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Hulk smash? Maybe not anymore: scientists block excess aggression in mice

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Pathological rage can be blocked in mice, researchers have found, suggesting potential new treatments for severe aggression, a widespread trait characterized by sudden violence, explosive outbursts and hostile overreactions to stress.

In a study appearing today in the *Journal of Neuroscience,* researchers from the University of Southern California and Italy identify a critical neurological factor in aggression: a brain receptor that malfunctions in overly hostile mice. When the researchers shut down the brain receptor, which also exists in humans, the excess aggression completely disappeared.

The findings are a significant breakthrough in developing drug targets for pathological aggression, a component in many common psychological disorders including Alzheimer's disease, autism, bipolar disorder and schizophrenia.

"From a clinical and social point of view, reactive aggression is absolutely a major problem," said Marco Bortolato, lead author of the study and research assistant professor of pharmacology and pharmaceutical sciences at the USC School of Pharmacy. "We want to find the tools that might reduce impulsive violence."

A large body of independent research, including past work by Bortolato and senior author Jean Shih, USC University Professor and Boyd & Elsie Welin Professor in Pharmacology and Pharmaceutical Sciences at

USC, has identified a specific genetic predisposition to pathological aggression: low levels of the enzyme monoamine oxidase A (MAO A). Both male humans and mice with congenital deficiency of the enzyme respond violently in response to stress.

"The same type of mutation that we study in mice is associated with criminal, very violent behavior in humans. But we really didn't understand why that it is," Bortolato said.

Bortolato and Shih worked backwards to replicate elements of human pathological aggression in mice, including not just low enzyme levels but also the interaction of genetics with early stressful events such as trauma and neglect during childhood.

"Low levels of MAO A are one basis of the predisposition to aggression in humans. The other is an encounter with maltreatment, and the combination of the two factors appears to be deadly: it results consistently in violence in adults," Bortolato said.

The researchers show that in excessively aggressive rodents that lack MAO A, high levels of electrical stimulus are required to activate a specific brain receptor in the pre-frontal cortex. Even when this brain receptor does work, it stays active only for a short period of time.

"The fact that blocking this receptor moderates aggression is why this discovery has so much potential. It may have important applications in therapy," Bortolato said. "Whatever the ways environment can persistently affect behavior — and even personality over the long term — behavior is ultimately supported by biological mechanisms."

Importantly, the aggression receptor, known as NMDA, is also thought to play a key role in helping us make sense of multiple, coinciding streams of sensory information, according to Bortolato.

The researchers are now studying the potential side effects of drugs that reduce the activity of this receptor.

"Aggressive behaviors have a profound socio-economic impact, yet current strategies to reduce these staggering behaviors are extremely unsatisfactory," Bortolato said. "Our challenge now is to understand what pharmacological tools and what therapeutic regimens should be administered to stabilize the deficits of this receptor. If we can manage that, this could truly be an important finding."

Provided by University of Southern California