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A focus on CXCR4 in Alzheimer's disease

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Abstract:

Alzheimer's disease (AD) is one of the most common and devastating aging-related neurodegenerative diseases. Besides the well-known role of chemokines and their receptors in the immune system, they are widely expressed in the nervous system, where they play roles in the regulation of cell migration and neurotransmission. The chemokine CXC motif receptor 4 (CXCR4) is evolutionarily highly conserved seven-transmembrane G-protein-coupled receptors (GPCRs). It has been demonstrated that CXCL12/CXCR4 signaling pathway involved in the pathologic process of AD. In this review, we demonstrated the GPCR family proteins and summarized the relationship between CXCR4 and GPCR, CXCR4 and AD. The review aimed to provide the novel insight of CXCR4 into the early prevention of mild cognitive impairment and in the diagnosis and treatment of AD.

Keywords:

Alzheimer's disease, CXCL12, CXC motif receptor 4, G-protein-coupled receptor

Introduction

G-protein-coupled receptors (GPCRs) are integral membrane proteins that convert extracellular signals into intracellular responses including responses to hormones and neurotransmitters. GPCRs, also called seven transmembrane (TM)-spanning receptors, represent the largest family of cell surface receptors and are the targets of intense drug discovery efforts. While a number of available drugs on targeting GPCR signaling pathways, overall <20% of GPCRs are targeted.[1] However, despite structural similarities, GPCRs have unique combinations of signal-transduction activities involving G-protein-dependent signaling pathways, as well as G-protein-independent signaling pathways and complicated regulatory processes.[2-4] Therefore, the development of new therapeutic targets on GPCRs could be a promising method to maintain the effect and control the side effects of inhibitors based on biased ligands or allosteric modulators.[5,6]

GPCR regulates and involves diverse system diseases including nerve system disease. Alzheimer's disease (AD) is one of the most common and devastating aging-related neurodegenerative diseases. ADs pathological characteristics in the brain are senile plaques (SPs) and neurofibrillary tangles (NFTs). Many mechanisms are involved in ADs pathological process including insulin signaling pathway,[7] mitogen-activated protein kinases (MAPK) pathway, and inflammatory signaling.[8]

The chemokine CXC motif receptor 4 (CXCR4) is an evolutionarily highly conserved GPCR family member. CXCR4 belongs to seven-TM GPCRs. CXCL12/CXCR4 pathway has been known to be involved and regulated inflammatory response. Interestingly, ADs pathological changes also include a variety of inflammatory phenomenon. However, whether and how CXCL12/CXCR4 molecular transduction plays a role in AD, especially inflammatory process is to be investigated.

The main purpose of our review is to provide an overview of the involvement of

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CXCR4 in AD. We summarized the signaling pathways and the current findings on the regulatory roles of CXCR4 in AD. It is expected that CXCR4 may serve as a novel target for treatment of AD.

G-protein-coupled receptor family

GPCR is one of the largest family of cell surface receptors. A GPCR is basically composed of three parts: the extracellular region, the TM region, and the intracellular region. The extracellular region contains N-terminus and three extracellular loops (ECL1–ECL3); the TM region contains seven TMα-helices (TM1–TM7); the intracellular region contains three intracellular loops (ICL1–ICL3); and an intracellular amphipathic short α-helix (H8) lying perpendicular to the membrane plane and the C terminus.[9,10] Although their molecules and functions are diverse, they consist of seven TM domains linked by intracellular and ECL.[11] Ligand was recognized and bind to extracellular domains, then it induces the conformation change of the receptor coupling to G proteins with intracellular domains.[12] This, in turn, leads to coupling and signaling activation of one or more G-proteins inside the cell.

