Review Article

Neuronal nitric oxide synthase and affective disorders

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ARTICLE INFO

ABSTRACT

Affective disorders including major depressive disorder (MDD), bipolar disorder (BPD), and general anxiety affect more than 10% of population in the world. Notably, neuronal nitric oxide synthase (nNOS), a downstream signal molecule of N-methyl-D-aspartate receptors (NMDARs) activation, is abundant in many regions of the brain such as the prefrontal cortex (PFC), hippocampus, amygdala, dorsal raphe nucleus (DRN), locus coeruleus (LC), and hypothalamus, which are closely associated with the pathophysiology of affective disorders. Decreased levels of the neurotransmitters including 5-hydroxytryptamine or serotonin (5-HT), noradrenalin (NA), and dopamine (DA) as well as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis are common pathological changes of MDD, BPD, and anxiety. Increasing data suggests that nNOS in the hippocampus play a crucial role in the etiology of MDD whereas nNOS-related dysregulation of the nitrergic system in the LC is closely associated with the pathogenesis of BPD. Moreover, hippocampal nNOS is implicated in the role of serotonin receptor 1 A (5-HTR1 A) in modulating anxiety behaviors. Augment of nNOS and its carboxy-terminal PDZ ligand (CAPON) complex mediate stress-induced anxiety and disrupting the nNOS-CAPON interaction by small molecular drug generates anxiolytic effect. To date, however, the function of nNOS in affective disorders is not well reviewed. Here, we summarize works about nNOS and its signal mechanisms implicated in the pathophysiology of affective disorders. On the basis of this review, it is suggested that future research should more fully focus on the role of nNOS in the pathomechanism and treatment of affective disorders.

Introduction

Affective disorders, with a lifetime risk of 10%–20%, are a family of serious mental disorders including major depressive disorder (MDD), bipolar disorder (BPD), and anxiety (Baldwin, 2007). Among them, MDD and BPD are usually classified as mood disorders (Sanacora et al., 2008). According to the surveys conducted by the World Health Organization (WHO), affective disorders will become the second leading cause of disability by the year 2020 and lead to great 'burden' worldwide (Sanacora et al., 2008; Murray and Lopez, 1996).

Nitric oxide synthases (NOS) are a family of catalytic synthases, including neuronal NOS (nNOS, or NOS1), endothelial NOS (eNOS, or NOS3), and inducible NOS (iNOS, or NOS2), which synthesize the production of NO, a gas signaling molecule (Alderton et al., 2001). The endothelial isoform, eNOS, is constitutively expressed in the endothelial cells, while the macrophage isoform, iNOS, is not constitutively expressed but is induced by cytokines (Hevel et al., 1991; Bredt and Snyder, 1990). In the brain, nNOS derived NO constitutes the largest proportion of NO. The protein nNOS exhibits a bidomain structure containing a reductase domain (C-terminal) plus an oxygenase domain

(N-terminal) and consists of 1434 amino acids (Boissel et al., 1998). Overall, the oxidation of L-arginine are catalyzed by nNOS to generate citrulline and NO as products in a wide range of tissues (Zhou and Zhu, 2009). Specifically in the CNS, nNOS is mainly located in neurons, astrocytes, and neuroanl stem cells (NSCs) in the mammalian central nervous system (CNS) (Luo and Zhu, 2011). Changes in nNOS expression have been detected in sevral CNS disorders such as MDD, BPD, anxiety, stroke, Parkinson's disease (PD), Alzheimer's disease (AD), and amytrophic lateral sclerosis (ALS) (Calabrese et al., 2007; Lopez et al., 2017; Zhang et al., 2018a; Suzuki et al., 2010). In excitory neurons, NMDAR and nNOS are linked by postsynaptic density protein 95 (PSD95) at glutamatergic synapses, mediating the glutamate signal (Craven and Bredt, 2000; Craven et al., 1999). Activation of nNOS depends on NMDARs-mediated calcium influx, incearsing the content of NO. Glutamate is the major excitatory neurotransmitter in the CNS. A growing body of evidence suggests that the dysfunction of glutamatergic neurotransmission is involved in the pathology of MDD, BPD and anxiety (Riaza Bermudo-Soriano et al., 2012; Amiel and Mathew, 2007; Cortese and Phan, 2005; Dutta et al., 2015; Gerhard et al., 2016; Ginsberg et al., 2012; Fountoulakis, 2012). The effects of glutamate in

the CNS are mainly mediated through glutamate receptors including NMDARs (Niciu et al., 2012).

The N-methyl-D-aspartate receptors (NMDAR) is one of the three types of ionotropic glutamate receptors. Stimulation of NMDARs results in activation of neuronal nitric oxide synthase (nNOS), an enzyme catalyzing the formation of nitric oxides (NO) from L-arginine (Garthwaite et al., 1989). NMDARs are predominantly concentrated in the limbic system, a brain area that has close relationship with MDD, BPD and anxiety (Paoletti et al., 2013; Buller et al., 1994; Mathews et al., 2012). It is found that the antagonists of NMDARs exhibit the property of antidepressants (Nowak et al., 1995; Yuen et al., 2009, 2011). More importantly, clinical antidepressants such as fluoxetine, metapramine, moclobemide and desipramine bind to the NMDARs and act directly as antagonists and reduce the activity and expression of NMDAR (Szasz et al., 2007; Mayer et al., 2009). Ketamine, a non-competitive NMDA receptor antagonist, repeated treatment of which or at a single low dose, was proved a fast-acting antidepressant response (Dutta et al., 2015; Galvez et al., 2018; Grunebaum et al., 2017; Gurnani and Khurshid, 2017; Medeiros da Frota Ribeiro and Riva-Posse, 2017; Taiminen, 2017; Yang et al., 2018; Zhang et al., 2018b; Li et al., 2010). Besides, clinical trials demonstrated ketamine's rapid activity in patients with treatment-resistant MDD, BPD, and anxiety (Ionescu et al., 2015; Murrough et al., 2013). Therefore, NMDAR and its downstream signaling would be considered as the potential targets for discovery of the fast-onset antidepressant (Abbasi, 2017; Jelen et al., 2018). The polymorphisms of NR1 subunit of NMDARs have a high association with BPD (Mundo et al., 2003). Decreased expression of the NR2 subunit in the anterior cingulate cortex was found in a post mortem study of BPD patients (Woo et al., 2004). Additionally, in-situ hybridization assessment revealed that the expression of both NR1 and NR2 A subunits in the hippocampus were reduced in the patient with BPD (McCullumsmith et al., 2007). Furthermore, it was observed that a wide variety of NMDARs antagonists have shown anxiolytic-like effects (Riaza Bermudo-Soriano et al., 2012). Converging lines of evidences suggest that NMDARs have important functions in the pathology of affective disorders and may be a novel therapeutic target (Sanacora et al., 2008; Mathews et al., 2012; Kemp and McKernan, 2002; Holden, 2003; Serafini et al., 2015; Williams and Schatzberg, 2016; Machado-Vieira et al., 2009). However, the high risk of neurotoxicity caused by NMDARs antagonists is concerning (Olney et al., 1991; Farber et al., 2002). In order to avoid the potential severe side effects, it is necessary to explore a safe drug target in the downstream signaling of NMDARs. Since nNOS works as a main downstream molecule of NMDARs (Mungrue and Bredt, 2004), these studies support a potentially important role of nNOS in the pathology of affective disorders and nNOS may be a practical and more selective drug target for treatment of affective disorders. Thus, in this review we will summarize the evidence of the roles of nNOS in the pathology of MDD, BPD, and anxiety, which could assist in new drugs discovery for treating affective disorders.

