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Altered circadian somatostatin expression linked to bipolar disorder

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Results of the first study of its kind to link abnormalities in circadian rhythms to changes in specific neurotransmitters in people with bipolar disorder will be published this week in the journal *Biological Psychiatry*.

The three-year study conducted by McLean researchers points to specific neuroanatomical changes in human subjects with these illnesses, and specifically to neurons that regulate anxiety and stress response, according to Harry Pantazopoulos, PhD, assistant neuroscientist at McLean's Translational Neuroscience Laboratory and instructor in psychiatry at Harvard Medical School.

"For more than 50 years, there's been evidence that there's something wrong with circadian rhythms in people with bipolar disorder, but there has been a huge gap in terms of what we understand about their brains and how altered circadian rhythms are contributing to their symptoms," noted Pantazopoulos, lead author of the study.

"Growing evidence points to a key role for somatostatin, a neurotransmitter in schizophrenia and bipolar disorder," he said. "In the amygdala, a part of the brain involved in anxiety and stress, somatostatin plays an important role in the regulation of anxiety and depression, often co-occurring in these disorders."

The paper provides three main, previously unreported findings:

- Somatostatin immunoreactive neurons are decreased in the amygdala in schizophrenia and in bipolar disorder.
- The expression of somatostatin in the human amygdala displays a healthy circadian rhythm of expression.
- This circadian somatostatin expression is altered in subjects with bipolar disorder.

This altered circadian function of somatostatin in subjects with bipolar disorder consists of a sharp decrease in somatostatin expression by neurons in the early morning, in comparison to a rise in the same neurons during this time interval in healthy control subjects, according to Pantazopoulos.

"We eventually saw that people with bipolar disorder have a very strong decrease of this protein in the beginning of the day while people without a psychiatric disorder normally have an increase in this protein," he said. "The decrease of the protein correlates very strongly with the established severity of depression and anxiety symptoms in people with mood disorders, in the morning. Therefore, our findings point to potential neural correlates of circadian rhythm abnormalities associated with specific symptoms in bipolar disorder."

The study was conducted using postmortem brains from the Harvard Brain Tissue Resource Center, in which 15 brains were used from healthy controls, 15 with bipolar disorder, and 12 with schizophrenia.

"Brain imaging technology doesn't have the resolution at the moment to allow us to examine these neurons in the brain in people with bipolar disorder because the changes are in very specific neurocircuits that we can't visualize very well," said Pantazopoulos. "With post mortem brain studies, we are able to look at changes microscopically."

While the study validates what many researchers have long suspected, Pantazopoulos is cautious about drawing conclusions. "We're only scratching the surface of learning what the rhythmic expression of these proteins does biologically and how this goes awry in psychiatric disorders. We have a long way to go, as this is just one brain region and one specific protein."

Pantazopoulos recently launched a new study that looks at neurotransmitters as well as the clock genes within the suprachiasmatic nucleus of people with bipolar disorder and those without psychotic disorders--to characterize how the proteins' rhythm of expression change.

"From studies on animals, we know we can treat the circadian rhythm of the suprachiasmatic nucleus non-pharmacologically by using light therapy. We could potentially correct the abnormalities in circadian rhythms in some areas, such as the amygdala--by resetting the circadian rhythm with bright light therapy," said Pantazopoulos. "The goal is to not only understand the pathology of these disorders, but to develop new diagnostic methods and treatments down the line, possibly patient-specific bright light therapy."

Source:
McLean Hospital