Preliminary evaluation of the value of small molecular nutrients in depression-specific local metabolic network in preventing and treating depression

Jiacheng Xu*

School of Food Quality and Safety, School of Food and Biological Engineering, Zhejiang Gongshang University, Hangzhou, 310018, China

Abstract: Depression, a severe mental disease, has become increasingly prevalent worldwide, leading to many negative social impacts. The discovery of a small molecular nutrient capable of preventing and treating depression is of great importance. In this study, the results of signal pathways involved in 19 depression-related genes show that only four depression-related genes (HIBADH, TKT, GMPPB, B3GAT3) are directly connected to the metabolic network, while the remaining genes are connected to the non-metabolic network. Additionally, based on the information in KEGG and STRING, we have constructed a local metabolic network (LMN) for depression. Using this network, we found a small molecule nutrient, 3-hydroxyisobutyrate (3-HIB), which has potential value in preventing and treating depression. Finally, we made a preliminary evaluation of its therapeutic potential for depression. In future, we can categorize patients with varying depression symptoms based on molecular profiles and provide nutrient prevention and treatment strategies in different metabolic pathways.

1. Introduction

Depression, as a prevalent mental disorder, has exhibited a notable escalation in prevalence in the past hundred years, which has attracted researchers to actively explore new means to treat and prevent this disease. In recent years, more and more studies have shown that some specific small molecular nutrients have a positive impact on the prevention and treatment of depression. For example, omega-3 fatty acids [1], vitamin D [2], and B vitamins (especially vitamin B6[3] and vitamin B12[4]) are reported to have potential benefits for the prevention and treatment of depression. However, the research on nutrients related to depression prevention and treatment still faces many challenges. For example, it has been observed that the known nutrients related to depression prevention and treatment have no obvious effect on depression [5], the evidence is unclear [6], and different individuals have different responses to small molecular nutrients [7]. Therefore, it is of great significance to find effective small molecular nutrients for the treatment of depression.

Metabolic network refers to the network structure composed of various metabolites and metabolic pathways in organisms. Local metabolic network (LMN) is a specific metabolic network composed of metabolites involved in disease-related genes, which can reflect the metabolic process and relationship in organisms, and reveal the mechanism of disease.

The metabonomics of depression have been previously reported [8]. At least 19 genes were observed to be associated with depression causation, primarily acting through cis-regulated brain protein dependencies [9]. In addition, studies have shown that branched-chain amino acids (BCAAs), such as isoleucine, leucine, and valine, may be biomarkers of major depression, which has a certain correlation with depression [10]. Creating a specific LMN of depression can help us to comprehensively understand the metabonomics information of depression. The database will automatically introduce some small molecules that have not been considered into the local network through a series of means such as text mining, so that it is easier to find potential nutrients to prevent and treat depression.

Therefore, based on the above considerations, this study aims to build a high-quality depression-specific LMN, look for small molecule nutrients with potential applicability in the prevention and treatment of depression, and preliminarily evaluate their effectiveness for depression. This could provide new avenues for investigating dietary interventions for depression prevention and treatment.

*Corresponding author's e-mail: 3581966072@qq.com

2. Research methods

2.1. Data sources

2.1.1 Database

In this paper, the KEGG (Kyoto Encyclopedia of Genes and Genomes) database was used to find out the biological metabolic pathways involved in various genes related to depression, and the information on protein interaction provided by STRING (Search Tool for Recurring Instances of Neighboring Genes) was used as a supplement. Based on the information in KEGG (Kyoto Encyclopedia of Genes and Genomes, a comprehensive database resource for understanding higher-order functional networks in biological systems) and STRING, we have constructed a local metabolic network (LMN) for depression. The STRING is Search Tool for the Retrieval of Interacting Genes/Proteins, a database of known and predicted protein-protein interactions). Using this network, we found a small molecule nutrient, 3-hydroxyisobutyrate (3-HIB), which has potential value in preventing and treating depression. A local metabolic network (LMN) is a specific part of the metabolic network that is directly related to the disease under study. As show in table 1.

Table 1. Data sources used in this study

Database	Website
KEGG	https://www.genome.jp/kegg/
STRING	https://string-db.org/

2.1.2 Depression-related genes

Thomas et al. [9] reported that 19 genes such as B3GLCT, GMPPB, CTNNDI, CNNM2, and EPHB2 were related to depression (Table 2.), and these depression-related genes were further studied in this study.

