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The Role of Neurotransmitters in Relation to Psychiatric Conditions Throughout the COVID-19 Epidemic

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A B S T R A C T

Various studies have reported the presence of psychiatric symptoms among individuals diagnosed with COVID-19, encompassing heightened stress levels, impaired cognitive function, depressive mood, anxiousness, post-traumatic stress disorder (PTSD), psychotic symptoms, and suicidal ideation. The objective of this review was to elucidate the involvement of neurotransmitters in psychiatric disorders following the COVID-19 pandemic. There are multiple variables that can influence the results of research studies examining the presence of symptoms or the initiation of psychiatric disorders in individuals diagnosed with COVID-19. Factors associated with mental health difficulties include direct involvement in the healthcare field, presence of a psychiatric disease within the family, limited social support, advanced age, solitary living arrangements, and the utilization of high dosages of steroids during the acute phase. Multiple types of neurotransmitters are involved in the modulation of stress levels inside the human body. The neurotransmitters implicated in this process include dopamine, serotonin, epinephrine and norepinephrine, acetylcholine, gamma-aminobutyric acid (GABA), and glutamate. In summary, cytokines have a pivotal role in modulating the hypothalamic-pituitary-adrenal (HPA) axis within the brain, hence potentially giving rise to psychiatric manifestations including impaired sleep, heightened stress, depressive affect, and several other psychological disturbances.

1. Introduction

On January 30, 2020, the World Health Organization (WHO) officially declared the novel coronavirus 2019-nCoV as a global public health emergency.[1] The COVID-19 pandemic has compelled governments in the countries most heavily impacted by the outbreak to implement stringent preventive measures, including lockdowns, in order to mitigate the spread of the virus among their populations. They included working from home, closing shops, schools, restaurants, and any other non-essential service or company to restrict the outbreak's spread and prevent the healthcare system from failing. The implementation of quarantine regulations resulted in the adoption of detrimental behaviors, hence exerting an adverse influence on the overall well-being of the populace.[2,3]

Psychiatric symptoms have been observed in individuals diagnosed with COVID-19 in several studies. These symptoms encompass heightened stress levels, impaired memory, feelings of melancholy, anxiety, post-traumatic stress disorder (PTSD), psychosis, and suicidal ideation. Furthermore, some individuals have also exhibited enduring negative effects. Individuals may experience cognitive impairments, sleep disturbances, heightened levels of stress, feelings of melancholy, worry, and symptoms associated with post-traumatic stress disorder (PTSD) for an extended period of time following the acute phase of the illness. Based on the crucial findings from

recent studies into the origins of neuropsychiatric disorders, researchers have successfully identified the brain mechanisms that underlie these impairments.[4,5] The objective of this review was to elucidate the involvement of neurotransmitters in psychiatric disorders following the COVID-19 pandemic.

Risk factor of mental health problem during COVID-19 outbreak

There are multiple variables that can influence the results of studies examining the presence of symptoms or the initiation of psychological disorders in individuals diagnosed with COVID-19.[6] Factors associated with mental health difficulties include direct involvement in the healthcare industry, the presence of a psychiatric disorder within the family, limited social support, advanced age, social isolation, and the utilization of high doses of steroids during the acute phase. The pressures associated with isolation encompass concerns related to illness, discomfort, and boredom, as well as limited access to essential supplies and information, all of which contribute to the duration of the period of confinement. Moreover, the scarcity of financial resources can pose a challenge during periods of quarantine. The consequences of individuals experiencing involuntary unemployment and abrupt career discontinuation can have enduring effects. The research analyzed indicates that the isolation resulted in notable socioeconomic challenges as a consequence of economic decline.[7] Following an extended period of quarantine, empirical evidence has substantiated its association with an increased susceptibility to mental disorders, including but not limited to anger and anxiety.

