Research on galanin can result in new drugs for depression

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Depression afflicts a large number of people over their lifetime. In addition to suffering and a risk for suicide, the disease is associated with major cost for society.

Different types of treatment are available, including pharmacological interventions such as SSRIs, e.g. Prozac. Even if this treatment is successful in around 60 percent of patients, there are problems with resistance, side effects and late onset of the therapeutic effect.

Against this background, researchers at Karolinska Institutet are searching for new targets for development of improved antidepressants. Among the targets are receptors for neuropeptides, a large group of neurotransmitters. Galanin is a 29/30 amino acid long neuropeptide that acts via three receptors, GalR1-3.

Studies show an anti-depressive effect

Galanin, which was purified from porcine intestine, was discovered more than 30 years ago by Viktor Mutt and his Ph.D. student Kazuhiko Tatemoto. This peptide has since then been studied with focus on depression by several groups at KI and Stockholm university. Extensive animal experiments suggest that the GalR1 antagonist could have antidepressive effect.

Swapnali Barde and collaborators have now investigated to what extent the results from animal experiments are relevant for humans. Five regions were studied in post-mortem brains from depressed women and men that had committed suicide and from controls.

"We use three methods for analysis of galanin and the three receptors: qPCR to measure levels of transcript (mRNA), prosequencing to measure DNA methylation (epigenetic changes) and radioimmunoassay, the latter, however, only to measure concentrations of galanin," says one of the authors, Tomas Hökfelt.

Results show a difference between sick and healthy brains, especially in the frontal lobe and in two nuclei in the lower brain stem. Various

anterior cingulum was not affected at all. Furthermore, it was especially the transmitter cells, that is, galanin and GalR3, that show changes. Both were upregulated in the brain stem nuclei and downregulated in the frontal lobe.

"At the same time, the methylation was changed in the opposite direction, which is in agreement with a theory that methylation suppresses synthesis. The changes were seen both in women and men," Tomas Hökfelt continues.

Fewer side effects expected

GalR3 coexists both with noradrenalin and 5-hydroxytryptamin in separate nerve populations in the nuclei of the lower brain stem. GalR3 is an inhibitor receptor that slows down activity in these nerve cells, and in this way, reduces release of NA and 5-HT in the forebrain. Since the transcript for both galanin and GalR3 are upregulated, these likely result in reduction in activity of these two monoamines in the forebrain in depression. A GalR3 antagonist could thus possibly have an antidepressant effect by inhibiting 'the break.'

"The end result is similar to what SSRIs and similar medicine cause, namely to increase the brain content of 5-HT and NA – but via a completely different mechanism. The expectation is that a GalR3 antagonist also would act faster, that is, without delay, as well as have fewer side effects," concludes Tomas Hökfelt.

More information: Swapnali Barde et al. Alterations in the neuropeptide galanin system in major depressive disorder involve levels of transcripts, methylation, and peptide, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1617824113