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The Role of GABA Pathway Components in Pathogenesis of Neurodegenerative Disorders

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Abstract

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. GABA regulates neuronal excitability, synaptic plasticity, and neuronal activity-dependent homeostatic adaptations in response to various stimuli. Disruption of GABA signaling has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Neuroinflammation, characterized by the activation of microglia and the release of cytokines and chemokines, has been recognized as a hallmark of neurodegenerative disorders. Recent studies have suggested that the dysfunction of GABA signaling exacerbates the neuroinflammatory response and contributes to the progression of neurodegenerative disorders. The activation of GABA receptors on microglia and astrocytes has been shown to modulate the production and release of various cytokines and chemokines, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

Keywords: GABA; gamma-aminobutyric acid; neurodegenerative disorders; neuroinflammation; astrocytes; microglia; cytokines; chemokines; Alzheimer's disease; Parkinson's disease; Huntington's disease; amyotrophic lateral sclerosis; multiple sclerosis; epilepsy; NMDA; glutamate; neurotransmitter; receptors; GABA receptors; neuroprotection; therapeutic targets

1. Introduction

γ-Aminobutyric acid (GABA), the mammalian central nervous system's (CNS) dominant inhibitory neurotransmitter, regulates neuronal excitability, synaptic plasticity, and activity-dependent homeostatic adaptations in response to various stimuli. Disruption of GABA signaling has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Neuroinflammation, characterized by the activation of microglia and the release of cytokines and chemokines, has been recognized as a hallmark of neurodegenerative disorders. Recent studies have suggested that the dysfunction of GABA signaling exacerbates the neuroinflammatory response and contributes to the progression of neurodegenerative disorders. The activation of GABA receptors on microglia and astrocytes has been shown to modulate the production and release of various cytokines and chemokines, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

1.1. GABAergic Neurons, Classification, Functions, and Implication in Neurodegenerative Disorders

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS), regulating neuronal excitability and synaptic plasticity. GABA is synthesized from glutamate by the enzymes glutamate decarboxylase (GAD) and transported into synaptic vesicles by vesicular GABA transporters (VGAT). Upon release, GABA binds to ionotropic GABA receptors (GABA$_A$ and GABA$_C$) and metabotropic GABA receptors (GABA$_B$), which mediate synaptic inhibition and modulate various cellular processes, including gene expression and protein synthesis. The GABAergic system plays a crucial role in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. The GABAergic system has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

1.2. Cytokines and Chemokines

Cytokines and chemokines are small proteins that act as signaling molecules, mediating the immune response and communication between cells in the body. Cytokines are a broad category of proteins that include interleukins, tumor necrosis factors, interferons, and growth factors. They can be produced by various cells, including immune cells, such as macrophages and lymphocytes, and non-immune cells, such as fibroblasts and epithelial cells. Cytokines can have pro-inflammatory or anti-inflammatory effects, depending on the context and the specific cytokine involved. Chemokines are a subfamily of cytokines that specifically mediate the chemotaxis of cells, meaning they can attract and guide the movement of cells to specific locations in the body. Chemokines are produced by various cells, including immune cells, such as macrophages and lymphocytes, and non-immune cells, such as fibroblasts and epithelial cells. They can be classified into several subfamilies, including CC, CXC, CX3C, and XC chemokines, based on the number and arrangement of cysteine residues in their protein structure. Cytokines and chemokines play a crucial role in the immune response and inflammation, regulating the recruitment and activation of various immune cells, the production of antibodies, and the resolution of inflammation. However, dysregulation of cytokine and chemokine production and signaling can lead to chronic inflammation and tissue damage, contributing to the pathogenesis of various diseases, including autoimmune disorders, cancer, and neurodegenerative disorders. The GABAergic system has been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

2. Cytokines and Chemokines Expression

Cytokines and chemokines are small proteins that act as signaling molecules, mediating the immune response and communication between cells in the body. The expression of cytokines and chemokines is a complex process that involves the activation of various signaling pathways and the production of transcription factors and other regulatory proteins. The GABAergic system has been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. The GABA and GABA receptors are expressed on various cells in the brain, including neurons, astrocytes, microglia, and immune cells, such as T cells and macrophages. The activation of GABA receptors can modulate the production and release of various cytokines and chemokines by these cells, which can have both pro-inflammatory and anti-inflammatory effects. For instance, GABA receptors have been shown to inhibit the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), in microglia and astrocytes, which can help to reduce neuroinflammation and protect against neuronal damage. The GABA receptors have also been shown to promote the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), in these cells, which can help to resolve inflammation and promote tissue repair. The expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. For instance, GABA receptors have been shown to inhibit the proliferation and cytokine production of T cells, which can help to reduce the inflammatory response in the brain. The GABA receptors have also been shown to promote the differentiation of regulatory T cells (Tregs), which are a subset of T cells that can suppress the immune response and promote tissue repair. The GABAergic system has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

2.1. Nuclear Factor Kappa B

Nuclear factor kappa B (NF-κB) is a family of transcription factors that play a crucial role in the immune response and inflammation. The GABA receptors have been shown to modulate the activation of NF-κB in various cells, including neurons, astrocytes, microglia, and immune cells, such as T cells and macrophages. The activation of GABA receptors can inhibit the activation of NF-κB in these cells, which can lead to a reduction in the production of pro-inflammatory cytokines and chemokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which can help to reduce neuroinflammation and protect against neuronal damage. The GABA receptors have also been shown to promote the activation of NF-κB in these cells, which can lead to the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which can help to resolve inflammation and promote tissue repair. The expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. For instance, GABA receptors have been shown to inhibit the proliferation and cytokine production of T cells, which can help to reduce the inflammatory response in the brain. The GABA receptors have also been shown to promote the differentiation of regulatory T cells (Tregs), which are a subset of T cells that can suppress the immune response and promote tissue repair. The GABAergic system has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

