The role of CXCR2 in Alzheimer's disease

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Abstract. Alzheimer's disease is associated with widespread expression of the C-X-C chemokine ligand (CXCL) 1 and its receptor, C-X-C chemokine receptor (CXCR) 2. The surface of neutrophils and monocytes/macrophages expresses CXCR2. Through the CXCL1/CXCR2 axis, these cells can be attracted to the lesion to take part in the inflammatory response. By activating certain neuronal pathways via the CXCL1/CXCR2 axis, CXCR2 expression in neurons will harm neurons. Astrocytes also express CXCR2, and when the receptor is active, the quantity of astrocytes increases but their functionality is compromised. Understanding the mechanisms underlying the CXCR2 impact during the progress of Alzheimer's disease may offer an appealing target for therapeutic therapy, as inflammation can arise at virtually any location of damage. The primary functions of CXCR2 in Alzheimer's disease are summarized in this review. CXCR2 affects the expression of Tau and Aβ, which may work in concert through microglial cells to cause Alzheimer's disease. The primary pathology associated with Alzheimer's disease is the accumulation of Tau and Aβ proteins. CXCR2's main functions in Alzheimer's disease are classified into the blood-brain barrier (BBB) disruption, γ-secretase, and neuroinflammation pathway, CXCR2 influences the production of Aβ protein in Alzheimer's disease. Additionally, it impacts Tau protein expression in Alzheimer's disease via the GSK 3 β and ERK/MAPK pathways.

Keywords: CXCL1, CXCR2, Alzheimer's disease, Neuroinflammation, BBB Disruption, ERK/ MAPK and GSK 3 β, γ-secretase.

1. Introduction

Neurological diseases dramatically impair physiological functions and reduce life expectancy. Since the axons of the central nervous system do not regenerate themselves, inflammation is brought on by a variety of substances released in response to nerve injury. The nervous system can be disrupted by ischemia, hypoxia, and mechanical injury, which can lead to the severance of connections between neuronal and supporting cells as well as disruption to the blood-nerve barrier. Neurotransmitters, lipid mediators, neurotrophic factors, cytokines, and chemokines are released in response to damage. These molecules bind to receptors to mediate immune cell-neuron-glia contact and sensitise neurons. Due to the activation and recruitment of immune cells and glial cells to the inflammatory areas, this frequently results in pain and inflammation.

Chemokines are the peptide superfamily bind to G protein-coupled receptors which can control immunological responses, tumour growth, and immune cell migration.

CXCL1, a component of the CXC subfamily, contributes to inflammatory disorders by stimulating immune cells. Primarily binding to CXCR2, CXCL1 also binds to NAP-3, GRO-α, and MGSA; activation of CXCR1 requires higher levels of binding to CXCR2. Inflammatory chemicals such as TNFα and IL-1β can trigger CXCL1, which is produced by platelets and megakaryocytes. This promotes CXCL1 gene transcription through the NF-κB pathway. CXCL1, which is constitutively produced in neurons, is increased in inflammatory conditions, attracting inflammatory cells and facilitating the development of illness. It plays a role in numerous types of neuropathies, such as Alzheimer's disease. The primary function of CXCL1 is to activate the CNS's CXCR2 receptor.

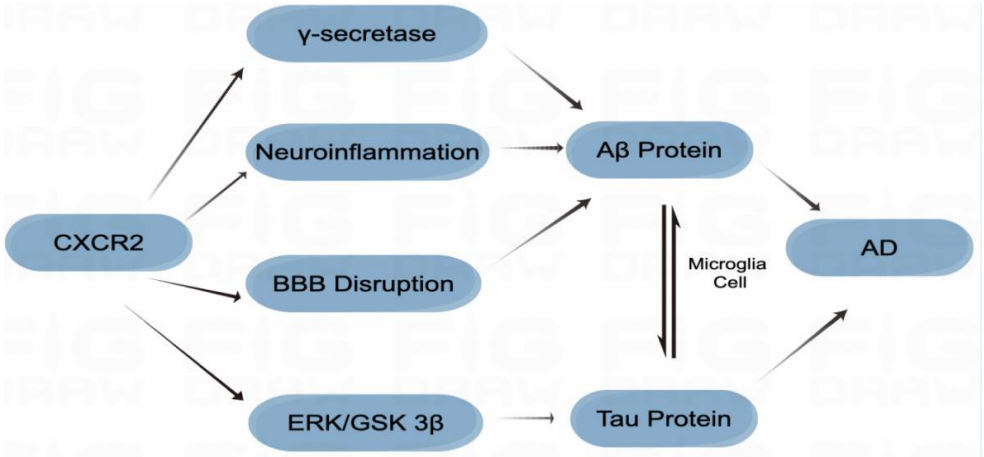
Like CXCR1, CXCR2 is a G protein-coupled receptor that, when it binds to CXCL1, activates distinct pathways. CXCR2, which is expressed in various types of cells and has been linked in diseases such as Alzheimer's disease, begins several signalling pathways. G proteins are activated by CXCL1/CXCR2 binding, which results in signalling through the PI3K/Akt pathway, activation of PLC-β, and control of intracellular Ca2+. Additionally, leukocyte migration is impacted by the

