How are endorphins a natural remedy for anxiety? (Are endorphins sufficient to alleviate anxiety? Under which conditions?)

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ABSTRACT

Generalized anxiety disorder (GAD) causes fear or anxiety responses to innocuous stimuli, exaggerated responses to concerning stimuli, affects over 300 million people globally, and is nearly twice as common in women as in men. This review discusses the underlying neurological changes, as well as the interactions between the brain,body, and sex in this complex disorder. The effects of not only societal expectations, but sex hormones, hormonal cycles, and environmental impacts are discussed. One intervention for anxiety with increasing evidence for its effectiveness is exercise, and specifically its impact on endorphins. Endorphins are opioid neuropeptides released when the body experiences stress or pain and act as the body's natural pain relievers. Endorphins are also released during exercise. Endorphins modulate stress-related brain activity by binding to mu-opioid receptors, thereby decreasing heart rate and restlessness. Gender also must be considered when evaluating anxiety disorders due to gendered societal expectations and differences in levels of testosterone and estrogen which affect endorphin production. While males and females have similar baseline endorphin levels, the hormonal fluctuations of the menstrual cycle affect endorphins, meaning that sex differences can impact anxiety.. By including multifactorial considerations in GAD, we continue to progress in understanding and improve treatment options and outcomes.

INTRODUCTION

Introduction to Function and Mechanism of Endorphins

The word endorphin is derived from the words "endogenous" and "morphine", meaning "morphine made inside of your body". Endorphins, coined "feel good chemicals", are opioid neuropeptides primarily made in the pituitary gland and hypothalamus, and their release is triggered by CRH in response to stress or pain (Ali et al.). (Ali et al.) Endorphins not only manage pain and stress, but influence mood, motor activity, breathing, regulate sexual behavior, hormonal cycles, and pituitary hormone secretion, due to their concentration in relevant regions of the brain (Ali et al.) ;(Zhang); (ABSTRACT). Once released, beta-endorphins (BE) in the peripheral nervous system (PNS) bind to mu-opioid receptors on sensory neurons and block pain signaling (Ali et al.).By binding to opioid receptors in the dorsal horn of the spinal cord, endorphins inhibit the release of substance P, a neuropeptide which transmits pain signals (Ali et al.), which stops pain signals from being sent to the brain. In the central nervous system (CNS), endorphins inhibit GABA, which in turn increases dopamine release—boosting mood and promoting feelings of pleasure (Shrihari). Laughter, or even the anticipation of something funny stimulates endorphin release(ABSTRACT). In more extreme cases, such as life-threatening or highly stressful situations, the adrenal medulla can release large amounts of endorphins, providing temporary pain resistance (Amir et al.). Importantly, in addition to being triggered by stress, pain or laughter , moderate-intensity aerobic activity for at least 20 minutes significantly increases BE (Shrihari).

The role of endorphins as the body's natural pain reliever also lies in interactions with other key neurotransmitters. For example, endorphins indirectly increase dopamine activity (the reward chemical) by inhibiting GABA, which normally suppresses dopamine neurons (Shrihari). This mechanism links endorphins to reward pathways and addiction-like behavior (Ali et al.), resulting in the association of endorphins and feeling good. Endorphins also indirectly interact with norepinephrine (NE), a neurotransmitter directly involved in the body's "fight or flight" response. NE acts to increase heart rate, blood pressure, alertness, and stress reactivity—all of which are heightened during anxiety (Ali et al.). Endorphins, particularly, BE modulate NE activity by binding to mu-opioid receptors located on noradrenergic neurons, especially in the brainstem and locus coeruleus (Ali et al.); (Amir et al.). When bound, endorphins inhibit the firing of these NE-producing neurons, reducing the release of NE into the synaptic cleft (Ali et al.)1)Reduction in NE decreases physical symptoms of anxiety such as rapid heart rate and restlessness. During acute stress, both endorphins and NE are released: NE activates the body, while endorphins serve as a counter-regulatory force, promoting calm and analgesia (Ali et al.);(Amir et al.).

