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PERSPECTIVE

Inflammation and lithium: clues to mechanisms contributing to suicide-linked traits

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Suicide is one of the leading causes of death in the United States, yet it remains difficult to understand the mechanistic provocations and to intervene therapeutically. Stress is recognized as a frequent precursor to suicide. Psychological stress is well established to cause activation of the inflammatory response, including causing neuroinflammation, an increase of inflammatory molecules in the central nervous system (CNS). Neuroinflammation is increasingly recognized as affecting many aspects of CNS functions and behaviors. In particular, much evidence demonstrates that inflammatory markers are elevated in traits that have been linked to suicidal behavior, including aggression, impulsivity and depression. Lithium is recognized as significantly reducing suicidal behavior, is anti-inflammatory and diminishes aggression, impulsivity and depression traits, each of which is associated with elevated inflammation. The anti-inflammatory effects of lithium result from its inhibition of glycogen synthase kinase-3 (GSK3). GSK3 has been demonstrated to strongly promote inflammation, aggressive behavior in rodents and depression-like behaviors in rodents, whereas regulation of impulsivity by GSK3 has not yet been investigated. Altogether, evidence is building supporting the hypothesis that stress activates GSK3, which in turn promotes inflammation, and that inflammation is linked to behaviors associated with suicide, including particularly aggression, impulsivity and depression. Further investigation of these links may provide a clearer understanding of the causes of suicidal behavior and provide leads for the development of effective preventative interventions, which may include inhibitors of GSK3.

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INTRODUCTION

In 2010, suicide was the 10th leading cause of death in the United States, accounting for more than 38 000 deaths, the suicide rate increased steadily during the previous 10 years, and an astounding approximately one million people in the US made a suicide attempt (Centers for Disease Control and Prevention website). Thus, it is evident that suicide is a major health problem that is not adequately treated, as well as being poorly understood. Clearly, there is a crucial need to develop improved strategies to understand the conditions that elicit suicidal behavior and to develop effective interventions.

Suicidal behavior is often, but certainly not always, associated with psychiatric illnesses, particularly major depression, bipolar disorder and schizophrenia. For example, a strong association was indicated by the finding that suicide is 60% comorbid with mood disorders,[1] and the risk of suicide is at least 15 times higher in patients with bipolar disorder than for the general population.[2] However, the perplexing question remains as to what differentiates the suicidal person from those with similar conditions that are not suicidal. This issue has led to numerous studies attempting to identify behavioral characteristics that contribute to suicidal behavior. Among the key characteristics that have been identified to be associated with suicidal behavior, impulsiveness, aggression and feelings of helplessness or depression demonstrate particularly strong links.[1,3–9] These associations raise the possibility that identification of mechanisms and therapeutic interventions that regulate these characteristics may provide insight into the causes of suicidal behavior and lead to methods for early detection and intervention. In this regard, there is increasing evidence that abnormal activation of the inflammatory system is linked to each of these individual behaviors in animal models, and to suicidal behavior in humans.

Here, we review evidence suggesting that inflammation may be a key factor precipitating suicidal behaviors in response to initiating stressors, we assess key aspects of suicidal behavior-linked endophenotypes that have been studied in rodents, and we examine the effects of lithium intervention that appears to diminish suicide-linked behaviors.

STRATEGIES TO STUDY SUICIDAL BEHAVIOR IN ANIMAL MODELS

The very nature of suicide limits direct investigation except postmortem, thus gaining a better understanding of suicidal behavior requires the development of indirect strategies. Two feasible approaches include studies in animal models of mechanisms that regulate suicide-associated behaviors, and studies of the mechanism of action of drugs that alter suicidal behavior. Thus, although suicide cannot be directly studied in animal models, rodents can be used to study factors that regulate suicide-relevant behaviors or endophenotypes. Using the endophenotype approach to investigate complex behaviors associated with numerous psychiatric and neurological conditions has been discussed by many investigators in a variety of fields,[10,11] and although not perfect, it remains the primary strategy available for studies in rodents. Thus, a better understanding of suicidal