NO plays an important role in the physiology of the CNS (Alderton et al., 2001; Garthwaite, 1995). However, it turns harmful when involved in some pathological processes mainly due to its reactivity with reactive oxygen species (ROS), forming peroxynitrite (ONOO·) which can nitrosylate extensive proteins, lipids, deoxyribonucleic acid (DNA), ribonucleic Acid (RNA), and other cell constituents (Anand and Stamler, 2012; Foster et al., 2009, 2003). Of note, biosynthesis of neurotransmitters can be regulated by NO (Trabace et al., 2004). Additionally, hippocampal neurogenesis, neuronal plasticity, nerve growth factor synthesis, hypothalamic-pituitary-adrenal (HPA) axis activity and other targets involved in depression are modulated by NO (Guix et al., 2005; Bishop and Anderson, 2005; Cardenas et al., 2005). It has been documented that the dysfunction of NO in the brain is related to the etilogy of MDD, BPD, and anxiety (Baranyi et al., 2015; Dhir and Kulkarni, 2011; Pitsikas, 2018). However, the function of nNOS pathway in affective disorders is not comprehensively reviewed. In the present review, we analyzed studies on the interaction between nNOS

and the signal molecules involved in affective disorders and recognize that nNOS plays a critical role in the primary pathological changes of affective disorders.

nNOS expression and distribution in the CNS

More than 10 differently spliced nNOS transcripts were reported, among which three isoforms of nNOS including nNOSα, nNOSβ, and nNOSμ are the principal (Kolesnikov et al., 2009). In the CNS, the 160 kDa nNOSα is the predominant splice variant, accounting for the great majority of catalytic activity in the brain (Mungrue and Bredt, 2004). A radioactive oligonucleotide in situ hybridization experiment employed the nNOSβ-specific probe indicated that nNOSβ may be responsible for the major portion of citrulline formation (Eliasson et al., 1997). The isoform nNOSμ is majorly expressed in striated muscle, important for muscle homogenates (Mungrue and Bredt, 2004; Kolesnikov et al., 2009; Percival et al., 2008). Among the three isoforms, nNOSα is well-studied in the CNS diseases, with wide distribution in other cell types including astrocyte and neural stem cells (NSCs), not only neurons, in the brain (Calabrese et al., 2007; Luo et al., 2010).

In the brain, nNOS is predominantly expressed in the hippocampus, cortex, hypothalamus, DRN, amygdala, and other regions (Wang and Nakai, 1995; Okere and Waterhouse, 2006; Tagliaferro et al., 2001; Leger et al., 1998; Simpson et al., 2003; Zhang et al., 2010), (Table 1), the areas of the brain related to stress and affective disorders. Almost all of the sub-regions of the hippocampus including detate gurus, hilus, CA3, CA1, and subiculum express nNOS in different cell types such as interneurons, granular neurons, and pyramidal neurons, indicating that nNOS plays an important role in the function of the hippocampus (Zhou et al., 2011a; Oliveira et al., 2008; Liang et al., 2013; Wendland et al., 1994). Both the periventricular and magnocellular nucleus of the hypothalamus harbor nNOS cells expressing LepRb or Sim1 (Leshan et al., 2012; Sutton et al., 2014). More importantly, it has been shown that NOS directly exist in corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) neurons and modulate the secretion of CRF (Orlando et al., 2008; Yuan et al., 2006; Harada et al., 1999) (Table 1). In the amyadala, nNOS is mainly found in the basolateral complex. Various types of neurons in different regions of the cerebral cortex also contain nNOS (Table 1), indicating diversified functions of nNOS in the cortex. Notably, nNOS and 5-HT are co-expressed in the same neurons in different areas of the dorsal raphe nucleus (DRN) (Tagliaferro et al., 2001; Okere and Waterhouse, 2006, 2006; Tagliaferro et al., 2001; Leger et al., 1998; Simpson et al., 2003), implying the interaction between nNOS and 5-HT in the biological function of DRN.

The level of nNOS in other places of the brain is relatively lower (Table 1). For instance, nNOS-expressing cells are found in the striatum, and there is evidence showing that nNOS in the striatum is implicated in the pathology of Aging (Del Moral et al., 2004), Parkinson's disease (Chalimoniuk and Langfort, 2007) and Huntington's disease (Table 1) (Norris et al., 1996). There is also data showing that nNOS in the locus coeruleus (LC) is involved in the pathology of BPD (Table 1) (Karolewicz et al., 2004). Furthermore, nNOS-positive cells are found in the basal ganglia, olfactory bulb, and cerebellar cortex, though the role of nNOS in these tissues needs further investigation (Table 1) (Hu et al., 2012a; Sanchez-Islas and Leon-Olea, 2001; Kishimoto et al., 1993; Crespo et al., 2003; Abbott and Nahm, 2004). A large number of nNOS positive cells and nNOS immunoreactive axons are also reported in the spinal cord, which is involved in the pathology of pain (Table 1) (Lukacova et al., 2012).

nNOS signaling in the brain

The dimer form is the active form of nNOS, requiring tetrahydrobiopterin (BH4), heme and L-arginine binding. Although the synthesized NO from endogenous L-arginine is the principle signaling mediator of nNOS, the featured structure of nNOS contributes to its

Table 1
The distribution of nNOS expression in the CNS.

Tissue in the CNS	Sub-region	Cell types
Hippocampus	CA1	Pyramidal cells and interneurons (Zhou et al., 2011a; Liang et al., 2013; Wendland et al., 1994)
	CA3	Pyramidal cells and interneurons (Zhou et al., 2011a)
	Granular layer	Granule cells (Zhou et al., 2011a; Liang et al., 2013)
	Molecular layer	Interneurons (Romay-Tallon et al., 2010)
	Hilus	GABA interneurons (Zhou et al., 2011a; Liang et al., 2013)
		GAD67 interneurons (Jinno et al., 1999)
	Subiculum	Interneurons (Oliveira et al., 2008)
Hypothalamus	Paraventricular Nucleus	LepRb neurons (Leshan et al., 2012);
		Sim1 neurons (Sutton et al., 2014);
		CRF neurons (Harada et al., 1999)
		8-arginine vasopressin neurons (Nylen et al., 2001)
	Magnocellular Nucleus	Oxytocin neurons (Nylen et al., 2001)
	Supraoptic nucleus	NA (Srisawat et al., 2004)
Amygdala	Basolateral complex	GABAergic interneurons (Wang et al., 2017; Vatanparast et al., 2013)
Cerebral cortex	Neocortex	GABAergic interneurons (Shlosberg et al., 2012)
	Prefrontal cortex	Interneurons (Zoubovsky et al., 2011; Spiers et al., 2016)
	Visual cortex	Calretinin- or parvalbumin-positive interneurons (Gu et al., 2015; Lee and Jeon, 2005)
	Entorhinal cortex	NA (Oliveira et al., 2008)
	Temporal cortex	GABAergic interneurons (Bernstein et al., 2014)
	Barrel cortex	GABAergic interneurons (Perrenoud et al., 2012)
Dorsal raphe nucleus	Dorsomedial area	5-HT neurons (Tagliaferro et al., 2001; Simpson et al., 2003)
	Ventromedial area	5-HT neurons (Tagliaferro et al., 2001; Simpson et al., 2003)
	Periventricular part	5-HT neurons (Leger et al., 1998; Simpson et al., 2003)
Striatum	Striatal matrix	Spiny nitregic neurons (Ramos et al., 2002)
Olfactory bulb	Periglomerular region	Periglomerular cells (Chen et al., 2004);
		GABAergic neurons (Crespo et al., 2003)
	Vomeronasal accessory	Granule cells (Kishimoto et al., 1993)
	Nasal Epithelium	Olfactory receptor neurons (Sanchez-Islas and Leon-Olea, 2001)
Basal ganglia	Corpus striatum	NA (Hu et al., 2012a)
Locus coeruleus	NA	Neuromelanin-containing neurons (Karolewicz et al., 2004; Bielau et al., 2012b; Karolewicz et al., 2008)
Spinal cord	Dorsal horn	NA (Lukacova et al., 2012; Davidova et al., 2009)
Cerebellar cortex	Molecular layer	Stellate, basket, Purkinje and granule cells (Abbott and Nahm, 2004; Martins et al., 2011)

