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Title of Research *	Intact Ovarian Function Protects Female Mice From the Hypermetabolic State Induced by Neonatal Sertraline Exposure
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**Introduction & Purpose \***

BACKGROUND: Up to 10% of all pregnancies are complicated by SSRI therapy. We have administered the most commonly prescribed SSRI (sertraline) to neonatal mice to model third trimester human exposure. Exposed male but not female mice had adult serotonin deficiency with phenotypes including hyperphagia, hyperactivity, tachycardia and increased resting metabolic rates. In female mice, estrogen increases tryptophan hydroxylase, the rate limiting enzyme in serotonin production.

HYPOTHESIS: We hypothesized that bilateral ovariectomy would unmask the effects of neonatal SSRI exposure on female mice.

**Experimental Design \***

METHODS: C57BL/6 pups were randomized to intraperitoneal injections of saline or sertraline (5mg/kg/d) on days of life 1 to 14. At 6 months, female mice underwent either sham surgery or bilateral paravertebral ovariectomy (OVX, N=6-9). After a month of recovery, adult phenotypes were assessed. Open field testing assessed locomotor activity, hemodynamics were measured by tail cuff, and resting metabolic rates were measured by indirect calorimetry. Data were compared by 2-way ANOVA. Tukey post-hoc testing was performed if statistically significant differences were detected ( $P < 0.05$ ). When a significant interaction was present, Student's t-tests were utilized.

**Results \***

RESULTS: Sertraline and/or OVX did not alter overall activity, but OVX shifted activity towards the periphery of the open field, suggesting increased anxiety ( $P = 0.001$ ). No significant differences were noted in tail cuff blood pressures or heart rates. Basal metabolic rate (resting oxygen consumption) was significantly increased in sertraline-exposed mice with post-hoc testing isolating the effect to sertraline-exposed/OVX mice ( $P < 0.05$ ). Although sertraline and/or OVX did not alter adult body weight, sertraline and OVX had interactive effects on adult food intake with OVX decreasing the intake of control mice and sertraline exposure increasing the intake of OVX mice (control/sham  $154 \pm 6$ , sertraline/sham  $148 \pm 8$ , control/OVX  $121 \pm 8$ , sertraline/OVX  $167 \pm 8$ ).

**Conclusions \***

CONCLUSION: OVX had independently effects on locomotor activity with a relative decrease in central movement (thigmotaxis, a marker of generalized anxiety). Sertraline exposure increased adult metabolic rate and food intake only in those mice with surgically-induced ovarian failure. We speculate neonatal SSRI exposure induces a compensatory

decrease in endogenous serotonin production that is partially masked in female mice by estrogen-stimulated tryptophan hydroxylase expression.

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