Oxytocin

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Disclosure

Devaki Lindsey Berkson, MA, CNS, DACBN, CAN, ND, is owner of Berkson Health in Austin, TX. She is employed at the Wiseman Family Practice Clinic in Austin, TX and the Integrations Health Center Tulsa, OK. Conflict of interest was resolved through peer review of slide content.

Professional Education Services Group staff have no financial interest or relationships to disclose.

Disclosure

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Learning Objectives

- At the conclusion of this activity, the participant will be able to:
  - Discuss how oxytocin is being used as treatment in various disease states, such as atrophic vaginitis, erectile dysfunction, obesity, and leaky gut.
  - Discuss the role oxytocin plays in the hormone family, immune system and the potential in treating immunologic disorders.
  - Review dosing and administrative routes for oxytocin.

Case One

- Women with attachment disorder starting at the end of 1st trimester in first marriage.
- Lozenge vs. intranasal
- Was able to re-establish attachment
- Oxytocin is known as the “peptide of attachment”

Case Two

- 36 yr.-old woman with life long history of severe constipation
- Colonoscopies revealed “necessity” for surgery
- She had tried colonics, digestive enzymes, exercise, diet, massage, fiber, fermented foods and yet could only go every 2 weeks with severe intervention; limited foods; severe pain bloat.
- Oxytocin Replacement: Success
- The intestinal area is lined with oxytocin receptors. Studies have shown oxytocin to have anti-colitis action in rats. In-vitro studies have shown it to protect enterocytes and to have protective gut anti-inflammatory, motility, and gut wall enhancing permeability actions.
Case Three

- 62 yr.-old woman with history of aggressive breast cancer, 6 years out, severe atrophic vaginitis; bleeding and pain on intercourse and osteoporosis secondary to history of aromatase inhibitors.
- Out of shape from surgeries, recovery, fear, insomnia, cortisol, etc.
- Possible answer for multiple issues: Oxytocin

Oxytocin and Atrophic Vaginitis

- Pilot study: 20 post-menopausal women with atrophic vaginitis confirmed by visual and colposcopic exam
- 10 women were given 1mg/ml oxytocin gel
- 10 women were given placebo
- After 7 days, 7/10 women in the treatment group had normalized vaginal epithelium vs. none in the control group.
- Circulating oxytocin and estradiol were not different between the two groups. It is NOT an estrogen agonist but has “estrogen-like actions” on mucous membranes.


Concerns with previous study

- Oxytocin is typically not dosed in mg. Instead it is dosed in units. IU/mg can change from one lot of Oxytocin to the next.
- Common dosing ranges from 100-120 IU
- Testimonial: One pharmacy used dosing of 1gm QHS X 7 days, then twice a week thereafter with positive results.

Oxytocin and Bone Health

- Osteoblasts and osteoclasts express OTR.
- Genetically modified mice with null OT and OTR develop osteoporosis that progressively worsens with age in BOTH genders.
- OT stimulates the development and maturation of osteoblasts.
- Mice without OTR, did not experience bone enhancing effects of 17b-estradiol.


Skeletal Muscles are Flush with OTRs

Both OT and OTR decline in the aging process

Researchers theorized OT may be linked with muscle health and preserving muscle mass in young and protecting against sarcopenia in aging.

Elabd C et al. Oxytocin is an age specific circulating hormone that is necessary for muscle maintenance and regeneration. Nat Commun. 2014 Jun 10;5:4082.

Oxytocin and Muscles

- Young (2-4 months) and old mice(18-24 months) had muscles injured for this study.
- Youthful healing = control.
- Researchers gave an OTR antagonist to a group of injured young mice. Then treated elder mice with subQ OT.
- After 5 days, the older mice’s muscle injuries healed comparably to the young mice.

Elabd C et al. Oxytocin is an age specific circulating hormone that is necessary for muscle maintenance and regeneration. Nat Commun. 2014 Jun 10;5:4082.
Oxytocin: anti-muscle aging tool?

- Another group of young and old mice injured the same as in first experiment.
- Researchers gave OTR antagonist (blocker) to the young injured mice.
- The older mice were not given subQ OT but now were the control group.
- The young mice, without OT signaling, healed like the older injured mice: muscle healing was "stunted".
- Mechanism of action: OT directly stimulates the MAPK/ERK signaling pathways.

