OXYTOCIN AND HEADACHES

Disclosures

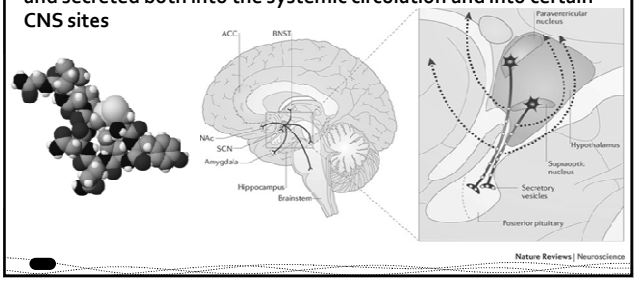
Professor David C Yeomans, Director of Pain Research, Stanford Medical School

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

Learning objectives

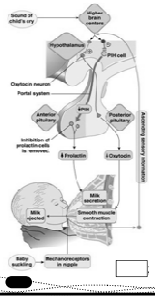
- Oxytocin chemical anatomy
- Involvement of endogenous oxytocin in migraine prevalence
- Effect of oxytocin on trigeminal neurons
- Effect of oxytocin in animal pain models
- Distribution of oxytocin after nasal application
- Importance of inflammation in analgesic efficacy of oxytocin in rodents and migraineurs
- Interaction between oxytocin and CGRP in vitro and in vivo
- Effect of addition of magnesium on efficacy of oxytocin

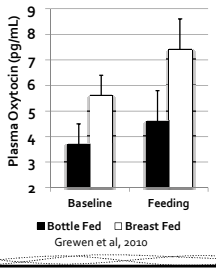
Oxytocin is a 9 amino acid polypeptide hormone/neurotransmitter which is made in the hypothalamus and secreted both into the systemic circulation and into certain CNS sites



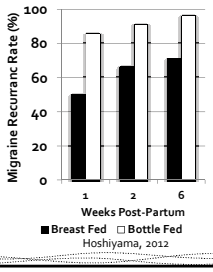
Circumstantial evidence that increases in oxytocin can lead to decreases in migraine

Breast feeding releases oxytocin and prevents migraines





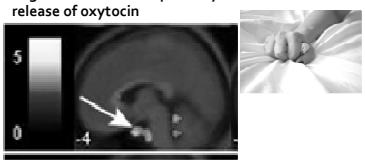
Grewen et al, 2010



Hoshiyama, 2012

Intercourse and orgasm release oxytocin and relieve migraines

Orgasm activates the pituitary release of oxytocin



Huynh et al., 2013

During orgasm, plasma oxytocin increases 42% in women, 73% in men

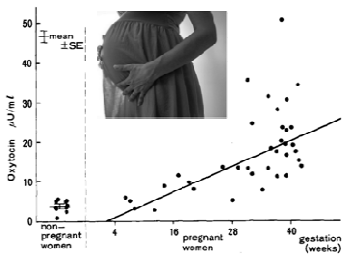
Carmichael et al., 1987

Intercourse and orgasm can alleviate migraine headache

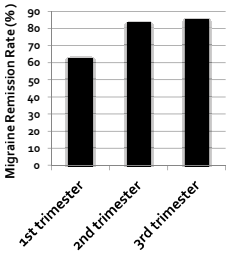
Degree of relief	No (%) of women N = 58
Complete relief	10 (17%)
Moderate relief	5 (9%)
Temporary relief (< 60 min)	7 (12%)
Relief only for mild headaches	5 (9%)
Any relief	27 (47%)
No relief	28 (48%)
Worse	3 (5%)

Adapted from Evans and Couch, 2001

Pregnancy increases oxytocin and decreases migraine



Kuwabara et al., 1987



Adapted from Hoshiyama, 2012

Case studies of alleviation of migraine by IV oxytocin

Case 1

A 37 yr old patient had a migraine during delivery. Following delivery, …"her only complaint was continued headache rated 8/10. Immediately after delivery of the placenta, oxytocin 20 units was administered in 300 mL of Lactated Ringers Solution, USP over 10 minutes. By the completion of the infusion, the patient experienced complete relief of her headache."

Case 2

"A ten-year-old Caucasian male presented with an acute migraine headache of eight hours duration… His pain intensity rating was 8/10…A peripheral intravenous line was started and 500 mL normal saline with 10 units of oxytocin was administered over 30 minutes. Twenty minutes after beginning the infusion his pain intensity decreased to 2/10."

