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Review Article

Introduction to Neurocircuitry and Neurobiology of Anxiety

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Abstract

Context: Nowadays, experiencing occasional anxiety is a common part of each person's life. The number of anxious people has increased in this modern life style. This study aimed to review some researches as to accelerate searching for new anxiolytic treatments.

Evidence Acquisition: Related articles were extracted from databases including PubMed, Google Scholar, Springer, Science Direct and Wiley. Forty-eight articles were chosen. The articles were carefully considered, and after extracting information, they were categorized and integrated in the appropriate sequences to meet the needs of this study.

Results: This review mentions the important brain regions involved in anxiety; it then continues with encapsulating some of the neurotransmitters' and neuropeptides' functions that cope with anxiety-like behaviors.

Conclusion: With regard to the results, it is suggested that anxiety can be caused by change in the brains' neurotransmitters level but more studies are needed to identify its exact mechanism.

Keywords: Anxiety, Neurotransmitter, Neurobiology, Neurocircuitry

1. Context

Anxiety is an overreaction to a situation [1, 2]. According to National Institute of Mental Health's report, approximately 18% of adults in the United States are suffering from anxiety [3]. Different factors associated with anxiety disorders such as alteration in releasing pattern of some neurotransmitters in the brain involves in anxiety-related behaviors [4].

In addition to neurotransmitter, reports demonstrate that some molecular mechanisms and organelles of the cells have important roles in anxiety-related disorders [4], for example Mitochondria as an energy center of cell and lysosome which is involved in disposal of wasted materials in the cells. Anxiety is a common phenomenon in some lysosomal storage diseases [5]. Also an indirect relation of cell membrane to anxiety has been proposed before. Microtubules are a component of the cytoskeleton in the cytoplasm. Microtubules are important in cell migration, mitosis, development and gene regulations; additionally, in indirect ways they can participate in anxiety-related behaviors. Peroxisome are organelles participating in catabolism of very long chain fatty acids and reduction of reactive oxygen species (ROS). It has been suggested that the increase in ROS production induces

anxiety. Also Endoplasmic reticulum function is related to anxiety as inhibition of endoplasmic reticulum stress decreases anxiety-like behavior induced by restrainer [6].

2. Evidence Acquisition

Related articles were extracted from databases including PubMed, Google Scholar, Springer, Science Direct and Wiley, with the following keywords or a combination of them: Anxiety; Neurotransmitter; Organelle; Neurobiology; Neurocircuitry. After a comprehensive search that was done based on the keywords, 48 articles were chosen. The articles were carefully considered, and after extracting information, they were categorized and integrated in the appropriate sequences to meet the needs of this study.

3. Results

The present study is a review article that was conducted in 2019. About 48 papers proved to be appropriate and after extraction, categorization and integration were formulated in the form of proper sequence for the purpose of the present study. Various methods such as behavioral tests, lesions studies and neuroimaging investigations have indicated that different parts of brain are engaged in anxiety disorders and anxiety-like behaviors [4]. Regions are listed below:

3.1 Amygdala

In the bottom segment of the temporal lobe, a complex of several nuclei comprise an almond-shaped structure called Amygdala [7, 8]. This includes excitatory projection to basal forebrain, hypothalamus and brainstem structures [9]. Amygdala deals with different behavioral processes including memory formation and decision-making [7].

3.2 Hippocampus

Hippocampus, a part of limbic system, has a key role in spatial navigation and consolidation of memory [10]. There is a direct correlation between hippocampal volume and anxiety symptoms in patients who suffer from depression, showing hippocampal contributions in anxiety behavior [7].

3.3 Frontal Cortex

Frontal Cortex in the mammalian brain is placed at the front of each cerebral hemisphere which has different functional divisions [11]. It comprises of the dorsolateral, ventromedial, and orbital sectors which, all together, have an important role in mammalian behaviors [11]. Amygdala activation causes an activation of anxiety neurocircuitry and Pre-Frontal Cortex (PFC) is responsible for regulating this activation [11]. Structural changes accrue from anxiety consequences in hippocampus and the PFC which could increase the next neuropsychiatric disturbances [11, 12]. Amygdala, hippocampus and PFC are correlated to Hypothalamic-Pituitary-Adrenal (HPA) axis in direct and indirect ways [13].

