Sadness and Major Depressive Disorder - The Biology Behind Emotions

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Abstract

Sadness is one of the most widely experienced emotions, and though appearing simple on the outside, it is quite complex. The feelings of sadness that we experience are the culmination of neurotransmitters, receptors, and different brain areas working together. We will go over the definition of sadness, the neurotransmitters and receptors involved, various disorders associated with sadness, and management/treatment options. This paper's primary goal is to detail the specific biological processes that cause sadness, and explain the factors that can cause disorders involving persistent sadness.

Introduction

Sadness is one of the six universal emotions (Ekman, 1999) and plays a crucial role in human experience. It can arise in situations including emotional processing after a tragic event, during social bonding, and the adaptation to loss or stress. While temporary sadness is normal, prolonged feelings of sadness can be a sign of a psychiatric disorder such as Major Depressive Disorder (MDD). Understanding the biological mechanisms underlying sadness can help explain emotional processing in the brain and why disruptions in these systems can lead to illnesses. To explore sadness and MDD, we will first examine neurotransmitters that control emotions.

Functions of Neurotransmitters

Neurotransmitters (NTs) are chemical messengers that bind to a receptor in order to convey a message or an emotion. Several NTs are involved in sadness, including, serotonin, dopamine, norepinephrine, and GABA. Serotonin is involved in mood regulation and maintaining emotional stability. It plays a key role in managing appetite, anxiety reduction, sleep, and digestion. On the other hand, dopamine's primary function is to reward and motivate. Low dopamine levels can be associated with anhedonia, or a reduced ability to experience pleasure. Norepinephrine, a catecholamine neurotransmitter, is often involved in stress response and emotional arousal. Low norepinephrine levels can result in low energy, poor concentration, and ultimately persistent sadness. Finally, GABA, the brain's primary inhibitory neurotransmitter, reduces neuronal activity by inhibiting signaling between neurons. When GABA signalling is reduced, emotional circuits can become hyperactive, contributing to anxiety and depressive symptoms.

Functions of Receptors

The above neurotransmitters exert their effects via receptors throughout the cortic and limbic systems. For instance, serotonin receptor 5-HT1A acts as an inhibitor that regulates mood and anxiety. This receptor regulates mood via hyperpolarizing neurons and decreasing synaptic

firing rates. 5-HT1A is located in the prefrontal cortex and the hippocampus. Another receptor, 5-HT2A, is an excitatory receptor involved in emotional processing and cognition. It can mediate cortical activity, cognitive flexibility, mood, and perception. Dopamine D1 receptors, critical for reward, motivation, and pleasure, function as excitatory receptors that enhance dopaminergic signaling. They are primarily located in the nucleus accumbens and the prefrontal cortex. D2 receptors, as inhibitory receptors, regulate the rewarding and motivating effects of dopamine. They can be found in the striatum and throughout the limbic system. Similarly to the effects of reducing dopamine levels, modified receptor activity can also contribute to anhedonia, a major symptom of depression. In other words, the receptors play an equally important role in mood regulation as the signaling molecules do. Finally, GABA-A receptors are ligand-gated chloride ion channels that facilitate the rapid inhibition of neurons. They are located in the amygdala and hippocampus. Essentially, different receptors can overlap in regulating different brain areas, and different subtypes of each receptor can inhibit or excite.

MDD and BDNF

While neurotransmitter and receptor activity can shape emotional responses, genetic and environmental factors can also affect sadness and how it presents itself. MDD is a relatively common disorder in the United States, having a lifetime incidence of 12% in men and 20% in women (Belmaker & Agam, 2008). In addition, MDD is also a moderately heritable psychiatric disorder, meaning that genetic variations affecting neurotransmitter systems and neural plasticity can increase an individual's risk of developing MDD. For instance, BDNF (brain-derived neurotrophic factor), a protein that supports neuron growth and synaptic plasticity, has a mutation called Val66Met. BDNF signaling is linked to mood regulation and antidepressant effects, and its impairment is implicated in the pathophysiology of depressive disorders (Castrén & Monteggia, 2021). Also, individuals with Val66Met present reduced hippocampal plasticity, increased vulnerability to stress, and ultimately a higher risk of depression under stressful conditions. However, environmental factors can also influence the presentation of sadness and MDD. Exposure to traumatic life events can disrupt dopamine levels and reward processing, which may contribute to anhedonia and depression.

Psychiatric and Neurological Disorders

While sadness alone does not inherently cause a neurological or psychiatric condition, it can be a prominent feature of certain disorders. However, in order to understand how sadness manifests in neurological and psychiatric disorders, it is important to identify the difference between the two. In neurological disorders, the physical makeup of the brain circuitry is altered. In psychiatric disorders, the overall structure of the brain remains largely intact, but the regulation of neurotransmitters and emotional brain circuits becomes dysregulated. For example, Parkinson's disease, primarily known for its motor symptoms, can also be dominated by sadness or depression as a non-motor symptom caused by neurochemical changes. On a molecular scale, Parkinson's disease involves degeneration of dopamine-producing neurons in the substantia nigra. Because these neurons are responsible for reward and motivation, patients

with Parkinson's disease experience reduced dopamine signaling, disrupting reward and motivation pathways, often leading to depressive symptoms. On the other hand, MDD exemplifies a psychiatric disorder as it involves the dysfunction of emotional brain circuits, particularly the prefrontal limbic system. Key affected regions include the prefrontal cortex, amygdala, and the hippocampus. Disturbances in these circuits can result in persistent negative emotional processing.

Management/Treatment

The management of depressive disorders can be challenging; however, there are several effective approaches. One major approach involves medication targeting neurotransmitters, with the purpose of restoring balance in emotional circuits. For example, selective serotonin reuptake inhibitors (SSRIs) increase serotonin availability by blocking its reuptake, thereby increasing its concentration in the synaptic cleft. Another important approach is psychotherapy. By learning cognitive patterns and emotional regulation techniques, a person can modify maladaptive thought processes that contribute to persistent sadness. For instance, a patient suffering from MDD may default to thinking "I always mess things up" when situations go wrong. Cognitive Behavioral Therapy (CBT) teaches patients to reframe these thoughts into more balanced statements, such as "I didn't do well this time, but I've succeeded before." This process strengthens top-down regulation from the prefrontal cortex and reduces excess activity within the amygdala. These simple emotional regulation techniques can appear insignificant; however, a study published in the NIH's Public Library of Medicine provides detailed evidence of CBT's effectiveness. The study examined 409 trials with 52,702 patients, and found clear evidence that CBT is effective in treating depression. In fact, the study reported a Hedges' g of 0.79, indicating a moderate to large positive effect of CBT in reducing depressive symptoms (Cuijpers et al., 2013). Also, lifestyle changes such as exercise and activity have been found to influence neurotransmitter systems that are important for emotional regulation, including serotonin and dopamine pathways (Pahlavani, 2024). On a molecular level, exercise increases levels of BDNF, a protein that supports neuronal growth, synaptic plasticity, and overall brain adaptability.

Conclusion

Sadness is not merely a subjective state, but rather a complex culmination of neurotransmitters, receptors, genetics, environmental conditions and neural circuits. Disruptions in these systems can result in psychiatric or neurological disorders, highlighting the biological effects of long term emotional distress. By understanding emotions such as sadness and their biological functions, doctors and researchers can better develop targeted treatments via pharmacology or psychotherapy to aid individuals with mental health conditions. Ultimately, approaching mental health from both the patient's feelings and a biological perspective creates a shared foundation of compassion over which we can build our collective knowledge of the complex workings of the brain.

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