TONIX PHARMACEUTICALS

NASDAQ: TNXP

TNX-2900

Prader-Willi Syndrome

HERBERT HARRIS, MD, PHD

RARE DISEASE INNOVATION AND PARTNERSHIP SUMMIT MARCH 23, 2023

PHILADELPHIA, PA

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TNX-2900*: Hyperphagia in Prader-Willi Syndrome
Intranasal Potentiated Oxytocin (OT) with Magnesium

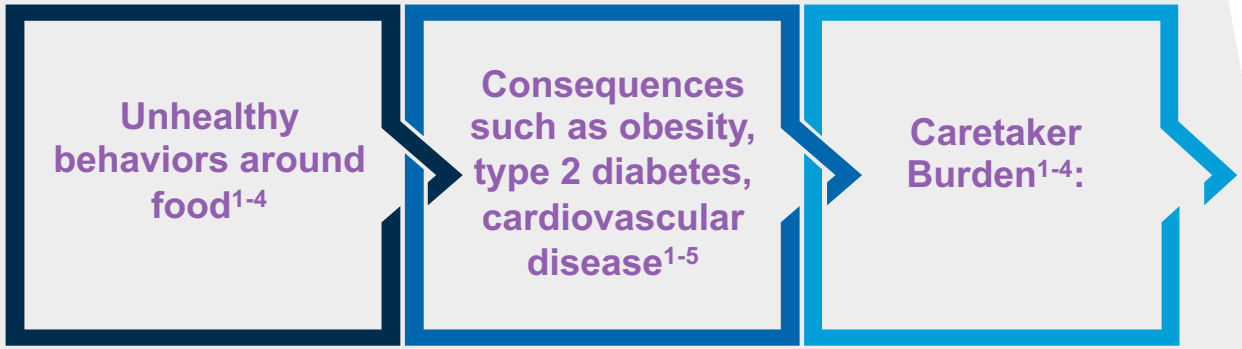
PROFILE

Prader-Willi Syndrome is the most common genetic cause of life-threatening childhood obesity

- Rare disease occurring in 1 in 10,000 to 1 in 30,000 births

Differentiator: No approved therapeutic currently on the market for hyperphagia in PWS

Dangers of PWS Hyperphagia:



Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Hyperphagia in Prader-Willi Syndrome

Additional Indications: Rare Hyperphagia Conditions

Status: Phase 2 ready

Next Steps: IND submission

*TNX-2900 is in the pre-IND stage of development and has not been approved for any indication.

[1]Miller JL, et al. *Am J Med Genet A*. 2011;155A(5):1040-1049.
[2]Butler MG, et al. *Genet Med*. 2017;19(6):635-642.
[3]Butler MG. NORD. Updated 2018. Accessed May 25, 2022. https://rarediseases.org/rare-diseases/prader-willi-syndrome/
[4]Prader-Willi Syndrome Association USA. Accessed May 25, 2022. https://www.pwsausa.org/what-is-prader-willi-syndrome/
[5]Muscogiuri G, et al. *J Endocrinol Invest*. 2021;44(10):2057-2070.

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TNX-2900*: Prader-Willi Syndrome
Intranasal Potentiated Oxytocin (OT) with Magnesium

RARE DISEASE PORTFOLIO

PROFILE

Prader-Willi Syndrome is the most common genetic cause of life-threatening childhood obesity

- Rare disease occurring in 1 in 10,000 to 1 in 30,000 births

Symptoms include lack of suckling as infants, poor muscle strength, and constant hunger (hyperphagia) in adolescents and young adults

- In animal models, OT has improved suckling and suppressed hunger
  - Tonix's patented potentiated OT formulation is believed to increase activity of OT at OT receptors (OXTR)

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Hyperphagia in Prader-Willi Syndrome

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Prader-Willi Syndrome (PWS)

Cause	~65% of cases are due to a new deletion on paternal chromosome 15; first genetic imprinting disorder recognized in humans
Prevalence	1 in 10,000 to 1 in 30,000[1,2]; most common syndromic cause of obesity
Symptoms	In infants, severe hypotonia and difficulty sucking. In children and adolescents, delayed global development, decreased growth resulting in short stature, intellectual difficulties, hypogonadism, hyperphagia, life-threatening obesity, behavioral problems
Diagnosis	Genetic testing: DNA methylation
Treatment	No cure, but human growth hormone treatment is FDA approved for growth failure in PWS children

[1]Angulo MA, et al. *J Endocrinol Invest.* 2015;38(12):1249-1263.
[2]McCandless, Shawn E et al. SUN-604 U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, *Journal of the Endocrine Society*, Volume 4, Issue Supplement_1, April-May 2020, SUN–604, https://doi.org/10.1210/jendso/bvaa046.993

Progression of Prader-Willi Syndrome[1]