recruitment of β-arrestin. The CXCL1/CXCR2 axis is important for neurological health because it plays essential functions in inflammatory and disease in the central nervous system. This review explores the role of CXCR2 in Alzheimer's disease, focusing on the different kinds of pathogenesis relevant to CXCR2 target and supporting to treat Alzheimer's disease [1].

2. The role of CXCR2 in Alzheimer's disease

Multiple studies have found that CXCR2 is highly expressed in diseased brains, where it mediates inflammatory responses that are detrimental to brain repair. Globally, in damaged brains, CXCR2 is overexpressed and induces inflammatory responses that limit brain regeneration. The brain endothelium expresses more CXCR2 in sepsis-associated encephalopathy (SAE) caused by lipopolysaccharide (LPS), which attracts neutrophils specifically and causes inflammation. CXCR2 inhibitors have a capacity to prevent this, revealing that CXCR2 could represent an effective therapeutic target to prevent brain neuritis induced on by purulent intoxication. Therefore, the CXCR2 is an important target in CNS disease such as Alzheimer's disease, although further research is required to determine if it affects other CNS diseases such as Alzheimer's disease.

This review summaries the main roles of CXCR2 in Alzheimer's disease. CXCR2 impacts on Alzheimer's disease by affecting expression of Aβ and Tau protein, which possibly acts synergistically via Microglial cells. Accumulation of Tau protein and Aβ protein is the main pathology of Alzheimer's disease. The main roles of CXCR2 in Alzheimer's disease are showed in the following flowchart (Figure 1). CXCR2 affects expression of Aβ protein in Alzheimer's disease via γ-secretase, Neuroinflammation and blood-brain barrier (BBB) disruption. While it also affects expression of Tau protein in Alzheimer's disease through ERK/ MAPK and GSK 3 β pathway.



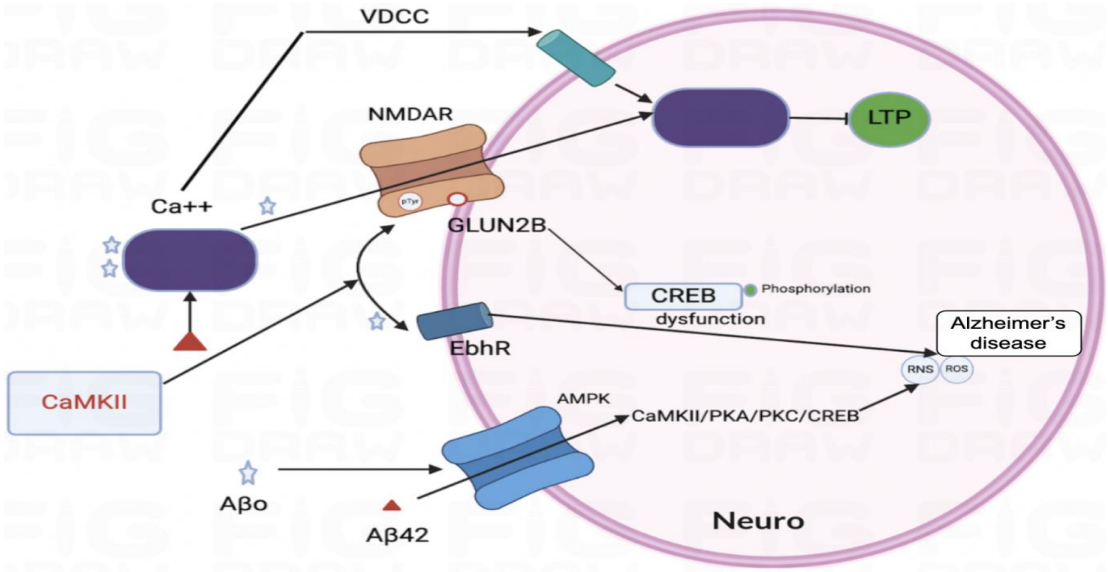
Note. CXCR2 pathway to AD. Created with figdraw.com using information from this review.