Finally, endorphins lessen the release of cortisol, the stress hormone, via the body's central stress response system, which involves the hypothalamus, pituitary gland, and adrenal glands, termed the hypothalamic-pituitary-adrenal axis (the HPA axis). When a person is stressed, the hypothalamus releases CRH. CRH signals the pituitary gland to release ACTH (adrenocorticotropic hormone). ACTH then signals the adrenal glands to release cortisol (Amir et al.). Endorphins are also produced in the pituitary gland in response to CRH, because they share the same precursor protein: POMC (proopiomelanocortin)(Amir et al.). When BE levels increase, they can suppress the HPA axis through negative feedback: endorphins inhibit CRH and ACTH release, further reducing secretion of cortisol. The result of these complex interactions is ultimately the quieting of many parts of the nervous system by endorphins, which promotes a state of calm.

Introduction of Central Nervous System Involvement in Anxiety

Anxiety is a complex, multi-modal disorder and as such involves many central nervous system regions. The core diagnostic features for GAD, as outlined in the DSM-IV,3 include excessive anxiety and worry that is difficult to control and pertains to several events or activities. The anxiety must occur more often than not for a period of at least 6 months and be accompanied by at least 3 of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbances (Abuse). Multiple regions in the brain are involved in the processing of emotions and the expression of anxiety, including the amygdala, prefrontal cortex (PFC), hippocampus, periaqueductal gray (PAG), and anterior cingulate cortex (ACC). Indeed, functional MRI studies reveal abnormal brain activation patterns during emotional processing tasks in GAD (Stein). The amygdala in particular is known to play a crucial role in processing emotions, specifically fear and fear response. In GAD, the amygdala shows heightened activation, which leads to exaggerated fear responses, both physically and experientially(Kim and Gorman). This increased activation is linked to not only heightened fear responses, but more pervasive anxiety responses (Stein). The PAG contributes to these defensive behavioral responses linked to fear and anxiety (Lawther et al.).

In addition to alterations in fear response, more complex thought and emotion patterns are altered in anxiety. The PFC is responsible for higher-order cognitive processes, including emotion regulation and control of anxiety. In GAD, altered activity has been shown, especially in dorsolateral and ventrolateral PFC, which may have a compensatory role in emotion regulation (Stein). Magnetic resonance spectroscopy (MRS) shows altered metabolite ratios in the PFC in GAD patients, suggesting neuronal changes (Stein). Both the alterations in neuronal metabolism and general neural activity indicates PFC function may be dysregulated, impairing the ability to control fear responses (Lawther et al.). The hippocampus also shows altered activity in anxiety, and is associated with memory, learning, and the context of fear (Kim and Gorman). Finally, the ACC is involved in both emotional awareness and self-reflection, and GAD is associated with increased activity in the ACC (Stein). People with anxious temperaments show more activity in the dorsal ACC, which is tied to worry and overthinking, and less activity in the ventral ACC, which helps process emotional experiences calmly (Simmons et al.). This imbalance may cause people with GAD to focus too much on potential threats and have a harder time calming down emotionally, even in uncertain or neutral situations. Taken together, GAD has effects across brain regions involved in emotional regulation, memory function, fear response regulation, and ability to self-reflect, which can decrease an individual's ability to modify or decrease their fear and anxiety responses.

