Metabolite-protein interaction (MPI) network analysis of obsessive-compulsive disorder (OCD) from reported metabolites

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ABSTRACT

Obsessive-Compulsive Disorder (OCD) is a lifetime mental condition with the prevalence of 1-3% in general population. Molecular evaluation of OCD is prominent to understand the complex basis of underlying mechanisms. Here, by the application of MPI construction of significant changed metabolites in OCD patients, it is tried to obtain a preliminarily insight of related molecular interactions. These interactions are fundamental for cell processes and drug design. For this purpose, a number of ten OCD related metabolites were obtained from literature, by the use of PubMed and Google Scholar Resources. Then, the ten candidate metabolites were examined by the application of STITCH 4.0 Online Resource, for investigating the ten significant linked proteins with our query metabolites and the related BPs. Top ten scored interacting proteins with the query metabolites were retrieved and the action types were identified. Some of the protein partners were previously detected as potential polymorphisms in OCD etiology. The Regulation of hormone secretion and regulation of phosphorylation are the most significant (corrected p value< 0.05) related biological process of the ten investigated metabolites in the whole network. The result suggests that, insulin may be influenced significantly in OCD profile as it is significantly regulated by the six of our metabolites in the whole network. In fact, either metabolites or proteins changes may influence each other levels and promotes OCD risk. Thus, further systematic analysis is suggested for confirmation and introduction of new biomarkers.

Keywords: Obsessive-Compulsive Disorder (OCD), Molecular Origin, Metabolite-Protein Interaction (MPI) Network.

Introduction

Obsessive-compulsive disorder is deliberating mental condition that is typical with obsessive thoughts and compulsive behavior (1). It has a lifetime prevalence of 1-2.5% in the general population (2). It has also recognized by WHO, as the leading mental disability that mostly people of the age of 15 to 44 are affected by this disorder (3). This complex illness is a combination of multifactorial interactions. The interaction of these factors can lead to manifestation of different subtypes with different kinds of comorbidities (1). The related disorders (comorbidity) are
commonly tourette syndrome, chronic hair pulling, trichotillomania, and anxiety (4) that made OCD as one of the prominent complex disorders for treatment approaches (5). Many different related polymorphisms have been identified in OCD risk with small effect. These polymorphisms have been introduced by clinical and neuroimaging investigation. However, the functional level of molecular origin and the complex interaction between these elements has been remained elusive (6). In addition, according to one study, gene expression level does not significantly associated to the reported OCD polymorphisms (7). On the other hand, many metabolites reported to be linked to OCD pathogenesis. Some of these metabolites are also important in other brain diseases. The changes in metabolites’ levels may indicate the disease state (8). In another way, specific kinds of metabolites may be recognized as potential biomarkers for disease determinations (9). These metabolites interact with other metabolites and proteins. Interaction between molecules can lead to specific condition of a disease (10). The analysis of molecular interaction on the bases on PPI and MPI is important to understand pathological process in the disorder. Here, the MPI analysis of the reported OCD metabolites has been examined to facilitate understanding OCD underling mechanisms.

Materials and Methods

Metabolites involved in OCD risk were obtained by the application of PubMed Database and Google Scholar Motor engine search. To conduct a systematic literature review, keywords used for searching in databases include “Obsessive-Compulsive Disorder”, “Metabolites”, and “Metabolome”. The compound’s identifiers were extracted from KEGG Database (http://www.genome.jp/kegg-bin/get_htext) for each metabolite. The IDs were then applied for network building and functional annotation enrichments. In a way that, ten metabolites were searched through STITCH 4.0 Resource (search tool for interacting chemicals), available at http://stitch.embl.de, in which predicted interactions of proteins and chemicals can be retrieved. The linkage between proteins and chemicals are extracted from experiments, databases and the literature (11). Confidence score is determined for interactions between elements. The network of each individual metabolite and the whole ten metabolites were constructed. The action view of the networks is helpful to understand the modes of it with defined scores. The annotation study of whole network provides another level of understanding of disease mechanism. For this purpose, enrichment analysis of network related to biological processes is also studied by STITCH 4.0 Resource. The statistical significance is determined by corrected p value < 0.05. The correction method for this evaluation is bonferroni test.

Results

OCD related metabolites were investigated through literature. A number of ten metabolites were assigned to OCD risk. The function of metabolites and their disease annotations are tabulated in table1.

