GPCR, Alzheimer's disease and their connection in drug discovery

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Abstract: G-protein coupled receptor (GPCR) is a big family of protein which serves as signal receptors in the surface of cells, induces various cell responses and is widely used in drug discovery. On the other hand, Alzheimer's disease (AD) is a kind of popular brain disease which causes memory loss, behavior changes and cognitive deficits. However, the connection between GPCR and AD, especially how can GPCR be used to treat AD has not been discussed thoroughly. Therefore, in this review, we introduce basic knowledge of GPCR and its perspective related to drugs. Besides, we conclude history, causes and symptoms of AD. In addition, several examples of GPCR pathways involved in AD treatment are fully discussed to explain connection between GPCR and AD. To summarize, this review provides detailed information about GPCR, AD and their connection, which shows bright future for drug invention via GPCR in AD.

1. Introduction

G-protein coupled receptor (GPCR) is the biggest family of cell surface receptors, which serves as drug targets for more than 50% currently used drugs. However, considering over 800 types of GPCR, only about 50-60 GPCRs have been used in drug design [1]. Besides, application of GPCR shifts from several specific fields to more popular diseases such as Alzheimer's disease (AD), diabetes and obesity [2]. Regarding these two factors, GPCR is one of the most promising drug targets and has a benefiting future for millions of people. On the other hand, Alzheimer's disease, a most common type of dementia, affects over 35 million people worldwide in an increasing rate [3]. Common symptoms of AD are cognitive degradation, changes in mood and social withdrawal [4], which make AD patients tormented. To date, current studies have found several causes of AD, such as accumulation of amyloid-beta protein (Aβ) and tau phosphorylation. Although numerous researches have been done, there is no effective drug for AD. As a result, researchers are trying to discover more drug targets, including GPCR to cure AD. Therefore, the relationship between GPCR and AD requires further research notwithstanding current knowledge for structure and function of GPCR.

The structures and functional features about GPCR are well-studied and the attempts in drug-design for curing AD has fascinated researchers for years. To be specific, the 3D structural analysis of GPCRs was largely accelerated by crystal determination and cryo-electron microscopy (cryo-EM), which indicated them as future drug targets in clinics [5]. Besides, the studies about the different GPCR's interactions with upper-pathway ligands, their coupling G proteins and arrestins were relatively complete. Thus, it becomes legitimate and accessible to summarize the GPCR pathways associated with AD. On the other hand, the experimental findings in the past decades indicates multiple factors to cause Alzheimer's disease, including Aβ generation, over-phosphorylation of tau protein and other genetic mutations [6]. However, even our understanding about pathological cause of AD has been improved a lot, few research can be found illustrating the roles of GPCRs in pathological signaling pathways. What's more, though there are several newly designed drugs targeting Aβ or Tau proteins under clinical trials, none of them show convincing effectiveness in

reversing the neurodegenerative progression in AD patients at late period. Thus, designing more GPCR targeted drugs remains to be essential in human's attempt to cure AD.

In this review, we introduce what GPCR is, illustrate GPCR signaling and explore new findings of it. Besides, history, causes and symptoms of AD are concluded. In addition, we offer several examples of GPCR pathways involved in AD treatment in order to fully explain the connection between GPCR and AD, and future AD drug treatments using GPCR is also discussed.

2. GPCR

2.1 Classification

As one of the most successful drug targets, G-protein coupled receptors (GPCRs) currently occupy over 50% market share. Specifically, GPCRs have six classes, and each class have different amino acid sequences. Among which, four classes (A, B, C, and F) exist in human body [7]. To begin with, class A receptors have short disordered N-terminal region, while some of them obtain opposite features. On the other hand, class B receptors include the secretin receptor and adhesion receptor. In fact, the former is characterized by a large extracellular domain which are sites for ligand binding. Additionally, class C receptors realize signaling function by forming special dimers and class F receptors contain the frizzled and smoothened receptors [7].

2.2 Structure and function

In common, GPCRs are composed of a common seven-transmembrane alpha-helical structure, and thousands of ligands can bind to it. Moreover, structure of GPCR definitely related to the signaling of GPCR. For instance, GPCRs can be bound to agonists, which forms an agonist-GPCR complex. Indeed, this complex triggers downstream signaling cascades. Besides, multiple ligand-dependent partial activation result in a microprocessor-like' action rather than an 'on-off' switch [8]. Furthermore, GPCRs are widely distributed in human body and are responsible for vision, smell, taste and neuronal transmission [8].

2.3 Advanced research

Considering the practical value of GPCR, numerous researches have recently been done and inspiring conclusions are raised. For example, only three types of GPCR (GPR4, GPR65, GPR68) are able to sense H+. Rowe et al. found that these GPCRs obtain buried acidic residues to sense H+ [9]. They used informatics platform pHinder and deep variant profiling to identify these unique residues and identified their contribution to pH sensing [9]. Additionally, beta-arrestins, which are regulators in the downstream of GPCR, are also researched in detail. For example, beta-arrestins are found to be left with a unique footprint by GPCR. Furthermore, related research team shows the orientation of arrestin and provides direct evidence for the formation of arrestin oligomers in the cell [10].

