NEW PERSPECTIVE ARTICLE

Neuroimmunological Responses to Social Isolation
Respuestas neuroinmunes al aislamiento social

Received: 15-XI-2015 Accepted: 16-XI-2015 Published Online First: 20-XI-2015

DOI: http://dx.doi.org/10.15517/ijds.v0i0.22032

ABSTRACT

Objective social isolation and perceived social isolation are psychosocial stressors that may impair the normal functioning of the neuroimmune system. Chronic activation of the neuro-immuno-endocrine communication and the consequent loss of homeostasis may lead to the appearance of pathologies and associated mood disorders. For example, alterations in the hypothalamic-pituitary- adrenal axis and sympathetic nervous system dynamics may account for the observed predisposition to inflammatory diseases following chronic social stress. Therefore, it is necessary to further study the underlying mechanisms in social isolation in order to prevent its deleterious effects on health. The objective of this New Perspective article is to supplement the understanding of the neuroimmunological responses to social isolation and provide a basis for future research in this topic.

KEYWORDS

Social isolation, Psychosocial stress, Neuroimmune responses.

RESUMEN

El aislamiento social objetivo y el aislamiento social percibido son estresores psicosociales que pueden afectar el funcionamiento normal del sistema neuroimmune. La activación crónica de la comunicación neuro-imuno-endocrina y la consequente pérdida de la homeostasis puede llevar a la aparición de patologías y desórdenes del comportamiento asociados. Por ejemplo, se puede atribuir las alteraciones en la dinámica del eje hipotalámico-pituitario-adrenal y el sistema nervioso simpático a la predisposición de enfermedades inflamatorios que se observa luego del estrés social crónico. Por lo tanto, es necesario estudiar más a fondo los mecanismos subyacentes del aislamiento social, con el fin de prevenir sus efectos adversos en la salud. El objetivo de este artículo de Nueva Perspectiva es suplementar el entendimiento de las respuestas neuroinmunológicas al aislamiento social y proveer una base para futuras investigaciones en este tema.

PALABRAS CLAVE

Aislamiento social, Estrés psicosocial, Respuestas neuroinmunes.

Objective social isolation and perceived social isolation are sources of psychosocial distress and have been associated with increased disease-related mortality and susceptibility to cardiovascular and neurological diseases (for review see Friedler et al., 2015). Perceived social isolation has been described as "how individuals evaluate their level and quality of social contact and engagement", while objective social isolation refers to the lack of social contacts (Victor et al., 2003). Large clinical epidemiological studies and pre-clinical research have reported detrimental effects of isolation on human and animal health (Friedler et al., 2015). The negative health consequences could be explained by potentially linking objective social isolation and perceived social isolation to the continuous activation of the stress-responsive hypothalamic-pituitary-adrenocortical (HPA) and sympathetic-adrenomedullary-endocrine systems, along with the sympathetic and parasympathetic nervous systems. Each may be a probable mechanism that mediates changes in systemic inflammation as well.

Psychosocial stressors stimulate the activation of the HPA axis and sympathetic nervous system, resulting in elevated levels of circulating glucocorticoids and catecholamines (Wohleb et al., 2015; Ramirez et al., 2015). For instance, chronic social isolation is a potent psychosocial stressor that activates the HPA axis promoting increased levels of corticotrophin-releasing hormone, adrenocorticortropic hormone, and corticosterone (Serra et al., 2005). Additionally, social isolation in rats leads to an extended exposure to glucocorticoids due to HPA axis hyperactivation (Butler et al., 2014), perhaps reducing the sensitivity of immune cells to anti-inflammatory feedback, which may contribute to inflammatory diseases.

Some of the immune effects of psychosocial stress have been characterized in animal studies (Ramirez et al., 2015; Wohleb et al., 2015). For example, social defeat, a pre-clinical model of psychosocial stress in mice, results in a shift of myelopoiesis and hematopoiesis with an increased production and egress of pro-inflammatory and glucocorticoid-resistant myeloid progenitor cells from the bone marrow into circulation and other organs such as the spleen and the brain (Wohleb et al., 2015). It is feasible social isolation may incite as well myelopoietic changes. Social defeat-induced shift in myelopoiesis is paralleled with increased IL-6 in plasma (Ramirez et al., 2015). Similarly, social isolation has been linked to elevated IL-6 concentrations in serum (Loucks et al., 2006).

