How do animal fear models inform our understanding of glutamate regulation by astrocytes in humans developing PTSD, and what similarities can be identified using these models for prediction and treatment possibilities?

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Abstract

Post-Traumatic Stress Disorder (PTSD) is an involved psychiatric mental illness that develops as a response to a traumatic event or series of scarring events. PTSD is one of the top three most common mental health illnesses, in fact, 7-8% of the global population will experience PTSD at some point in their lives. Understanding the neurobiological basis of PTSD would be important for clinical research behind possible treatment plans to help individuals relieve themselves of prior trauma. This research article will discuss the importance of astrocytes and their function in terms of regulating glutamate. By analyzing the PTSD-like behaviors from animal fear models, we will be connecting the astrocyte function for regulating glutamate for the pathogenesis of PTSD.

Introduction

Stress is a ubiquitous dimension of human life, and its effects on the brain have become a new-found interest between scientists and doctors. In response to acute or chronic stressors, the brain undergoes complex changes at the neural and molecular levels. These changes -including alterations in neurotransmitter systems, neuroplasticity, and hormonal responses- can affect one's mental health. These variations in brain structure and function can lead to more extreme dysregulation, often causing post-traumatic stress disorder (PTSD).

Post-Traumatic Stress Disorder (PTSD) is the fourth most common psychiatric condition that can develop in individuals who may have experienced acute or chronic trauma that has caused alterations in their brains (World Health Organization 2022). Just to name a few common causes, individuals may be suffering from war trauma, experiencing critical accidents, being assaulted, and being abused. While its exact etiology is not fully known and is dependent on numerous factors, it is well-established that chronic stress plays a central role in its development and persistence (Maeang and Milad 2017). Understanding the specific pathways that have undergone alterations and learning its impacts on one's pathophysiology of PTSD is extremely critical to deepen our understanding of this psychiatric disorder.

Scientifically, this project is vital because it strives to understand the intricate ways underlying stress can cause brain alterations. By pinpointing these pathways, we can gain insights into the biological basis of stress-related disorders, particularly PTSD. This understanding can drive the development of more effective diagnostic tools, therapies, and treatment opportunities to improve patients' mental health.

To approach this issue, this paper will focus on the pathophysiology of astrocytes, its relation to glutamate regulation, and how this can affect an individual with symptoms of PTSD. This paper will also discuss which and how animal fear models can be best used

to simulate stress environments to understand the pathogenesis of this psychiatric disease.

Glutamate Regulation by Astrocytes

Astrocytes are a variety of glial cells that are specific to the brain. They help maintain the balance of neurotransmitters (e.g., glutamate), regulate the blood-brain barrier, and promote synapse formation (Wei and Harrison 2023). The glutamates' excitatory characteristics help manage neuroplasticity, along with brain functions including brain development, memory, and cognition (Li et al 2019). Increased glutamate has had previous ties to neurodegenerative diseases such as Parkinson's Disease and Huntington's Disease (Sheldon and Robinson 2007), however recent studies suggest that an increasing range in glutamate may also be present within individuals suffering from PTSD. As the glutamate concentrations in the brain increase or decrease more than baseline, the brain can suffer from brain cell damage and death (Cleveland Clinic 2024). The impairment of astrocytes often leads to these physiological symptoms. These cells recycle the glutamate neurotransmitters from glutamate into glutamine in order to remove ammonia and promote nutritional support for depression by encouraging gut health. It is also extremely important for the synthesis of excitatory amino acids such as glutamate (Glu) and Aspartate (Asp), and inhibitory amino acids such as γ-amino butyric acid (GABA) (Albercht et al 2010). These excitatory and inhibitory neurotransmitters are responsible for the amino acids responsible for muscle tissue growth and function along with anxiety regulation and sleep respectively. The conversion of glutamate between these two forms is important for communication between neurons.

However, the role of astrocytes and their impact in regulating glutamate is an emerging area of research. After experiencing a traumatic event, many pathways in the brain will have been chemically altered causing the overstimulation of glutamate. This glutamate dysregulation can also be caused by the lack of astrocytes or their function and can be detrimental to an individual's mental health.

These cells are significantly abundant and unique to the brain and are located in the Central Nervous System (CNS) that provides chemical and physical support to neurons. These star-shaped cells are identifiable by their protein called the glial fibrillary acidic protein (GFAP). This protein allows the cell to communicate with other cells with support from the surrounding neural networks. Astrocytes can be categorized into four main types: interlaminar, protoplasmic, varicose projection, and fibrous. Interlaminar astrocytes are specific to primates, are relatively small in size, and have a substantial amount of GFAP fibers. Protoplasmic astrocytes are the largest type of astrocytes that make up the CNS and are responsible for the regulation of glutamate and synaptic transmission (Tabata 2015). These cells are much larger in size and have large round GFAP densities that branch out into smaller and finer processes. In comparison, the protoplasmic astroglia relay around white matter tracts. These are the largest type of astrocyte cells and therefore express fewer processes in comparison to the other types of astrocyte

cells. Researchers predict that these cells regulate synaptic activity through communication with other neural structures to regulate metabolism and maintain homeostasis within the CNS (Wei and Morrison 2023). Lastly, the varicose projection astroglia connect with other cells using their spiny branches. Although their unique function is still unknown, researchers believe that these astroglia are responsible for higher-order cognitive reprocessing as it has only been found in the nervous system of primates. To better understand the biological role of astrocytes in PTSD, we can turn to animal models which allow us to better target the role of specific biological functions in behavior.

