Synapses: Pandora's box of clues for autism

The Center for Synaptic Brain Dysfunction, prepared for another challenge

"When I called my son's name, he ignored me. I thought he must be lonely, but he was actually sick. He was diagnosed with autism, which had advanced so much…"
This is a story that Mr. Tae Won Kim, a famous guitarist and leader of the group "Boohwal," painfully confessed in a TV program last year. It was hard for him to accept that his son who had shown abnormal symptoms around his first birthday had finally been diagnosed with autism. He also said that his life had become miserable. Fortunately, Mr. Kim has been recovering his image as a good father according to another TV program. However, many parents of children with autism have lived painful lives like Mr. Kim.

With improvements in human rights and medicine the understanding and consideration of patients with autism has increased and majority of developed countries are very interested in autism. However, people with social deficiencies are still being isolated in society. The picture is from an experience game called Auti-Sim that was submitted to Hacking Health, which is a Canadian medical conference. The game caused people to experience the auditory hypersensitivity of a patient with an autistic disorder in order to help them better understand patients with autism.

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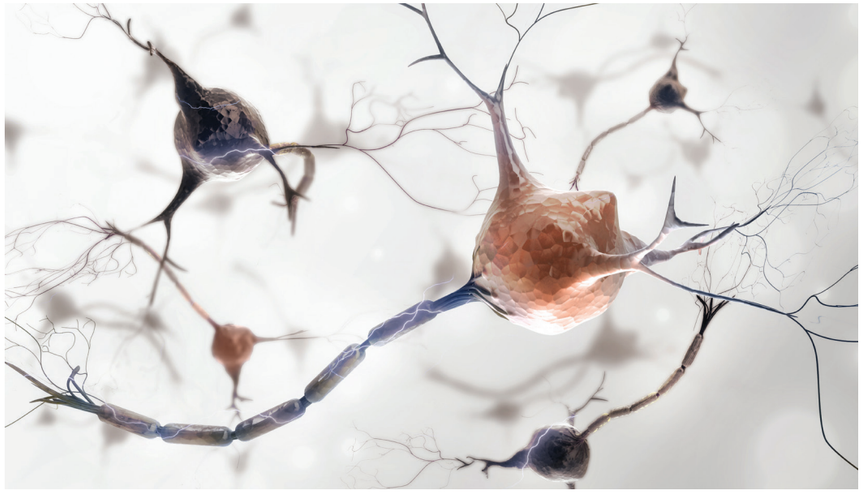
Autism (autistic disorder), together with intellectual disabilities, is a type of developmental disability. Of the 2,501,111 people with disabilities in Korea, 196,997 have developmental disabilities, which accounts for 7.9% of the total according to statistics announced by the Ministry of Health and Welfare at the beginning of this year. A total of 18,133 people have autistic disorders, which corresponds to 0.7% of the total number of disabled people.
The biggest problem in autism is the lack of treatment, even though there are drugs that can treat the secondary symptoms that often accompany autism, such as hyperactivity, poor motor skills, aggression, and irritability. To date, the medical community has no particular measures of the core symptoms of autism, which are social deficiency and repetitious behavior. For this reason, The Center for Synaptic Brain Dysfunction (Director: Eunjoon Kim) in The Institute for Basic Science has focused on autism. Director Eunjoon Kim is quite confident that the key to autism lies in synapses, which link numerous nerve cells in the brain.