NA means no answer.
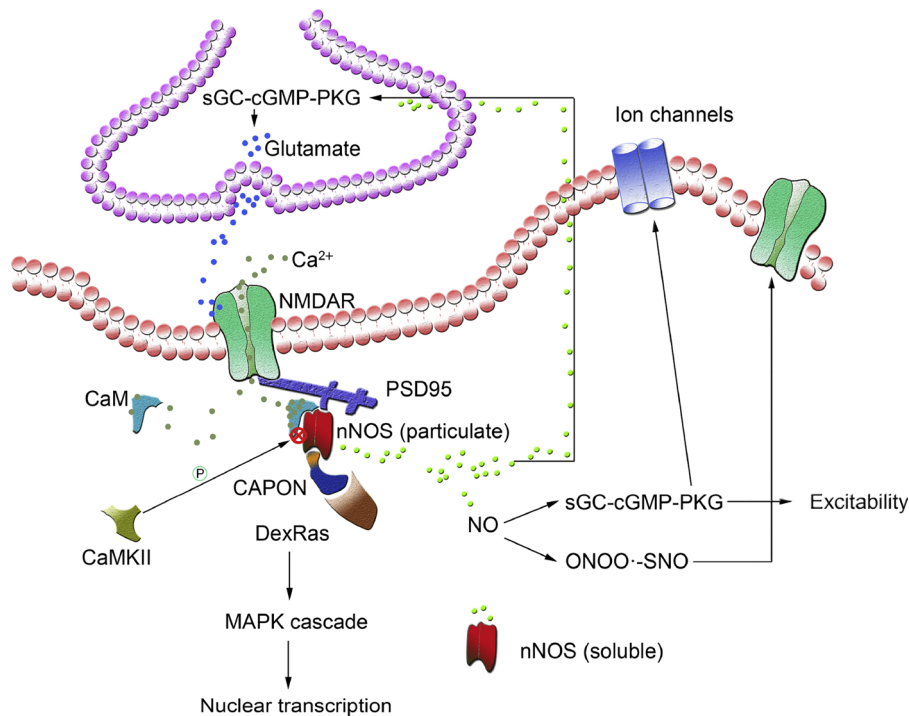
Fig. 1. A descriptive model for the signaling pathway of nNOS in excitatory neurons.

flexible signal transduction pathway (Zhou and Zhu, 2009; Luo and Zhu, 2011). There are two non-overlapping binding sites in the structure of nNOS, including a canonical PDZ domain (residues 1–99) that binds PDZ motifs inside other proteins (Jaffrey et al., 1998; Manivet et al., 2000; Riefler and Firestein, 2001; Chanrion et al., 2007a) and an "internal" PDZ motif (residues 100–130) that binds PDZ domains of other proteins (Christopherson et al., 1999; Hillier et al., 1999). Neuronal NOS is an important enzyme in the downstream cascade of the

NMDARs. The PDZ domain of nNOS binds to the second PDZ domain of the postsynaptic density protein-95 (PSD-95), which in turn binds to the cytosolic tail of the NMDARs (Christopherson et al., 1999) (Fig. 1). When a large volume of glutamate is released from pre-synapse into the synaptic gap, NMDARs on the post-synaptic membrane opens in response to glutamate binding, allowing Ca^{2+} influx into the cell (Fig. 1). The elevated cytosolic Ca^{2+} concentration is required for Calmodulin (CaM) to interact with nNOS, leading to activation of nNOS by phosphorylation of nNOS, increasing NO production. The nNOS are attached to the plasma membrane via adapter proteins such as PSD-95, creating the particulate form of nNOS with a higher probability of activation by CaM compared to soluble nNOS in the cytoplasm. However, the interaction between nNOS and CaM is blocked by the Calmodulin protein kinase (CaMKII) via phosphorylation of nNOS (Fig. 1). The triple-complex of NMDAR/PSD-95/nNOS plays an important role in a range of normal neuronal functions including learning and memory and synaptic plasticity (Garthwaite, 1995; Jaffrey and Snyder, 1995; Garthwaite et al., 1988), as well as pathophysiological disorders of the brain such as stroke and pain (Zhou et al., 2010; Aarts et al., 2002; Florio et al., 2009). The membrane-localized nNOS further physically couples with another adapter protein called CAPON linked to DexRas 1 to regulate the nitrosylation of DexRas 1 (Jaffrey et al., 1998; Fang et al., 2000), activating a downstream MAP kinase (MAPK) cascade and modulate nuclear transcription of cAMP-response element binding protein (CREB), N-myc proto-oncogene protein (N-Myc), nuclear factor-kappa B (NF-κB), Tumor protein (p53), and histone deacetylase 2 (HDAC2), *etc*. (Fig. 1).

The function of nNOS is majorly mediated by the NO-activated soluble guanylate cyclase (sGC)- cyclic guanosine monophosphate (cGMP)- protein kinase G (PKG) pathway, affecting postsynaptic neuronal excitability and targeting several ion channels including sodium, voltage-gated calcium, calcium-activated and ATP-sensitive potassium, and cyclic nucleotide-gated channels, as well as AMPA receptors (AMPARs) to modulate synaptic strength (Calabrese et al., 2007). Meanwhile, NO also diffuses to presynaptic region and regulates presynaptic neurotransmitter release (Fig. 1). Excessive amounts of NO produced under pathological conditions are associated with increased inflammation and oxidative stress reacts with superoxide anion oxygen (O2)·, to form ONOO· (Pacher et al., 2007). Nitrosylation including S nitrosylation and nitrotyrosination of proteins are important in physiological and pathological signaling (Anand and Stamler, 2012; Foster et al., 2009, 2003). Functionally, some receptors such as NMDARs, sodium channels are inhibited by nitrosylation while other channels or receptors such as L-type calcium (Ca) channel, calcium activated potassium channel, and GABA-A receptor are activated by nitrosylation (Choi et al., 2000; Manzoni et al., 1992). The different effects on channels and receptors precisely regulate a wide spectrum of physiological processes including cell death and injury, synaptic function, redox response, mitochondrial function, and transcriptional control (Calabrese et al., 2007). Particularly, nNOS may represent a central component that regulates synaptic transmission and intercellular signaling, through negative regulation of the NMDARs by S-nitrosylation (Kim et al., 1999) (Fig. 1). Beside of excitatory neurons, the signaling pathway of nNOS in interneurons and astrocytes are not well studied and remain unclear.

Overall, the catalytic activity, protein-protein interaction, and subcellular localization of nNOS are the key factors in its signal transduction.

Glutamate synthesized and released in the pre-synapse binds to the NMDARs at the post-synapse, leading to influx of Ca^{2+} which then activates nNOS and its signaling pathway.

Affective disorders

Affective disorders, mainly including MDD, BPD, and anxiety disorders, are a set of psychiatric diseases characterized by dramatic changes or extremes of mood (Baldwin, 2007). MDD is characterized by feelings of extreme sadness, hopelessness, and a proportion of patients have suicide attempts (Wong and Licinio, 2001). The clinical medication for MDD include tricyclic antidepressants (TCAs), tetracyclic antidepressant, SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), dopamine reuptake blocker, 5-HTR1 A antagonist, 5-HTR2 antagonists, 5-HTR3 antagonist, monoamine oxidase inhibitors (MAOIs), and noradrenergic antagonist. Classic BPD is featured by switching of two periods of mood including depression and mania (Goodwin and Jamison, 2007). The treatment for BPD includes lithium, an old mood stabilizer, and atypical antipsychotics with greater side effects, such as aripiprazole, risperidone, quetiapine, ziprasidone, and clozapine. Anxiety disorders are characterized by feelings of nervousness, anxiety, and even fear (Gross and Hen, 2004). Medication used for alleviating the symptoms of generalized anxiety disorder includes benzodiazepines including alprazolam, clonazepam, chlordiazepoxide, diazepam, and lorazepam, SSRIs, SNRIs, and some of the tricyclic antidepressants. Although similar symptoms and cure strategy and drugs cause difficulty in precise treatment of affective disorders, these disorders can be distinguished and divided into several subtypes according to diagnosis criteria with different treatment guidance and principle.

The pathogenesis of affective disorders involves both neurology and psychiatry; however the molecular mechanism is not fully understood. Increasing hereditary evidence shows that the affective disorders are influenced by the interaction between genetic and environmental factors (Baldwin, 2007). In a given genetic background, dysfunction of neurotransmitters and hormones in the brain in response to environmental factors, such as stressful life events, play a major role in the development of affective disorders (Lex et al., 2017; Won and Kim, 2016; Lupien et al., 2009a; de Kloet et al., 2005a). Life events, such as a traumatic event, personal loss, health problem, family issue, and alcohol or drugs abuse, can trigger the pathological changes related to affective disorders.