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behavior may benefit from studies of endophenotypes in rodents, particularly impulsive behavior, aggression and depression-like behaviors that have been linked to suicidal behavior. Another strategy to examine mechanisms regulating suicidal behavior is to consider the actions of an agent that reduces attempted and completed suicides. Substantial evidence demonstrates that lithium, the classical mood stabilizer used to treat bipolar disorder, reduces suicidal behavior and mortality during long-term treatment.[5,12] This conclusion is supported by several meta analyses and has been reported in patients with unipolar and bipolar depression (the patient populations most often treated with lithium), in responders and nonresponders to the mood stabilizing action of lithium, and the antisuicidal effect of lithium is not matched by other mood stabilizers or antidepressants.[6,8,13–16] Furthermore, several studies have found that relatively high levels of lithium in the public drinking water are associated with reduced risk of suicide in the general population.[17] Thus, studies in rodents of individual behaviors associated with suicidal behavior, in conjunction with studies of lithium, which is able to diminish suicidal behavior, provide feasible investigative strategies to better understand the underlying causes of suicidal behavior and to develop effective interventions.

STRESS INDUCES INFLAMMATION WHICH IS ASSOCIATED WITH SUICIDAL BEHAVIOR

Stress is a common precursor of suicidal behavior.[18] Stress also increases inflammation, and inflammation is linked to increased impulsive, aggressive and depressive behaviors, leading to the hypothesis that stress-triggered inflammation has an important role in provoking suicidal behavior (Figure 1). Multiple types of psychological stress have been shown to cause activation of the inflammatory response, which is indicated by elevated levels of inflammatory cytokines.[19–45] However, comparative studies have not been reported to determine if different types of stress induce different patterns of inflammatory cytokine production, and which inflammatory molecules are most closely associated with suicidal behavior. The common finding that stress induces inflammation has been interpreted in evolutionary terms as a logical mechanism to enhance survival. Historically, many stressors had the potential to lead to injury and infection, therefore pre-activation of the immune system would enhance survival and recovery.[46] However, as psychological stress has increased in modern societies, and drugs are available to combat life-threatening infections, these evolutionary mechanisms to improve survival after injury may now have deleterious effects on behaviors, including promotion of multiple suicide-linked behaviors, as discussed below.

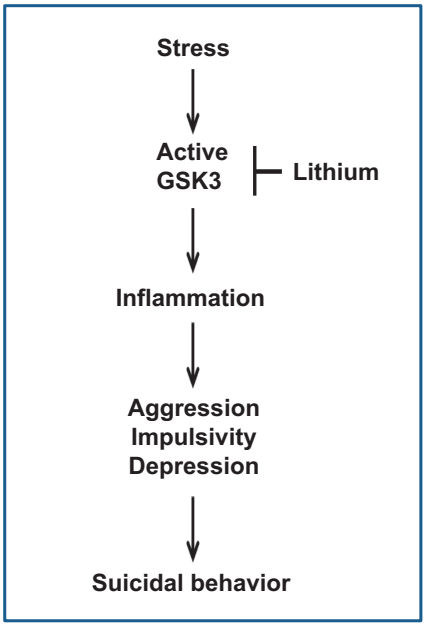

Figure 1. Scheme of a potential mechanistic pathway that may lead to suicidal behavior. The scheme displays a hypothetical component of mechanisms contributing to suicidal behavior. Stress is established to cause activation of GSK3 in rodent brain, and lithium is an established inhibitor of GSK3, which we propose may contribute to its antisuicidal actions. Active GSK3 promotes inflammation, and we hypothesize that inflammation, one of multiple signaling systems regulated by GSK3, contributes to provoking components of suicidal behavior, such as aggression, impulsivity and depression. GSK3, glycogen synthase kinase-3.