YRS: 0 | 1 | 2 | 4 | 8 | 16 | 24 | 32

0 yrs

0 to 9 months

9 to 25 months

2 to 4.5 years

4.5 to 8 years

8 years to adulthood

Adulthood

Phase 0
Low birth weight

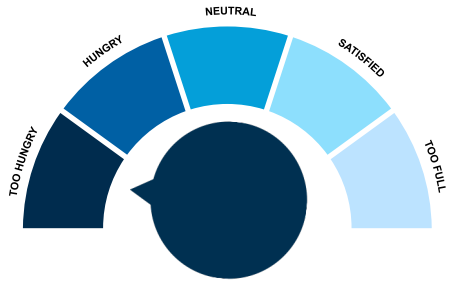
Phase 1a
Failure to thrive, feeding difficulties, hypotonia, increased infant mortality

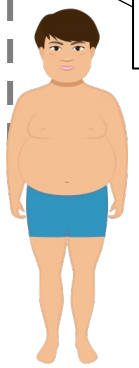
Phase 1b
Normal growth

Phase 2a
Weight increase without appetite increase

Phase 2b
Weight and appetite increase; obesity occurs if allowed to eat what they want

Phase 3
Hyperphagia





Average age at death: 29.5 years[2]

Phase 4
Return to normal appetite; this phase is not often reached

RARE DISEASE PORTFOLIO

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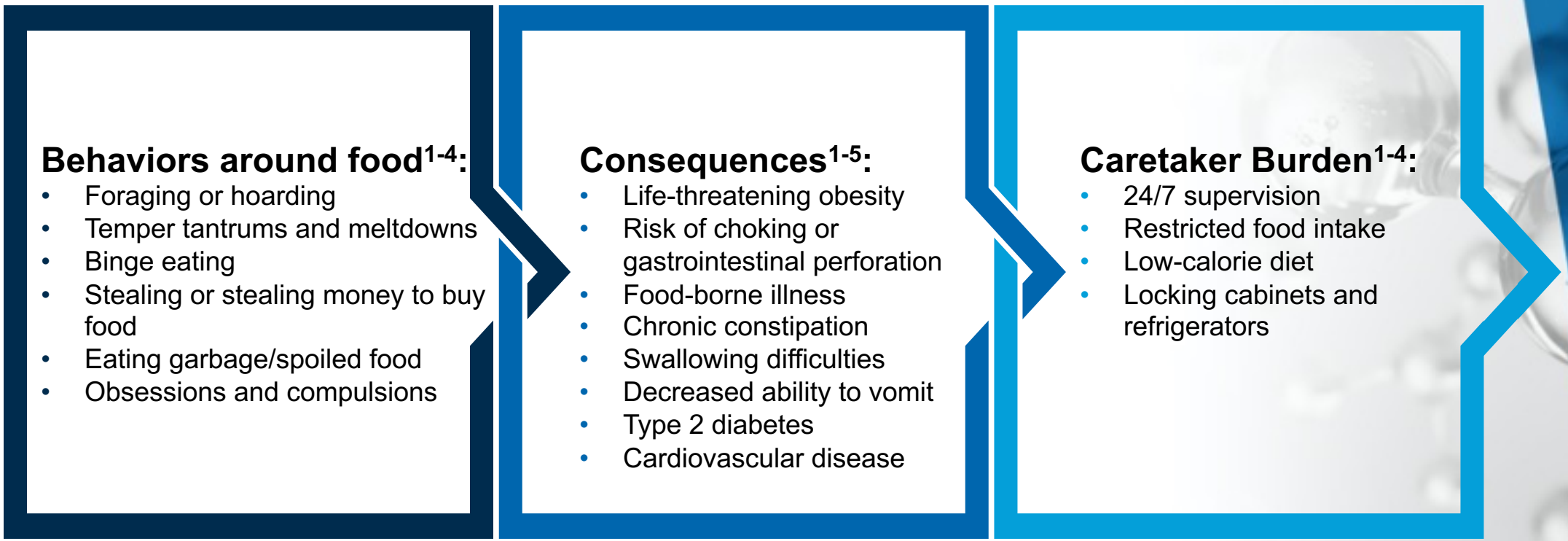
1. Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.
2. Butler MG, et al. *Genet Med*. 2017;19(6):635-642.

Dangers of PWS Hyperphagia



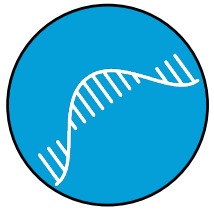
There is no treatment for PWS-related hyperphagia[4]

1. Miller JL, et al. *Am J Med Genet A*. 2011;155A(5):1040-1049.
2. Butler MG, et al. *Genet Med*. 2017;19(6):635-642.
3. Butler MG. NORD. Updated 2018. Accessed May 25, 2022. https://rarediseases.org/rare-diseases/prader-willi-syndrome/
4. Prader-Willi Syndrome Association USA. Accessed May 25, 2022. https://www.pwsausa.org/what-is-prader-willi-syndrome/
5. Muscogiuri G, et al. *J Endocrinol Invest*. 2021;44(10):2057-2070.

Abnormalities of the Oxytocin System in Patients with PWS

PWS patients have

Increased oxytocin in blood plasma[1,2]



Decreased oxytocin mRNA[1]

Low levels of oxytocin receptor expression[2]

Decreased or abnormal oxytocin neurons (especially in the PVN)[1]

PVN=paraventricular nucleus.

1. Correa-da-Silva F, et al. *J Neuroendocrinol*. 2021;33(7):e12994.
2. Jurek B, et al. *Physiol Rev*. 2018;98(3):1805-1908.