3.4 Ventral Tegmental Area (VTA)

Ventral tegmental area (VTA) is an accumulation of neurons adjacent to midline on the basis of midbrain [14]. VTA has significant role in anxiety behavior [14].

3.5 Nucleus Accumbens (NAc)

Nucleus Accumbens (Nac) is a mass of neurons, participating in cortico-basal ganglia-thalamic loop [15] Nac is the inferior part of the striatum and is predominantly linked to the limbic system [15]. Nac is one of the most crucial brain regions, involved in psychiatric disorders especially those related to anxiety and substance addiction such as Bipolar Disorder, Attention Deficit Hyperactivity Disorder (ADHD) and Post-Traumatic Stress Disorder (PTSD) [16, 17].

3.6 Transmitters Involved in Anxiety

Dopamine is one of the most important neurotransmitters vital in the variation of anxiety in different parts of the brain [18, 19]. Anxiety-like behaviors induced by anxiogenic or anxiolytic drugs are adjusted by mesocortical and mesolimbic pathways of dopaminergic system [19]. Furthermore, according to various studies, a vast range of brain functions like learning, memory and fear are modulated by dopamine receptors [19].

Histaminergic fibers rise from rat's tuberomammillary nucleus (TMN) and its damage can induce anxiolytic-like effects but, anxiogenic-like responses were promoted by the injection of histamine into the dorsal and ventral hippocampus and also Amygdala in mice [20, 21]. Effect of histamine on anxiety and other emotional states could be mediated by its effect on other neurotransmitters. Some effective anxiolytic drugs like Buspirone and Diazepam could reduce the production level of histamine in the rats' brain [21]. Histamine injection in different parts of the brain has different effects on anxiety related behavior. For example, its injection in the ventral hippocampus and CeA has anxiogenic-like effects while its injection in dorsal hippocampus results in anxiolytic-like behaviors in the EPM test [22].

Acetylcholine is a neurotransmitter with distinct effects including arousal, attention, memory and motivation [23]. Cholinergic innervation from the basal forebrain to the cerebral cortex and hippocampus are involved in cognition [23]. There are two main types of cholinergic receptors, namely nicotinic and muscarinic ones [24].

The possibility of anxiety could be amplified in smoking persons, according to clinical studies based on tobacco consumption [25]. Nicotine increases activity of some parts of the brain such as CeA and NAc and also the firing rate of VTA dopaminergic neurons [26]. Lots of neurotransmitters in the CNS for instance acetylcholine, noradrenaline, dopamine, GABA, serotonin, glutamate and neuropeptides are affected by nicotine administration [27].

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter [28]. First-line pharmacological treatment for anxious people is selective serotonin re-uptake inhibitors (SSRIs), such as anxiolytic agents which reduce the activity of amygdala and may attenuate serotonin formation; and yet, it has been shown that chronic administration of SSRI decreases serotonin synthesis [29].

The derivative substance is from the bark of Yohimbe, an evergreen tree found in Central and Western Africa, known as Yohimbine with indole alkaloid structure [30]. In high concentrations it interacts with serotonin and dopamine receptors [31]. Researches demonstrated that anxiety could be increased by releasing of 5-HT from the dorsal raphe nucleus (5-HTDRN), in mice [32].

Glutamate is one of the main excitatory neurotransmitters in the CNS is Glutamate [33]. Glutamate has different roles in cognitive and non-cognitive processes comprising neurodevelopment, learning and memory, pathogenesis of anxiety-related disorders, psychiatric conditions like schizophrenia and mood disorders [33]. Glutamate has different ionotropic and metabotropic receptors existing in high density in regions like the cortical and limbic [18]. The role of glutamate N-methyl-D-aspartate receptor NMDARs subtype in anxiety-like behavior is clearly recognized [34]. Studies have shown that in anxiety-like behaviors, the hippocampal glutamate N-methyl-D-aspartate receptor (NMDAR)s play important roles [35].

