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Insight into the genetics of autism offers hope for new drug treatments

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Drugs to increase insulin signaling may be effective for treating autism say Lancaster University researchers, who have discovered how a genetic change impacts on insulin signaling and glucose metabolism in the brain.

In the human genome small sections of DNA have been found to be duplicated or deleted in some people, a phenomenon known as Copy Number Variation.

Some of these genetic changes cause neurodevelopmental problems and dramatically increase someone's risk of developing disorders such as autism, schizophrenia and Tourette's syndrome.

For example, people with a DNA deletion at chromosome 2p16.3, which results in deletion of the Neurexin1 gene, commonly experience neurodevelopmental delay and cognitive problems.

People with the 2p16.3 deletion are also around 14 to 20 times more likely to develop neurodevelopmental disorders including autism, schizophrenia and Tourette's syndrome than people without the deletion.

There are an estimated two to three million people worldwide who have this type of DNA deletion but there are currently no effective drug treatments for their resulting cognitive problems.

For the first time, in research funded by The Royal Society, scientists have demonstrated that Neurexin1 gene deletion reduces glucose metabolism in the prefrontal cortex, a key brain region involved in higher-level cognitive functions including cognitive flexibility and paying attention. Neurexin1 deletion was also found to reduce insulin receptor signaling in the prefrontal cortex, which likely underlies the reduced glucose metabolism seen in this region.

The research, published in the journal Autism Research, give valuable new insight into how this leads to cognitive deficits, behavioural changes and dramatically increases the risk of developing a range of neurodevelopmental disorders.

The key finding that Neurexin1 deletion impacts on insulin signaling and glucose metabolism in the prefrontal cortex suggests that using drugs to increase insulin signaling may be an effective therapeutic strategy.

Lead researcher Dr. Neil Dawson from Lancaster University said: "There is an urgent need to further understand the underlying neurobiology of neurodevelopmental disorders in order to develop new treatments. Drugs to help people with their cognitive and social problems are particularly urgently needed, as these symptoms dramatically impact on their quality of life."

In addition, the researchers also showed that Neurexin1 deletion causes deficits in cognitive functions that depend on the prefrontal cortex, including a deficit in the ability to be flexible.

The research also found that the reduced glucose metabolism in the prefrontal cortex that results from Neurexin1 deletion was linked with being hyperactive when experiencing novel situations.

A second brain region identified as being impacted by Neurexin1 deletion was the dorsal raphé, which showed increased activity. This region is the origin of serotonin neurons that project throughout the brain, suggesting that Neurexin1 deletion also makes the serotonin neurotransmitter system dysfunctional.

Dr. Neil Dawson said: "In addition, the observation that the serotonin system may be dysfunctional requires further research, and suggests that drugs targeting this neurotransmitter system may also be useful. We can now test the ability of drugs that target these mechanisms to restore these translational changes seen as part of ongoing research to develop better treatments for people with 2p16.3 deletion, autism, schizophrenia and Tourette's syndrome".

More information: Rebecca B. Hughes et al, Altered medial prefrontal cortex and dorsal raphé activity predict genotype and correlate with abnormal learning behavior in a mouse model of autism-associated 2p16.3 deletion, *Autism Research* (2022). DOI: 10.1002/aur.2685