Figure 1. CXCR2 Pathology pathway to AD.

3. Aβ Pathology

Neuritic plaques and NFTs have significantly accumulated in the afflicted brain regions. The main progress of Aβ in Alzheimer's disease is showed in the following figure (Figure 2). Deficit in APP metabolism results in elevated levels of Aβ generation. The prevailing belief is that amyloid plaques are formed when Aβ collects in the extracellular space after being secreted. APP and the cleavage product Aβ regulate synaptic activity in a homeostatic approach. Amyloid plaques, extracellular aggregates, and Aβ are all harmful to the nearby neurons. Consequently, amyloid plaque development, cognitive decline, and synaptic dysfunction are brought on by the intraneuronal buildup of Aβ. The nidus of plaque development is neurotic/synaptic Aβ buildup. Normally, the APP is carried down to the neurites, where it transforms at synapses into Aβ. Early Aβ accumulation and abnormal tau phosphorylation in AD develop at synapses, changing the synaptic makeup in the early stages of the

disease. Additionally, Phospho-tau levels in Aβ-positive synaptosomes rise during this phase. The presence of soluble oligomers in surviving neocortical synaptic terminals indicates the development of dementia. This phenomenon aligns with the "amyloid cascade hypothesis," which postulates that phosphorylated tau accumulation and synaptic spread are driven by oligomeric Aβ. Early in the course of the disease, endogenous tau is crucial to the neurotoxicity of both tau and Aβ. Both direct and indirect deleterious consequences of hyperphosphorylated tau and Aβ can be observed, affecting immunological response, axonal transport, signaling cascades, neurotransmission, and organelle function. All these causes lead to loss of synapses and abnormalities in the release of neurotransmitters. Intraneuronal Aβ accumulation is decreased by synaptic activity, which also protects against Abeta-related synaptic changes. Both glutamatergic and gamma-aminobutyric acid (GABA) ergic primary neurons involved in APP/presenilin-1 (PS1) processing accrues varying levels of endogenous Aβ42. Following the cleavage of APP C-terminal fragments by gamma-secretase, Aβ is also generated inside neurons. After exposure to Aβ 42, autophagy is inhibited. Phosphorylated ERK1/2 (pERK1/2) is upregulated by autophagic activation, which also alleviates hippocampus cell dysfunction. Certain GABAergic stress tests may be advantageous for detecting elderly people who are cognitively normal since reduced GABAergic tone emerges in the preclinical stage of AD.



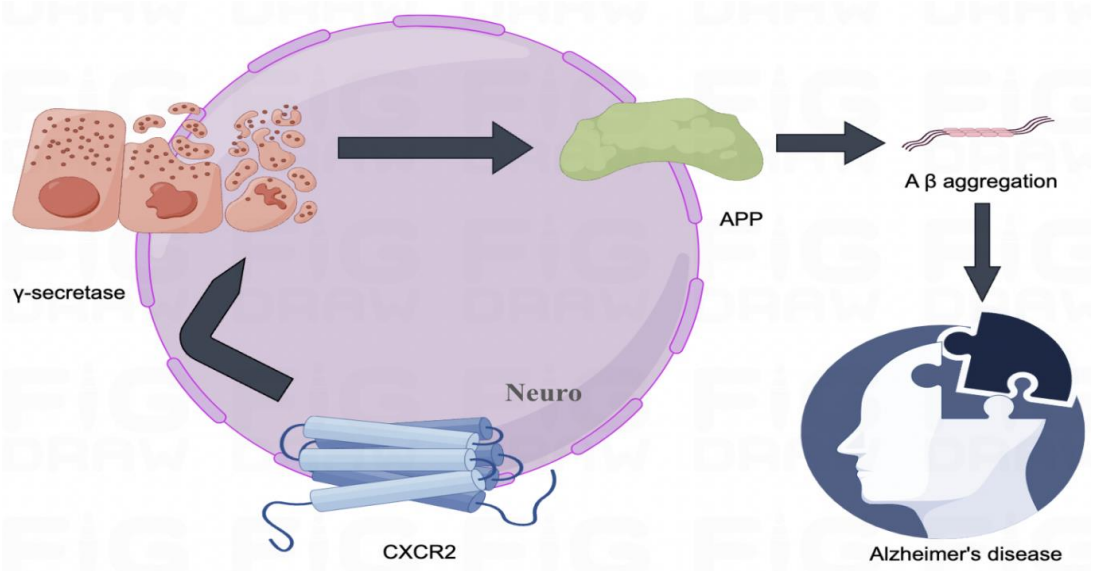
Note. Aβ Pathology pathway to AD. Created with figdraw.com using information from Engin, 2021. [2]