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Neuro Transmitters and Neurochemical Systems Involved in Anxiety

Altered neurotransmitter signaling also plays a role in GAD. Several neurotransmitters and neuropeptides such as gamma-aminobutyric acid (GABA), serotonin (5-HT), norepinephrine (NE), and corticotropin-releasing factor (CRF) have been implicated in this disorder. GABA is the main inhibitory neurotransmitter in the brain and typically helps calm neural activity, and as such, reduced GABAergic function is associated with increased anxiety (Jetty et al.). Serotonin plays a more complex role in anxiety regulation. Serotonergic neurons, primarily in the dorsal raphe nucleus, modulate anxiety-related behaviors. Serotonin signaling can both increase and decrease anxiety, depending on brain region and receptor subtype (Lawther et al.). NE is directly involved in stress response. Increased noradrenergic activity has been linked to anxiety symptoms (Jetty et al.); (Kim and Gorman). Finally, CRF is a neuropeptide that activates the HPA axis, and is known to influence anxiety and stress responses (Kim and Gorman). Together, these neurochemical changes disrupt the brain's ability to regulate both fear and stress, a large contributing factor symptoms seen in individuals diagnosed with GAD.

How Does Anxiety Develop?

The general framework for how anxiety develops is a two-hit hypothesis, which consists of a combination of genetic predisposition and postnatal environmental experiences (examples include trauma or toxins). GAD has an estimated heritability of 15-20% (Stein). Additionally, GAD has a strong genetic correlation with neuroticism, a personality trait linked to anxiety and depression (Stein), and linkage studies identify chromosome 18q11.7 as a possible region involved in neuroticism and GAD susceptibility (Stein). This genetic work indicates shared biological pathways between GAD and major depressive disorder (MDD) (Stein), resulting in the fact that the majority of individuals with GAD experience depression during their lifetime (Stein).

Additionally, variations in glutamic acid decarboxylase (GAD1) genes also may influence susceptibility to GAD by affecting GABA synthesis (Stein). Environmental stressors (like trauma) interact with these biological systems to increase anxiety risk (Kim and Gorman); (Jetty et al.).

How Do Endorphins Counteract Physical Anxiety Symptoms?

Endorphins play a key role in alleviating the symptoms of both anxiety and depression. One way that endorphins help alleviate anxiety is by counteracting physical symptoms. By modulating NE activity, by binding to mu-opioid receptors located on NE neurons, endorphins inhibit the firing of these NE-producing neurons, reducing the release of NE into the synaptic cleft (Ali et al.), which lessens both rapid heart rate and restlessness. Endorphins also inhibit HPA axis activation, resulting in decreased cortisol release, reducing physical anxiety symptoms such as increased heart rate and muscle tension (Jayakody et al.); (Kandola and Stubbs). Endorphins suppress excessive sympathetic arousal, lowering heart rate and muscle tension (Jayakody et al.). By activating opioid receptors, endorphins reduce pain perception and bodily discomfort often heightened during anxiety episodes (Kandola and Stubbs). Although exercise increases endorphin production, which reduces effects of anxiety, it has been shown to be effective as an adjunctive treatment but generally less effective than antidepressants alone . However, when combined with cognitive behavioral therapy, exercise shows additional benefits as a treatment method, specifically in individuals diagnosed with social anxiety disorder (Jayakody et al.). Taken together, exercise-induced endorphins modulate a number of physical symptoms of anxiety and can reduce the discomfort associated with the anxious state.

How do endorphins Counteract Anxiety On a Neurochemical Level?

Endorphins also counteract anxiety on a neurochemical level. Endorphins are produced mainly in the pituitary gland and hypothalamus during stress and exercise (Jayakody et al.) and bind to G-protein coupled mu-opioid receptors, which inhibit excitatory neurotransmitter release, reducing the neuronal excitability linked to anxiety (Kandola and Stubbs). Endorphins reduce glutamate-mediated excitatory signaling in the amygdala, a brain region central to anxiety and fear responses. The amygdala's hyperexcitability drives anxiety and fear responses (LeDoux). Endorphins reduce glutamate release in the amygdala by activating opioid receptors, lowering excitatory neuronal firing and dampening anxiety circuits (Ressler). This neurochemical modulation underpins the anxiolytic (anxiety-reducing) effects of endorphins (Jayakody et al.). Endorphins also indirectly increase the activity of serotonin and dopamine, neurotransmitters involved in mood regulation and anxiolytic effects (Jayakody et al.);(Kandola and Stubbs).Endorphins and exercise reduce oxidative stress and inflammation in the brain, factors linked to anxiety pathology (Moylan et al.);(Kandola and Stubbs). The neurochemical balance of the brain when endorphins are high is biased towards decreased activation, low oxidative stress, and decreased inflammation.

