# New class of potential drugs inhibits inflammation in brain

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Scientists at Emory University School of Medicine have identified a new group of compounds that may protect brain cells from inflammation linked to seizures and neurodegenerative diseases.

The compounds block signals from EP2, one of the four receptors for prostaglandin E2, which is a hormone involved in processes such as fever, childbirth, digestion and blood pressure regulation. Chemicals that could selectively block EP2 were not previously available. In animals, the EP2 blockers could markedly reduce the injury to the brain induced after a prolonged seizure, the researchers showed.

The results were published online this week in the Proceedings of the National Academy of Sciences Early Edition.

"EP2 is involved in many disease processes where inflammation is showing up in the nervous system, such as epilepsy, stroke and neurodegenerative diseases," says senior author Ray Dingledine, PhD, chairman of Emory's Department of Pharmacology. "Anywhere that inflammation is playing a role via EP2, this class of compounds could be useful. Outside the brain, EP2 blockers could find uses in other diseases with a prominent inflammatory component such as cancer and inflammatory bowel disease."

Prostaglandins are the targets for non-steroid anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. NSAIDSs inhibit enzymes known as cyclooxygenases, the starting point for generating

prostaglandins in the body. Previous research indicates that drugs that inhibit cyclooxygenases can have harmful side effects. For example, sustained use of aspirin can weaken the stomach lining, coming from prostaglandins' role in the stomach. Even drugs designed to inhibit only cyclooxygenases involved in pain and inflammation, such as Vioxx, have displayed cardiovascular side effects.

Dingledine's team's strategy was to bypass cyclooxygenase enzymes and go downstream, focusing on one set of molecules that relay signals from prostaglandins. Working with Yuhong Du in the Emory Chemical Biology Discovery Center, postdoctoral fellows Jianxiong Jiang, Thota Ganesh and colleagues sorted through a library of 262,000 compounds to find those that could block signals from the EP2 prostaglandin receptor but not related receptors. One of the compounds could prevent damage to neurons in mice after "status epilepticus," a prolonged drug-induced seizure used to model the neurodegeneration linked to epilepsy.

The team found that a family of related compounds had similar protective effects.

Dingledine says that the compounds could become valuable tools for exploring new ways to treat neurological diseases. However, given the many physiological processes prostaglandins regulate, more tests are needed, he says. Prostaglandin E2 is itself a drug used to induce labor in pregnant women, and female mice engineered to lack the EP2 receptor are infertile, so the compounds would need to be tested for effects on reproductive organs, for example.

**More information:** J. Jiang et al. Small molecule antagonist reveals seizure-induced mediation of neuronal injury by prostaglandin E2 receptor subtype EP2. *PNAS* 2012, doi:10.1073/pnas.1120195109