History of Oxytocin Use

Synthetic oxytocin has been used to induce labor for over 65 years[1]

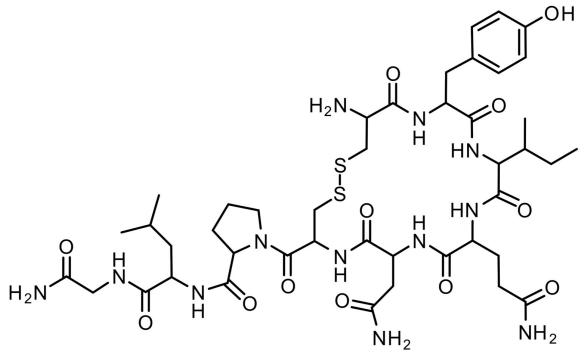
Due to the role of endogenous oxytocin in pain regulation and social behavior, the administration of exogenous oxytocin has been studied in a wide variety of therapeutic areas[2]

Intravenous application of oxytocin has been met with many challenges:

- Short half-life:
  - Intravenous oxytocin has a half-life of roughly 3 minutes[3]
- Difficulty crossing the blood-brain barrier[4]

[1] den Hertog CE, et al. *Eur J Obstet Gynecol Reprod Biol*. 2001;94(1):8-12.
[2] Bakermans-Kranenburg MJ, et al. *Transl Psychiatry*. 2013;3(5):e258.
[3] Oxytocin. Package insert. Hikma Pharmaceuticals USA Inc.; 2011.
[4] Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.

Functions of Natural and Therapeutic Oxytocin



Childbirth[1-3]:

Natural

- Stimulates uterine contractions during childbirth

Therapeutic

- Widely used for the induction of labor in an estimated 25% of women in Western countries

Breastfeeding[1,4,5]:

Natural

- Oxytocin is responsible for the let-down reflex
- Contracts the muscles around the glands that produce milk

Therapeutic

- Approved to stimulate milk production, but discontinued in the US

Behavioral regulation[1,6]:

Natural

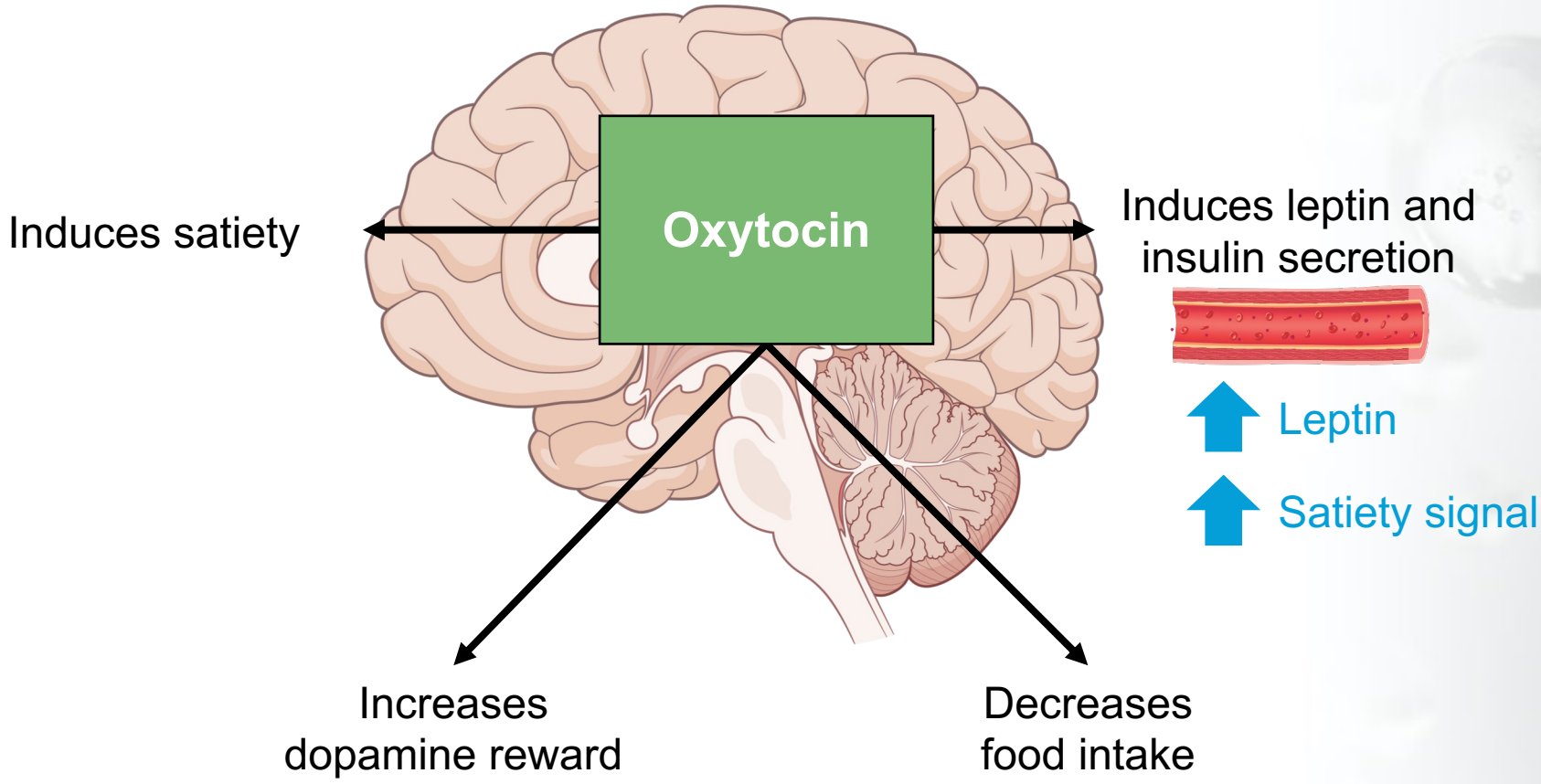
- Oxytocin plays a role in prosocial behaviors and bonding
- Signals satiety and suppresses appetite

