The Unappreciated Role of Hormones and the Gut

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The widespread expression of the sex steroid, thyroid and adrenal receptors (Satellite dishes) in gastric and intestinal mucosal lineages, particularly the epithelium, suggest regulatory roles of these hormones on digestion, immune function, metabolism, growth, differentiation and even as you will soon learn, sex steroid hormone maintenance.
Evolution of New Appreciation

- Autoimmunity Gender Bias
- Female : Male
- Gut driven - 2013!
- Cross-talk of microbiome with gut
- Gut wall hormone cross-talk - Barzi, Berkson
- Sex Steroids and Gut Function (estrogen, estrogen metabolites, testosterone, progesterone, thyroid)
Markle

- Gender bias appreciated in auto-immunity but mostly thought due to F or M. Puzzling feature of auto-immune diseases.
- This gender bias may be due to commensual microbiota of the host not just host. IE Lupus.
- We demonstrate that early-life microbial exposures determine sex hormone levels and modify progression to autoimmunity.
- Transfer of gut microbiota from adult males (MASCULINIZED MICROBIOTA) to immature females altered the recipient's microbiota, resulting in elevated testosterone and metabolomic changes, reduced islet inflammation and autoantibody production, and robust T1D protection.
- PROTECTION CAN BE TRANSFERRED.
- AND IS DEPENDENT ON THE ANDROGEN RECEPTOR & microbiome.
Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity.

- **Markle JG**, et al

- Program in Genetics and Genome Biology, Hospital for Sick Children Research Institute, Toronto, Ontario, Canada.

Cross Talk
Sex hormone - microbiome

- If microbiome can influence gender bias in auto-immune diseases
- Can it do this with sex hormones?
- It’s being suggested to be so, by Harvard researchers.
- In other words, the microbiome appears to be “genderized”.
Welcome to the Microgenderome

- Venus and Mars and the Microbiome
- Flak MB, Neves JF, Blumberg RS.
- Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School and Harvard Digestive Diseases Center, Boston, MA 02115, USA.
Microgenderome

- Observed that the composition of the commensal microbiota of male and female animals diverged at the time of puberty, which implies that maleness and femaleness exerted specific influences on the composition of the microbiota.

- REMOVE MICROBIOTA IN FEMALES - MORE T

- REMOVE MICROBIOTA IN MALES - LESS T.

- Bi-directionality between T levels and microbiota.

- Commensal microbiota may “record” the state of maleness, when is then “played back” to the host in a self-reinforcing program of masculinizing action.
Gender Bias in Autoimmunity is influenced by the Microbiota

- **Yurkovetskiy L**, et al
- Committee on Microbiology, The University of Chicago, Chicago, IL 60637, USA.
Gender bias and the role of sex hormones in autoimmune diseases are well established.

In specific pathogen-free nonobese diabetic (NOD) mice, females have 1.3-4.4 times higher incidence of type 1 diabetes.

Germ-free (GF) mice (no microbiome) lost the gender bias (female-to-male ratio 1.1-1.2).

Gut microbiota differed in males and females, a trend reversed by male castration, confirming that androgens influence gut microbiota.

Our results favor a “two-signal model” of gender bias, in which hormones and microbes together trigger protective pathways and communicate with each other.
Testosterone: more than having the guts to win the Tour de France.

- **An D, Kasper DL.**
- Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA 02115, USA.
- Sex bias in susceptibility to autoimmune diseases is evident but poorly characterized.
Translation into practice

- T - important as part of HT in women, not just males
- T - metabolites boost ER beta and hormonal cancer prevention
- T - anxiolytic
- Anti-androgens EDCs
- Family of hormones
- Gut protection
Thoughts

- Fecal transplants: Should they be gender specific if donor’s age is after puberty? FDA approved.
- Taking hormone therapy but not getting results?
- Want to boost immunity in certain patient populations: consider Testosterone therapy SOON WILL SEE THIS WITH ANY GUT SURGERIES
The Good Estrogen Dominance

• Molecular Pathways: Estrogen Pathway in Colorectal Cancer (AS WELL AS T & E CROSS-TALK)

• Afsaneh Barzi et al.

