Selective serotonin reuptake inhibitor exposure in utero and during breastfeeding results in abnormalities in enteric nervous system development and gastrointestinal function

Virginia Saurman*, Korey Stevanovic*, Sam Li*, George Anderson$, Narek Israelyan*, Michael Gershon* and Kara Gross Margolis*
Columbia University Medical Center, Departments of *Pediatrics and *Pathology; Yale School of Medicine, Child Study Center

Introduction

• Depression during pregnancy occurs in 14-23% of women
• Selective serotonin reuptake inhibitors (SSRIs) are first-line treatment
  – Antenatal SSRI use has increased from 1.5% to 6.4% nationally
• Good safety profile
• SSRIs cross the placenta
  – Two-fold increased risk of congenital malformations
  – Alter central nervous system development
  – Alter brain circuitry
  – Maladaptive behaviors that persist into adulthood
• SSRIs inhibit the serotonin reuptake transporter (SERT)
  – Increase in serotonergic neurotransmission

Introduction

• Serotonin plays critical roles in:
  – ENS development
  – GI motility
  – Intestinal epithelial proliferation
• Little known about the effects of ante- and post-natal SSRIs exposure on subsequent ENS or GI function
  – Children exposed in utero to SSRIs & tricyclic antidepressants require laxatives 10-fold more often
  – SERT inhibition during development may lead to abnormal ENS development and disturbed GI motility
Hypothesis
• Administration of an SSRI (fluoxetine) from gestation through weaning will inhibit SERT and thus enhance serotonin-mediated effects to alter ENS development.
  – The resulting ENS abnormality will lead to long-lasting changes in:
    • GI motility
    • Intestinal epithelial homeostasis

Will fluoxetine alter ENS development and GI function?
• Dams given fluoxetine or water by oral gavage daily during pregnancy and breastfeeding
• No exposure to Fluoxetine for 3-5 weeks
• Fluoxetine-exposed and control pups examined at 6 weeks
  - ENS development
  - Motility
  - Intestinal epithelial homeostasis
• Concurrent experiments done with SERTKO mice
  - Rule out off-target drug effects

The ENS of fluoxetine treated mice is hyperplastic
• Hyperplasia of:
  – Total neurons
  – Serotonin-dependent (late-born) neurons
    • Submucosal
      – Dopaminergic
      – CGRP-expressing
    • Myenteric
      – GABAergic
The ENS of SERTKO mice is hyperplastic
- Hyperplasia of:
  - Total and serotonin-dependent (late-born) neurons.
- Submucosal
  - Total
  - Dopaminergic
  - CGRP-expressing
- Myenteric
  - Total
  - GABAergic

In vivo intestinal transit is slower in fluoxetine-exposed mice

In vivo motility is slower in SERTKO mice
CMMCs are enhanced in fluoxetine-treated mice

- Peristaltic reflex (CMMC) measured in vitro
  - Independent of extrinsic neuronal influence
  - ENS-dependent
- Spatio-temporal maps constructed with video imaging
  - Frequency, velocity, and length of CMMCs greater in fluoxetine-treated mice
- In vivo motility slower
- In vitro motility faster

Chemical sympathectomy reverses fluoxetine-induced slow GI transit

- Exposure of mice to fluoxetine during development affects ENS and CNS
  - Measurements of GI motility in vivo are stressful
  - Sympathectomy reverses stress-mediated slowing of the gut
  - Likely a central effect
- Sympathectomy eliminates fluoxetine-induced slow transit
  - Likely a sympathetic nerve-mediated slowing of the gut
  - In vivo measurements of GI motility

Fluoxetine treatment enhances mucosal growth and permeability

- Small intestine
  - Control
  - Fluoxetine
  - Significant difference
- Small intestine
  - Control
  - Fluoxetine
  - Significant difference
- Colon
  - Control
  - Fluoxetine
  - Significant difference
- Intestinal Permeability
  - Control
  - Fluoxetine
  - Significant difference
Conclusions

• We tested the hypothesis that SERT inhibition with an SSRI (fluoxetine) during development potentiates serotonin and alters the ENS to cause long-lasting changes in GI function.
  – Fluoxetine-treatment from gestation to weaning:
    • Neuronal hyperplasia
    • Slow in vivo GI transit due to increased sympathetic discharge
    • Enhanced CMMCs in isolated bowel
    • Enhanced mucosal growth and permeability
• Similar findings in SERTKO mice
• The coincidence of effects of fluoxetine treatment and SERTKO support the idea that serotonin and SERT are critical regulators of ENS development

Conclusions

• Potential effects of SSRI exposure on the developing ENS should be further investigated
• The exquisite sensitivity of ENS development to SERT activity may underlie the pathophysiology of gut-brain axis disorders

Thank You
Villus height, crypt depth, and intestinal epithelial permeability are greater in SERTKO mice than WT.