HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Biol Psychiatry. 2016 July 01; 80(1): 4–5. doi:10.1016/j.biopsych.2016.04.019.

Inflammasome activation in Major Depressive Disorder: A Pivotal Linkage Between Psychological Stress, Purinergic Signaling and the Kynurenine pathway

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Major depressive disorder (MDD) is the most common psychiatric disorder representing a leading cause of disability worldwide. The clinical and financial burdens of depression go well beyond the neuropsychiatric manifestations, particularly when considering the comorbid conditions of advanced ageing, inflammation, metabolism and obesity. These comorbid conditions appear to arise from common mechanisms of pathogenesis, rather than the symptomatology of depression, as supported by epidemiologic studies, as well as the pathogenic mechanisms involved in these diseases, where stress and inflammation promote both Major Depressive Disorder (MDD) and accelerated aging. The paper by Iwata et al. (1), in this issue, presents novel findings with importance to our understanding of the mechanism whereby psychological stress induces inflammation, depression, as well as associated comorbidities including cardiovascular disease, diabetes, obesity, pain, psoriasis, inflammatory bowel disease, and cancer (2). The authors of this work have previously proposed an “inflammasome hypothesis” through which the protein complex known by this name is responsive to both pathogens as well as cell damage and stress, including the sensing of extracellular ATP (3). Through the induction of the inflammasome cascade, psychological stress has been proposed to promote both depression as well as peripheral comorbid conditions (3). The work presented here provides important new data in an animal model in further support of the inflammasome hypothesis demonstrating first, that psychological stress induces the release of extracellular ATP, and furthermore, the interaction of extracellular ATP with purinergic type 2X7 receptor mediates the activation of the NLRP3 inflammasome cascade, with the resultant release of IL-1β and further activation of Tumor Necrosis Factor alpha (TNFα). The results presented in this article also further support the conclusions of previous in vivo studies by this same group demonstrating the role of P2X7 receptor antagonists in modulating responses to stress and associated depression (3).

This study by Iwata et al., demonstrates that glutamate, rapidly released during stress, stimulates the release of ATP from astrocytes, as an initiating step in the pathogenesis of

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Conflicts of Interest: There are no conflicts of interest to disclose related to this work by any of the authors.

MDD (1). This step appears to provide a bridge between important upstream and downstream events as we discuss here. ATP release into the extracellular space is usually mediated by three major mechanisms including vesicular transport, cell death and opening of a hemichannel. Interestingly, opening of Connexin 43 (CX43) and Pannexin1 (Panx1) hemichannels in astrocytes has been described to increase during stress, with the resulting release of both ATP and glutamate, thus, identifying the possible mechanism of ATP and glutamate secretion during stress (4). Furthermore, since blocking both P2X7 and NMDA resulted in a reduction in both CX43 and Panx1 hemichannel activity, specific receptors for ATP and glutamate appear to positively regulate the release of these molecules. This evidence helps elucidate a potential stress pathway in which the onset of stress activates NMDA and P2X7 receptors resulting in hemichannel opening and the release of gliotransmitters such as ATP and glutamate, promoting a chain of events resulting in the development of depression as well as other comorbidities.

As the Iwata paper demonstrates, inflammasome activation (as determined by IL-1β release) occurs rapidly and somewhat transiently in response to stress-induced ATP release, followed by subsequent TNFα activation/secretion (1). TNFα appears to be activated to a higher percentage of baseline level, but also importantly remains elevated for a longer duration. TNFα, therefore, may both amplify and prolong the initial stress response. Recent studies, demonstrate the role of TNFα in mediating stress-induced depression by upregulating the enzyme indoleamine 2,3-dioxygenase (IDO), the first step in tryptophan catabolism, in a mouse model of chronic stress (5). Excess tryptophan catabolism, induced by TNFα, would then directly promote depression in part by reduced serotonin production from 5-hydroxytryptophan, and/or potential effects of dysregulation via kynurenine metabolites. It is likely therefore, that the longer-term effects initiated by stress, the NLRP3 inflammasome and IL-1β, are mediated by TNFα-induced tryptophan catabolism via the kynurenine pathway.

