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REVIEW ARTICLE

Nitric oxide as a modulator of stress and reproductive axis: a review

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Abstract

Anxiety and depression are the major disorders among the present world population with 3.6% of the global population suffering from anxiety and 4.4% from depression. Anxiety and depression are comorbid conditions and are reported to be gender biased, being more prevalent in females than males. Various factors that were reported to be responsible for the development of such conditions in an individual are environmental, genetic as well as epigenetic. Thus, the body has an elaborate interconnected system to maintain homeostasis and is regulated by various molecules. Among such systems are the hypothalamo-pituitary-adrenal axis, responsible for the regulation of stress in the body and the hypothalamo-pituitary- gonadal axis, responsible for reproductive functions. These axes again have an intricate system of neural circuitry comprising neuromodulators and neurotransmitters modulating its functioning. One such molecule is the ubiquitously present nitric oxide. This nitric oxide is implicated to be involved in various physiological processes through cyclic guanosine 3′5′-monophosphate (cGMP), including the functions of the brain. Nitric oxide is produced as a byproduct in the enzymatic conversion of L-Arginine to L-Citrulline in the presence of NADPH, cofactors and the enzyme nitric oxide synthase (NOS), NOS has three isoforms in the body neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS), all playing different roles in the body physiology. Of the three isoforms, nNOS expression has been found to be distributed in various brain regions such as the cerebellar cortex, dorsal raphe, cerebral cortex, amygdala, hippocampus, preoptic area and also paraventricular, magnocellular, the supraoptic nucleus of the hypothalamus. These regions, especially the amygdala, hippocampus, and dorsal medial thalamus of the subcortical limbic regions have been reported to be associated with mood disorders such as anxiety and depression. nNOS has been implicated in a varied range of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, anxiety, stroke and also learning and memory and neuropsychiatric disorders, including depression. NO produced in the brain is linked to be involved in regulating the HPA axis. On the other hand, NO is shown to be localized and expressed in the hypothalamus, hypophysis and gonads and can act on the hypothalamo-hypophyseal-gonadal (HPG) axis to regulate the synthesis and release of GnRH and thus reproduction, as GnRH and NO-producing neurons occupy similar positions in the hypothalamus. NO has also been reported to regulate spermatogenesis, sperm motility, sperm capacitation, fertilization, oogenesis (follicle development/folliculogenesis), gonadal hormones and steroidogenesis. Nitric oxide is also involved in the embryonic development of the brain and gonads, affecting the overall development of the HPA and HPG axis. Various studies have shown that nitric oxide is intricately involved in the modulation of both the HPA axis and HPG axis and thus in the pathology of neurodegenerative disorders and mood disorders and consequently affecting reproductive behaviour and fertility. This review is an attempt to highlight the crosstalk between the HPA and HPG axis and the role nitric oxide plays in regulating both the axis and mood disorders.

Keywords: Hypothalamus; Stress; Anxiety; Depression; Pituitary; Nitric Oxide; Gonads

1. Introduction

The current lifestyle has led to one of the major disorders, i.e., anxiety and depression, in the human population. Anxiety and depression though considered to be two distinct entities according to the diagnostic criteria are co-morbid (Fawcett and Kravitz, 1983; Schoevers et al., 2005; Cairney et al., 2008; Goldberg and Fawcett, 2012; Choi et al., 2020). Humans having anxiety disorders commonly have depression while the vice-versa is true for patients with depression, i.e., they would often have anxiety disorders (Tiller, 2013). The anxiety disorder recognized clinically as mental disorders in humans include generalized anxiety disorder, acute and chronic post-traumatic stress disorder, panic disorder, and obsessive-compulsive disorder. This also includes various phobias such as social phobia, agoraphobia, and specific phobia (eg, fear of flying) (Hang et. al., 2015; Manchia and Fanos, 2017; Hyman, 2021). These disorders are sex-dependent, being increased in females than males in humans (Holden, 2005; Boyd et al., 2015; Riecher-Rössler, 2017; Yu, 2018; Rehm and Shield, 2019; Kokkosis and Tsirka, 2020). The above hypothesis is supported by the gonadic theory, suggesting that women have a wider range of fluctuations in hormone levels than men. This fluctuation in hormone levels affects the brain regions (hypothalamus, prefrontal cortex, hippocampus) that are known to be involved in the modulation of mood and behavior (Faravelli et.al., 2013). Neuroimaging techniques like magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have shown the brain regions namely cortical brain areas, and subcortical limbic brain regions to be associated with depression. The dorsal and ventral anterior cingulate cortex, the dorsal and medial prefrontal cortex, the orbital frontal cortex and the insula of the cortical brain areas are responsible for anxiety disorders while the hippocampus, amygdala and the dorsomedial thalamus of the sub-cortical limbic brain regions are said to be implicated in depression (Rigucci et al., 2009; Desmyter et al., 2011; Pandya et al., 2012).

