Intranasal (IN) Oxytocin Relieves Pain and Depressive Behavior in a Rodent Model of Mild Traumatic Brain Injury (TBI)

TONIX PHARMACEUTICALS

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DISCLOSURES

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Consequences of TBI

- Post traumatic headaches (PTH)
- Cognitive deficits in memory, attention, and concentration
- Somatic complaints of fatigue, disordered sleep, dizziness
- Affective complaints of irritability, anxiety, and depression
- Post Traumatic Stress Disorder (PTSD)

Hoffman et al 2020

Post Traumatic Headache (PTH) is a Disabling Symptom of TBI

- TBI is the most common brain disorder, the incidence of which exceeds that of dementia, epilepsy and stroke
- 1.7 million TBIs are sustained each year in the United States, most of which are of mild initial severity
- 5.3 million Americans live with TBI-related disability
- PTH is one of the most prevalent TBI sequelae (up to 89% of patients suffer from it), is one of the longest lasting post-concussion symptoms, causes significant morbidity, and might be associated with slower neurocognitive recovery

Finkel et al 2012

CGRP and PACAP are Believed to Play a Critical Role in Post-traumatic Headache (PTH)

- Most PTH are migraine like in character (Finkel 2012)
- Some PTH have autonomic features (Finkel 2012)
- CGRP (Friburg 1994) and PACAP (Amin 2014) are elevated in jugular blood during migraine attack
- CGRP injection causes migraine headache in 63% of migraineurs
- PACAP-38 injection induces migraine headache in 73% of migraineurs
- CGRP antibodies are highly effective in approx. 50% of chronic migraine pts
- PACAP has been implicated in 15-40% of chronic migraineurs (Vollesen 2017)
- CGRP has been implicated in animal models of PTH (Navratilova et al., 2019)
- In an open label study, a CGRP antibody was found effective in PTH (Ashina et al, 2020)

Intranasal Oxytocin (IN OT) as a Treatment for PTH

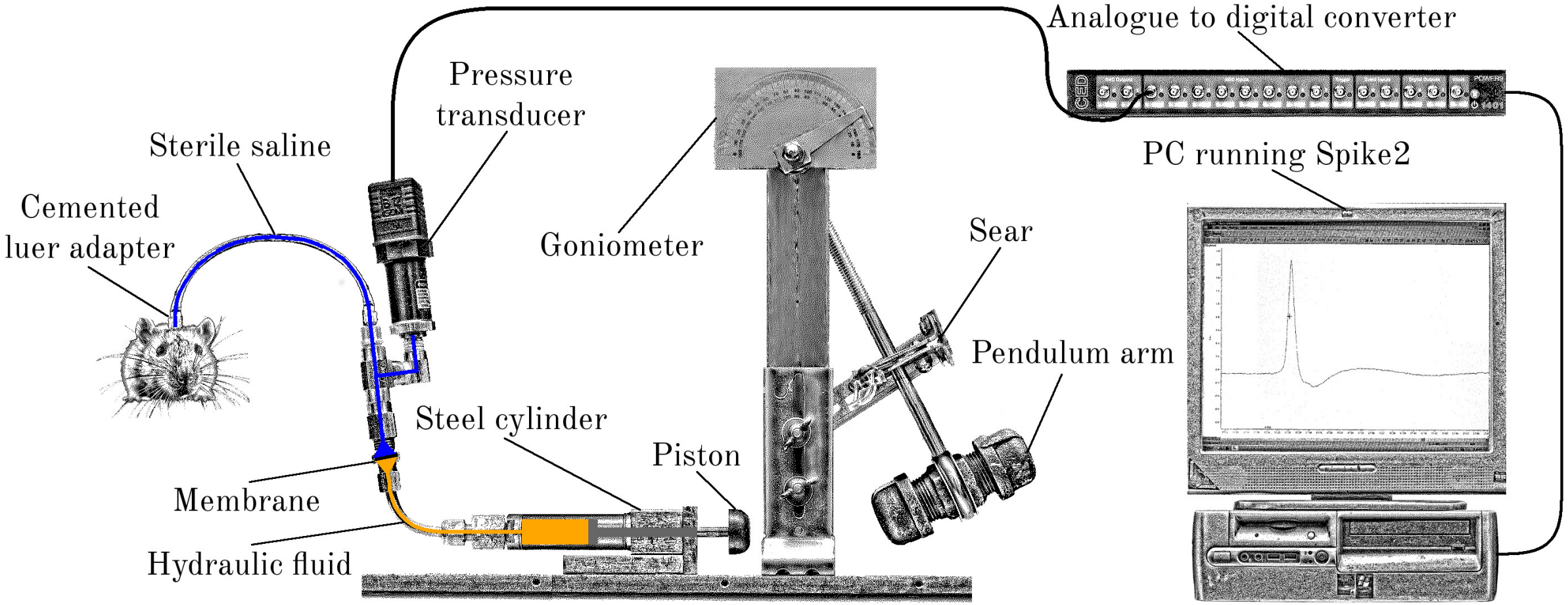
- Natural hormone, deficiency of which is believed to lower pain threshold
- Intranasal oxytocin is taken up by trigeminal (TG) system and believed to act in TG
- Has multiple mechanism of action, suppresses trigeminal nociceptive transmission, blocks CGRP and PACAP
- Has little systemic effect, and hence does not appear to block CGRP or PACAP elsewhere in the body
- Believed to have anti-dependence effect and has been used in treating PTH patients with medication overuse headache (MOH)
- Believed to have anti-anxiety effects, a common co-morbidity in TBI patients
- Extensive history of use and tolerability: clinically use for more than 60 years
- No recognized addictive potential, and no tachyphylaxis has been described