2.2. Mitogen-Activated Protein Kinases

Mitogen-activated protein kinases (MAPK) are a family of serine/threonine kinases that play a crucial role in various cellular processes, including cell proliferation, differentiation, and apoptosis. The GABA receptors have been shown to modulate the activation of MAPK in various cells, including neurons, astrocytes, microglia, and immune cells, such as T cells and macrophages. The activation of GABA receptors can inhibit the activation of MAPK in these cells, which can lead to a reduction in the production of pro-inflammatory cytokines and chemokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which can help to reduce neuroinflammation and protect against neuronal damage. The GABA receptors have also been shown to promote the activation of MAPK in these cells, which can lead to the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which can help to resolve inflammation and promote tissue repair. The expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. For instance, GABA receptors have been shown to inhibit the proliferation and cytokine production of T cells, which can help to reduce the inflammatory response in the brain. The GABA receptors have also been shown to promote the differentiation of regulatory T cells (Tregs), which are a subset of T cells that can suppress the immune response and promote tissue repair. The GABAergic system has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

2.3. Nuclear Factor Erythroid 2-Related Factor 2

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that plays a crucial role in the cellular response to oxidative stress and inflammation. The GABA receptors have been shown to modulate the activation of Nrf2 in various cells, including neurons, astrocytes, microglia, and immune cells, such as T cells and macrophages. The activation of GABA receptors can inhibit the activation of Nrf2 in these cells, which can lead to a reduction in the production of pro-inflammatory cytokines and chemokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which can help to reduce neuroinflammation and protect against neuronal damage. The GABA receptors have also been shown to promote the activation of Nrf2 in these cells, which can lead to the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which can help to resolve inflammation and promote tissue repair. The expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. For instance, GABA receptors have been shown to inhibit the proliferation and cytokine production of T cells, which can help to reduce the inflammatory response in the brain. The GABA receptors have also been shown to promote the differentiation of regulatory T cells (Tregs), which are a subset of T cells that can suppress the immune response and promote tissue repair. The GABAergic system has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

3. Conclusion

The GABA pathway plays a crucial role in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The loss of GABAergic interneurons and the dysfunction of GABA receptors have been implicated in the hyperexcitability and excitotoxicity observed in these disorders. The GABAergic system also interacts with other neurotransmitter systems, such as glutamate and dopamine, and has been shown to modulate the release and uptake of these neurotransmitters. The GABAergic system has also been implicated in the regulation of neuroinflammation and the immune response in the brain. For instance, GABA receptors have been shown to modulate the production and release of various cytokines and chemokines by microglia and astrocytes, which can either promote or suppress neuroinflammation and neurodegeneration. Moreover, the expression of GABA receptors on immune cells, such as T cells and macrophages, has been found to be altered in response to neuroinflammatory stimuli, suggesting that GABA may also modulate the immune response in the brain. This review provides a comprehensive overview of the role of GABA signaling in the pathogenesis of various neurodegenerative disorders, with a focus on the potential mechanisms by which GABA receptors on microglia and astrocytes may modulate neuroinflammation and neurodegeneration. We will discuss the evidence from preclinical and clinical studies that have investigated the effects of GABA receptor agonists, antagonists, and allosteric modulators on the production and release of various cytokines and chemokines, as well as the potential therapeutic implications of these findings.

Author Contributions

Conceptualization, P.K. and A.A.K.; Methodology, P.K. and A.A.K.; Formal analysis, P.K. and A.A.K.; Investigation, P.K. and A.A.K.; Resources, M.K.-B. and P.B.; Data curation, P.K. and A.A.K.; Writing – original draft preparation, P.K. and A.A.K.; Writing – review and editing, P.K. and A.A.K.; Visualization, P.K. and A.A.K.; Supervision, A.A.K.; Project administration, A.A.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

ACh	4-Aminobutyrylcholine
AD	5-Methoxysuccinic
ALS	Amyotrophic lateral sclerosis
BDNF	Brain-derived neurotrophic factor
BPD	Bipolar Disorder
CBD	Cannabidiol
CBP	Cannabinol
CBPA	Cannabidiol-type phenolic acid
CFTR	Cannabidiol Valine
CNS	Central nervous system
CRP	Corticotropin Factor
CSF	Cerebrospinal fluid
CXCR	Chemokine/Receptor Cross
DA	Dopa Supplement
DAT	Dopamine Transporter Receptor
DMNT	Dehydro-Methyl-Nicotine Tartrate
FAD	Fragile X Syndrome
FTD	Frontotemporal Dementia
GABA	γ-aminobutyric acid
GABA$_A$	Gamma-Aminobutyric Receptor
GABA$_B$	Gamma-Aminobutyric Receptor
GABA$_C$	Ionotropic Gamma-Aminobutyric
GAP	Cyclic-AP Function
HPLC	Methanol Gradi
HPLC	Major Depressive Disorder
HPLC	Hydrophilic Interaction Chromatography
HPLC	Small Molecule Gene Recognition Function
HPLC	Phenolic Protein Tetragonal
HPLC	Phenolic Acid
HPLC	Transport Chlorophyll
HPLC	Protein Bifurcation
HPLC	Phenolic Acid
HPLC	Neurotoxin Inhibitor Polypeptide Cornetic
GAP	Single Nucleotide Polymorphism
GABA	Ionotropic Glutamate
GABA	Synaptic Gamma
GABA	Ionotropic

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