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Full-length Article

Gut microbiota-expressed sulfotransferase sulfonates 25-hydroxyvitamin D3 and promotes depression

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Highlights

- *Escherichia coli* from patients with depression could degrade 25[OH]D3.
- Sulfotransferase in *Escherichia coli* sulfonates 25[OH]D3 into 25[OH]D3-3- sulfate.
- 25[OH]D3 decline and 25[OH]D3-3-sulfate production could induce depressive-like behaviors.
- The prevalence of *Escherichia coli* and sulfotransferase are higher in depressive patients.

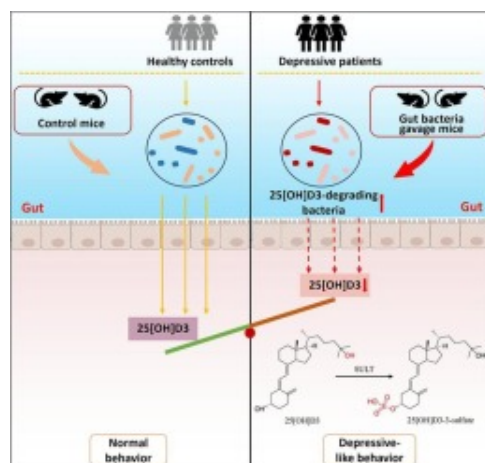
Abstract

Vitamin D deficiency (VDD) has been associated with depressive symptoms, but the underlying cause of this deficiency remains unclear. Here, we isolated and cultured *Escherichia coli* (*E. coli*) from the feces of depressive patients with VDD and found that this

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The gene encoding the 25[OH]D3-metabolizing enzyme in *E. coli* was identified as a sulfotransferase (SULT). A recombinant strain engineered for heterologous expression of SULT similarly reduced serum 25[OH]D3 levels and induced depressive-like behaviors. Interestingly, 25[OH]D3-3-sulfate, the sulfonation product of 25[OH]D3, also produced depressive-like behaviors in mice. Finally, both the prevalence of *E. coli* and the abundance of the *SULT* gene were strongly increased in depressive patients when compared to healthy controls. Our findings indicate that SULT expressed by gut microbiota may contribute to depressive symptoms by promoting 25[OH]D3 sulfonation and increasing 25[OH]D3-3-sulfate levels. However, further clinical and mechanistic studies are required to translate these findings to human depression.

Graphical abstract



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Keywords

Gut microbiota; 25-Hydroxyvitamin D3; Sulfotransferase; Depression

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~~substantial healthcare costs and contributes to increased disability~~
worldwide (Agrawal et al., 2022). Despite its high prevalence, the etiology and pathogenesis of depressive disorder remain incompletely understood. Recent advances have highlighted a potential role for vitamin D in mood regulation. Vitamin D status has been increasingly linked to cognitive decline and mental disorders, and vitamin D deficiency (VDD) has been proposed as a potential contributor to depression (Milaneschi et al., 2014; Anglin et al., 2013). Accumulating evidence indicates that vitamin D plays important roles in brain development, neurotransmission, neuroprotection, and immunomodulation (Cui et al., 2017). Studies in humans have demonstrated that vitamin D receptors (VDRs) were expressed in microglia within the brain, and VDR-deficient microglia exhibit a more primed proinflammatory phenotype characterized by increased secretion of neuroinflammatory cytokines (Cui et al., 2023, Menéndez et al., 2024). Through VDR-mediated gene transcription, vitamin D regulates inflammatory pathways that have been implicated in the pathophysiology of depressive disorder (Jarkas et al., 2024, Goldsmith et al., 2016).

In both humans and animals, vitamin D is converted in the liver by 25-hydroxylase to 25-hydroxyvitamin D3 (25[OH]D3). This metabolite is subsequently converted in the kidney into the biologically active form, 1,25-dihydroxyvitamin D3 (1,25[OH]₂D3), by 1 α -hydroxylase, or into the inactive metabolite 24,25-dihydroxyvitamin D3 (24,25[OH]₂D3) by 24-hydroxylase (Rosen 2011). The active vitamin D metabolite contributes to neuronal integrity by upregulating neurotrophic factors in brain regions such as the hippocampus and neocortex (Skoczek-Rubińska et al., 2025, Dawoud et al., 2023). Therefore, VDD may lead to reduced levels of the active metabolite, impair neuronal function, and further promote the occurrence of depression. However, the mechanisms by which VDD develops in patients with depression remain poorly understood.

Emerging evidence suggests that serum vitamin D status is closely correlated with the composition, diversity, and functional activity

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2019), whereas *Carnobacterium maltaromaticum*, in combination with other microbiota, could induce intestinal vitamin D production and activate host VDRs, thereby suppressing colorectal cancer development (Li et al., 2023). The above observations indicate that microbial regulation of vitamin D metabolism may affect the onset or progression of various diseases. Notably, sulfotransferases expressed by human gut bacteria have been shown to sulfonate compounds containing a flat 5 α *trans*-fused steroidal ring system, including 25[OH]D3 (Yao et al., 2022). However, whether the gut bacterium in patients with depression possesses an enhanced capacity to metabolize 25[OH]D3 through sulfonation, thereby contributing to VDD, remains largely unknown.

Here, we hypothesized that specific gut microbiota present in patients with depression may metabolize 25[OH]D3 through sulfonation, leading to reduced circulating 25[OH]D3 levels and subsequent depressive symptoms. To test this hypothesis, we examined whether gut microbiota from patients with depression reduces circulating 25[OH]D3 levels and induces depressive-like behaviors in mice.

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Healthy controls and patients with depression, aged 19–65 years, were recruited in our study. Participants underwent comprehensive medical examinations and psychiatric interviews by a professional psychiatrist, and met the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Exclusion criteria were as follows: substance abuse within the past 3 months, history of heart or kidney disease, infection, cancers, obesity and major somatic diseases. To avoid the ...

Circulating 25[OH]D3 levels are reduced in patients with depression

A growing body of evidence suggests that VDD is associated with depression (Milaneschi et al., 2014; van den Berg et al., 2021). To investigate whether serum 25[OH]D3 levels are reduced in depressive patients, we enrolled healthy controls (n=66) and patients with depression (n=72) in this study. Serum 25[OH]D3 levels were detected using LC-MS/MS. The serum level of 25[OH]D3 in patients with depression [(12.19±0.73) ng/mL] was significantly lower than that in healthy controls ...

Discussion

Here, we isolated *E. coli* from fecal samples of depressive cases with VDD and demonstrated that *E. coli* can metabolize 25[OH]D3 *in vitro*. We further identified SULT expressed by *E. coli* as the key enzyme responsible for 25[OH]D3 sulfonation. Heterologous expression of this enzyme in engineered bacteria induced sulfonation of 25[OH]D3 and subsequently induced depressive-like behaviors in mice. Our data suggest that 25[OH]D3-metabolizing bacteria and the SULT enzyme may be underlying therapeutic ...

CRedit authorship contribution statement

Zijun Li: Formal analysis, Data curation, Conceptualization. **Junchi**

Mei: Resources, Project administration, Methodology,

Uncited references

Jang et al., 2018a, Jang et al., 2018b, Kim et al., 2020, Kim et al., 2020, Milaneschi et al., 2014a, Milaneschi et al., 2014b. ...

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ...

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