Further, the above neurocircuitry system comprising of the anterior cingulate cortex (ACC) (hypothalamus, amygdala, ventral striatum, insula, periaqueductal grey, and the ventral regions) and the pre-frontal cortex (PFC) (specifically ventromedial PFC and orbitofrontal cortex) are also reported to be involved in fear and anxiety response (Quirk et al., 1995; Phelps and LeDoux, 2005; Phillips et al., 2008; Mah et al., 2016). During these psychiatric disorders, both structural and functional abnormalities have been found in these areas. Moreover, there are reports that in India 14.3% of the total population of the country has mental disorders (Khambaty and Parikh, 2017). The report further reveals that one among every seven people in India has a mental disorder, which ranges from mild to severe. Among the mental disorders prevalent among the population, both anxiety and depressive disorders are of high prevalence (3.3% - 3.1-3.6 for depressive disorders and 3.0–3.5 for anxiety disorders) (Khambaty and Parikh, 2017). In another study by Sahoo and Khess (2010), symptoms of clinical depression and generalized anxiety disorder were 12.1% and 19.0% respectively in a stratified sample of college students. In the same study, of the total population analyzed, 18.5% population had depressive symptoms, while 24.4% had anxiety and 20% of the population had stress symptoms, which ranged from mild to severe conditions. There are also reports as per the National Mental Health Survey of India-2016 that females in India are more prone to depressive disorders, especially among the 40-49 age group (Gururaj et al., 2016). Further, depression disorders are more in females residing in urban metros than in rural areas. Among the Indian population, nearly 1 in 40 and 1 in 20 suffer from past and current depression (Gururaj et al., 2016). In the same survey, it was also reported that the prevalence of mental disorders was nearly twice as much in urban metros as compared to rural areas.

Similar to these reports, the recent global COVID-19 pandemic has also affected the global mental health of the population. In a study on the South Asian population, the COVID-19 pandemic resulted in anxiety and depression disorders at the rate of 34.1% to 41.3% in pooled patient samples (Hossain et al., 2021; Taylor, 2022). Salari et al (2020) also reported a similar result with 31.9% for anxiety and 33.7% for depression in the population affected by the global effect of the COVID-19 pandemic, with females showing more anxiety and depression symptoms than males. This finding is in accordance with generalized findings before the occurrence of the pandemic, that anxiety and depression disorders are prevalent more in females than males (Markkula and Suvisaari, 2017). In general, the pandemic impacted the general health of the population in low and middle-income categories (Kola et al., 2021), with anxiety and depression disorders in 25.6% and 27.6%, respectively in the general population, when the effect of the COVID-19 was adjusted in the said population of the study (Santomauro et al., 2021). Thus, the study shows that mental health disorders such as anxiety and depression are commonly prevalent today also among the population and their aetiology needs to be explored and understood. Like many other human diseases, most of the clinical studies of mood disorders have been performed on rodents because of their similarity to humans in anatomy, physiology, and genetics. Rodents are small and have a short generation time hence provide easy handling with controlled modification of variables, availability of different models, with the possibility of creating new models and also the availability of controls. They are cost-effective and have been proven to be an efficient tool to speed research and also the development of drug therapies (Vandamme, 2015). Behavioural and physiological responses to fear in rodents can be seen by the animal's tendency to show escape and avoidance behaviours from the potentially dangerous situation by displaying activities like flight, avoidance, freezing, defensive threat, defensive attack and risk assessment (Edmunds, 1974; Blanchard et al., 2003; Toth et al., 2013). They have also been observed to bury novel, unpleasant, or potentially dangerous stimuli (Treit et al., 1981; Dixit et al., 2020). Litvin et al (2007) has reported that rats have around 22kHz ultrasonic alarm cries in their defense pattern in response to a predator threat. They also demonstrate cessation of ongoing behaviour (Estes and Skinner 1941). Behaviour changes are studied by observing the animals in various behaviour tests, like elevated plus-maze, light/dark box and open-field tests are used to evaluate anxiety-like behaviours while forced-swim, tail suspension tests and marble burying tests are some tests for assessing depression. In these tests, the natural behaviors of rodents, such as exploratory behaviour, locomotor activity, rearing or food and water consumption, have been described to be decreased (Vuralli et al., 2019). Mental disorders such as anxiety and depression are of multifactorial origin, comprising environmental, psychological and genetic components. Research on these mental disorders in relation to neurotransmitters and small peptide molecules has yielded specific results and has vastly contributed to the understanding of the disorder.