Table 2. Basic information on depression-related genes

	humanGene Name	Gene ID	KEGG ORTHOLOGY	Definition
1	B3GALTL	145173	K13675	Beta 3-Glucosyltransferase
2	GMPPB	29925	K00966	GDP-Mannose Pyrophosphorylase B
3	EPHB2	2048	K05111	EPH receptor B2
4	PSMB4	5692	K02736	Proteasome 20S Subunit Beta 4
5	HIBADH	11112	K00020	3-hydroxyisobutyrate dehydrogenase
6	TKT	7086	K00615	Transketolase
7	B3GAT3	26229	K10158	Beta-1,3-glucuronyltransferase 3
8	CTNND1	1500	K05690	Catenin Delta 1
9	TMEM33	55161	K20724	Transmembrane protein 33
10	P2RX7	5027	K05220	Purinergic receptor P2X 7
11	CACNA2D2	9254	K04859	Calcium voltage-gated channel auxiliary subunit alpha2delta 2
12	LMBRD1	55788	K14617	LMBR1 domain containing 1
13	SLC25A12	8604	K15105	Solute carrier family 25 member 12
14	NEK4	6787	K08857	NIMA related kinase 4
15	CNNM2	54805	K16302	Cyclin and CBS domain divalent metal cation transport mediator 2
16	THUMPD3	25917	—	THUMP domain containing 3
17	FAHD2B	151313	—	Fumarylacetoacetate hydrolase domain containing 2B
18	CDH13	1012	K06808	Cadherin 13
19	TRPT1	83707	K10669	tRNA phosphotransferase 1

2.2. Construction of depression-specific local gene network

There are often direct or indirect connections between genes in cells, which are either physical (the encoded protein can be combined to form a protein compound machine) or functional. Therefore, any group of genes can form at least one local gene network and the local gene network composed of depression-related genes is called depression-specific local gene network.

Using the drawing function on the STRING website, 19 genes related to depression (Table 2) are connected through protein-protein interaction (PPI), metabolic reaction, metabolic pathway-transmembrane transport, catalytic regulation, transcription regulation, etc. In addition, we supplemented the network diagram with the information in reference [9] and drew a local gene network (LGN). (Figure 1.)

2.3. The local gene network of depression is coupled with branched-chain amino acid metabolism

In this study, we tried to couple the degradation pathways of valine, and leucine isoleucine provided in the KEGG database with depression LGN and finally formed a local metabolic network. (Figure 2.)

3. Research results

3.1. Depression-specific local metabolic network

Table 3. Signal Pathways Involved in Depression-related Genes

Pathway ID	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12	G13
hsa00514	√												
hsa00051		√											
hsa00520		√											
hsa01100		√			√	√	√						
hsa01240		√											
hsa01250		√											
hsa04015								√					
hsa04520								√					
hsa04670								√					
hsa04360			√										
hsa03050				√									
hsa05010				√									
hsa05012				√									
hsa05014				√				√					√
hsa05016				√									
hsa05017				√									
hsa05020				√									
hsa05022				√									
hsa00030						√							
hsa01200						√							
hsa01230						√							
hsa03013									√				
hsa04020										√			
hsa04080										√			
hsa04621										√			
hsa04010											√		
hsa04260											√		
hsa04261											√		
hsa04921											√		
hsa05410											√		
hsa05412											√		
hsa05414											√		
hsa00280					√								

N00852					√								
hsa04977												√	
hsa00532							√						
hsa00534							√						

According to the pathways involved in 19 depression-related genes (Table 2) sourced from the KEGG website, we constructed a corresponding table of genes and pathways (Table 3.). From Table 3, we can see that G4, G8, and G13 all participate in the R14 pathway, and only four genes G2 (GMPPB), G5 (HIBADH), G6 (TKT), and G7(B3GAT3) are directly involved in the R4 pathway. Other genes are connected to the non-metabolic network, which shows that the specific local molecular network of depression mainly contains regulatory genes and a small number of metabolic genes, so we speculate that depression is more likely to be a regulatory disease than a metabolic disease.

Furthermore, we analyzed the connectivity of these genes in many aspects, including PPI, metabolic reaction and metabolic pathway-transmembrane transport, catalytic regulation, transcription regulation, etc., and used the STRING database to map. At the same time, we finally constructed the LGN results of these genes by combining the information of the PPI network among 25 potential depression-related proteins [9]. As shown in Figure 1, the gene PSBM4 is physically related to HIBADH, SLC25A12, and GMPPB respectively, and P2RX7 is also physically related to CACNA2D2, which proves that PSBM4 and HIBADH are physically related.