Therapeutic

- No approved oxytocin therapy

1. McCormack SE, et al. *Endocr Rev*. 2020;41(2):121-145.
2. Kuwabara Y, et al. *Arch Gynecol Obstet*. 1987;241(1):13-23.
3. Boie S, et al. *Cochrane Database Syst Rev*. 2018;8(8):CD012274.
4. World Health Organization. World Health Organization; 2009. https://www.ncbi.nlm.nih.gov/books/NBK148970/
5. MPR. December 12, 2013. Accessed June 23, 2022. https://www.empr.com/home/news/retrophin-to-reintroduce-syntocinon-nasal-spray/
6. Bartz JA, et al. *Trends Cogn Sci*. 2011;15(7):301-309.

Oxytocin Plays Major Role in Satiety[1-3]



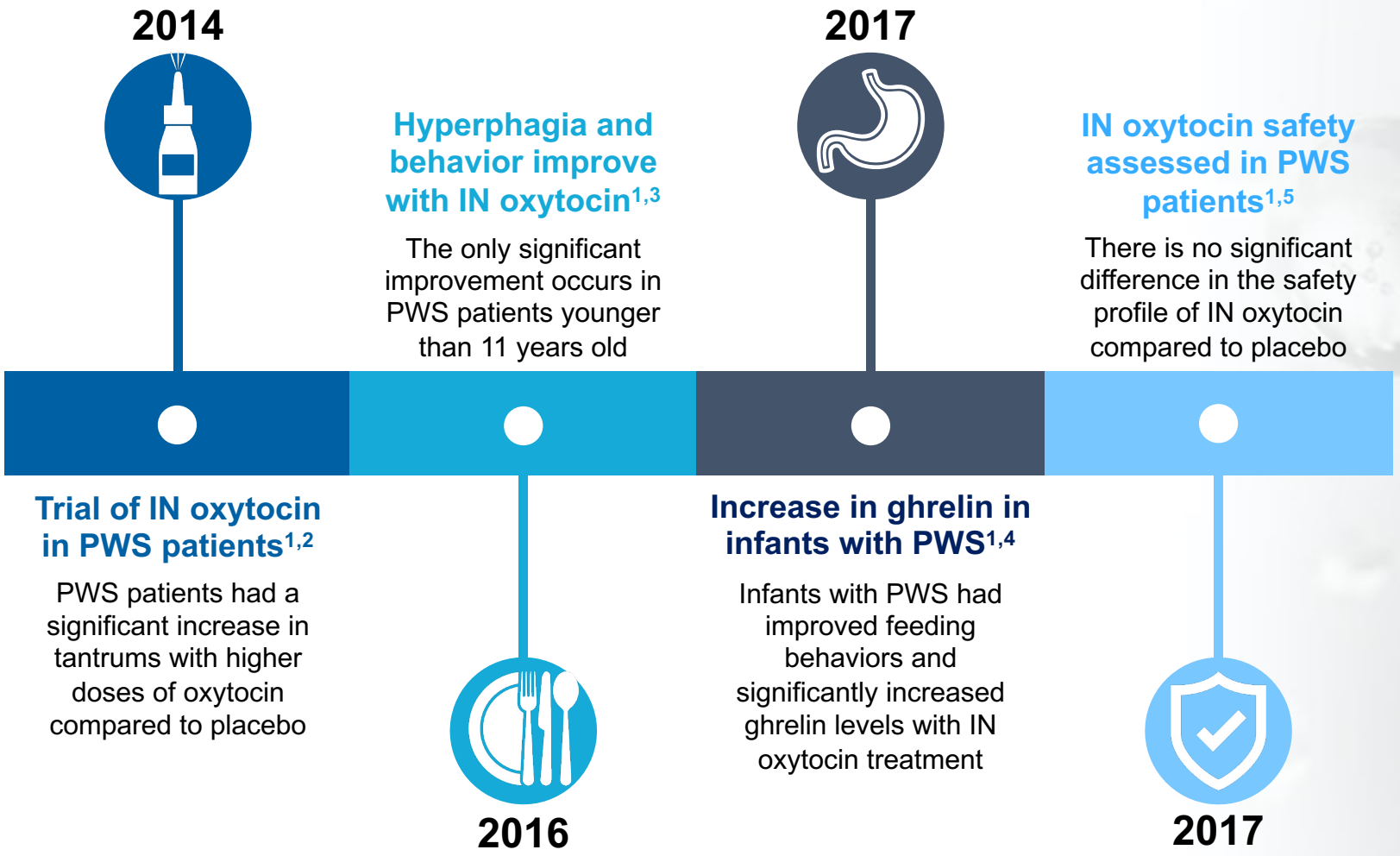
1. Correa-da-Silva F, et al. *J Neuroendocrinol.* 2021;33(7):e12994.
2. McCormack SE, et al. *Endocr Rev.* 2020;41(2):121-145.
3. Kerem L, et al. *Int J Mol Sci.* 2021;22(14):7737.

