Autism & the Microbiome

BY: GABA-DABA-DOOOO

THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.

YOU CALL THIS LIVING?
Agenda

- Introduction
  - Autism Spectrum Disorder (ASD)
  - Overview: Oxidative stress + inflammation + acetaminophen exposure in the induction of ASD
  - Overview: U.S. ASD epidemic + Tylenol + Roundup
  - Focus Paper Overview: Microbial-Mediated Changes in Mouse Models of ASD

- Methods
- Results
- Discussion
- Conclusion
What is ASD?

Brief Introduction

★ Overview
- Intro to ASD
- Biological factors
- U.S. Autism Epidemic
Intro: Autism Spectrum Disorder (ASD)

- **ASD** = catchall term for autism, asperger syndrome, pervasive development disorder
- Heterogenous neurodevelopmental disorder that starts from birth to 3 years
  - characterized by:
    - social deficits
    - repetitive behaviors
    - language deficits
- With each new edition of the DSM, the criteria for the diagnosis of ASD have expanded → increase in ASD prevalence
- Influenced by both genetic and environmental factors, and continues to increase worldwide
  - Occurs in all racial, ethnic, and socioeconomic groups
- No single causative mechanism
- Effective treatments remain elusive
  - Current treatment: ABA Therapy
Biological Factors of ASD

- Early brain overgrowth may underlie specific neurofunctional and clinical phenotypic subtypes in ASD in the first years of life
- Consequences of brain overgrowth
  - Slowed phase or eventual decline of growth
  - Excess neuron proliferation but reduced synapse formation
    - Found an average of 67% extra neurons in the frontal cortex
  - Dysregulation of cell cycle hub genes
U.S. Autism Epidemic

- Epidemic began in the 1980s
  - pre-1980s
    - 50-60% of autistic children were autistic at birth
    - 40-50% regressed into autism at ~18 months
  - Prevalence increased 10x by 1995
- 2015 incidence of autism was 1 in 45 children
  - 4:1 ratio are boys
- Parents who have a child with ASD have a 2%-18% chance of having a second child who is also affected
- Gene expression for autism is turned on/off by epigenetic mechanisms
  - Environmental Toxins
The role of oxidative stress, inflammation and acetaminophen exposure from birth to early childhood in the induction of autism

William Parker, Chi Dang Hornik, Staci Bilbo, Zoie E. Holzknecht, Lauren Gentry, Rasika Rao, Shu S. Lin, Martha R. Herbert, and Cynthia D. Nevison

● Overview:
  ○ Autism, Inflammation, and Oxidative Stress
  ○ Proposed triggers of autism epidemic
    ■ Aspartame
    ■ Ethyl mercury and vaccines
  ○ Autism and Acetaminophen
Autism and Inflammation

- Factors associated with the induction of autism are typically linked with either inflammation and/or oxidative stress.
- Risk factors for inflammation associated with autism:
  - Maternal
  - Paternal
  - Autoimmune Diseases
  - Maternal Obesity
  - Febrile Episodes in the First 2 Trimesters
  - obesity
- An increase in inflammation in Western Societies may contribute to an increase in autism.
Autism and Inflammation

- Since children with Autism are 7 times more likely to be born with cerebral palsy, some scientists suggest its associated with inflammation
  - Cerebral palsy is associated with chorioamnionitis
    - Stimulates fetal production of inflammatory cytokines including IL-6.
- Maternal exposure to severe emotional distress in childhood may be another risk factor for autism.
  - This may be rooted in the link between childhood and adolescent adversity and immune dysregulation and inflammation
Autism and Oxidative Stress

- Oxidative stress is a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses.
- Oxidative stress, like inflammation, is associated with cancer, coronary artery disease, and a number of psychiatric disorders.
- Maternal exposure during gestation to agricultural pesticides such as organophosphates, organochlorines, and pyrethroids has been identified as a moderate-to-high risk factor for autism.
  - dependent at least in part on the proximity to the applied chemical and the trimester during which the exposure took place.
  - Evidence for exposure to pesticides after birth as a risk factor for autism is non-existent.
Autism and Oxidative Stress

