Reviewer's report

Title: Aspirin: A review of its neurobiological properties and therapeutic potential for mental illness

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Reviewer: Christopher A Lowry

Reviewer's report:

In this manuscript, the authors provide a concise and informative review of the neurobiological properties of aspirin and its potential for therapeutic use in the treatment of a number of psychiatric and neurological conditions associated with inflammation, including major depressive disorder (MDD), bipolar disorder, schizophrenia, and Alzheimer’s disease. The authors make a convincing argument that further preclinical and clinical studies are warranted. The review is well-written and appropriate for a general audience.

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

There are three questions that are raised by this review that I believe warrant at least a brief discussion. First, it’s proposed that aspirin may have therapeutic potential in different affective disorders, schizophrenia, and Alzheimer’s disease, but clearly these conditions have different symptoms and diagnostic criteria. Do the authors think that increased inflammation or increased stress-induced inflammation is a risk factor for each of these diverse conditions, and therefore, decreasing inflammation or inflammatory responses would reduce risk and/or have therapeutic value, or do the authors think that these diverse conditions are driven by unique patterns of inflammatory dysregulation that determine clinical symptoms, each of which would be effectively targeted by aspirin? If the former is the case, then it would be predicted that only a subset of patients (those with the risk factor, increased inflammation or inflammatory responses) would benefit from treatment. It would be useful to deal with this explicitly. Second, would the authors predict that treatment with aspirin would only be beneficial in that subset of patients that have increased inflammation (baseline inflammatory markers prior to treatment), or in that subset of patients with increased inflammatory responsiveness prior to treatment, or in all patients? There is evidence from a recent clinical trial of the tumor necrosis factor antagonist infliximab that treatment with anti-inflammatory agents may only be beneficial in patients with elevated baseline inflammatory markers (Raison et al., 2012). Third is the issue of prevention versus treatment. Are the authors arguing that aspirin would be beneficial for prevention, treatment, or both?

Minor issues not for publication

There are currently no disclosure statements for HD, JJM, CGD, or MM
1. Abstract, line 15, “mood disorders, schizophrenia” should be “mood disorders and schizophrenia”

2. Introduction, para. 2, line 6, should “L-8” be “IL-8”? 

3. Introduction, para. 5, line 13, “psychiatric diseases, have” should be “psychiatric diseases have”

4. Inflammation and redox dysregulation in mental disorders, para. 2, line 5, “IL-1” should this be IL-1alpha or IL-1beta?

5. Inflammation and redox dysregulation in mental disorders, para. 2, line 9, “reduce the inflammatory markers levels CRP and IL-6” should be “reduce levels of the inflammatory markers CRP and IL-6”

6. Inflammation and redox dysregulation in mental disorders, para. 2, line 10, “elevated inflammatory markers levels” should be “elevated levels of inflammatory markers”

7. Inflammation and redox dysregulation in mental disorders, para. 2, line 16, “MDE” should be “MDD”?; next line, reference 25 is cited twice; two lines down, remove question mark from the end of the sentence.

8. Inflammation and redox dysregulation in schizophrenia, para. 2, line 4, “Toxoplasma gondii” should be italicized.

9. Inflammation and redox dysregulation in schizophrenia, para. 2, line 7, “…IL-8 is” should be “IL-8 are”; next line, “independant” should be “independent”; next line, “mediating” should be “modulating”?; “dysregulated in schizophrenia” should be “dysregulated in schizophrenia,”

10. General comment, for a general audience, it would be good to define many of the abbreviations that are used, such as PTX3, PAI-1, OPG, ICAM-1, metS, etc. If consistent with journal style, it would be useful to have an abbreviation list.

11. Inflammation and redox dysregulation in schizophrenia, para. 3, line 17, “schizophrenia and the meta-analysis” should be “schizophrenia, consistent with the meta-analysis”

12. Inflammation and redox dysregulation in Alzheimer’s dementia, para. 2, line 6, “which when coupled with” should be “which, when coupled with”

13. The association between psychiatric disease, dementia, and auto-immunity, para. 1, line 9, “autoimmune responses” should be “autoimmune response”; also line 16

14. The association between psychiatric disease, dementia, and auto-immunity, para. 2, line 11, “autoimmune disorders” should be “autoimmune disorder”

15. Activated microglia in psychiatric disorders, para. 4, line 6, quinolinic acid is listed as a terminal breakdown product in the kynurenine pathway of tryptophan metabolism, but quinolinic acid is further broken down to NAD+

16. Activated microglia in psychiatric disorders, para. 6, line 2, “Alzheimer” should be “Alzheimer’s”

17. Role of aspirin in Alzheimer’s disease; clinical data, para. 1, line 5, “than
those not use aspirin” should be “than those that do not use aspirin”
18. Conclusion, line 6, “thus far is promising” should be “thus far are promising”
19. Author contribution, line 6, “neurodegernative” should be “neurodegenerative”
20. Tables 1 and 2, many abbreviations are not defined in the footnote; unfortunately, parts of Tables 1 and 2 were cut off in the review copy of the manuscript.
21. Table 1, Landi 2003, “impaire” should be “impair”?
22. Table 1, Cornelius 2004, “Defferences” should be “Differences”; “examinations” should be “examinations”
23. Table 1, the meaning of the shading in the table is not indicated.
24. Table 1, Arvanitakis 2008, “catholic” should be “Catholic”
25. References 7, 8, 10, 62, 84, 101, 102, 105, 122, and 123 are missing volume and/or full page numbers.

Reference List

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
Declaration of competing interests. C.A. Lowry has consulted for Enlight Biosciences, and has received travel reimbursement for consultation with Immodulon Therapeutics.