Intranasal Use of Oxytocin

- Intranasal oxytocin was introduced as a lactation aid in the early 1960s[1]
- Numerous studies have investigated chronic and acute intranasal oxytocin for the treatment of neuropsychiatric disorders and pain[2]
  - Intranasal oxytocin has been studied in anxiety disorders,[3] autism,[4] PTSD,[5] schizophrenia,[6] and pain[7]
- Chronically administered intranasal oxytocin is generally very well tolerated[8-11]
- Intranasal oxytocin has been found to be generally safe and well tolerated in a variety of healthy populations ranging from infancy to old age[12,13]

1. Skarsten KW. *Tidsskr Nor Laegeforen*. 1962;82:8-10.
2. Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
3. Jones C, et al. *Dialogues Clin Neurosci*. 2017;19(2):193-201.
4. Guastella AJ, et al. *Biol Psychiatry*. 2010;67(7):692-694.
5. Pitman RK, et al. *Psychiatry Res*. 1993;48(2):107-117.
6. Feifel D, et al. *Biol Psychiatry*. 2016;79(3):222-233.
7. Boll S, et al. *Neuroscience*. 2018;387:149-161.
8. Rung, JM, et al. *Psychopharmacology (Berl)*. 2021;1-14.
9. Horta M, et al. *Neurosci Biobehav Rev*. 2020;108:1-23.
10. Finger E, et al. *Neurology*. 2015;84(2):174-181.
11. Barraza JA, et al. *Exp Clin Psychopharmacol*. 2013;21(2):85-92.
12. DeMayo MM, et al. *Drugs*. 2017;19(5):391-410.
13. Verhees MWFT, et al. *Psychopharmacology (Berl)*. 2018;235(8):2471-2477.

Intranasal (IN) Oxytocin As PWS Treatment



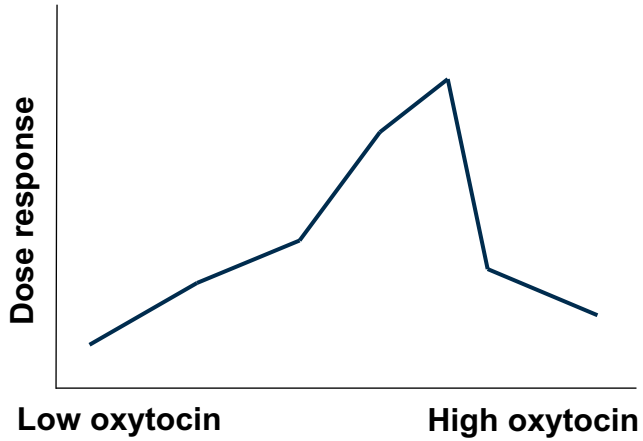
Despite strong evidence for the role of OT in satiety, there are challenges in using OT for the treatment of PWS

1. McCormack SE, et al. *Endocr Rev*. 2020;41(2):121-145.
2. Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
3. Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.
4. Tauber M, et al. *Pediatrics*. 2017;139(2):e20162976.
5. Miller JL, et al. *Am J Med Genet A*. 2017;173(5):1243-1250.

Challenges in Intranasal Oxytocin Studies in PWS

- No significant difference with IN oxytocin treatment but significantly increased tantrums at higher doses in humans[4]
- Significant improvement in hyperphagia but only in patients younger than 11 years old[5]

- Central oxytocin levels are difficult to measure[1]
- Dose response in animals is not linear but an inverted-U shape[1,2]

