Reviewer's report

Title: An Overlooked Connection: Serotonergic Mediation of Estrogen-Related Physiology and Pathology

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Reviewer: Sarah L Berga

Reviewer's report:

The authors propose an important link between estrogen effects on the serotonergic system and a variety of estrogen-mediated effects cataloged in human physiology and pathology. They review data from disciplines such as endocrinology, molecular biology, neuroscience, and epidemiology to form a proposal that serotonin may mediate many of the observed effects of estrogen and estrogen deficiency in these systems. The authors note that, in the CNS, estrogen influences pain transmission, headache, dizziness, nausea, and depression, all of which are known to be consequences, in part, of serotonergic signaling pathways. Similar comparisons are drawn from estrogenic (and serotonergic) effects on the immune system, the clotting cascade, bone metabolism, and breast cancer. The paper is well-written. Some comments follow:

1) The paper can best be described as theoretical: it is, in fact, an opinion piece based upon a review of the literature and speculation that follows this review. The observations are important, and interesting, but reach only the level of hypothesis. There is no new data presented which tests the hypotheses that are offered. The speculated interplay between estrogen levels and serotonergic pathways include mechanisms whereby estrogens affect serotonin production (via TPH enzyme) and metabolism (via SERT concentration and activity), as well as 5HT receptor levels and activity.

2) There is no mention of data from ER null mice or 5HT receptor null mice as a means of further testing the author's hypotheses.

3) There is little, if any, mention of any model system in which the interplay of estrogens and serotonin are NOT readily explained by current data. Surely the authors found conditions in which there were mutually exclusive activities of estrogens and serotonin as pertains to human physiology or pathophysiology?

4) On page nine of the manuscript, regarding estrogen effects on bone, the authors write that: “These effects are consistent with observations that bone is maintained until menopause and begins to weaken following menopause or when E2 function is otherwise compromised.” This is not the case, and bone loss occurs in both men and women starting at approximately 30 years of age, and seemingly independent of normal estrogen production in women in this early age group (the 30s).

(accept as editorial or opinion piece with minor revisions)

What next?: Accept after discretionary revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests.