The Role Of Mitofusin-2 And Mitochondrial Dysfunction In The Nucleus Accumbens During Depression And Anxiety

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Abstract

Depression is a mood disorder characterized by symptoms that include anhedonia, a lack of energy, dysregulation of sleep, and thoughts of suicide. Depression is often comorbid with anxiety disorders, which are mood disorders characterized by increased arousal and other specific behavioral patterns such as restlessness and difficulty concentrating that can interfere with daily activities. These disorders are of considerable interest to current neurological research, especially to find new means of efficacious treatment due to the delayed onset of efficacy and inadequate response/remission rate of typical antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are the primary class of antidepressants currently in use, developed alongside the monoamine theory of depression. However, the introduction of new hypotheses, like the neuroplasticity hypothesis of depression recontextualizes the understanding of current antidepressants, leaving room for the development of new therapeutic methods. Specifically, the nucleus accumbens (NAc) has been of considerable interest to research surrounding these mood disorders due to its projections to and from various regions of the forebrain that have been associated with the comorbid behaviors found in anxiety and depression. The NAc is largely composed of medium spiny neurons (MSNs), which are divided based on the specific expression of dopamine receptors. MSNs specifically express dopamine type 1 (D-1) or dopamine type 2 (D-2) receptors. Within these neurons, mitochondrial proteins have been shown to influence depressive and anxiety-like behavior, introducing them as a novel target for future therapeutic efforts.

Introduction

Depression is a common but serious mood disorder that causes severe symptoms including, but not limited to, anhedonia, lack of energy, dysregulation of sleep and appetite, and thoughts of suicide, affecting an estimated 3.8% of the world population(“WHO” n.d.). Chronic stress has the potential to be biologically damaging, branding it as the main environmental risk factor associated with mood disorders(Duman 2010). Often, depression is modeled in animal populations through repeated exposure to stress. According to a study by Yale University’s Department of Psychiatry, more than 60% of those with depression also experience symptoms of anxiety disorder (REF).

Anxiety disorders are characterized by increased arousal, and other specific behavior patterns that can interfere with daily activities, and can be accompanied by feelings including but not limited to restlessness, fatigue, and difficulty concentrating. These behavioral predispositions in those with anxiety are associated with negative mood, and implies vulnerability to depressive disorders (Duman 2010; “NIMH » Depression” n.d.). In animal models, anxiety is usually classified from data obtained through multiple behavioral tests, such as the Elevated Plus Maze (EPM), to screen for specific measures of anxiety-like behavior in rodent models to create ”derived“ variables that offer a description of behavioral profiles (Steimer 2011). The nucleus accumbens (NAc) is a critical part of the brain’s reward system because it interfaces with regions of the forebrain that have been associated with comorbid behaviors found in anxiety and depressive disorders, and its functionality is often altered during their expression (Ho 2022).

This introduces it as a promising target of study for the treatment of depression and anxiety mood disorders.

The NAc is primarily composed of medium spiny neuron (MSN) projections, which have classically been shown to exhibit alterations in neuronal plasticity in both depression and anxiety. Research has been predominantly focused on experience-dependent plasticity mechanisms within the NAc, with theories connecting dopamine (DA) and glutamate signals to synaptic plasticity of MSNs (Liu et al. 2017). Recently, however, scientists have begun to study other mechanisms influencing dendritic arborization and spine density, including mitochondria signaling transduction. Mitochondria have long been implicated in the regulation of dendritic arborization as well as spine and synapse formation (Liu et al. 2017). Mechanistically, however, molecular players in mitochondrial function have not been the subject of mood disorder research until recently. Emerging research suggests a central role of the mitochondrial GTPase Mitofusin-2 in the NAc for the regulation of anxiety/depression symptomatology, promising novel approaches to future research and therapeutic efforts of these illnesses. This review aims to discuss the newly developing role for Mitofusin-2 in anxiety and depressive disorders, and its role in the future of research surrounding these comorbid disorders and their treatment.