Two main types of treatments available for affective disorders are medication and psychotherapy (DeRubeis et al., 2008). There are many different medications available for relieving the symptoms (Manji and Young, 2002; Mitchell, 2002; Montgomery, 2002; Nemeroff and Owens, 2002; Raison et al., 2002). However, the solution of affective disorder remains still impossible under current typical clinic therapy merely, driving scientists to search new therapeutic targets. The 'Monoamine-Deficiency Hypothesis', developed from clinical observations cannot fully explain the mechanism of depression (Berton and Nestler, 2006). However, abnormality of monoamine level couldn't completely interpret for depression, indicating that other signal molecules may be critical in the pathological development of affective disorders. The distribution of nNOS-positive neurons in the brain, mainly in the hippocampus, cortex, hypothalamus, DRN, and amygdala (Table 1), implies a strong link between nNOS and affective disorders. Interestingly, the interaction between nNOS and monoamine was found important in the antidepressive effect of classic antidepressants (Smith and Whitton, 2000; Segieth et al., 2001; Chiavegatto et al., 2001; Strasser et al., 1994; Asano et al., 1997; Bryan-Lluka et al., 2004; Fossier et al., 1999). Collectively, increasing evidences are showing that nNOS in different regions of the brain play fundamental roles in the pathology of MDD, BPD, and anxiety.

nNOS and MDD

MDD is a chronic, recurring and potentially life threatening mental illness that causes marked diminished interest or pleasure and a persistent feeling of sadness (Belmaker and Agam, 2008; Ignacio et al., 2018). The diagnosis of MDD requires a distinct change of mood characterized by sadness or irritability which last a minimum of 2 weeks (Belmaker and Agam, 2008). Since its development in 1960 by Dr. Hamilton, the Hamilton Depression Rating Scale (HAM-D) has been widely applied to diagnose depression (Hamilton, 1960). The core

symptom of MDD is accompanied by at least several psychophysiological changes, such as sleep disturbances, reduced appetite, slowed thinking, suicidal thoughts, and angry outbursts (Belmaker and Agam, 2008).

Numerous theories of the etiology of depression have been developed. The 'Monoamine-Deficiency Hypothesis', an early milestone in the pathophysiology of depression, is demonstrated by the facts that monoamine is decreased in the brain and antidepressants effectively recover it (Millan, 2004). However, serious gaps and limitations have been revealed in the 'Monoamine-Deficiency Hypothesis'(Berton and Nestler, 2006; Millan, 2004). For instance, it takes at least 3–4 weeks to exert antidepressant effects while the concentrations of monoamine increase rapidly after antidepressant treatment. Despite this, only a subset of patients shows recovery after antidepressant treatment by increasing the concentration of monoamine. Hyperactivity of the HPA axis is also observed in the majority of patients with depression, as manifested by hyper-secreted CRF from the hypothalamus and adrenal hyper-responsiveness to circulating adrenocorticotropic hormone (ACTH) (de Kloet et al., 2005a; Parker et al., 2003; Wong et al., 2000). Over the years, the hypotheses on the pathophysiology of depression and on the molecular mechanisms of antidepressants have greatly extended (Wong and Licinio, 2001; Berton and Nestler, 2006). Depression is associated with impairments of structural plasticity and cellular resilience. Numerous preclinical and clinical studies have shown that signaling pathways involved in regulating cell survival and cell death are long-term targets for the actions of antidepressants, including brain derived neurotrophic factor (BDNF), CREB, and molecules regulating adult hippocampal neurogenesis (Eisch et al., 2003; Koch et al., 2002). Furthermore, the glutamatergic system and gamma aminobutyric acid (GABA) system also have been demonstrated to be involved in the pathophysiology of depression (Machado-Vieira et al., 2009; Luscher et al., 2011).

The major function of nNOS is synthesis of NO. There are various evidences that have demonstrated an imperative role of NO derived from nNOS positive neurons in MDD (Baranyi et al., 2015; Dhir and Kulkarni, 2011; Akpinar et al., 2013; Herken et al., 2007; Yu et al., 2003). Neurons expressing nNOS are predominantly located in the hippocampus, cortex, hypothalamus, DRN, amygdala (Wang and Nakai, 1995; Okere and Waterhouse, 2006; Tagliaferro et al., 2001; Leger et al., 1998; Simpson et al., 2003; Zhang et al., 2010), strongly implicated in MDD (Table 1). More and more studies revealed indispensable roles of nNOS-NO pathway in the etiology and treatment of MDD, which are discussed in the following sessions.

Antidepressant properties of nNOS inhibitors

More and more clinical and pre-clinical studies strongly suggest the implication of the NO cascade in the pathology of depression (Dhir and Kulkarni, 2011; Wegener and Volke, 2010; Ostadhadi et al., 2016a; Zomkowski et al., 2010; Jesse et al., 2010, 2008; Dhir and Kulkarni, 2007a; Almeida et al., 2006; Harkin et al., 1999, 2004). Jefferys and Funder showed that L-N-arginine methyl ester or N[G]-nitro-L-arginine methyl ester (L-NAME), a type of general NOS inhibitor, decreased immobility of rats in the Porsolt forced swimming test, which was reversed by pre-treatment with L-arginine (the NOS substrate) (Jefferys and Funder, 1996). Both acute and chronic treatment of L-NAME produced antidepressive-like response in FST (Harkin et al., 1999). N[G]-monomethyl-L-arginine (L-NMMA), another NOS inhibitor, also elicited antidepressive-like effect in FST (Harkin et al., 1999). In line with this finding, studies found that NG-nitro-L-arginine (L-NA or L-NNA), another type of non-preferential NOS inhibitor, resulted in antidepressant-like effects in the forced swimming test (FST) and augmented the behavioral effect of antidepressants (Gigliucci et al., 2010; Karolewicz et al., 2001; Harkin et al., 2003) (Table 2). Co-treatment with the non-selective 5-HT receptor antagonist metergoline, preferential 5-HTR2 A antagonist ketanserin, or the 5-HTR2C antagonist RO-430440, but not

5-HTR1 A antagonist WAY 100,635 or the 5-HTR1B antagonist GR 127935, attenuated the L-NA-induced reduction in immobility in FST (Gigliucci et al., 2010). Administration of lipopolysaccharide (LPS) is a model of depression in rodents. It was found that NOS inhibitors, including L-NAME, aminoguanidine, and sildenafil prevented the LPS-induced depression-like behavioral and neurochemical alterations (Tomaz et al., 2014).

Selective nNOS inhibitors produced acute antidepressant-like effects in behavioral measurement (Volke et al., 2003; Joca and Guimaraes, 2006; Silva et al., 2012). For instance, 7-nitroindazole (7-NI), a preferential inhibitor of nNOS, and 1-(2-trifluoromethylphenyl)imidazole (TRIM), a stronger preferential inhibitor of nNOS, decreased immobility time in the FST (Volke et al., 2003; Joca and Guimaraes, 2006; Silva et al., 2012; Ulak et al., 2010). Moreover, 7-NI augmented the behavioral effects of imipramine and fluoxetine in FST (Harkin et al., 2004). Studies showed an increase in Fos expression in several brain regions after stress which were attenuated by 7-NI similar to fluoxetine and venlafaxine, suggesting that these drugs share common neurobiological substrates [Silva et al., 2012]. Consistently, acute stress-induced increase in c-FOS immunoreactivity in the brain was reduced following treatment with L-NA or TRIM (Sherwin et al., 2017). Additionally, 7-NI administration altered the expression of genes related to transcription in the cAMP response element-binding pathway, which possibly account for the antidepressant-like effects induced by nNOS inhibition (Ferreira et al., 2012). The antidepressive property targeting nNOS was also documented by the effect of Nω-propyl-L-arginine (NPA), another preferential nNOS inhibitor (Garthwaite et al., 1989; Sales et al., 2017). Notably, microinjection of NPA into the dorsal hippocampus induced dose-dependent antidepressant-like effects, which were counteracted by a 5 H TR1 A antagonist (Hiroaki-Sato et al., 2014). It was recently shown that acute stress exposure increased nNOS expression, the concentration of NO in the hippocampus, and both NPA and [1H-[1,2,4] Oxadiazole[4,3-a]quinoxalin-1-one] (ODQ), an inhibitor of sGC, induced an antidepressant-like effect [Sales et al., 2017; Heiberg et al., 2002; Pereira et al., 2015; Diniz et al., 2016]. Carboxy-PTIO (c-PTIO), a type of NO scavenger, produced antidepressant-like effects in the FST (Pereira et al., 2015; Diniz et al., 2016; Poleszak et al., 2007). Interestingly, hippocampal NO was shown to play a role in the antidepressant-like effect of ketamine (Liebenberg et al., 2015). Our lab found that nNOS knockout mice possess an antidepressant-like phenotype (Zhou et al., 2007). More importantly, we found that chronic stress caused overexpression of nNOS in the hippocampus and inhibition of nNOS activity reversed chronic stress-induced depressive behaviors (Zhou et al., 2011a, 2007). Repeated treatment with 7-NI (30 mg/kg), at which dose increased BDNF protein levels in the hippocampus, attenuated learned helplessness development (Sherwin et al., 2017). Although the selectivity of 7-NI was concerned, the dose exerting antidepressive effect (30 mg/kg) did not changed the enzymatic activities of iNOS and eNOS (Zhou et al., 2007). Additionally, it was shown that repeated administration of TRIM improved the depression behavior of mice exposed to chronic stress (Mutlu et al., 2009).