2. Hypothalamo-Pituitary-Adrenal (HPA) axis

In a normal circumstance, the endocrine response to stress is the secretion of glucocorticoids (Sapolski et al., 2000; Gjerstad et al., 2018; Scherholz et al., 2019), they are the systemic effector hormone of HPA axis and their secretion is dependent on environmental and experiential events (Herman et al., 2016; Joseph and Whirledge, 2017; Spencer and Deak, 2017). Apart from many pathological and biomedical disorders such as hypertension, chronic fatigue syndrome, etc., an altered HPA axis is associated with mental health disorders like depression, post-traumatic stress disorder (PTSD), and schizophrenia (Heim and Nemeroff, 2009; Dean and Keshavan, 2017). Cortisol is the principal circulating glucocorticoid hormone in humans, many other mammals and most fish, whereas in rats, mice, birds and most reptiles it is the corticosterone (Norris and James, 2013). Cortisol/corticosteronereadily crosses the blood-brain barrier therefore this hormone can directly target the brain, and therefore is responsible for glucocorticoid negative feedback (Weil-Malherbe et al., 1959; Spiga et al., 2014). HPA axis encompasses a population of cells located within the hypothalamus, pituitary gland and adrenal gland, secreting hormonal signal that makes up this system (Joel and Baram, 2009). In the hypothalamus, the parvocellular cells of the paraventricular nucleus (PVN) produce a corticotropin-releasing hormone (CRH), which is the central player in the HPA axis. CRH-producing neurons receive neural input from various regions of the brain and their terminals project to the median eminence of the hypothalamus. CRH is a stimulator of the anterior pituitary for the secretion of adrenocorticotropic hormone (ACTH) (Herman et al., 2003). Mature ACTH after cleavage of prohormone Pro-opiomelanocortin (POMC) is stored in vesicles of the anterior pituitary for secretion upon receiving a signal from CRH for exocytosis (Cawley et al., 2016). ACTH further triggers the cells of zona fasciculata of the adrenal cortex to synthesize and secrete cortisol/corticosterone, which diffuses into circulation after secretion to give its various physiological effector functions in the body in response to the stressor (Thrivikraman et al., 2000).

HPA axis activity and their corresponding effect on the cortisol/corticosterone activity has been reported to be in a rhythmic fashion, the amplitude of their release into the blood show modulation depending upon the daytime (ultradian) as well as circadian rhythm, some species even showing seasonal dependency (Dickmeis et al., 2013). Sex differences are also observed in the corticosterone level in rats, with females displaying higher corticosterone levels and higher HPA axis response when exposed to the same stressor, indicating the role of gonadal steroids. These sexual differences could be due to the sexual dimorphism in mammals resulting from genetic and hormonal events that begin early during development and may continue throughout the lifespan (Becker et al., 2005).