Section 1: Definitions and Literature Review

The nucleus accumbens is a subcortical region of the brain composed of two subregions with unique features: the shell and core. The shell and core differentially express neuromodulators and receptors including enkephalin and *Gamma*-aminobutyric acid (GABA) type A receptors. Inversely, substances like substance P and dopamine (DA) are preferentially located within the shell (For more information, see: (Salgado and Kaplitt 2015)). DA has been a molecule of interest in the study of the NAc due to its implication as an agent of motor stimulant mediation, and its role in the natural reward system of the brain. GABAergic MSNs are a major cell type of the NAc, making up around 95% of the cells present. These GABAergic neurons play an important role in major efferent projection from the NAc (including various areas of the mesencephalon and basal ganglia) (Salgado and Kaplitt 2015). MSNs are defined by their expression of either dopamine receptor 1 (D-1) or dopamine receptor 2 (D-2), distinguished by their projections to target regions. D-1 MSNs target the VTA and VP, while D-2 MSNs target the VP specifically (Castro and Bruchas 2019).

The remaining 5 percent of the NAc is composed of local interneuron populations, characterized into (1) fast-spiking (FSI) and parvalbumin-releasing (PV), (2) persistent low threshold and somatostatin-releasing (SOM), and (3) tonically active and acetylcholine-releasing (CIN) interneurons. The second group of interneurons are highly concentrated with neuropeptide somatostatin (SOM), neuropeptide Y (NPY), and nitric oxide synthase (NOS) (Salgado and Kaplitt 2015). Due to their central role in NAc projections and accumbal DA function, which have been shown to play a key role in the expression of anxiety and depression mood disorders (Dunlop and Nemeroff 2007), this review will be focusing on D-1 and D-2 MSNs. For more information on the functional role of interneurons and other neuromodulators found in the NAc, please reference Review (Castro and Bruchas 2019).

Accumbal activation has been observed to be reduced in patients with mood disorders, and animal models of depression have revealed various alterations in the VTA-NAc pathway (Xu et al. 2020). Specifically, reduced excitatory input and dendritic complexity within D-1 MSN have been observed to contribute to stress-induced depressive and anxiety-like behaviors. This theory of neuroplasticity as a key element of depression and anxiety has been the focus of research surrounding depression and has informed the consensus around these comorbid mood disorders (ref) (insert a ref for a well known review or multiple studies supporting this statement).

Section 2: Overview

The monoamine theory of mood disorders, a precursor to widely-accepted contemporary theories such as the neuroplasticity hypothesis, was the primary hypothesis of MDD for more than 50 years (Liu et al. 2017). It suggests that imbalances in the monoamine neurotransmitters serotonin, noradrenaline, and dopamine contribute to the development and treatment of MDD. This theory initially stemmed from unintentional findings around the efficacy of chemical compounds inhibiting reuptake of monoamine neurotransmitters in treating depression. This led to the development of the selective serotonin reuptake inhibitors (SSRIs), the primary class of antidepressant medications currently in use, and the monoamine theory informed the development of antidepressants from the 1980s–2000s
(Liu et al. 2017; Chu and Wadhwa 2023). However, this theory has been criticized for being too simplistic, and the emergence of clinical observations inconsistent with the theory including the delayed onset of efficacy and inadequate response/remission rate of typical antidepressants (Liu et al. 2017). This has led to the need for modification of the monoamine theory, or the development of new hypotheses like the monoaminergic receptor hypothesis, the signaling hypothesis, or the neuroplasticity hypothesis (Racagni and Popoli 2008).

