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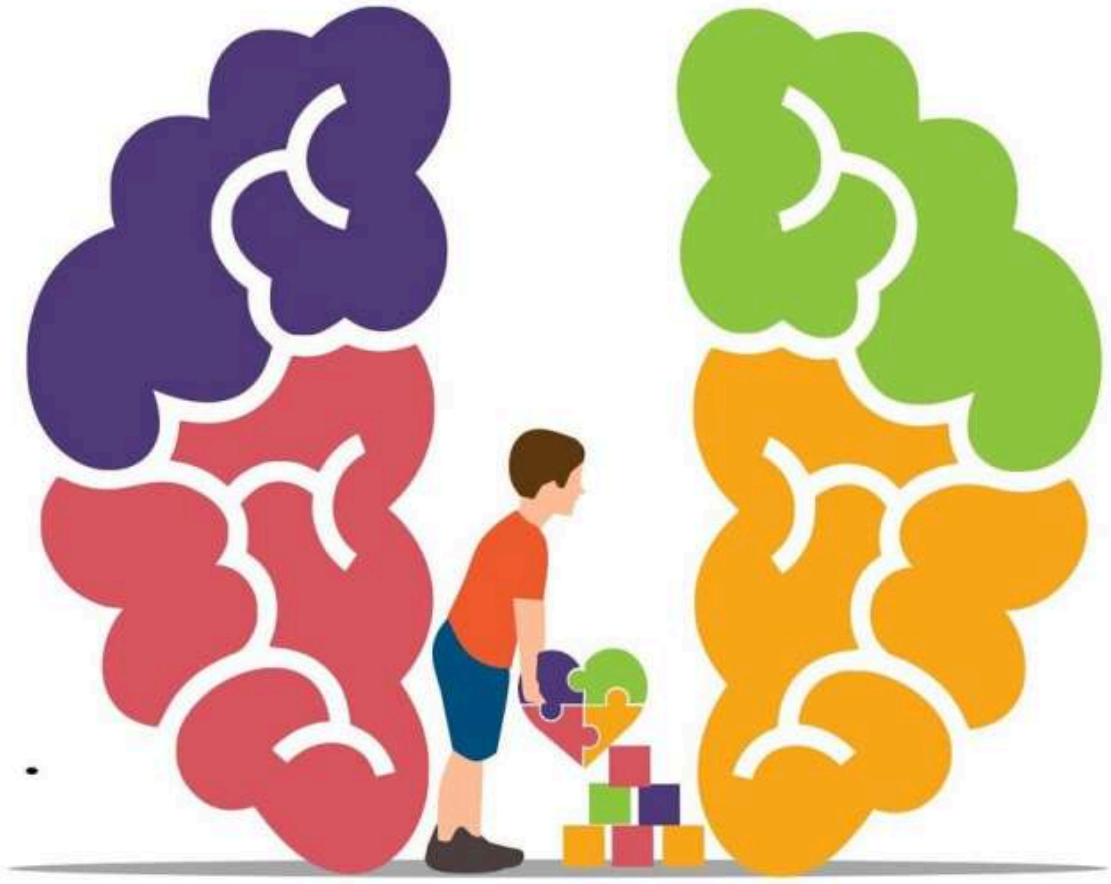
Editors' notes

Metabolism of autism reveals developmental origins

by University of California - San Diego



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Researchers at the University of California San Diego School of Medicine have shed new light on the changes in metabolism that occur between birth and the presentation of autism spectrum disorder (ASD) later in childhood. The researchers discovered that a small number of biochemical pathways are responsible for the majority of these changes, which could help inform new early detection and prevention strategies for autism.

"At birth, the physical appearance and behavior of a child who will develop autism over the next few years are indistinguishable from that of a neurotypical child. Indeed, in most cases the fate of the child with regard to autism is not set at birth," said Robert Naviaux, M.D., Ph.D., professor in the Departments of Medicine, Pediatrics and Pathology at UC San Diego School of Medicine.

"We're starting to learn about the governing dynamics that regulate the transition from risk to the actual appearance of the first symptoms of ASD. Early diagnosis opens the possibility of early intervention and optimal outcomes."

ASD is a developmental disorder characterized by difficulties in socializing and communication, as well as repetitive and/or restrictive behaviors. For the majority of people with ASD, the condition is a significant disability, with only 10–20% of children diagnosed before 5 years of age able to live independently as adults.

While autism is known to have strong genetic risk factors, there are also environmental risk factors that play a role in the development and severity of ASD. Naviaux and other researchers are discovering that the development of autism is governed by the real-time interaction of these varied factors. By studying the developmental biology of metabolism and how it differs in autism, new insights are emerging in ASD and other complex developmental disorders.

"Behavior and metabolism are linked—you cannot separate them," added Naviaux.

To learn more about the early metabolic changes that occur in children with autism, researchers studied two cohorts of children. One cohort consisted of newborn children, in whom autism can't be detected. The second cohort consisted of 5-year-old children, some of whom had been diagnosed with autism.

When comparing the metabolic profiles of children in the cohort who were eventually diagnosed with autism to those who developed neurotypically, they found striking differences. Of the 50 different biochemical pathways the researchers investigated, just 14 were responsible for 80% of the metabolic impact of autism.

The pathways that were most changed are related to the cell danger response, a natural and universal cellular reaction to injury or metabolic stress. The body has biochemical safeguards in place that can shut down the cell danger response once the threat has passed, and Naviaux hypothesizes that autism occurs when these safeguards fail to develop normally. The result is heightened sensitivity to environmental stimuli, and this effect contributes to sensory sensitivities and other symptoms associated with autism.

"Metabolism is the language that the brain, gut and immune system use to communicate, and autism occurs when the communication between these systems is changed," added Naviaux.

The cell danger response is primarily regulated by adenosine triphosphate (ATP) the body's chemical energy currency. While these ATP-signaling pathways do not develop normally in autism, they may be partially restorable with existing pharmaceutical drugs. In 2017, Naviaux and his team completed early clinical testing for suramin, the only drug approved in humans that can target ATP signaling and which is normally used to treat African sleeping sickness.

Now, the researchers hope that by revealing the specific ATP-related pathways that are altered in autism, their work will help scientists develop more drugs that target these pathways to manage the symptoms of ASD.

"Suramin is just one drug that targets the cell danger response," he said. "Now that we're closely interrogating how metabolism changes in ASD, we could be at the beginning of a drug renaissance that will create new options for treatment that never existed before."

The study is published in the journal *Communications Biology*.

More information: *Communications Biology* (2024). www.nature.com/articles/s42003-024-06102-y

Journal information: Communications Biology