- Maternal exposure to traffic-related air pollutants also carries risk factors for autism.
  - Maternal exposure to other traffic-related toxins is a moderate-to-high risk factor for autism.
Autism, Oxidative Stress, and Vitamin B

- High levels of maternal vitamin B12 and vitamin B9 (folate) are additional risk factors linked to autism.
  - While B9 (potentially in the form of folic acid) is necessary for neural development, women who consumed more folic acid than recommended were at a greater risk for having an autistic child.
- While high levels of folate are associated with autism, anti-folate receptor autoantibodies have been prevalent in children with autism.
Autism, Oxidative Stress, and Inflammation

- Isolated risk factors alone are not great predictors of autism risk.
- Oxidative stress and inflammation alone cannot account for the rise of instances of autism since the 1980s.
  - May be an effect of increased awareness and changing criteria.
Proposed triggers of the autism epidemic

Inflammation and Oxidative Stress are not the only mediators of ASD?

- How do we know this?
  - Rapid “increase” in autism incidence show the importance of environmental factors and increased awareness
- Proposed triggers
  - Aspartame
  - Ethyl mercury and vaccines
  - Acetaminophen
- Ongoing research
Aspartame

- Artificial sweetener use since the start of autism epidemic
- Releases methanol when broken down
- Findings: not associated with autism
Ethyl mercury and Vaccines

What is Ethyl Mercury?
- A cation that is a metabolite of thiomersal
- Used in the preservation of vaccines

Counter-Argument Against Vaccines as a Proposed Trigger
- Elimination of thimerosal from vaccines = no reduced rate of autism
- Vaccines have existed longer than the autism epidemic and is a necessary preventative for infections
Autism and Acetaminophen

- Drug History
- Prostaglandin Synthesis
- Drug Metabolism: Phase 1 and 2
Drug History - Acetaminophen

19th Century: Issue with Parasites

1886: Drs. Arnold Cahn and Paul Hepp of France -- Accidental use of acetanilide shows analgesic and fever reducing properties

1899: Karl Morner of Germany -- Relationship between Acetaminophen and Acetanilide is defined: Metabolism of acetanilide produces acetaminophen

1909: Joseph Freiher Von Mering -- Acetaminophen is synthesized

1949: Interest in Acetaminophen resurfaces with end of WW2

1966: Acetaminophen Overdose is possible

1980: Aspirin is Linked to Reye’s syndrome; People switch over to Acetaminophen
Acetaminophen Consumption

● Who uses it?
  ○ Anyone **INCLUDING** babies and newborns*
  ○ * Only in cases of negative response to vaccines; under close supervision and super small dosage
  ○ * Babies’ first vaccine is the Hepatitis B, immediately following birth

● What does it do?
  ○ Fever Reduction
  ○ Pain Reduction
Metabolism of Acetaminophen

Non-toxic metabolites

Highly toxic metabolite (NAPQI)

Phase I Metabolism

Phase II Metabolism

Acetaminophen

= sulfation dependent, impaired in children with autism

= glutathione dependent, impaired in children with autism

Inhibition of COX-2 enzyme, maybe others

Prostaglandin H2 production inhibited

Prostaglandin D2 production inhibited (potentially important for brain development and function)

Prostaglandin E2 production inhibited (alters firing rate of neurons in the hypothalamus and may play a role in resolution of inflammation)
Prostaglandin Synthesis

- Prostaglandins are lipid autacoids ("fat hormones") derived from arachidonic acid
- Necessary to sustain homeostatic function and mediate pathogenic mechanisms (i.e. Inflammatory response)
- Found to be generated by cyclooxygenase (COX) isoenzymes
- Biosynthesis is blocked by NSAIDs
Prostaglandin Synthesis

Prostaglandin H2 production inhibited

Prostaglandin D2 production inhibited (potentially important for brain development and function)

Prostaglandin E2 production inhibited (alters firing rate of neurons in the hypothalamus and may play a role in resolution of inflammation)
Further Studies Showing Negative Results:

- Found in Rats:
  - ANY exposure during early postnatal life was linked to LONG TERM modifications to brain development, decreased social interactions, and reduced sensory functions (Only in Male)

- In vitro studies with human cells:
  - Acetaminophen can cause “an immediate, reversible, dose-dependent loss of oxygen uptake followed by a slow, irreversible dose-independent death”
    - Short Term: affects oxygen uptake by cells
    - Long Term: Cell Death / Toxicity in tissues other than the liver

- In human adults:
  - Low-dose acetaminophen triggers immune system activation and oxidative stress responses
Metabolism of Acetaminophen

Non-toxic metabolites

Highly toxic metabolite (NAPQI)

Phase II Metabolism

Phase I Metabolism

Acetaminophen

Inhibition of COX-2 enzyme, maybe others

Prostaglandin H2 production inhibited

Prostaglandin D2 production inhibited (potentially important for brain development and function)

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= sulfation dependent, impaired in children with autism

= glutathione dependent, impaired in children with autism
Drug Metabolism Phase 1 - 2

- Phase 1: Metabolism and Drug Activation
  - Uses heme-containing enzymes oxidases
    - Note: Heme binds to oxygen
  - Enzymes unmask or introduce (-OH, -O) to drug molecule
    - Make hydrophilic drug more water loving
  - Activates Drug
  - Production of NAPQI (TOXIC)

- Phase 2: Conjugation and Drug Inactivation
  - Uses enzymes transferases
    - “Transferring small polar molecules onto a drug to make more water soluble”
  - Different from the previous because oxygen isn’t needed
    - Enzymes used: Glucuronate, glutathione, sulfate, acetate
  - Inactivates Drug

NOTE: You don’t need to go through phase 1, but if you do then you MUST go through phase 2
Drug Metabolism Cont.

- **Non-toxic metabolites**
- **Acetaminophen**
- **Highly toxic metabolite (NAPQI)**

- **Phase I Metabolism**
- **Phase II Metabolism**

- ⭐️ = sulfation dependent, impaired in children with autism
- ⭐️⭐️ = glutathione dependent, impaired in children with autism
Environmental Toxins & Autism: Aggravating the U.S. Autism Epidemic

Overview
- Acetaminophen Toxicity
- Gut Microbiome Disruption
- Damage Reversal
Acetaminophen in ASD

- Considered a normal key mechanism in Autism
- In Children Pre-Puberty regressed to Autism Found:
  - Dec Sulfate and Glutathione
  - Less DHEA-S
- Which they assumed that Prenatal/Postnatal Estrogen Depleted
- Immature asymmetric brain myelin sheaths (white matter)
  - Dec Blood Brain Flow, Dec Serotonin (Behavior: Easily excitable and Repetitive behavior)
  - Dec Oxytocin (Behavior: Social Anxiety)
Tylenol + Enzymes

- Children who regress to autism:
  - decreased methionine, glutathione and cysteine
- Sulfate derived from Cysteine
- Dec Sulfation in the Liver
  - used to make foreign/domestic molecules soluble for excretion
- Decrease Liver's Glutathione :( 
  - What is Glutathione?
    - antioxidant for your body/brain
- Dec Metallothionein
  - transports and binds metals
Tylenol Molecular Mechanisms

- Bind Acetaminophen to Selenium binding proteins
- Selenoproteins underlie glutathione system
- Mercury binds Selenium
- Acetaminophen + Mercury (Not Good Combo)
Tylenol in the Brain

- Excess Acetaminophen leads to depleted brain Glutathione
  - premature Purkinje cell death
- Estrogen necessary for mature myelin sheaths or white matter
- In Autism Spectrum Disorder WM inc within hemispheres and dec between hemispheres
  - means: reduced connectivity between parts of the brain
  - inc testosterone which inc WM within hemispheres
Taking Acetaminophen will decrease the Sulfate and Glutathione required to detoxify Acetaminophen!
Roundup