Altogether, extensive evidence indicates that the nNOS-NO-sGC pathway plays an important role in depression-related behavior and the signaling of 5-HT in the hippocampus is implicated in the antidepressive effect of nNOS inhibitors (Table 2).

nNOS as the target of stress

Life stress is a primary cause of depression (Bech, 2005). The cortex, hippocampus, amygdala, and the HPA axis are all involved in the pathology of depression (Krishnan and Nestler, 2008; Shelton, 2007). Increasing data suggest that life stress leads to enhancement of nNOS expression and activity in these brain regions. Acute restraint stress evoked an increase in the content of NO_2/NO_3 in the dorsal hippocampus (Moraes-Neto et al., 2014). Five days after a single or repeated restraint stress, there was an additional increase in NADPH- or nNOS-

Table 2
Antidepressant properties of nNOS inhibitors.

Drugs	Species	Condition	Treatment	Test (post treatment)	Mechanism
L-NAME	Rat	Physical state	50 mg/kg, i.p., 1 time	FST (30 min)	Nitric Oxides (Jefferys and Funder, 1996)
	Mice	Physical state	10 mg/kg, i.p., 1 time	FST (1 hour)	Nitric Oxides (Harkin et al., 1999; Zhu et al., 2018)
	Mice	Physical state	5mg/kg, i.p., 1 time	FST (1 hour)	Nitric Oxides (Chaudhari et al., 2010)
	Mice	Physical state	5mg/kg, i.p., 1 time	FST (1 hour)	5-HTR1 A/5-HTR1B (Chaudhari et al., 2010)
	Mice	Physical state	5mg/kg, i.p., 1 time	FST (1 hour)	Adrenergic system (Chaudhari et al., 2010)
	Mice	LPS treatment	30 mg/kg, i.p., 1 time	FST, SPT (24 hours)	NO-cGMP pathway (Tomaz et al., 2014)
	Mice	Clonidine treatment	10 mg/kg, i.p., 1 time	FST (1 hour)	NA (Chaudhari et al., 2010)
	Mice	Reserpine treatment	10 mg/kg, i.p., 1 time	FST (1 hour)	NA (Chaudhari et al., 2010)
L-NMMA	Mice	Physical state	30 mg/kg, i.p., 1 time	FST (1 hour)	Nitric Oxides (Harkin et al., 1999)
L-NA	Rat	Physical state	20 mg/kg, i.p., 1 time	FST (1 hour)	5-HT (Harkin et al., 2003)
	Rat	Physical state	10 mg/kg, i.p., 1 time	FST (1 hour)	Neuronal activation in the DG, CA1, and DRN (Sherwin et al., 2017)
	Mice	Physical state	1 mg/kg, i.p., 1 time	FST (1 hour)	Nitric Oxides (Karolewicz et al., 2001)
	Mice	Physical state	10 mg/kg, i.p., 1 time	FST (5 or 24 hours)	5-HT, 5-HTR2 A, 5-HTR2C (Gigliucci et al., 2010)
7-NI	Rat	Physical state	Intrahippocampal injection, 100nmol	FST (30 min)	Nitric Oxides in the dorsal hippocampus (Joca and Guimaraes, 2006)
	Rat	Physical state	30 mg/kg, i.p., 1 time	FST (1 hour)	5-HT (Silva et al., 2012)
	Rat	Physical state	20 mg/kg, i.p., 1 time	FST (1 hour)	5-HT (Harkin et al., 2003)
	Mice	Physical state	50 mg/kg, i.p., 1 time	FST (50 min)	Nitric Oxides (Volke et al., 2003)
	Mice	Physical state	50 mg/kg, i.p., 7 days	FST (1 hour)	Hippocampal 5-HT (da Silva Leal et al., 2017)
	Mice	Chronic stress	30 mg/kg, i.p., 4 days	Coat State, FST, TST (1 month)	Hippocampal neurogenesis (Zhou et al., 2007)
	Mice	Corticosterone	30 mg/kg, i.p., 7 days	FST, TST, SPT (1 month)	Glucocorticoids receptor (Zhou et al., 2011a)
	Mice	Learned helplessness	30 mg/kg, i.p., 7 days	LH development (24 hours)	Hippocampal BDNF level (Sherwin et al., 2017)
TRIM	Rat	Physical state	50 mg/kg, i.p., 1 time	FST (50 min)	5-HTR1 A (Ulak et al., 2010)
	Rat	Physical state	50 mg/kg, i.p., 1 time	FST (1 hour)	Neuronal activation in the DG, CA1, and DRN (Sherwin et al., 2017)
	Mice	Physical state	50 mg/kg, i.p., 1 time	FST (50 min)	Nitric Oxides (Volke et al., 2003)
	Mice	Chronic stress	30 mg/kg, i.p., 35 days	Coat State, Splash test (3 weeks)	Nitric Oxides (Mutlu et al., 2009)
NPA	Rat	Acute stress	Intrahippocampal injection, 0.01 pmol	FST (1 hour)	Hippocampal 5-HTR1 A (Hiroaki-Sato et al., 2014)
	Rat	Acute stress	Intrahippocampal injection, 0.001 nmol	FST (24 hours)	NO-sGC pathway in the dorsal hippocampus (Sales et al., 2017)

NA means no answer.

positive neurons in the CA1, CA3 sub-region of the hippocampus, and the entorhinal cortex (Echeverry et al., 2004). In addition, 21 days CMS exposure increased nNOS expression in all fields of the hippocampus (CA1, CA3, DG, and subiculum) (Zhou et al., 2011a, b). The total hippocampal nNOS activity, nNOS protein levels and mRNA expression were increased after stress in the Flinders rat, a genetic animal model of depression (Wegener et al., 2010).

After 2 h of immobilization stress, nNOS mRNA expression in the anterior pituitary and adrenal cortex was up-regulated with 1.5 and 2-fold respectively (Kishimoto et al., 1996). The nNOS mRNA signals in hypothalamic paraventricular nucleus (PVN) significantly increased after the stress for 6 h (Joung et al., 2012). However, some studies showed that NOS$^+$ cell density and number in the PVN were significantly decreased in rats after chronic stress, and in humans with depression (Gao et al., 2014; Bernstein et al., 1998; de Oliveira et al., 2000). Thus, how nNOS changes in the PVN after stress or in patients with depression require more evidence. Acute restraint stress induced a significant increase in the density of neurons expressing NADPH-d and nNOS in the amygdala nuclei (Echeverry et al., 2004). In addition, a significant increase of NOS enzyme activity in the anterior pituitary, adrenal cortex, and adrenal medulla was observed in the stressed animals (immobilization of 6 h) as compared to non-stressed control rats (Kishimoto et al., 1996; Krukoff and Khalili, 1997).

