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A review of Monoaminergic Systems in Anxiety Disorders: Current Status and Future Directions

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ABSTRACT:

Anxiety is mental condition characterized by disturbances of mood as well as of thinking, behaviour, and physiological activity. It is a state of mood when the subject feels fear for known or unknown sources of future threats. Anxiety occurs due to an imbalance between neurotransmitters like GABA, monoamines (serotonin, norepinephrine, and dopamine). These neurotransmitters are also involved in other neurological disorders like depression. In anxiety, the affected parts include the limbic brain in association with the amygdala, prefrontal cortex and hippocampus. Monoamines play a significant role in the progression of anxiety due to its frequent modulation activity in brain. Monoamines behave as neurotransmitters as well as neuromodulators containing a single amino moiety, together with an aromatic ring for two carbon chains. Monoamines are derived by the action of decarboxylase enzymes on aromatic amino acids (phenylalanine, tyrosine and tryptophan). This review elaborates the roles of monoamines in anxiety disorder with their brief pathway and associated dysregulation.

Introduction-

In the current scenario, anxiety becomes the most common mental disorder of the central nervous system (Mahendra and Bisht, 2011). People with anxiety evolve at a rate of substantially higher than the general with cardiovascular, cerebrovascular, gastrointestinal, and respiratory disorders (Andreescu and Lee, 2020). Anxiety disorders are not known to be a particular condition, but they are the group of disorders marked by recurrent emotions of elevated anxiety and intense pain and stress (Stein et al., 2017). According to WHO 2017 report almost 264 million of world population is affected from anxiety (Fig.1). Mainly motor stress, sympathetic hyper responsiveness and anticipation of danger are the indication of anxiety (Daviu et al, 2019). Basically, anxieties are classified as generalised anxiety disorder, phobic anxiety, panic anxiety, obsessive-compulsive anxiety and post-traumatic anxiety (Himanshu and Deepa, 2020). Furthermore, anxiety is mostly found in females as compared to males due to menstrual imbalance, variation in brain chemistry (Remove lined ref). Anxiety is mostly affected in females at the mid-age of life between 40-49 years (WHO reported on 2017). According to multiple systems, symptoms of anxiety are cognitive, physiological, and behavioural (Asmundson et al, 2006). The cardinal symptoms of anxiety are awareness of threat, irritability, and lack of concentration, palpitation, difficulty in breathing, tremor, sweating, giddiness, paraesthesiae and gastrointestinal disturbance (Tyrer, 1984). Mental stress, psychology trauma, exaggerated pressure, uncertainty threats and

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lack of sleep are the major consequence of anxiety (Grupe and Nitschke, 2013). Anxiety and depression are common psychiatric conditions that not only co-occur, but also co-occur with other neurologic illness (Shah and Han., 2015).

