NEWS

Studies implicate gut bacteria in autism

BY **EMILY ANTHES**

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Autism, with its constellation of behavioral and cognitive symptoms, might seem to be all in the brain. But intriguing new studies suggest that some aspects of the disorder might originate in the gut.

For decades, doctors have heard anecdotal reports that **children with autism have frequent gastrointestinal problems**, suffering from bloating, abdominal pain, constipation, diarrhea and more.

The latest research, conducted over the past several years, probes the **controversial possibility** that whatever is amiss in the gut is not just a symptom of autism, but **one of the causes**. The work is an offshoot of mounting scientific interest in the human microbiome, the stew of bacteria that make their homes in our gastrointestinal tracts.

A new study, published 31 January in the *Proceedings of the National Academy of Sciences*, suggests that these microbial residents may direct brain development, ultimately shaping behavior[1].

"It's a big eye opener," says lead investigator **Sven Pettersson**, professor of microbiology at Karolinska Institute in Sweden. "If you would have said 20 years ago that bacteria would have anything to do with brain function, people would have laughed at you."

Healthy guts are home to a vast number of bacteria, of a variety of different species. "You have more bacteria in your gut than you have cells in your body," says **Derrick MacFabe**, director of the Kilee Patchell-Evans Autism Research Group at the University of Western Ontario in Canada, who was not involved with the study.

Far from being pathological, these microscopic stowaways are critical players in normal biological functioning.

Microbial passengers:

Some studies have found a higher incidence of gastrointestinal disturbances in children with autism. A 2006 study revealed, for instance, that 70 percent of children with autism suffer from gastrointestinal problems, compared with only 28 percent of typically developing children[2].

In 2005, **Anne McCartney**, a microbiologist and senior research fellow at the University of Reading in the U.K., found that children with autism have higher-than-normal concentrations of *Clostridium* bacteria, a microbial group that can produce neurotoxins. Other researchers have reported similar findings[3].

"There does seem to be a case to suggest that both the numbers and types of certain bacteria in the gut are different in autistic and non-autistic children," McCartney says.

Armed with these findings, researchers began to explore whether changes in gut bacteria, rather than being mere symptoms of autism, contribute to the disorder. Anecdotal evidence suggested that might be the case — parents often reported that their children's behavior seemed to get worse when their gut symptoms were exacerbated.

In the new study, researchers set out to determine whether gut microbes can shape brain development. They examined two sets of mice: one group has a normal stew of the microbes, whereas the other has squeaky-clean guts devoid of bacteria.

Comparing the behavior of these two groups, the researchers found that the bacteria-free rodents are more hyperactive and more likely to take risks than those with microbes. The sterile mice also show abnormalities in the expression of dozens of genes and in the way they process several neurotransmitters — including noradrenaline, dopamine and serotonin.

To investigate whether gut microbes are responsible for these differences, the scientists exposed bacteria-free pups to a full complement of microbes taken from the normal mice. The sterile mice no longer grew into hyperactive and risk-taking adults. In fact, they acted just like the mice born with normal gut bacteria.

Though Pettersson and his colleagues weren't looking specifically at autism, the study provides compelling evidence that the microbes in our bellies can influence behavior, perhaps by guiding brain development.

"This phenomenon seems to take place very early in life," Pettersson says. Indeed, transfusing bacteria-free adult mice with gut microbes has no effect on their behavior. "One of the striking findings is that in order to change the behavior pattern of the animals, we have to expose the mice at a young age to that bacteria," Pettersson says.

Autism models:

The next step for researchers is to unravel the mechanism underlying this gut-behavior link.

One possibility is that microbes influence brain development by altering the level of hormones circulating in the bloodstream. Alternately, gut bacteria might be communicating with the brain through the vagus nerve, which runs from the head all the way down to the abdomen.

MacFabe is investigating whether gut microbes can influence the brain in ways that explain the symptoms of autism spectrum disorders. He is using rats to study fatty acids produced by the microbes that live in the gut, focusing particularly on **propionic acid**, which is produced by *Clostridia*, the bacteria that seem to be present at higher levels in children with autism.

When MacFabe and his colleagues injected propionic acid directly into the brains of rats, they became hyperactive, began engaging in repetitive behaviors and lost interest in social interactions[4].

Subsequent studies have reinforced these findings. In young and adult rats alike, propionic acid seems to cause repetitive and antisocial behaviors, cognitive impairments and patterns of brain inflammation that resemble those seen in children with autism[5,6,7].

"There are compounds that gut bacteria make that can make animals do some very weird things," MacFabe says, "some very specific things that have similarity to autism."

The research is provocative, but there's still much to do before gut microbes can be established as a real contributor to autism. Even if the connection holds up, it's unclear whether changing the gastrointestinal environment would have any benefits for children with autism. "I'm not convinced at this point that we can say, 'If we modulate the gut flora we can alleviate autism,'" McCartney says.

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