Hippocampal interneurons and treatment for major depressive disorder

Major depressive disorder is a widespread and often debilitating mental illness, negatively affecting the quality of life of those experiencing it. Understanding the mechanisms behind depression and its treatment is key to improving therapy. Signaling involving serotonin has a major role in depression, and SSRIs are a popular class of antidepressant that target the disorder. Dr Yotam Sagi from The Rockefeller University, New York, examines the role of hippocampus interneurons in depression. Recent studies by Dr Sagi on parvalbumin and cholecystokinin interneurons in the hippocampus have revealed the mechanisms behind p11 in depression and its treatment.

According to the WHO, more than 264 million people worldwide suffer from depression. This mental illness can stem from a multitude of factors, leading to symptoms such as low self-worth, lack of energy, and loss of enjoyment and motivation. It is estimated that 7.2% of Americans had a depressive episode in 2018. Many different medications for depression are available, with selective serotonin reuptake inhibitors (SSRIs) being some of the most popular. Between 2015 and 2018, 13.2% of American adults had recently used antidepressants.

Given the widespread use of antidepressants and their importance for treating an often debilitating mental illness, it is vital that we understand how they work in as much detail as possible. Dr Yotam Sagi, a Senior Research Associate at The Rockefeller University, New York, has authored multiple studies that delve into the molecular mechanisms of how SSRIs act on neurons in the hippocampus.

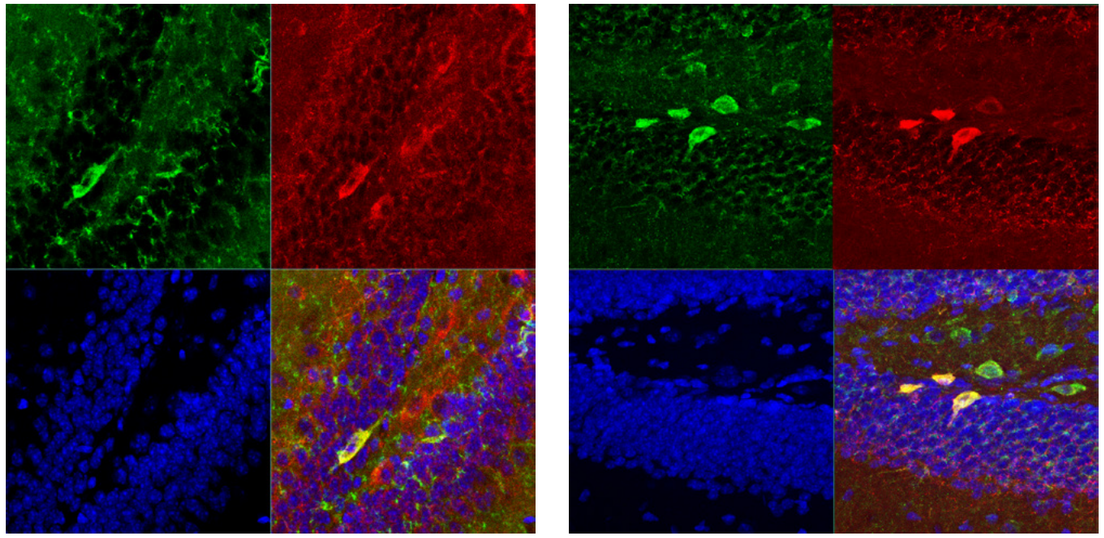
HOW DO SSRIs WORK?

A lot has been discovered about the mechanism behind the therapeutic effects of SSRIs; however, a lack of knowledge is still a barrier to treating depression. Serotonergic neurons are neurons that signal using the neurotransmitter serotonin, which is involved in regulating mood. SSRIs block the reuptake of serotonin from the cleft between these neurons, meaning more serotonin remains in the cleft, thus increasing serotonergic transmission.

