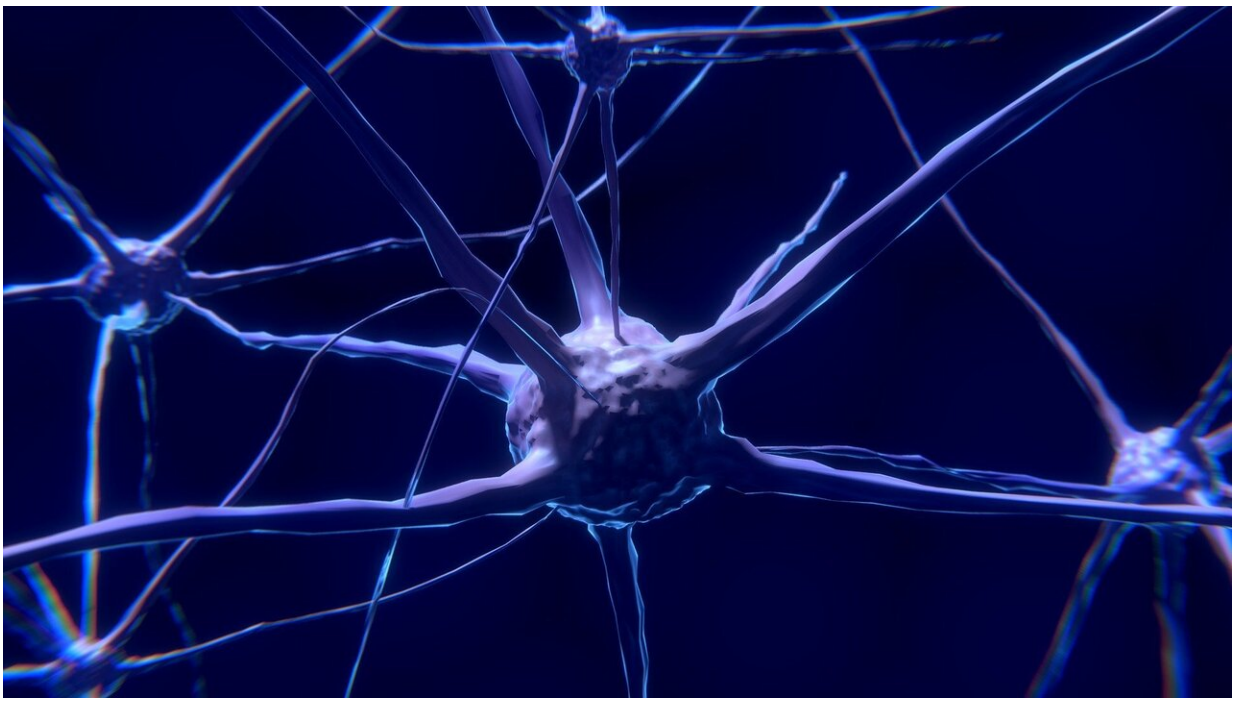
Prescription drug improves symptoms of autism by targeting brain's chemical messengers

January 27 2020



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Bumetanide—a prescription drug for oedema (the build-up of fluid in the body) - improves some of the symptoms in young children with autism spectrum disorders and has no significant side effects, according to a new study from researchers in China and the UK.

Published today in *Translational Psychiatry*, the study demonstrates for the first time that the drug improves the symptoms by decreasing the ratio of the GABA to glutamate in the brain. GABA and glutamate are both neurotransmitters—chemical messengers that help nerve cells in the brain communicate.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder estimated to affect one in 160 children worldwide. It is characterised by impairments in social communication, which manifest as problems with understanding emotions and with non-verbal communication, such as eye contact and smiling, and in failures to develop, maintain and understand social relationships. People with ASD also tend to have restricted interests and show repetitive behaviour. In mild cases of ASD, people are able to live independently, but for some the condition can be severe, requiring life-long care and support.

Although the biological mechanisms underlying ASD remain largely unknown, previous research has suggested that it may result from changes in brain development early in life, and in particular in relation to GABA, a neurotransmitter, a chemical in the brain that controls how nerve cells communicate. In the adult brain, GABA is inhibitory, which means it switches nerve cells 'off'. In fetal life and early postnatal development, it is mostly excitatory, switching nerve cells 'on' and making them fire, playing a key role in the development and maturation of nerve cells. Alterations in the GABA-switch (from excitatory to inhibitory) can cause a delay in when the developing neural circuits reach functional maturity, with consequences for network activity. This implies that intervening at an early age may help reduce some of the symptoms that can make life challenging for people with ASD.