Rosy prospects for the market for drugs that treat sociality

Recently, *Nature*, an English science magazine, published a study that collated genes related to autistic symptoms in a detailed gene analysis from several thousands of people. A huge number of studies on autism, including the study in *Nature*, have been published in recent years. Taken together, these studies suggest that the number of genes that are predicted to be related to autism is as many as 630.
Animal experiments are needed to determine if problems with a particular gene cause or inhibit autistic symptoms. In other words, an animal that has an alteration in the gene of interest must be examined in order to determine if any changes occurred because of the altered gene. Considering it takes about 3–5 years for one gene to be thoroughly examined with this animal experiment technique, vast amounts of work is yet to be completed by scientists. Because of the widespread awareness about this situation, numerous scientists have devoted themselves to autism research.
In particular, pharmaceutical companies have been fiercely competing in the race to develop drugs to treat autism. Anyone in the pharmaceutical industry who develops a drug that improves social deficiency, a major symptom of autism, would not have to worry about their financial situation for at least the next 20 years. In addition, because such a drug could be used to treat other mental disorders besides autism that have similar symptoms, the first company to develop such a drug would, as is commonly expressed, be rolling in the dough.
About 40 candidate drug for the treatment of autism are being examined in clinical trials. About three target the N-methyl-D-aspartate (NMDA) receptor, which is a gatekeeper protein localized at the end of nerve cells and that binds neurotransmitters to transduce signals to neighboring nerve cells through synapses. Several studies focusing on NMDA receptors indicate that many scientists, including those at The Center for Synaptic Brain Dysfunction, agree that a better understanding of NMDA receptors would provide significant answers to the riddle of autism.

The secret of receptors in synapses

Recently, the number of studies on the involvement of NMDA receptors in autism has increased because two studies on the entire protein structure of the NMDA receptor were published in *Nature* and *Science* last July and May, respectively. The elucidation of the receptor's structure provides decisive



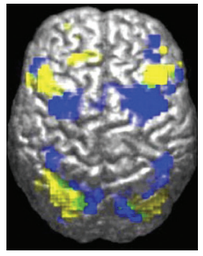
According to research results that have accumulated for a long time, it is now clear that the key to treatment for autism lies in synapses. This means that treatment for numerous neural psychiatric disorders lie in the very narrow gaps between synapses that are responsible for neuronal signal transduction.

clues to scientists studying protein functions. The shape of the NMDA receptor, which was illustrated in *Nature* and *Science*, is like that of a mortar. The mortar-like receptor has a vertical channel that spans the center of the receptor and that controls signals by holding or releasing neurotransmitters while it spins.

Many research groups across several countries, including those in The Center for Synaptic Brain Dysfunction, speculate that autism is induced when the signal transduction function of the NMDA receptor is out of its normal range and is greatly increased or inhibited. Director Kim published a study in *Nature* 2 years ago that identified that mice with reduced NMDA receptor activity exhibited autistic symptoms. This study was conducted in collaboration with Professor Bong-Kiun Kaang's group at the Biological Sciences Department of Seoul National University and Professor Min Goo Lee's group at the College of Medicine of Yonsei University. A contrasting study published in the Proceedings of the National Academy of Sciences of the USA before Director Kim's study reported that hyperfunctioning of the NMDA receptor also resulted in autism-like symptoms. Director Kim has now submitted a manuscript, which is currently in review, to an international journal reporting results that identify this opposite mechanism. Scientists were confused by these studies. Similar responses to both the up- and down-regulation of the activity of a receptor suggest that it will be difficult to determine which mechanism to be targeted by drugs designed to treat actual patients. In fact, a number of recent studies have applied drugs that are used to treat mental disorders and that function through these two different mechanisms.

For example, memantine, which is a medicine used to treat Alzheimer's disease, is well known to downregulate and normalize hyperfunctioning NMDA receptors. To date, as many as 10 studies have reported that the administration of memantine to patients with autism improved their symptoms. In contrast, treatment with D-Cycloserine, a drug that increases and normalizes the activity of hypofunctioning NMDA receptors, has been shown to improve the symptoms of patients with autism.

Some interested patients and guardians were aware of these unusual phenomena. Director Kim received an e-mail from the father of a child with autism in another country. It said, "When I gave my child a D-Cycloserine-like medication, the child's social interactions improved. Memantine treatment had an effect on the child's language skills. I am wondering why these effects occured." Director Kim suggests that a clue lies in the fact that nerve cells are present in various forms. In terms of function, nerve cells are divided into excitatory and inhibitory cells. Of course, NMDA receptors



It is known that patients with autism use different brain areas compared to people without autism. The picture is a functional magnetic resonance image that highlights the brain areas activated during visuomotor movement. Clear differences can be observed between people without autism (green) and patients with autism (yellow).

