Effects of stress on brain cells offer clues to new anti-depressant drugs

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Research from King's College London reveals the detailed mechanism behind how stress hormones reduce the number of new brain cells - a process considered to be linked to depression. The researchers identified a key protein responsible for the long-term detrimental effect of stress on cells, and importantly, successfully used a drug compound to block this effect, offering a potential new avenue for drug discovery.

The study, published in *Proceedings of the National Academy of Sciences* (*PNAS*) was co-funded by the National Institute for Health Research Biomedical Research Centre (NIHR BRC) for Mental Health at the South London and Maudsley NHS Foundation Trust and King's College London.

Depression affects approximately 1 in 5 people in the UK at some point in their lives. The World Health Organisation estimate that by 2030, depression will be the leading cause of the global burden of disease. Treatment for depression involves either medication or talking therapy, or usually a combination of both. Current antidepressant medication is successful in treating depression in about 50-65% of cases, highlighting the need for new, more effective treatments.

Depression and successful antidepressant treatment are associated with changes in a process called "neurogenesis"- the ability of the adult brain to continue to produce new brain cells. At a molecular level, stress is known to increase levels of cortisol (a stress hormone) which in turn acts on a receptor called the glucocorticoid receptor (GR). However, the

exact mechanism explaining how the GR decreases neurogenesis in the brain has remained unclear.

Professor Carmine Pariante, from King's College London's Institute of Psychiatry and lead author of the paper, says: "With as much as half of all depressed patients failing to improve with currently available medications, developing new, more effective antidepressants is an important priority. In order to do this, we need to understand the abnormal mechanisms that we can target. Our study shows the importance of conducting research on cellular models, animal models and clinical samples, all under one roof in order to better facilitate the translation of laboratory findings to patient benefit."

In this study, the multidisciplinary team of researchers studied cellular and animal models before confirming their findings in human blood samples. First, the researchers studied human hippocampal stem cells, which are the source of new cells in the human brain. They gave the cells cortisol to measure the effect on neurogenesis and found that a protein called SGK1 was important in mediating the effects of stress hormones on neurogenesis and on the activity of the GR.

By measuring the effect of cortisol over time, they found that increased levels of SGK1 prolong the detrimental effects of stress hormones on neurogenesis. Specifically, SGK1 enhances and maintains the long-term effect of stress hormones, by keeping the GR active even after cortisol had been washed out of the cells.

Next, the researchers used a pharmacological compound (GSK650394) known to inhibit SGK1, and found they were able to block the detrimental effects of stress hormones and ultimately increase the number of new brain cells.

Finally, the research team were able to confirm these findings by

studying levels of SGK1 in animal models and human blood samples of 25 drug-free depressed patients.

Dr Christoph Anacker, from King's College London's Institute of Psychiatry and first author of the paper, says: "Because a reduction of neurogenesis is considered part of the process leading to depression, targeting the molecular pathways that regulate this process may be a promising therapeutic strategy. This novel mechanism may be particularly important for the effects of chronic stress on mood, and ultimately depressive symptoms. Pharmacological interventions aimed at reducing the levels of SGK1 in depressed patients may therefore be a potential strategy for future antidepressant treatments."

More information: Anacker, C. et al. 'A role for the kinase SGK1 in stress, depression and glucocorticoid effects on hippocampal neurogenesis' *Proceedings of the National Academy of Sciences* (*PNAS*) (May 2013) www.pnas.org/cgi/doi/10.1073/pnas.1300886110

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