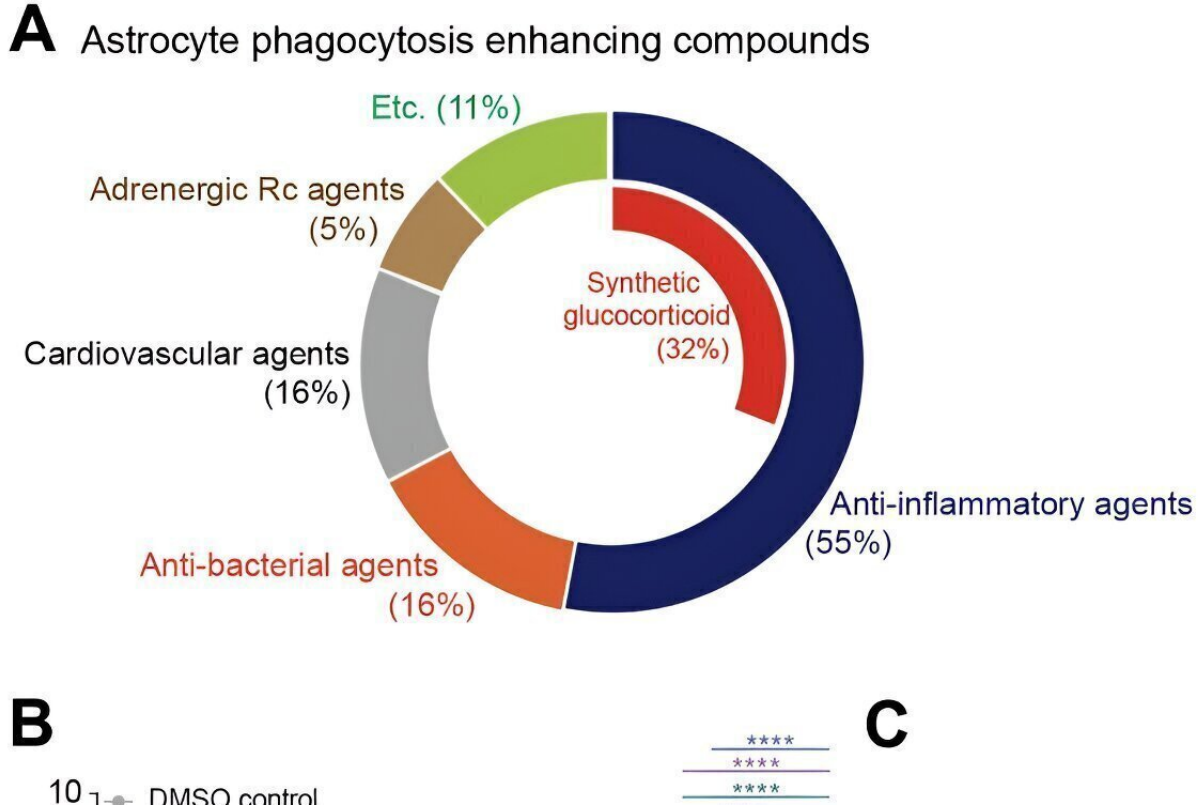
Research team identifies a cause of mental illnesses induced by childhood abuse

August 4 2023



Results of screening for compounds that increase astrocyte phagocytosis (A) Discovered that synthetic glucocorticoid (stress hormone) increases the phagocytosis of astrocytes through screening of FDA-approved clinical compounds. (B-C) When treated with stress hormones, the phagocytosis of astrocytes is greatly increased, but this phenomenon is strongly suppressed by the GR antagonist (Mifepristone). CORT: corticosterone (stress hormone), Eplerenone: mineralocorticoid receptor (MR) antagonist, Mifepristone: glucocorticoid receptor (GR) antagonist . Credit: *Immunity* (2023). DOI:

10.1016/j.immuni.2023.07.005

Childhood neglect and/or abuse can induce extreme stress that significantly changes neural networks and functions during growth. This can lead to mental illnesses, including depression and schizophrenia, but the exact mechanism and means to control it were yet to be discovered.

On August 1, a KAIST research team led by Professor Won-Suk Chung from the Department of Biological Sciences announced the identification of excessive synapse removal mediated by astrocytes as the cause of mental diseases induced by childhood abuse trauma. Their paper titled, "Stress induces behavioral abnormalities by increasing expression of phagocytic receptor MERTK in astrocytes to promote synapse phagocytosis," was published in *Immunity*.

The research team discovered that the excessive astrocyte-mediated removal of excitatory synapses in the brain in response to stress hormones is a cause of mental diseases induced by childhood neglect and abuse.

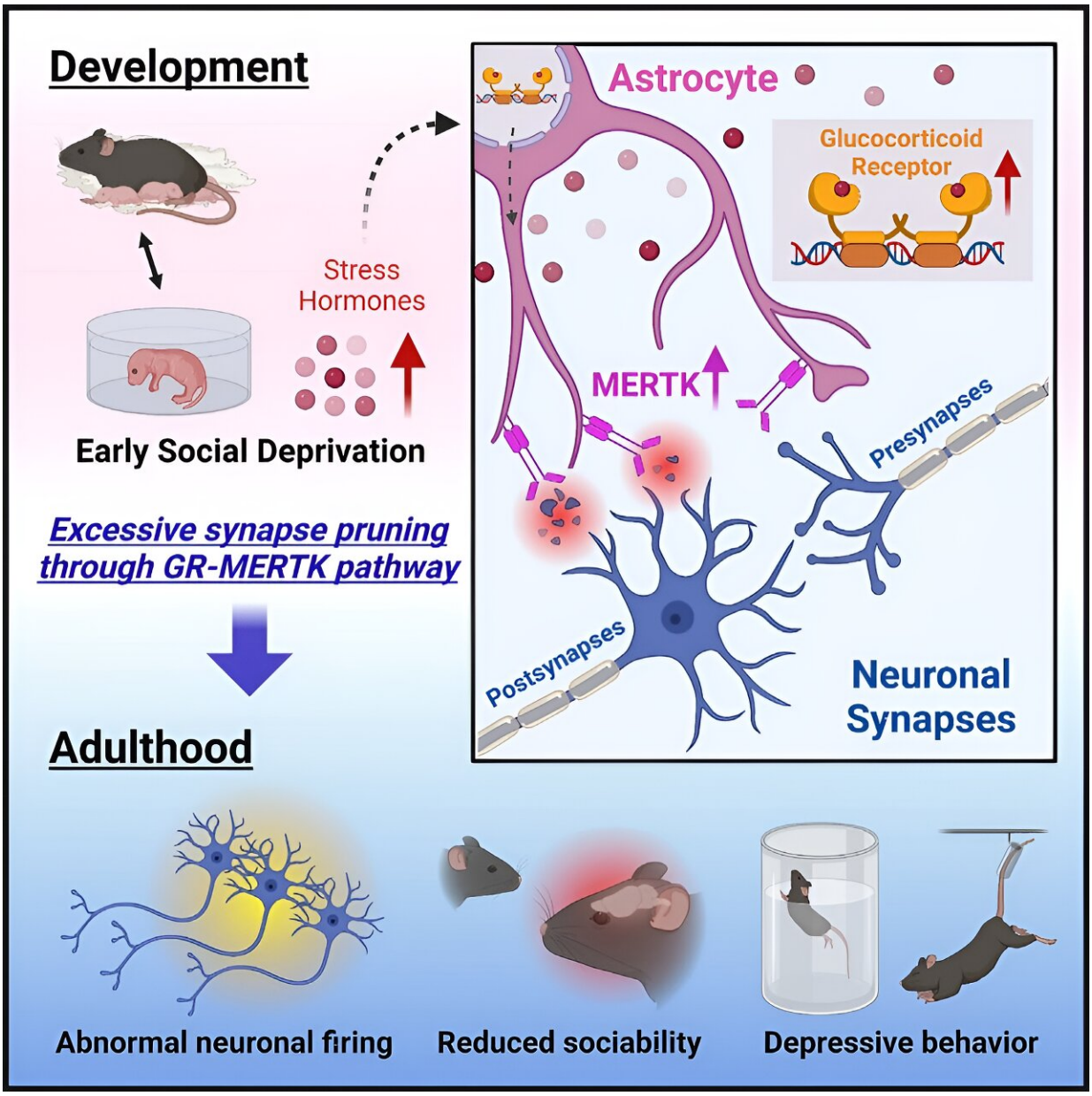
Clinical data have previously shown that high levels of stress can lead to various mental diseases, but the exact mechanism has been unknown. The results of this research therefore are expected to be widely applied to the prevention and treatment of such diseases.