3. AD

3.1 History of AD

Alois Alzheimer diagnosed a woman in 1907.Her symptoms were memory deficits, cognitive loss and pathological jealousy. With the help of autopsy, neurofibrillary tangles (NFTs) and senile plaques (SPs) were viewed as the main symptoms of Alzheimer's disease. Alzheimer's disease (AD) is the most common cause of dementia in people who are over 65 years old. It is a dual retinopathy disease defined by a widespread but regionally specific pattern of intraparenchymal diffuse and neuritic ß-amyloid (Aß) plaques and intracytoplasmic (initially), then extracellular, neurofibrillary tangles with synaptic and neuronal loss and gliosis [11]. The most typical feature of AD is dementia. Patients have varying degrees of impairment in multiple areas of cognitive function and behavior. Unlike normal aging, AD also includes emotional changes. Symptoms of depression and anxiety are common in the

early clinical stages. In the later stages of the disease, patients are usually mute, incontinent, bedridden, and often die of complications [12].

3.2 Diagnosis of AD

The pathological diagnosis of Alzheimer's disease considers any amount of Alzheimer's neuropathy to be abnormal. For example, the NIA-AA standard defines three distinct preclinical stages using the amyloid cascade hypothesis: the first is amyloid lesions, the second is Tau pathology that causes neurodegenerative changes, and the third is the occurrence of subtle cognitive changes [13]. Besides, current standard uses an ABC scoring system, which requires the presence of amyloid plaques and Tau tangles to describe the number of AD neuropathological changes, ranging from none too high. Score A was determined by Thal staging, score B by Braak staging, and score C by CERAD score of neuritis plaque [14].

3.3 Treatment for AD

The main treatments for Alzheimer's include non-drug therapy and drug therapy. Non-drug therapy is improving the patient's psychiatric symptoms through the nursing method. Drug therapy mainly uses anti-Alzheimer's drugs to relieve and suppress patients' symptoms. Only cholinesterase inhibitors (ChEIs) and the N-Methyl-D-Aspartate (NMDA) have been approved by the FDA to treat AD dementia. Memantine uncompetitively blocks the NMDA receptor42 and, thus, may be neuroprotective by preventing neuron loss, as well as improving symptoms by helping to restore function of damaged neurons [15]. In addition, Memantine and cholinesterase inhibitors have also been clinically proven to be effective as a combination therapy.

4. GPCR pathways involved in AD treatment

4.1 Innovation

GPCRs provides a pathway for therapeutic intervention in AD. Drugs targeting GPCRs could diversify the symptomatic treatment portfolio for AD and potentially offer disease-modifying therapies [16]. For example, Alzheimer’s disease (AD) is affected by acetylcholine signal transduction, which receptors are involved in calcium homeostasis. GPCRs regulate calcium homeostasis by different molecular mechanisms. For example, β_2AR is involved in creation of Aβ and calcium dysregulation by influencing γ -secretase activity, and mGluR induces excitatory toxicity and calcium dysregulation through glutamate binding and chemokine receptor induced inflammation in disease conditions [17]. Furthermore, functional GPCR classification may enhance the therapeutic potential of GPCRs and contribute to the development of GPCR candidates for AD.

4.2 Potential drugs

There is not a drug which can cure AD, because AD is too complex that scientists do not fully understand mechanisms behind it. Current drugs focus on moderating symptoms of AD. On the other hand, this review discusses some potential drugs which provide insights in AD treatment,

Pancreatic amylase affects AD in a variety of ways, such as improving blood glucose, reducing body weight, or acting directly on AD. Since Amylin mimics the structure of Aβ and Tau, Amylin and its corresponding GPCR may be a key pathway for destruction by accumulation of Aβ and pTau, especially their aggregation form [18]. Amylin or pramlintide may be used as a single novel therapeutic agent to target multiple indicators of brain neurodegeneration in AD.

AchEI (Acetylcholinesterase inhibitors) is designed to increase acetylcholinesterase levels, and has been approved by FDA for commercial treatments of AD [19]. mAChR, an important neurotransmitter receptor in learning and memory, mediates the effect of acetylcholine.

Caffeine, which is a non-selective antagonist for adrenergic receptors (AR), has been proved to enhance memory, lower Aβ levels and improve cognitive function in AD mice models. Similarly, A2AR antagonist, SCH58261, is protective to cognitive impairment induced by Aβ [19].

A highly selective antagonist to CRHR1 (corticotrophin-releasing hormone receptor 1) has been proved to reduce depression symptoms in AD patients. CRHR1 is rich in the pituitary gland, which shrinking is related to mental symptoms of AD [20].

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