- Roundup
- Monsanto/Agricultural Industry
- Glyphosate-Based Herbicide
  - Vertebrate-safe
- Western Diet
- Type 2 Diabetes
- Shikimate Metabolic Pathway
- Microbiome Bacteria Disruption
Augmentin & the Microbiome

- Amoxicillin & Clavulanate Potassium
- Launched in 1981
  - Widespread use in day care centers
- Elimination of normal gut flora
  - Tryptophan
  - Spares anaerobes
- Lactobacillus especially vulnerable
Amoxicillin & Autism

- GABA is only inhibitory after birth
  - Excitatory for development & ASD
- In development, GABA exports Cl\(^-\) to fight overhydration
  - Children with ASD have overhydrated white matter
- Maternal oxytocin might signal mature GABA function
  - Dehydrates neurons
  - GABA switch
Damage Reversal

- Significant focus on **oxytocin**
- Bumetanide
  - Significant improvements in communication and repetitive behavior
- IGF-1
  - Reduces excitability
  - Stimulates oxytocin
  - Stimulates oligodendrocytes
  - Improves neural connectivity in SZ
- Cannabidiol: stimulates oxytocinergic neurons

Oxytocin: a key molecule in ASD
Colon

DETOXIFICATION
ASD: social deficits, language deficits, and repetitive behavior
  ○ Nature v. Nurture
  ○ May be mediated by inflammation and oxidation
★ Increasing prevalence since 1980
★ 3 Main Environmental Toxins
  ○ Acetaminophen (Tylenol)
  ○ Amoxicillin (Augmentin)
  ○ Glyphosate (RoundUp)
★ Toxins kill important microbes in the gut

Quicc Recap
Brought to you by Anthony

Tylenol & Other Environmental Toxins
Can we rescue social deficits caused by ASD?

How does the gut microbiome influences human development?

Gut-Brain Axis

New mechanistic insight into the gut-brain-axis signaling by which *L. reuteri* influences CNS function and selective behaviors
Intro: Microbes with High Hopes

- The gut-microbiome-brain axis
- Maternal High-Fat Diets (MHFDs) induce social deficits and reduce \textit{L. reuteri} populations
  - Human maternal obesity is increasing
- \textbf{New Evidence:} \textit{L. reuteri} can rescue impairments in social behavior
- Vagus nerve is the platform for the GBA
- Reward Pathway Divergence

Focus Microbe: \textit{Lactobacillus Reuteri}
Methods

1. General Overview
2. Social Interaction Task (behavioral setup)
3. In-depth: How to create knockout mice

Etc.
- Cell count, fluorescence intensity, PCoA (principal coordinates analysis), NMDAR/AMPAR ratios

Most papers will follow this template:

1. Previous studies show: __
2. Ask the new question(s)/hypothesis: __
3. Test the hypothesis by: __
4. Findings: _

5… Ask another question… Test hypothesis… etc.

= Understand something better about science
Previous studies show: MHFD (maternal high fat diet) mice → social deficits & change in gut microbiota (specifically, L. reuteri)

**Question:** Can we apply this to ASD-like mice and rescue? What’s a possible cause? Maybe gut bacteria?

**Test:** Check bacteria levels (L. reuteri) in Shank3b/- and BTBR mice

**Finding:** Explained by Selin in Results (levels are going to be high/low/unchanged)

**Question:** Can we rescue social deficit by using L. reuteri?

**Test:** (Give/removing) L. reuteri to these mice

**Finding:** Paper Title: Yes, we rescue

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**Question 1:** What’s the mechanism of L. reuteri in ASD model? Possibly **vagus nerve**

**Test:** Remove vagus nerve (vagotomy). Can we still rescue?

**Finding:** Explained by Selin in Results

**Question 2:** What’s the mechanism of L. reuteri in ASD model? Possibly **oxytocin**

**Test:** Give oxytocin and (give/remove) L. reuteri

Check inside brain (PVN) and count cells/intensity. Can we still rescue?