Unfortunately, SSRI treatment does come with some downsides. As well as users experiencing side effects, the drugs can take a while to show therapeutic effects, sometimes even months. For this reason, Dr Sagi studies how SSRIs affect cells in the hippocampus before and after chronic, or long-term, use. This is because hallmarks of major depressive disorder include impairments in the hippocampus. Much of this research focuses on how parvalbumin expressing (PV) and cholecystokinin expressing (CCK) interneurons are involved in stress and SSRI response. These interneurons use the neurotransmitter GABA and are inhibitory, meaning that they reduce the excitability of other neurons in the hippocampus.

NEURENSIN-2 AND MOOD

In one of two studies recently published in *Molecular Psychiatry,* Dr Sagi explores the role of Neurensin-2 and SMARCA3 in depression and antidepressant action. Neurensin-2 is a protein that associates with neurons that receive nerve impulses (called postsynaptic neurons), and is highly expressed in some GABAergic neurons, including PV and CCK expressing interneurons. SMARCA3 is a chromatin remodeler that regulates gene transcription, also highly expressed in PV and CCK interneurons.



Microscopic images of protein p11 in CCK (left) and PV (right) neurons in the hippocampus. p11 is depicted in green, CCK and PV are imaged in red. The cell nucleus in blue shows the shape of the dentate gyrus of the hippocampus.

Dr Sagi's research studies how SSRIs affect cells in the hippocampus during interim use.

In the study, it was found that deleting SMARCA3 in CCK interneurons caused impaired emotional behaviour in mice. In behavioural tests, deleting SMARCA3 in CCK interneurons caused anhedonia-like behaviour – anhedonia is the inability to feel pleasure – as well as anxiety and despair-like behaviour. The despair-like behaviour was not observed when SMARCA3 was deleted from PV interneurons.

Dr Sagi's team then used a method called translating ribosome affinity purification (TRAP) to identify genes regulated by SMARCA3 in CCK interneurons. They found that many of these genes encode proteins that regulate postsynaptic excitatory input. 26% of these genes were associated with AMPA receptor signaling. Reduction in AMPA receptor subunits cells, miniature postsynaptic currents (mPSCs) caused by AMPA were reduced by 75%.

is an impairment in the hippocampus associated with depression in previous studies, but a direct molecular mechanism that explains this impairment was unknown. An impairment in AMPA receptor signaling was then confirmed physiologically. When SMARCA3 was deleted in CCK

The researchers then identified Neurensin-2 as a gene regulated downstream by SMARCA3, as Neurensin-2 was upregulated in cells with SMARCA3 deletion. This caused the team to hypothesise that SMARCA3 could have a role in repressing the expression of Neurensin-2. When chronic stress was

Given the widespread use of antidepressants, it is vital that we understand exactly how they work.

induced in mice, both SMARCA3 and Neurensin-2 levels changed. SMARCA3 levels in hippocampal cell nuclei went down, whereas Neurensin-2 levels in the cytoplasm went up. In these experiments, mice more susceptible to stress had a lower frequency of AMPA receptor mPSCs.

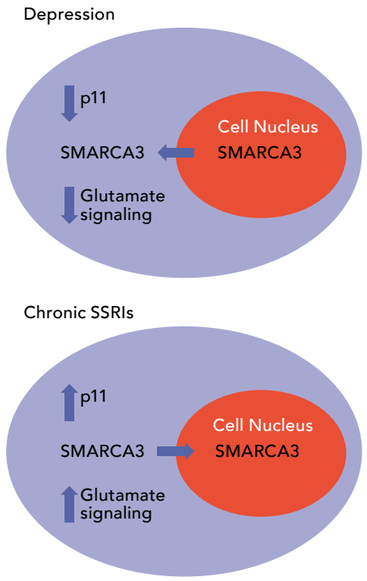
When Neurensin-2 was deleted and stress was induced in mice, they showed less social avoidance, anxiety-like behaviour, and anhedonia than control mice. The opposite effect was seen when Neurensin-2 was overexpressed, impairing social interaction and nesting behaviour as well as increasing anxiety-like behaviour. When Neurensin-2 was overexpressed, an increase in AMPA-induced mPSCs was also seen in CCK interneurons.

