Author's response to reviews

Title: Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways.

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Author's response to reviews: see over
To Dr. Sabina Alam, Ph.D.

Editor BMC Medicine

Re: Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways

Dear Dr Alam,

We have revised the above paper according to the points raised by the referees:

1. Reviewer: Dr. J.C Leza

The authors review the relationships between clinical depression and sickness behaviour from a translational point of view. Some minor changes are suggested: - delete chronic fatigue from key words (no much about in the text); change point-comma for comma in series such those in line 5, first para. Introduction section, the initial part of the 2nd para. in Introduction section.

In the Introduction we have changes the ; into ,:

- explain the rationale about activation of bacterial production after loss of iron in diet (3rd line, 2.3 section (S. B and anorexia and weight loss)

This now explained in the text, see secion 2.3 line 4: Iron is one of the nutrients employed by bacteria for their growth.

- change body temperature units (ºC instead of ºF).

Degrees ºC are now added. However, the data in ºF are still included. Also the SDs cannot be transformed.
- Excessive non standard abbreviations: SIRS, CARS, CIRS, TRYCAT, PIC...

We have deleted the use of SIRS and CARS from the revision.

We have added a list with abbreviations (just before the Acknowledgements).

PICs: this abbreviation is commonly used is the literature.

CIRS: is a new abbreviation that denotes “compensatory (anti)inflammatory reflex system”. In any case we need an abbreviation to describe this reflex, also in the figures.

TRYCAT: we were the first to use this abbreviation in 2011. Now also other authors start to use TRYCAT.

- To what "translational data" refers the inicial sentence 2nd para. page 18 (section 5.2)?

This is now explained on page 18, last paragraph:

These TRYCAT data obtained in animal experiments are, however,

Reviewer Dr.C.Pariante:

I really enjoyed this thorough review which brings together established concepts with novel ideas. My main (compulsory) recommendation is that more space should be given to the discussion of the action of antidepressants on inflammatory pathways, both in terms of clinical evidence and of potential mechanisms. This would be an ideal translational angle to add to the review.

We have added a new section (see section 8) on antidepressants:

8. Antidepressive treatments

Antidepressants have significant immunoregulatory and immunosuppressive effects in normal volunteers. Tricyclic antidepressants (TCAs) and selective 5-HT reuptake inhibitors (SSRIs) attenuate the production of PICs, e.g. IL-1β, TNFα and IL-6, and Th1-like cytokines, including IL-2 and IFNγ [177]. Most antidepressants, i.e. TCAs, SSRIs, reversible inhibitors of monoamine oxidase A, 5-HT and noradrenaline reuptake inhibitors, and atypical antidepressants (e.g. tianeptine) all increase the production of IL-10, a negative immunoregulatory cytokine and / or lower the production of IFNγ, resulting in a decreased IFNγ / IL-10 production ratio [178]. There is also evidence that SSRIs and TCAs inhibit the production of IL-1β, TNF-α, and IL-6 in brain cell cultures [65]. Also, in animal models antidepressants have antiinflammatory effects [65]. For example, mice challenged with a lethal dose of LPS were protected by bupropion administration, which significantly reduced the production of IFNγ, TNFα and IL-1β [179]. There is also evidence that antidepressants...
may attenuate inflammation-induced sickness behaviours. For example, tianeptine may reduce sickness behaviours induced by peripheral (but not central) administration of LPS and IL-1β [180]. Treatments that target inflammation, e.g. etanercept blocking TNFα functions, may attenuate IL-1β-induced sickness behaviours [181].

In depressed patients, on the other hand, the in vivo effects of antidepressants are less clear. Subchronic treatments with antidepressants do not consistently attenuate inflammatory signs in depressed patients [182,183]. Accordingly, a recent meta-analysis showed that antidepressant subclasses other than SSRIs did not attenuate the concentrations of pro-inflammatory cytokines [184]. Thus, despite the well established immunoregulatory effects of antidepressants targeting inflammation (attenuate), Th1 (downregulate) and T regulatory (upregulate) functions, clinical remission in depression is not associated with normalization of immuno-inflammatory pathways [182-184]. Thus, clinical depression appears to be accompanied by a “resistance” to the immunosuppressive effects of antidepressants [183]. This may suggest that the immuno-inflammatory pathways are continuously activated by processes that can not be blocked by antidepressants, for example, by the autoimmune responses directed against neoantigenic determinants [133] and increased translocation of gram negative bacteria [157]. There is also evidence that antidepressants target O&NS (attenuate), antioxidants (increase) and neuroprogressive processes (attenuate) [183]. Despite these effects, increased activity and sensitization of immuno-inflammatory pathways, O&NS pathways, autoimmune responses, and neuroprogression determine in part staging of depression, e.g. treatment resistance and recurrence of depression [52]. Thus, these pathways may in part explain why in many trials the clinical efficacy of antidepressants does not outperform placebo [185] and why despite being treated with antidepressants, depressed patients show high relapse rates [186]. Therefore, new combinatorial treatment strategies are developed in clinical depression with drugs that target inflammation, Th1 activation, O&NS and lowered antioxidant levels, and/or neuroprogression, e.g. celecoxib, statins, acetylsalicylic acid, minocycline, zinc, N-acetyl cysteine, curcumin, etc. [183].

Editorial remarks:

Authors' contributions: are now described:

MM and MB participated in the design of this review, while all authors helped to draft the paper. The authors would like to thank Bruce Charlton for extensive discussion of the text.

Competing interests and non-financial competing interests; these are now described:

MM and MB participated in the design of this review, while all authors helped to draft the paper. The authors would like to thank Bruce Charlton for extensive discussion of the text.

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The other authors declare that they have no competing interests.

We hope that the paper is now in acceptable format,

Kind regards,

Michael Maes