this is love.

under the microscope:

oxytocin

❤️oxytocin❤️

IT'S NOT LOVE.
IT'S OXYTOCIN.
The Prairie Vole Story
Clinical Manipulations of Oxytocin

- “Pitocin” — artificial oxytocin — is used to induce labor in delivery rooms

- Labor induction rate in the U.S. is 30-40%

- Oxytocin antagonists are used to delay preterm labor

Kenkel et al., 2014
Pharmacological Manipulation of Oxytocin

- Gregory et al., 2013 showed that male children who underwent labor induction or augmentation had a 23% higher chance of an autism diagnosis (35% if they received BOTH labor induction and augmentation)
- Female children whose mother’s labor was induced or augmented also had a higher risk of autism (but lower than in males)
- These studies modeled PITOCIN or ATOSIBAN administration
Methods

- On day 1 of life, vole pups received an injection of either:
  - 1) Oxytocin (OT)
  - 2) Oxytocin antagonist (OTA)
  - 3) Saline (SAL)
  - 4) They are handled only (HAN)
- Tested: alloparental care, partner preference, plus-maze, and intrasexual aggression
Exposure to OTA reduces alloparental care in males

Bales et al., Developmental Psychobiology, 2004
OT shows a dose-response on pair-bonding in females

Bales et al., Hormones and Behavior, 2007
Male dose-response

Carter et al., 2008
Early OT/OTA changes reproductive potential in males

Bales et al., Physiology & Behavior, 2004
Results of Neuroanatomical Studies

- No changes in OT production at 60 days (Kramer et al., 2007)
- No changes in OT receptors or dopamine D2 receptors at 60 days (Bales et al., 2007)
- Multiple changes in vasopressin V1a receptors in both sexes (Bales et al., 2007)
Monogamous, New World primates

Small family groups

Adult pair-mates form a bidirectional social bond

Titi monkeys (Callicebus cupreus)
Intranasal Oxytocin

- Chronic intranasal OT is already in clinical trials for use in schizophrenia, autism, social anxiety, etc.
- No previous animal testing for long-term effects
- GOAL OF THIS SERIES OF STUDIES: DETERMINE LONG-TERM EFFECTS OF DEVELOPMENTAL EXPOSURE TO INTRANASAL OXYTOCIN IN:
  - A socially monogamous rodent
  - A rodent model of autism
  - A socially monogamous primate
- Focus on social behavior, repetitive behavior, and neural substrates
Intranasal oxytocin
Study Timeline - Voles

Intranasal Oxytocin Treatments

<table>
<thead>
<tr>
<th>Week 1: two acute observations</th>
<th>Week 2: two acute observations</th>
<th>Week 3: two acute observations</th>
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Days 1-20
- Birth to Weaning

Days 21-42
- Weaning to Sexual Maturity

Days 43-60
- Sexual Maturity to Adulthood

Alloparental Care
- Plus Maze
- Open Field
- Juvenile Affiliation
- Partner Preference
Partner Preference Testing (Approx. 2 weeks after end of OT administration)

Males

- Partner
- Stranger

Females

- Partner
- Stranger

Saline  Low OT  Med OT  High OT
Intranasal OT administration in mice

- BTBR T+ LtpIr3tf/J (BTBR) mice are a mouse model of low sociability
- C57BL/6J mice are a strain control
- Results: Few to no effects of intranasal OT
Sociability

Conspecific vs control object

“Crawley test”
Diagram from Millan and Bales 2014
4a. Males Chamber Time

4b. Females Chamber Time

4c. Males Sniff Time

4d. Females Sniff Time

Bales et al.,
Translational Psychiatry, 2014
Intranasal Oxytocin Administration

- Treated monkeys once per day from the age of 12 to 18 months

- Chronic intranasal OT at 0.8 IU/kg dissolved in 50μl of saline (n=6) or saline (n=5)

- Medium dose (based on clinical studies)

- Late juvenile and pubertal period
Titi monkey Parent Preference Test

Prairie vole Partner Preference Test
Williams et al. 1992

Carp, Rothwell, et al., in review
( Unpublished data slides removed)
Conclusions – intranasal studies

- Effects of intranasal oxytocin may be long-lasting, different by sex, may differ between rodent species and between rodents and primates.

- Obstetric and other clinical uses of oxytocin may have long-lasting effects on offspring – and the effects on mothers are mostly unstudied.
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Questions??