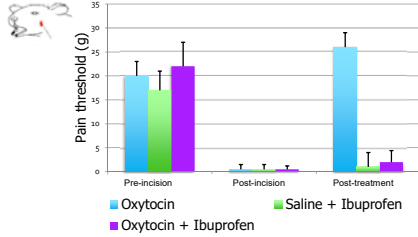
The OTR gene promoter has multiple response elements for the inflammatory cytokine IL-6



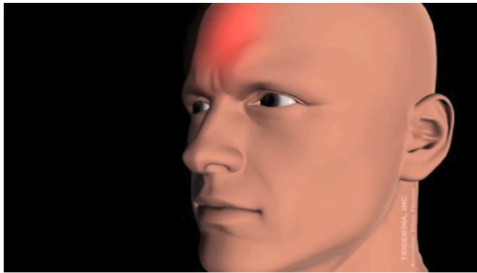
Inflammation increases trigeminal Oxytocin receptor expression



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



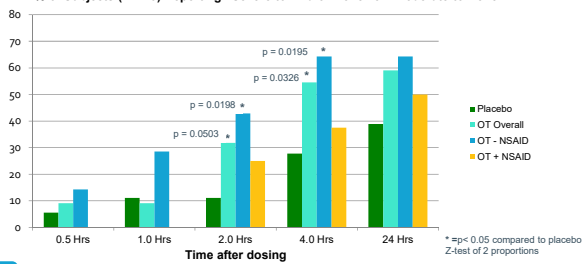
Nasal delivery of oxytocin to the trigeminal system of humans

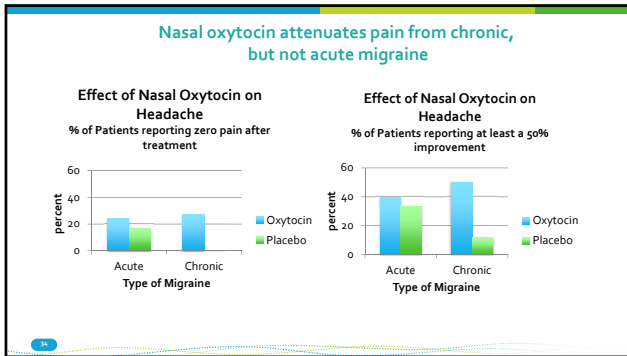


Pilot Clinical Study: Nasal Oxytocin Reduces Pain In Chronic Migraineurs

Excluding patients who took NSAIDs within 24 hours increases efficacy

% of Subjects (n = 40) Reporting "Severe to Mild or None" or "Moderate to None"





Summary: Evidence for OXTR modulation of migraine

Oxytocin Levels

- Oxytocin receptors on trigeminal ganglia neurons decrease excitability
- As endogenous oxytocin levels increase, migraines decrease
- Estrogen modulates oxytocin levels
- Nasally applied oxytocin concentrates in the trigeminal system

OXTR affinity

- Mg++ and cholesterol positively affects OXTR affinity; Na++ negatively affects OXTR affinity
- Mg++ levels lower in migraineurs especially during attacks
- Mg++ increases trigeminal ganglia neurons inhibition by oxytocin
- Mg++ is therapeutic for migraine
- Na+ levels higher in migraineurs
- Cholesterol levels increase with migraine frequency and severity but drop with estrogen drop

OXTR expression

- Estrogen increases OXTR expression
- Inflammation (IL-6) increases OXTR expression and efficacy in rat trigeminal pain models
- Nasal oxytocin is effective in chronic migraineurs who have not taken NSAIDs

Hugging, massage, sex, looking at your dog, and shooting your gun release oxytocin – and perhaps could help prevent migraines

under the microscope

oxytocin

Science

A lasting bond

The secrets of our deep ties with dogs

Healing touch

How massage and touch help us heal



Thank you!
