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Evaluation of Δ9-tetrahydrocannabinol Effect on Autism Inflammatory Factors by Molecular Docking Study

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder and is characterised by social communication difficulties. Inflammation and immune system activation is reported as pathogenicity of ASD. It has been demonstrated that cannabis consumption improves interpersonal communication and reduces hostile feelings. In this study, we evaluated the beneficial effect of Δ9-tetrahydrocannabinol (THC) on ASD's inflammatory factors with bioinformatic tools. Molecular docking showed THC interact with ASD's inflammatory factors specially IL12B and RELA. It seems that THC alleviates inflammation in ASD by targeting ASD's inflammatory factors.

Keywords: Autism, Δ9-tetrahydrocannabinol, THC, Inflammation, Molecular docking

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, with an estimated prevalence of 1.9%. ASD is clinically defined by core characteristics such as social communication difficulties, restricted, repetitive behaviours and interests [1]. According to a 2014 prevalence survey conducted in the United States, one out of every 69 children aged 8 to 11 years old has autism. This proportion has significantly increased to one in every 60 children in 2016 [2]. Although behavioural therapy, speech and social therapy, and dietary/nutritional/medical treatments are effective treatments for ASD, no medical treatment has been approved to treat core symptoms of ASD, such as social communication difficulties and repetitive behaviours [3].

Inflammation has been more and more recognized as a major contributor to central nervous system (CNS) injury in both the developing and adult brain over the last several decades. The brain is especially vulnerable during pregnancy, infancy, and early childhood, and insults that occur during these critical courses have the potential to cause long-term damage. ASD, schizophrenia, cerebral palsy, epilepsy, cognitive impairment, and depression have all been linked to early-life immune activation and inflammation [4]. For many years, a growing number of studies have suggested that the immune-inflammatory system plays an important role in ASD [5].

Cannabis consumption has been shown to improve interpersonal communication and reduce hostile feelings. The main phytocannabinoids (components of

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the cannabis plant) are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [6]. Moreover, oral cannabidiol use in children with ASD can decrease symptoms of self-injury, rage attacks, hyperactivity, sleep problems and anxiety [7]. In addition, THC has a protective effect against inflammation and oxidative stress [8].
In the present study, the effect of THC on inflammatory factors which increase in autism was investigated. The purpose of this study is to answer the question of whether THC can improve autism by reducing inflammation?

Materials and Methods

Inflammatory factors including IL12B, CCL5, IL6, TNF, CXCL8, CCL2, IL1B, IL4 and TGFB1 were selected from the Psychiatric Disorders book as the main inflammatory/immunological factors for ASD patients [9].

Protein-Protein Interaction (PPI) Network

The PPI network was created using the STRING database to better understand the relationship between ASD's inflammatory proteins. PPI of ASD's inflammatory factors plotted by STRING v.11.3 [10]. The hub genes in the ADS' inflammatory protein network were identified according to degree using Cytoscape software

Transcription factor prediction

Transcriptional Regulatory Relationships Unraveled by Sentence-based Text mining database (TRRUST version 2.0), a manually curated database of human transcriptional regulatory networks [11], was used to identify transcription factor target genes.

Molecular docking

Molecular docking was performed by Pyrx 0.8 to evaluate THC interaction with ASD's inflammatory proteins. Crystal structures were prepared before docking by Chimera 1.8.1 by correcting residues with missing atoms and side chains, adding hydrogen atoms, and deleting water molecules and ligands. For the molecular docking studies, the seven co-crystal structures of target proteins CCL2 (protein data bank [PDB] ID: 3IFD), CCL5 (PDB ID: 6FGP), CXCL8 (PDB ID: 4QTAN2U), IL1B (PDB ID: 5R8M), IL6 (PDB ID: 1IAR), IL12B (PDB ID: 5MXA), NFKB1 (PDB ID: 1SVC), RELA (PDB ID: 1NFI), TGFB1 (PDB ID: 5VQP) and TNF (PDB ID: 5M2J) in complex with their respective inhibitors were obtained from the Uniprot(https://www.uniprot.org/).