The network view of ten metabolites retrieved individually from STITCH Source is represented in figure 1. The whole MPI network composed of interacting proteins with our ten investigated metabolites (See figure 2). Biological process enrichment of the OCD ten metabolites by the use of STITCH 4.0 is depicted in table2.
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Discussion

Metabolite-protein interactions are the essential parts of system biology. The interactions may be as allosteric regulation or enzymatic function (32). These biochemical pathways are run by those connections, and are also important for pharmaceutical interventions (32). Cellular functions and drug impact on cells can be studied by analyzing MPI networks (11). In OCD molecular profile, there are many important metabolites as shown in table 1. These metabolites are also fundamental in other brain diseases. Furthermore, to provide insight into the connectivity and topology of these related metabolites of OCD, network map of MPI is evaluated. As indicated in figure 1, the investigated metabolites interact with other proteins that some of them express higher connectivity. Top ten related proteins for each individual metabolite are included in each network. Cholesterol as one of the important reduced elements in the serum of OCD patients has a noteworthy connection to apolipoprotein A-I (APOA1) in its network. Apolipoprotein A-I participates in the reverse transport of cholesterol from tissues to the liver regulation. APOA1, beside activation role has other functions including inhibition and catalysis. APOA1 is reported to have decreased level in the serum of schizophrenia patients (36). It may also have some roles in cholesterol reduction levels in OCD patients. Proteomic analysis of serum of OCD patients can be helpful in this regard. In N-acetyl aspartate interaction topology, the only binding formed between N-acetyl aspartate and caspase 1 (CASP1). Vitamin B12, folate, and homocysteine play important roles in production of serotonin and other monoamine neurotransmitters. These metabolites contributes in carbon

Table 1. The list of identified metabolites from literature (PubMed and Google Scholar)

<table>
<thead>
<tr>
<th>Metabolite Name</th>
<th>KEGG Compound ID</th>
<th>Function in Brain</th>
<th>Other Brain Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol(12)</td>
<td>C00187</td>
<td>Membrane permeability (12)</td>
<td>Schizophrenia (13), Alzheimer’s Disease(14)</td>
</tr>
<tr>
<td>N-acetyl aspartate(15)</td>
<td>C01042</td>
<td>Neuronal protein synthesis regulation, Myelin production Neurotransmitters’ production (16)</td>
<td>Schizophrenia (17), Bipolar (18) Parkinson’s disease (19)</td>
</tr>
<tr>
<td>C6H9NO5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12(20)</td>
<td>C05776</td>
<td>Neurotransmitter production (20)</td>
<td>Schizophrenia, Autism (21)</td>
</tr>
<tr>
<td>(cobalamin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate (vitamin B9)(20)</td>
<td>C00504</td>
<td>Neurotransmitter production (20)</td>
<td>Depressive disorder (22), Autism (23), Bipolar (24)</td>
</tr>
<tr>
<td>Homocysteine (20)</td>
<td>CE1401</td>
<td>Neurotransmitter production (20)</td>
<td>Depressive disorder (22), Autism (25), Bipolar (24)</td>
</tr>
<tr>
<td>Creatine (15)</td>
<td>C00300</td>
<td>Energy supplier (26)</td>
<td>ADHD (27), Bipolar, Schizophrenia (28)</td>
</tr>
<tr>
<td>Glucose (29)</td>
<td>C00293</td>
<td>Energy supplier (29)</td>
<td>Schizophrenia, Autism (30), Bipolar (31)</td>
</tr>
<tr>
<td>Glutamate (32)</td>
<td>C00025</td>
<td>Neurotransmitter (32)</td>
<td>Addiction (33), Schizophrenia</td>
</tr>
<tr>
<td>Dopamine (34)</td>
<td>C03758</td>
<td>Neurotransmitter (34)</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Serotonin (5-HT)(35)</td>
<td>C00780</td>
<td>Neurotransmitter (35)</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>
Figure 1. Action view of MPI networks of ten investigated metabolites. Different edge colors indicate the interaction type. The connections are determined by confidence score. The top ten interacting proteins with the query metabolites are determined in each individual network.
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Transfer metabolism (methylation), which is a part of neurotransmitter production (20). Low levels of vitamin B₁₂ and B₉ and high levels of homocysteine in serum are linked to abnormal cognitive tasks, decline and dementia (20). These changes are also reported for OCD risk (20). Folate is highly connected to dihydrofolate reductase (DHFR) with the score of 0.998. DHFR role is binding, inhibition and catalysis of folate.