NO primarily mediates the biological function of nNOS (Zhou and Zhu, 2009). Researchers provide evidence that NO mediates the function of nNOS after stress exposure. An early study found elevated plasma nitrate levels in patients with major depression compared with both patients with anxiety disorder and normal control subjects (Suzuki et al., 2001). It was also showed that plasma NOx levels among suicidal depressive patients are higher than among non-suicidal depressive patients and normal controls (Kim et al., 2006). More specifically, stress caused activation of NO-producing neurons in the brain of rat (Krukoff and Khalili, 1997). Furthermore, following treatment of depressed patients with paroxetine, levels of serum nitrate and nitrite, both of which are degradation products of NO, was significantly reduced. The same authors showed that paroxetine indeed inhibited conversion of L-arginine to citrulline and NO in vitro (Kim et al., 2006). Consistently, NO levels in the plasma were significantly increased in rats exposed to chronic unpredictable stress (Gao et al., 2014). Our previous work demonstrated that hippocampal injection of SIN-1 induced depressive behavior in mice and clearance of NO by c-PTIO in the hippocampus counteracted chronic stress-induced depressive behavior (Zhou et al., 2011a). Collectively, increasing evidences show that nNOS located in several regions of the CNS such as the hippocampus, hypothalamus and pituitary is reactive to stress stimuli, indicating an important role of nNOS in the development of MDD.

The role of nNOS in serotonergic signaling in depression

The monoamines including 5-HT, NA, and DA are involved in the pathogenesis of affective disorders (Shelton, 2007; Hornykiewicz, 1974). Particularly, the role of the 5-HT pathway is well established and recognized in the pathogenesis of depression (Castren, 2005). A deficiency of 5-HT was discovered very early from post-mortem studies of patients with major depression [Hornykiewicz, 1974; Shaw et al., 1967; Asberg et al., 1976]. Based on this result, several types of antidepressants increasing the concentration of 5-HT in the synaptic cleft were developed. In the brain, several places including the hippocampus, amygdala, frontal cortex, and hypothalamus (post-synaptic tissues) receive serotonergic input from the DRN (pre-synaptic tissues). The dysfunction of serotonergic neurons is found both in the pre-synaptic tissues and post-synaptic tissues. The central theory of depression supported by these findings is called 'Monoamine-Deficiency Hypothesis' or 'Monoamine theory'. Nitric oxide is ubiquitously

synthesized by nNOS in these tissues, playing a fundamental role in extensive physiological and pathological processes. The coexistence of the two transmitters offers the high probability that they act together in depression.

A growing body of evidence suggest that nNOS regulates the synthesis, release, and uptake of 5-HT. Tryptophan hydroxylase (TH), the rate-limiting enzyme in biosynthesis of 5-HT, is inactivated by ONOO·, which is mediated by sulfhydryl oxidation, in a concentration-dependent manner (Kuhn and Geddes, 1999; Kuhn et al., 1999; Ara et al., 1998). In addition, NO donor S-nitroso-N-penicillamine (SNAP) was shown to decrease 5 H T release in the raphe nucleus but increase release in the frontal cortex (Smith and Whitton, 2000). Both local infusion of 7-NI into the hippocampus and systemic administration significantly increased extracellular level of 5-HT (Segieth et al., 2001). Consistently, Chiavegatto et al revealed that nNOS knockout mice had increased levels of 5-HT in several brain regions regulating emotion, including cerebral cortex, hypothalamus, hippocampus, and amygdala (Chiavegatto et al., 2001). In contrast, administration of L-Arg, the substrate for catalyzing NO, decreased the level of 5-HT in the hippocampus (Strasser et al., 1994). Sodium nitroprusside (SNP), a NO donor, inhibited the uptaking of 5-HT into synaptosomes in the rat brain without effecting the 5-HT transporter (Asano et al., 1997). However, other types of NO donors such as (Z)-1-[N-methyl-N-[6-(N-methy-lammoniohexyl)-amino]]diazen-1-ium-1,2-diolate (MAHMA/NO) and 5-amino-3-(4-morpholinyl)-1,2,3-oxadiazolium chloride (SIN-1) inhibited 5-HT uptake by SERT in COS-7 cells expressing human SERT (Bryan-Lluka et al., 2004). In an early study, it was shown that SERT was transformed into an inactive form to reduce 5-HT in the presence of 3-morpholinosydnonimine, a nitric oxide donor or endogenous nitric oxide synthase was activated (Fossier et al., 1999). The activation of NMDA receptors has been substantially linked to the production of the signaling molecule NO in the CNS (Garthwaite, 1995). Previous studies demonstrated that the NMDA receptor antagonists, MK-801 and D-AP5, increased extracellular levels of 5-HT and DA in the ventral hippocampus in vivo (Whitton et al., 1994). Thus, it is possible that endogenous NO functions through negative control of the levels of 5-HT in the hippocampus. Furthermore, the antidepressive effect of inhibition of NO synthase depends on the level of 5-HT (Harkin et al., 2004, 2003). In the hippocampus, postsynaptic 5-HTR1 A is an important signal mediator of 5-HT (Zhang et al., 2010). Post-mortem studies find diminished 5-HTR1 A numbers and lowered receptor affinity in the hippocampi of depressed suicide victims. Stress and high concentration of glucocorticoid similar to the level under stressful conditions stimulates a great quantity of NO production by up-regulating nNOS expression and activity in the hippocampus (Zhou et al., 2011a). Both glucocorticoid and chronic stress also have been shown to induce downregulation of 5-HT$_{1A}$ receptor density and messenger RNA (mRNA) content in the hippocampus. Additionally, our research found that NO donor DETA/NONOate (100 μM) depressed hippocampal 5-HTR1 A expression in vitro and in vivo (data not published). These data together let us postulate that high concentration of glucocorticoids responding to the stimulation of stressful life events enhance nNOS function in the hippocampus. Therefore, endogenous NO derived from nNOS under chronic stressful stimuli in the hippocampus may participate in the pathophysiology of depression by negatively regulating the 5-HT pathway (Fig. 2).

Interestingly, nNOS in turn works in downstream of the 5-HT cascade. Activation of hippocampal 5-HTR1 A inhibits postsynaptic Ca^{2+} influx through the NMDARs. Serotonin 5 H TR1B agonists abolished NMDAR-evoked enhancement of NOS activity. Administration of serotonergic antidepressants decreased hippocampal nNOS activity (Wegener et al., 2003; Luo and Tan, 2001). Interestingly, other lines of antidepressant targeting NA and DA also involved in suppression of NOS (Krass et al., 2011; Ostadhadi et al., 2016b). Methylene blue with structural similarities to tricyclic antidepressants had antidepressant properties. It was also found that methylene blue treatment reduced
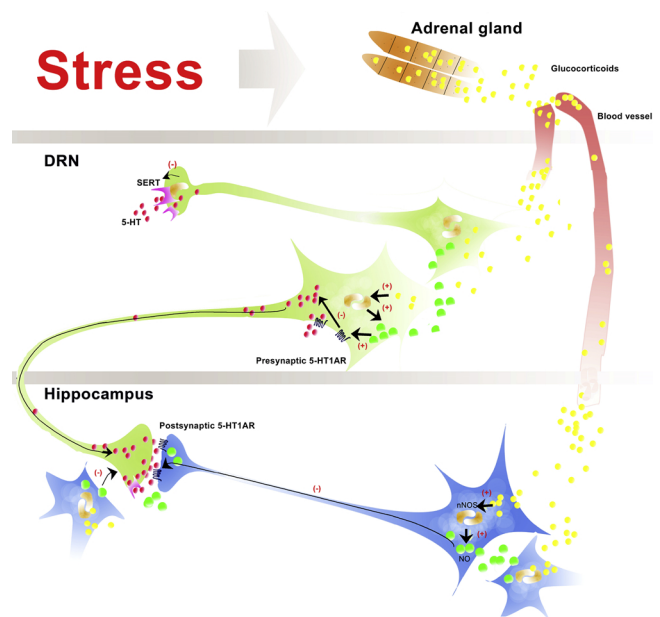

Fig. 2. The interaction between nNOS and serotonergic signaling in depression.