3. Hypothalamo-Pituitary-Gonadal (HPG) axis

As the HPA axis physiologically adapts by responding to the stressor, it also intercedes the activity of the Hypothalamo-Pituitary-Gonadal (HPG) axis- the reproductive axis of the body. There is an inhibitory response in reproductive physiology and behaviourin both sexes (Spencer and Deak, 2017). HPG axis constitutes the hypothalamus, pituitary and gonads (testis in males and ovary in females). The main player in the HPG axis is the gonadotropin-releasing hormone (GnRH) (Millar, 2005). GnRH stimulates the gonadotroph cells of the pituitary to synthesize and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This FSH and LH further act on the ovary to regulate oocyte maturation, ovulation and steroid hormone production (Richards and Pangas, 2010) and on testis for hormonal regulation of testicular functions, acting through

their receptors in Sertoli and Leydig cells (Kaprara and Huhtaniemi 2017). GnRH neurons originate outside the CNS, during development, GnRH neurons migrate from the medial olfactory placode of the developing nasal cavity across the nasal septum, together with vomeronasal axons, and enter into the forebrain with the nervus terminalis, arching into the septal-preoptic area and hypothalamus (Yoshida et al., 1995). Processes are then extended from the hypothalamus to the median eminence, and GnRH is released into capillaries of the hypophysial portal system that reaches the anterior pituitary gland and modulates its gonadotropin synthesis and secretion (Millar, 2005). One way the GnRH secretion occurs is in a pulsatile way by regulating the ovarian cycle and normal folliculogenesis, this pulsatile secretion of GnRH occurs via Kiss1/NKB/Dyn (KNDy) neurons in the arcuate nucleus of the hypothalamus (Plant, 2020). Kisspeptin has been well accepted as the coordinator of secretion of reproductive hormones, acting at the apex of the hypothalamic-pituitary-gonadal (HPG) reproductive axis affecting puberty and fertility (Trevisan et al., 2018). Along with reproduction, kisspeptin also modulates behaviour, mood and emotions through its extensive distribution in the limbic system. Kisspeptin has also been identified as a hypothalamic anorexigenic factor (Bond and Smith, 2014; Mills et al., 2018). The other way GnRH secretion occurs is in the surge, particularly in females, this causes a preovulatory LH surge that leads to ovulation (Maeda et al., 2010). The pulsatile secretion of GnRH is dependent on various other neural inputs like norepinephrine, dopamine, serotonin, GABA, glutamate, neuropeptide Y (NPY), galanin and also the kisspeptin-neurokinin B-opioid pathway (Kaprara and Huhtaniemi 2017). As a consequence of this pulsatile GnRH secretion, FSH and LH are secreted from the anterior pituitary and enter the circulation to reach their target organs testis and ovary. The testis is the male reproductive organ and it has two chief functions: the production of spermatozoa (spermatogenesis) and the production of steroids (steroidogenesis). The steroid hormone, testosterone, regulates the development of spermatozoa and the growth, development and maintenance of the accessory reproductive glands. It also influences the development of secondary sex characteristics and, to some extent, sexual behaviour. The testis is divided into pyramidal lobules, each containing numerous convoluted seminiferous tubules that produce the spermatozoa and loose connective tissue that contains Leydig cells, the endocrine cells producing