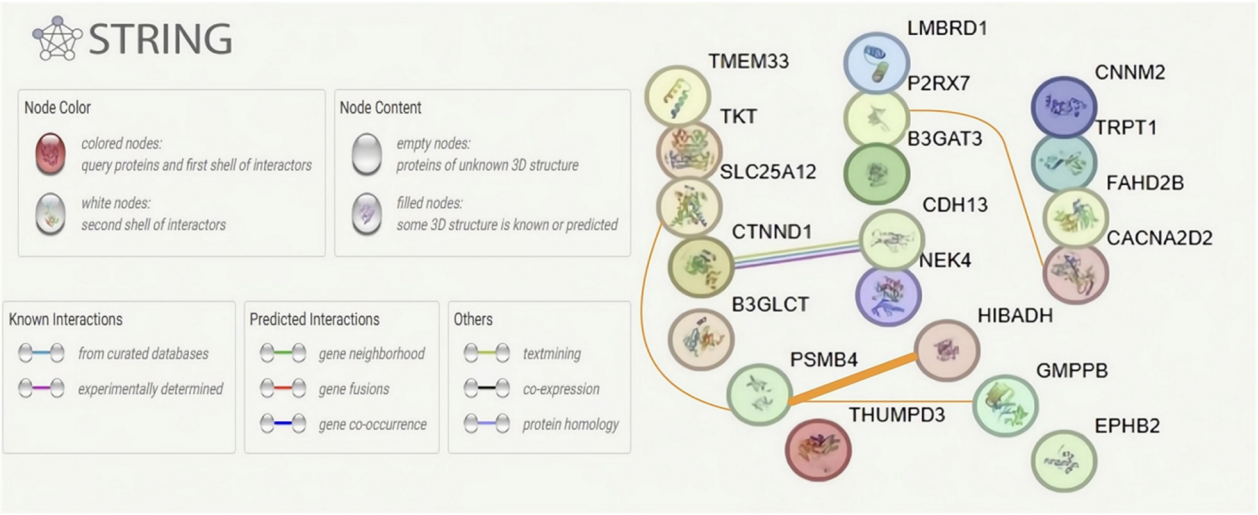

Fig. 1. Local Gene Network

The local gene network (LGN) of depression-related genes is drawn based on the STRING website (https://string-db.org/), in which TMEM33, TKT, and SLC25A12 are all abbreviations of depression-related genes (Table 2). Genes connected by lines in the figure, such as CTNND1 and CDH13, are Functional related. In the figure, the yellow lines represent the association between genes from Text mining, the blue lines represent the association from form preserved databases, and the purple lines represent the Experimentally Determined association. Genes with overlapping parts, such as TMEM33 and TKT, have a physical relationship, and their coded protein can be combined to form a protein compound machine. The orange lines represent physical PPI, and the thickness of the lines is proportional to the evidence for the PPI.

BCAAs such as isoleucine, leucine, and valine are reported to be potential biomarkers of major depression, which has a certain correlation with depression [10], so we focus on the metabolism of BCAAs. Here, we coupled the degradation pathway of valine, leucine, and isoleucine with depression LGN, and found that only the small molecule 3-HIB encoded by the HIBADH gene in the LGN was included in the metabolic pathway of BCAAs (Table 3.). Therefore, we considered the synthesis and decomposition pathways of 3-HIB and its isomer 3-Hydroxybutyrate(3-HB) and finally constructed an LMN (Figure 2.) including the LGN, the degradation process of BCAAs and the synthesis and decomposition process of its related small molecules (3-HIB, 3-HB). The figure describes the relationship between 19 genes related to depression and the metabolism process of BCAAs. From the figure, we can see that only 4 of the 19 genes related to depression are directly connected to the metabolic network, and 3-HIB is the metabolite of valine, which is only encoded by HIBADH, and the concentration of 3-HIB is consistent with the concentration of valine.