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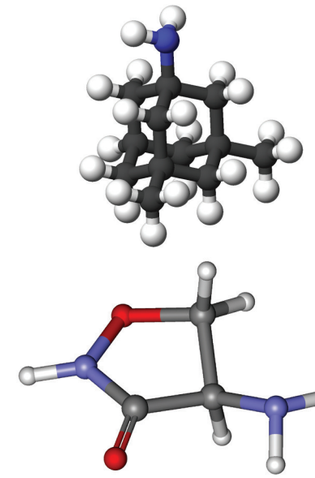
are present in both cell types. For example, when a drug that increases the activity of NMDA receptors reaches NMDA receptors of inhibitory receptors of nerve cells, excitability of inhibitory nerve cells increases, which in turn inhibits the excitatory nerve cells that receive signals from inhibitory nerve cells. These effects result in an outcome similar to the inhibition of NMDA receptors in excitatory nerve cells. The opposite situation is also possible. In conclusion, Director Kim predicts, "Fine control of the balance between excitation and inhibition will be the key to the development of autism medicine."

Zinc, another target

Numerous research findings suggest that a drug for autism that targets NMDA receptor mechanisms will soon be available. In agreement, Director Kim says, "Drug development is actually a matter of time." However, he predicts that it would not be easy for two reasons. First, NMDA receptors are involved in other mental disorders as well as autism. Scientists have postulated that autism shares some mechanisms with schizophrenia (which means splitting of the mind) as well as Alzheimer's disease. This indicates that autism-targeted drugs may affect other aspects of brain function. Thus, the drug might cause unexpected adverse reactions or it might be evaluated as a narcotic.

Second, the complex structure of the NMDA receptor is an issue. Although most nerve cells have NMDA receptors, their subunits differ slightly. Furthermore, some subunits appear or disappear in particular nerve cells depending on the developmental stage of the brain. Hence, it is confusing which cells or which stages are to be targeted when designing a drug.

Therefore, the Research Center has set up another target—Zinc. Scientists have become interested in zinc in relation to autism based on the environmental effects on autism. If autism is caused only by genetic factors, then, if one monozygotic twin has autism, the other must have autism too. However, cases of monozygotic twins both having autism account for about 80% of all cases. The remaining 20% suggest the involvement of environmental effects. It is well known infants born to pregnant women who experience severe immunological diseases or viral infections or who take antiepileptic drugs have an increased risk of developing autism. Recently, some clinicians have claimed that these kinds of



The molecular structures of memantine (top) and D-Cycloserine (bottom). Both are candidate drugs for autism, but their functional mechanisms and effects are different. These seemingly confusing results are speculated to be due to the diversity of nerve cells.