Figure 2. Aβ Pathology pathway to AD. Abbreviations: AD: Alzheimer's disease, Aβ42: Amyloid beta 42 peptide, AβO: Amyloid beta oligomer, AMPK: AMP activated protein kinase, CaMKII: Ca^{2+}-calmodulin dependent protein kinase, CREB: cAMP regulatory-element-binding protein, EbhR: ephrin receptor, GLUN2B: subunit of NMDAR, mainly reside at extra synaptic sites, LTP: long-term potentiation, NMDAR: N-methyl-D-aspartate receptor, PKA: cAMP-dependent protein kinase A, PKC: protein kinase C, ROS: reactive oxygen species, RNS: reactive nitrogen species, VDCC: voltage-dependent Ca^{2+} channels; APP–amyloid precursor protein; Source: own elaboration.

Alzheimer's disease-related synapse dysfunction. Oxidative stress is brought on by amyloid-β activating stress-related protein kinases through NMDARs. Apoptosis is brought on by the phosphorylation of ERK1/2 and MEK1/2 by MAPK. Amyloid-β either directly activates numerous protein kinases or activates NMDAR, causing mitochondrial dysfunction. The Bcl-2-CypD-Caspase pathway causes AD and synapse loss. Amyloid-β causes oxidative stress and increased cytoplasmic Ca2+ levels, which might have a direct or indirect effect on mitochondria. After membrane depolarization, hazardous levels of Ca2+ are released into the cytoplasm through the opening of NMDAR and VDCC. Neural injury is brought on by oxidative stress in the mitochondria, cytochrome c release, activation of caspase-9, and then caspase-3. Microglia are stimulated by amyloid-β

oligomers to produce cytokines, which in response lead to a rise in peIF2α, pJNK, pPKR, and pIKKβ as well as the suppression of brain insulin transmission. In addition to contributing to synapse loss and decreased long-term potentiation, these processes work to increase insulin resistance [2]. (Abbreviations: AD: Alzheimer's disease, Aβ42: Amyloid beta 42 peptide, AβO: Amyloid beta oligomer, AMPK: AMP activated protein kinase, CaMKII: Ca2+-calmodulin dependent protein kinase, CREB: cAMP regulatory-element-binding protein, EbhR: ephrin receptor, GLUN2B: subunit of NMDAR, mainly reside at extra synaptic sites, LTP: long-term potentiation, NMDAR: N-methyl-D-aspartate receptor, PKA: cAMP-dependent protein kinase A, PKC: protein kinase C, ROS: reactive oxygen species, RNS: reactive nitrogen species, VDCC: voltage-dependent Ca2+ channels).

4. γ-secretase pathway



Note. γ-secretase pathway to AD. Created with figdraw.com using information from Korbecki, 2022. [3]

Figure 3. CXCR2 increases γ-secretase activity. This results in increased release of amyloid β (Aβ) and increased amyloid plaque formation. Abbreviations: CXCR2—CXC motif chemokine receptor 2; APP–amyloid precursor protein; Source: own elaboration.