testosterone. The seminiferous epithelium consists of Sertoli cells and spermatogenic cells. Spermatogenic cells are proliferating populations of cells at various stages of the differentiative process of spermatogenesis. The cells are in the spermatogonial phase, spermatocyte phase (meiosis) and spermatid phase or spermiogenesis. The arrangement is such that the most immature cells are located near the basement membrane. As the cells proliferate and undergo differentiation, they move towards the lumen. Leydig cells in response to LH release from the anterior pituitary produce an increasing amount of testosterone. This testosterone along with FSH from the anterior pituitary stimulates the process of sperm production within the seminiferous epithelium (Ross and Reith, 1989; Zirkin, 1998; Holdcraft and Braun, 2004; Hess and Renato de Franca, 2008). In females, the ovary is the reproductive organ responsible for the production of gametes by oogenesis and the production of steroids. The ovarian hormones are further in control of the regulation of oocytes and the growth and development of secondary sex organs and mammary glands. In the ovary, the peripheral portion, the cortex, contains the ovarian follicles, embedded in compact, richly cellular connective tissue. Each ovarian follicle contains an oocyte, the developmental state of the oocyte is determined by the size of the follicle. During the early embryonic developmental stage of the ovary, the primordial germ cells migrate to the genital ridges. In the early fetal life, these primordial germ cells develop into oogonia and undergo rapid proliferation by mitotic division. Oogonia enlarge to form primary oocytes. When the ovarian stromal cells form a flattened layer of follicular cells around each oocyte, primordial follicles are formed. The primary oocyte within the primordial follicles undergoes the first meiotic division before birth, but the process gets arrested at the diplotene stage and resumes the meiotic division only at puberty when a group of follicles begin their cyclic development. As the first meiotic division is completed in the mature follicle, each daughter cells of the primary oocyte receive an equal share of the chromatin, but one daughter cell receives a majority of the cytoplasm and becomes the secondary oocyte. As the secondary oocyte surrounded by a mass of cumulus cells leaves the follicle at ovulation, the second meiotic division is in progress. This division is arrested at the second metaphase and is not completed unless the secondary oocyte is penetrated by a spermatozoon. The polar body formed from the first and second division undergoes degeneration. During the development, a large number of primordial follicles are lost to atresia during the fetal, early postnatal and puberty, i.e., the follicles degenerate and disappear. After puberty, follicles can undergo atresia at any stage of its maturation and involves, invasion of granulosa cell layers, sloughing of the granulosa cells into the antrum of the follicle, hypertrophy of the theca interna cells, the collapse of the follicle and invasion of the connective tissue into the cavity of the follicle. The oocyte undergoes degeneration by autolysis and disappears. The FSH and LH secreted by the anterior pituitary help the ovary in maintaining the ovarian cycle by secreting steroid hormones estrogen and progesterone from the granulosa cells and theca cells of the ovary (Ross and Reith, 1989; Sen and Caiazza, 2013; Bilinski et al., 2017).