Elabd C et al. Oxytocin is an age specific circulating hormone that is necessary for muscle maintenance and regeneration. Nat Commun. 2014 Jun 10;5:4082.

Introducing Oxytocin

- Oxytocin is a peptide hormone.
- Peptide hormones are made of amino acids. A peptide is a link of two or more amino acids.
- As far as peptide hormones go, oxytocin is a small thing, with only nine amino acids. In comparison, thyroid-stimulating hormone (TSH) contains 201.
- Sometimes oxytocin is referred to as a nonapeptide, since nona means "nine."

Oxytocin historically

- Oxytocin is historically appreciated for its role in pregnancy.
- It signals uterine contractions, lets down milk for lactation, and deepens bonding between mother and child.
- Now, new research and clinical evidence reveal ever-expanding possibilities for oxytocin replacement in the clinical trenches.
- For example, oxytocin therapy is being used to treat autism spectrum disorder, schizophrenia, obesity, addiction, erectile dysfunction, orgasm disorders, and as a libido, orgasm, and emotional "bonding" enhancer. Viagra = mood enhancer. Why? Boosts oxytocin production.

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Oxytocin

- Oxytocin is produced in the hypothalamus. It is made by the neurons of the paraventricular and supraoptic nuclei of the hypothalamus (the same areas of the brain turned on by orgasm; the bigger the orgasm, the more these cells are “turned on”). These hypothalamic neurons have axons that deliver OT both locally and peripherally.


Oxytocin: brain/spinal chord

- The brain has high levels of OTRs. Oxytocin acts as a neurotransmitter signaling the amygdala (seat of faith vs. fear), the nucleus accumbens (sense of well-being), and the hippocampus (home of short-term memory and confidence).

- Oxytocin traverses cerebral regions by diffusing across neural tissue, like you would cut across lanes to get to an off-ramp on a freeway.

- There are OTR receptors throughout the entire spinal cord.


Oxytocin: Connection (the new Vitamin C)

- Animal model research emphasizes a strong relationship between the expression of OT in the brain and the ability to have socially monogamous attachment behavior. These investigations began with the vole.

- Two closely related species of voles have exact opposite relationship styles: one is monogamous, mating for life, while the other is promiscuous, choosing to be a forever player. What’s the biological difference? The monogamous prairie vole has many more oxytocin and vasopressin (a playmate with oxytocin) receptors and activity in the brain. In comparison, the polygamous vole has much less such bonding receptors, and thus, more sleuthing mating behaviors.

- Researchers have gone to the trouble of reversing these mating behaviors. They engineered typically promiscuous male voles to be more monogamous, and typically monogamous male voles to become more promiscuous. They also manipulated oxytocin and vasopressin levels (both androgens and estrogens) in female voles.


Oxytocin: cuddle chemical

- Young and Wang manipulated three attachment hormone musketeers (oxytocin, vasopressin and dopamine) and influenced preference of one beloved over another.
- They “gene-jerry-rigged” whom the animals would choose to mate. They named this the neuro-biological model of pair bonding.
- A number of researchers have pleaded the case that this is how humans basically meet, mingle and mate, too.
- We know moms and babes bond through oxytocin. Magnetic imaging of the brains of mothers who see photos of their own infants (compared to pics of matched control infants not known to them), show the areas of the brain that “activate” are flush with oxytocin, vasopressin, and dopamine receptors.


Case Three and Four

- 39-year old woman was married to a 25-year old man who was a photographer in the model industry. She had gained weight and he had lost interest. He was used to looking at slim models all day long. He loved her but he no longer desired or enjoyed sex as much with her. She was on life-long antidepressants (which she felt had put on her weight) and couldn’t get off due to fierce historical rebound issues. They wanted her to lose weight and him to gain interest and perhaps even for her to get off antidepressants.
- They both went on oxytocin (24 IU in one nostril TID) and also before and during any sexual encounter. They informed me that within several days their intimacy was better than it had been in years. They felt their marriage was back on track. It’s half a year later and they are doing better than ever.
- She has more stable moods and higher quality of life than ever, but still has not gone off antidepressants. Her historic rebound issues were so severe she is still to frightened to attempt to do so.