Adrenaline (epinephrine) or noradrenaline (norepinephrine) system has three types of receptors including α1, α2 or β-adrenergic receptors. α1-adrenergic receptors antagonists may be used in anxiety treatment [36]. IP injection of alpha-1 adrenergic antagonist (Prazosin) has an anxiolytic effect among rats [37]. Likewise,

in other studies, the anxiogenic properties of α- and β-adrenergic neurotransmissions have been revealed [38]. Systemic blockade of α2-adrenoceptors (using Yohimbine) led to a decrease of fear [39]. Salbutamol, known as adrenergic β2 receptor agonists (the highest dose), decreased anxiety [39]. Anxiolytic response occurred by the cooperation of salbutamol and ineffective dose of morphine [39]. The basolateral amygdala complex (BLA) administration of beta-adrenergic antagonist propranolol (4µg/rat) decreased OAT% [39].

Nitric Oxide (NO) system plays an underlying role in relaxation of blood vessels, and also regulates many biological processes in CNS including anxiety [40]. In stressful situations, synthesis of NO increases as a neuromodulator that can change other messengers' activities [41].

NO is synthesized by the function of a group of enzymes called Nitric Oxide synthase (NOS) which mediates the conversion of L-arginine to L-citrulline to produce NO as a byproduct [21]. Neuronal NOS usually exists in neuronal cell bodies, dendrites, and axons, mostly expressed in the CNS, containing the cerebral cortex, hippocampus, striatum, hypothalamic and amygdaloidal nuclei, and mesencephalon constructions that are suggested to dramatize the variation of anxiety-like conditions in the brain [21]. NO has a role in learning and memory processing by regulating long-term potentiation and long-term depression, so it is involved in neural plasticity and mood related disturbances like anxiety [42]. To date, different/opposite effects of NO on anxiety have been reported, manifesting dose and time dependent effects of NO [42].

Gamma-Aminobutyric Acid (GABA) is an inhibitory neurotransmitter [43, 44]. The effect of GABA on anxiety depends on its combination with other neurotransmitters. GABA content within ventromedial prefrontal cortex (vmPFC) is important in the physiology of anxiety [45]. Glutamic acid decarboxylase 2 (Gad2) GAD2 is an enzyme catalyzing the decarboxylation of glutamate to GABA and CO2 [46]. Genetic studies both on animal and human investigations have revealed an important role of it in anxiety disorders [46]. Synthesis of Neurosteroids as allosteric modulators of the GABAA receptors is regulated by stress and by anxiogenic stimuli [42]. The results of studies suggest that during early-life, anxiety- and depression-related behaviors can be influenced by GABA-A receptor, signaling in a time- and dose-dependent manner in later life [47]. Among different regions of the brain, the ventromedial prefrontal cortex (vmPFC) has a vital role in processing and regulation of emotion [47]. It is suggested that dysfunction of vmPFC can lead to disinhibition of amygdala, causing high anxiety levels [48]. The flow of information to amygdala is shaped by GABA inter-neurons within vmPFC. Therefore, studies assume that GABA content within vmPFC can be associated with anxiety [48].

4. Conclusion

Fear is an emotional response in a normal range to threatening stimuli [49]. In anxiety disorders, the response is not normal and disturbs daily life [49]. Anxiety can be caused by aversive experiences, and also change in the brains' neurotransmitters level [38]. Further studies are needed to identify promising treatments, using animal models based on neurobiology of this disorder, especially among women. Most of the experimental studies are in male, but it is widely accepted that the rate of anxiety in women is more than men [50].

This review summarized some recent researches on mediators, moderators and associations between the different brain regions, transmitters, molecules and anxiety. As mentioned in the manuscript, the imbalance in the brain neurotransmitters can alter mood and behavior situations, leading to anxiety. Based on widespread studies, anxiety disorder is a result of both genetic and inappropriate environmental

factors. Knowing the biochemistry related to this behavior can pave the path for curing it.

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Conflict of Interest
The authors declare no conflict of interest.

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