GPCR is the largest and most diverse protein families in the mammalian cells. The G-proteins consist of three subunits: α, β, and γ. It has been demonstrated that five identified genes encode the β subunit, 12 encode the γ subunit, and 17 encode the α subunit.[13] Activation of G proteins dissociates the Gα subunit from the Gβγ subunits of GPCRs. The Gβγ subunits activate the downstream effectors such as enzymes and ion channels.[14] Moreover, the Gα subunits have a key role in determining the receptor coupling specificity and influencing the efficiency of ion channel modulated by Gβγ subunits.[15] On the basis of their G protein-coupling preference, it can be broadly classified into four subfamilies: Gs, Gq/11, Gi, and G12/13.[16]

All chemokines exert their biological effects through the activation of an extended family of seven TM GPCRs. Approximately 19 chemokine receptors (CKR) have been characterized to date, including six CXC receptors (CXCR1–6), ten CC receptors (from CCR1-10), one lymphotactin receptor (XCR1), and one fractalkine receptor (CXC3CR1). CKRs are notoriously promiscuous. Chemokines are small proteins consisting of about 100 amino acids. More than 50 different chemokines have been identified in higher vertebrates.[17] Chemokines have been classified into four families: C, CC, CXC, and CX3C according to their conserved N-terminal cysteine residues.[18] These residues can be adjacent (CC) or separated by amino acids (CXC and CX3C). Most chemokines are members of the CC (CC motif and β-chemokine) and CXC (α-chemokine) subfamilies. CC subfamily chemokines contain two contiguous cysteines near the amino terminus of the molecule, whereas a single amino acid separates the two cysteines in members of the CXC subfamily. Chemokines in the CX3C (δ-chemokine) subfamily have three amino acids between the two cysteines. The fourth subfamily comprises chemokines with a single cysteine designated the C (γ-chemokine) subfamily. Each subfamily of chemokines acts on a group of related GPCRs.[18] It has been observed in *in vitro* that a single chemokine can activate more than one receptor; conversely, a single cloned receptor can frequently be activated by more than one chemokine although it is probable that their selectivity is actually higher *in vivo*.[19] There are, however, instances when a CKR is activated by a single chemokine, i.e., the CXCR4 receptor has only one known ligand, stromal-derived factor-1 alpha (CXCL12).

CXC motif receptor 4 and G-protein-coupled receptor

Besides the well-known role of chemokines and their receptors in the immune system, they are widely expressed in the nervous system, where they play roles in the regulation of cell migration and neurotransmission. Meanwhile, chemokine signaling is also important in the regulation of neuroinflammatory responses. Chemokines are small chemoattractant cytokines that are expressed in discrete anatomical locations. Chemokines are responsible for specific recruitment of leukocytes during inflammation.[10] Chemokines act on CKR, members of the seven-TM domain GPCR superfamily. Classically, one of the CKR ICLs interacts with heterotrimeric, pertussis toxin-sensitive G proteins called Gαi, initiating a cascade of signal transduction events in response to ligand binding.[18]

CXCR4, encoded on chromosome 2q21, is an evolutionarily highly conserved GPCR expressed on monocytes, B-cells, and naïve T-cells in the peripheral blood. Human CXCR4 was originally identified as a receptor for CXCL12 by screening CKR orphan genes for their ability to induce intracellular Ca^{2+} in response to human CXCL12. Its ligand, CXCL12, is a homeostatic chemokine, which controls hematopoietic cell trafficking, adhesion, immune surveillance, and development. The amino-terminal domain of CXCL12 binds the second ECL of CXCR4 and activates downstream signaling pathways. The ICL3 of CXCR4 is necessary for Gαi-dependent signaling, and ICL as well as the C-terminus of CXCR4 are required for chemotaxis.[10,20,21]

CXCL12 binding to CXCR4 triggers multiple signal transduction pathways that are able to regulate intracellular calcium flux, chemotaxis, transcription, and cell survival.[22] CXCL12 binding promotes CXCR4 conformation changing Gαi protein dissociation into