The neuroplasticity hypothesis, evolving from the monoamine hypothesis, has recently been subject to a lot of attention from researchers
(Cramer et al. 2011; Egeland, Zunszain, and Pariante 2015)(ref). It is based on the neural system's ability to adapt to stimuli by altering its structure, function, and connections in response to stimuli including stress, linking changes in neuronal structure and activity to the development of stress-induced MDD. This recontextualizes the understanding of current antidepressants, explaining their efficacy through more thorough pathways that affect neuroplasticity
(Racagni and Popoli 2008; Andrade and Rao 2010; Serafini 2012; Harmer and Cowen 2013). The theory provides a framework for understanding the relationship between stress, the brain, and the effectiveness of antidepressant medications. While the molecular mechanisms behind neuroplasticity are not yet fully understood, this hypothesis offers a promising approach to understanding the causes and treatment of depression. A rapid onset of action and a deeper understanding of the changing theories about depression and anxiety can challenge the SSRI's wide usage as a first-line treatment for psychiatric conditions and introduce the potential for new and effective drugs

Section 3: Evidence and discussion

Mitochondria are important organelles responsible for producing a majority of the ATP required for a cell's metabolic processes. As a result, defects in the mitochondria can have negative effects on cell health, and cause injury or death. Mitochondrial function has been credited with a central role in neuronal function, but research has only recently begun to develop understanding of specific mitochondrial mechanisms in the context of stress-induced behavioral changes such as anxiety and depression(Picard and McEwen 2018). Mitofusin proteins (Mitofusin-1 and Mitofusin-2) have been implicated as key mediators of mitochondrial fusion and fission, with Mitofusin-2 (MFN-2) specifically having a role in the dendritic and spine complexity of D-1 MSNs in the NAc (Gebara et al. 2021; Li et al. 2004; Misgeld and Schwarz 2017). Since reduced dendritic complexity hinders neuronal plasticity, the length of D-1 MSN dendrites is shown to be reduced in a chronic social defeat model of depression(Chandra et al. 2017) in accordance with the neuroplasticity hypothesis of depression, suggesting a role of MFN-2 in depressive symptomatology.

A more recent study conducted in 2021 by Gebara et al. establishes a direct causal relationship between MFN-2 expression, reduced dendritic length and complexity, and mood disorders (Gebara et al. 2021). Rats that were classified as high anxiety, defined by a tendency to perceive events as threatening as measured through the elevated plus maze and open field tests displayed lower MFN2 expression in accumbal D-1 and D-2 MSNs compared to low anxiety rats. When MFN2 overexpression was virally induced, all of these behavioral, mitochondrial, and neuronal phenotypes were reversed. High anxiety rats also displayed increased depression-like behaviors, substantiating the comorbidity of these mood disorders and MFN-2's relevance to the two(Gebara et al. 2021). This introduces accumbal MFN-2 as a novel target for therapeutic efforts against both anxiety and depression. Specifically, Rho GTPases such as RhoA have recently been implicated in a possible functional role for dendritic atrophy due to their function as regulators of dendritic structure and plasticity. Since their activation has the capacity to control mitochondrial distribution and dynamics, future research has the potential to establish a relationship between RhoA and MFN2 in the context of anxiety and depression as a direction for new ways to address these comorbid diseases.

Section 4: Conclusion

While many classical theories like the monoamine theory of mood disorders shaped the understanding around anxiety and depression, the neuroplasticity theory of depression has been the primary focus of research in recent years. It allows for a better understanding behind current antidepressant medication, such as SSRIs, by observing the effects of stress on the synaptic strength in various areas of the brain, like the NAc. The NAc has been implicated as a critical part of the brain's reward system, and therefore is a promising target of study in the context of these comorbid mood disorders. While the neuroplasticity theory has been effective in examining the effectiveness of current medication, research has been lacking in understanding molecular function in this context. Specifically, the mitochondrial GTPase Mitofusin-2 has been implicated in a central role in neuronal function and shown to directly impact dendritic length and complexity. While Mitofusin-2 has been studied in the context of human neuropathy, research

has been limited regarding their role in regulating mood disorders (ref). This puts them in a unique place as a target for future therapeutic efforts to address the comorbid anxiety and depression disorders more effectively.

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