VIEWPOINT

Are Anti-inflammatory Therapies Viable Treatments for Psychiatric Disorders?
Where the Rubber Meets the Road

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Accumulating data indicate that inflammation may play a role in a host of psychiatric illnesses.[1] These data reveal reliable associations of inflammatory markers with psychiatric disorders, the induction of psychiatric symptoms following administration of inflammatory stimuli, the association of inflammation-related genes with psychiatric disease, and the elucidation of neurobiological and immunological mechanisms by which inflammation targets neurotransmitters and neurocircuits to change behavior. Nevertheless, whether therapeutic strategies that inhibit inflammation will be effective in treating psychiatric illnesses remains unclear. This question is not trivial given the pressing need for novel therapeutics based on the high rates of treatment resistance across disorders and on our relatively limited psychopharmacologic repertoire.

As reflected in recent reviews of the efficacy of anti-inflammatory drugs in treating depression and schizophrenia, including a recent meta-analysis on depression published in *JAMA Psychiatry*,[2] the experimental strategies used to date are the ones that have failed to yield new drugs for psychiatric disorders. Clinical trials using anti-inflammatory agents with multiple off-target effects on nonselected populations of patients, using nonspecific measures of outcome without evidence of target engagement, provide limited information and run the risk of repeating an approach that, although familiar, is no longer viable. It is this very approach that has led the National Institute of Mental Health to demand more rigorous standards regarding clinical trials, including an "experimental medicine" approach to avoid the mistakes of the past.[3] In the case of inflammation, these mistakes are being repeated despite the existence of a treasure trove of data that can inform future studies and ultimately determine whether inhibiting inflammation holds therapeutic promise. A brief evaluation of what we know and how it can guide future study design is a necessary first step toward making this determination. The following tenets are proffered as initial guideposts to address the challenge.

Inflammation

Inflammation is not for everyone. What has become increasingly clear is that no psychiatric disorder is an inflammatory disorder, and only subgroups of patients with any given psychiatric disease exhibit an increased number of inflammatory markers.[4] Thus, treatment trials of anti-inflammatory agents should preselect patients with increased inflammation. To our knowledge, no clinical trials in published meta-analyses of anti-inflammatory therapies for major depression or schizophrenia have enriched for patients with increased inflammation,[2] and only 1 trial of patients with depression considered baseline inflammation as a relevant predictor of response.[4] Standard inflammatory markers that are clinically available, such as C-reactive protein, appear to be adequate for initial attempts at response prediction. Indeed, C-reactive protein is one of the best predictors of response to anticytokine therapies in inflammatory disorders, such as ulcerative colitis and Crohn disease,[4] and was recently found to predict a differential response to distinct classes of antidepressants.[5] It should be noted, however, that more nuanced profiles of inflammatory proteins and gene expression, as well as cellular immune parameters, likely represent the future for predictors and targets of response to anti-inflammatory therapies.

Primum Non Nocere

Above all, do no harm. Although using anti-inflammatory strategies for those with increased inflammation may show therapeutic promise, laboratory animal studies demonstrate that inflammatory cytokines play a pivotal role in learning and memory, as well as in neuronal integrity (including neurogenesis and synaptic pruning).[6] Moreover, data suggest that response to antidepressants may in part be dependent on the induction of inflammatory cytokines. Thus, the indiscriminant use of anti-inflammatory treatments for psychiatric patients without inflammation (as has been done in every clinical trial to date) may reduce the likelihood of detecting a response and could potentially lead to the exacerbation of the disease.

Symptom Specificity

Symptom specificity is the rule not the exception. An emerging literature has revealed specific subcortical and cortical circuits that are targets of inflammation. Notable among these are reward circuitry in the basal ganglia and cortical circuits (eg, dorsal anterior cingulate cortex, amygdala, and anterior insula) that mediate anxiety, arousal, and alarm.[1] Evolutionary considerations regarding the engagement of these neurocircuits by inflammation suggest that inhibition of motivation and activation of arousal may subserve shunting of energy resources to fight infection and heal wounds while increasing vigilance against attack.[1] Thus, the prototypical and evolutionarily conserved responses of anhedonia and anxiety to inflammatory stimuli provide an excellent starting point for the examination of specific neurocircuits and symptoms as primary end points for anti-inflammatory therapies as reflected in National In-

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stitute of Mental Health Research Domain Criteria related to positive and negative valence systems. To our knowledge, no previous study has taken advantage of this conceptual framework to shape trial design and focus end points on those circuits and symptoms that are most likely to be responsive to anti-inflammatory therapeutics.

Anti-inflammatory Drugs

Not all anti-inflammatory drugs are created equal. A significant drawback to current studies examining anti-inflammatory strategies in psychiatric disorders is that the "anti-inflammatory" drugs commonly used have a multiplicity of "off-target" effects. Such drugs may inhibit inflammation and improve symptoms, but they might do so through mechanisms unrelated to their anti-inflammatory activity, thereby confounding the interpretation of results. For example, celecoxib, the drug used in the majority of trials for major depression,[2] has effects on several pathways relevant to the pathophysiology of depression, but these effects do not involve inflammation, including the effects on the glucocorticoid receptor, as well as cadherin-11, an adhesion molecule involved in synaptic plasticity and fear- and anxiety-related responses.[7] Minocycline hydrochloride, a drug used in schizophrenia trials owing to its inhibitory effects on microglial activation, is an antibiotic and, therefore, has direct effects on the gut microbiome, which has been shown to modulate behavior.[1] It is also possible that psychiatric disorders may cause inflammation, and with successful treatment, the number of inflammatory markers may be reduced. Such may be the case with some antipsychotic and antidepressant drugs that have been associated with a decreased number of inflammatory markers following disease improvement.

Relevant to proof-of-concept studies, optimal drug candidates are biologic agents (typically monoclonal antibodies) that specifically target individual inflammatory cytokines such as tumor necrosis factor and interleukin 1. These medications have demonstrated marked efficacy in patients with inflammatory disorders and have no off-target effects. The major limitations of these drugs include immune suppression and the associated risk of infection, notably the reactivation of tuberculosis.

Trust But Verify

A major advantage of using anti-inflammatory agents is that there are definitive readouts of target engagement. The majority of anti-inflammatory therapies have effects on inflammatory markers, and therefore it can be determined whether a treatment is indeed "hitting the target," at least as represented in peripheral blood. Given recent data that blood-borne inflammatory cells are transporting inflammatory signals to the brain, peripheral inflammatory markers may be even more relevant than previously thought.[1] Only 2 clinical trials[2,4] have used inflammatory markers to monitor target engagement, and in both cases, the level of inflammation was decreased, and this decrease was associated with treatment response. Although the relationship between peripheral and central inflammatory markers remains understudied, in the absence of reliable measures of inflammation in the brain, peripheral markers represent an excellent starting point for target verification. Moreover, to assist in the interpretation of the literature, the assessment of a standardized subset of inflammatory markers is recommended, including the levels of C-reactive protein, tumor necrosis factor, and interleukin 6, which have been found to be reliably elevated in a variety of psychiatric disorders.

Conclusion

The stage is set for well-informed, proof-of-concept studies to determine whether inflammation is a viable therapeutic target for psychiatric disease or an epiphenomenon of limited therapeutic relevance. Guidelines derived from what we know about inflammation and its effects on the brain can support intelligently designed clinical trials, potentially opening the door to a host of therapeutics targeting the immune system in order to treat disease.

ARTICLE INFORMATION

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