Researchers identify novel mechanism to reduce nervous system inflammation

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Researchers at Georgetown University Medical Center have discovered a new way to limit inflammation caused by the activation of microglia - key immune cells in the brain. Although the role of such cells is to "clean up damage" after injury, they often worsen the damage by releasing toxic inflammatory factors.

In the October issue of the journal *Glia,* now published online, the scientists say that the type of chemical they used to deactivate these cells could possibly be developed as a drug to treat a variety of acute and chronic disorders marked by brain cell damage – including stroke, head and spinal cord injury, and possibly Alzheimer's disease and Parkinson's disease.

"Inflammation associated with the activation of microglial cells is an important factor that appears to contribute to tissue damage and disability in many of the important neurodegenerative disorders. By decreasing this inflammatory response, tissue loss after injury can be reduced. Thus, what we found in this study has important potential therapeutic implications for the treatment of a number of important neurological disorders," says the study's senior investigator, Alan I. Faden, M.D., a professor of neuroscience and director of the Laboratory for the Study of Central Nervous System Injury.

The research, led by investigator Kimberly Byrnes, Ph.D., an assistant professor in Faden's laboratory, centered on microglial cells, which react against pathogens that invade the brain, and also remove foreign material

and damaged cells.

Byrnes describes microglial cells as just a little too good at their jobs. "They overdo it, perhaps because they don't have very good stop signals. They secrete a number of toxic chemicals designed to clear up infections and damaged tissue-- but in the process they can kill sensitive brain cells."

In this study, Byrnes, Faden and a team of four other researchers looked to see whether microglial cells express a certain receptor on their surface that Faden and his laboratory had previously found could be turned on in brain neurons to prevent cell death in response to injury. The receptor, the group I metabotropic glutamate receptor 5 (mGluR5), which also plays a critical role in modulating pain and addiction, was previously found in other types of brain cells.

The researchers found the receptor protein in microglia in cell culture. "That's a first," Byrnes says. They then showed that a selective activator of this receptor type, CHPG, could turn off microglial activity. This is the same chemical that Faden discovered could shut down certain kinds of suicide cell death (apoptosis) in neurons.

"We found that if we stimulate just this receptor, we can markedly reduce microglial release of key inflammatory factors and the ability of activated microglia to kill nerve cells," Byrnes says.

The receptor, therefore, appears to be a switch-off mechanism, a brake on the damaging effects of microglial activity. "This is possibly a way that the brain has designed to turn microglia off, but the problem is that these cells get many other signals that keep them turned on after injury."

Treating brain injury with a selective compound may be challenging, the researchers add. "Microglia also releases good chemicals, such as growth

factors, to promote nerve cell regrowth and regeneration, so the trick will be to discretely use it after injury for a period of time."

But brain and spinal cord injury studies in animals, conducted after the present experiments were completed, have been very encouraging, Byrnes says. Those studies have not yet been published.

Source: Georgetown University