New insights into autoimmunity and depression

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Systemic lupus erythomatosus (SLE), often simply called lupus, is a complex autoimmune disease marked by joint pain, skin rashes, extreme fatigue, and depression, among other symptoms. Some studies have described a possible link between SLE's most severe psychiatric manifestation, psychosis, and a protein autoantibody associated with the central nervous system, anti-ribosomal P.

To investigate how an autoantibody could stimulate behavioral changes by interaction with the brain, researchers at Tel Aviv University set out to induce depressive hallmarks in mice. Their findings, presented in the March 2007 issue of *Arthritis & Rheumatism*, shed light on the brain pathways of depression in general and in central nervous system dysfunction in SLE in particular.

Healthy female mice received injections, directly into the brain, of human anti-ribosomal P antibodies extracted from the blood sample of an SLE patient. For control purposes, equal numbers of mice were injected with normal human immunoglobin G. All the mice were then subjected to a series of tests: a forced swimming test in a glass beaker partially filled water to evaluate escape-oriented behaviors, such as rearing and jumping; rotarod and grip strength tests to gauge motor function; a staircase test; a swim T-maze test to assess cognitive function; and a passive avoidance test to measure the ability of mice to remember a foot shock delivered 24-hours earlier.

Depression-like behavior was strongly observed in the performance of

anti-ribosomal P antibody-injected mice on the forced swimming test. The immobility time of these mice was twice as high as that of the control group, indicating a state of despair. In the remaining tests of cognitive and motor functions, there were no significant differences detected between the mice in each group, ruling out neurological damage.

In an additional experiment, the "depressed" mice were randomly divided into treatment groups. Some mice were treated with fluoxetine, the antidepressant marketed as Prozac, and some mice were treated with haloperidol, a psychotropic drug used to treat anxiety, addiction, and depression. To determine the effectiveness of each therapy, mice were subjected to repeating the forced swimming, staircase, and rotarod tests. Depression-like behavior was significantly blocked by long-term treatment with fluoxetine, but not by short- or long-term treatment with haloperidol.

At the culmination of the experiments, the brains of mice were sectioned and scrutinized through immunostaining. The staining pattern delineated the limbic system, which regulates the automatic nervous system's response to stress. It also highlighted areas of the brain associated with the sense of smell.

These findings provide a novel line of research into the mechanisms underlying the limbic and olfactory pathways in depression. Imaging studies both in patients with clinical depression and patients with SLE could help determine whether these pathways are similarly affected in humans.

"The relevance of the results to the involvement of the central nervous system in SLE is another intriguing aspect of the present study," notes its leading author, Yehuda Shoenfeld, M.D., while emphasizing the need for further investigation through large-scale clinical studies. "Elucidating the

mechanisms by which anti-ribosomal P induces behavioral changes may lead to novel therapeutic advances for SLE patients with depression," Dr. Shoenfeld reflects.

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