• USC Norris Comprehensive Cancer Center, Los Angeles; and Azusa Pacific University, Azusa, California


• Published online 2013 Aug 21. doi: 10.1158/1078-0432.CCR-13-0325
Barzi - ER beta

• Worldwide, colorectal cancer has a higher incidence rate in men than in women, suggesting a protective role for sex hormones in the development of the disease.

• Preclinical data support a role for estrogen and its receptors in the initiation and progression of colorectal cancer and establishes that protective effects of estrogen are exerted through ERβ.

• Hormone replacement therapy in postmenopausal women as well as consumption of soy reduces the incidence of colorectal cancer.

• Soy - unique isoflavone that only upregulates ER beta.
In the Women's Health Initiative trial, use of HRT in postmenopausal women reduced the risk of colon cancer by 56%. A recent meta-analysis showed that in women, consumption of soy reduced the risk of colon cancer by 21%.

We hypothesize that sometime during the tumorigenesis process ERβ expression in colonocytes is lost and the estrogen ligand, HRT, or soy products, exerts its effects through preventing this loss.

Thus, in the adenoma-to-carcinoma continuum, timing of HRT is a significant determinant of the observed benefit from this intervention.

We further argue that the protective effects of estrogen are due ERβ.
In 1996, Kuiper and Jan-Ake Gustafsson described the expression of a novel subtype of the estrogen receptor (ER) in rat prostate and ovary. (TULANE)

The data suggest that ERβ may be considered as a dominant-negative regulator of ERα modulating transcriptional responses to estrogens.

The ratio of ER α vs. β. within a cell may determine the cell sensitivity to estrogens and its biological responses to the hormone.

*It is not the ligand, it is the multiplicity of receptors which determines the plethora of estrogen actions.*
ER beta vs. ER alpha

- Growth vs. Controlled Growth
- Biest. T metab.
- Rhubarb extract
- 5ALPHA
- Androstane, 3B,
- 17b-diol
- (3B0diol)
Healthy Digestion

- Vagal
- Vagus Nerve
- Buddha Nervew

Vagus nerve is oxytocin pathway where ER beta, 3B-diol and oxytocin all connect to keep it vagal.

- Patient with long term constipation.
- Patient with UC/colectomy.
- Gut Barrier Function Protectors
Oestradiol decreases colonic permeability through oestrogen receptor beta-mediated up-regulation of gut protective proteins (occludin and junctional adhesion molecule-A) in epithelial cells.

Braniste V, et al

Institut National de la Recherche Agronomique, Toulouse, France.

Adhesive Molecules/Gut

- IgA - antiseptic paint
- Licking
- Gut wall held TIGHT by adhesion molecules
- ER beta
- Oxytocin
- Metabolite of T
- Soy
JAM-A & ERB & Tight Junctions

- Estradiol modulates paracellular permeability and tight junction (TJ) function in endothelia and reproductive tissues.

- Oestrogen receptors are expressed in intestinal epithelial cells and oestradiol regulates epithelium formation and function.

- We examined the effects of oestrous cycle stage, oestradiol benzoate, and progesterone on colonic paracellular permeability in the female rat, and whether EB affects expression of the TJ proteins in the rat colon and the human colon cell line Caco-2.
ER beta - gut barrier function

- Oestradiol increased occludin mRNA and protein in the colon.
- These data show that oestrogen reinforces intestinal epithelial barrier through ER beta-mediated up-regulation of the transmembrane proteins
  - Occludin and
  - JAM-A.
- These findings highlight the importance of the ER beta pathway in the control of colonic paracellular transport and mucosal homeostasis.
- Tightners vs Openers
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 cells.