Hypothalamus pituitary adrenal (HPA) axis

Neurohormones and neurotransmitters play a crucial role in modulating behavior and psychological activity inside neural networks. These signaling molecules activate G-protein-coupled receptors, which have an effect on the brain's neural circuitry. This could change behavior and the movement of neurons in vertebrates and invertebrates like nematodes and drosophila. Stress hormones, specifically glucocorticoids, which play a role in both metabolic and immunological processes, activate the hypothalamic-pituitary-adrenal (HPA) axis when people experience a lack of social interaction.[8,9]

The anterior pituitary secretes the adrenocorticotropic hormone, which in turn stimulates the adrenal cortex to produce cortisol. Cortisol is a type of glucocorticoid steroid hormone that has the ability to traverse the blood-brain barrier and penetrate the brain. The hypothalamus and pituitary gland exhibit an inhibitory feedback reaction to cortisol, thus accomplishing the homeostatic circuit. The prefrontal cortex, hippocampus, and amygdala exhibit a substantial density of cortisol receptors, encompassing both mineralocorticoid and glucocorticoid receptors. The impact of cortisol on memory and concentration processes is contingent upon various circumstances, such as the severity of the cortisol rise. The negative impacts of intense stress on behavior are mitigated by the hyperactivation and sensitivity of the serotonergic system. Exercise, on the other hand, seems to enhance stress resilience by promoting adaptability in serotonergic neurons. Moreover, it has been observed that social isolation has a detrimental effect on the hypothalamus, leading to the release of oxytocin and vasopressin, which are known to play a crucial role in regulating behavioral patterns in both humans and other animal species. The levels of toll-like receptors TNF-α, IL-4, IL-10, and ACTH in the plasma, as well as the levels of receptors IL-6 and TNF-α in the hippocampus, are elevated in rats subjected to social isolation stress. Based on a recent comprehensive investigation, there exists a correlation between the experience of negative consequences and the states of isolation and loneliness.[10-12]

Neurotransmitters

Multiple types of neurotransmitters are involved in the modulation of stress levels inside the human body. The neurotransmitters implicated in this process include dopamine, serotonin, epinephrine,

norepinephrine, acetylcholine, gamma-aminobutyric acid (GABA), and glutamate.[13]

Dopamine

Dopamine plays a crucial role in dopaminergic dysfunction, and there exists a correlation between reward-related memory performance and certain mental disorders such as depression and schizophrenia. It is very important for reward-related learning pathways to be involved in the development of addiction, as the feedback loop between the hippocampus, ventral striatum, ventral tegmental region, and hippocampus is very important. The transmission of dopamine from the ventral tegmental region (VTA) to the hippocampus plays a crucial role in the consolidation of declarative memories into long-term memory. Many parts of the mouse brain, like the hippocampus, prefrontal cortex, striatum, midbrain, and pons-medulla, have significantly higher levels of dopamine and its metabolites after a single exercise session. The positive impact of exercise on cognitive functioning has also been associated with the neurotransmitter dopamine.[14,15]

Serotonin

Serotonin is a chemical neurotransmitter that facilitates the transmission of signals between neurons inside the central nervous system. Neurons that are susceptible can be observed in several regions of the brain. The synthesis of serotonin occurs within the brainstem and plays a crucial role in regulating a range of processes, such as self-regulation and emotional equilibrium. The benefits of exercise in alleviating symptoms of depression and anxiety have been associated with the modulation of serotonin levels. Prolonged engagement in physical activity has been found to yield therapeutic effects comparable to those of antidepressant medication in individuals. A prior investigation revealed that serotonergic neurons played a role in the acute modulation of depressive and anxiety-like behaviors during exercise. Serotonin is hypothesized to be involved in the cognitive advantages associated with acute exercise. Serotonin has a crucial role in regulating various aspects of human physiology, including mood, emotion, sleep, and appetite. On the other hand, dopamine is responsible for controlling essential cognitive processes such as motivation, memory, recognition, and excitation.[16,17]