Except for the initial insult, stress appears to utilize many of the same mechanisms as pathogens to induce an inflammatory response, although much still remains to be learned about the details of the stress-induced signaling pathway. The stress response is most well-characterized for signaling through Toll-like receptor 4 (TLR4), the receptor for lipopolysaccharide (LPS), which is the most widely used agent to study inflammation experimentally and is the major cause of sepsis. TLR4 is activated by both pathogen-associated molecular patterns of microbes, and insult-induced endogenous ligands, called danger- or damage-associated molecular patterns (DAMPs).[47] DAMPS induce TLR4 signaling outcomes that respond to the need for rapid danger-recovery and restoration of homeostasis.[48] DAMPs that activate TLR4 include a broad range of molecules, such as heat-shock proteins,[49] hyaluronan oligosaccharides,[50] high-mobility group protein box-1,[51] modified lipids[52] and several others, which are produced by a variety of stressors in the central nervous system as well as peripherally. Thus, stress-induced DAMPs can set in motion an inflammatory response that appears to be equivalent to that induced by pathogens. TLR4 is expressed by microglia, astrocytes and neurons, as well as immune cells.[48,53–57] TLR4 expression is dynamic and is often upregulated in conditions that are associated with increased levels of pathogen-associated molecular patterns or DAMPs,[52,58] including evidence of dynamic changes in the expression of TLR4 in the brain. For example, TLR4 expression in rodent brain increased in response to ischemia/reperfusion injury, which was partially attributed to DAMPs arising from oxidative stress.[55,59] Furthermore, chronic mild stress increased TLR4 expression in rat prefrontal cortex,[42] and administration of a TLR4 antagonist reduced stress-induced neuroinflammation.[45] Thus, TLR4 can be activated in response to stress, not only by pathogens, and is involved in stress-induced inflammation, including in the central nervous system.

There is much evidence linking an activated inflammatory response with suicidal behavior. Elevated levels of inflammatory cytokines, particularly interleukin-6 (IL-6), were found in the blood and CSF of patients who attempted suicide compared with nonsuicidal depressed patients and controls.[60–64] Elevated markers of inflammation and microglial activation also were found in postmortem brains of suicide victims.[65–67] Conversely, therapeutic administration of cytokines increases suicide risk.[68–71] Particularly interesting is the recent finding from a postmortem brain study that protein expression of TLR4 is higher in depressed suicide victims than in depressed nonsuicide subjects and controls.[72] Notably, alterations in genes involved in inflammation have been found to be associated with suicidal behavior in multiple studies of potential candidate genes.[73–76] In addition, inflammation activates the enzyme indoleamine-2,3-dioxygenase, which catalyzes the formation of kynurenine, and plasma kynurenine levels were higher in depressed patients with a history of suicide attempts than in nonsuicidal depressed patients and healthy controls.[77] The authors suggested that elevated kynurenine levels may be a marker of suicide attempt risk, independent of depression severity, and that kynurenine metabolites may

contribute to the aggression/impulsivity and neurocognitive deficits proposed as endophenotypes associated with suicidal behavior.[1,18,77–79] Thus, multiple lines of evidence demonstrate a consistent relationship between elevated markers of inflammation and suicidal behavior. Therefore, it is important to identify which components of suicidal behavior may be induced by activation of the inflammatory response.

AGGRESSIVE BEHAVIOR

Aggression has been linked to suicidal behavior in many studies[1,3–5,7,8,79] and an increasing number of reports demonstrate that inflammation is associated with increased aggressive behaviors.[80] Elevated aggressive traits were associated with increased serum TNF,[81] with the inflammatory marker C-reactive protein,[82–84] and with multiple cytokines.[84,85] Increased serum IL-6 levels correlated with personality traits of aggression in healthy controls[83] and with aggression traits in female patients with eating disorders.[86] Furthermore, aggressive traits were increased in patients treated with cytokines therapeutically.[87,88] Thus, in humans, aggressive behaviors are well correlated with increased markers of inflammation.