α and βγ subunits.[22,23] In turn, different subtypes of the α subunit impart different signals: Gαi subunits inhibit cyclic adenosine monophosphate formation through inhibition of adenylyl cyclase activity, and αq subunits activate phospholipase C-β, generating diacylglycerol and inositol 1,4,5 trisphosphate, controlling the release of intracellular Ca^{2+}. While inhibiting adenylyl cyclase, the Gαi subunits activate the nuclear factor-kappa B, Janus-activated kinase-signal transducers and activators of transcription (STAT), and phosphatidylinositol 3-kinase-AKT pathways as well as mammalian target of rapamycin, and the Jun N-terminal kinase/p38 MAPKs, regulating cell survival, proliferation, and chemotaxis.

CXCR4 is a major type of receptor for CXCL12. CXCL12/CXCR4 chemokine signaling plays a critical role in modulating various nervous system developmental processes and in regulating synaptic plasticity. CXCR4 is widely expressed in the peripheral and central nervous system (CNS) and exerts functions as modulation of neurotransmission, synaptic plasticity, and neuroglial interactions.[22,24] In a central neuropathic diseases model, CXCL12/CXCR4 were upregulated in neurons, astrocytes, microglia/macrophages, and leukocytes in the lumbar spinal cord.[24] Unlike the α subunits, βγ dimer subunits promote RAS-mediated MAPK signaling, thereby regulating cell proliferation and chemotaxis.[20] Finally, in addition to these classic signaling pathways, CXCR4 triggers Bruton tyrosine kinase (BTK) phosphorylation and downstream MAPK in mantle cell lymphoma and primary acute myeloid leukemia blasts, suggesting a potential interaction of CXCR4 on BTK and a potential for concomitant CXCR4 and BTK inhibition, as the treatment targets.[24]

CXC motif receptor 4 and Alzheimer's disease

Alzheimer's disease and aging

Since older individuals (those over 65 years of age) will double between 2000 and 2050, the population is aging.[25] Aging is a natural physiological process, a progressive deterioration of the overall homeostatic brain mechanisms, accompanied by cognitive decline. A consequence of normal aging is a greater susceptibility to learning and memory impairments generally attributed to a decrease in neuronal plasticity of the cortex and hippocampus. Cognitive processes mediated by hippocampus and prefrontal cortex are most vulnerable to aging process.[26] Both brain regions suffer cellular and synaptic changes during aging that can be directly related to the decline of cognitive performance.[27] Considering that the life expectancy of the population has increased, the senescence has been the primary risk factor for the development of aging-related diseases such as AD.[28] Cognitive deficits are the most common consequences of aging process and AD.[29] Both aging process and AD are characterized by a progressive deterioration of learning and memory.[28,.30,31] This strong relationship between aging and AD is important to investigate the pathophysiological mechanism in each event such as the involvement of the neurotrophic factors in these processes.

Many cellular mechanisms in AD including insulin signal pathway,[7] MAPK signaling,[8] and extracellular-signal-regulated kinase pathway[32] have been well explored. Nowadays, chemokine/CKR offers a novel navigation in AD managements and mechanisms. It is well known that chemokine/CKR pathway involved the inflammation. Inflammatory phenomenon also occurs in AD. It might not be a surprise that chemokine/CKRs may affect ADs pathological progress. However, the exact molecular mechanisms are unknown and need to be further determined.

Chemokines and chemokines receptors in Alzheimer's disease

AD is one of the most common and devastating aging-related neurodegenerative diseases. The disease poses a great threat to older individuals and their families, becoming a serious social problem with increasing longevity. The clinical manifestation of disease occurs usually after the age of 65.[33] This illness is characterized by massive neuronal loss, cognitive dysfunction, and loss of memory. The incidence and prevalence continuously increase with advancing age.[34]