Presence of a stressor, activation of HPA axis, causes suppression of HPG axis by inhibition of GnRH and GnRH receptor (GnRHR) synthesis, disruption in pituitary release of FSH and LH, and enhanced function of the gonadotropin-inhibitory hormone (GnIH; mammalian ortholog gene Rfrp3) neurons (Joseph and Whirledge, 2017). The intricate functioning of various brain axis is under regulation by numerous neurotransmitters, hormones, neuropeptides and neuromodulators. One such neuromodulator is nitric oxide which has a ubiquitous presence and has been well documented to be involved in both the HPA axis and HPG axis along with its varied functions.

3.1. Nitric Oxide

Nitric oxide (NO), a biological messenger molecule, has various physiological functions in the brain i.e., regulation of neurotransmission, synaptic plasticity, development of hypothalamic nuclei etc. (Tanda et al., 2009; McClellan et al., 2010; Bellefentaine et al., 2011). In general, nitric oxide is derived from the enzymatic conversion of L-arginine to citrulline by nitric oxide synthase (NOS) in the presence of nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH) and other co-factors (Bonthuis et al., 2010). NO mediates its signalling by interacting with soluble guanylyl cyclase (sGC) and stimulating its activity. There are three isoforms of nitric oxide synthases (NOS) including neuronal NOS (nNOS, or NOS1), endothelial NOS (eNOS, or NOS3), and inducible NOS (iNOS, or NOS2) (Alderton et al. 2001). iNOS is not expressed in the cell normally but its expression can be induced if there is some appropriate inducer like in macrophage the bacterial cytokines can illicit iNOS expression as its cytotoxic response, and once induced, it can remain active without the regulation by intracellular Ca^{2+} (Nathan and Hibbs, 1991). In the brain expression of the inducible nitric oxide synthase (iNOS) in glia can lead to killing of neurons by the astrocytes and microglial phagocytosis of neurons resulting in neurodegeneration (Brown and Neher, 2010). eNOS is expressed in the endothelial cells and Ca^{2+}-activated calmodulin is important for the regulation of its activity (Hemmens and Mayer, 1998). eNOS is a homeostatic regulator of numerous essential cardiovascular functions, dilating all types of blood vessels by stimulating soluble guanylyl cyclase and increasing cyclic GMP in smooth muscle cells, it also has a critical role in post-natal angiogenesis, is vasoprotective and also has an anti-atherosclerotic effect (Forstermann and Sessa, 2012). Of the three isoforms of nitric oxide synthase (NOS) (nNOS, eNOS, iNOS), NO derived from nNOS has been implicated in the modulation of neurophysiological functions (Kourosh-Arami, 2020), including neuroendocrine regulation of GnRH (Bellefontaine et al., 2011). In the brain, distribution of nNOS expression has been reported to be in the area of the hippocampus, the paraventricular, magnocellular and supraoptic nucleus of the hypothalamus, amygdala, cerebral cortex, dorsal raphe nucleus, striatum, olfactory bulb, basal ganglia, locus coeruleus, spinal cord and cerebellar cortex (Zhou et al., 2018). Numerous studies have suggested nNOS to be involved in the pathology of affective disorders such as major depressive disorder (MDD), borderline personality disorder (BPD) and anxiety disorder. In human suffering from schizophrenia and depression, the nNOS-containing neurons were localized in several hypothalamic nuclei of the postmortem brains, with the vast majority of nNOS neurons in the paraventricular nucleus (PVN). Cell counts of immunoreactive (ir)-nNOS neurons revealed a significant

reduction of cell density in the PVN of depressed and schizophrenic patients compared to the controls, while the total amount of ir-nNOS cells in the PVN was smaller in depressive and schizophrenic patients (Bernstein et al., 1998). It was either reduced or of abnormal size and branching pattern in the putamen of schizophrenic patients (Laurer et al., 2005). It was also shown that a small subset of ir-parvocellular PVN co-localize corticotrophin-releasing hormone (Bernstein et al., 1998). Thus, it was postulated that the reduced expression of ir-nNOS in the PVN in depressive and schizophrenic patients may be due to the involvement of nitric oxide in the release of CRH, arginine vasopressin and oxytocin, which have been shown to over-express in depressive-like conditions (Bernstein et al., 1998). Early genetic indications of nNOS function were provided by knockout mice with a deletion of exon 2 (Huang et al., 1993) and displayed aggressive behaviour and abnormal nocturnal motor coordination and cognitive performance (Weitzdoerfer et al., 2004; Nelson et al., 2006). Brueniq et al., 2017 have investigated the two genes of the nitric oxide pathway NOS1AP and NOS for their potential involvement in post-traumatic stress disorder (PTSD) and suggested that the genes from the nitric oxide pathway are likely to play a key role in PTSD, and other conditions related to it and in its resilience. Neurobiology of disorders such as anxiety, stress, and neuropsychiatric diseases has been observed to be associated with the dysfunction of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) cascade. Hyperactivity of the HPA axis is one of the most consistent biological findings in anxiety- and depression-related disorders. Experiments involving the administration of nitric oxide donors or inhibitors also further add to prove the role of nitric oxide in anxiety and depression behaviour such as social isolation stress as well as nitrite levels in the cortex of isolated conditioned mice (Amiri et al., 2015). Moreover, disorders like anxiety- and depression-like behaviour lead to dysfunction of the hypothalamo-hypophyseal-adrenal axis, the axis responsible for the endocrine stress response. Nitric oxide has been reported to be involved in the neural network linking GnRH reproductive neuroendocrine axis during food deprivation and stress-related disorders. Administration of a NO donor like 3-morpholinosydonimine (SIN-1) reverses the inhibitory GnRH and LH responses and normalises the KISS1 and RF-amide related peptide 3 (RFRP-3) mRNA profiles indicating the nitric oxide signalling interaction with the neurotransmitters (Shakya et al., 2018).

