Biological Psychiatry

Commentary

Microglial Activation and Response to Anti-inflammatory Treatment in Major Depressive Disorder: Another Piece in the Inflammation–Mood Disorders Puzzle

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There is good news and bad news when it comes to our understanding of inflammation in the pathogenesis and treatment of major depressive disorder (MDD). The bad news is that, like the dexamethasone suppression test or the efficacy of antidepressants before it, inflammation is oversold as an answer to the mystery of depression and its treatment. The good news is that an unusually replicable set of findings (for psychiatry) increasingly paints a consistent picture of the ways in which inflammation is of value in understanding MDD. In the current issue of *Biological Psychiatry*, Attwells *et al.* (1) simultaneously extend and confirm what we know already about how brain and body work together when it comes to inflammation and its role in MDD.

So, what do we know already?

We know that inflammation influences mood acutely and promotes depression when chronic. However, we also know that inflammation is not an equal opportunity inducer of emotional misery. Pre-exposure factors that increase the risk for MDD in general, including female sex and past and current depressive status, also increase the risk for depression and related symptoms following an immune stimulus. Similarly, how depressed a person becomes after an inflammatory challenge has much to do with the ways in which systems that interact with the immune system respond to the challenge. Abnormalities associated with idiopathic MDD also predict increased depression in the context of inflammation. In particular, changes in central nervous system (CNS) functional activity and monoamine and glutamatergic neurotransmitter metabolism, as well as alterations in sleep, hypothalamic-pituitary-adrenal axis activity, peripheral cytokines, and intracellular second messenger pathways, are all associated with an increased risk of depression induced by inflammation (2).

It follows logically that if inflammation induces depression, MDD should be associated with increased inflammation. Indeed, a vast array of studies reliably report that as a group, patients with MDD demonstrate increases in circulating inflammatory biomarkers, especially interleukin-6, tumor necrosis factor, and C-reactive protein (2). Early on, many of us suspected that the link between inflammation and depression might explain at least a portion of the association between medical illness and MDD but wondered where the inflammation could possibly be coming from in medically healthy individuals with MDD. The answer was not long in coming as studies showed that psychological stress (both early-life adversity and exposure to a laboratory stressor) and increased adiposity drove inflammation even in the absence of an infectious stimulus. Because stress and increased adiposity are strong predictors of depression, the case seemed airtight, with a beautiful symmetry often desired but seldom seen in mental health research. Based on the beauty of these findings, those of us working in the field expected to find the obvious corollary that anti-inflammatory agents would have robust antidepressant effects.

We were wrong.

Anti-inflammatory agents do not appear to be all-purpose antidepressants. It is true that small studies have reported strikingly large effect sizes for nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase-2 (COX-2) inhibitors and have contributed disproportionately to meta-analyses claiming benefits for anti-inflammatories, especially as antidepressant augmenting agents (3). However, studies with larger sample sizes have generally failed to find antidepressant benefits for these agents, including a large recent study that found no benefit for daily aspirin versus placebo in either reducing or preventing depressive symptoms (4).

Moreover, NSAIDs and COX-2 inhibitors have a number of "off-target" effects unrelated to inflammation that might enhance or impair their capacity as antidepressants and that therefore complicate any interpretation of results, positive or negative. On the other hand, cytokine antagonists offer a far more specific and definitive test of inflammation as a therapeutic target. Here the results to date could not be more decisive. In medically healthy patients with treatment-resistant MDD (TRD) or bipolar depression, the tumor necrosis factor antagonist infliximab showed no benefit over saline placebo, which was numerically superior in the TRD study (5,6). Whether studies underway testing interleukin-6 antagonism will produce different findings is a question for the future; however, an abstract report suggests that interleukin-6 antagonism before bone marrow transplant might actually increase, rather than attenuate, subsequent depressive symptoms (7).

If results from cytokine antagonist studies conducted to date are decisive, they are not disappointing.

Although these results may refute earlier hopes that inflammation would finally provide a long hoped for "unified field theory" of mood disorders, they align nicely with the more nuanced, and increasingly consistent, picture provided by research over the last decade. This view highlights the fact that mood disorders writ large are not inflammatory conditions.

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https://doi.org/10.1016/j.biopsych.2020.08.003
Biological Psychiatry October 15, 2020; 88:594–596 www.sobp.org/journal
ISSN: 0006-3223

Indeed, the depression–inflammation literature is a classic example of mean values hiding more than they reveal. Depressed populations do not have elevated inflammation because all members are mildly inflamed. Rather, differences between depressed and nondepressed populations reflect the presence of a subgroup of depressed patients who have inflammatory values significantly above those observed in comparison with groups of healthy, nondepressed individuals (2). These patients typically comprise between 25% to 35% of the larger MDD population, depending on the inflammatory metric used and the demographics of the sample. They are not in the majority, but they are different in all the ways one would expect if inflammation contributes to depression in patients with increased inflammation, but not in those without it.