Fig 1.World population affected with anxiety

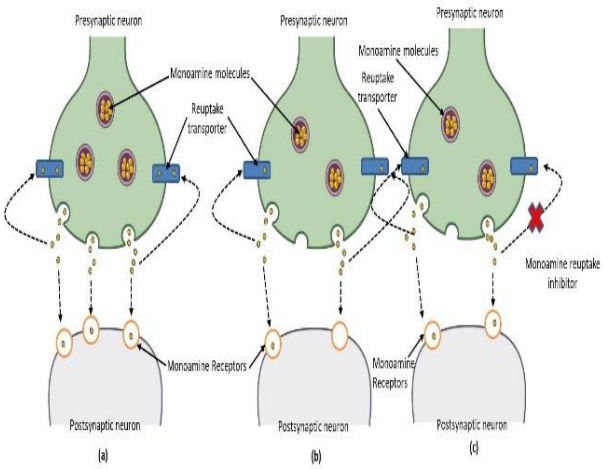

Fig 2. Monoamine transmission in anxiety disorder

Monoamines are the neurotransmitters, chemically it comprises single amino group that is coupled with a two-carbon chain aromatic ring. They are produced from the aromatic amino acids (such as phenylalanine, tyrosine and tryptophan) by the action of decarboxylase enzymes (Niyonambaza et al, 2019). Monoamines are released at the synapse from presynaptic neurons and exert their action by activating monoamines receptor at postsynaptic neurons. Monoamines become non-functional by the action of the reuptake transporters which can be inhibited by monoamine reuptake inhibitor and reverse the action of monoamines (Fig. 2). Also action of monoamines terminated through degradation of monoamines and deactivation of monoamines receptor (J Masson and M Hamon, 2009). Monoamines are active in the supervision of the endogenous pain system, or in some kinds of injuries, specifically in neuropathic pain, peripheral and central monoaminergic impairment has been illustrated (Bravo et al., 2019). The monoaminergic system is involved in the control of nervous system homeostasis and among its various roles, monoamines control the endogenous pain system (Bannister et al., 2009). Research findings indicate that the neurophysiological anxiety process is being associated with serotonergic, noradrenergic, glutamatergic as well as GABAergic transmission dysregulation. Some drugs that modify the role of two of the main neurotransmitter monoamine systems in the brain (noradrenergic and serotonergic) have been shown to alter the level of fear and anxiety in animal models, stable individuals and patients. For people with anxiety, stimulation of the 5-hydroxytryptamine (5-HT or serotonin) system does not cause marked abnormalities, but activation of Norepinephrine (NE) system causes irregular chances in parameters of fear, somatic complaints, heart rate and NE metabolite and hydrocortisone concentrations in ill people with panic disorder however not in patients with generalised anxiety, obsessive-compulsive disorder, depression or schizophrenic disorder (Heninger and Charney, 1988). Despite the fact that it has so many unpleasant side effects, such as relaxing, muscle relaxation, ataxia, amnesia, ethanol, barbiturate potentiation and resistance, benzodiazepines are the main class of anti-anxiety (Mahendra and Bisht, 2011). Neurological systems engaged in significant depressive disorders as well as anxiety brain disorder, a growing body of research highlights the role of serotonin, noradrenaline as well as dopamine mechanism for dysfunction. Physiological activities underlying serotonin, norepinephrine as well as dopamine irregular singling it could be due to one of the decreased presynaptic producer of such neurotransmitters or abnormal signal transmission, as such, contributing to modification in the expression or function of receptors

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and disrupted intracellular signal distribution (Liu et al., 2018).

Serotonin role in anxiety disorder

The loss and abundance of serotonin in the brain will play a significant role in managing the psychological anxiety state of the disease. Seven classes in 5-HT receptors have been recognised, from including their subgroups 5-HT to 5-HT7 receptor (Hoyer et al., 1994). On multiple cell types, various 5- HT receptor subgroups differently expressed contribute to 5-HT neurotransmission possessing anti-anxiety as well as anxiogenic effects (Chopin and Briley, 1987). The anxiolytic impact can be induced by the activation of the 5-HTA receptor in hippocampus tissue (Albert et al., 2014). Reserpine interacts with serotonin synaptic vesicles, depletes 5-HT brain stocks and raises urine concentrations of 5-HT major 5-hydroxyindoleacetic acid (5-HIAA) metabolites, triggering depressive symptoms in humans (Shore et al., 1955). 5-HT brain deficiency can increase MDD adverse emotions, including depression, ego, critique, anger, terror, anxiety, aggression, tiredness and insecurity (Coppen, 1967). The serotonergic disruption involved in the production of MDD primarily involves low 5-HT neuronal synthesis and abnormal 5-HT receptor activity (Artigas, 2013). Ligands can produce both antidepressant (Choi et al., 2012) and anxiolytic products with 5-HT1A agonist activity (Vianna and Carrive, 2009). Elevated 5-HT1A autoreceptors, postsynaptic receptor inhibition or reduced 5-HT neurotransmission can contribute to the phenotype of anxiety, while downregulation of 5-HT1A improves the impact of anti-anxiety. In the amygdala, 5-HT2A receptor agonism can induce symptoms of anxiety and insomnia (Bystritsky et al., 2008). Findings of 5-HT2C activate the receptor in the elevated plus-maze framework of anxiety produce contradictory outcomes (Charney et al., 1987). In social anxiety disorder, observation indicated decreased attachment of the 5-HT1A receptor in the insula, amygdala, and anterior cingulate cortex (Lanzenberger et al., 2007). For people who suffer with MDD, antidepressant medications boot 5-HT neurotransmission. Many forms of affective disorders, including panic disorder and generalised anxiety disorder (GAD) may also enhance (Kahn et al., 1988).