Fear Learning Models

Animal fear models have long served as invaluable tools in understanding the complex interplay between stress, and the development of post-traumatic stress disorder (PTSD)-like phenotypes in animals. These models, typically involving rodents, provide researchers with a controlled environment to study the physiological and behavioral responses to traumatic experiences. By inducing fear or exposing animals to stressors that mimic traumatic events, scientists can gain insights into the mechanisms by which the brain undergoes chemical changes causing symptoms of PTSD, a condition that affects not only a wide range of animal species but also humans. Investigating the parallels between animal stress responses and PTSD-like symptoms offers valuable insights into the biological foundation of this debilitating disorder, and potentially paving the way for more effective treatments for both humans and animals alike.

Animal fear models are the most common models used for medical studies aimed toward understanding brain structures, neurotransmitter systems, neural circuits, and the applications of fear and anxiety. These models are specifically designed to simulate natural environments to observe behavioral changes based on the experiment. Different types of fear models can be employed by researchers to study various factors. For example, the most common types of animal models include the following: single-prolonged stress, restraint stress, foot shock,
stress-enhanced fear learning, and underwater trauma (Borghans and Homberg 2015). Regarding PTSD, the single prolonged stress (SPS) model is often used to study symptoms such as anxiety and reduced social behavior using pathways such as restraint for psychological studies, forced group swimming for physiological studies, and pharmacological studies (Lisieski et al 2018). Restraint stress models involve inducing the animals with physiological responses by restricting its free movement. Foot shock models are used to study the neurobiology of stress and neuropsychiatric disorders by inducing electric shocks to animal subjects and studying emotional, physical, and behavioral changes (Modrak 2023). Stress-enhanced fear learning (SEFL) models were designed to examine fear sensitization and to study exposures to traumatic stressors using a series of unsignaled shocks (Nishimura et al 2022). Lastly, underwater trauma

models are specific to studying acute and chronic stressors and comparing their ethological relevance (Ardi et. al 2013).

The most important factor for evaluating the effectiveness of these fear models depends on their validity. Specifically, studying the efficacy of new changes in behavior is extremely crucial for capturing the complexity of PTSD manifestations and symptoms. This validity is not single-handedly determined by the mere presence of PTSD-like behaviors in the test subject but instead by the etiological relation, these behaviors will have to real-life situations. Identifying similar behavioral traits between the fear models and real-life circumstances is pivotal to validating the model in accurately reflecting the intricacies of PTSD. Anxiety expressions within these fear models are often used to validate the model and establish translational relevance to PTSD in humans, including signs such as anxiety, defensiveness, reductions in social interactions, and sexual behaviors (Blanchard et. al 2001). Understanding the order of measurement is vital for establishing the temporal dynamics of these anxiety expressions and their correlation with PTSD-like responses. Furthermore, the examination extends to the similarities between the elicited behaviors in fear models and those observed in actual traumatic events, elucidating the model's capacity to mimic the intricacies of real-life trauma. Ultimately, assessing general similarities in phenotypes between fear models and PTSD contributes to a comprehensive understanding of the model's ability to faithfully represent the multifaceted nature of post-traumatic stress disorder.

Use of Fear Learning Models to Study the Role of Astrocytes in PTSD

Fear learning models have also been used for understanding the role astrocytes play in mammalian behavior, such as regulating and responding to neuronal activity. These models have been specifically employed to study how astrocytes regulate contextual fear memory, and dysregulation that leads to pathological fear-related disorders. These numerous glial cells support the brain’s function by increasing systolic Ca2+concentrations as a response to neuronal activity (Li et al 2019). This change causes a trigger to gliotransmitters and feedback regulation of neuronal activity and synaptic transmission. These transductions can be results of remembering traumatic events which could further lead to a change in behavioral responses and physical and psychological harm. These recollections are what lead to individuals suffering from disorders such as PTSD, anxiety disorders, depression, and various phobias. Researchers have used the channelrhodopsin-2 (ChR2) gene expression to investigate the role of glia on rodent behavior by manipulating their Ca2+levels. Studies on astrocytes and glutamate modulation in animal fear models for fear conditioning are extremely

important for understanding the biological involvement in changes in the molecular composition of synaptic transmission and neuronal signaling. The study conducted by Li and colleagues, (2020) resulted in data that claimed that adenosine and adenosine receptors were responsible for fear memory and the anxiolytic effect (Li et al, 2020). By targeting key chemical messengers, the researchers were able to reduce the abnormal excitability of neurons in the rodents' brains. They specifically altered the ChR2 gene to control its induction of calcium in astrocytes.

Conclusion

This review provides crucial insights into the complex mechanisms in which underlying fear-related behaviors relate to the potential involvement of astrocytes in regulating glutamate therefore producing new behavioral changes. All of these models are crucial for analyzing the different effects of fear models on various aspects of the animals' behavior, by focusing on the biological processes, such as neural activity and synaptic transmission. By elucidating the specific involvement of glutamate and astrocytes towards fear and memory recollection, researchers may be able to uncover the target methods and models for treating PTSD and other related psychiatric disorders. Overall, the incorporation of fear learning models for investigating astrocyte function concerning glutamate regulation represents a topic that needs to be further researched in the interest of understanding the pathogenesis of PTSD and using this to further improve the development of more effective treatment options to alleviate its debilitating symptoms.

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