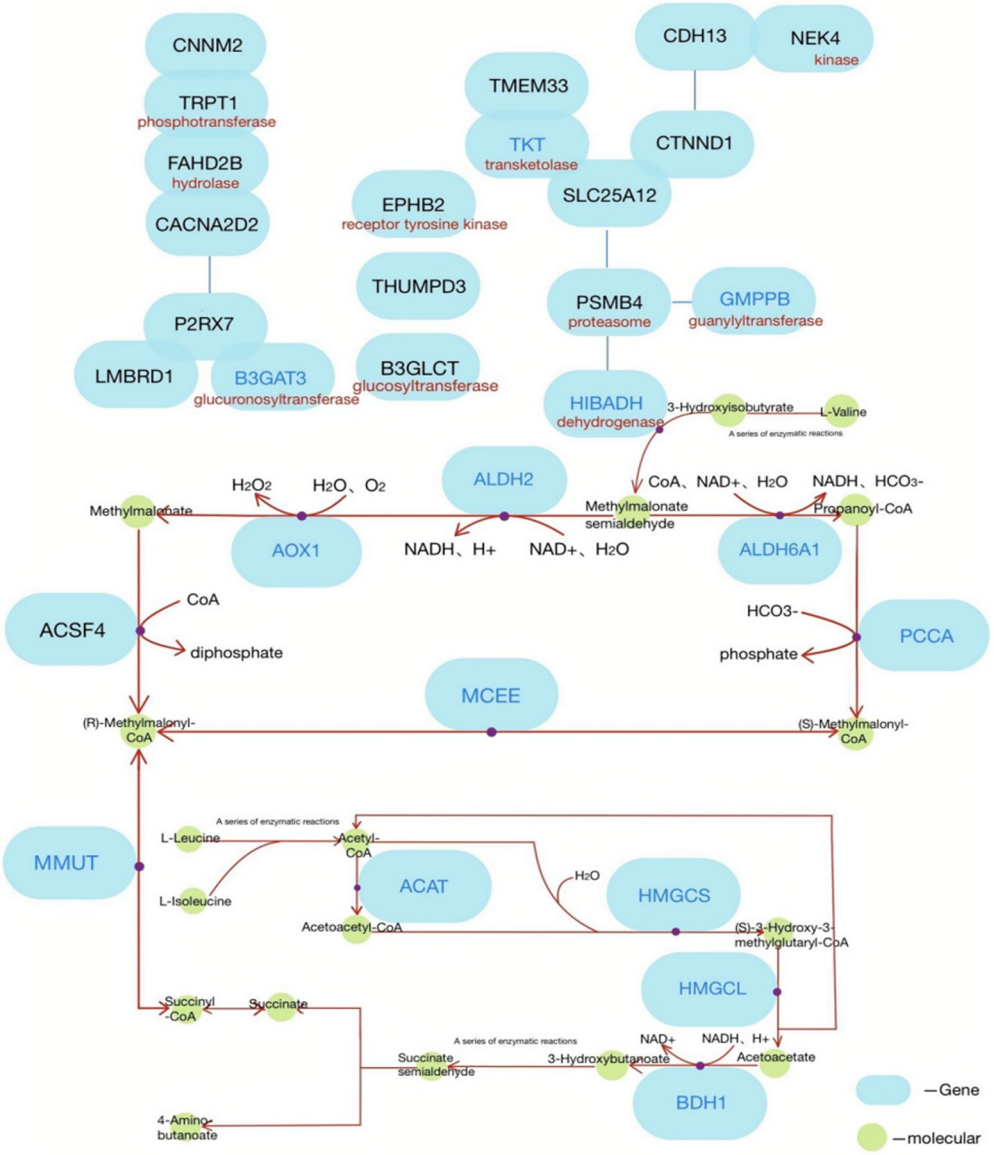

Fig. 2. Local Metabolic Network (LMN)

Depression-specific local metabolic network diagram, in which overlapping genes indicate a physical relationship and genes connected by lines in the diagram have a functional relationship. In the figure, the genes in blue indicate the genes directly connected to the metabolic network, and the words in red indicate the types of gene expression products. 'A series of enzymatic reactions' indicates omitted partial enzymatic reaction processes. This graph is derived from the integration of valine, leucine, and isoleucine degradation map and butanoate metabolism map (https://www.genome.jp/kegg/).

After identifying 3-hydroxyisobutyrate (3-HIB) as a potential nutrient for preventing and treating depression, we conducted a preliminary evaluation that included a review of existing literature on 3-HIB's role in metabolic processes related to depression, an analysis of its interactions with other molecules within the constructed local metabolic network (LMN), and an assessment of how 3-HIB levels correspond to the severity of depressive symptoms. Our evaluation suggests that 3-HIB could modulate the metabolic pathways implicated in depression, potentially offering a novel avenue for therapeutic intervention.