**Finding:** Explained by Selin in Results
7 Figures have commonality: 2 different measures

Measure **bacteria levels**

Measure **interaction time**
We need a way to quantify this “social deficit” in ASD-like mice (Shank3b-/- and BTBR mice).
A Method that may be useful to you

HOW TO CREATE KNOCKOUT MICE

Shank3b -/- mouse
You will often notice mention of: **Shank3b-/-** mice (also BTBR)

A mouse model that exhibit behaviors similar to autism spectrum disorder (ASD)

Note:

(-) = missing gene  
(+) = wildtype

-/- refers to **knockout**

+/- refers to **wildtype** ('control')

+/- refers to **hemizygote** (one copy deleted)
SHANK3b-/- mice exhibit ASD-like behaviors

- Social deficits
- Self-injurious repetitive grooming.

- Function: *scaffolding that supports the connections between neurons*

**What is SHANK3?**

**Ribosomes produce protein (Shank3) from mRNA**

**Ribosome takes information from mRNA copied from DNA (in cell nucleus)**

**Gene (region of DNA)**

**Chromosome**

**Region of DNA in a chromosome has the gene for Shank3 protein to be made**

**Goal:** remove Shank3b gene in the chromosome so mouse can’t produce Shank3b protein

Shank3b-/- means...

- Shank3b gene removed
- Shank3b protein can’t be created
- Without Shank3b ➔ ASD behavior
How do we breed/knockout this Shank3B/-/- Mouse?

1. Find the chromosome and part of strand that Shank3B gene is located

2. Manufacture a vector (virus that delivers a gene to a target cell) with disrupted Shank3B.

3. Mark Shank3b vector with Neo and Herpes-TK to help enrich recombination (quality control)

4. Insert plasmid backbone to protect from nucleases

Goal: -remove Shank3B gene in chromosome
-insert modified gene into embryonic stem cells
= baby mouse grows without Shank3B gene

Within chromosome 22...

- Target gene = Shank3

- Neo (marks Shank3b) (helps enrich recombination)
- Homology arm
- Herpes-TK (helps enrich homologous recombination events over random insertion)
- Backbone protects from nuclease
1. Find the chromosome
2. Make gene inoperable
3. Mark strand with Neo/Herpes-tk
4. Create viral vector

5. Use electroporation to open membrane of stem cells and insert DNA

5. Inject modified stem cells to pregnant mouse embryo

6. Collect chimera baby mouse from foster mother

7. Let chimera breed with a normal mouse produces wildtype and knockout mice

8. Collect knockout (Shank3b-/-) for studying
How to create a knockout mouse

1. **Determine** a gene you want knocked out/inactivated
2. **Find** the chromosome associated with gene
3. **Engineer** altered gene sequence with inoperable target gene + homologous arms
4. **Add** markers + plasmid backbone to ensure recombination (cell will die if recombination was messed up)
5. **Obtain** embryonic stem cells from pregnant wildtype mice
6. **Add** vector to embryonic stem cell for recombination and incorporation of new sequence
7. **Inject** modified embryonic stem cell back into pregnant mother
8. **Obtain** chimera mice with hemizygote traits (+/-)
9. **Breed** chimera with normal WT mice
10. **KNOCKOUT MICE BORN**
Results: Shank3B−/− Mice Show Alterations in the Composition of the Gut Microbiota, and Treatment with L. reuteri Rescues Their Social Deficits

- Mice lacking the Shankb isoform of the Shank3 gene exhibit ASD-like behaviors
  - Do shankb mice display alteration of their gut microbial composition?
    - Bacterial composition
    - Bacterial diversity
- Shank3B−/− mice were treated with either vehicle or L. reuteri
  - Shank3B−/− mice had impaired sociability
  - Shank3B−/− mice: normal preference for social novelty
  - Treatment with L. reuteri rescued sociability in Shank3B−/− mice
Environmental factors can change the microbial composition of the host, and affect brain physiology and function via the gut-microbiota-brain axis.