NO, involved in various physiological processes implying pathophysiology of different conditions, may be connected and molecular mechanisms or pathways may be shared under certain conditions. In the stress physiology and stress-related disease processes, NO has a detrimental effect but also has ameliorating effect suggesting an important role in stress and adaptive response to it (Esch et al., 2002).

Central administration of inhibitors of NO, N_{ω}-Nitro-L-arginine methyl ester hydrochloride(L-NAME) attenuated the plasma ACTH response to intermittent electroshocks and concurrently decreased hypothalamic NOS activities. This suggests that NO exerts a stimulatory influence on the HPA response to physico-emotional stressors and that the hypothalamus is the critical site of their action. The study also confirmed the specificity of action of L-NAME at suppressing NOS (Kim and Rivier, 1999). Further, it has been established that enkephalin and dynorphin systems of the rat hypothalamus exhibit expression of NOS by nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-diaphorase) activity or by labelling with antibodies such as methionine enkephalin (M-Enk) or dynorphin B (Dyn-B) in the paraventricular, arcuate and ventromedial nuclei (Murakami, 1994). A high ratio (37%-84%) of NADPH-diaphorase activity was reported in the Dyn-B neurons of the supraoptic and parvocellular and magnocellular PVN neurons in the rat hypothalamus. Hence, the study revealed that dynorphin and enkephalin have the ability to produce nitric oxide. The study also suggested that the increased expression of nitric oxide in magnocellular neurosecretory dynorphin-containing neurons may help the NO in the control of neurohypophyseal hormone secretion along with dynorphin (Murakami, 1994). In the Dyn-induced spinal cord injury (SCI), treatment with various NOS inhibitors (L-NAME, 7-NI and Aminoguanidine (AG), NO donor 3-propanediamine, N-{4-[l-(3-aminopropyl)-2-hydroxy-2-nitrosohydrazino] butyl} (Spermine NONOate, Sper/NO), and NOS substrate (L-arginine - L-Arg) show therapeutic effects, suggesting a differential role of NO/NOS in DYN induced SCI. Pretreatment with Sper/NO or L-Arg 10 min prior to i.t. Dyn A(l-17) not only prevented Dyn-induced elevations of nNOS and iNOS activities but also inhibited the basal nNOS and iNOS activities, implying that their neuroprotective mechanisms against Dyn-induced SCI may involve its inhibition of NOS after Dyn-induced paralysis has occurred as well as its initial vascular dilation (Hu et al., 1999). Further, the inhibition of NOS activity in heat stress attenuated the dynorphin immunoreaction and cell injury, indicating that dynorphin-induced neurotoxicity in hyperthermia is mediated via a mechanism involving nitric oxide (Sharma and Alm, 2001). Thus, it may be speculated that the enkephalin and dynorphin systems may be involved in mood disorders such as anxiety and depression-like behaviour.

In the time-dependent sensitized model of a stressed animal, stress–restress evoked a long-lasting increase in hippocampal NOS activity that was accompanied by a reactive downregulation of hippocampal NMDA receptors and dysregulation of inhibitory GABA pathways. Also, treatment with iNOS inhibitor aminoguanidine blocked stress-induced NOS activation. This prominent role of NO in neuronal toxicity and the important regulatory role for glutamate and GABA, throws some light on the stress-related hippocampal degenerative pathology and cognitive deficits seen in patients with PTSD (Harvey et al., 2003).