3.2. 3-HIB Prevention and Treatment of Depression Value Analysis

Insulin resistance (IR) is a common consequence of obesity, and it is also the main driving factor for the prevalence of type 2 diabetes (T2D) and related diseases worldwide. Some studies have shown that IR is related to the increase of circulating BCAAs concentration. 3-HIB is an intermediate product of the catabolism of valine, and studies show that the circulating 3-HIB level increases with the increase of blood sugar level. Another study on 3-HIB also proved that the increase of 3-HIB level in plasma is a sign of the risk of T2D. 3-HIB is a paracrine regulator of trans-endothelial fatty acid transport in mouse skeletal muscle. 3-HIB secreted by muscle cells enhances its fatty acid intake, leading to increased lipid

accumulation and systemic IR induction. Inhibition of 3-HIB synthesis may reduce the uptake of fatty acids by skeletal muscle microvascular endothelial cells and prevent IR.

Studies have shown that depression and T2D often have a bi-directional relationship. A study on middle-aged women in Korea shows that middle-aged women with T2D often have high levels of depressive symptoms and are at risk of depression. Depression also increases the risk of diabetes, because antidepressants have a negative impact on insulin sensitivity and blood sugar control. The content of BCAAs in venous blood is positively correlated with diabetes, negatively correlated with depression, and the small molecule 3-HIB in the BCAAs degradation pathway is also positively correlated with diabetes [10]; In addition, some literature shows that the concentration of valine is consistent with the concentration of 3-HIB, which can also be seen from the catabolic pathway of Valine.

Therefore, we speculate that the concentrations of valine and 3-HIB in plasma or body fluids of patients with depression should be at a low level, but this speculation still needs further study to be finalized. If it is true, providing 3-HIB as a nutrient to patients with depression may be helpful for prevention and treatment. However, the above observation and speculation may not be applicable to patients with depression and other diseases. For example, Chen JJ et al. reported that although the BCAAs metabolism of patients with depression and anxiety symptoms is still abnormal, the content of 3-HIB in them is higher than that of normal controls. In addition, Ciocan D et al. showed that the content of isoleucine in some depressed patients (taking some drugs) decreased significantly, while according to Whipp AM et al., the Valine and leucine in depressed patients decreased significantly, but there was no obvious relationship between the content of isoleucine and depression. However, Baranyi et al. [10] reported that the contents of three BCAAs in patients with depression were lower than those in normal people. The above results suggest that there are abnormalities in the catabolism of BCAAs in patients with depression, but the degree of abnormality in the catabolism of three amino acids is different in patients with different symptoms. In future, patients with depression can be classified according to their individual metabolic characteristics, and nutrient prevention strategies in different metabolic pathways can be provided.

4. Conclusion

Small molecular nutrients have been reported to play a positive role in the prevention and treatment of depression, so it is of great significance to study effective small molecular nutrients for the treatment of depression. By constructing a specific local metabolic network for depression, it is found that only four depression-related genes (HIBADH, TKT, GMPPB, B3GAT3) are directly connected to the metabolic network, while other genes are connected to the non-metabolic network, so depression is more likely to be a regulatory disease than a metabolic disease. The evaluation of the value of 3-HIB in preventing and treating depression shows that 3-HIB has potential value in preventing and treating depression. However, we also found that the level of 3-HIB is different in patients with different symptoms, so the value of 3-HIB in preventing and treating depression still needs further study.

At present, since some database information is difficult to obtain, a considerable number of small molecular substances lack effective information or even incomplete information, which makes it difficult for us to find enough references. However, when looking for small molecular nutrients that can improve depression, a large number of compounds often need to be considered. Therefore, due to the above limitations, the current research is often limited to a few small molecules in the metabolic pathway network and carried out on a smaller scale. In addition, the local metabolic network drawn at present lacks the analysis of the dynamic process, and only static results can be selected for analysis in the drawing process. Although the static results of several points can be analyzed, it is difficult to guarantee its timeliness. Moving forward, the development of personalized medicine approaches for depression treatment will benefit from advancements in genomics, metabolomics, and proteomics. Specifically, techniques such as next-generation sequencing (NGS) can be employed to analyze genetic variations among individuals with depression. Metabolomic profiling using mass spectrometry (MS) and nuclear magnetic resonance (NMR) will allow for a detailed characterization of the metabolic signatures associated with different depressive symptoms. Additionally, data science methodologies, including machine learning algorithms and bioinformatics tools, can be utilized to process large-scale molecular data and identify patterns that correspond to specific patient subtypes. This will enable the customization of nutrient-based interventions and the development of precision treatment strategies tailored to an individual's unique molecular profile.

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