Oxytocin: Stress

- Oxytocin helps buffer stress by influencing hormonal influence over the hypothalamus/pituitary/adrenal axis (HPA axis). At various levels OT helps the host cope with stress and promotes anti-anxious reactions.

Oxytocin and Sex Hormones

- Sex steroid hormones—estrogen, testosterone and progesterone—intimately interact with OTR and are part of sex hormonal influence over human emotions.

- Estrogens act synergistically with OT by enhancing its anxiolytic effects and increasing OTR levels. A single dose of estradiol increases plasma OT levels in women (one of the many reasons estrogen replacement makes many women enjoy happier moods and avoid anti-depressants).

- A metabolite of testosterone (nicknamed 3beta-diol) has similar input in the brain and other critical areas, such as within the HPA axis, as it boosts ER beta which is intimately linked to OT.


Oxytocin – Estrogen Receptor Beta.

- Estrogen has two major receptors that receive estrogen signals: ER alpha and ER beta.

- ER beta is an oncoprotein suppressor (protects against cancer) and anti-inflammatory molecule balancing out the pro-growth signals of ER alpha. Areas in the brain with OTRs stunningly overlap exact location of ER beta receptors.

- Approximately 85% of OT neurons in the pituitary co-express ER beta!

- Activation of ER beta normalizes HPA axis activity and acts to buffer stress and anxiety.

- There is “crosstalk” between OT and ER beta throughout the body.


Oxytocin ER beta

- There also appears to be a “threesome” between a metabolite of testosterone (3B-diol—itself a promoter of ER beta) and ER beta and OT.

- All three synergize, especially in the brain and the vagus nerve.

Oxytocin Vagal Nerve

- Vagus nerve; Cellular Big Brother

- Healthy vagal tone creates calm. Everyone has their own vagal footprint. The better the vagal tone, the less rattled we are by stress and the more calm we seem to enjoy. A healthy digestive tract is mostly para-sympathetically "vagal."

- The healthier your vagal tone, the lower your level of cellular inflammation, or the faster you bring inflamed tissues back to normal after infection, or the more peaceful your moods or the faster recovery back to calm after an emotional storm has hit.

- Oxytocin appears to be a major hormone player traveling vagal highways, maintaining calm, hormonal satiety and peace, suppressing inflammation and more. Being a hormone of connectivity, oxytocin upregulation in the vagal nerve—this massive internal feedback loop—may be part of feeling well and right with the world. Meditation boosts vagal tone and oxytocin.


OT, Vagus Nerve, Estrogen Hypothalamus (Cross-Talk Yet Again)

- The vagus nerve is not only flush with oxytocin receptors, this large feed back nerve also influences the number of estrogen receptors in the nervous system and brain.


Romantic Love

- Adults shown photos of a romantic partner with whom they are "intensely in love" light up brain areas flush with oxytocin, vasopressin, and dopamine receptors .

Oxytocin Intimacy

- Oxytocin replacement has been shown to create more pleasurable orgasms and a stronger sense of empathy in both men and women. Men given OT intranasally report the biggest bang, perhaps since they naturally, during orgasm, make less oxytocin than women, so any bump up might be more noticeable.
- Since men produce less oxytocin, which is a bonding hormone, men are less vulnerable to intimacy attachment compared to women.
- The highest experimental recorded levels of oxytocin, shown to be achieved in women who were multi-orgasmic. Behnia B et al. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. Horm Behav. 2014 Mar;65(3):308-18.

Oxytocin - Orgasms

- When orgasming, oxytocin levels are significantly increased in the brains of both men and women. But, oh so much more in ladies. Oxytocin remains elevated for about five minutes and then levels rapidly decline. Much less is produced by masturbation or sex without orgasm.
- Women’s pituitary’s are boosted more by orgasm than men proven by Pet Scan Imaging.

