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Targeting proline: Old and new treatment approaches for Schizophrenia

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There are multiple genetic links between schizophrenia and a deficit of proline dehydrogenase (PRODH) enzyme activity. There is also evidence that excess proline can disrupt both glutamatergic and dopaminergic signaling, with neurotoxic effects. We have found that over 25% of schizophrenic patients at an acute short-stay psychiatric hospital have hyperprolinemia. Hyperprolinemic patients had a significantly later age of first psychiatric hospitalization, suggestive of later onset, and hospital stays 46% longer than non-hyperprolinemic subjects. Thus hyperprolinemia has implications in the etiology of schizophrenia, and for the clinical management of these patients.

Vitamin D deficits have been associated with schizophrenia susceptibility, and in a follow-up study we reported that vitamin D, a potent transcriptional modulator, can upregulate the PRODH gene. Hypothesizing a link between vitamin D insufficiency and schizophrenia risk, via loss of PRODH regulation and proline elevation, we showed that patients with vitamin D insufficiency have three times the odds of being hyperprolinemic and that hyperprolinemia is a significantly mediating phenotype that may explain over one third of the effect of vitamin D insufficiency on schizophrenia risk.

The aim of this presentation is to discuss both novel and longstanding treatment approaches for schizophrenia that may, directly or indirectly, regulate the PRODH pathway and modulate proline level. We will review the current field, plus will present some new data suggesting that pharmacogenomic methodologies, coupled with treatment approaches that target proline, may yield significant symptom benefit in patients with psychiatric illness.

Disclosure: Catherine Clelland is a co-inventor on a US patent application that is related to this work.

Biography

Catherine Clelland received her PhD in molecular genetics from University College London, and completed her postdoctoral training at Mount Sinai School of Medicine, New York. In 2007, she joined the faculty of the Department of Pathology and the Taub Institute at Columbia University Medical Center. Her work has been funded by the Bright Focus Foundation, the National Institute of Aging, and the National Institute of Mental Health, and she has been the recipient of fellowships from the Charles H Revson Foundation and the Gray Matters at Columbia. She has published more than 15 papers in peer-reviewed journals and she serves as an academic editor for the Journal Medicine.

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