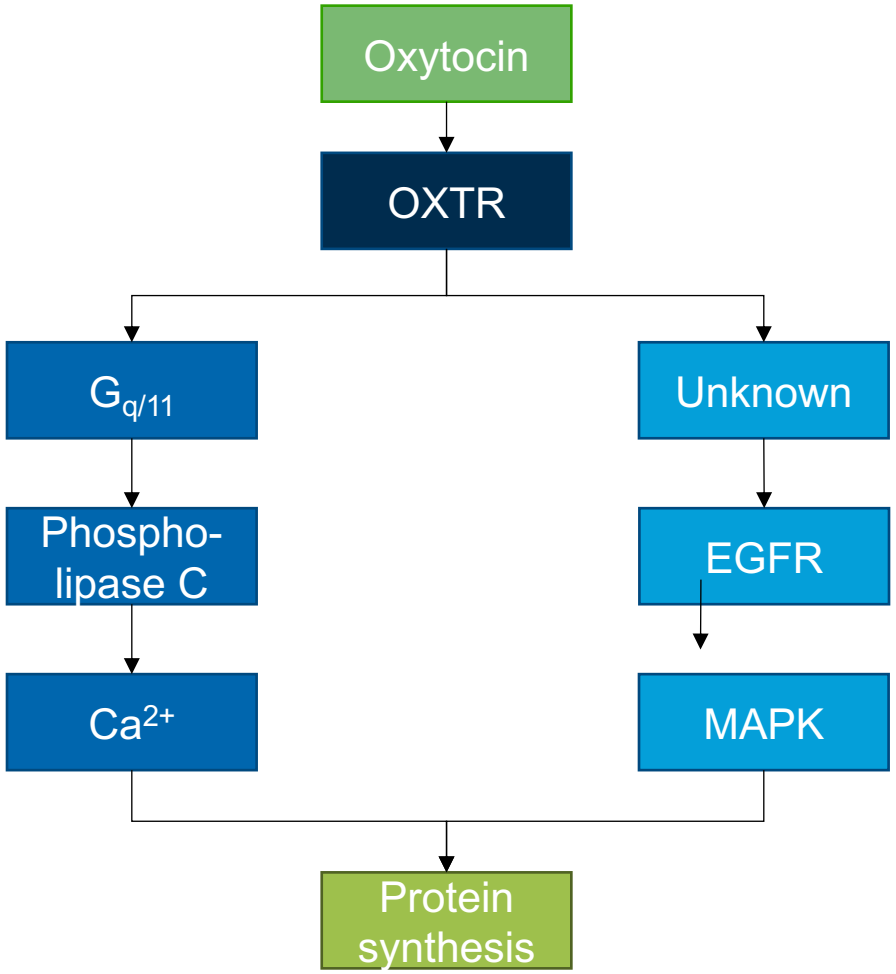


- Recent reports in animals show that magnesium is needed for full oxytocin receptor binding[2,3]
- Magnesium enables a full dose response[2,3]

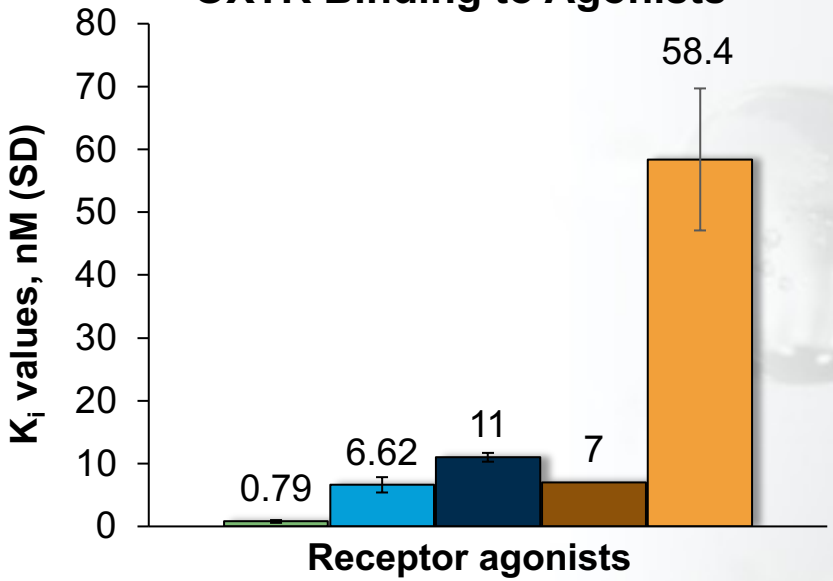
1. Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
2. Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.
3. Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.
4. Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
5. Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.

Oxytocin Receptor (OXTR)

OXTR Signaling Cascade



OXTR Binding to Agonists[1]



