Blood Biomarker acetyl-L-carnitine (LAC) May Help Depression Diagnosis

Researchers Find a “Lack of LAC” in Cases of Major Depressive Disorder

Acetyl-L-carnitine acts on neurons (pictured here) that release the neurotransmitter glutamate. Researchers believe that, by altering glutamate levels, the molecule affects systems involved in depression. [Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University]

- It may be possible to diagnose depression using more than just a patient’s behavioral symptoms. New findings suggest that people with major depressive disorder (MDD) have lower levels of the molecule acetyl-L-carnitine (LAC) in their blood than healthy controls. In addition, the degree of LAC deficiency reflects the severity and the age of onset of MDD—making LAC a tool that could transform depression diagnosis and treatment.

- This type of breakthrough, says Scott Russo, Ph.D., associate professor of neuroscience and the director of the Center for Affective Neuroscience, is something that “we’ve been talking about for generations.” He adds that a test like this is “exactly what we need” and that the field has relied on “symptom clusters” and ignored biology for too long.

- Giulio Pasinetti M.D., Ph.D., professor of neurology at the Icahn School of Medicine at Mount Sinai agrees, telling GEN that “identifying easily obtainable biomarkers that accurately diagnose depression is an imperative for improving mental health,” adding that “depression, when
undiagnosed and untreated, increases an individual’s risk to develop more severe symptoms.”

- Carla Nasca, Ph.D., a member of the McEwen lab at The Rockefeller University, the lead author on this study entitled “Acetyl-L-carnitine deficiency in patients with major depressive disorder,” published in the Proceedings of the National Academy of Sciences (PNAS), has been studying the role of LAC in stress and depression for years. LAC donates acetyl groups to histones, regulating the expression of genes important for synaptic plasticity, including those genes that regulate levels of glutamate—the major excitatory neurotransmitter in the brain. Too much glutamate in the brain leads to excitotoxicity, which can result in cell death, a loss of resilience to stress, depression, and other stress-related mental disorders.

- In the current paper, Dr. Nasca and her colleagues, in collaboration with Natalie Rasgon, M.D., Ph.D., at Stanford University, have published a translational study looking at the LAC levels in two non-overlapping patient populations.

The image depicts an artistic interpretation of the LAC working model in which glutamatergic overflow, symbolized by the heavy raindrops, has
been suggested as brain target regulated by LAC in a key brain region, the seahorse-shaped ventral hippocampus, whose epigenetic protection can shield from the rain. [Maria Rita Schillaci]

- When asked when she first hypothesized that LAC may play a pivotal role in depression, Dr. Nasca responds that “results from several rodent studies generated [a] hypothesis for a deficiency in LAC in major depression.” She adds that “rodents with behavioral abnormalities have a LAC deficiency that signals impaired neural and systemic functions such as hippocampal glutamatergic dysfunction, abnormal structural plasticity, as well as systemic insulin resistance.” These traits were improved in the rodents by supplementation with LAC, suggesting a possible role for LAC as a treatment for depression in humans.

- Regarding the use of LAC as a treatment for depression, Dr. Russo says that “the data from the animal model experiments years ago look convincing, with a rapid and robust reversal of behavioral symptoms.” Although he states that “mice aren’t people,” he adds that these data are a “very good starting point.” Dr. Russo is particularly excited by how rapidly the animals’ symptoms were reversed when given LAC. He explains that a rapidly acting anti-depressant would be a huge benefit for treatment because many of the drugs currently found in the anti-depressant arsenal take 4–6 weeks to see any effect. Rapidly acting drugs could save lives, especially in the suicidal patient population.

- Dr. Rasgon cautions against people self-medicating with LAC, which is available over the counter. "We've identified an important new biomarker of major depression disorder. We didn't test whether supplementing with that substance could actually improve patients' symptoms. What's the appropriate dose, frequency, duration? We need to answer many questions before proceeding with recommendations, yet. This is the first step toward developing that knowledge, which will require large-scale, carefully controlled clinical trials."

- Huda Akil, Ph.D., the co-director and research professor at the Molecular and Behavioral Neuroscience Institute (MBNI) at the University of Michigan, tells GEN that “severe, untreatable depression is remarkably difficult to unpack biologically with multiple paths to becoming depressed (genetic, development, metabolic, social).” Because of this complexity, “one treatment will not work for everyone.”

- In addition to finding that patients with MDD have less LAC in their blood, the researchers were able to identify subtypes of patient populations based on their LAC levels. More specifically, they found that
the deficiency in LAC is stronger in patients that don’t respond to standard antidepressants (treatment resistant depression) and is linked to a severe, childhood trauma-associated type of depression. They found that, in particular in women, a history of childhood trauma predicted the decrease in LAC. These findings indicate that LAC may serve as a precision medicine biomarker with LAC levels being used together with clinical characteristics (e.g., depression severity, age of onset and history of childhood trauma) to aid the diagnosis of biological based depression subtypes.

- It is this point that makes Dr. Nasca’s paper “a very important contribution” according to Dr. Akil. She adds that there is “a critical need to define subtypes based on combinations of variables to begin to personalize the treatments.”

- Dr. Pasinetti adds that “by defining a biologically distinct subtype of patients with depression, the use of LAC as a biomarker may identify individuals who may specifically benefit from individualized mechanistic treatments.” He adds that “this is important to consider, as certain treatments may be more appropriate for specific subgroups of patients, and supports expanding research into individualized treatments for patients with depression.”

- Dr. Nasca is hopeful, adding that their latest study opens the possibility of “using a panel of biomarkers to identify and study novel therapeutic targets related to central glutamatergic dysfunction in specific subtypes.”

- Dr. Russo says that, “LAC is not going to be the end-all-and-be-all of depression.” Dr. Pasinetti agrees that “depression is a multifactorial disease that depends upon a complex mosaic of environmental and genetic factors.” However, both agree that these translational findings into LAC levels are very exciting, with Dr. Pasinetti adding that “future investigations may show that altered LAC levels may drive other symptoms and pathologies in depression, and vice versa.”

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