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Rat models on the rise in autism research

Neuroscientists switch to rats as genetically modified strains become increasingly available.

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Put two young mice in a cage and they will politely sniff one another. Two rat pups, by contrast, quickly become a blur of fur as they begin some “really rough-and-tumble play”, says Richard Paylor, a neuroscientist at Baylor College of Medicine in Houston, Texas. Such behaviour makes rats an ideal animal model for studying autism spectrum disorder, given that children who have the disorder are often less interested in play than children without it.

Paylor is one of the first scientists to use transgenic rats to study neurodevelopmental diseases such as autism, and presented his team’s work at the Society for Neuroscience meeting in Washington DC last week. Transgenic rats, Paylor and others say, are a better proxy than mice for the behavioural and cognitive problems experienced by people with autism. And because rats are a preferred model for the pharmaceutical industry, their use in basic research may speed new treatments.

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Rats are making a comeback as the lab animal of choice for neuroscientists.

“I think they’re the future,” says Joseph Buxbaum, a neuroscientist at the Seaver Autism Center at Mount Sinai School of Medicine in New York. “I could name 20 high-complexity behavioural tests that you can do in a rat that nobody’s ever done in a mouse.” At the meeting, he debuted his lab’s own transgenic rat strain, which is missing a working copy of a gene called *Shank3*. People with this same mutation usually develop a neurodevelopmental condition, often autism.

Rats were once neuroscientists' animals of choice. They learn more quickly than mice, and their bulkier brains and bodies make many invasive experiments easier and tissues simpler to collect. But the development of genetically modified mice more than two decades ago, and their subsequent wide availability, instead led many scientists to adopt mouse models in their experiments.

Ready-made mutants

However, in the past few years scientists have developed an efficient way to make transgenic rats. There are now nearly two dozen strains of knock-out rats for sale, including several that are missing genes implicated in autism and other neurodevelopmental conditions, such as fragile X and Rett syndromes.

Paylor revealed the first results of a battery of behavioural tests on two strains of transgenic rats at the neuroscience meeting last week. One strain lacks a copy of the *Fmr1* gene — having a similar effect to the mutation that causes fragile X syndrome in humans — while the second strain is missing neuroligin-3, a gene implicated in autism.

Paylor's early results suggest that rats with these mutations display traits that may be analogous to autistic characteristics in humans. When paired together in a cage, two rat pups each lacking a working copy of *Fmr1* spend less time playing and produce fewer ultrasonic calls than normal rats. Adult females missing one copy of neuroligin-3 tend to throw errant pups back towards their nest, whereas normal females carry the rodents back. Paylor isn’t sure what to make of this habit, but it could be a proxy for the problems in social interaction seen in humans with autism.

Both rat strains exhibit the repetitive behaviours that are a core feature of autism. Adult female rats lacking neuroligin-3 gnawed at the hard plastic water bottles in their cages so voraciously that the bottles leaked. Paylor’s team gave the animals blocks of soft wood and measured how much of the block remained after a day. The rats lacking *Fmr1* munched on more wood than normal rats. Meanwhile, rats missing neuroligin-3 chewed through no more wood than other rats because they were too busy gnawing at their water bottles, Paylor says.

Experimental expense

Transgenic rats have their downsides. The animals are more expensive to house and test than mice — a potential deterrent for some

academic labs, notes Matthew Anderson, a neuroscientist and physician at Harvard Medical School in Boston, Massachusetts. The mutations currently available in transgenic rats are not as sophisticated as those in mice. For instance, it is not yet possible to create rat strains that are missing large chunks of chromosomes — a type of mutation in humans that is linked to many neurodevelopmental diseases.

In many behavioural tests, the transgenic rats performed comparably to mice lacking the same genes, says Paylor. And Buxbaum's team and others have seen the same electrophysiological defects in mice with a defective copy of *Shank3* that they saw in rats missing the gene.

Still, Paylor thinks that rats offer better analogies of human behaviour, particularly the rough social play that is common among young rats. And Buxbaum points out that many electrophysiological tests, such as recording bursts of electrical activity in the neurons of live animals, are far more difficult in mice — in some cases, such tests are not possible because the mouse brain regions are too puny.

But the main virtue of the latest transgenic rat models may be to bridge the gap between basic research and drug development, and hopefully lead to new treatments. Rats are used in the pharmaceutical industry to predict how humans will metabolize drugs, and to identify potential side effects. Such tests must be completed before phase I safety trials can begin in humans.

If researchers can identify pathways and even drugs that ameliorate autistic characteristics in rat models, rather than in mice, drug companies may be more willing to put up the money needed to test the drugs in humans and bring them to market, says Robert Ring, vice-president for translational research at the charity Autism Speaks in New York, and former head of Pfizer's autism research unit.

"When they test a drug in the rat, they feel like they're getting a much better sense of what it's going to do in patients," says Buxbaum. "For people like me who are really translationally oriented, I want to short-circuit two years of wasted time."

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