Researchers see a 'picture' of threat in the brain: Work may lead to new model of neuroinflammation

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A team of researchers is beginning to see exactly what the response to threats looks like in the brain at the cellular and molecular levels.

This new information, including the discovery that a model of social stress can increase inflammation among brain cells, should provide new insight into how the stress response affects inflammatory and behavioral responses.

It may also provide new targets for drugs treatments in the continuing struggle to curtail depression and anxiety.

Scientists from Ohio State University's Institute of Behavioral Medicine Research reported their results in the latest issue of the Journal of Neuroscience.

John Sheridan, professor of oral biology, and Jonathan Godbout, an assistant professor of molecular virology, immunology and medical genetics, turned to colonies of mice to make their discoveries.

Groups of mice living together quickly adopt a hierarchy ranging from dominant to subordinate. This vaguely political system controls the interaction among the animals. Once these patterns had been established, the researchers then added an additional, highly aggressive mouse to the mix for a two-hour period each day to disrupt the social hierarchy.

With no place to retreat, the mice were forced into conflicts with the new aggressor. After as few as three episodes with the aggressor, the original mice showed distinct signs of what the researchers considered "anxiety-like behaviors." This kind of experiment creates a "social disruption" within the group of mice and is widely used to mimic psychological stress.

"These animals can't flee, so they have to stand and fight," Sheridan explained. "In doing so, they're repeatedly defeated, creating a condition called "learned helplessness," a condition closely linked to depression.

What Sheridan and Godbout saw was that the animals' anxiety continued for a long time after the termination of the stressful episodes of defeat. "For two weeks or more after we stopped the stressor, we could still see this anxiety-like behavior," Sheridan said.

The real discoveries came when the researchers analyzed what was happening in the animals' brains and in their immune response.

"We found that in the stressed animals, a certain type of immune cell (myeloid progenitor cell, or MPC), produced in the bone marrow, entered the circulatory system and migrated to the brain," explained Godbout.

These MPCs might normally relocate in this way to deal with an infection or an injury in the brain, but in this case, they moved solely because of the response to a social stressor, he said. The experiments showed that the number of these cells more than tripled in the brain following the stress.

Other immune cells called microglia, normally residing in the brain, also triggered an inflammatory response because of the stress. The researchers also noted that the stressor caused a particular activation

pattern of neurons, or nerve cells, within the brain.

The response to social stress also caused an increase in the amounts of some inflammatory cytokines in the brain, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a) which are linked to inflammation. These cytokine responses correlated with an insensitivity of MPCs to glucocorticoids, hormones that normally inhibit inflammation in the body.

So the research team saw these and other cellular changes occurring in the brain following the stress, at the same time they were seeing the behavioral changes – the anxiety-like behavior.

The findings are evidence of a two-way communication that's existing between the body and the brain in times of stress, Sheridan said.

To test that apparent connection, they gave the mice injections of propranolol -- a so-called "beta-blocker" drug often used for cardiac conditions -- before they encountered the more aggressive mouse. In this case, the researchers saw no increase in IL-1 or TNF-a, no glucocorticoid insensitivity, and no long-lasting anxiety-like behavior in the test animals.

"If we treated the animal with a beta-blocker each night before we put the intruder in, it completely blocked the signal. The anxiety-like behavior never developed," Godbout said.

"What this basically argues is that we may now have a new target for individuals who have extended anxiety-like behavior," Sheridan said. "We may have a new target cell to think about in terms of new therapies.

"And since that cell (the MPCs traveling from the bone marrow) is coming from the periphery of the body, we might not need to resort to

psychoactive drugs that can have adverse effects on the brain."

Proving that, however, will take more animal studies and subsequent large studies using humans before this approach could be used clinically, he said.

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