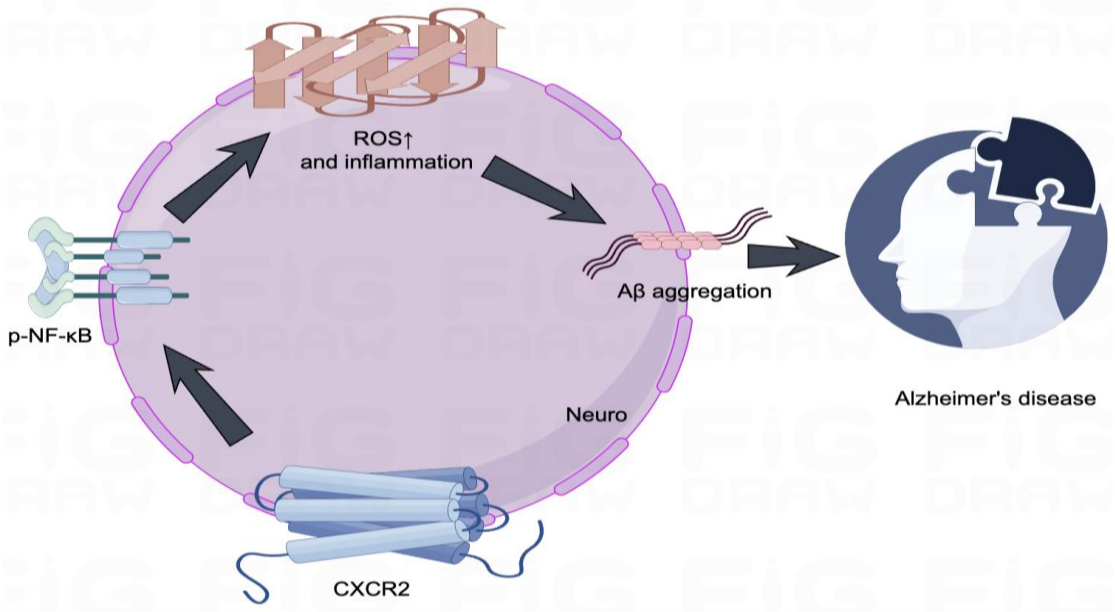
CXCR2 impact on Alzheimer's disease via increasing γ-secretase activity. This results in increased release of amyloid β (Aβ) and increased amyloid plaque formation which can cause Alzheimer's disease. Korbecki and colleagues (2022) argue that activation of CXCR2 increases the activity of γ-secretase, which is a protease that uses amyloid precursor protein (APP) as a substrate could cause AD as figure 3 showed. This results in the release of Aβ, which aids in the development of amyloid plaques. Furthermore, Aβ increases CXCR2 expression in brain microvascular endothelial cells. This suggests that the trans endothelial migration of monocytes into the brain is caused by the CXCL1/CXCR2 axis. These monocytes initiate differentiation into microglia produced from bone marrow, which play a crucial role in removing Aβ plaque deposits and preventing the development of Alzheimer's disease [3].

Additionally, Zuena and colleagues (2019) summary that Microglia and astrocytes, as well as neuritic plaques of AD tissue, have all been shown to have elevated levels of CXCR2. Aβ release is inhibited when CXCR2 is knocked down or pharmacologically blocked with the antagonist SB225002, as this inhibits γ-secretase. On the other hand, Aβ is increased when CXCR2 is activated by exogenous chemokines such hrIL8 and hrGRO-α. Additionally, the injection of Aβ1-42 intrahippocampally triggers a microglial chemotactic response, which entails the time-dependent increased expression of CXCL8/CXCR2 in the hippocampus. An enhanced T cell entrance into the brain is linked to the up-regulation of CXCR2 in peripheral T cells, which is also brought on by the

hippocampus Aβ1-42 injection. Intraperitoneal injection of the CXCR2 antagonist SB332235 reduces these effects and validates activation of CXCR2 increases the activity of γ-secretase and cause AD [4].

Moreover, Bakshi and associates (2011) also have shown in vitro that while activating CXCR2 with exogenous chemokines hrIL8 and hrGRO-α results in an increase in Aβ, knocking down or pharmacologically blocking it with the antagonist SB225002 causes an inhibition in Aβ release through inhibition of γ-secretase. The same scientists have verified these findings in in vivo experiments where they have shown an inhibition in γ-secretase and a decrease in Aβ in Cxcr2 defective animals [4].

5. Neuroinflammation pathway



Note. Neuroinflammation pathway to AD. Created with figdraw.com using information from [1].

Figure 4. Neuroinflammation pathway to AD. CXCR2 induces Neuroinflammation which lead to the aggregation of Aβ. Abbreviations: CXCR2—CXC motif chemokine receptor 2; ROS–Reactive Oxygen Stress; p-NF-κB-the phosphorylated form of Nuclear Factor kappa B; Source: own elaboration [1].

