European College of Neuropsychopharmacology – press release

Researchers find that Antidepressants may improve brain function

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- Type of research: peer reviewed/experimental study/people

Researchers have found that SSRI (*Selective Serotonin Reuptake Inhibitors)* antidepressants have the potential to improve certain cognitive functions, such as verbal memory. They measured brain function in patients before and after taking the SSRI escitalopram and correlated this to a drop in the level of one of the serotonin receptors in the brain and to cognitive improvements during treatment. This work is presented for the first time at the ECNP Conference in Milan, after recent publication in the journal *Biological Psychiatry*.

Serotonin is often described as a 'feel good' chemical, and higher levels of serotonin circulating in the brain contribute to a sense of well-being, and can ease clinical depression in most sufferers. There are several serotonin receptors in the brain, and all will serve to regulate well-being by regulating circulating serotonin's interaction with the brain. However, this work concentrated on only one serotonin receptor, the $5HT_4$ receptor.

The researchers began by scanning the brains of 90 depressed patients, to measure the quantity of $5HT_4$ receptor which serotonin binds to. At the same time, patients were given a series of tests to measure mood and cognitive abilities.

Patients were given daily doses of escitalopram, and at the end of an 8-week period, 40 patients were rescanned to measure the quantity of $5HT_4$ receptor in the brain. The mood of the patients had improved, but the team also found that the levels of $5HT_4$ receptor had dropped by around 9% possibly due to adaptations to increased levels of serotonin. When they asked these patients to undertake more cognitive tests, they found that their performance had improved, so that *the less* the $5HT_4$ receptor had changed the better the cognitive outcome. This phenomenon was particularly prominent for the ability to recall words.

"*This is potentially significant*" said researcher Vibeke Dam (Copenhagen University Hospital, Rigshospitalet, Denmark), "*It seems that the SSRI medication contributes to an improvement on cognitive function, at the same time as helping improve mood. Our work ties the improvement in cognitive function to the specific $5HT_4$ receptor and suggest that direct serotonin 4 receptor stimulation may be in important pro-cognitive target to consider in optimizing outcomes of antidepressant treatment. It also reinforces the idea that serotonin is crucial to mood improvement*.

Co-researcher Vibe Froekjaer (Copenhagen University Hospital, Rigshospitalet, Denmark), added, *"This is a first result, so we need to do a lot more work to look at the implications. Poor cognitive function is very hard to treat efficiently and may*

require extra treatment. This work points to the possibility of stimulating this specific receptor so that we can treat cognitive problems, even aside from whether or not the patient is has overcome the core symptoms of depression".

The researchers note that this was a real-world study, so there is no placebo control.

The team's next step is to treat patients with drugs which specifically stimulates the $5HT_4$ receptor to see the effect on cognitive function; interestingly, serotonin is also found in the gut, and there are drugs available to treat irritable bowel syndrome which specifically bind to and stimulate $5HT_4$, which the team may repurpose in these trials.

Commenting, Professor Philip Cowen, Professor of Psychopharmacology at the University of Oxford said:

"In the context of recent controversies about the role of brain serotonin in clinical depression, it is noteworthy that the PET studies of the Copenhagen Group provide unequivocal evidence that brain 5-HT4 receptors are decreased in unmedicated depressed patients. Their work also demonstrates the intimate role of brain 5-HT4 receptors in cognitive function. This confirms recent work from Oxford showing that the 5-HT4 receptor stimulant, prucalopride – a drug licensed for the treatment of constipation- improves memory in both healthy participants and people at risk of depression".

This is an independent comment, Professor Cowen was not involved in this work.

Article in Press, Biological Psychiatry: https://www.biologicalpsychiatryjournal.com/article/S0006-3223(24)01537-3/abstract

Please note that all comments derive from the conference, they do not appear in the publication.