Results

PPI network analysis

PPI network plotted by STRING database then analyzed by Cytoscape. Except for nodes TGFB1 and IL12B, which got degree 7, the rest of the nodes got degree 8 (Figure 1). Network analysis showed that ASD's inflammatory proteins are closely related to each other and they can have many interactions with each other.

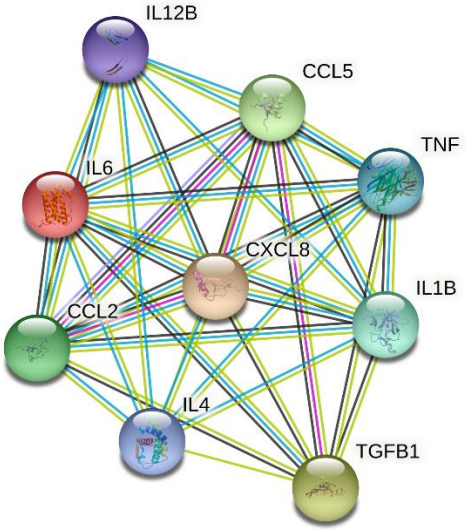

Figure 1. PPI network for ADS' inflammatory proteins

Transcription factor prediction

According to PPI network analysis, ASD's inflammatory proteins have close interactions which are why upstream transcription factor was evaluated for them. For this purpose, TRRUST database was

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employed for transcription factor prediction. 37 transcription factors were obtained for ASD's inflammatory proteins (Not all of them are shown in the figure) the two transcription factors that regulated the largest number of these proteins were selected. NFKB1 and RELA can regulates 8 and 7 of these protein expressions respectively (Figure 2).

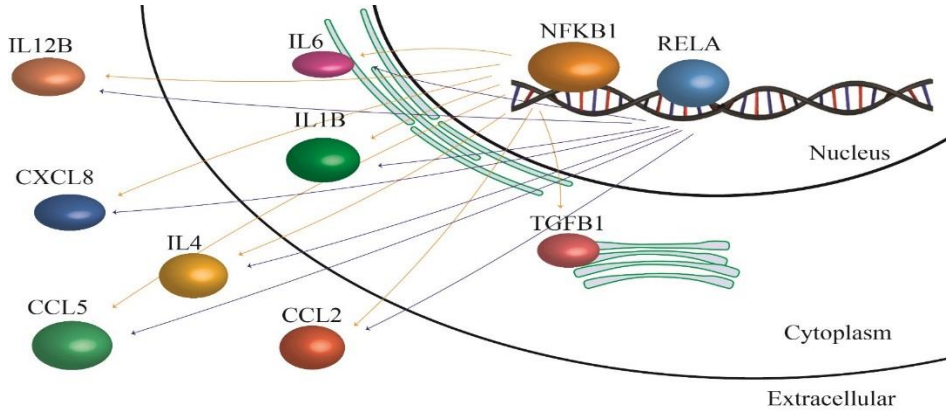

Figure 2. NFKB1 and RELA regulate most of the ASD's inflammatory proteins expression

Molecular docking

Molecular docking was performed for all ASD's inflammatory proteins and NFKB1 and RELA as upstream regulators. Docking results showed that THC not only can target ASD's inflammatory proteins it can target NFKB1 and RELA (Figure 3). The highest binding affinity was devoted to IL12B and RELA by -7.5 and -7.4 Kcal/mol respectively (Table 1). Moreover, THC interacts to CCL2 and TGFB1 by 3 hydrogen bonds.