VPA administration during gestation leads to ASD-like behaviors in rodents:
- Alterations in microbial ecology

Treatment with *L. reuteri* improves social deficits in the offspring from VP mice:
- *L. reuteri* corrects the social deficits in this environmental model of ASD (VPA) with alterations in the gut microbiome

**Results:** The VPA Mouse Model of ASD Shows Alterations in the Composition of the Gut Microbiota + Treatment with *L. reuteri* Rescues Its Social Deficits
Results: BTBR Mice Show Alterations in the Composition of the Gut Microbiota, and Treatment with L. reuteri Rescues Their Social Deficits

- No genetic variants in ASD risk genes have been identified in the BTBR genome → idiopathic
- BTBR mice harbor a different microbial community in the gut: reduction in L. reuteri levels
- Treatment with L. reuteri improved the social deficits in the three chamber and reciprocal social interaction tasks in the BTBR mice
- Treatment with L. reuteri selectively reverses the ASD-like social deficits in genetic, environmental, and idiopathic models of ASD.
Results: L. reuteri Rescues Social Deficits Independent of Other Gut Microbes

- Treatment with *L. reuteri* did not alter the microbial profile of Shank3B/mice or BTBR mice
- *L. reuteri* has no significant impact in the overall microbial composition of the host
- Germ-Free Mice
  - Displayed social deficits
  - *L. reuteri* to reversed the social deficits in GF mice
  - *L. reuteri* rescues social behavior in the absence of other members of the community
Results: L. reuteri Reverses Deficits in Social Behavior via the Vagus Nerve

- Bidirectional gut-microbiota-brain axis
- Alterations in gut permeability have been described in individuals with ASD
- Shank 3B/mice did not experience major changes in gut permeability when tested.
- Tested whether the vagus nerve could serve as a channel of communication between the gut and the brain for L. reuteri
- If the vagus nerve is required for the relevant gut-microbiota-brain communication, L. reuteri should fail to rescue the social deficits in vagotomized Shank3B / mice
  - Consistent with this hypothesis, we found that L. reuteri rescued social behaviors in control mice, but not in vagotomized Shank3B / mice (Figures 4D and 4F).
- Thus, L. reuteri reversed the social deficits in Shank3B / mice in a vagus nerve-dependent manner.
● Oxytocin modulates numerous aspects of social behaviors and is implicated in ASD

● *L. reuteri* increases oxytocin levels
  ○ Reduction in oxytocin-positive neurons in the PVN of *Shank3B* / mice compared to WT littermates
  ○ *L. reuteri* treatment increased the number and fluorescence intensity of oxytocin-positive neurons in *Shank3B* /
  ○ Intranasal oxytocin reversed the social deficits in *Shank3B* / mice

● Oxytocin improved the social behaviors that are deficient in VPA, BTBR mice, and partially in GF mice, all models in which *L. reuteri* effectively rescues their social deficits.

● Oxytocinergic signaling is involved in the mechanism by which *L. reuteri* selectively restores social behavior in several ASD mouse models

Results: Oxytocin Rescues Social Behavioral Deficits in Genetic, Environmental, and Idiopathic Models of ASD
Results: L. reuteri Restores Social Interaction-Induced Synaptic Potentiation in the Ventral Tegmental Area of Shank3B−/− Mice, but Not in Mice Lacking the Oxytocin Receptor in Dopaminergic Neurons

- Since the oxytocinergic system is impaired in Shank3B / mice → social interaction-induced VTA plasticity would be deficient in these mice
- Recorded direct social interaction-evoked long-term potentiation (LTP) in VTA DA
- Reciprocal social interaction increased the AMPAR/NMDAR in VTA DA neurons from control mice → but the same procedure failed to induce synaptic potentiation in Shank3B / mice.
- Baseline AMPAR/NMDAR ratios were similar in Shank3B / mice and WT littermates,
  - A single injection of cocaine, which increases the AMPAR/NMDAR ratio in VTA DA neurons, evoked LTP in VTA DA neurons of Shank3B / mice
  - Synaptic potentiation associated specifically with social reward is impaired in Shank3B / mice.
  - L. reuteri rescues the deficits in social interaction-induced VTA plasticity in Shank3B / mice
  - Intranasal oxytocin administration also rescued the impaired LTP in VTA DA neurons from Shank3B / mice.