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Gender Differences in Anxiety from a Biological and Social Perspective

Endorphins have a modulatory effect on anxiety, but GAD and other anxiety disorders are highly multifactorial. Another factor that can affect anxiety presentation is gender identity. Anxiety is a disorder that must be looked at through a gendered lens due to differences in both biological makeup and the strong influence of societal normalities on reporting. Societal norms dictate that women should be emotionally expressive and empathetic, which may increase their willingness to report anxiety (Cavanagh et al.). Men, on the other hand, are socialized to suppress vulnerability, often causing them to express anxiety through physical symptoms rather than admitting to it, which can be seen as a sign of weakness (Caballo et al.). These patterns may lead to overdiagnosis in women and underdiagnosis in men, despite generally comparable stress levels (Caballo et al.)(Cavanagh et al.). In Australian psychologist offices, 48% of women reported high anxiety vs. 32% of men, with depression rates showing similar gender gaps (Cavanagh et al.). A large cross-cultural study with over 30,000 participants across 18 countries further highlighted this gap, finding that women report higher social anxiety than men in most contexts (Caballo et al.). Women particularly reported more anxiety regarding: public speaking, interactions with authority, fear of embarrassment, and opposite-sex interactions (Caballo et al.). It was also found that gender differences are less significant for interactions with strangers or assertive expression of annoyance (Caballo et al.). This suggests that women experience less pronounced anxiety in more impersonal instances. Among clinical populations diagnosed with social anxiety disorder, men and women report similar symptom severity, suggesting that gender differences in community samples may reflect reporting style rather than actual experienced anxiety (Caballo et al.). This poses the question of whether women are actually more susceptible to anxiety than men or if they are simply more inclined to report experiencing symptoms.

Beyond this obvious impact of social normalities on reported anxiety levels across genders, differing levels of estrogen and testosterone have been shown to affect the brain's response to stress. Estrogen modulates the HPA axis, which is the primary biological system regulating the body's response to stress. Fluctuations in estrogen levels across the menstrual cycle, pregnancy, and menopause contribute to greater mood variability and increased emotional reactivity in women (Cavanagh et al.). These hormonal fluctuations influence BE production, which plays a role in regulating stress and anxiety responses, increasing vulnerability to anxiety disorders in women during certain menstrual cycle phases (Cavanagh et al.). Testosterone, on the other hand, is associated with emotional suppression, which may contribute to the comparatively lower reported anxiety rates in men (Cavanagh et al.). Both social and biological factors play a role in the manifestation of anxiety and its diagnosis. In order to avoid reinforcing societally imposed gender biases in diagnosis, clinicians must remain aware of these combinatorial influences.

Differences between female and male responses to endorphins

Gender identity also affects endorphin response. Although men and women show similar resting BE levels, their responses to stress are different both in terms of timing and amount of BE production (Goldfarb et al.). Studies in male and female rats found greater BE increases in

the hypothalamus and pituitary in response to both pain and morphine in males than females, suggesting innate biological sex differences in opioid and pain regulation (Aloisi et al.). In humans, men show greater increases in BE during high-intensity exercise than women (Goldfarb et al.). Women exhibit slightly lower BE levels after exercise regardless of what menstrual phase they are in. This is further enhanced at lower exercise intensities (Goldfarb et al.). These findings highlight the fact that men experience stronger endogenous opioid effects during physical stressors such as pain or exercise. Since BEs have such positive effects on pain and mood, lower BE responses in women during stress or exercise contribute to the higher prevalence of anxiety and greater pain sensitivity in females.