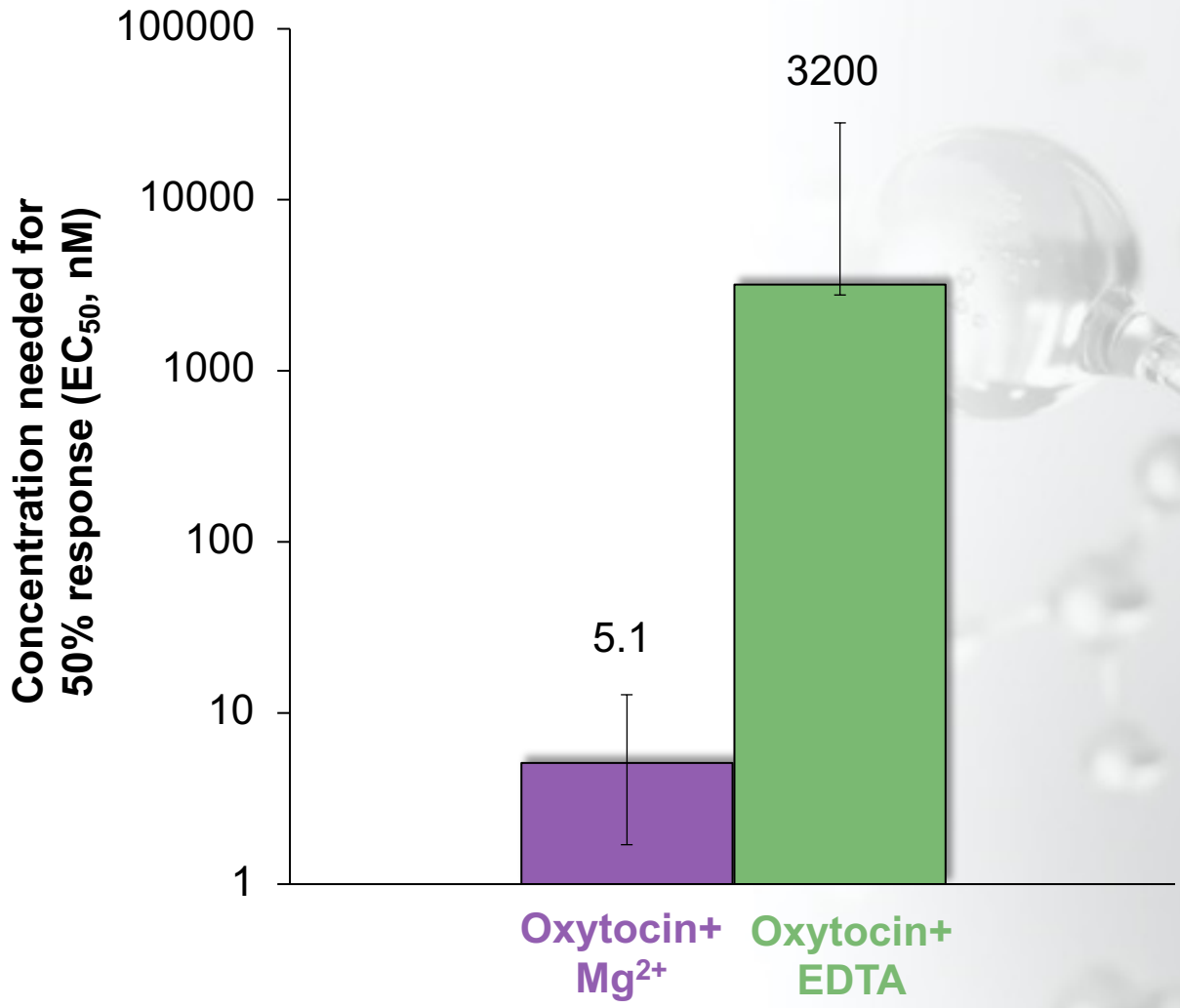
- **Oxytocin**
- **TGOT** = highly selective agonist
- **Atosiban** = functionally selective agonist (can act as an antagonist depending on the G-protein coupled to OXTR)
- **Carbetocin** = oxytocin analog – weak agonist with mixed antagonist activity[2]
- **WAY 267,464** = nonpeptide agonist more specific for the vasopressin receptor

EGFR=epidermal growth factor receptor; MAPK=mitogen activated protein kinase; OXTR=oxytocin receptor

[1] Jurek B, et al. *Physiol Rev*. 2018;98(3):1805-1908.
[2] Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.

Oxytocin+Mg^{2+} Activates OXTR Secondary Messengers

Magnesium is needed not only for oxytocin binding to OXTR but also for OXTR activation



