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PhD Candidate

Social Stress Induces Immunoenhancement During Allergic Airway Inflammation and Infection

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VITA

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ABSTRACT

Stress is commonly considered to be immunosuppressive, but in some disease states like asthma or infection stress can be immunoenhancing. The immunoenhancement has been associated with glucocorticoid resistance in immune cells that renders the cells insensitive to the anti-inflammatory effects of glucocorticoids. A unique murine social disruption stress paradigm, SDR, can model the stress-induced glucocorticoid resistance and exacerbation of inflammation, which can be relevant to inflammatory diseases in humans. In the context of SDR, stress enhances inflammation and delays resolution in an Aspergillus fumigatus (Af) allergic airway inflammation model. In stressed and Af challenged mice, gene expression data suggested increased inflammation (IL-1β, TNF-α, GM-CSF) with histology confirming the increase was due to infiltrating inflammatory cells. Furthermore, stress and Af challenge most prominently increased granulocytes in the lung compared to controls. Bone marrow chimeras demonstrated that the increase in immune cells was bone marrow-derived, and that stress induced myeloid progenitor cell egress and trafficking to lung. Closer examination of the granulocytic population, identified many as neutrophilic. Using the antibodies to CD16 and CD49d, several distinct neutrophil populations were visualized including apoptotic, mature, activated, or immature neutrophils. Stress and Af challenge significantly increased the immature neutrophil population in both the lung and blood. In the clinic, it has been shown that a rapid release of immature neutrophils from the bone marrow can occur during times of stress and immune challenge. The consequences of this state of neutrophilia on disease are still being determined, but it is known these neutrophils have a higher capacity to induce inflammation and exacerbate patient symptoms. Neuropeptide Y (NPY), norepinephrine (NE), and IL-1β are putative mediators in the periodontal inflammatory and stress responses. NPY, via Y1 receptors (Y1Rs), modulates NE that subsequently modulates cytokines like IL-1β via β-adrenergic receptors (βARs). In turn, IL-1β modulates NPY and NE via IL-1 receptor type 1 (IL-1R1) to precipitates inflammation. We examined the consequences of Y1R, β-AR, and IL-1R1 in a murine model of periodontal inflammation and in stress-exacerbated inflammation. We antagonized the Y1R or βAR or used IL-1R1 knockout mice in the absence or presence of SDR. Porphyromonas gingivalis (P. gingivalis) or vehicle
was injected into calvarial tissue of Y1R or βAR antagonized or IL-1R1 knockout non-stressed mice or SDR mice. After 24 hours, proinflammatory gene expression was determined. Y1R or βAR antagonist-treated *P. gingivalis*-infected mice had increased expression of proinflammatory cytokines compared to vehicle-treated *P. gingivalis*-infected mice. In non-infected animals, SDR increased proinflammatory gene expression as compared to control mice. In infected animals, SDR further exacerbated *P. gingivalis*-induced proinflammatory gene expression as compared to control animals, and this increase was abrogated by blocking Y1Rs and β-ARs during stress. IL-1R1 deficiency abrogated proinflammatory cytokine expression in non-stressed or stressed conditions. Altogether, the Y1R, βAR, and IL-1R1 are important mediators in inflammatory and stress-exacerbated inflammatory processes, thus elucidating potential mechanisms for the connection of stress to periodontal inflammation. Overall, stress enhances disease states such as allergic airway inflammation and periodontal inflammation through increased immune cell trafficking and through neuronal systems.
RECENT PRESENTATIONS

Reader BF. Neuropeptide Y Y1, IL-1RI, and Adrenergic Receptors Modulate P. gingivalis-Induced Inflammation. American Association for Dental Research/National Institutes of Health Dental and Craniofacial Research Conference. Tampa, FL. March 21, 2012.

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