Vitamin B₁₂ tightly connected to gastric intrinsic factor (vitamin B synthesis), (GIF), which activates absorption of the essential vitamin cobalamin (Cb) in the colon (37). Homocysteine binding to 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) is the most significant interaction in its network. MTR catalyzes the transfer of a methyl group from methylcobalamin to homocysteine. Low levels of folate

Figure 2. The metabolite-protein interaction network of ten metabolites using STITCH 4.0. Different colors of edges indicate functional properties.
is reported to cause homocysteine accumulation (38). One of the important proteins in creatine network is creatine kinase that catalyzes the conversion of creatine. Phosphocreatine is used as an energy supplier of brain. Another essential interacting agent with creatine is solute carrier family 6 (SLC6A8), which is required for creatine transportation to brain. Increased creatine level of medial prefrontal cortex is reported in OCD patients (15).

**Table 2.** Two top ranked biological processes of OCD ten related metabolites (corrected p value<0.05), the terms are ordered based on statistical significance.

<table>
<thead>
<tr>
<th>Term</th>
<th>Number of Genes</th>
<th>P value bonferroni</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation of hormone secretion</td>
<td>5</td>
<td>2.21E-04</td>
</tr>
<tr>
<td>Regulation of phosphorylation</td>
<td>7</td>
<td>4.61E-04</td>
</tr>
</tbody>
</table>

Glucose as another essential element that its metabolisms changes in OCD state has strong reaction with insulin (INS) in the network. Dopamine as vital neurotransmitter in brain has many connections. As indicated in its network, proteins including dopamine transporters and receptors are essential parts of its network. DRD1, DRD2, DRD3 and SLC6A3 as receptors and transporter respectively, were previously reported to be involved in OCD risk with different types of polymorphisms. Furthermore, polymorphisms of other related proteins including catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAOA) are also showed to have contributions in OCD profile. There are other highly interacting proteins (MAOB, TAAR1 and SST) in dopaminergic system that may be involved in OCD risk. In glutamate network profile, glutamate receptor (GRIN) and solute carrier (SLCA) are one of the previously recognized polymorphism in OCD development. The modes of actions between GRIN and glutamate are divers including activation, binding, catalysis and reaction. In addition, glutamate receptor (GRM5) activated by glutamate, is the most significant related functional partner. Serotonin is another vital neurotransmitter in brain mood regulation (35). Examining ten most related interacting proteins show that serotonin receptors (HTR family) have direct interactions and possesses high relation scores. Solute carrier (SLC6A4) also contributes for serotonin transportation. All these loci have been verified to have associations with OCD. This fact implies on the importance of these interactions that level changes of either metabolites or proteins may induce pathogenesis processes of OCD. In other word, expression changes of proteins or metabolites levels may due to imbalance the metabolome profile and protein regulation, respectively. In addition, some of the interactive proteins to the designated metabolites were previously investigated in the genetic level with different kinds of polymorphisms for OCD (35). In this regard, this finding can justify the fact that, these polymorph genes may have presented in the functional level as their interacted metabolites demonstrated significant changes in OCD psychopathology. However, systematic molecular investigation is required for validation of this claim. Moreover, examining interacting elements in the whole metabolic network of the ten metabolites provides a better understanding of OCD underlying mechanisms. Based on figure2, GCK, DRD2, APOA1, GRM5, HK1, INS, HTR1A, HTR2C, GALM and LDLQ3 indicate high confidence of interactions with the investigated metabolites. Network topology of the ten metabolites show that some of these molecules are in close relations. Serotonin and dopamine
have significant interaction with combined score of 0.995. This evidence suggests the reaction link between these two metabolites. Glucose binds to glutamate and previous findings confirmed that glucose metabolism is relevant to glutamate concentration changes in brain (39). Hypermetabolism of glucose in some parts of OCD patients’ brain may intricate to this psychopathology process. Insulin is regulated by many of the metabolites including glucose (inhibition and activation), serotonin (inhibition and activation), dopamine (inhibition and expression), homocysteine (inhibition), cholesterol (inhibition and activation), glutamate (activation). In this regard, regulation of insulin secretion may be disrupted widely in OCD patients. On the other hand, enrichment analysis of the whole network map (table2), identifies two most statistical significant biological processes that are regulation of hormone secretion and regulation of phosphorylation that may play important role in OCD development.

Conclusion
In conclude, for better understanding OCD associated mechanisms, evaluation of other related partners in MPI network of OCD is recommended by adding more agents (lower confidence score) to the studied networks. However, application of systems biology approach including metabolic as well as proteomic investigations is a requirement for clarifying the complex nature of OCD.

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Conflict of Interest
The authors declare no conflict of interest.

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