Efficacy of IN OT Has Been Demonstrated in Other Headache Models

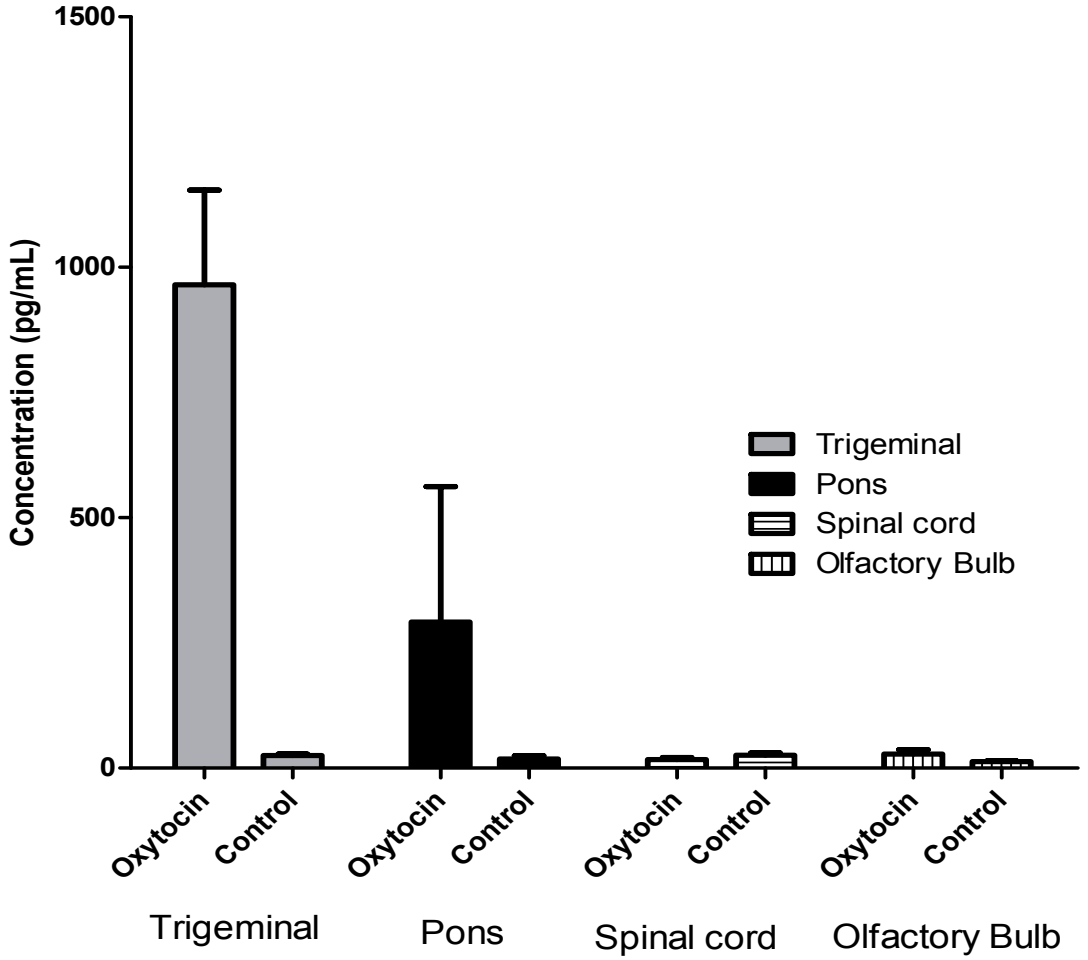
- Synergistic action between oxytocin and Mg demonstrated
- Naso-cerebral pathway proved by radiolabeling studies
- Decreased action potentials in TG cells demonstrated by elegant electrophysiological studies
- Blockage of CGRP and PACAP release by oxytocin demonstrated*
- Pain relief in TG system by intranasal oxytocin, but not IV oxytocin, demonstrated in animal models of TMJ inflammation and trigeminal neuropathy
- Oxytocin receptors demonstrated in SPG, a key parasympathetic contributor to cranial pain persistence