Phillips et al., 2006

Oxytocin is released by hugging, massage, sex, looking at your dog, and shooting your gun

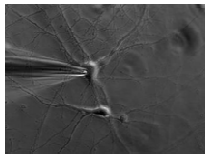
DID YOU KNOW?

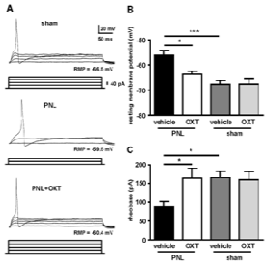
Your body releases the same hormone (Oxytocin) while shooting a gun as having an orgasm?

Oxytocin and trigeminal pain

Oxytocin immunoreactivity on trigeminal ganglia neurons

Oxytocin inhibits injured trigeminal ganglia neurons *in vitro*





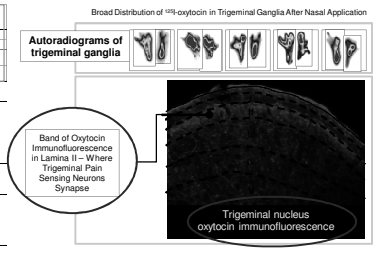
Kubo et al., submitted

Nasal application of oxytocin

Oxytocin is preferentially transported throughout the trigeminal system after nasal delivery

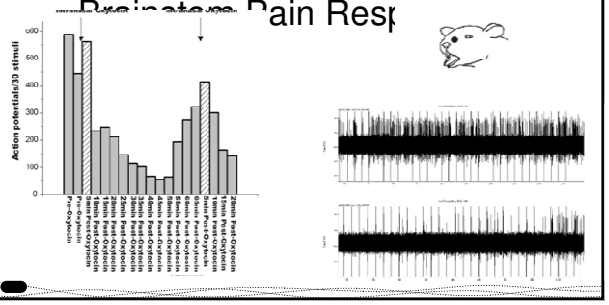
Oxytocin tissue levels (nM) after intranasal administration*			
TRIGEMINAL NERVE	Ganglion	574	±191
	Maxillary branch	471	±117
	Mandibular branch	676	±235
	Ophthalmic branch	423	±143
OLFACTORY NERVE	Nucleus	34	±10
	Bulbs	33	±13
BRAIN	Cortex	29	±8
	Caudate	39	±12
	Thalamus	15	±6
	Midbrain	23	±12
	Cerebellum	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

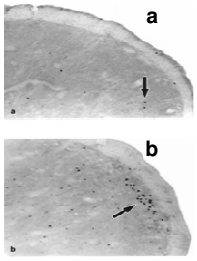


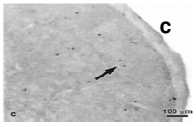
Intranasal Analgesia: Oxytocin Inhibits Brainstem Pain Resp

Nasal oxytocin inhibits pain responses of trigeminal nucleus neurons *in vivo*



Nasal oxytocin decreases nitroglycerin-induced c-fos expression in the trigeminal nucleus

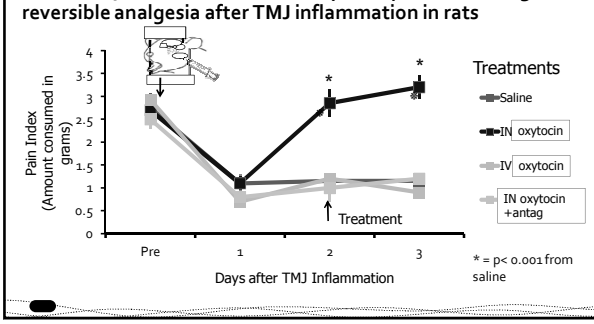




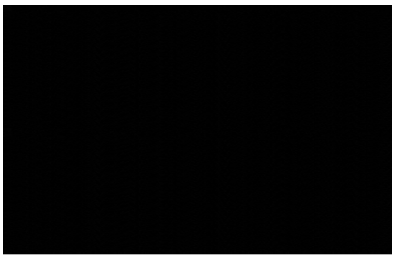
Nitroglycerin can induce migraines in humans

C-fos Expression change in the Trigeminal nucleus before (a) and After (b) nitroglycerin infusion, and (c) after nasal oxytocin treatment

Intranasal, but not intravenous oxytocin produces antagonist-reversible analgesia after TMJ inflammation in rats