GI functions and OT effects were compared in OTR-knockout (OTKO) 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.
Healthy Gut Has Vagal Tone

- Oxytocin/ ERB help contribute to this.
- Meditation boosts vagal tone and oxytocin blood levels.
Oxytocin - TJs

- 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.

Effects of intranasal oxytocin on steroid hormones in men and women.

- In randomized, double-blind experiments, we administered oxytocin (24 IU) or saline placebo to 97 healthy participants. Saliva samples were collected before and at several time points after the oxytocin/placebo administration to assess the levels of cortisol, progesterone, and testosterone.

- Oxytocin had no effects on testosterone, progesterone, or cortisol in women or men.

- Is not sex steroid agonist

- Does not have a direct impact on the human hypothalamic-pituitary-adrenal or hypothalamic-pituitary-gonadal axes under non stressful circumstances.

Aging Gut - OT as new anti-aging tool

• As the literature shows that oxytocin is profoundly involved in parenting and in bonding throughout life, it is highly likely that oxytocin plays a role in grandparenting and bonding between grandparents and grandchildren as well.

• In addition, ageing impairs neurocognitive processes that are profoundly affected by oxytocin (including some aspects of memory and emotion recognition) and is associated with alterations in both structure and function of the amygdala, and the gut.

ERB + Oxytocin synergy

- Brain
- Brain Stem
- Vagus Nerve
- ERB regulates OT gene expression, they are very intimate indeed.
Tighteners vs. Openers

- Tighteners - mucus, vitamin A, B1, ERB, T metab, oxytocin
- Openers - super glue sticky molecules, lectins. Glutenins, gliadins,
- Digestive Enzyme insufficiencies
- Large polypeptides mechanical damage
Oestradiol increased occludin mRNA and protein in the colon, but not zona occludens.

Further, ERB and DPN (ER beta agonist) enhanced occludin and junctional adhesion molecule (JAM)-A expression in Caco-2 cells, an effect blocked by antagonists.

These data show that oestrogen reinforces intestinal epithelial barrier through ER beta-mediated up-regulation of the transmembrane proteins occludin and JAM-A determining paracellular spaces. These findings highlight the importance of the ER beta pathway in the control of colonic paracellular transport and mucosal homeostasis. P had no effect.
ER beta

- This is in support of the hypothesis that high plasma oestrogen level during the follicular phase of the reproductive cycle limits TJ opening in the normal colon, through up-regulation of transmembrane proteins leading to the reinforcement of the structural integrity of TJs, an effect suppressed during the luteal phase. (Pregnancy - IBD protection - Berkson)

- Because impaired paracellular permeability is a trigger for inflammatory bowel disorders and chronic inflammation in humans (Meddings, 1997; Shen & Turner, 2006), the ERβ pathway may represent a novel target to prevent or limit the epithelial barrier defect in these diseases.

- Lung/Brain
Sex hormones play an important role in the maintenance of the mucosal barrier function as well as the mucosa associated immune function in both genders.

Clinical Translation

- Mucosal Repetitive Issues think mucosal supporters
- Including hormonal
- This is often the forgotten bigger picture.
- I especially think this with Chronic Inflammatory Bowel Diseases (Crohn’s, UC, Diverticulitis, smoldering diverticulitis)
And inflammation

- JAM-related proteins in mucosal homeostasis and inflammation.

- JAMs have multiple functions that include regulation of endothelial and epithelial paracellular permeability, leukocyte recruitment during inflammation, angiogenesis, cell migration, and proliferation. Lung, Brain, bladder.

- Indole 3 carbinol, iodine, estriol

Estriol - ER beta - endothelium

- Metabolite ligands of estrogen receptor-beta reduce primate coronary hyper-reactivity. (3beta-diol)

- Mishra RG, Stanczyk FZ, Burry KA, Oparil S, Katzenellenbogen BS, Nealen ML, Katzenellenbogen JA, Hermsmeyer RK. (He Who... Jumps)

- Dimera Incorporated, 2525 NW Lovejoy, Suite 311, Portland, OR 97210, USA.