Inflammatory stimuli cause functional changes in the ventral striatum and cingulate cortex, and medically healthy patients with MDD and increased inflammation show similar changes in these brain regions. Inflammation alters the metabolism of serotonin and glutamate and impairs dopamine signaling (2). Although awaiting replication in prospective studies, post hoc analyses suggest that patients with MDD or bipolar disorder and increased inflammation are generally resistant to selective serotonin reuptake inhibitors and respond preferentially to the NMDA receptor antagonist ketamine and to agents with dopaminergic effects in the brain, such as bupropion and nortriptyline (2). Finally, randomized, placebo-controlled trials have shown that cytokine antagonists, minocycline, and anti-inflammatory omega-3 fatty acids, while having no overall antidepressant properties, produce a placebo-adjusted antidepressant effect in the subgroup of patients with MDD or bipolar disorder and increased inflammation (5,8,9), consistent with meta-analyses suggesting that cytokine antagonists demonstrate modest antidepressant properties when used in patients with autoimmune/inflammatory diseases (10).

Enter the Attwells *et al.* study (1) on the role of CNS inflammation in antidepressant responses to the COX-2 inhibitor celecoxib. Starting with an assumption that the mixed findings on celecoxib augmentation in previous trials might reflect a failure to consider baseline CNS inflammatory status, the investigators used positron emission tomography to assess translocator protein distribution volume (TSPO V_T) in the prefrontal and anterior cingulate cortices of 41 patients with TRD who subsequently underwent 8 weeks of open-label treatment with celecoxib (200 mg a day). The investigators report that reductions in Hamilton Depression Rating Scale (HDRS) scores showed a strong sigmoidal relationship with prefrontal cortex and anterior cingulate cortex microglial activation, as measured by TSPO V_T. Patients with low TSPO V_T had no response to celecoxib. As TSPO V_T increased, so did improvements in depression—up to a point, after which no further gains were noted.

The study is an important contribution for several reasons. It adds another piece of evidence to a growing database that patients with MDD and inflammation are different from other MDD patients in ways that might matter clinically. And while many studies have reported associations between peripheral inflammatory biomarkers and therapeutic response in MDD, this is the first study to our knowledge to observe a similar association between response to an anti-inflammatory and a marker of CNS inflammation. Moreover, the strong s-shaped association between TSPO V_T and response suggests that NSAIDs and COX-2 inhibitors may reduce depression primarily via anti-inflammatory mechanisms, rather than their off-target effects.

Finally, it is important not to let our enthusiasm blind us to the fact that in this TRD population celecoxib had minimal effects on depressive symptoms, even in patients with increased TSPO V_T. Precision medicine is a lofty goal, but no pharmacologic augmenting strategy would make it to market based on the whisper of an effect seen even in the most responsive patients (i.e., a 4-point reduction in HDRS score from baseline). Importantly, this modest effect is consistent with placebo-adjusted effect sizes seen with cytokine antagonists and may suggest that inflammatory pathways are too generalized and far “upstream” to be viable clinical options.

Of all the limitations admirably listed by Attwells *et al.* (1), the lack of a placebo comparator may be the most important, and for an intriguing reason. While not universally observed, some evidence suggests that anti-inflammatory agents may actually be counterproductive in patients with MDD and low levels of inflammation (i.e., they respond better to placebo) (5,8). This curious finding is well worth deeper exploration because it suggests that the story of inflammation in mood disorders may be less consistent than this commentary has attempted to suggest, and that in fact inflammation may be relevant for depression more generally, but not in the simple linear way that those of us in mental health so often crave.

Acknowledgments and Disclosures

CLR serves as a consultant for Usona Institute, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Institute of OM Foundation, and Emory Healthcare.

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Received Aug 1, 2020; accepted Aug 5, 2020.

References

1. Attwells S, Setiawan E, Rusjan PM, Xu C, Hutton C, Rafiei D, *et al.* (2020): Translocator protein distribution volume predicts reduction of symptoms during open-label trial of celecoxib in major depressive disorder. Biol Psychiatry 88:649–656.
2. Felger JC (2019): Role of inflammation in depression and treatment implications. Handb Exp Pharmacol 250:255–286.
3. Bai S, Guo W, Feng Y, Deng H, Li G, Nie H, *et al.* (2020): Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: A systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry 91:21–32.
4. Berk M, Woods RL, Nelson MR, Shah RC, Reid CM, Storey E, *et al.* (2020): Effect of aspirin vs placebo on the prevention of depression in older people: A randomized clinical trial. JAMA Psychiatry Jun 3: e201214.
5. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, *et al.* (2013): A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. JAMA Psychiatry 70:31–41.

6. McIntyre RS, Subramaniapillai M, Lee Y, Pan Z, Carmona NE, Shekotikhina M, *et al.* (2019): Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: A randomized clinical trial. JAMA Psychiatry 76:783–790.
7. Raison CL, Knight JM, Pariante C (2018): Interleukin (IL)-6: A good kid hanging out with bad friends (and why sauna is good for health). Brain Behav Immun 73:1–2.
8. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, *et al.* (2016): Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: A proof-of-concept study. Mol Psychiatry 21:71–79.
9. Savitz JB, Teague TK, Misaki M, Macaluso M, Wurfel BE, Meyer M, *et al.* (2018): Treatment of bipolar depression with minocycline and/or aspirin: An adaptive, 2x2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. Transl Psychiatry 8:27.
10. Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM (2018): Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 23:335–343.