Serotonin signalling pathway

5-HT, in relation to GABA, performs a significant role in the growth and progression of anxiety conditions. Various surveys have also shown the elevated in the brain, 5-HT concentration also improves anxiety and decreases anxiety by reducing the 5-HT level (Celada et al., 2013). The modification of hunger, power, sleep, attitude and cognitive function in anxiety includes serotonergic neurons (Chaput, 2014). Its importance in anxiety is confirmed by its activating effects on the amygdala and its predictions on the locus coeruleus. Serotonergic receptors are triggered by anxiety and fear (Hen, 1993).

Current knowledge of fear and anxiety neurology focuses mainly on three interacting factors: HPA (hypothalamic-pituitary-adrenal) axis, amygdala, and neuromodulators (e.g., serotonin) (Curran and Chalasani, 2012). The physiological correlation between the serotonin system and anxiety is strongly implied by the good track record of SSRIs. The bulk of the animal world uses serotonin, a monoamine neurotransmitter, as a neural circuit modulator. Serotonin modulates a broad variety of activities in mammals, including experience of pain, sleep, anger, serotonin neurons reside in the brain stem, it migrates to frontal brains and limbic system (e.g. amygdala, thalamus, hypothalamus, hippocampus and frontal cortex) from the dorsal and median raphe nuclei, hence establishing a serotonin circuit (Weiger, 1997). In the nucleus of the dorsal raphe, fear, as well as anxiety, triggers selectively stimulate serotonergic neurons that then translated through the amygdala and the hypothalamic portion of the HPA axis. In the plasma membrane of the presynaptic serotonin neuron, serotonin is produced from tryptophan through tryptophan hydroxylase, then serotonin packed into vesicles monoamines transporters, such vesicles are fused with the lipid bilayer and the retained neurotransmitter are released into the serotonin bound synaptic gap on the surface of postsynaptic cells receptors (Carre-Pierrat et al., 2006). While reabsorbing unbound serotonin by reuptake transporters returning to the presynaptic cell, the signal is eliminated thus restricting the spreading of 5 HT intensity (Kandel and Schwartz, 2000). Anxious behaviours associate with differences in serotonin pathway function (Goddard and Charney, 1997). Investigators have correlated a short human serotonin transporter gene (SLC6A4) promoter allele (5-HTTLPR) with anxiety-related character attributes, such as

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apprehension of situation, integrating functional imaging with genomic research. Higher fear in specimens bearing the short allele of the serotonin transporter promoter, 5HTTLPR display increased amygdala activation during an anxiety inducing interpersonal communication function relative to long allele carriers, consistent with these results. These studies indicate that the behaviour in the amygdala that is important to anxiety can be inhibited by 5HT.

Role of norepinephrine in anxiety disorder

NE is received by the tyrosine transporter into the noradrenergic nerve endings via the precursor synthesis of tyrosine and norepinephrine transformed to norepinephrine through a sequence of modification (Wang et al., 2016). It was thought that signs of anxiety were triggered by NE hyperactivity in the CNS. Corticotrophin releasing hormone may stimulate the NE energy transporter in the locus coeruleus-temporal hippocampus under stress condition, which activates NE and induces symptoms of wakefulness and anxiety (Fig. 4). In patients with GAD, researchers found elevated serum catecholamine concentrations, suggesting an abundance of NE (Homan et al., 2015). Initial data suggest that adrenergic receptor activity requires single nucleotide polymorphism as a susceptibility factor for general anxiety disorder (Wang et al., 2016). Animal study observation has shown that beta-adrenergic receptor antagonism within the central nervous system can attenuate cocaine's anxiogenic effects and disrupts anxiety-like gene variants involving aversion, apprehension and stress like behaviours (Kindt et al., 2014; McCall et al., 2017).