CXCR2 impact on Alzheimer's disease via inducing Neuroinflammation. As Figure 4 showed, CXCR2 influence p-NF-κB and increase ROS which cause inflammation. This results in increasing aggregation of amyloid β (Aβ) and amyloid plaque formation which can cause Alzheimer's disease.

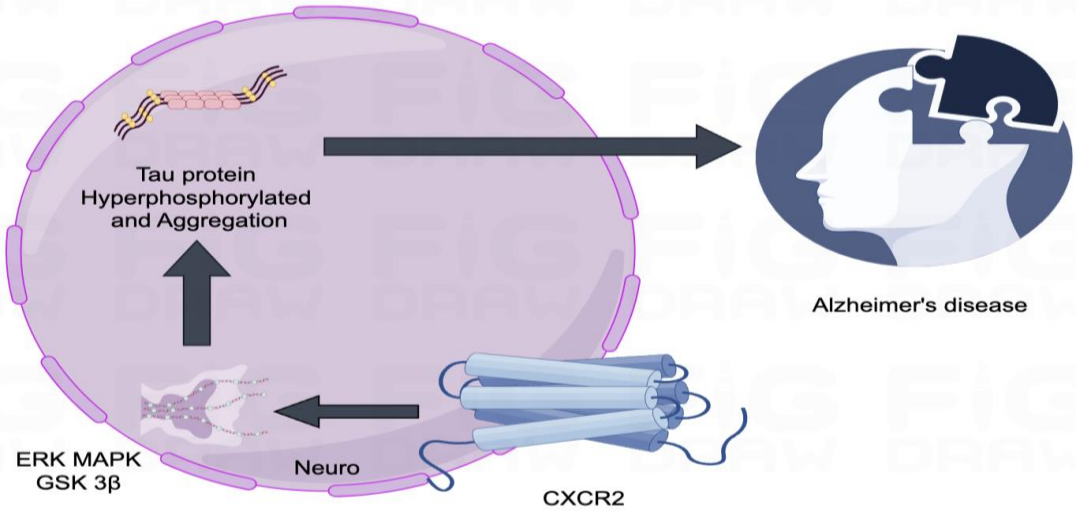
Oxidative stress (OS) and reduced inflammatory responses are intimately associated with neurodegenerative diseases. OS and neuroinflammation frequently worsen one another because reactive substances secreted by inflammatory cells both induce OS and increase inflammation by intracellular signalling. A balanced redox environment in a healthy condition facilitates a protective inflammatory response. However, this equilibrium is upset by redox imbalance in neurodegenerative diseases. Important participants in neuroinflammation, activated microglia emit cytotoxic and inflammatory substances that cause neurodegeneration. Insufficient removal of accumulated Aβ in Alzheimer's disease (AD) intensifies neuroinflammation and OS, underscoring the involvement of microglial activation in both mechanisms [5].

Perez-Nievas and colleague (2021) also argue that the significant function of the chemokine CXCL1 and its receptor CXCR2 play in the pathogenesis of Alzheimer's disease (AD) is examined in the study. According to the study, reactive astrocytes are triggered by β-amyloid (Aβ) and subsequently secrete a considerable amount of CXCL1, which interacts with CXCR2 receptors on neurons. It is demonstrated that this interaction mediates synaptotoxic consequences, resulting in a

significant decline in dendritic spine density—a crucial sign of synaptic health. The authors argue that neurons damaged by conditioned media from Aβ-stimulated astrocytes have reduced neurite length and complexity, which are essential for preserving synaptic connections. Significantly, the application of a CXCR2 antagonist (SB225002) successfully averts these synaptic toxic consequences, indicating that inhibiting the CXCL1/CXCR2 pathway may be a viable therapeutic approach to shield neurons from the deleterious effects of Aβ. The results emphasise the role of astrocytic signaling in AD and demonstrate how the CXCL1/CXCR2 axis plays a part in the neurodegenerative processes linked to the disease. This study provides up the possibilities for future research focused on targeting this ligand-receptor pair to develop novel interventions for AD, potentially mitigating cognitive decline and improving neuronal health in affected individuals. This is because it clarifies the mechanisms through which CXCL1 promotes synaptic dysfunction. All things considered, the research contributes to the increasing amount of proof suggesting non-neuronal cells—in particular, astrocytes—have a major influence on the development of Alzheimer's disease [6].