Estriol -

- Selectively binds ER beta

- Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? PostGrad Med. 2009;121(1):1-13.
Estriol

- Now you can see why estriol is anti-inflammatory
- Useful in MS
- Useful in chronic inflammatory diseases like chronic interstitial cystitis
- Useful in autoimmune diseases such as endometriosis
- Useful in inflammatory bowel diseases like UC and even GERD and EoE
- Given topical, IM, IV and by suppository.
Does testosterone prevent early postoperative complications after gastrointestinal surgery?

TESTOSTERONE IS A STABILIZER OF THE MICROBIOME

- Sah BK et al The role of sex hormones in the early postoperative complications of gastrointestinal diseases.

- A total of 65 patients who underwent operations for gastric and colorectal diseases (mainly malignant diseases) were included in the study. The only study endpoint was analysis of postoperative complications.

- Patients of both sexes were uniform but postoperative complication rate was significantly higher in female patients.

- There was no significant association of estradiol and progesterone with postoperative complications. Testosterone levels in complicated patients were significantly lower than in uncomplicated patients.

- A lower value of testosterone was a predictor for higher complication rate, and a lower value of testosterone at later times after surgery was a better predictor of complications. (history of GI surgery)

- Patients with low testosterone level were prone to higher postoperative complications, which was evident in BOTH sexes. World J Gastroenterol. 2009 Nov 28;15(44):5604-9.
Estrogen – Liver-Pit-Gastric Cross Talk

- Gastric 17β-estradiol has a pivotal role in the regulation of the gastro-hepato-pituitary axis.
- Presence of aromatase and active production of gastric 17β-estradiol in parietal cells.
- Hepatic dysfunction causes changes in gastric 17β-estradiol levels in the systemic circulation;
- HIGH gastric 17β-estradiol affects pituitary function(s).

Gastric Parietal Cells: Potent Endocrine Role in Secreting Estrogen as a Possible Regulator of Gastro-Hepatic Axis

Estrogen Hepato Gastric Axis

- Aromatase activity and production of E2 in the gastric mucosa were demonstrated.
- Parietal cells exhibited strong signals for aromatase mRNA.
- Estrogen receptor α mRNA and immunoreactive protein were demonstrated in hepatocytes.
- These findings indicate that gastric parietal cells play a potent endocrine role in secreting estrogen that may function as a regulator of the gastro-hepatic axis.
New Theory  -  Estrogen Hepato-Gastric Axis

• Under normal physiological conditions, a large quantity of estrogen equivalent to ovary is secreted from an unidentified region of the gastrointestinal organs into the portal vein and most of it is then trapped in the liver, but in the case of increased portal-systemic shunting, it overflows into the systemic circulation, resulting in the elevation of systemic E2 concentration, to cause estrogen-excess signs associated with liver cirrhosis.

• Until now, however, little attention has been given to the possibility that estrogen may be produced in the gastrointestinal tract.
**Gut-Estrogen-Liver-GB-Pituitary Axis**

- EXCESSIVE Estrogenic symptoms often occur with liver disease and biliary tract disorders.

- Wistar female rats were used, and the common bile duct was ligated twice and transected completely at 7 days before termination. Estrogen levels increased almost three times blood levels prior.

- These results suggest that the increment of serum 17β-estradiol levels in obstructive cholestasis induced by BDL is derived from 17β-estradiol secreted from the parietal cells in females as well as males.

HORMONE/GUT ISSUES NEED LIVER SUPPORT


- In females, estradiol regulates liver metabolism via estrogen receptors by decreasing lipogenesis, gluconeogenesis, and fatty acid uptake, while enhancing lipolysis, cholesterol secretion, and glucose catabolism.