AD is the most common cause of dementia in the elderly. AD is characterized by pathological findings in the brain: SPs and NFTs. The former are extracellular aggregates composed of amyloid β peptides,[35] while the latter are intracellular aggregates composed of hyperphosphorylated Tau protein. Its pathological changes also include a variety of "inflammatory" phenomenon such as activation of microglia and astrocytes. The pathological significance of inflammatory responses elicited by resident CNS cells has drawn considerable attention in recent years.[5] Chemokines belong to a rapidly expanding family of cytokines, the primary function of which is control of the correct positioning of cells in tissues and recruitment of leukocytes to the site of inflammation. Study of this very important class of inflammatory cytokines may greatly help our understanding of inflammation in the progress of AD, as well as other neurodegenerative diseases. So far, a number of chemokines and CKR have been demonstrated in resident cells of the CNS, and upregulation of some chemokines and receptors is found associated with AD pathological changes. The expressions of chemokines and their receptors in the CNS are significantly different under physiological and pathological conditions.

CXCL12/CXC motif receptor 4 axis signaling as a novel target of Alzheimer's disease management

Chemokines are small chemoattractant molecules playing a key role in inflammation and immunity.[36,37] In addition to their role in neuroinflammation, chemokines, such as CXCL12, have been shown to participate in neuronal signaling.[38,39] Chemokine CXCL12 and its receptor CXCR4 have been previously shown to modulate neuronal firing and neuron/glia communication.[40] Moreover, it has been previously shown that inflammatory responses in AD correlated with cognitive decline.[41,42] Decreased mRNA and protein levels of CXCL12, a chemokine involved in neuron-glia communication, may affect memory through altered communication in the CNS. CXCR4, the receptor for CXCL12, is concurrently decreased at the protein level in transgenic mice compared to age-matched nontransgenic controls. Importantly, it is demonstrated that CXCL12 and CXCR4 levels are decreased in AD patients as compared to nondemented controls, supporting a role for this chemokine in cognitive functioning. The decreased levels of CXCL12 might interfere with proper neuronal signaling and may therefore negatively affect memory. The results of young nontransgenic mice treated with a CXCL12 receptor antagonist AMD3100 show deficits in learning and memory.[43]

In addition, the lack of CXCL12/CXCR4 impaired memory provides further evidence supporting a role of this chemokine and its receptor in learning and memory. In conclusion, a potential new pathway is in part responsible for aspects of cognitive functioning and can thus represent a novel target in disorders affecting learning and memory. Hence, it has been identified a novel pathway mediated through CXCL12 that directly affects learning and memory and may be responsible for the dementia component of AD.

Conclusion

The pathologic changes in dendritic spines and synapses play key roles in cognitive dysfunction. Downregulated CXCR4, as a traditional GPCR, inhibits learning and memory. Therefore, the signaling CXCL12/CXCR4 might be involved in the pathological dysfunction of AD. The prevalence of AD is increasing as the population ages, posing serious threats to the health and lives of elderly people and creating significant socioeconomic burdens for families and the society. Effectively preventing and managing AD has become an important aim. However, the exact mechanisms of CXCL12/CXCR4 axis regulating downstream molecular in AD still need to be further determined. Therefore, targeting on the mechanisms of action, regulatory molecules, and signaling pathways of CXCR4 will be helpful for a comprehensive understanding of the pathogenic mechanisms of AD, particularly early stages. In addition, such studies will provide evidence for early clinical interventions for learning, memory, and for the discovery effective AD diagnosis and therapy.

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Conflicts of interest

There are no conflicts of interest.