Combined with microglia, astrocytes are becoming increasingly recognized to play an essential role in neuroinflammation in Alzheimer's disease (AD). In this investigation, reactive markers such lipocalin-2 (Lcn2) and GFAP were more abundant in astrocytes treated with Aβ-containing medium (TGCM), indicating inflammatory signalling that included enhanced NF-κB phosphorylation. In astrocyte-conditioned media, TGCM treatment elevated cytokines such as CXCL1, according to cytokine array analysis. In astrocytes exposed to Aβ, researchers observed a considerable rise in CXCL1, which is high in AD brains and linked in tau pathology. Tau phosphorylation and caspase-3 activation are facilitated by CXCL1, which results in tau breakage and mislocalization. According to this experience, TGCM therapy elevated neuritic tau and cleaved caspase-3 in neurons, which is consistent with the idea that synaptic disruption may be facilitated by CXCL1-induced tau truncation [6].

6. ERK MAPK and GSK 3 β pathway



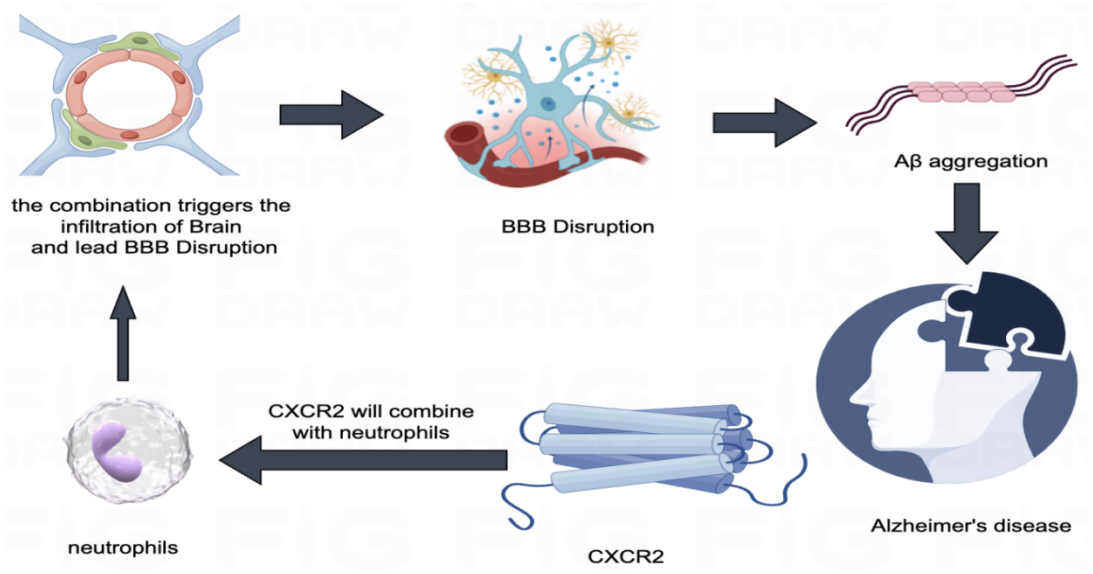
Note. Activation of ERK MAPK and GSK 3 β lead to the hyperphosphorylation Pathology pathway to AD. Created with figdraw.com using information from Korbecki, 2022 [3].

Figure 5. Activation of ERK MAPK and GSK 3 β lead to the hyperphosphorylation Pathology pathway to AD. CXCR2 causes hyperphosphorylation of tau protein which leads to a proteolytic cleavage of tau protein, which enables the formation of a neurofibrillary tangle. Abbreviations: CXCR2—CXC motif chemokine receptor 2; ERK—extracellular signal-regulated kinase; GSK3β—glycogen synthase kinase 3β; MAPK—mitogen activated protein kinase; Source: own elaboration.

CXCR2 impact on Alzheimer's disease via activation of ERK MAPK and GSK 3 β lead to the hyperphosphorylation Pathology pathway to AD. CXCR2 causes hyperphosphorylation of tau protein which leads to a proteolytic cleavage of tau protein, which enables the formation of a neurofibrillary tangle and causes Alzheimer's disease as shown in Figure 5 above.