The menstrual cycle also has an influence on endorphin production. The menstrual cycle's hormonal fluctuations (estrogen and progesterone) modulate BE levels and HPA axis activity (Goldfarb et al.). BE levels tend to be slightly higher during the follicular phase than the luteal phase, though this difference is not statistically significant (Goldfarb et al.).During phases when BE release is lower (e.g., luteal phase or during strenuous exercise with menstrual disruption), women may be more vulnerable to anxiety symptoms. Endorphin increases during high-intensity exercise were similar in both phases (Goldfarb et al.). Estrogen may enhance BE synthesis by acting on the HPA axis; female athletes with higher estrogen had suppressed LH levels and elevated BE, showing strong hormonal regulation (Ihalainen et al.). Strenuous exercise can cause menstrual irregularities due to increased BEs and catechol estrogens suppressing gonadotropin releasing hormones, which disrupt normal cyclic rhythms (Keizer and Rogol). Increased BEs and catechol estrogens from high training loads can disrupt normal reproductive hormone signaling, worsening mood and anxiety regulation (Keizer and Rogol). This hormonal disruption can lead to both reproductive and mood disturbances in female athletes ((Keizer and Rogol). Practically, female athletes should monitor training intensity and menstrual health closely to avoid these effects, and maximize anxiety regulation.

CONCLUSION

Anxiety is a widespread disorder, considered to be the most common mental health challenge globally, which affects hundreds of millions of individuals. The development of anxiety is due to both inborn vulnerability and environmental exposures. One example of inborn risk is the genetic linkage of GAD and depression by the personality trait neuroticism, explaining why most people who experience one disorder during their lifetime also experience the other. Another factor that contributes to anxiety is dysregulation in the brain. In GAD, alterations in key brain regions such as the amygdala, PFC, hippocampus, and ACC heighten fear responses and impair emotional regulation. GAD is also characterized by neurochemical disruptions, specifically involving GABA, serotonin, NE, and CRF, which further compromise the brain's ability to regulate stress and anxiety. Finally, gender influences anxiety prevalence due to both societal normalities and biological factors, including likelihood to report symptoms as well as interactions between sex hormones and stress hormone systems.

One way to manage this dysregulation is by providing the brain with a counter-regulatory component. Endorphins are opioid neuropeptides produced primarily in the pituitary gland and hypothalamus that modify pain, mood, and stress through interactions with neurotransmitter systems such as dopamine, norepinephrine, and GABA. Endorphins mitigate the physical

symptoms of anxiety such as restlessness and rapid heart rate by reducing norepinephrine activity, and suppressing cortisol release. Endorphins are produced during exercise, which has led to the use of exercise as an adjunctive therapy to help modulate anxiety. High-intensity exercise, defined as physical activity performed at approximately 70–85% of an individual's maximum heart rate, is the most effective form of exercise to help manage anxiety symptoms. Sex-specific hormonal fluctuations impact endorphin production. For example, BE levels are slightly higher during the follicular phase than the luteal phase, due to high estrogen production in the follicular phase, and the progesterone dominance of the luteal phase, which contributes to reduced BE synthesis. Practically, this means that women will be better able to molecularly modulate stress in the follicular phase than the luteal phase, an ability which is enhanced with high-intensity exercise. Given its multifactorial nature, no single intervention method entirely addresses GAD, but integrating exercise with cognitive behavioral therapy or pharmacotherapy can optimize treatment effectiveness.

Endorphins naturally produced by the body serve as an accessible and effective treatment option for everyone affected by this disorder. Exercise is an effective adjunctive intervention for anxiety, due to its production of endorphins which combat anxiety on both a neurochemical and physical level. In order for women to achieve this effect, they should engage in high- intensity exercise, but all people with anxiety are likely to experience some symptom alleviation from exercise.

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