The neuro-inflammatory perspectives on the application and utilization of ursodeoxycholic acid in schizophrenia

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Abstract

Various research methods to treat schizophrenia have experienced conflicting etiological theories through their evolution, with diverse emphasis on genetic, physiological, biochemical, and psychological aspects. However, major breakthroughs have not been reached despite decades of research on schizophrenia. This article aims to provide perspectives on research findings and cast light on the potential involvement of bile acid metabolism in schizophrenia and its impacts on the neuro-inflammatory response. These results can be exploited to identify new leads for drug treatment through an enhanced understanding of disease pathophysiology.

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Schizophrenia is defined as a disabling disorder whose etiology is unknown and for which there is no definite cure.[1] A lot of evidence has suggested that at least a third of patients with schizophrenia have a peripheral proinflammatory state and neuroinflammation.[2] In this respect, over the past decade, neurobiological research has illustrated that orbitofrontal white matter neural density was augmented in schizophrenia cases with high transcription levels of pro-inflammatory cytokines compared to those with low transcription levels and controls.[3] The above neuropathological mechanism is likely to contribute to functional and structural disconnectivity, even in the first episode of psychosis.[3]

Recent evidence has depicted the potential involvement of bile acid metabolism in schizophrenia and how it affects the neuro-inflammation response. It is therefore of high importance to comprehensively examine bile acids and their role in schizophrenia development.[4,5]

Bile acids, mainly ursodeoxycholic acid and its conjugated species, tauroursodeoxycholic acid, have long been known to possess anti-apoptotic, anti-oxidant, and anti-inflammatory properties. Ursodeoxycholic acid/tauroursodeoxycholic acid are critical signaling molecules that modulate metabolic processes by binding to nuclear and membrane receptors, namely the farnesoid X receptor (FXR), the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), and the takeda G protein-coupled receptor 5 (TGR5).[4]

FXR-mediated bile acid signaling has the capability to modulate bile acid synthesis, glucose, lipid, and energy metabolism, inflammation, and the transcription of several genes, including brain-derived neurotrophic factor (BDNF).[4,6] NF-κB-mediated bile acid signaling prevents the generation of nitric oxide and pro-inflammatory cytokine tumor necrosis factor α (TNF-α). Also, TGR5-mediated bile acid signaling in immune cells has been found to reduce pro-inflammatory cytokine production and phagocytic activity, *i.e.*, an immunomodulatory action of bile acids. Since a wide range of research has revealed that elevated levels of pro-inflammatory cytokines, aberrant glucose and lipid metabolism, and abnormal expression of BDNF are associated with schizophrenia, it is feasible that variations in bile acid signaling pathways, such as changes in bile acid pool size or composition, could have a key role in the pathophysiology of this disorder.[4,6,7]

In this respect, a recent study by Qing *et al*. indicated that ursodeoxycholic acid and its precursor, 7-keto lithocholic acid, were depleted in schizophrenia patients.[4] Ursodeoxycholic acid is broadly employed to treat cholestatic liver disease, and a recent case report shows that ursodeoxycholic acid supplementation exhibits clinical efficacy and safety in treatment-refractory schizophrenia, which suggests that ursodeoxycholic acid is likely to be a viable therapeutic target for personalized schizophrenia treatment.[8]

Qing *et al*. also illustrated lower FXR affinity indices in schizophrenia patients than in healthy controls, which implies ameliora-

tion of FXR-mediated repression of *CYP7A1* for producing bile acids through the classic pathway.[4] These results, which illustrate diminished activation of FXR signaling, may contribute to a rise in intestinal permeability and upregulation of C-reactive protein and interleukin-6 in schizophrenia patients.[4]

All in all, these findings give a comprehensive snapshot of serum bile acid profiles in schizophrenia patients and ascertain changes in bile acid pool size and composition, which provide novel insights into the pathophysiology of schizophrenia.[4] Although they show the association of schizophrenia with abnormal bile acid profiles, they cannot prove the causal relationship between bile acids and schizophrenia.[1-8] In this regard, future preclinical or clinical studies on the microbiota - bile acids -FXR/-TGR5/-NF-κB signaling pathways are warranted to identify the causality between bile acids and schizophrenia.

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