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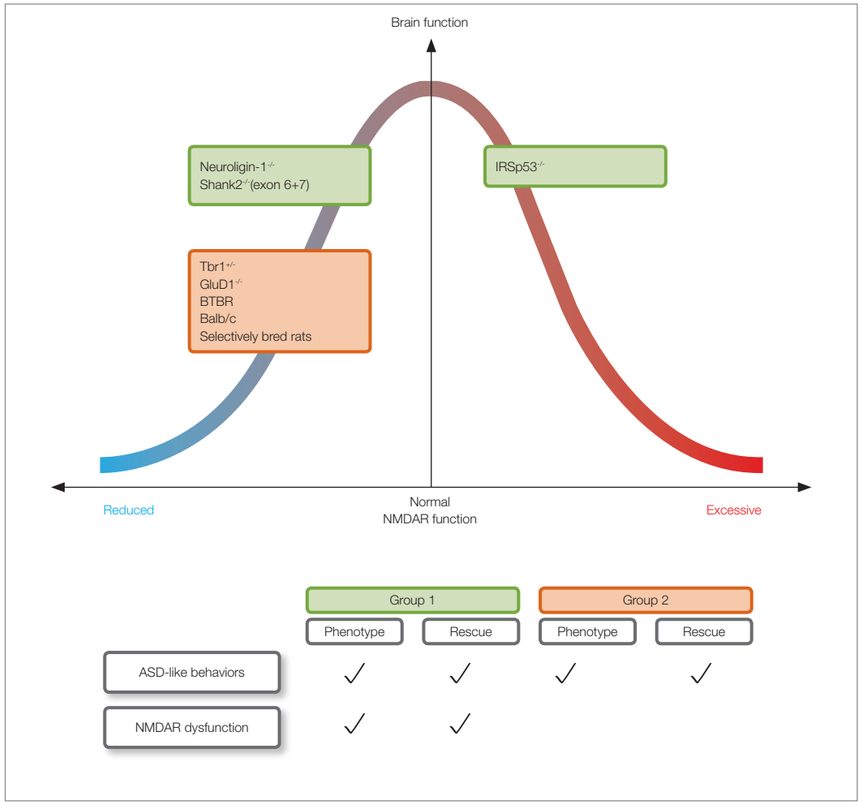
Zinc, which is an important nutrient, is a major component of enzymes and proteins in the body. The results of recent studies suggest that zinc plays an important role in the treatment of autism.



The hyperfunction or hypofunction of NMDA receptors is likely to cause autism. This hypothesis is supported by the results of behavioral studies and drug treatment studies of genetically modified mouse models with altered NMDA receptors.

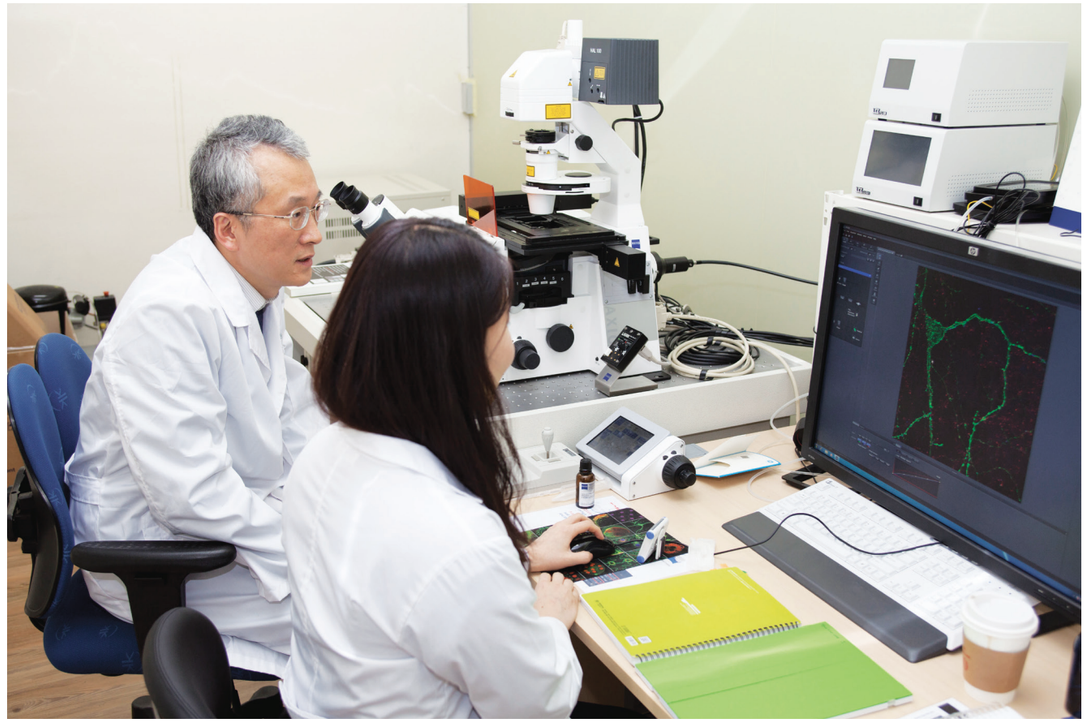
environmental effects account for up to 50% of the cases.