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Notes for Editors

This work is presented at the 37th ECNP Congress, taking place in Milan and online 21-24 September 2024, see https://www.ecnp.eu/Congress2024/ECNPcongress. With more than 6,000 participants the ECNP Congress is Europe's leading platform for the latest research in disease-related neuroscience.

Conference abstract: P2085 Serotonin 4 receptor and its associations with clinical outcomes and verbal memory over the course of antidepressant treatment in depression

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Background: The serotonin 4 receptor (5-HT_4R) has been highlighted as a promising treatment target in major depressive disorder (MDD) particularly for cognitive symptoms [1]. We previously showed that cerebral 5-HT4R binding is ~7% lower in unmedicated patients with MDD compared with healthy individuals and that low 5-HT_4R binding is associated with poorer verbal memory performance in the depressed patients [2]. We here

for the first time map 5-HT_4R binding in patients with MDD over the course of standard antidepressant treatment.

Aim: To investigate the relationship between cerebral 5-HT_4R binding, clinical symptom outcomes, and cognitive function in patients with MDD who initiate selective serotonin reuptake inhibitor (SSRI) drug treatment.

Methods: Ninety moderately to severely depressed patients (64 females; mean age=27.1, range 18–57) underwent molecular brain imaging with the [^{11}C]SB207145 radiotracer to measure 5-HT_4R brain binding and cognitive testing prior to starting 12 weeks of standard antidepressant treatment with the SSRI escitalopram [3]. A subsample of 40 patients we rescanned again after 8 weeks and all patients completed cognitive testing again after 12 weeks of treatment. Clinical depressive symptoms were assessed with Hamilton depressive rating scale 6 ($HAMD_6$) at baseline and after 4, 8 and 12 weeks of treatment.

We used logistic regression to assess if pretreatment cerebral 5-HT_4R binding in neocortex, neostriatum and hippocampus can predict patient status (remission vs non-response) after 8 weeks of treatment. In addition, latent variable models (LVMs) were used to assess if global pretreatment 5-HT_4R is correlated with reduction in $HAMD_6$ scores after 4, 8 and 12 weeks of treatment. LVMs were also used to assess change in 5-HT_4R binding for a subgroup of patients (n=40) who were rescanned again after 8 weeks of treatment and to assess the correlation between change in 5-HT_4R binding and change in $HAMD_6$ scores and change in verbal memory performance.

Results: Pretreatment 5-HT_4R binding did not predict clinical recovery status at week 8 (all AUC<0.57, all p_{adj}=1.0) nor was it associated with change in $HAMD_6$ after 4 (r=0.08, p_{adj}=1.0), 8 (r=-0.09, p_{adj}=1.0) or 12 (r=-0.11, p_{adj}=1.0) weeks. After 8 weeks of antidepressant intervention global 5-HT_4R levels were significantly reduced (p<0.001) irrespective on antidepressant response status. At a regional level, the decrease in binding constituted 9.0% in neostriatum (p_{adj}<0.0001), while no significant change was observed in neocortex (-1.4%, p_{adj}=1.0) or hippocampus (-1.7%, p_{adj}=1.0). While change in 5-HT_4R binding was not correlated with change in $HAMD_6$ scores at week 8 (r=0.06, p=0.73), it was positively correlated with change in verbal memory symptoms (r=0.40, p=0.04).

Interpretation: We here show that 5-HT_4R is downregulated over the course of SSRI treatment which is consistent with the notion that antidepressants increase cerebral extracellular serotonin. Meanwhile, our findings also suggest that patients whose 5-HT_4R levels did not decrease experienced the largest improvement in memory performance, highlighting the potential importance of 5-HT_4R as a treatment target in MDD for cognitive symptoms. These findings offer insights to mechanisms underlying antidepressant effects and point to new directions for precision medicine treatments in MDD.

References

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Article in press, Biological Psychiatry: Effect of antidepressant treatment on 5-HT_4 receptor binding and associations with clinical outcomes and verbal memory in major depressive disorder
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