Reviewer’s report

Title: Perinatal exposure to a chemical mixture based on Arctic maternal body burden results in a long-term elevation of hypothalamic cytokines.

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Reviewer: John D Johnson

Reviewer’s report:

Review of ‘Perinatal exposure to a chemical mixture based on Arctic maternal body burden results in a long-term elevation of hypothalamic cytokines”. The authors address an important issue of whether perinatal exposure to environmental toxins common to pollutants found in Northern Canada alter basal or stimulated levels of brain cytokines.

Major Compulsory Revisions

1) There is emphasis on the possible contribution that environmental toxins, particularly the Arctic chemical mixture, play on cognitive neurological impairments, yet the only brain region examined was the hypothalamus. The authors indicate they ‘chose to focus on the hypothalamus given that this region has higher than normal levels of most cytokines and the fact that most research indicates a critical role of hypothalamic functioning in cytokine induced neuronal alterations’. While true, higher levels of brain cytokines are expressed in the hypothalamus that are thought to mediate many sickness responses such as fever, decreased food/water intake, HPA and sympathetic nervous system responses, cognitive impairment including learning/memory and attention deficits are typically not thought to be mediated by cytokines in the hypothalamus, but in brain areas such as the hippocampus and prefrontal cortex. Including additional brain areas would strengthen the paper and better allow the authors to discuss the possible role environmental toxins have in altering cytokine production in brain areas that mediate higher order cognitive processes. If other brain areas were not dissected or cannot be included, then at least further discussion of the kinds of physiological responses that might be altered by cytokine changes in the hypothalamus might be warranted.

2) The ‘mixture preparation’ section of methods needs clarifying. For example the manuscript states, “The dosing solution for the high dose of the full mixture (5.0 mg/ml) was then prepared by combining 0.84 g of the OC stock solution, 0.37 g of the PCB stock solution, 0.34 g of the MeHg stock solution and 0.59 g of corn oil.’ Table 1 lists the concentration in micrograms per ml, not mg/ml. Also, when combining the stock solutions it seems odd to report a weight instead of a volume, and it would take 15.85 liters of OC stock solution (reported to be at a final concentration of 0.053 mg/ml) to get 0.84g. Overall, it is unclear how the calculations result in the reported concentrations.

Minor Essential Revisions
1) Results (first paragraph): Include F values (df) for basal IL-1 in results. Also, p=0.07 is listed after ‘LPS treatment’ but do the authors mean the basal levels presented in Figure 1 as inferred by the post-hocs analyses?

2) Results (last paragraph): Include ‘Figure 4-5’ in description

3) Methods: What was the brain tissue homogenized in?

4) Discussion (first paragraph): ‘exposure to realistic levels of environmental chemicals provoked long-term inflammatory cytokines’. Equating concentrations of drugs across species is always a tricky issue as the absorbance, metabolism, clearance of the drugs may be different. While it’s nice the authors took the time to determine a ‘realistic’ level of toxin to administer, some discussion of the precautions/limits should be discussed as well.

Discretionary Revisions

1) Discussion (paragraph three): Authors may not want to abbreviate CNS since this is not a brain journal.

Minor issues not for publication:

1) Abstract (Methods): ‘cytokine levels were measured with a suspension-based array system and differences were determined using ANOVA’

2) Methods (first sentence): ‘nulliparous’ is spelled nulliparous

3) Methods (Mixture preparation section): ‘because it is not lipophilic and it’s contribution to the mixture’; no apostrophe is needed

4) Methods (Mixture preparation section next sentence): “Because a number of the chemical had extreme values’; chemical should be plural

5) Methods (mixture preparation; second paragraph): “This PCB stock solution was then transferred’; change to ‘was’

6) Methods (statistical analyses): “was modified by the perintal chemical exposure”; should be perinatal

7) Methods (statistical analyses): “animals also received the adult LPS injection”; reword to indicate animals received LPS injections when they were adults

8) Results (last paragraph): ‘post hoc analyses based on out a priori’; should be ‘our’

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I declare that I have no competing interests.