SSRI TREATMENT, NEURENSIN-2, SMARCA3, AND P11

In a second paper in *Molecular Psychiatry,* Dr Sagi's team investigated how long-term treatment with the SSRI fluoxetine – otherwise known as Prozac – is intertwined with the action of Neurensin-2, SMARCA3, and p11. Studies on the protein p11 have indicated that it has a role in regulating mood, especially in depression and SSRI treatment, due to interaction with proteins involved in serotonergic signaling. A previous study has shown that p11 and SMARCA3 bind together to form a complex following long-term SSRI treatment, which has been theorised to alter gene transcription.

In this paper, the researchers started by giving mice two weeks of treatment with a range of SSRIs, all of which caused downregulation of the gene that encodes for Neurensin-2, Nrsn2. Fluoxetine showed the most marked effect, with the gene being downregulated by 20.5%. A single dose of fluoxetine did not alter Nrsn2 levels, but downregulation was already detected after 7 days of treatment. While Nrsn2 was downregulated with fluoxetine treatment, p11 was shown to be upregulated after 7 days of treatment, implying that these early changes start before the behavioural response to SSRIs is established.

In mice where p11 was deleted, both Nrsn2 transcript and the levels of Neurensin-2 protein were increased. SMARCA3 deletion also increased



The protein p11 regulates excitatory (Glutamate) signaling and emotional behavior via its interaction with the chromatin remodeling factor, SMARCA3.

While Nrsn2 was downregulated with fluoxetine treatment, p11 was shown to be upregulated.

the expression of Nrsn2. However, SMARCA3 transcription was unchanged with fluoxetine treatment. This made the researchers theorise that SSRI treatment upregulating p11 could increase the amount of SMARCA3 in the cell nucleus. This idea was supported when 60% more SMARCA3 was found in cell nuclei after two weeks of treatment.

The researchers then determined where in the hippocampus this cascade acts by deleting p11 from either CCK or PV interneurons of mice and treating them with SSRI. Upregulation of p11 was observed after treatment with the SSRI citalopram. However, this effect was not seen when p11 was deleted from PV interneurons. Deletion of SMARCA3 in PV interneurons attenuated the downregulation of Nrsn2 by fluoxetine. These mice did not show anhedonia but lost their behavioural response to fluoxetine. The researchers then hypothesised that the downregulation of Neurensin-2 in PV interneurons by p11 and SMARCA3 is important for the behavioural response to antidepressants. Overexpression of Neurensin-2 in PV interneurons resulted in loss of the antidepressant response by fluoxetine. The physiological implications of fluoxetine treatment were then studied. 21 days of fluoxetine treatment increased the frequency of AMPA receptor-mediated mPSCs by 160% in mice with Neurensin-2 deleted from their PV interneurons. Wild-type mice showed a frequency increase of 72% after fluoxetine treatment. However, when Neurensin-2 was overexpressed, there was no increase in mPSC frequency.

WHAT THESE RESULTS MEAN

These studies identify how this protein cascade in neurons of the hippocampus have a role in both susceptibility to depression and the responsivity to SSRI treatment. This helps us understand what goes on in the brain over the course of treatment with SSRIs, and could be useful in identifying ways to improve treatment for depression.

Through his research, Dr Sagi aims to improve treatment for depression.

Behind the Research

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Research Objectives

Dr Sagi's research elucidates how neurons of the hippocampus regulate the susceptibility to depression and the response to its treatment.

Detail

Bio

Dr Yotam Sagi is a Senior Research Associate at the Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York. His research focuses on identifying molecular mechanisms implicated in stress related disorders and drug abuse.

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Personal Response

How could these findings impact the future of depression treatment?

"The main challenges involving treating major depressive disorder (MDD) include the delay in the clinical response, resistance to treatment, and worsening of symptoms. Because not all patients respond to every treatment, many MDD patients need to try different treatments before a beneficial effect is reached, leading to poor compliance and relapse. Our goals are to develop unbiased tools to predict the responsivity to antidepressants after short treatment, and to develop a new class of short-term treatments that could facilitate the clinical response to the slow-acting antidepressants."

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