Neuroinflammation in Alzheimer’s Disease and Major Depression

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Alzheimer’s disease (AD) is an irreversible progressive neurodegenerative disorder and the major cause of dementia. The disease symptoms in sporadic cases usually start after the age of 60. Time between the first expression of behavioral disease symptoms and death might be up to 10 years. Thirty-five million people worldwide are estimated to suffer from AD, and in the United States alone 5.3 million people are diagnosed with the disease. According to the World Health Organization, AD is the fifth leading killer, and presently there is no cure for the disease.

The core symptom of AD is impaired cognitive function. Alzheimer’s disease brain pathology is characterized by extracellular depositions of amyloid-β, intracellular aggregates of the protein τ, and loss of cholinergic forebrain innervation. These neuropathological hallmarks of AD are mainly present in brain regions involved in cognition, like cortex, hippocampus, and amygdala.

Besides neuronal loss and protein deposits in the brain, inflammatory processes play an important role in AD. Although inflammation per se is a protective reaction of the body against intruding parasites, bacteria, or viruses, inflammation is also a major component of chronic degenerative diseases. In fact, investigating immune responses in brain diseases is a relatively new science, mainly because the brain was considered an “immune privileged site.” Today, we know that almost all components of the immune system are also present within the brain.

Microglia are the macrophages of the brain and comprise 10%-12% of the total cell number of the brain (1). Within the brain, microglia strongly interact with astrocytes, neurons, and blood vessels. After injury or stress, microglia get activated, their morphology is changed, and they start to secrete proinflammatory cytokines.

Prolonged inflammation, such as interleukin (IL)-1, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ), coordinate the local and systemic inflammatory response to pathogens (2).

The innate immune response is paramount in maintaining tissue homeostasis. Therefore, not all immune responses should be considered per se as damaging. This is especially clear for the cytokine TNF-α and its receptors. Upon local challenges such as ischemia (in stroke) or amyloid precipitations (in Alzheimer’s disease), TNF and its receptors become strongly expressed. Tumor necrosis factor does not necessarily damage brain tissue via activating TNF receptor 1. Stimulation of TNF receptor 2 by TNF antagonizes TNF receptor 1 death signals by inducing a neuroprotective signaling cascade that requires the activation of protein kinase B/Akt and nuclear factor κB (3).

Neuroinflammation plays an important role in AD as well as in depression. Alzheimer’s disease is often accompanied by symptoms of depression, anxiety, irritability, and mood instability. In many cases, patients have undergone long-time treatments against these psychiatric symptoms before being clinically diagnosed for AD. In those cases, anxiety or depression is not just a side effect of AD but rather an integral part of the typical behavioral symptoms. Interestingly the affective status might even be of predictive value for disease development.

It is well-established that indoleamine 2,3-dioxygenase (IDO) is induced under several pathological conditions, including AD. Reduction of tryptophan levels by IDO activity affects serotonin (5-HT) synthesis, which is implicated in a variety of psychiatric disorders, but also affects cerebral plasticity, because 5-HT can increase production of neurotrophic peptides, such as brain-derived neurotrophic factor. Finally, the end product of the catabolic tryptophan pathway, induced by IDO, is a neurotoxic activator of the α-methyl-D-aspartate receptor, called quinolinic acid. This factor can also contribute to excitotoxic effects in neurodegenerative diseases. These observations suggest that the tone of cerebral 5-HT should be kept within a narrow range, because deranged 5-HT levels compromise various brain functions. There is mounting evidence that IDO is a prominent player in the relation between chronic inflammation and depression, as we know from the effects on IDO of toxins like lipopolysaccharide or proinflammatory cytokines, such as TNF-α and IFN-γ. Both experimental (4) as well as clinical studies point to a role of IL-2, IFN-α, or IFN-β in major depressive disorders (5,6).

Su et al. (7) report in this issue of Biological Psychiatry that 28% of the patients with a chronic viral hepatitis C infection, treated with IFN-α, developed depression. In this study they showed that two enzymes, phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2), which are involved in the metabolism of polyunsaturated fatty acids, are critically involved in cytokine-induced depression and sickness behavior. They also showed that the genetic variations of the PLA2 and the COX2 genes increase the risk of IFN-α-induced depression as well as in major depression unrelated to cytokine treatment. These genetic effects seem to be mediated by the regulation of the polyunsaturated fatty acid levels. The PLA2 “at risk” genotype is associated with higher PLA2 activity, subsequently with lower eicosapentaenoic acid levels, which could explain the higher risk of developing IFN-α-induced depression. In control studies, lower eicosapentaenoic acid levels were reported to be associated with an increased risk of major depression. This genetic variation was also related to more somatic symptoms of depression. The COX2 “at risk” genotype was found to be associated with lower docosahexaenoic acid levels, which is consistent with other studies showing lower docosahexaenoic acid levels in patients with major depression.

One of the strongest factors involved in IFN-α-induced depression is higher depressive symptoms at baseline. However, there are no differences in the baseline Beck Depression Inventory scores between “at risk” or “low risk” genotypes of PLA2 and COX2 genes. This indicates that, specifically in response to IFN-α, these genes increase the risk of developing depression (7).

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Received Jan 22, 2010; revised Jan 26, 2010; accepted Jan 27, 2010.
In this same issue of *Biological Psychiatry* Baune et al. (8) report their observations on cytokines and inflammatory processes in major depression. They have investigated the negative effect of the IL-1β gene on pharmacological response and amygdala and anterior cingulate cortex function. Their findings show that two genetic variants of the IL-1β gene increase the risk of nonremission over 6 weeks of antidepressant treatment in major depression. The IL-1β was also described to reduce tryptophan levels and therefore to affect 5-HT synthesis. The effect of the gene variations as described by Baune et al. on IL-1β levels in vivo, however, is not yet clear.

Conclusions on the generally presumed relationships among brain inflammatory processes, lower tryptophan and 5-HT, and depression should be drawn with the necessary precautions. In patients with low blood tryptophan in the circulation due to excessive peripheral degradation of the amino acid via IDO, depression was not the major psychopathology. Rather, aggressiveness and lack of impulse control correlated with low tryptophan levels in the circulation (9). These observations might either point to possibly differential consequences of peripheral and cerebral effects on mood or the way depression is being assessed and diagnosed.

In summary, there is growing evidence that inflammatory processes play a key role in major depression as well as in neurodegenerative diseases like AD and might be partly responsible for the depression symptoms in AD patients. Interestingly, it was recently shown in a mouse model of AD that imipramine, a tricyclic antidepressant (10), can prevent cognitive decline and amyloid-β accumulation by TNF-α inhibition.

*Mrs. Dobos and Drs. Korf, Luiten, and Eisel reported no biomedical financial interests or potential conflicts of interest.*