Scientists find a new mechanism underlying depression

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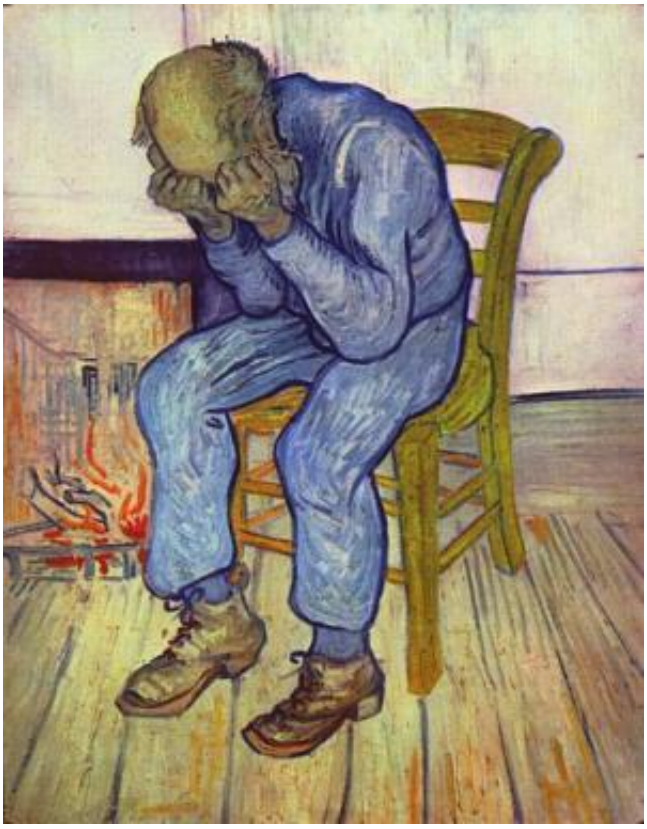

Vincent van Gogh's 1890 painting

(Medical Xpress)—The World health Organization calls depression "the leading cause of disability worldwide," causing more years of disability than cancer, HIV/AIDS, and cardiovascular and respiratory diseases combined. In any given year, 5-7% of the world's population experiences

a major depressive episode, and one in six people will at some point suffer from the disease.

Despite recent progress in understanding depression, scientists still don't understand the biological mechanisms behind it well enough to deliver effective prevention and therapy. One possible reason is that almost all research focuses on the brain's neurons, while the involvement of other brain cells has not been thoroughly examined.

Now researchers at the Hebrew University of Jerusalem have shown that changes in one type of non-neuronal brain cells, called microglia, underlie the depressive symptoms brought on by exposure to chronic stress. In experiments with animals, the researchers were able to demonstrate that compounds that alter the functioning of microglia can serve as novel and efficient antidepressant drugs.

The findings were published in *Molecular Psychiatry*, the premier scientific journal in psychiatry and one of the leading journals in medicine and the neurosciences.

The research was conducted by Prof. Raz Yirmiya, director of the Hebrew University's Psychoneuroimmunology Laboratory, and his doctoral student Tirzah Kreisel, together with researchers at Prof. Yirmiya's laboratory and at the University of Colorado in Boulder, USA.

The researchers examined the involvement of microglia brain cells in the development of depression following chronic exposure to stress. Comprising roughly 10% of brain cells, microglia are the representatives of the immune system in the brain; but recent studies have shown that these cells are also involved in physiological processes not directly related to infection and injury, including the response to stress.

The researchers mimicked chronic unpredictable stress in humans—a leading causes of depression—by exposing mice to repeated, unpredictable stressful conditions over a period of 5 weeks. The mice developed behavioral and neurological symptoms mirroring those seen in depressed humans, including a reduction in pleasurable activity and in social interaction, as well as reduced generation of new brain cells (neurogenesis)—an important biological marker of depression.

The researchers found that during the first week of stress exposure, microglia cells undergo a phase of proliferation and activation, reflected by increased size and production of specific inflammatory molecules, after which some microglia begin to die. Following the 5 weeks of stress exposure, this phenomenon led to a reduction in the number of microglia, and to a degenerated appearance of some microglia cells, particularly in a specific region of the brain involved in responding to stress.

When the researchers blocked the initial stress-induced activation of microglia with drugs or genetic manipulation, they were able to stop the subsequent microglia cell death and decline, as well as the depressive symptoms and suppressed neurogenesis. However, these treatments were not effective in "depressed" mice, which were already exposed to the 5-weeks stress period and therefore had lower number of microglia. Based on these findings, the investigators treated the "depressed" mice with drugs that stimulated the microglia and increased their number to a normal level.

Prof. Yirmiya said, "We were able to demonstrate that such microglia-stimulating drugs served as effective and fast-acting antidepressants, producing complete recovery of the depressive-like behavioral symptoms, as well as increasing the neurogenesis to normal levels within a few days of treatment. In addition to the clinical importance of these results, our findings provide the first direct evidence that in addition to

neurons, disturbances in the functioning of brain microglia cells have a role in causing psychopathology in general, and depression in particular. This suggests new avenues for drug research, in which microglia stimulators could serve as fast-acting antidepressants in some forms of depressive and stress-related conditions."

More information: Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis, *Molecular Psychiatry* , (17 December 2013): www.nature.com/mp/journal/vaop … full/mp2013155a.html

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