New research shows how chronic stress worsens neurodegenerative disease course

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The evidence is accumulating on how bad stress is for health. Chronic stress can intensify inflammation and increase a person's risk for developing central nervous system infections, neurodegenerative diseases, like multiple sclerosis (MS), and other inflammatory diseases, say researchers presenting at the 115th Annual Convention of the American Psychological Association (APA). These researchers have demonstrated for the first time that stress-related increases in central nervous system inflammation are behind the adverse effects of stress in an animal model of MS.

Researchers from Texas A & M University used mice to show what role social stress plays in the immune process to influence the course of an MS-like disease. They proposed that stress-induced increases of pro-inflammatory cytokines, which are proteins that regulate immune and inflammatory functions, inhibit the clearing of a virus and allow the inflammatory process to run amok. Stress, say the authors, may interact with viral infections to increase vulnerability to diseases such as MS. Meta-analysis of studies investigating the impact of stressful events in patients with MS show an increased risk of worsening symptoms of the disease.

In a series of experiments on mice, the authors showed that increases in a particular cytokine – interleukin-6 (IL-6), which is released during stress and regulates the part of the immune system that fights infection – can make socially stressed mice vulnerable to MS-like illnesses.

The researchers used a social disruption model (SDR) to simulate social stress for mice and then infected the mice with Theiler's murine encephalomyelitis (TMEV). Infection with TMEV results in an acute infection of the central nervous system followed by a chronic autoimmune disease similar to that seen in humans with MS. Their laboratory has previously shown that exposure to social stress prior to infection exacerbates both the early viral infection and the later autoimmune demyelinating MS-like phase of the disease.

To create a stressful environment, researchers housed three young male mice together for several weeks. After the mice established a stable social hierarchy, researchers introduced an older aggressive male into the residence for a couple of hours. The intruder exhibits aggressive behavior – posturing, fighting, wounding, pursuit – that results in submissive behaviors and social defeat in the younger resident mice. This procedure was repeated for three consecutive nightly two-hour sessions with one night off, followed by an additional three nightly sessions. To keep the mice from getting used to the intruder, a new intruder was introduced for each session.

What they found was this stress appears to elevate levels of IL-6, which subsequently increases the severity of the MS-like illness. Furthermore, using specific IL-6 neutralizing antibody treatments during the stress exposure can prevent the stress-related worsening of the disease, said the authors.

In one experiment, they showed that mice exposed to social disruption had elevated central and peripheral levels of IL-6. However, infusing the neutralizing antibody into the brain prevented this stress-induced increase in IL-6. This demonstrated that the antibody could effectively reverse the stress-related increases in IL-6 in brain and in circulating blood.

Results from a second experiment showed that administering the IL-6 neutralizing antibody during the stress exposure prevented worsening of the TMEV infection. By blocking the stress-induced elevation of IL-6, TMEV infection was weakened, which lessened some of the disease symptoms, such as motor impairment, inflammation in the brain and spinal cord, and the viral level in the central nervous system. Based on these findings, Dr. Mary Meagher, the lead researcher, proposes that the adverse effects of stress-induced IL-6 on TMEV infection are enough to create a pro-inflammatory environment that interferes with the immune response to infection. Because the early immune response shapes the later specific immune response to infection, impairment of the early response could account for the increased viral level, prolonged viral infection, increased CNS inflammation, and the subsequent exacerbation of the chronic autoimmune disease.

There is a growing body of evidence in both animal and human studies that suggests that exposure to stress can increase and sustain the release of pro-inflammatory cytokines following an assault on the immune system. Thus, the present findings might help scientists unravel which biobehavioral mechanisms offset the adverse health effects of chronic social stress in humans. “Similar to mice exposed to repeated social defeat by an aggressive intruder, people exposed to chronic social conflict experience high levels of stress and consequent dysregulation of the immune system, thereby increasing vulnerability to infectious and autoimmune disease,” said Meagher. “The cytokine response during chronic stress appears to play a key role in exacerbating the acute CNS infection and the development of subsequent autoimmune responses.”

Furthermore, interventions that prevented or reversed the stress-induced increases in IL-6 in the mouse model may have implications for humans, said Meagher. It is possible that the adverse effects of social conflict on people who are vulnerable to certain inflammatory diseases may be prevented or reversed by treatments aimed at blocking increases in this

cytokine. Recent evidence suggests that some potential interventions include certain anti-inflammatory drugs, exercise, antidepressant medication, omega-3 fatty acids, and mindfulness relaxation training. However, human clinical trials are needed to fully evaluate this issue.

Source: American Psychological Association