hippocampal nitrate levels (Harvey et al., 2010). The antidepressant-like effect of bupropion [(+/-)-alpha-t-butylamino-3-chlor-opropiophenone], a dopamine reuptake inhibitor, was prevented by pretreatment with L-arginine, the substrate for nitric oxide synthase. Additionally, pretreatment of mice with 7-nitroindazole potentiated the effect of bupropion (Dhir and Kulkarni, 2007b). Treatment with nNOS inhibitor, 7-nitroindazole, augmented the behavioral effects of imipramine and fluoxetine, respectively (Harkin et al., 2004). The antidepressant-like effect of venlafaxine (8 mg/kg, i.p.) was prevented by pretreatment with L-arginine (750 mg/kg, i.p.), the substrate for nitric oxide synthase, demonstrating that the antidepressant-like effect of venlafaxine in the FST involved an interaction with the L-arginine-NO-cGMP pathway (Jesse et al., 2010, 2008; Dhir and Kulkarni, 2007a). An article found that treatment with 1-(2-trifluoromethylphenyl)-imida-zole (TRIM) (20 mg/kg), a nNOS inhibitor, augmented the behavioral effect of tricyclic antidepressant imipramine, selective serotonin reuptake inhibitor (SSRI) citalopram and fluoxetine or selective serotonin reuptake enhancer tianeptine (Ulak et al., 2008). Although pretreatment with L-arginine counteracted the antidepressant-like effect of imipramine, venlafaxine, bupropion but not fluoxetine, our research revealed that the blockage of nNOS accounted for the modulation of anxiety-related behavior of fluoxetine (Zhang et al., 2010(Krass et al., 2011).

DRN as the resource of 5-HT is critically linked to the occurrence of depressive symptoms and the effects of antidepressants (Soiza-Reilly and Commons, 2014). However, the role of DRN in depression is completely different from the hippocampus. In the DRN, 5-HT reduces the firing rate of neurons by stimulating the 5-HTR1 A which serves as the predominant autoreceptor, implicated in mental illness (Albert et al., 2011). Higher raphe autoreceptor binding and expression are detected in patients with depression and in post-mortem raphe tissue from depressed suicide victims (Stockmeier, 1997; Stockmeier et al., 1998). Moreover, these autoreceptors desensitized after 2–3 weeks of antidepressant treatments (Gray et al., 2013). A recent study demonstrates that 5-HT1 A autoreceptor levels determine vulnerability to stress and response to antidepressants (Richardson-Jones et al., 2010). A large number of nNOS immunoreactive cells co-labeled with 5-HT or SERT are found in the DRN (Chanrion et al., 2007b; Lu et al., 2010). Moreover, a study found that 7-NI, a selective nNOS inhibitor, decreased raphe 5-HT release with a concomitant increasing in the frontal cortex. Chanrion et al. found that nNOS had a physical association with

the SERT by PDZ domain, reducing SERT activity in DRN (Chanrion et al., 2007a). The expression of nNOS or the interaction between nNOS and SERT in the DRN may be regulated by elevated glucocorticoids after stress, accounting for the dysfunction of the postsynaptic serotonergic pathway (Fig. 2).

This model describes the potential role of the interaction between nNOS and serotonergic signaling in depression. Increased glucocorticoids after stress arrive at the hippocampus and DRN via circulation. In the hippocampus, glucocorticoids up-regulate the expression of nNOS, causing reduced postsynaptic 5-HT$_{1A}$R content. In the DRN, glucocorticoids modulate the 5-HT release by influencing the interaction between nNOS and SERT.

nNOS in the hyperactivity of HPA axis

The HPA axis is a multifaceted regulatory system that integrates neuronal and endocrine function (de Kloet et al., 2005b, c). It comprises the tissues of the hypothalamus, pituitary and adrenal cortex, and the associated regulatory inputs, releasing factors and hormones. In brief, the neurosecretory cells of the PVN of the hypothalamus secrete CRF and arginine vasopressin (AVP) into the circulatory system of the pituitary stalk. These hormones induce the release of ACTH from the anterior lobe of the pituitary into systemic circulation. In turn, ACTH, promotes the release of the glucocorticoids (cortisol in human, corticosterone in rodent) from the adrenal cortex (Lupien et al., 2009b). The effects of glucocorticoids are mediated mainly by two types of intracellular, specialized steroid receptor family subtypes (de Kloet et al., 2005b): type I, the high-affinity mineralocorticoid receptor (MR), and the type II, low-affinity glucocorticoid receptor (GR). Decreased levels of GR in the hippocampus are thought to be the primary etiology of HPA axis hyperactivity in depression. Hyperactivity of the HPA axis is a characteristic feature of depressive illness. New data suggested an important role of the nNOS-NO pathway in HPA axis hyperactivity (Zhou et al., 2011a).

The hippocampus is the primary negative regulator of HPA axis activity in the brain (Jankord and Herman, 2008). The loss of this negative control contributes to HPA axis hyperactivity after chronic stress (Herman et al., 1989). Glucocorticoids mediate chronic stress-induced hippocampal nNOS overexpression via activating MR (Zhou et al., 2011a; Zhu et al., 2014a). In turn, hippocampal excessive NO significantly down-regulates local GR expression through soluble guanylate cyclase (sGC)/cGMP and ONOO·/extracellular signal-regulated kinase signaling pathways (Zhou et al., 2011a) (Fig. 3). By creating transgenic mice blocking neurogenesis, Snyder et al. showed that killing newborn neurons in the adult hippocampus causes elevated HPA axis activation, contributing to the etiology of depression (Snyder et al., 2011). Therefore, overexpressed nNOS in the DG may lead to HPA hyperactivity via reduction of hippocampal neurogenesis.

The PVN of the hypothalamus, which drives the HPA axis, provides a negative feedback of the activity of the HPA axis. The mRNA of nNOS is detected in the PVN in rats by *in situ* hybridization histochemistry (Kurose et al., 2001). The NO generated in the PVN is involved in regulating HPA axis activity (Reis et al., 2003). Direct intracerebroventricular injection of NO donor 3-morpholino-sydnonimine (SIN-1) up-regulated transcription of CRF and vasopressin in the PVN, causing increased releasing of adrenocorticotropic hormone (ACTH) (Lee et al., 1999). In contrast, intracerebroventricular injection of S-nitroso-N-acetylpenicillamine (SNAP), which spontaneously breaks down to form NO, caused a transient dose-related decrease in the plasma vasopressin concentration (Ota et al., 1993). Administration of 7-nitroindazole (7-NI), a specific neuronal inhibitor of nNOS abolished the stimulatory action of CRF on ACTH (Gadek-Michalska and Bugajski, 2008). However, no evidence shows that excessive amount of NO is produced in the PVN in patient with MDD or in animal model of depression. While the expression level of nNOS mRNA is up-regulated by nociceptive and endotoxin stimulation, the nNOS expression in the PVN

is not altered by stress (Zhu et al., 2014a; Uribe et al., 1999). Although glucocorticoids elevated throughout the body including the hippocampus and the hypothalamus, nNOS in the PVN of the hypothalamus does not contribute to HPA axis hyperactivity due to a low level of MR in the PVN compared with the hippocampus (Zhu et al., 2014a) (Fig. 3).

This model describes the mechanism of the different roles of glucocorticoids in the hippocampus and hypothalamus in modulation of the HPA axis. Acute stress-stimulated glucocorticoids bind to MR in the hippocampus, up-regulating nNOS expression and NO production. The excessive NO down-regulates GR via the sGC/cGMP pathway, impairing the negative feedback modulation of the synthesis of CRF in PVN neurons in the hypothalamus. However, glucocorticoids in the hypothalamus exert negative regulation on the synthesis of CRF in PVN neurons due to a lack of MR content in the hypothalamus.