One of the major environmental factors that results in differences among individuals is nutrition. This is because many proteins that are involved in physiological functions in the body become structurally stable or fully functional from the effects of zinc that is ingested with the food. In fact, zinc concentrations tend to be lower in the hair of children with autism compared with the hair of children without autism. Zinc is essential for the maintenance of nerve cell functions. Therefore, nerve cells especially contain more zinc compared with other cells. A manuscript submitted by Director Kim is currently under review; it describes a study wherein mice administered a drug that transports zinc from nerve cells to synapses showed improvement in symptoms of autism.

Why is head circumference measured in childhood?

Despite many of the unanswered riddles that remain at the levels of cells and proteins, it is now clear that autism is a disease of synapses, which is supported by the fact that autism mostly starts in childhood, which is when nerve cells and synapses in the brain develop most vigorously. Autism is clinically diagnosed when a child repeats the same behavior or cannot directly look into other people's eyes before 3 years of age.

In addition, findings that events during pregnancy greatly affect the presence or absence of autism are one of the major pieces of evidence that suggests a relationship between autism and brain development. The fate of synapses, including their numbers and composition, is mostly determined during the prenatal period. Synapses are actively formed when information, such as sounds or movements, is transferred from the outside to the fetus through sensory cells 1–2 months before birth. Because sensory information rapidly increases from the moment of birth, synapses also increase exponentially. The acceleration of synapse development reaches a peak around 2 years of age. Thereafter, synapse development pauses, and then the number of synapses reduces to about half in adolescence. Therefore, the number of synapses that will be available throughout the life span is decided in adolescence. Director Kim said, "To secure the diversity of brain neural circuits, about twice the number of synapses is made and then discarded later." He explained, "That is the reason why education is important in childhood." Synapses and neuroglial cells play an essential role in signal transduction between nerve cells during brain development. Once nerve cells



Director Kim says it will be 20 years next year since he began studying synapses. In addition, he mentions that curing autism is one of the most important goals of the Research Center, and he hopes that his research will help relieve the difficulties of the affected patients and their families.

are formed, they extend branches to other nerve cells to form synapses; neuroglial cells are produced after nerve cells in order to support these connections. These neuroglial cells make up about 80% of the entire brain volume. If the brain is thought to be a rice bowl that contains rice and beans, the neuroglial cells are the rice and the nerve cells are the beans. The brain gradually grows due to the developmental processes. If a problem occurs during this developmental process, the chances of mental disorders, including autism, are higher. This is one of the reasons why head circumference is included in medical checkups of infants and toddlers. Abnormally big or small heads are often found in children with autism.

Physical substance that creates sociality

If a person glances at their watch during a conversation, most people think that that person must have other business and that they should finish the conversation soon. However, patients with autism are not aware of the meanings in these kinds of actions. Hence, it is hard for them to smoothly communicate with others, and they are diagnosed with deficiencies of sociality.

The human brain usually has about a 100 billion nerve cells, and each nerve cell is connected to about 1,000 synapses. It is hard to conclude that human sociality is exclusively attributed to those nerve cells or synapses. However, for the spontaneous production and function of sociality, which is a complex concept, in the human body, which is a collection of organic materials, a minimum amount of physical substance is required. Scientists believe that this substance is the synapse-based neural circuits in the brain. Director Kim said, "It will have been 20 years by next year since I started studying synapses," and, "Despite the seriousness of the difficulties for patients with autism and their families and the social costs, there is no appropriate medicine for autism. The Research Center wants to help cure autism."