Further, the NOS inhibitor, L-NAME has been reported to decrease the ACTH response to shock. L-NAME has also been shown to decrease the upregulation of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) peptides in the paraventricular nucleus of the hypothalamus due to exposure to neurogenic stressors. There have also been reports of an increase in the number of CRH and AVP transcripts following intracerebroventricular administration of NO in the paraventricular nucleus of rats (Nelson et al., 1997), suggesting that nitric oxide has a stimulatory role in the hypothalamus. Also, the role of nNOS in depression has been reported in chronic mild stress (CMS) mice (Zhou et al., 2018) using pharmacological and genetic approaches. CMS-exposed mice displayed impaired neurogenesis in the hippocampus and behavioural changes typical of depression. Deletion of the nNOS gene in the mice leads to the prevention and reversal of the effects of the CMS-exposed mice. Administration of nNOS inhibitor to the mice also had similar effects (Zhou et al., 2018). Moreover, nNOS knockout mice displayed antidepressant-like properties. This finding leads to the suggestion that overexpression of nNOS in the hippocampus of the brain is critical for CMS-induced depression. Further, the inhibition of nNOS signaling in the brain may lead to a novel approach to the etiology of depression-like disorders (Echeverry et al., 2004). It has also been reported that rats treated with 7-nitroindazole (7-NI), N_{ω}-Nitro-L-arginine (l-NOARG) and L-NAME produced anxiolytic-like behaviour in the elevated plus maze (EPM) test (Volke et al., 2003). Further, when the light/dark exploration test was performed on the rats, which were treated with the NO donor, 3-morpholinosydnonimine (SIN-1), displayed an anxiolytic-like response (Tsuchiya et al., 1997; Perez-Nievas et al., 2007).

During fear exposure, NO concentration increases in some areas of the limbic system and is also involved in the modulation of aversive memory, increasing fear and anxiety-like behavior. Sodium nitroprusside administration has an anxiolytic effect in rats, contrastingly, administration of L-NAME also induces an anxiolytic effect in rats, indicating nitric oxide has a positive modulatory function (Medeiros et al., 2022). The characteristic feature of depressive illness is the hyperactivity of the HPA axis, which is a result of the decreased glucocorticoid receptor (GR) in the hippocampus that in turn is due to the glucocorticoid-induced hippocampal nNOS upregulation. Chronic mild stress (CMS) and corticosterone exposures cause hippocampal nNOS overexpression, suggesting hippocampal nNOS could be important for stress-related depression, also apparent because the inhibition of hippocampal nNOS almost abolishes both CMS- and corticosterone-induced depressive behaviours (Zhou et al., 2011). Pair housing increases anxiety-like responses in male mice, inhibition of nNOS by gene deletion or treatment with inhibitor 3-Br-7-NI affects the ability of the animal to respond behaviorally to social stimuli in pair-housed mice. It reduced open arm exploration in single-housed mice, but in pair-housed mice, nNOS inhibition increases open arm exploration indicating that nNOS inhibition is anxiolytic in group-housed male mice (Workman et al., 2008). Impairing NO and ROX pathway by creating double knockout mice by deleting the p47phox and nNOS genes in

C57BL/6 mice show that deletion of these genes synergizes to impair cognitive function relevant to schizophrenia and social behaviours relevant to autism (Walton et al., 2013). Male mice with nNOS gene deleted also displayed a dramatic loss of behavioural inhibition resulting in elevated aggression and mating behaviour (Nelson et al., 2006).

4. Conclusion and future directions

Evidence indicates that anxiety and depression have always accompanied humans and animals. However, the concrete treatment regimen for the said disorder has been elusive to date. The research on anxiety and depression disorders has improved the patient's quality of life, but with limiting results. At times, some of the clinical symptoms are misinterpreted or completely missed. Thus, studying molecules involved in controlling anxiety and depression disorders becomes essential, which may help improve understanding of the etiology of the mental disorder. Moreover, future research on such mood disorders like integrating the HPA-HPG axis in the etiology of anxiety- and depression-like behaviour and reproductive functions will further add to the plethora of information available on anxiety- and depression-like behaviour and help add a connecting link in understanding the disorder better.

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Authors contributions

PK conceptualized the idea and initiated the review work. All the authors have equally contributed in literature survey, drafting and finalization of the manuscript. All the authors read and approved the manuscript before submission for publication.

Conflict of interests

The authors declares that we have no conflict of interests.

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