Nasal delivery of oxytocin to the trigeminal system of humans



Pilot clinical study: effect of nasal oxytocin in episodic migraine

Percent of patients showing improvement at 2 hrs

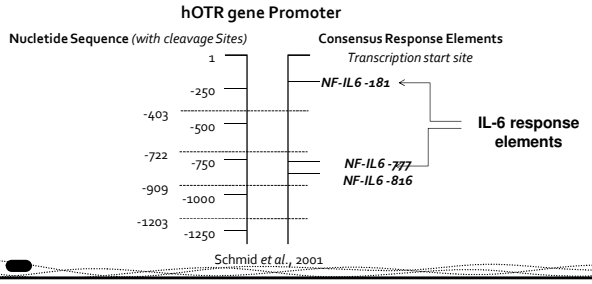
	IN Oxytocin	IN Placebo
Pain reduction	33%	26%
Photophobia	21%	9%
Phonophobia	16%	2%
Nausea	27%	17%

Rating at 24 hrs

	IN Oxytocin	IN Placebo
Excellent	14%	2%
Good	14%	7%
Fair	11%	17%
Poor	61%	74%

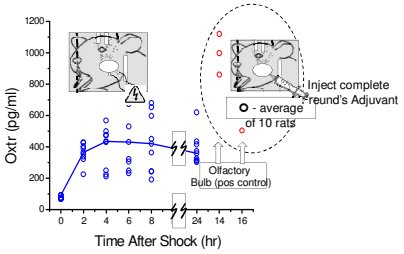
Inflammation and oxytocin analgesic efficacy

Oxytocin gene promoter has multiple response elements for Inflammatory cytokine IL-6

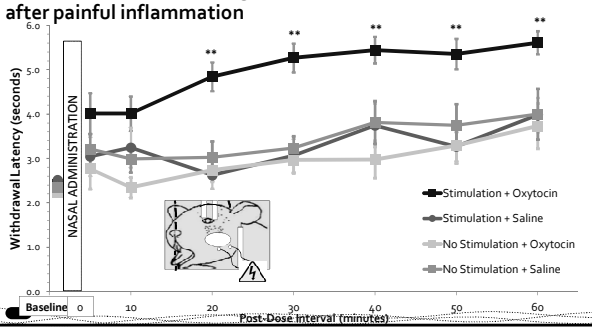


Schmid *et al.*, 2001

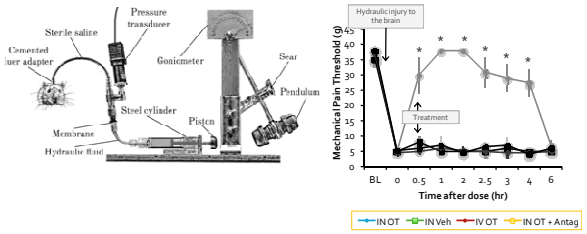
Inflammation increases expression of oxytocin receptors on trigeminal ganglia neurons 5-10 fold



Nasal oxytocin reduces trigeminal thermal nociception only after painful inflammation

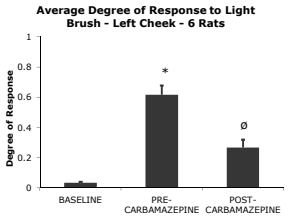


Nasal, but not IV oxytocin is analgesic for head pain after brain injury



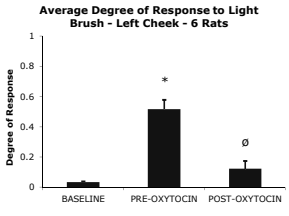
Nasal oxytocin is as effective as multiple doses of carbamazepine in a rat model of trigeminal neuralgia

Multi-Dose Carbamazepine



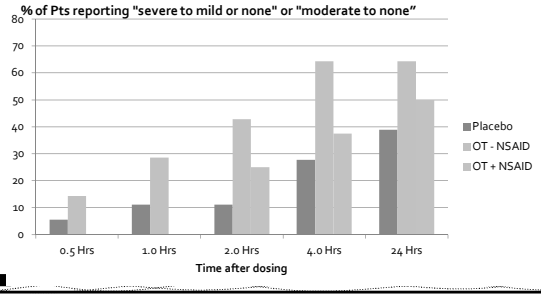
* = p < 0.001 vs baseline
Ø = p < 0.001 vs Pre-Carbamazepine

Single Dose Nasal Oxytocin



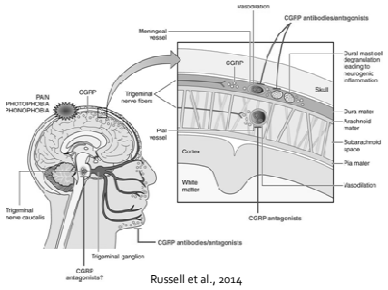
* = p < 0.001 vs baseline
Ø = p < 0.001 vs Pre-Oxytocin