*Yeomans et al 2017

Efficacy of nasal OT was tested in a rat model of mild-moderate traumatic brain injury (TBI)



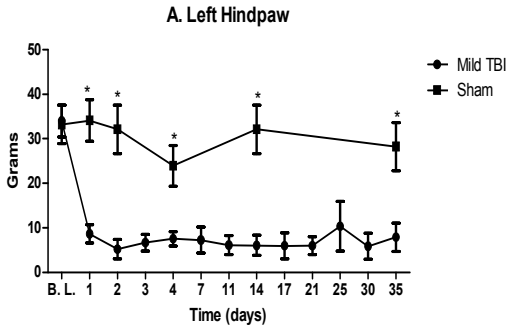
Elevated levels of OT in trigeminal ganglia and pons after nasal application of OT vs vehicle control

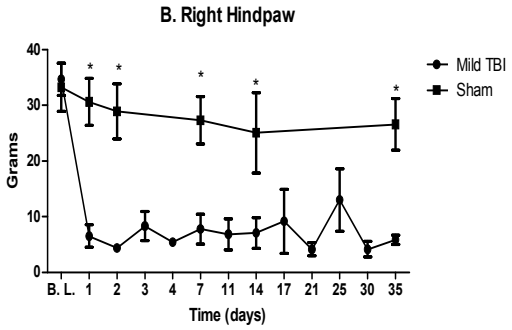


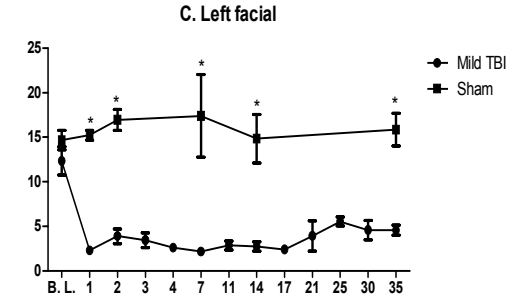
Nasal OT effects on post-TBI pain

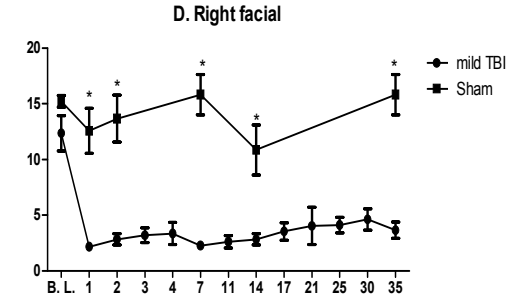
Mechanical sensitivity (von Frey) after mild TBI or sham surgery