Norepinephrine signalling pathway in anxiety

Norepinephrine (NE) is a significant neurotransmitter of monoamine that has massive impacts in many brain areas to control anxiety and behavioural changes. The NE cortical system's essential role is to combine alertness activity with concentrated attention on specific external stimuli and anxiety condition. The main norepinephrine mechanism is inherently controlled in the stress hormone mechanism, and the pathogenicity of anxiety and depression has been identified in dysregulation within the NE system. Consequentially, essential norepinephrine function has both anxiogenic or anxiolytic effects, depending on which stress is acute and chronic over time, either fear is stable and unexpected, and also which areas of the structural brain are influenced (Goddard et al., 2010). In situations of chronic stress, hypothalamic-pituitary-adrenal system dysfunction of the NE system operation can transform a homeostatic stress response into a pathological stress response (Goddard et al., 2010). Analysis indicates that neurobiological acceptability of pathophysiological condition of anxious depression may be exerted by the NE association with the serotonin system. The majority of noradrenergic neurons in the brain stem are distributed in multiple small groups and allocated cell classes A1 to A7, which includes the locus coeruleus (LC) (A4, A6 cell groups) (Baker, 1989). Under groups of noradrenergic nuclei, like the prefrontal cortex, project their axons diffusely across the brain (from groups of cells A1/A2), hypothalamus (from groups of cell A1/A2), thalamus, hippocampus, and amygdala). Cortical effects on the ascending brainstem NE system may help crucial modulation of inputs and take part in a vital role in the response to emotional distress and psychological disorders linked to stress. Precise activity specific to NE dependent behavioural actions can be guided by task-related judgement processes taking place in the prefrontal cortex. The orbitofrontal cortex is known to process the assessment of incentives within the prefrontal cortical regions, while the anterior cingulate cortex tracks success failures and overall expressing negative stimuli, like discomfort, financial loss, and social isolation. Direct inputs from both the orbitofrontal and anterior cingulate cortical regions can therefore create a powerful cognitive and emotional feedback "top-down'' effect on neuronal functioning of the brainstem NE(Bao et al., 2008).

Role of dopamine in anxiety disorder

DA is a neurotransmitter which is a crucial neurological substrate for reinforcement, attention, encouragement, cognitive function frequency and the desire to feel pleasure in the hypothalamus and pituitary, which may contribute to modulating human feelings (Coppen, 1967). It has shown that dopaminergic activity is implicated in depressive (Ryan et al., 2012) Or nervous activity (Vicario et al., 2017). Inadequate DA neuron can induce a sign of depression, such as helplessness as well as insufficient desire (Dunlop and Nemeroff, 2007;

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Kasch et al., 2002). Two subtypes, the D1and D2receptors, have DA receptors. In patients with social anxiety disorder, studies have shown decreased density of dopamine transporter and D2 receptor binding in the striatum compared with healthy controls (Dunlop and Nemeroff, 2007; Schneier et al., 2000). DA blockers may enhance the severity of the symptoms of social fear (Clausius et al., 2009). The amount of homovanillic acid, a cerebrospinal fluid dopamine metabolite reduced in stressed comorbid patients who have socially affected anxiety (Jokinen et al., 2007).

Dopamine signalling pathway

In fear and anxiety, dopamine plays a crucial role in controlling the anxiogenic function of the amygdala by a cortical brake exerted by the medial prefrontal cortex and seems to have a significant influence on the transmitting signals in between the basolateral amygdala (BLA) and the central nucleus. Rostrolateral dominant and Para capsular intercalated islands, and lateral central amygdala nucleus, are preferentially innervated by afferents of dopamine from the ventral tegmental region, stimulating non-overlapping D1 and D2 receptor group found in these sites (de la Mora et al, 2010). Anxiolytic and anxiogenic effects on conditioned and non-conditioned forms of stress or worry are caused by the intra-amygdaloidal infusion of D1 agonists and antagonist, respectively, implying an anxiogenic role for amygdala D1 receptors (Zarrindast and Khakpai, 2015). Analysis of the impact of D2 agonists and antagonist suggests that whether anxiogenic or anxiolytic effects are elicited based on the extent of danger animal faces in anxiety models. It is proposed that the receptors of D1 and D2 dopamine in the amygdala can play a different role in anxiety regulation (de la Mora et al, 2010). The likelihood part D1 receptors participating in hazard identification is thus discussed, encouraging conditioned-unconditioned interactions through restoring the efficacious characteristics of unconditional stimulus and controlling the transmission of signals via cortical and BLA regions to BLA and central nucleus, whereas D2 receptors perform a part in supporting behavioural mechanism to cope with apprehension(de la Mora et al., 2010).