References

1. Allen JA, Roth BL. Strategies to discover unexpected targets for drugs active at G protein-coupled receptors. Annu Rev Pharmacol Toxicol 2011;51:117-44.
2. Azzi M, Charest PG, Angers S, Rousseau G, Kohout T, Bouvier M, *et al*. Beta-arrestin-mediated activation of MAPK by inverse agonists reveals distinct active conformations for G protein-coupled receptors. Proc Natl Acad Sci U S A 2003;100:11406-11.
3. Rosenbaum DM, Rasmussen SG, Kobilka BK. The structure and function of G-protein-coupled receptors. Nature 2009;459:356-63.
4. Rajagopal S, Rajagopal K, Lefkowitz RJ. Teaching old receptors new tricks: Biasing seven-transmembrane receptors. Nat Rev Drug Discov 2010;9:373-86.
5. Nickols HH, Conn PJ. Development of allosteric modulators of GPCRs for treatment of CNS disorders. Neurobiol Dis 2014;61:55-71.
6. Violin JD, Crombie AL, Soergel DG, Lark MW. Biased ligands at G-protein-coupled receptors: Promise and progress. Trends Pharmacol Sci 2014;35:308-16.
7. Chami B, Steel AJ, De La Monte SM, Sutherland GT. The rise and fall of insulin signaling in Alzheimer's disease. Metab Brain Dis 2016;31:497-515.
8. Du LL, Chai DM, Zhao LN, Li XH, Zhang FC, Zhang HB, *et al*. AMPK activation ameliorates Alzheimer's disease-like pathology and spatial memory impairment in a streptozotocin-induced Alzheimer's disease model in rats. J Alzheimers Dis 2015;43:775-84.
9. Venkatakrishnan AJ, Deupi X, Lebon G, Tate CG, Schertler GF, Babu MM. Molecular signatures of G-protein-coupled receptors. Nature 2013;494:185-94.
10. Zhao J, Deng Y, Jiang Z, Qing H. G protein-coupled receptors (GPCRs) in Alzheimer's disease: A focus on BACE1 related GPCRs. Front Aging Neurosci 2016;8:58.
11. Tao YX. Constitutive Activation of G Protein-Coupled Receptors and Diseases: Insights into Mechanisms of Activation and Therapeutics. Pharmacol Ther 2008; 120:129-48.
12. Lu ZL, Saldanha JW, Hulme EC. Seven-transmembrane receptors: Crystals clarify. Trends Pharmacol Sci 2002;23:140-6.
13. Hur EM, Kim KT. G protein-coupled receptor signalling and cross-talk: Achieving rapidity and specificity. Cell Signal 2002;14:397-405.