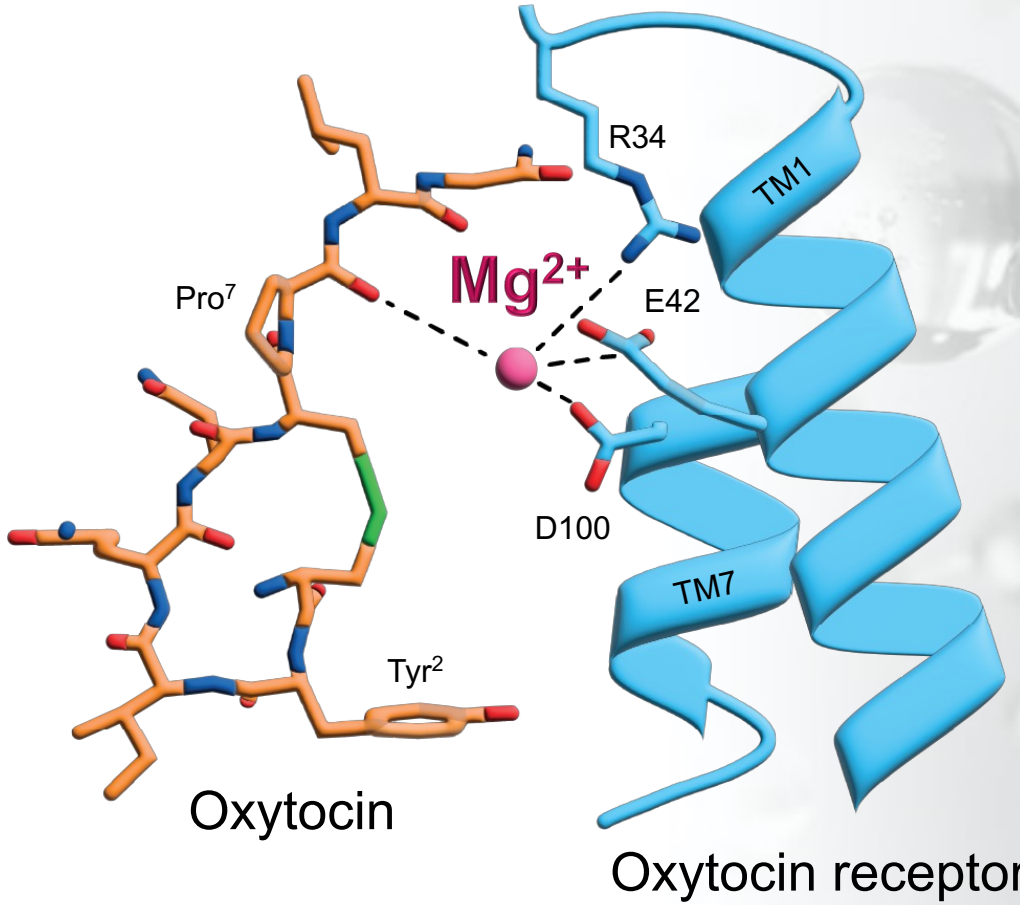
BRET assay in HEK-293 cells

BRET=bioluminescence resonance energy transfer; EDTA=etheylenediaminetetraacetic acid; HEK=human embryonic kidney; OXTR=oxytocin receptor.

Meyerowitz JG, et al. *Nat Struct Mol Biol.* 2022;29(3):274-281.

Oxytocin Requires Magnesium for Receptor Binding

- OXTR exists in 2 conformational states[1]:
  - Low affinity
  - High affinity
- Magnesium ions are necessary for the high-affinity state[1,2]
- Without magnesium ions present, oxytocin cannot achieve full binding to OXTR[2]

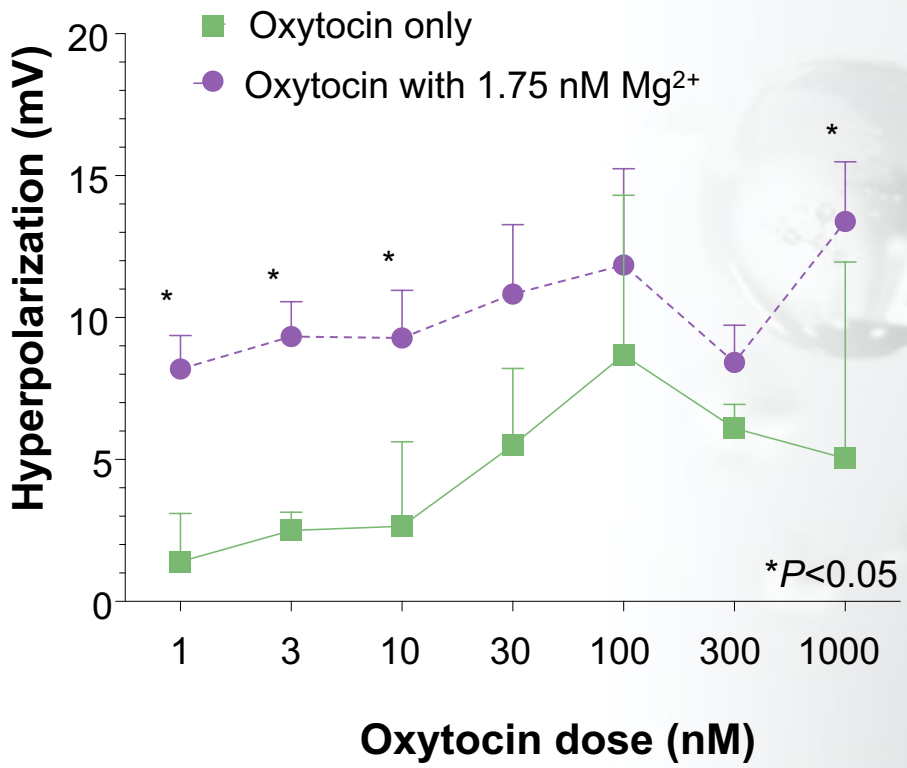


OXTR=oxytocin receptor.

1. Jurek B, et al. *Physiol Rev*. 2018;98(3):1805-1908.
2. Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.

Addition of Mg^{2+} Expands the *in vivo* Useful Dose Range of Intranasal Oxytocin in Animals

- A nonlinear dose response has been demonstrated in the use of intranasal oxytocin
- This decreases efficacy at higher doses
- Addition of Mg^{2+} rescues the efficacy of oxytocin at high doses



In vitro whole-cell voltage-clamp recordings of rat trigeminal nerves exposed to oxytocin solution with and without additional magnesium ions

Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.

Highlights

- Hyperphagia in Prader-Willi syndrome (PWS) is severe and life-threatening
  - There is currently no treatment for hyperphagia in adolescents and young adults with PWS
- Oxytocin is one of the hormones responsible for signaling satiety
- The oxytocin receptor requires magnesium ions for the high-affinity conformation for signaling satiety
- TNX-2900* combines oxytocin with magnesium for improved receptor binding and potentially improved therapeutic action
- TNX-2900 is in development to treat hyperphagia in adolescents and young adults with PWS

*TNX-2900 is an investigational drug in the pre-IND stage of development and has not been approved for any indication

THANK YOU