A few studies of rodents have also examined links between aggression and inflammation. In rodents, aggression is often measured using the social dominance tube test and the aggression test. Mice bred for high aggression had increased cytokine levels[89] and knockout of both tumor necrosis factor receptor-1 and tumor necrosis factor receptor-2 resulted in the remarkable absence of aggressive behavior.[90] Thus, there appears to be a strong link between aggression and activation of the inflammatory system in rodents, but further studies are needed to verify this association and to delineate which inflammatory molecules mediate the interaction and the mechanisms that are involved.

Substantial evidence shows that lithium can reduce aggressive behavior. Lithium is well documented to reduce aggressive behavior in a variety of human populations, for example, children, adults and the elderly, which has been related to its antisuicidal actions.[5,6,8,91,92] As reviewed in detail previously,[5,92,93] many studies have shown that aggressive behavior in rodents also is consistently reduced by lithium treatment. Thus, lithium significantly reduces aggressive traits and inflammation, but these two outcomes of lithium administration have not yet been examined together.

IMPULSIVE BEHAVIOR

As noted in the Introduction, impulsive behavior may frequently be an important component of suicidal behavior. Only a limited number of studies have tested if there is a relationship between inflammation and impulsive behavior. In a study of nearly 5000 individuals, elevated levels of IL-6 were associated with impulsivity-related traits.[94] A novel study of 5652 people over a period of 3 years identified a strong correlation between impulsiveness and increased lymphocyte numbers that are indicative of immune activation, and the authors concluded that 'impulsiveness was a predictor of chronic inflammation'.[95]

Links between inflammation and impulsive behavior appear not to have been examined in animal models, but there is evidence that lithium administration reduces impulsive behavior in humans and rodents. Three controlled studies of lithium in humans concluded that lithium reduces impulsive behavior, but further studies would strengthen this conclusion.[96–98] In rodents, impulsive behavior exemplified by choosing a small or poor reward that is available immediately, in preference to a larger but delayed reward, is often measured using the three-choice serial reaction time task,[99] in which mice are trained to respond to a flash of light occurring in one of three locations with a nose poke, which releases a food reward. In the subsequent test phase, mice are trained to choose between two light cues, one giving a larger food reward than the other. In subsequent trials, the delivery of the larger food reward is delayed, so mice must choose the immediate smaller reward or the delayed larger reward, and wild-type mice predominantly choose the latter. Increased impulsive behavior results in mice choosing the immediate smaller reward rather than the delayed larger reward. There is some indication that lithium treatment reduces impulsive behavior in rodents, but the data are limited. Lithium administration suppressed impulsive behavior in the three-choice serial reaction time task in male Wistar/ST rats, a strain that has been shown to be more impulsive than Lister hooded rats.[100] Lithium reduced premature responses and increased the latency of the correct responses in the three-choice serial reaction time task in male Wistar/ST rats, without affecting response latency and without affecting the amount of food consumption or other motivation-related measures.[101] Lithium also reduced impulsivity in mice in the delay discounting task in which mice receive larger rewards after a delayed response than after an immediate response.[102] Thus, the links between impulsive behavior and inflammation, as well as its control by lithium, remain sparse but supportive of these associations.