Evaluation of adult leukocyte gene profile in perceived social isolation found a significant increase in pro-inflammatory gene expression in these cells and a decreased antiviral gene expression in these individuals (Cole et al., 2007). Moreover, it has been reported perceived social isolation is associated with a lower natural killer cell activity and augmented levels of Epstein Barr Virus antibodies in circulation (Glaser et al., 1985; Kielcot-Glaser et al., 1984). These data suggests that social isolation imparts immunological changes, increasing the risk of infections.

The immune dysfunction promoted by psychosocial stressors results in deleterious inflammation in the peripheral immune system that is propagated to the central nervous system through microglia activation and production of pro-inflammatory molecules in the brain (Wohleb et al., 2015). Stress-induced monocyte infiltration to the brain parenchyma and perivascular spaces (Ramirez et al., 2015) likely potentiates neuroinflammatory signaling through afferent neuroimmune communication pathways. In fact, it has been shown social isolation causes increases in brain IL-1ß, which is related to increases in cytokines in plasma (Maier 2003). The enhanced expression of IL-1 ß is probably paralleled by an elevated expression of other pro-inflammatory

cytokines and chemokines that stimulate the recruitment of peripheral-derived monocytes with an inflammatory phenotype. This stress-induced neuroinflammatory profile is likely mediated by the activation of microglia and brain macrophages, since these cells are the main regulators of the inflammatory response in the central nervous system (Wohleb et al., 2015). Microglia activation induced by objective social isolation and perceived social isolation are relevant since these cells may be more reactive if an immune challenge is given. For instance, ex-vivo mitogen-stimulation of microglia from socially defeated animals expressed exaggerated mRNA levels of IL-1ß, IL-6, and TNF-α even 24 days after stress cessation (Ramirez et al., 2015).

Enhanced neuroinflammatory signaling due to stress-associated immune dysregulation may precipitate the neurobiology of mood disorders as well (Wohleb et al., 2015). Stress-induced depressive-like behavior has been linked with an enhanced production of pro-inflammatory cytokines in both the peripheral immune system and in the central nervous system, paralleled with an increase of HPA axis products (Ramirez et al., 2015). Also, objective social isolation and perceived social isolation are stressors that have been associated with anxiety (Cruces et al., 2014).

The augmented expression of pro-inflammatory molecules in the brain associated with stress may lessen the expression neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which may provoke neurogenic deficits and neuronal atrophy (Koo and Duman 2008). Also, pro-inflammatory cytokine production may reduce neurogenesis (Monje et al., 2003). In fact, social isolation in a pre-clinical model of stroke induced depressive symptoms and decreased levels of BDNF and neurogenesis two months after the challenge (Friedler et al., 2014). Perturbations of neuronal plasticity by chronic stress such as social isolation may impart changes in cognition and may contribute to more devastating forms of cognitive deterioration including dementia and Alzheimer's disease.

Given the risk for morbidity and mortality associated with objective social isolation and perceived social isolation (Friedler et al., 2015), more investigation is needed to determine the extent of immunological changes elicited by these two stressors. It is apparent cytokines play a potential role in the physiological processes that link objective social isolation and perceived social isolation with increased risk for disease and mental health disturbances.

In consideration of these findings, objective social isolation and perceived social isolation can contribute to illness processes through the influence of psychosocial stress. Future research should further characterize how these two psychosocial stressors affect neuroimmune pathways and associated social deficits. Chronic activation of physiological pathways could end up compromising health over time. Thus, identifying intervening neuroimmune mechanisms to help explain why these stressors contribute to diverse diseases may help bridge the gap between epidemiological and biological levels of analysis. Finally, it would be valuable to elucidate the underlying mechanisms by which immunity is affected by objective social isolation and perceived social isolation in order to target and prevent the detrimental health effects in these patients.

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Karol Gabriela Ramírez Chan DDS, MSc, Phd[1]

1. Profesora, Departamento de Ciencias Restaurativas, Facultad de Odontología, Universidad de Costa Rica, Costa Rica. Investigadora Asociada, Laboratorio de Investigación y Capacitación en Ciencias de la Facultad de Odontología (LICIFO), Facultad de Odontología, Universidad de Costa Rica, Costa Rica. Investigadora Asociada, Centro de Investigación en Neurociencias, Universidad de Costa Rica, Costa Rica.

E-mail address: karol.ramirez@ucr.ac.cr, Phone: (506) 2511-8022, Fax: (506) 2511-4827.