Sequestered prion protein takes the good mood away, suggests new hypothesis on depression

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The discovery of antidepressant drugs in the 1950s led to the first biochemical hypothesis of depression, known as the monoamine hypothesis. This hypothesis proposes that an imbalance of certain brain chemicals is the key cause of depression. Research has investigated whether and to what degree the "reward and pleasure" chemical

dopamine and, more recently, the "happiness" chemical serotonin, could be the neurotransmitters involved in the malady. However, the monoamine hypothesis does not seem to fully explain the complexity of human depression. Now a new study offers one more important key that may increase our understanding of the pathogenesis behind clinical depression and neurodegenerative disorders.

Proteinaceous infectious particles, also known as prions, are proteins in which the complex molecular three-dimensional folding process has simply gone astray. For reasons not yet understood, the misfolding nature of prions is associated to their ability to sequester their normal counterparts and induce them to misfold as well. The ever-growing crowd of misfolded proteins form the aggregates seen in the brains of patients with neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Patients with these disorders manifest progressive neurological deterioration and clinical depression, among other symptoms.

Although the misfolded counterparts have historically received all the attention, the spotlight is now on the native protein, namely the prion protein, which is the one that has not undergone misfolding. What role do the native proteins play? An interesting hypothesis is that these particles serve as a hub where some cellular components assemble. For instance, it has already been shown that the prion protein participates in events such as cell proliferation, differentiation and survival. Now a team led by Dr. Rafael Linden from the Institute of Biophysics Carlos Chagas Filho, at the Federal University of Rio de Janeiro, in Brazil, proposes that the prion protein plays a role in depression.

In an article entitled "Prion protein modulates monoaminergic systems and depressive-like behavior in mice" and published in the *Journal of Biological Chemistry*, the group shows that mice lacking normal prions show a depressive-like behavior similar to depression symptoms found

in patients with Alzheimer's and prion diseases, namely Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), Gerstmann-Sträussler-Scheinker syndrome, Fatal Familial Insomnia and kuru. Human prion diseases frequently show clinical symptoms such as depression, anxiety, and hallucinations, and the monoamine hypothesis has been called to explain such deficits.

The research conducted by the group shows that mice with no prion protein have increased levels of the receptors that bind to serotonin. Additionally, the levels of the enzyme that makes dopamine, and dopamine itself, are also higher in mice deprived of the prion protein. Interestingly, the study shows that although these animals have high levels of dopamine, they do not show the normal response that should occur when dopamine binds to its receptor, despite the fact that the levels of the receptor for dopamine are normal in these animals. According to Danielle Beckman, the first author of the paper "it is possible that the lack of interaction between dopamine and its receptor results from a desensitization of the receptor precisely because there is too much dopamine".

Another important observation made by the group, and which supports the hypothesis that prions have a role in depression, is the fact that the prion protein is found in the same places in the cell as the dopamine and serotonin receptors. Additionally, the authors observed that the prion protein might bind to the dopamine receptor.

The group believes that in normal individuals, the prion protein works as a scaffold for multiple molecular interactions. When prion protein molecules are sequestered by their misfolded counterparts, they can no longer work as a scaffold for all these molecular interactions, which impairs the mechanisms evoked by the brain chemicals important for mood.

These findings open the door for future research considering the prion protein as a potential target in the development of treatments for major depression and related disorders.

More information: *Journal of Biological Chemistry*, www.jbc.org/content/early/2015 … 666156.full.pdf+html

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