DEPRESSIVE BEHAVIOR

Depression is often linked with suicidal behavior, although, in contrast to the commonly held assumption, many suicidal patients are not depressed.[1,4,5,7,9,78,103] There is abundant evidence that inflammation is associated with the onset and severity of depression, as inflammatory molecules are upregulated in the serum and postmortem brains of depressed patients, as discussed in detail in several reviews.[104–109] Furthermore, administration of interferon-α to bolster immunity induces depression in susceptible people.[103,110] Moreover, LPS administration induces symptoms of depression in humans,[111] and a mild stimulation of the primary host defense system has negative effects on emotion, which is thought to be caused by elevated cytokines.[110,112] As noted above, psychological stresses that can induce depression increase inflammatory cytokine production in humans and rodents.[113,114] Inflammation in patients with major depression is associated with resistance to antidepressant treatment, and anti-inflammatory drugs can improve antidepressant actions.[106–108,114-116] Raison and Miller[46] recently summarized results demonstrating that many genetic changes identified in patients with major depressive disorder involve the inflammatory system. In rodents, administration of inflammatory cytokines or the inflammation-stimulant LPS causes depression-like behaviors that are attenuated by antidepressants.[105] Specific inflammatory cytokines that have been identified as promoters of depression-like behavior in rodents include IL-6,[117] TNFα[118] and IL-1β.[119] Thus, there is much evidence that inflammation can precipitate depression and impair therapeutic responses.

Lithium is not used therapeutically as a direct antidepressant, but is often used to augment antidepressants in treatment-resistant depression, and inflammation is reduced by lithium. In mice, lithium has a wide variety of antidepressant-like effects. For example, in mice, lithium administration produces antidepressant-like effects in the learned helplessness paradigm[120] and in the forced swim test.[121] The antidepressant actions of lithium are often attributed to its action as an inhibitor of glycogen synthase kinase-3 (GSK3), as discussed in the following section, because pharmacological or molecular inhibition of GSK3 has similar antidepressant effects in animal models.

GSK3 INHIBITORS REDUCE INFLAMMATION

GSK3 refers to two paralogs, GSK3α and GSK3β, that are encoded by different genes but retain 85% homology and are commonly

referred to as isoforms. GSK3 is primarily regulated by phosphorylation on serine-21-GSK3α and serine-9-GSK3β, which inhibits GSK3 activity. Homozygous GSK3α/β$^{21A/21A/9A/9A}$ knockin mice express both GSK3 isoforms with serine-to-alanine mutations at these sites, S9A-GSK3β and S21A-GSK3α. This maintains GSK3 maximally active, since it cannot be inhibited by serine phosphorylation, but within the physiological range because GSK3 is expressed at normal levels.[122] GSK3 may be a feasible therapeutic target to diminish suicidal behaviors because it promotes several suicide-linked behaviors in rodents and promotes inflammation, and lithium is a well-established inhibitor of GSK3, which may contribute to the capacity of lithium to reduce suicide.

A variety of evidence has raised the possibility that activated GSK3 may contribute to suicidal behaviors. GSK3 is activated in mouse brain by stress,[123] a response that may promote suicide-linked behaviors, and GSK3β activity was found to be elevated in postmortem brains of depressed suicide victims.[124] Clear evidence has demonstrated that GSK3 promotes aggressive behaviors, as reduced expression of either GSK3 isoform decreased aggressive behaviors in mice.[125,126] The contribution of GSK3 to impulsive behaviors has yet to be examined, except for the studies of lithium discussed above, but an evaluation of SNPs in the GSK3β gene revealed that a genetic variability in the GSK3β gene is associated with increased impulsive behavior in patients with bipolar disorder.[127] Many studies have shown that GSK3 promotes depression-like behaviors in rodents.[128] These include clear antidepressant effects of a variety of new small molecule inhibitors of GSK3, in addition to lithium, in rodents,[121,129–132] including on depressive behavior exhibited by tryptophan hydroxylase-2 mutant mice with deficient serotonin.[125] Also, overexpression of a dominant-negative mutant of GSK3 to reduce GSK3 actions promoted resilience in the social defeat stress test of depression-like behavior.[133] In addition, inhibition of GSK3 is required for the rapid antidepressant effect of ketamine in the learned helplessness model of depression in mice.[120] Antidepressants increase serotoninergic signaling, which inhibits GSK3 by increasing its serine phosphorylation, and increase signaling by Wnt2, which inhibits GSK3 in the Wnt signaling pathway.[134,135] Importantly, antidepressants inhibit GSK3 in mouse brain after *in vivo* administration of clinically relevant doses.[125,135] Furthermore, oppositely to inhibiting GSK3, expression of constitutively active GSK3 in mice results in increased susceptibility to stress-induced depression-like behavior in mice.[123]