14. Neves SR, Ram PT, Iyengar R. G protein pathways. Science 2002;296:1636-9.
15. Jeong SW, Ikeda SR. Effect of G protein heterotrimer composition on coupling of neurotransmitter receptors to N-type Ca(2+) channel modulation in sympathetic neurons. Proc Natl Acad Sci U S A 2000;97:907-12.
16. Pan HL, Wu ZZ, Zhou HY, Chen SR, Zhang HM, Li DP, *et al.* Modulation of pain transmission by G-protein-coupled receptors. Pharmacol Ther 2008;117:141-61.
17. Ragozzino D. CXC chemokine receptors in the central nervous system: Role in cerebellar neuromodulation and development. J Neurovirol 2002;8:559-72.
18. White FA, Wilson NM. Chemokines as pain mediators and modulators. Curr Opin Anaesthesiol 2008;21:580-5.
19. Rot A, von Andrian UH. Chemokines in innate and adaptive host defense: Basic chemokinese grammar for immune cells. Annu Rev Immunol 2004;22:891-928.
20. Hirsch E, Katanaev VL, Garlanda C, Azzolino O, Pirola L, Silengo L, *et al.* Central role for G protein-coupled phosphoinositide 3-kinase gamma in inflammation. Science 2000;287:1049-53.
21. Sasaki T, Irie-Sasaki J, Jones RG, Oliveira-dos-Santos AJ, Stanford WL, Bolon B, *et al.* Function of PI3Kgamma in thymocyte development, T cell activation, and neutrophil migration. Science 2000;287:1040-6.
22. Oh SB, Tran PB, Gillard SE, Hurley RW, Hammond DL, Miller RJ, *et al.* Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci 2001;21:5027-35.
23. Gillard SE, Lu M, Mastracci RM, Miller RJ. Expression of functional chemokine receptors by rat cerebellar neurons. J Neuroimmunol 2002;124:16-28.
24. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, *et al.* The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21:531-43.
25. Evandro F F, Morten SK, Heiko J, Juan Li, Li L. A research agenda for aging in China in the 21st century.Ageing Res Rev 2015;24:197-205.
26. Barrientos RM, Kitt MM, Watkins LR, Maier SF. Neuroinflammation in the normal aging hippocampus. Neuroscience 2015;309:84-99.
27. Morrison JH, Baxter MG. The ageing cortical synapse: Hallmarks and implications for cognitive decline. Nat Rev Neurosci 2012;13:240-50.
28. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010;464:529-35.
29. Chuu JY, Taylor JL, Tinklenberg J, Noda A, Yesavage J, Murphy GM Jr., *et al.* The brain-derived neurotrophic factor val66Met polymorphism and rate of decline in Alzheimer's disease. J Alzheimers Dis 2006;9:43-9.
30. Baquer NZ, Taha A, Kumar P, McLean P, Cowsik SM, Kale RK, *et al.* A metabolic and functional overview of brain aging linked to neurological disorders. Biogerontology 2009;10:377-413.
31. Samanez-Larkin GR, Knutson B. Decision making in the ageing brain: Changes in affective and motivational circuits. Nat Rev Neurosci 2015;16:278-89.
32. Feld M, Krawczyk MC, Sol Fustiñana M, Blake MG, Baratti CM, Romano A, *et al.* Decrease of ERK/MAPK overactivation in prefrontal cortex reverses early memory deficit in a mouse model of Alzheimer's disease. J Alzheimers Dis 2014;40:69-82.
33. Mufson EJ, Mahady L, Waters D, Counts SE, Perez SE, DeKosky ST, *et al.* Hippocampal plasticity during the progression of Alzheimer's disease. Neuroscience 2015;309:51-67.
34. Budni J, Bellettini-Santos T, Mina F, Garcez ML, Zugno AI. The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. Aging Dis 2015;6:331-41.
35. Amemori T, Jendelova P, Ruzicka J, Urdzikova LM, Sykova E. Alzheimer's disease: Mechanism and approach to cell therapy. Int J Mol Sci 2015;16:26417-51.
36. Feng L. Role of chemokines in inflammation and immunoregulation. Immunol Res 2000;21:203-10.
37. Murdoch C, Finn A. Chemokine receptors and their role in inflammation and infectious diseases. Blood 2000;95:3032-43.
38. Limatola C, Giovannelli A, Maggi L, Ragozzino D, Castellani L, Ciotti MT, *et al.* SDF-1alpha-mediated modulation of synaptic transmission in rat cerebellum. Eur J Neurosci 2000;12:2497-504.
39. Rossi D, Zlotnik A. The biology of chemokines and their receptors. Annu Rev Immunol 2000;18:217-42.
40. Bezzi P, Domercq M, Brambilla L, Galli R, Schols D, De Clercq E, *et al.* CXCR4-activated astrocyte glutamate release via TNFalpha: Amplification by microglia triggers neurotoxicity. Nat Neurosci 2001;4:702-10.
41. Bajetto A, Bonavia R, Barbero S, Florio T, Schettini G. Chemokines and their receptors in the central nervous system. Front Neuroendocrinol 2001;22:147-84.
42. Parachikova A, Agadjanyan MG, Cribbs DH, Blurton-Jones M, Perreau V, Rogers J, *et al.* Inflammatory changes parallel the early stages of Alzheimer disease. Neurobiol Aging 2007;28:1821-33.
43. Parachikova A, Cotman CW. Reduced CXCL12/CXCR4 results in impaired learning and is downregulated in a mouse model of Alzheimer disease. Neurobiol Dis 2007;28:143-53.