- In males, testosterone works via androgen receptors to increase insulin receptor expression and glycogen synthesis, decrease glucose uptake and lipogenesis, and promote cholesterol storage in the liver.
Sex hormone receptors could be potential promising targets for the prevention of hepatic steatosis.


- **Sex Hormones and Their Receptors Regulate Liver Energy Homeostasis.**
Ulcers

- T may increase risk as boosts gastric acid secretion (PART OF AGING, LESS T, CONTRIBUTES TO LOWER STOMACH ACID LEVELS)


- T delays and P accelerates preexisting lingual and gastric ulcers

- 1) major male T and female P sex hormones exhibit opposite effect on healing of preexisting ulcers in the oral cavity and stomach because testosterone markedly delayed while progesterone significantly accelerated this healing;

- 2) testosterone-induced delay in ulcer healing involves significant increase in gastric acid secretion and the fall in the gastric microcirculation at the margin of lingual and gastric ulcers and the excessive production and release of proinflammatory cytokine IL-1 beta; and

- 3) testectomy improved the gastric ulcer healing due to inhibition of gastric acid secretion and the rise in plasma gastrin, which exerts gastroprotective, trophic and ulcer healing action on the gastric mucosa.
Thyroid disease is common, and its effects on the gastrointestinal system are protean, affecting most hollow organs.

Hashimoto disease, the most common cause of hypothyroidism, may be associated with an esophageal motility disorder presenting as dysphagia or heartburn.

Dyspepsia, nausea, or vomiting may be due to delayed gastric emptying due to hypothyroidism.

Thyroid

- Reduced acid production possible in both hypo and hyper.
- Ascites in myxedema is characterized by a high protein concentration.
- Graves' disease accounts for 60% to 80% of thyrotoxicosis. Hyperthyroidism is accompanied by normal gastric emptying with low acid production, partly due to an autoimmune gastritis with hypergastrinemia.
- Transit time from mouth to cecum is accelerated, resulting in diarrhea.
- The gastrointestinal manifestations of thyroid disease are generally due to reduced motility in hypothyroidism, increased motility in hyperthyroidism, autoimmune gastritis, or esophageal compression by a thyroid process. Symptoms usually resolve with treatment of the thyroid disease.
Clinical Translation/Assessment

- Thyroid
- All hormones including oxytocin
- Can treat with HT, nutrients and herbs
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.”
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

- 40 yr.-old woman with life long history of UX and cholecystectomy 18 years ago and colectomy 15 years ago.
- Went from 25 bloody diarrhea/d to 8.
- 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.
- DGL and oxytocin - firmed stools, 3X, no blood, game changer, visualized and 1st time no sign of UC.


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.

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 17β-estradiol. (OT + E)

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 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.


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 accumben (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) vole research

- 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 promiscuous male voles to become more monogamous. By reducing or increasing oxytocin (and vasopressin) signals in the brain, they altered desire for monogamy or preference for bigamy (though some say this should be dubbed “pig-amy”).


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 unknown to them), show the areas of the brain that “activate” are flush with oxytocin, vasopressin, and dopamine receptors.


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.

- Empathy from crisis - more OT, more empathy

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 anti-depressants her historic rebound issues were so severe she is still to frightened to attempt to do so.
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 oncogene 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 ruffled we are by stress and the more cast iron stomachs 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 noticed.

- 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.


*Huynh HK, Willemsen AT, Holstege G.* *Neuroimage.* 2013 Aug 1;76:178-82. Female orgasm but not male ejaculation activates the pituitary. A PET-neuro-imaging study.
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

Presented at the Endocrine Society Annual Conference, March 2015
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. Some cases up to 60 to 80 IU per spray.

- Episodic: 30 minutes prior to intercourse and during: 24-58 IU

- Administration routes:
  - Intranasal most researched - different issues, different timing to see results.
  - 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.

- 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 as breast tissue protector. Oxytocin might even be linked to stimulating the newly found *happiness epicenter* in the brain.


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