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Brief Commentary

Inflammation and impulsivity: Is lithium the chill-pill?

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Who has never experienced the elation of buying the latest hi-tech gadget (or a new pair of shoes!) on the spur of the moment? It feels fantastic for a while, or at least until the credit card bill arrives. Impulsive actions are small thrills that color our lives, and for most of us they are relatively harmless. However, when unchecked behavior becomes pervasive and difficult to manage it can lead to disastrous consequences. Such is the case in bipolar disorder.

Impulsivity is a core feature of bipolar disorder. High trait impulsivity, in particular motor impulsivity or behavioral disinhibition, correlates with high frequency manic episodes and a worse clinical prognosis because of its associations with prevalent comorbidities of bipolar disorder that include substance abuse, pathological gambling, and suicide attempts (Stanford et al., 2009).

Lithium is, to date, still the first-line therapy for bipolar disorder, proving superior as monotherapy to other pharmaceuticals in ameliorating mania, depression, general functioning, cognition, and structural brain changes (Post et al., 2019). Given the strong association of behavioral disinhibition with bipolar disorder, an interesting question is whether lithium can also decrease impulsive behavior. Although not exhaustively addressed, some supporting evidence to this effect has been reported in the clinical literature (Dorrego et al., 2002). However, the question has not been addressed mechanistically in animal models.

In this issue of Brain, Behavior and Immunity, Adams et al. (2020) use a translationally validated rodent test for behavioral inhibition, named the 5-choice serial reaction task, to present evidence that chronic lithium administration decreases motor impulsivity in rats. This is accompanied by reduced levels of proinflammatory cytokines, such as interleukin (IL)-6, IL-1β and the chemokine RANTES, within the orbitofrontal cortex (OFC), a prefrontal cortex region preeminently engaged during behavioral inhibition tasks. The authors suggest that lithium decreases motor impulsivity in part by decreasing inflammation.

Altered peripheral proinflammatory markers are well documented in bipolar disorder (Knijff et al., 2007; Nassar and Azab, 2014). A recent meta-analysis found an abnormal inflammatory profile associated with bipolar disorder that included elevated levels of IL-4, IL-10, IL-1β and IL-6, tumor necrosis factor (TNF)-α, and prostaglandins (Modabbernia et al., 2013). Less known is the relationship between impulsive behavior and inflammation, but evidence for an association between impulsivity-related traits and higher levels of pro-inflammatory markers in humans has recently emerged (Brundin et al., 2017).

Lithium has profound effects on inflammatory mediators; indeed, one of the initial side-effects of lithium use observed in humans was that it increased leukocyte numbers. To date the documented anti-inflammatory effects of lithium include inhibition of proinflammatory cytokine production (IL-6, IL-1β, TNFα, INF-γ), inhibition of nitric oxide signaling, and inhibition of prostaglandin synthesis (Nassar and Azab, 2014). What is the mechanism linking lithium to inflammation and how does it affect the brain? Lithium can displace divalent magnesium ($Mg2+$) and inhibit several enzymes that use $Mg2+$ as a co-factor. Notable among the direct targets of lithium inhibition are glycogen synthase kinase-3 beta (GSK3β) and inositol monophosphatase (IMP), two enzymes that affect a wide array of cellular processes including autophagy, oxidative stress, and inflammation. In particular, GSK3β is an activator of both JAK/STAT and NFκB signaling and inhibition of this enzyme may account for the decrease in the diverse classes of proinflammatory markers observed by Adams et al. In the brain, lithium reduces microglia activation and microglia-driven secretion of proinflammatory molecules known to have marked neurotoxic effects. Therefore, one hypothetical mechanism behind the results presented in this paper is that lithium, by inhibiting GSK3β activity in microglia, reduces production of inflammatory molecules and protects neuronal function, thus reducing impulsive behavior.

Some important questions remain still unanswered, as the study focuses on the effects of lithium in uncompromised animals, i.e., in the absence of either inflammation or impaired behavioral inhibition. For example, we do not know if the same inflammatory molecules reduced by lithium actually increase in contexts where inhibitory control is compromised. Mechanistic studies to determine which of the signaling molecules regulated by lithium, if any, may be responsible for disrupting inhibitory control will provide a natural extension of these findings and add to their clinical relevance.

A noteworthy aspect of the study is that lithium reduced inflammatory markers more robustly in the OFC, but not in other regions such as the medial prefrontal cortex, hippocampus, or nucleus accumbens. This is significant because the OFC has a crucial role in motor impulsivity and it suggests the possibility that dysregulated inflammatory signals in this area of the prefrontal cortex are associated with impulsive phenotypes. In support of this idea, increased expression of proinflammatory cytokines were found in the orbitofrontal cortex of suicide victims (a population with high trait impulsivity) (Tonelli et al.,

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2008). Studies exploring inflammatory indexes in the OFC under conditions of heightened impulsive behavior (for example induced by stress or drugs of abuse) might test further this idea in rodent models. An additional mechanistic question that arises from these findings, and worthy of further investigation, is how such regionally localized regulation of inflammatory mediators occurs.

Another interesting notion that surfaces from this work is that only a subgroup of animals responded to lithium treatment, suggesting the possibility that individual differences in the expression of impulsivity (well-documented in animal models of impulsive behavior) may affect the response to lithium. This is an area that deserves further investigation, with several intriguing questions still open. For example, what neurobiological mechanisms underlie the individual's impulsivity set-point? How do these mechanisms become challenged or are resistant to therapies like lithium? Is a propensity for proinflammatory activity a contributing element to individual differences in therapeutic success?

Finding molecular endpoints of lithium actions that impact behavioral disinhibition is relevant to the development of improved therapies not only for bipolar disorder but also for other disorders characterized by increased impulsivity, such as addictive behaviors, attention deficit disorder, and pathological gambling. While lithium is a useful and effective drug, it does come with a number of side effects. Efforts are currently being made to establish if lithium-mimetic drugs can be safely used as alternatives to lithium to decrease impulsivity (Barkus et al., 2018), and it will be interesting to see if they too reduce inflammation. If inflammatory events contribute to the exacerbation of impulsive behaviors, it may be useful in the future to explore if selective anti-inflammatory drugs offer benefits, in conjunction with mood-stabilizers, to relieve deficits of impulse-control.

The relationship between impulsivity and inflammation in the brain has scarcely been addressed in animal models, and in this context the paper by Adams et al timely sets the stage for in-depth functional studies to address this complex and clinically significant question.

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