Social interaction-induced synaptic plasticity is impaired in Shank3B / mice but restored by treatment with L. reuteri or oxytocin
Results: L. reuteri Restores Social Interaction-Induced Synaptic Potentiation in the Ventral Tegmental Area of Shank3B−/− Mice, but Not in Mice Lacking the Oxytocin Receptor in Dopaminergic Neurons

- The effect of L. reuteri on social behavior and related changes in social-induced plasticity in the VTA depends on oxytocin signaling
  - Conditionally deleted oxytocin receptors (Oxtr) in DA neurons
  - Deletion of Oxtr in DA neurons in DA-Oxtr / mice → no impact on the levels of L. reuteri in the gut
  - Mice lacking Oxtr in DA neurons (DA-Oxtr /) were socially impaired
- Treatment with either L. reuteri or oxytocin failed to rescue the deficits in social behaviors and related changes in VTA DA synaptic function in DA-Oxtr / mice
- Cocaine was able to induce LTP in VTA DA neurons of DA-Oxtr / mice
- L. reuteri treatment promotes social behaviors and social interaction-mediated synaptic potentiation in an oxytocin-dependent manner.
Quicc Recap
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Methods and Results

- Shank3b\(^{-/-}\) mice model ASD in humans
- L. reuteri presence is sufficient in rescuing social deficits
  - Genetic Model: Shank3b\(^{-/-}\)
  - Environmental Models: GF, VPA, MFHD
  - Idiopathic: BTBR
- L. reuteri use vagus-dependent signaling
- Oxytocin is critical for social reward
Discussion

What does all this mean?
&
What do we do now?
What does this mean?

- This changes how we view neurological diseases
  - It’s not all about the brain anymore
- We have a promising sign of future ASD treatment
- Importance of the gut-brain axis
  - Link to multiple diseases
- There’s a strong link between oxytocin and ASD
What do we do now?

Transition into human trials!

1. Demonstrate robustness of microbial intervention
   - Different models
   - Non-mouse trials (rats, NHPs, pigs)
2. Determine whether the effect is direct or indirect
   - If indirect, identify the main players
3. Have a decent understanding of the mechanisms
   - L. reuteri modulate oxytocinergic and dopaminergic signaling
Cool Future Stuff

- Optogenetics: genetically modifying neurons to respond to light
  - Artificial gut-brain axis modulation
- Precision Medicine with germs
- Microbiota as reliable indicators for disease
- Increased understanding of genetics
- Enlisting viruses as antibiotics
Concluding Remarks

Autism linked with inflammation and oxidative stress

Mediators of ASD?
- NO Correlation shown Aspartame, Ethyl Mercury and Vaccines

Actual Environmental Toxins?
- Acetaminophen! Amoxicillin and Glyphosate Depletion

L. Reuteri shown to:
- revere social deficits in maternal high-fat-diet offspring
- rescues social deficits in several models of ASD
- Vagus nerve dep manner--rescues social interaction-induced synaptic plasticity in the VTA of ASD onset--Oxytocin deficiency?
Looking Ahead...

"Indeed, we think that our findings have strengthened the rather unconventional idea that it might be possible to modulate specific behavior through the gut microbiome using select bacterial strains."

The latest state-of-the-art vagus nerve and gut-microbiota-brain axis research from the Costa-Mattioli Lab might be a game changer. The findings by Sgritta et al. could lead to revolutionary treatments that could improve sociability for everyone who is touched by the social deficits associated with ASD. "We have begun to decipher the precise mechanism by which a microbe in the gut modulates brain function and behavior. This could be key in the development of new and more effective therapies,” Costa-Mattioli concluded.
FOCUS PAPER:

ADDITIONAL RESOURCES:
- “Phase I vs. Phase II Metabolism.” Phase 1 vs Phase 2 Metabolism - Pharmacology - Medbullets Step 1, Medbullets Step 1, 2016, step1.medbullets.com/pharmacology/107006/phase-i-vs-phase-ii-metabolism.