Lithium is an established inhibitor of GSK3, and lithium and other GSK3 inhibitors are remarkably effective in reducing inflammation. Therapeutic levels of lithium, ~1 mM, inhibit GSK3 both directly[136,137] and by an indirect mechanism that causes increased inhibitory serine phosphorylation of GSK3.[138,139] GSK3 inhibitors have been shown to be effective anti-inflammatory drugs, reducing by 67–90% inflammatory IL-6, IL-1β and TNFα production by microglia,[140] astrocytes,[141–146] human monocytes and peripheral blood mononuclear cells[147] and other immune cells.[143,146–149] Remarkably, *in vivo* administration of lithium provided protection from endotoxin shock sufficiently enough to allow the survival of most mice from an otherwise lethal (LD100) dose of LPS.[147] Thus, GSK3 inhibition effectively reduces inflammation throughout the periphery and the central nervous system.[150] Reduced LPS-induced inflammatory cytokines attained by inhibiting GSK3 was found to be due to inhibition of the transcriptional activity of NF-κB, a transcription factor that mediates upregulation of many inflammatory molecules,[147] in accordance with reports that GSK3 promotes NF-κB activity, as we reviewed.[151] GSK3 inhibitors also block signal transducer and activator of transcription-3 (STAT3) activation, a key transcription factor in inflammatory signaling.[141] Remarkably, GSK3 regulates the anti-inflammatory cytokine IL-10 in an opposite manner, so GSK3 inhibition increases anti-inflammatory IL-10 levels three- to fourfold *in vivo* and *in vitro*.[147] This is mediated by GSK3 inhibition of the CREB and AP-1 transcription factors to reduce their expression of anti-inflammatory IL-10, which underlies the increase in IL-10 levels induced by GSK3 inhibitors.[147,152] The anti-inflammatory actions of GSK3 inhibitors likely contribute to their beneficial effects that have been found in multiple animal models of inflammatory diseases, including endotoxic shock,[147] arthritis and peritonitis,[152,153] endotoxemia,[154] colitis[155] and traumatic brain injury.[156] Furthermore, GSK3 inhibitors alleviate inflammatory disease severity in the mouse model of multiple sclerosis.[146,157]

In summary, GSK3 may be a feasible therapeutic intervention for suicidal behavior. GSK3 is activated by stress, is a strong promoter of inflammation, promotes in rodents aggressive and depression-like behaviors, and is inhibited by lithium, which diminishes suicidal behavior.

PERSPECTIVE

Altogether, there is substantial evidence that suicidal behavior and individual impulsivity, aggression and depression are all associated with increased inflammation, which itself can be induced by stress. Thus, we propose the concept that stress activates GSK3 and induces inflammation, which, in turn, promotes the suicide-linked endophenotypes of impulsivity, aggression and depression-like behaviors. We speculate that different inflammatory molecules are produced following different types of stress and that different inflammatory molecules may mediate each of the behavioral outcomes, perhaps accounting, in part, for why not all suicidal patients exhibit each behavior. Furthermore, it is likely that differential effects of inflammatory molecules on the specific brain regions and neural circuits that mediate each of the suicide-linked behaviors influence the cumulative behavioral outcome, which also must be regulated by genetic and epigenetic characteristics of affected subjects. Identification of the inflammatory and behavioral responses to stress that are attenuated by lithium may begin to provide information about its mechanism for reducing suicidal behavior, and why it is not effective in all patients. Furthermore, we suggest that inhibition of inflammatory signaling and inhibition of GSK3 may provide mechanisms to diminish in tandem both the inflammatory response to stress and suicide-related behaviors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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