Pilot clinical study: Nasal oxytocin reduces pain in chronic migraineurs Blocking IL-6 with NSAIDs decreases efficacy



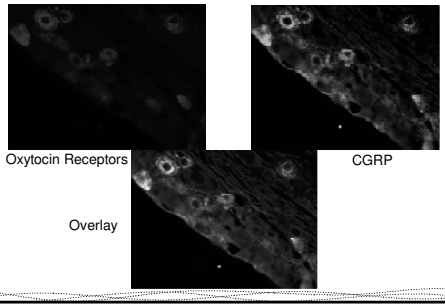
Oxytocin and CGRP: mechanism to reduce migraine frequency

Dural CGRP release appears to be critical to migraine



Russell et al., 2014

Oxytocin Receptors are co-expressed on CGRP + Trigeminal Neurons



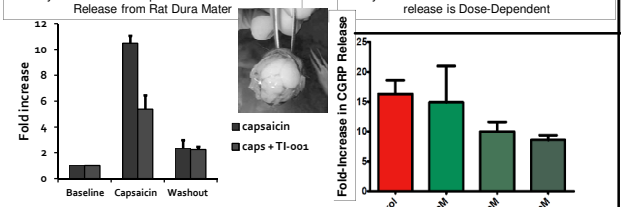
Oxytocin Receptors

CGRP

Overlay

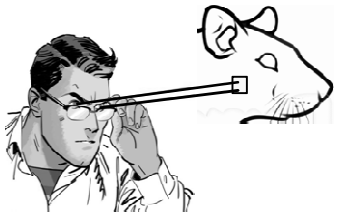
Oxytocin's Inhibition of trigeminal neurons decreases dural (and likely central) CGRP release

Oxytocin Reduces Capsaicin-Induced CGRP Release from Rat Dura Mater

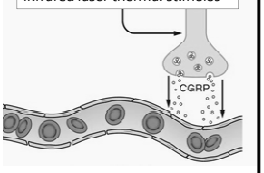


Oxytocin- induced Reduction of Dural CGRP release is Dose-Dependent

Laser stimulation of the cheek induces CGRP release-dependent flare



Infrared laser thermal stimulus

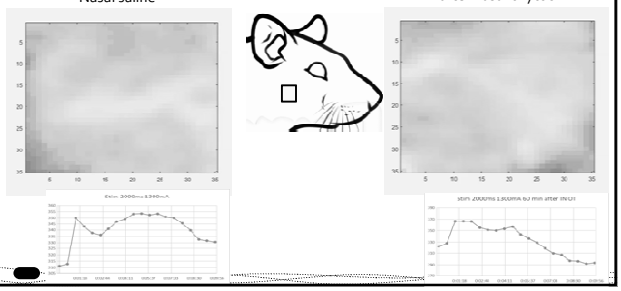


Adapted from Russell et al., 2014)

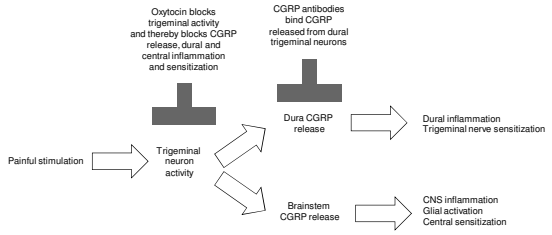
Nasal oxytocin reduces flare response to laser pulse measured by scanning laser doppler after cheek inflammation

Nasal saline

1 hr after nasal oxytocin

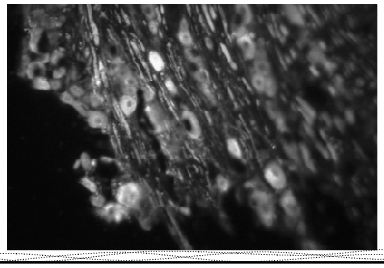


Oxytocin blocks release of CGRP and so could directly block both peripheral and central sensitization

