The Role of Neuropeptide Y and its Receptors in the Immune System and Immune Disorders

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LAY SUMMARY

A Molecular Link Exists Between Stress and Immune Suppression: Does it Contribute to Disease?

A hormone secreted during psychological stress that interferes with immune defenses has recently been found. Researchers will examine in mice how this relationship works at a molecular level and explore whether it may play a role in autoimmune diseases, inflammatory diseases, or possibly even schizophrenia.

The investigators have discovered that a neuropeptide (called neuropeptide Y, or “NPY”), a hormone secreted during psychological stress, interferes with immune responses in two ways. First, Y1 receptor signaling inhibits responses by “innate” immune sentries. These are the body’s first line defenders, which recognize an invader and summon “adaptive” immune cells to attack. Second, Y1 receptor signaling suppresses activation of these adaptive immune lymphocytes. This finding links the hormone and its receptor with immune suppression. Although NPY and its Y1 receptor are not produced in the immune system, they may play an immune regulatory role that is as important as that of conventional immune factors.

Now, using animal models, the researchers will see what other immune functions the NPY/Y receptor system, and a related peptide, called “PYY,” may control. They will assess how these newly discovered immune functions fit with known processes of immune regulation. Additionally, they will explore whether malfunctions in these regulatory processes may be related to immune cell destruction of the body’s own tissues as occurs in autoimmune diseases (in which immune cells errantly attack the body’s own tissues), or in inflammatory diseases.

Significance: The discovery of a molecular link between stress and immune suppression opens up new avenues for exploring the role of stress in diseases in which immune responses are inadequate. It also suggests the possibility of developing therapeutic approaches, outside the immune system, for suppressing immune attacks against the body’s own tissues that occur in autoimmune diseases.

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The primary role of the immune system is the containment of pathogens, cancer cells, and infections. It also plays a role as a sentinel, preventing the emergence of abnormal lymphocytes, which can attack tissues and cause autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis. Stress and strong emotional episodes dramatically reduce our resistance to infection, and sometimes cancer. Yet, up until now, the relationship between our mental state and our immune defences is still not known. At the Garvan Institute, we recently discovered that neuropeptide Y (NPY), a hormone secreted during psychological stress, interferes with immune defences and inhibits the response of important immune cells via the Y1 receptor. This was an important discovery as, for the first time, we established a new link between psychological stress and immuno-suppression.
Using unique animal models, we propose to dissect the NPY/Y receptor system further and uncover additional immune functions controlled by NPY and a related ligand peptide YY (PYY) via each of their 5 shared Y receptors, in the normal immune system. We will assess how these new immune functions fit with known immuno-regulatory systems and whether their dysregulation may contribute to some immune diseases. We will investigate how Y1 receptor signalling on immune cells interferes with signalling via conventional immune receptors, thereby identifying potentially useful new therapeutic targets. Finally, as several human psychological and neurological disorders are associated with immune disorders, we will investigate the status of the NPY/Y1 system in these patients and also investigate the possibility of an association between some autoimmune/inflammatory diseases with a dysregulation of the NPY/Y1 system.

Findings from this work will help us design an entirely new generation of future immuno-therapies which will offer the possibility to intervene two ways: either interfere with the NPY system and immuno-stimulate individuals undergoing severe psychological stress, or take advantage of the inhibitory role of NPY and its receptors to regulate exacerbated immune responses in inflammatory and autoimmune diseases.