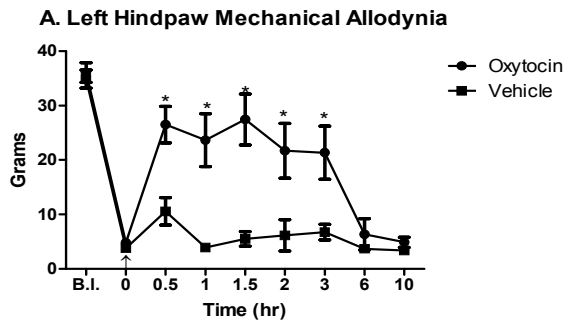
The effect of nasal oxytocin on allodynia after mild TBI.

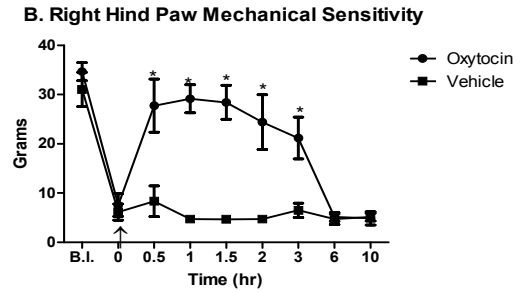


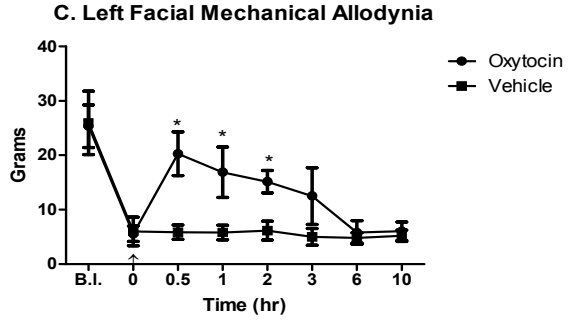


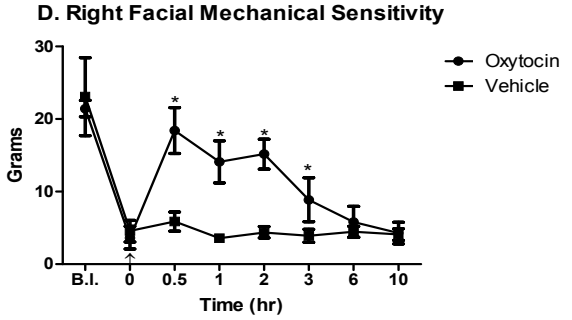








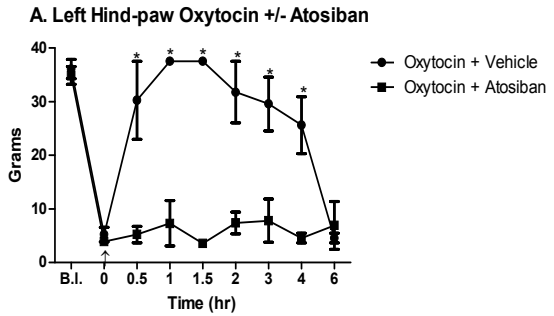


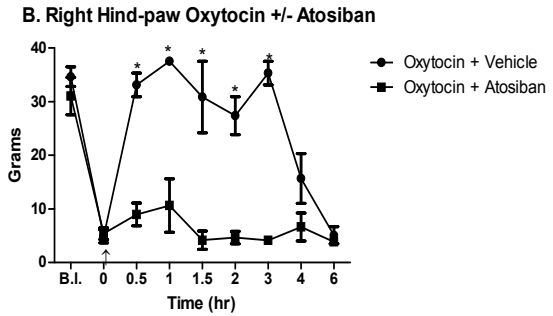


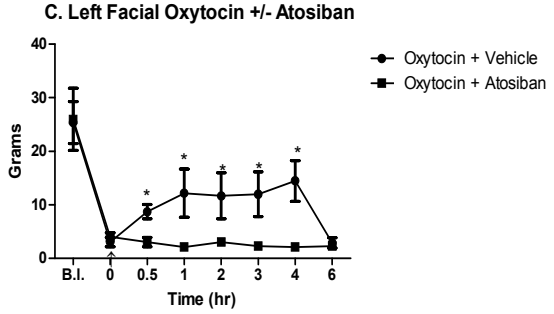
Nasal OT effects on post-TBI pain

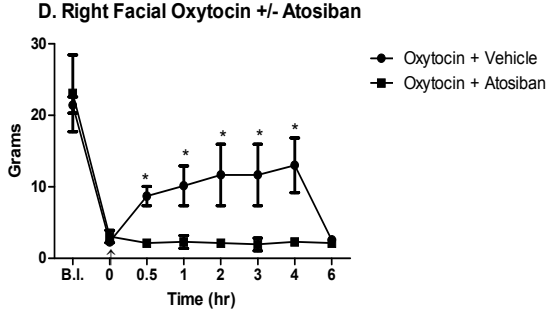
Anti-allodynic effect of nasal OT is blocked by the OT antagonist Atosiban

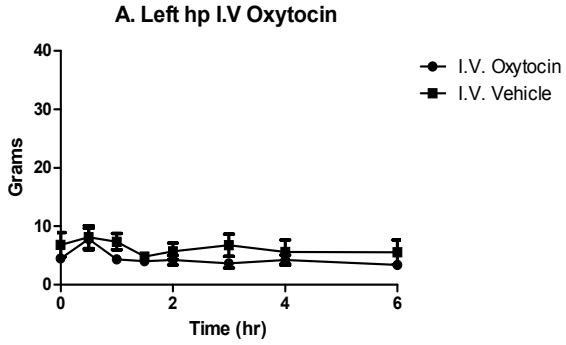
IV OT is ineffective in preventing post-TBI allodynia