Oxytocin - Orgasm

- When a woman orgasms, her pituitary is turned on to secrete more oxytocin and prolactin. So, when she orgasms, she longs to bond and has tremendous satisfaction (from the prolactin, a satiety hormone in this scenario) with that sensation.
- No matter how much a “friend with benefits” male lover might insist a liaison is only a friendly wham bang, if it’s done repetitively enough, and she orgasms enough, she’ll bond with him.
- Her brain and hormones make her do it.
Oxytocin - Weight

- Massachusetts General Hospital researchers gave 25 healthy men a single dose oxytocin nasal spray (24 IU)
- One hour before breakfast
- Half the men were overweight
- The men on OT averaged 122 fewer kcals and 9g less fat compared to placebo
- No side effects reported other than intake reduction

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Oxytocin - Appetite Control and Weight Reduction

- Case Five. Woman in her late 20's with trouble with portion control. She had a history of ulcerative colitis and would have flare-ups if she ate too much, which kept her in a flare-up loop, as she continuously ate too much. One week on 24 IU intranasal spray in one nostril BID accomplished nothing, but when we increased it to one spray in each nostril TID right before eating, she was able to eat less, lose weight, and avoid continuous flare-ups. Oxytocin has also been shown to act as an anti-inflammatory in the gut.

Contra-indications: Prostate Cancer

- Certain prostate cancer cell lines express OTR, and in vitro studies have suggested that oxytocin plays a role in migration of malignant cells.
- It is unproven whether exogenous oxytocin can influence intra-prostatic metabolism.
- Theoretical concern may lower cortisol but no studies yet.

Dosing

- General: 10-24 IU one to two nostrils, one to three times a day
- Episodic: 30 minutes prior to intercourse and during: 24-58 IU
- Administration routes:
  - Intranasal most researched
  - Sublingual spotty anecdotal evidence from compounding pharmacies
  - Oral contraindicated as peptide should not well survive intact, after exposure to gut milieu

Oxytocin

- Can be measured in 24-hr urine
- Supports hormone family: boosts estrogen receptor production in brain, boosts ER beta and T metabolite functioning, and
- The “Oxytocin-secreting system” is a major part of the neuroendocrine regulation, similar to HPA axis.


Oxytocin - Immune

- Interactions between the nervous system and immune system have been studied extensively. But mechanism?
- In this review, we provide a comprehensive examination of current evidence on interactions between the immune system and hypothalamic oxytocin-secreting system.
- We highlight the fact that oxytocin may have significant effects in the body, beyond its classical functions in lactation and parturition.
- Similar to the hypothalamo-pituitary-adrenal axis, the oxytocin-secreting system closely interacts with classical immune system, integrating both neurochemical and immunologic signals in the central nervous system and in turn affects immunologic defense, homeostasis, and surveillance.
- Lastly, this review explores therapeutic potentials of oxytocin in treating immunologic disorders.
**Oxytocin - bright future**

- May even be used to decrease leaky gut and systemic inflammation, and possibly be used as a breast protector to decrease breast feeding pain.
- Up with oxytocin. Or shall I say, up your nose with it.


**Oxytocin - Leaky Gut**

- Enteric neurons express oxytocin; moreover, enteric neurons and enterocytes express OT receptors. We tested hypotheses that OT/OTR signaling contributes to enteric nervous system-related gastrointestinal physiology protecting transit time, permeability and proliferation and renewal of cell wall epithelial cells.
- GI functions and OT effects were compared in OTR-knockout (OTRKO) and wild-type (WT) mice.
- Villi and crypts were shorter in OTRKO than in WT mice, and transit-amplifying cell proliferation in OTRKO crypts was deficient. Macromolecular intestinal permeability in OTRKO was greater than WT mice, and experimental colitis was more severe in OTRKO mice; moreover, OT protected WT animals from colitis.
- Observations suggest that OT/OTR signaling acts as a brake on intestinal motility, decreases mucosal activation of enteric neurons, and promotes enteric neuronal development and/or survival. It also regulates proliferation of crypt cells and mucosal permeability; moreover OT/OTR signaling is protective against inflammation.

**Oxytocin - Gut’s new BEST FRIEND**

- Had to figure out dosages that would NOT cause weight loss.
- The intestinal mucosa is abnormal in OTRKO mice.
- The intestinal barrier is significantly more permeable in OTRKO mice than in WT littermates.
- The severity of experimental colitis in OTRKO mice is significantly greater than that in WT littermates.
- Exogenous OT protects mice from TNBS-induced colitis.

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