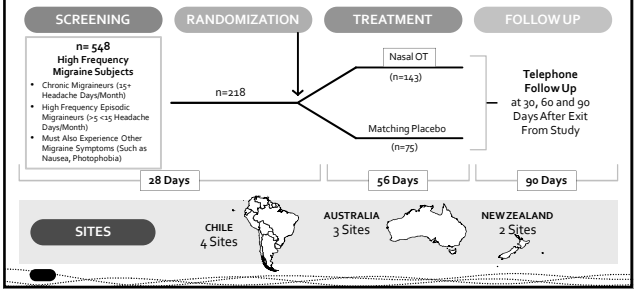


Oxytocin Receptors also co-express with PACAP in trigeminal ganglia neurons

Overlay of OXTR (Green) and PACAP-38 (Red) immunoreactivity

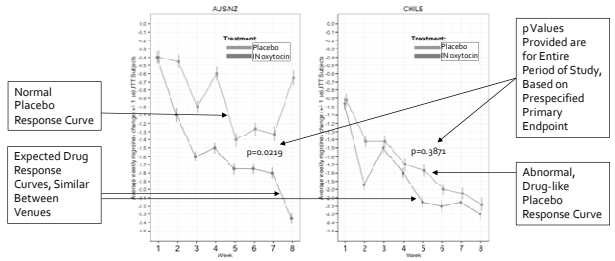


Pilot study: effect of nasal oxytocin on migraine day frequency



Placebo in Australia/New Zealand vs. Chile

Geographical Comparison in Weekly Migraine Headache Days (MHD) Reduction



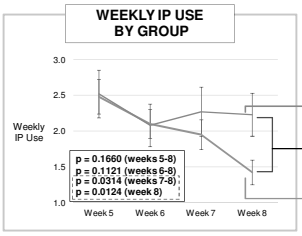
Normal Placebo Response Curve

Expected Drug Response Curves, Similar Between Venues

p Values Provided are for Entire Period of Study, Based on Prespecified Primary Endpoint

Abnormal, Drug-like Placebo Response Curve

IP Use Lower in Treatment Arm Compared to Placebo



DOSING

IP 'as needed' (PRN) use required when patients experienced headaches → **P Values** for IP use indicate statistical significance in final weeks of study

RESULTS

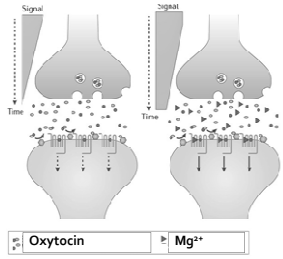
PLACEBO SUBJECTS: Continued to take **higher levels of IP**

80% HIGHER Usage of IP by the placebo group

SUBJECTS IN TREATMENT ARM: **Used less IP** week-by-week as headache days declined

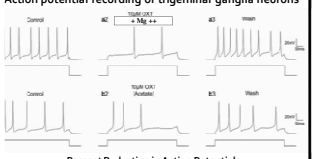
TI-001, a novel, magnesium containing oxytocin formulation

Magnesium ions act as positive allosteric modulators at the oxytocin receptor, increasing the potency of oxytocin *in vitro*

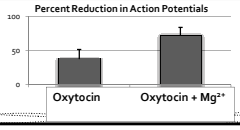


Wooten et al., 2013

Action potential recording of trigeminal ganglia neurons



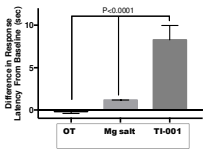
Percent Reduction in Action Potentials

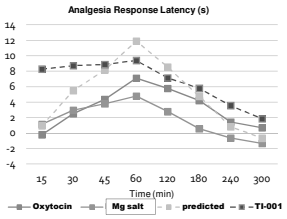


Nasal TI-001 analgesia is superior to oxytocin alone

TI-001 PRODUCES SYNERGISTIC IMPROVEMENT COMPARED TO OXYTOCIN IN ***ANALGESIC EFFECT***

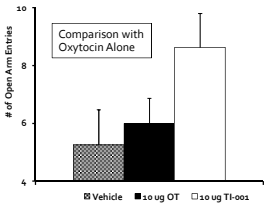
TI-001 synergy at 15 min post-dosing: immediate onset





Nasal TI-001 is more effective than oxytocin for Autism/FXS symptoms, e.g., anxiety

Elevated Plus Maze Test of Anxiety



Summary

- As oxytocin levels increase, migraines decrease
- Oxytocin receptors are present on trigeminal ganglia neurons
- Oxytocin decreases excitability of injured trigeminal ganglia neurons
- Nasally applied oxytocin concentrates in the trigeminal system and inhibits central neuronal responses and behavioral responses to painful stimuli
- Nasal oxytocin has minimal effect in low frequency episodic migraine
- Inflammation drives upregulation and enables efficacy in rat trigeminal pain models
- Nasal oxytocin is analgesic in chronic migraineurs who have not taken NSAIDs
- CGRP is co-expressed in trigeminal ganglia neurons; CGRP release is blocked by oxytocin
- PRN nasal oxytocin decreases migraine frequency in chronic migraineurs, presumably via blocking CGRP release
- Addition of magnesium salt to oxytocin produces synergistic, analgesic effects and results in a proprietary formulation

Thank you!