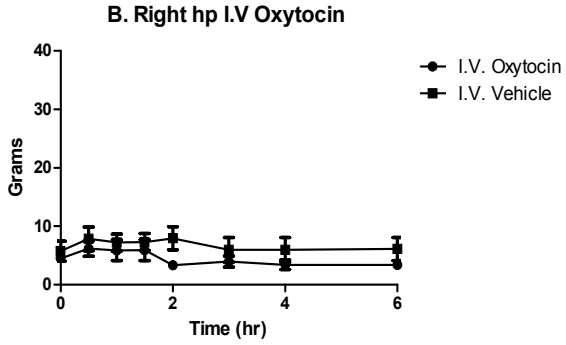


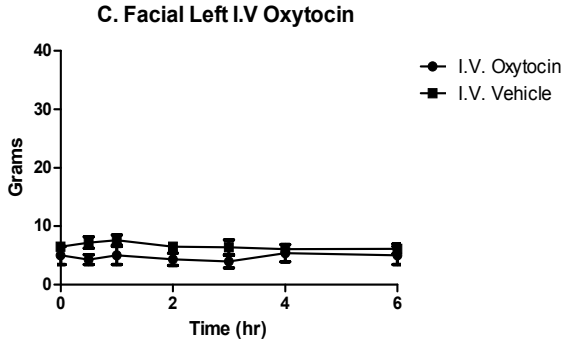


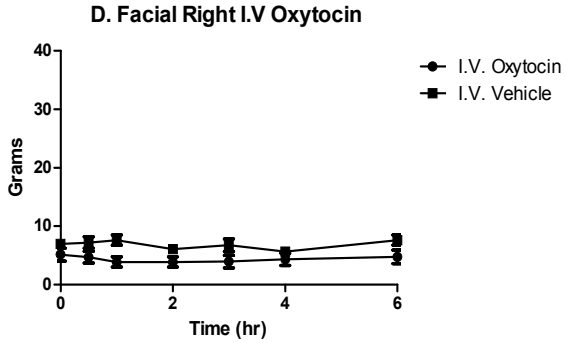








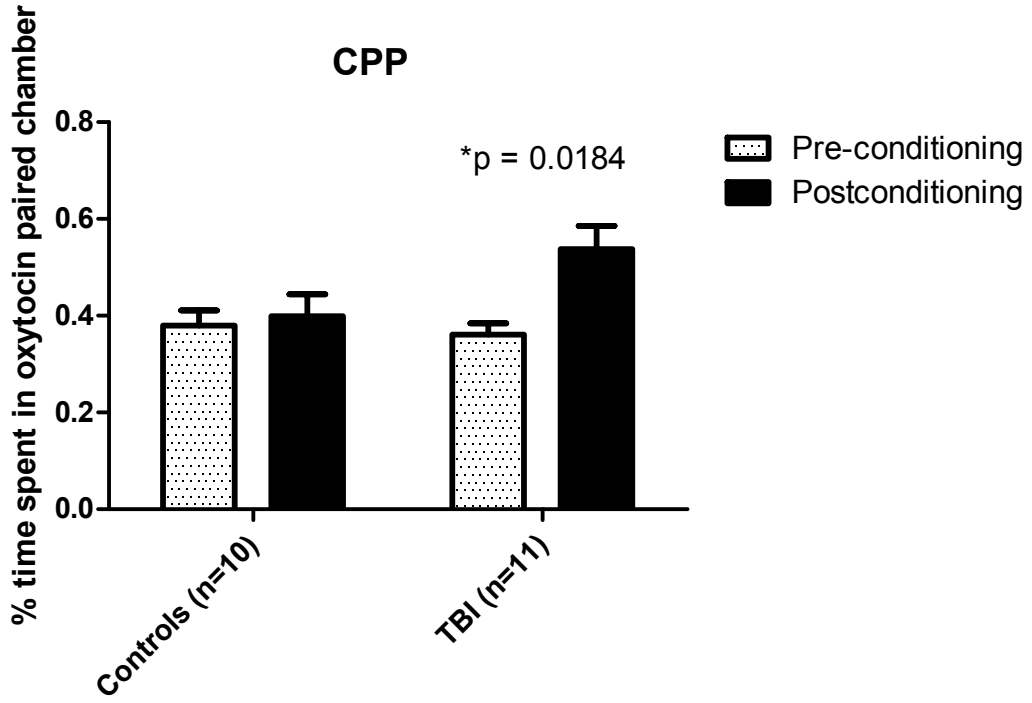


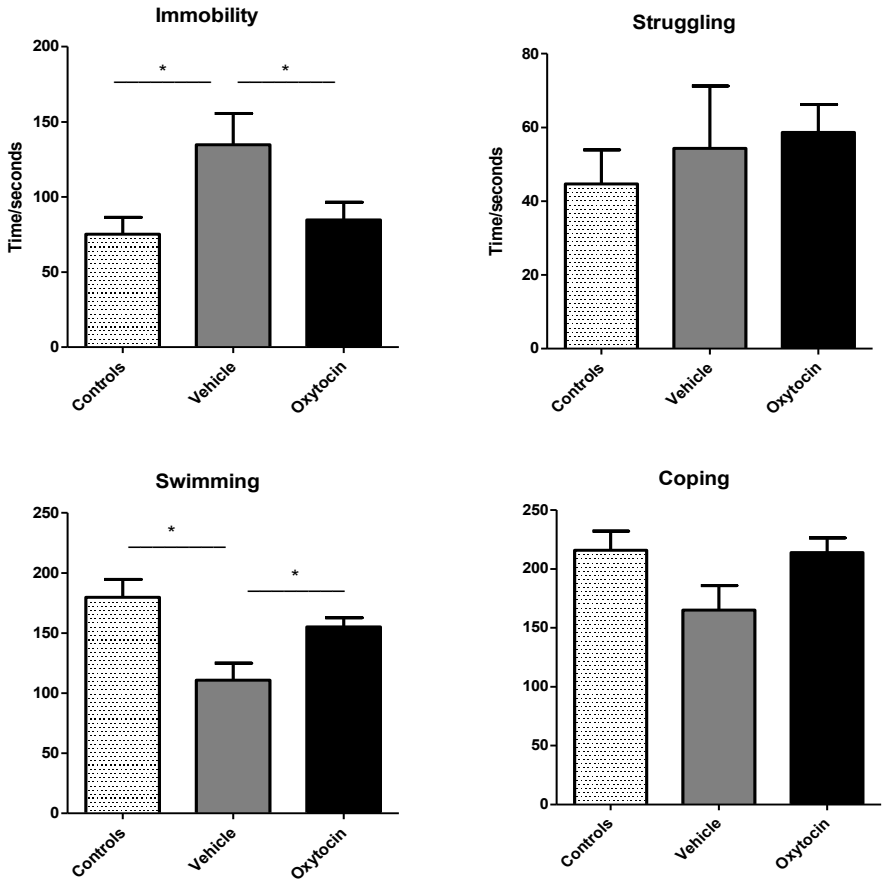


Nasal OT effects on post-TBI pain

Nasal OT has no effect on Conditioned Place Preference in control animals: analgesia without addictive potential

Nasal OT is effective in some aspects of post-TBI Depression in the forced swim test