Korbecki and colleague (2022) summaried that Alzheimer's disease patients' brains and cerebrospinal fluids had increased amounts of CXCL1. The brains of Alzheimer's disease patients include neurons that produce CXCL1. However, in pathological brain tissue, CXCL1 attaches itself to the CXCR2 receptor on neurons, activating GSK3β and ERK MAPK. This leads to hyperphosphorylation of tau and the eventual development of Alzheimer's disease. Then, caspase-3 cleaves Tau at Asp421 in neurons exposed to CXCL1 for a prolonged amount of time. This kind of short tau protein may serve as the foundation for neurofibrillary tangles. Additionally, hyperphosphorylated tau proteins are more likely to aggregate. This implies that CXCR2 mediates monocyte trans endothelial migration into the brain. These monocytes initiate the process of differentiating into bone marrow-derived microglia, which are essential for eliminating Aβ plaque deposits and inhibiting the development of Alzheimer's disease [3].

7. BBB Disruption Pathway



Note. BBB Disruption pathway to AD. Created with figdraw.com using information from Peng, 2021 [6].

Figure 6. BBB Disruption pathway to AD. CXCR2 will combine with neutrophils which trigger the infiltration of Brain and lead BBB Disruption, which enables causes Aβ protein aggregation. Abbreviations: CXCR2—CXC motif chemokine receptor 2; BBB-blood-brain barrier; Source: own elaboration.

CXCR2 impacts on Alzheimer's disease via Blood-Brain Barrier (BBB) disruption as shown in Figure 6 above. CXCR2 combines with neutrophils and triggers the infiltration of Brain and leads BBB disruption, which contributes to causes Aβ protein aggregation and causes Alzheimer's disease [7].

Wang and colleague (2021) summarized that peripheral immune cells are typically kept away from the brain by the blood-brain barrier (BBB), however, when the barrier fails to function properly, these cells can penetrate brain tissue and aggravate chronic inflammation and BBB dysfunction. Alzheimer's disease (AD) causes essential transporters including LRP1, RAGE, and P-gp, which control the flow of Aβ within the BBB, which causes the BBB's disintegration. This process involves pathological components such ROS, MMPs, NF-κB, and Ca2+-CaN. Empirical data indicates that Aβ deposition is exacerbated by BBB failure, which also impedes the substance's natural transit.

Because of this malfunction, β- and γ-secretases become more active, which increases the synthesis of amyloid-beta (Aβ), and abnormal Aβ accumulation is caused by decreased BBB transportation [8].

Another research group Peng and colleague (2021) argues that anti-inflammatory drugs for Alzheimer's disease (AD) may target chemokine receptors like CXCR2, which activate and draw microglia to cause neuroinflammation. CXCR2 also combines with neutrophils to initiate brain infiltration, which can compromise the integrity of the blood-brain barrier. Chemokine overexpression prolongs neuroinflammation and neurodegenerative processes by increasing immune cell infiltration, activating glial cells, and releasing more chemokines [9].

8. Conclusion and Future Prospect

CXCR2 regulates the expression of Tau and Aβ, which could operate in concert through microglial cells and lead to Alzheimer's disease. The primary pathology associated with Alzheimer's disease is the accumulation of Tau and Aβ proteins. Through disruption of the blood-brain barrier, neuroinflammation, and γ-secretase, CXCR2 influences the production of Aβ protein in Alzheimer's disease. Additionally, it influences Tau protein expression in Alzheimer's disease via the GSK 3 β and ERK/MAPK mechanisms. Therefore, the application of CXCR2 antagonists in Alzheimer's disease will be established well in the future. However, there are still many concerns about CXCR2 in Alzheimer's disease. Initially, the modern drug design methods structure-based drug design and fragment-based drug design can assist to discovery CXCR2 antagonists to treat Alzheimer's disease. Additionally, machine learning and artificial intelligence will be also applied in CXCR2 antagonists drug design. Moreover, CXCR2 antagonists can be discovered from natural product which is a novel method in the progress of drug design. Finally, because of the existing blood-brain-barrier problem, a variety of potential drugs for treating CNS diseases are restricted in the process of drug application. It is time to discovery novel drug delivery system to support CXCR2 antagonists to cross BBB and treat Alzheimer's disease. Therefore, focused research on CXCR2 responses will lead to more precise targeting treatments in advanced neurological diseases.

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