

Agent reduces autism-like behaviors in mice

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A mouse pays a social visit to a novel animal. Credit: MuYang, Ph.D., and Jacqueline Crawley, Ph.D., NIMH Laboratory of Behavioral Neuroscience

National Institutes of Health researchers have reversed behaviors in mice resembling two of the three core symptoms of autism spectrum disorders (ASD). An experimental compound, called GRN-529, increased social interactions and lessened repetitive self-grooming behavior in a strain of mice that normally display such autism-like behaviors, the researchers say.

GRN-529 is a member of a class of agents that inhibit activity of a subtype of receptor protein on [brain cells](#) for the [chemical messenger glutamate](#), which are being tested in patients with an autism-related syndrome. Although [mouse brain](#) findings often don't translate to humans, the fact that these compounds are already in clinical trials for an

overlapping condition strengthens the case for relevance, according to the researchers.

"Our findings suggest a strategy for developing a single treatment that could target multiple diagnostic symptoms," explained Jacqueline Crawley, Ph.D., of the NIH's National Institute of Mental Health (NIMH). "Many cases of autism are caused by [mutations](#) in genes that control an ongoing process – the formation and maturation of synapses, the connections between neurons. If defects in these connections are not hard-wired, the core symptoms of autism may be treatable with medications."

Crawley, Jill Silverman, Ph.D., and colleagues at NIMH and Pfizer Worldwide Research and Development, Groton, CT, report on their discovery April 25th, 2012 in the journal *Science Translational Medicine*.

"These new results in mice support NIMH-funded research in humans to create treatments for the core symptoms of autism," said NIMH director Thomas R. Insel, M.D. "While autism has been often considered only as a disability in need of rehabilitation, we can now address autism as a disorder responding to biomedical treatments."

Crawley's team followed-up on clues from earlier findings hinting that inhibitors of the receptor, called mGluR5, might reduce ASD symptoms. This class of agents – compounds similar to GRN-529, used in the mouse study – are in [clinical trials](#) for patients with the most common form of inherited intellectual and developmental disabilities, Fragile X syndrome, about one third of whom also meet criteria for ASDs.

To test their hunch, the researchers examined effects of GRN-529 in a naturally occurring inbred strain of mice that normally display autism-relevant behaviors. Like children with ASDs, these BTBR mice interact and communicate relatively less with each other and engage in repetitive

behaviors – most typically, spending an inordinate amount of time grooming themselves.

Crawley's team found that BTBR mice injected with GRN-529 showed reduced levels of repetitive self-grooming and spent more time around – and sniffing nose-to-nose with – a strange mouse.

Moreover, GRN-529 almost completely stopped repetitive jumping in another strain of mice.

"These inbred strains of mice are similar, behaviorally, to individuals with autism for whom the responsible genetic factors are unknown, which accounts for about three fourths of people with the disorders," noted Crawley. "Given the high costs – monetary and emotional – to families, schools, and health care systems, we are hopeful that this line of studies may help meet the need for medications that treat core symptoms."

More information: Silverman JL, Smith DG, Rizzo SJS, Karras MN, Turner SM, Tolu SS, Bryce DK, Smith DL, Fonseca K, Ring RH, Crawley, JN. Negative allosteric modulation of the MGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism. April 25, 2012, *Science Translational Medicine*.

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