Pathophysiology of anxiety disorder

The propensity to anxiety disorders is maternal, and some other variables may contribute to the likelihood of anxiety, such as environmental influences. The pathologic cause for anxiety disorders is the subject of this clinical review. It gives short overviews of panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, social anxiety disorder and posttraumatic stress disorder (Bandelow et al, 2012, Cheng et al, 2015). Anxious conditions usually pass via parenting style systems in the same way as behavioural characteristics are passed down from generation to generation. In people, the fear response includes a sequence of hormone levels, such as secretion of corticotrophin-releasing hormone (CRH), this effect induces activation of corticotrophin, this will contribute to the secretion from the adrenal cortex of depressing hormones (glucocorticoids and epinephrine) (Naughton et al, 2014). Usually, glucocorticoids take negative hypothalamus feedback, thereby reducing the secretion of corticotrophin-releasing factor (CRF). Even then, reaction to primate anxiety can not only be activated by the physical battle, but also by the sheer expectation of a homeostatic challenge. As a consequence, when people frequently and incorrectly assume that a homeostatic threat is about to happen, they reach the level of psychosis, fear as well as hysteria. The amygdala is the main stimulator in the sensations causing worry. The input receives the amygdala in the hippocampus, from neurons. Sensory feedback that bypass the cortex often receives the amygdala and hence appears to be unconscious. Sensory feedback that overrides the cortex often receives the amygdala and hence appears to be subconscious. The amygdala promotes areas of the brain stem and midbrain when triggered, triggering automatic hyperactivity, which can be carried out attributed to the sign of physiological anxiety. Therefore, the stress reaction requires the activation of the axis of the hypothalamic-pituitary-adrenal. In mental illness and anxiety disorders, this axis is hyperactive. The peptide forty-one amino acid corticotrophin-releasing factor, a central nervous system neurotransmitter that serves as a great potential to contribute to response to involuntary muscle, cognitive, inflammatory and endocrine stress . The peptide that is Gamma aminobutyric acid (GABA) prevents the release of CRF (Roberto et al, 2010) . It tends to be anxiogenic (Nurnberger et al, 1986), depress

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genic, and proinflammatory and contributes to an enhanced perception of pain. The locus coeruleus is stimulated by glucocorticoids, which gives a strong stimulating projection away to the amygdala. Thus amygdala then carries out much more CRF, leading to more secretion of glucocorticoids that leads to a continuous feedback loop between the brain and the body. Persistent CNS sensitivity to glucocorticoids hormones ultimately reduces the amount of norepinephrine within the coeruleus locus. Norepinephrine is an essential neurotransmitter, concentration, carefulness and enthusiasms as well as inspiration are involved. In the operation, there can subsequently be the onset of depression. It appears that serotonin is also implicated in the pathophysiology of anxiety disorders. Hippocampal 5-HT1A receptors can be activated by agents that enhance serotonin neurotransmission, thereby to promote neuroprotection and neurotransmission and generating an anti-anxiety effect. Another neurotransmitter thought to be naturally inhibitory is gamma-aminobutyric acid, the key inhibitory neurotransmitter throughout the central nervous system. The pathology of anxiety disorders is concerned in contrast with those in control subjects, GABA levels appear to decrease in the cortex of patients with PD (Long et al, 2013). Benzodiazepines enhance neurotransmission of GABA and may thus improve anxiety (Giacobbe and Flint, 2018). (Fig. 3)