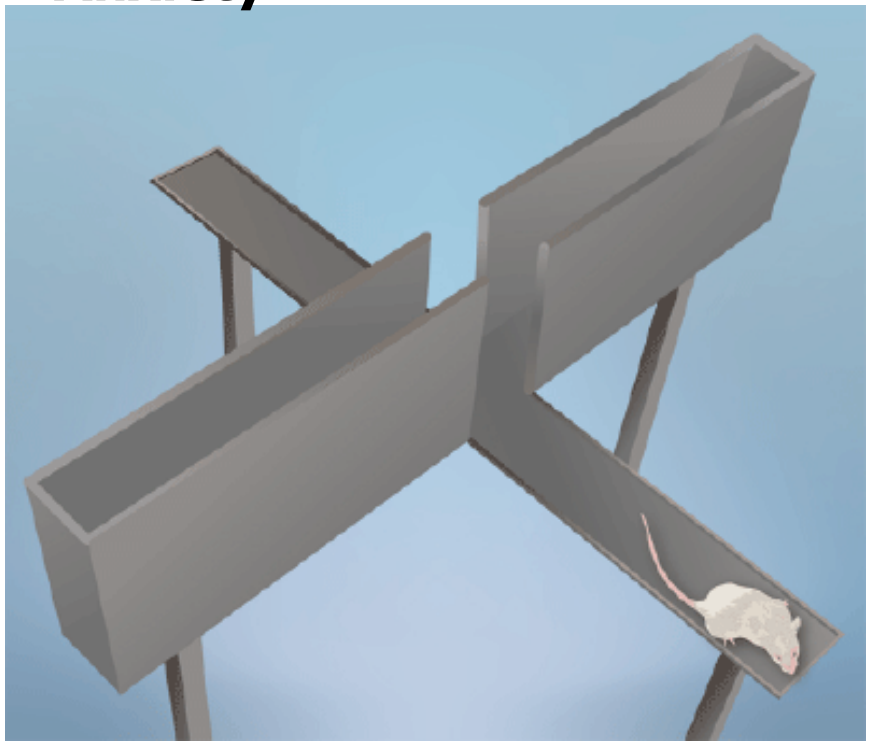


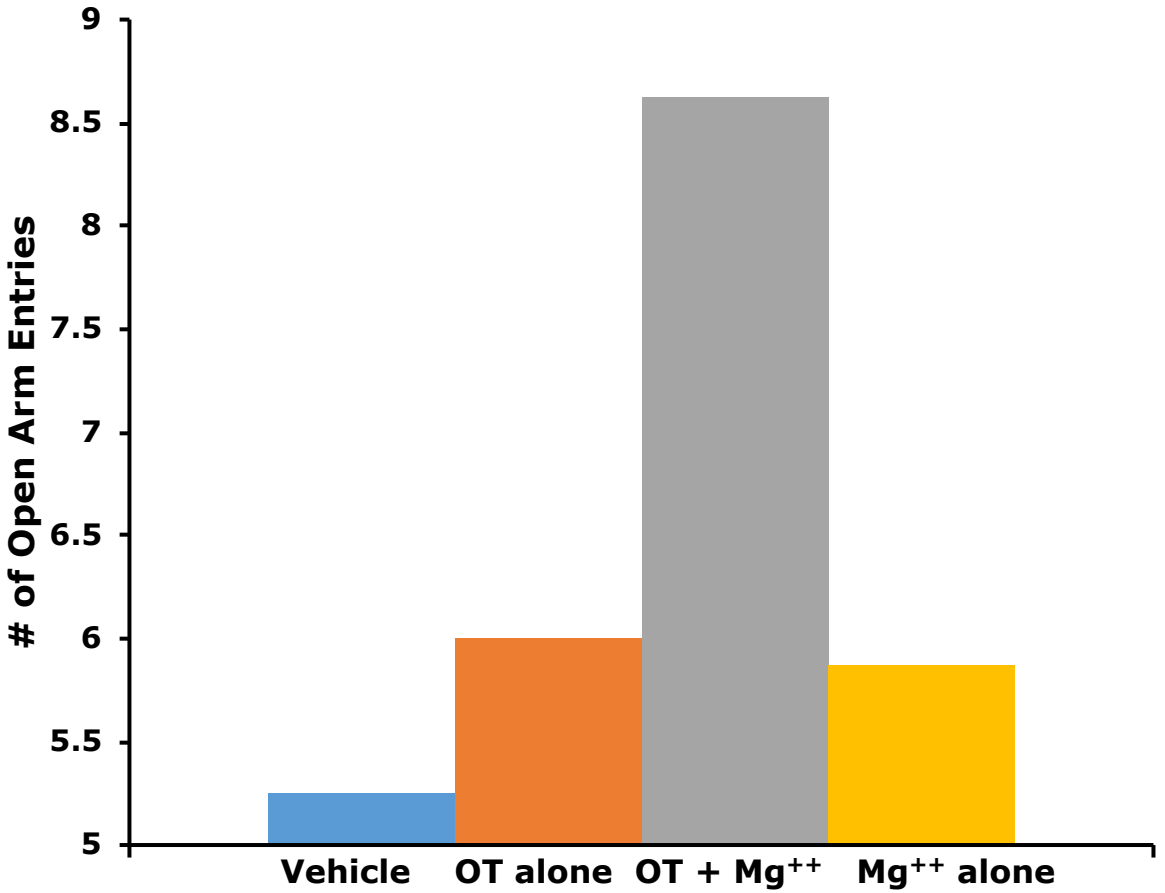


IN OT for Core PTSD Symptom of Anxiety

- Proprietary Formulation of Nasal Oxytocin Plus Mg++ Provides Synergistic Improvement in Elevated Plus Maze test of Anxiety

Elevated Plus Maze Test of Anxiety





Conclusions: IN Oxytocin in Post-traumatic Headache (PTH)

- After intranasal application, oxytocin concentrates in the trigeminal system
- Intranasal, but not IV Oxytocin attenuates pain responses in a rat model of traumatic brain injury without addictive potential
- These analgesic effects can be blocked by an oxytocin antagonist showing receptor specificity
- Intranasal oxytocin also attenuates post-TBI depressive and anxiety behaviors
- Addition of magnesium enhances the effects of intranasal oxytocin