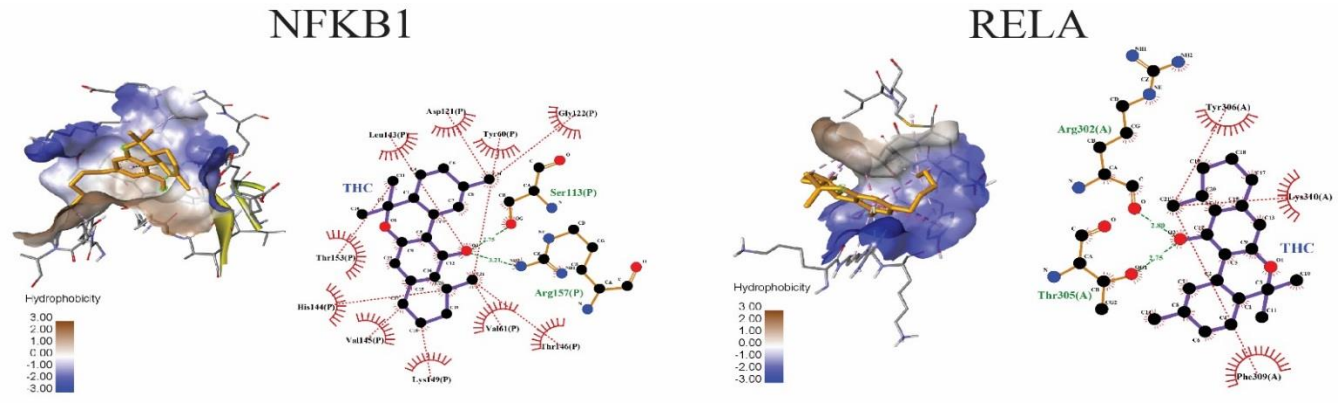

Figure 3. 2D and 3D images of THC interaction to NFKB1 and RELA.
In 2D structure, green and red lines show hydrogen and hydrophobic bonds

Table 1
Energy bonding of THC and ASD's inflammatory proteins

Protein	Binding Affinity (kcal/mol)	Hydrogen bonds	non-Hydrogen bonds
CCL2	-5.6	3	6
CCL5	-5.4	1	1
CXCL8	-6.6	-	7
IL1B	-6.6	-	14
IL4R	-6.4	-	14
IL6	-6.8	-	9
IL12B	-7.5	1	7
TGFB1	-5.9	3	1
TNF	-6.6	1	12
NFKB1	-6.8	2	10
RELA	-7.4	2	3

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Discussion

Autism is a developmental disorder that appears in early childhood. Autism is defined by an inability to learn social skills, repetitive behaviours, and a failure to develop speech and nonverbal communication skills [12]. Current diagnostic practices have been linked to a 20-fold increase in the reported prevalence of ASD over the last 30 years. Fragmenting the autism phenotype into dimensional "autistic traits" leads to the alleged recognition of autism-like symptoms in any psychiatric or neurodevelopmental condition, as well as in individuals decreasingly distant from the typical population, and prematurely dismisses the relevance of a diagnostic threshold [13]. Autism spectrum disorders (ASD), schizophrenia, cerebral palsy, epilepsy, cognitive impairment, and depression have all been linked to early-life immune activation and inflammation (4). ASD is associated with severe inflammation and immune system dysfunction, and several cell types contribute to the initiation and maintenance of these processes [14]. Increased numbers of reactive microglia and astrocytes have been found in both ASD postmortem tissue and animal models [15].

A growing body of evidence suggests that cannabinoids are beneficial for a variety of clinical conditions, including pain, inflammation, epilepsy, sleep disorders, multiple sclerosis symptoms, anorexia, schizophrenia, and others [16]. Cannabinoids appear to act on inflammation via mechanisms distinct from those used by nonsteroidal anti-inflammatory drugs (17).

In this study, we evaluated THC interaction with ASD's inflammatory factors. Our data showed that THC could interact with ASD's inflammatory factors, especially with IL12B and RELA (Table 1). Based on molecular docking data, THC interacts with RELA as an important inflammation regulator [18].

Conclusion

ASD is a neurodevelopmental disorder that characterizes by communication difficulties. Inflammation and immune activation have been reported in ASD patients. THC is an anti-inflammation compound and it could interact with NFKB1 and RELA. It seems that THC alleviates inflammation in ASD by targeting ASD's inflammatory factors.

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