Current treatments for ASD at preschool age are mainly behavioural interventions, such as using play and joint activities between parents and their child to boost language, social and cognitive skills. However, with

limited resources there is an inequality in access to these treatments across the globe, particularly in developing countries.

Previous studies in rats and small clinical trials involving children with ASD suggest that the drug bumetanide, which has been approved for use in oedema, a condition that results in a build-up of fluid in the body, could help reduce symptoms of ASD.

Now, an international collaboration between researchers at a number of institutions across China and at the University of Cambridge, UK, has shown that bumetanide is safe to use and effective at reducing symptoms in children as young as three years old. ASD can be reliably diagnosed at age 24 months or even as early as 18 months of age.

The team recruited 83 children aged three to six years old and divided them into two groups. A treatment group of 42 children received 0.5mg of bumetanide twice a day for three months, while a control group of 41 children received no treatment. The researchers assessed symptoms using the Childhood Autism Rating Scale (CARS), which is used to rate behaviour such as imitation, emotional response and verbal and non-verbal communication. Children scoring above 30 on the scale are considered to have ASD.

Before treatment, both groups had similar CARS scores, but afterwards, the treatment group now had a mean total score of 34.51 (compared to the control group mean score of 37.27). Also, importantly, the treatment group showed a significant reduction in the number of items on the CARS assigned a score greater than or equal to three, with the average number of 3.52 items in the treatment group compared to 5.49 items in the control group.

Dr. Fei Li from Xinhua Hospital, Jiao Tong University School of Medicine, the clinical lead of the study, said: "I have many children with

autism spectrum disorder under my care, but as psychological treatment resources are not available in many places, we are unable to offer them treatment. An effective and safe treatment will be very good news for them.

"The mother of a four year old boy living in a rural area outside Shanghai who received the treatment told me that he was now better at making eye contact with family members and relatives and was able to participate more in activities. In future, we hope to be able to ensure all families, regardless of where they are living, can receive treatment for their child."

To understand the mechanisms underlying the improvements, the researchers used a brain imaging technique known as magnetic resonance spectroscopy to study concentrations of neurotransmitters within the brain. They found that in two key brain regions—the insular cortex (which plays a role in emotions, empathy and self-awareness) and visual cortex (responsible for integrating and processing visual information) - the ratio of GABA to glutamate decreased over the three-month period in the treatment group. GABA and glutamate are known to be important for brain plasticity and promoting learning.

Professor Ching-Po Lin of National Yang-Ming University said: "This is the first demonstration that bumetanide improves brain function and reduces symptoms by reducing the amount of the brain chemical GABA. Understanding this mechanism is a major step towards developing new and more effective drug treatments."

Professor Barbara Sahakian from the Department of Psychiatry at the University of Cambridge said: "This study is important and exciting, because it means that there is a drug that can improve social learning and reduce ASD symptoms during the time when the brains of these children are still developing. We know that GABA and glutamate are key

chemicals in the brain for plasticity and learning and so these children should have an opportunity for better quality of life and wellbeing."

The team say the discovery that bumetanide changes the relative of concentrations of GABA to glutamate could provide a useful biomarker—a tell-tale biological measure—of how effective a treatment is. However, they cautioned that further research is needed to confirm the effectiveness of bumetanide as a treatment for ASD.

Dr. Qiang Luo from Fudan University said: "These findings are very promising and suggest we will be able to use the biomarker measure to identify which children with ASD will benefit most from bumetanide. Further studies in a larger number of children will hopefully confirm whether bumetanide is an effective treatment for children with autism spectrum disorder."

More information: Lingli Zhang et al. Symptom improvement in children with autism spectrum disorder following bumetanide administration is associated with decreased GABA/glutamate ratios. *Translational Psychiatry*; 27 Jan 2020

Provided by University of Cambridge

Citation: Prescription drug improves symptoms of autism by targeting brain's chemical messengers (2020, January 27) retrieved 4 May 2024 from https://medicalxpress.com/news/2020-01-prescription-drug-symptoms-autism-brain.html

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