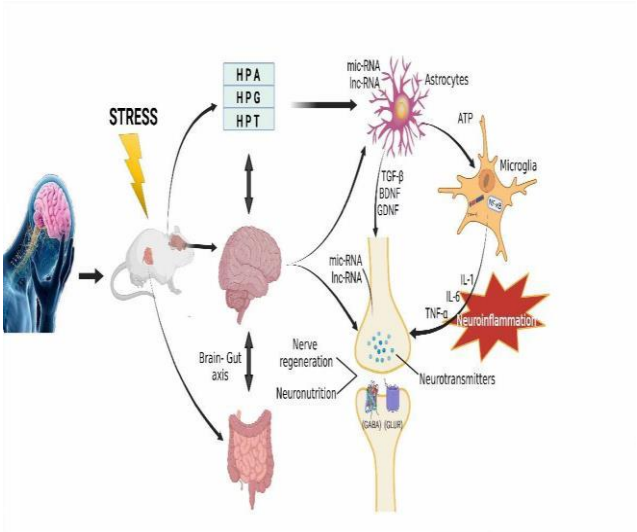

Fig 3 .Monoamine transmission in the brain in mood disorder

Current scenario of anxiety in the population

According to the World health organisation (WHO) major depressive disorder (MDD) becomes the world's second major illness by 2020(Murray and Lopez, 1997). One in five individuals globally meets the clinical criteria for an anxiety disorder at least once in a lifetime (Kessler et al., 2005). The research shows a number of mechanisms behind anxiety disorder including reuptake, neuroreceptor binding and channel transporter function, neuronal connectivity regulation and hypothalamic-pituitary-adrenal axis (HPA) (Liu et al., 2015). In terms of these mechanisms, a variety of medication, selective serotonin reuptake inhibitor (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs) and benzodiazepines for example are deemed helpful to fight anxiety disorders (Tyrer and Baldwin, 2006). During this decade the analysis of fear also grown into a central field of psychotherapeutic science. Peoplewith anxiety also have insomnia. A subjective complaint is the most common sleep disorder that it is unable to initiate or sustain sleep or that sleep is non-restorative with low quality and quantity (Association, 2013). The relationship between major depression, insomnia and anxiety disorders influences the role in the cardiovascular as well as immune systems (Taylor et al., 2003). Far more attention has been focused on the pathophysiology underlying depression on the damage to monoamine transmission mechanism over the past few years, such as decreased hydroxytryptamine (5-HT), norepinephrine (NE) and dopamine concentrations (DA) (Hindmarch, 2001; Sulser et al., 1962). The aetiology of anxiety and depression and the effect of anxiolytic and antidepressant medications, at least in part, are based on 5-HT1A receptors (Lesch and Mössner, 1999). The BDNF level of expression decreases in the dentate gyrus as well as the pyramidal cell layer of the hippocampus in rats and mice in response to stress, acute or chronic (Smith et al., 1995). Many of the most prominent results of psychiatric research have also contributed to a role, in particular, in anxiety disorders, for CRF and noradrenergic system dysregulation. A significant regulator of behavioural responses to anxiety and stress is the CRF system. CRF system dysfunction is hypothesized to be the cause of many conditions, like anxiety. The associations between monoaminergic and CRF systems in anxiety-related behaviour in mouse

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models have been shown by recent studied (Dirks et al., 2003; Groenink et al., 2003). Worldwide, monoamines are used in many disease therapies, such as Parkinson's disease, Alzheimer disease, depression (Lundgren et al., 2020). Current imaging mass spectrometry (IMS), enables small molecule tissue localization, including monoamines neurotransmitters, such as serotonin, dopamine and norepinephrine to be visualised (Sugiyama et al., 2020). A challenging clinical manifestations in cardiovascular is unobserved anxiety. Anxiety leads to repeated visits to the emergency room and neds for multiple medical tests to find out cardiovascular disease (Tully et al., 2016).

Future prospects

Since March 2020, the pandemic of the coronavirus (COVID-19) has dramatically increased anxiety and altered individual behaviour. Questions remain about the basic functions of the amygdala, medial prefrontal cortex, insula, and hippocampus in anxiety disorders. Besides, the most common and essential concerns are perhaps whether the cognitive changes present in anxiety disorders represent developed indications of disease or sensitivity factors that influence the chance of experiencing disorders.

Conclusion

This review typically suggests the roles of monoamines in anxiety disorders with their brief pathway. Serotonin, dopamine, and norepinephrine are the monoamines involved in the signalling pathway of anxiety. Generally, there is a dysregulation of this monoamine neurotransmitter, which causes anxiety disorder.

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Conflict of interest

No conflict of interest.

List of abbreviations

GABA- Gamma aminobutyric acid

NE- Norepinephrine

5-HT- 5-hydroxytryptamine or serotonin

DA- Dopamine

MDD- Major Depressive Disorder

Ads- Anxiety disorders

5-HIAA -5-hydroxyindole acetic acid

GAD- Generalised anxiety disorder

SSRIs- Selective serotonin reuptake inhibitors

BDNF- Brain-derived neurotrophic factor

CRF- Corticotrophin releasing factor

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