The research team clinically screened an FDA-approved drug to uncover the mechanism that regulates the phagocytotic role of astrocytes, in which they capture external substances and eliminate them.

As a result, the team found that synthetic glucocorticoids, namely stress hormones, enhanced astrocyte-mediated phagocytosis to an abnormal

level.

Glucocorticoids play essential roles in processes that maintain life, such as carbohydrate metabolism and anti-inflammation, but are also secreted in response to external stimuli such as stress, allowing the body to respond appropriately. However, excessive and long-term exposure to glucocorticoids caused by chronic stress can lead to various mental diseases including depression, cognitive disorders, and anxiety.



A schematic diagram of the study published in Immunity. Excessive stress hormone secretion in childhood increases the expression of the MERTK phagocytic receptor through the glucocorticoid receptor (GR) of astrocytes, resulting in excessive elimination of excitatory synapses. Excessive synaptic elimination by astrocytes during brain development causes permanent damage to brain circuits, resulting in abnormal neural activity in the adult brain and psychiatric behaviors such as depression and anti-social tendencies. Credit: *Immunity* (2023). DOI: 10.1016/j.immuni.2023.07.005

To understand the changes in astrocyte functions caused by childhood stress, the research team used mouse models with early social deprivation, and discovered that stress hormones bind to the glucocorticoid receptors (GRs) of astrocytes. This significantly increased the expression of Mer tyrosine kinase (MERK), which plays an essential role in astrocyte phagocytosis.

Surprisingly, out of the various neurons in the cerebral cortex, astrocytes would eliminate only the excitatory synapses of specific neurons. The team found that this builds abnormal neural networks, which can lead to complex behavioral abnormalities such as social deficiencies and depression in adulthood.

The team also observed that microglia, which also play an important role in cerebral immunity, did not contribute to synapse removal in the mice models with early social deprivation. This confirms that the response to stress hormones during childhood is specifically astrocyte-mediated.

To find out whether these results are also applicable in humans, the research team used a brain organoid grown from human-induced pluripotent stem cells to observe human responses to stress hormones.

The team observed that the stress hormones induced astrocyte GRs and phagocyte activation in the human brain organoid as well, and confirmed that the astrocytes subsequently eliminated excessive amounts of excitatory synapses. By showing that mice and humans both showed the same synapse control mechanism in response to stress, the team suggested that this discovery is applicable to mental disorders in humans.

Prof. Won-Suk Chung said, "Until now, we did not know the exact mechanism for how childhood stress caused brain diseases. This research

was the first to show that the excessive phagocytosis of astrocytes could be an important cause of such diseases." He added, "In the future, controlling the immune response of astrocytes will be used as a fundamental target for understanding and treating brain diseases."

More information: Youkyeong Gloria Byun et al, Stress induces behavioral abnormalities by increasing expression of phagocytic receptor, MERTK, in astrocytes to promote synapse phagocytosis, *Immunity* (2023). DOI: 10.1016/j.immuni.2023.07.005

Provided by The Korea Advanced Institute of Science and Technology (KAIST)