The intimate linkage of these pathways discussed above, likely presents a rationale and mechanism for the close association between MDD and comorbid conditions associated with inflammation and accelerated aging. The serum of patients with depression demonstrates an increase in proinflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) (6). It is worth noting that IFNγ and TNFα are two potent cytokines involved in the upregulation of IDO and the consequent promotion of tryptophan catabolism. Since quinolinic acid is a downstream metabolite of the kynurenine pathway and agonist of glutamate receptors (capable of inflammasome activation), tryptophan catabolism may serve to further exacerbate the initiating stress response via a vicious cycle involving the NLRP3 inflammasome cascade, with further TNFα-induced tryptophan catabolism. In support of this notion, deregulation of kynurenine metabolites, with increases in quinolinic acid are particularly evident in suicidal patients (7). The linkage of these pathways further provides a rationale for the development of comorbid conditions in patients with depression as well as the development of depression in patients with other initiating inflammatory conditions.

Since tryptophan catabolism via the kynurenine pathway ultimately provides for *de novo* NAD^+ synthesis, it is possible that increased NAD^+ hydrolysis and/or turnover may be

contributory in driving tryptophan breakdown. If NAD^+ levels were to be compromised, this would further promote inflammation and IDO activation, since the action of Sirtuin 1 (SIRT1) an NAD^+ dependent histone type III deacetylase, modulates the activity of NF-κB (8), a transcription factor involved in TNFα induction of IDO. SIRT1 has been associated with protection from both senescence as well as with several MDD comorbidities such as cardiovascular disease, obesity and diabetes (9). Indeed, several SIRT mRNAs appear to be reduced in states of depression in patients with MDD, suggesting an additional, yet inter-related mechanism for reduced control of inflammation (10).

The common pathobiology and epidemiologic convergence of stress, inflammation, and comorbid inflammatory conditions is particularly striking and emphasizes the need to address mental and physical disorders, including depression, from psychiatric, immunologic, and biochemical perspectives. Toward this end, the paper by Iwata et al., provides a major step forward in our understanding of the pathogenesis of major depression. These findings and the discussion herein, point to multiple targets for therapeutic intervention, including Pannexin channels, modulation of the purinergic receptor P2X7, the cytokines IL-1β, TNFα, IFNγ, and their cognate receptors, tryptophan catabolism and its effect on serotonin synthesis, NAD^+ metabolism, and/or sirtuins, may provide important targets for therapeutic intervention in MDD. Here we suggest a relationship between initiating stressors, inflammation, and a vicious cycle linking the inflammasome, the kynurenine pathway, major depression and other comorbid conditions. Furthermore, factors that are involved in the initiation, maintenance, and exacerbation of depression may represent distinct yet interrelated steps in the molecular pathogenesis of MDD. Thus, an increased understanding of the pathobiology of major depressive disorder and comorbid inflammatory conditions may permit more effective and personalized strategies to patient care.

Acknowledgments

JR is supported by R01 (RO1MH101010) and PO1(P01MH105303) grants from the National Institute of Mental Health. SV is supported by a NIDA supported Ruth L. Kirschstein Train grant (T32 DA007237, Unterwald, PI).

References

1. Iwata M, Ota KT, Li XY, Sakaue F, Li N, Dutheil S, et al. Psychological Stress Activates the Inflammasome via Release of Adenosine Triphosphate and Stimulation of the Purinergic Type 2X7 Receptor. Biol Psychiatry. 2015
2. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140:774–815. [PubMed: 24417575]
3. Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav Immun. 2013; 31:105–114. [PubMed: 23261775]
4. Orellana JA, Moraga-Amaro R, Diaz-Galarce R, Rojas S, Maturana CJ, Stehberg J, et al. Restraint stress increases hemichannel activity in hippocampal glial cells and neurons. Front Cell Neurosci. 2015; 9:102. [PubMed: 25883550]
5. Liu YN, Peng YL, Liu L, Wu TY, Zhang Y, Lian YJ, et al. TNFalpha mediates stress-induced depression by upregulating indoleamine 2,3-dioxygenase in a mouse model of unpredictable chronic mild stress. Eur Cytokine Netw. 2015; 26:15–25. [PubMed: 26083579]
6. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:201–217. [PubMed: 15694227]

7. Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Traskman-Bendz L, Guillemin GJ, et al. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. Brain Behav Immun. 2015; 43:110–117. [PubMed: 25124710]
8. Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004; 23:2369–2380. [PubMed: 15152190]
9. Yao H, Rahman I. Perspectives on translational and therapeutic aspects of SIRT1 in inflammaging and senescence. Biochem Pharmacol. 2012; 84:1332–1339. [PubMed: 22796566]
10. Abe N, Uchida S, Otsuki K, Hobara T, Yamagata H, Higuchi F, et al. Altered sirtuin deacetylase gene expression in patients with a mood disorder. J Psychiatr Res. 2011; 45:1106–1112. [PubMed: 21349544]