Epinephrine and norepinephrine

The act of engaging in acute exercise elicits an increase in plasma levels of norepinephrine and epinephrine in individuals. The plasma lactate level has a strong correlation with the exponential rise of these two catecholamines during the peak workout phase. The term "catecholamine threshold" refers to the point at which lactate and ventilatory levels increase simultaneously. Glycogenolysis, the enzymatic breakdown of glycogen in the liver, serves as a crucial energy supply for the muscles engaged in physical activity. The actions of norepinephrine and epinephrine within the peripheral nervous system facilitate this process. Despite the inability of catecholamines to traverse the blood-brain barrier, a certain investigation revealed that engaging in maximally rigorous exercise led to an elevation in noradrenergic levels within the cerebral spinal fluid. This finding suggests that physical activity has the potential to augment norepinephrine levels within the brain. Despite the involvement of norepinephrine in several cognitive processes, few studies have been conducted to explore its impact on acute changes in cognitive performance resulting from physical activity.[7,18]

Acetylcholine

Acetylcholine (ACh), a neurotransmitter found in the brain, plays a crucial and extensively studied role in the process of active system consolidation. The essential role of acetylcholine (ACh) in learning has been the subject of extensive investigation. Previous studies in humans have demonstrated that the inhibition of muscarinic ACh receptors results in a decline in subsequent performance shortly after the encoding of crucial information. This finding suggests

that these receptors play a crucial role in facilitating the transmission of information from the brain to the hippocampus, where the formation of associative connections takes place. In contrast, it is imperative to have reduced levels of consciousness during sleep since they facilitate the process of knowledge consolidation by reversing the direction of information flow.[19]

The active systems consolidation idea proposes that cholinergic tone has a role in directing the direction of communication between the hippocampus and neocortex, which is crucial for the transfer of declarative memory. Future research should prioritize the establishment of a more explicit connection between cholinergic mechanisms responsible for plasticity and the varied characteristics of network features. It is evident that there exists a correlation between acetylcholine and the direction of information sharing within the hippocampus cortical system.[16-19]

Acetylcholine is transiently released from the neuromuscular junction and preganglionic neurons of the autonomic nervous system, thereby playing a role in physical movement, as anticipated. Upon initiation of physical exercise, there is a notable increase in the levels of acetylcholine inside the cortex and hippocampal regions of the brain. The augmentation of acetylcholine levels leads to an elevation in the formation of theta waves in the hippocampus, hence enhancing synaptic plasticity and cognitive processes. A significant decrease of 40% in plasma choline levels, a constituent of acetylcholine, has been seen during marathon running. According to existing research, acetylcholine, which is similar to serotonin and dopamine, can contribute to the development of exercise-induced fatigue.[10,12]

Glutamate and gamma-aminobutyric acid (GABA)

The neurotransmitters glutamate and GABA, which play a significant role in activating and inhibiting brain activity, have received limited attention in studies investigating the acute effects of exercise. Acute physical activity induces an increase in the levels of glutamate and GABA activity within the brain, consistent with previous findings on neurotransmitter modulation. GABAergic neurons, primarily located in the ventrolateral preoptic area, have been identified as pivotal in the start and maintenance of sleep due to their capacity to suppress arousal centers in the brainstem, hypothalamus, and basal forebrain.[13,19]

The initial focus on GABA-A receptors for the treatment of sleep disorders, such as insomnia, has been accompanied by the recognition of adverse effects, notably the occurrence of atypical sleep patterns associated with the drugs employed in this approach. Within this particular context, it is possible to distinguish between GABA-A-positive receptors and GABA-A agonists. The former has the ability to boost shallow non-REM sleep and promote sleep spindle movement, but at the expense of slow-wave sleep (SWS) and rapid eye movement (REM) sleep. On the other hand, the latter has the capacity to improve both SWS and REM sleep. In contrast to its predecessor, the current intervention does not prioritize the improvement of slow-wave sleep (SWS) and the accompanying non-rapid eye movement (non-REM) sleep activity at the cost of other rapid eye movement (REM) sleep stages.[7,8]

2. Conclusion

Cytokines have a pivotal role in modulating the hypothalamic-pituitary-adrenal (HPA) axis inside the brain, leading to the manifestation of psychiatric symptoms like worse sleep quality, heightened stress levels, feelings of melancholy, and several other psychological disturbances.

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