The role of nNOS in neurogenesis: implication in depression

In the last decade, it has been shown that neurogenesis persistently occurs mainly in two regions of adult brain: the subventricular zone (SVZ) of lateral ventricle (LV) and the subgranular zone (SGZ) of the hippocampus (Lledo et al., 2006; Gould, 2007). Clinical studies suggest decreased hippocampal volume which was consistent with decreased neurogenesis and neuron degeneration in patients with depression (Sapolsky, 2000). The causal relationship between hippocampal neurogenesis and depression is supported by multiple aspects of research. (i) Different types of stress cause reduced neurogenesis in the DG of the hippocampus. (ii) Almost all antidepressant therapies stimulate the hippocampal neurogenesis. (iii) Hippocampal neurogenesis is required for the behavioral effects of antidepressant (Santarelli et al., 2003; Henn and Vollmayr, 2004; Steckler and Prickaerts, 2004; Sapolsky, 2004). Therefore, in recent years, decreased hippocampal neurogenesis is considered a common pathway of the etiology of depression. The molecules involved in the modulation of hippocampal neurogenesis may be a novel target for developing antidepressant in the future.

nNOS is an endogenous factor that dampens the neurogenesis in the adult brain (Packer et al., 2003). The number of new cells generated in the hippocampus is strongly augmented in nNOS knockout mice(Zhou et al., 2007; Packer et al., 2003). Administration of nNOS inhibitors increases proliferation of neural stem cells (NSCs) and survival rate of newborn neurons in the adult hippocampus (Zhou et al., 2007; Fritzen et al., 2007; Luo et al., 2007). The antidepressant effects of nNOS inhibition requires hippocampal neurogenesis (Zhou et al., 2007). Chronic stress up-regulates the expression of nNOS in the hippocampus (Zhou et al., 2007). Overexpression of nNOS-induced reduction in hippocampal neurogenesis contributes to the depressive behavior after chronic stress (Zhou et al., 2007). It has been shown that glucocorticoids decreases new cell formation in the hippocampus (Cameron and Gould, 1994; Cameron and McKay, 1999; Gould and Tanapat, 1999). The elevation of corticosterone, the glucocorticoids in rodents, accounts for the nNOS overexpression in the hippocampus induced by stress (Zhou et al., 2011a). Corticosterone represses the proliferation of progenitor cells in the hippocampus in part through increased nitric oxide formation (Pinnock et al., 2007).

Telomerase, which maintains the length of telomere by adding DNA bases, is crucial for prolonged persistence of stem cells (Rufer et al., 1999; Sarin et al., 2005; Zhou et al., 2017). Telomerase reverse transcriptase (TERT) knockout mice exhibit aggressive and depressive phenotypes (Zhou et al., 2016). Inhibition of TERT activity by 3′-azido-deoxythymidine (AZT) generates depression-like behavior and suppresses hippocampal neurogenesis. Meanwhile, overexpression of TERT exerts antidepressant-like effect, which is blocked by the disruption of hippocampal neurogenesis via X ray-irradiation (Zhou et al., 2011b). Most notably, repression of TERT catalytic activity counteracts the antidepressant-like effects of nNOS inhibition (Zhou et al., 2007). It is possible that nNOS interacts with TERT in regulating hippocampal neurogenesis and depressive mood.
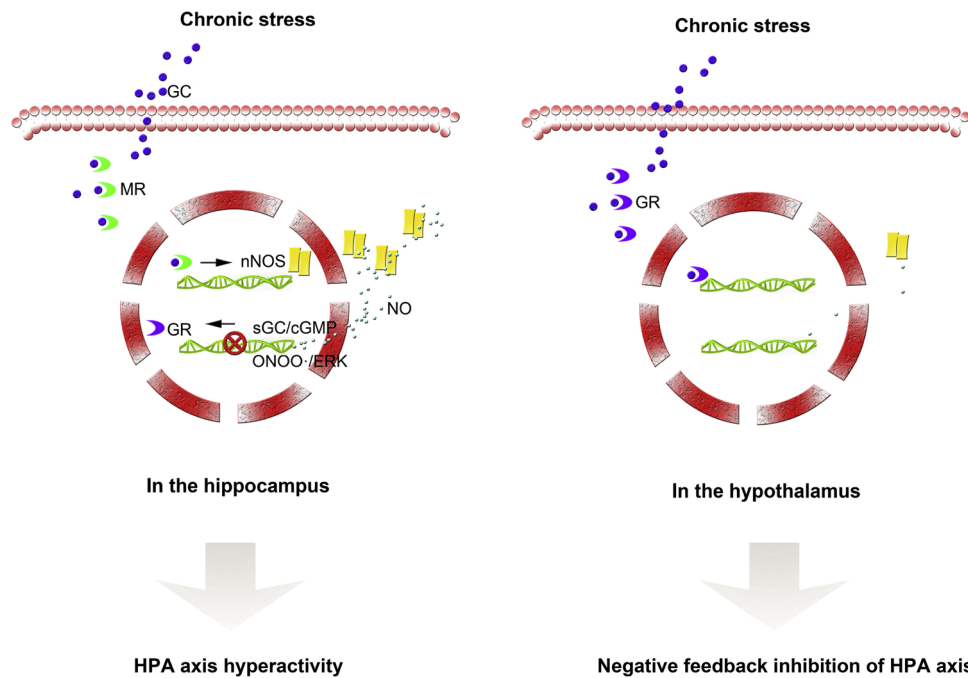
Fig. 3. The role of nNOS in regulating the HPA axis.

The role of nNOS in depression: the gender difference

Neurological illnesses, such as MDD, Alzheimer's disease (AD), anxiety disorders, schizophrenia, stroke, autism, and addiction, show sex differences in their incidence (Shors, 2002; Klein and Corwin, 2002; Jazin and Cahill, 2010). Sexual dimorphism including behavioral differences, anatomic characteristics, and molecular distinctions generally exists in the brain of different genders [Jazin and Cahill, 2010; Godfroid, 1999). These substantial differences underlie the sex gap in neurological disorders (Fischette et al., 1983; Chiari et al., 1999). Markedly, men and women exhibit significant sex differences in the development of depression and anxiety disorder (Payne et al., 1983). Notably, epidemiological investigations found that the prevalence of MDD for women is much higher for men (Gordon and O'Dell, 1983). Gender differences were demonstrated in both monoamine transmitter system and HPA axis, which may be the fundamental bases for differential susceptibility to MDD. Sex differences in monoaminergic changes, including serotonin, norepinephrine as well as dopamine, and their receptors expression and binding were observed between male and female rats (Fischette et al., 1983; Zhang et al., 1999; Dervola et al., 2015; Bernardi et al., 2015; Pohjalainen et al., 1998; Bangasser et al., 2016, 2013). Pronounced sex differences in several aspects of basal HPA axis function were documented: 1) Higher secretion and concentration of corticosterone was detected in females; 2) Females exhibited a greater duration of HPA in response to stressors (Oldehinkel and Bouma, 2011; Uhart et al., 2006; Seeman et al., 2001). Although extensive sex dimorphism in gene expression levels in the rodent brain were observed (Yang et al., 2006), the underlying molecular mechanisms for gender difference in MDD are not well characterized.

Sex hormones including testosterone and estrogen contribute to the mental state via androgen receptor (AR) and estrogen receptor (ER) in different gender (Fink et al., 1996, 1998). Interestingly, it was found that estrogen rather than testosterone determined the gender difference in the expression level of nNOS. An early study found that estrogen stimulated the expression of nNOS and the production of NO in human neutrophils, whereas a reduction of nNOS in the adult hippocampus was detected after estrogen treatment in later studies (Garcia-Duran et al., 1999; Grohe et al., 2004; Hu et al., 2012b). It was shown that ERα involved in the regulation of nNOS in preoptic area while ERβ was

responsible for the nNOS expression change in the hippocampus [Hu et al., 2012b; Scordalakes et al., 2002). The regulation of nNOS by estrogen may be involved in the estrogen-mediated neuroprotective effect(Wen et al., 2004). Several researches demonstrated that chronic stress increased nNOS expression and activity in the hippocampus of male mice and rat, contributing to stress-induced depressive behavior (Zhou et al., 2007; Wegener et al., 2010; Chen et al., 2015). In contrast, the expression of nNOS in the hippocampus was diminished after chronic stress in female mice, accounting for stress-related deficit in learning and memory (Palumbo et al., 2007). In our lab, Hu et al found a much higher basal level of NO in the hippocampus of male mice than female mice [Hu et al., 2012b]. The diversity was caused by different expression level of nNOS in the hippocampus, which due to the repressive regulation of nNOS expression by estrogen via ERβ, accounting for the sex difference in depression-like behaviors [Hu et al., 2012b]. Additionally, it was shown that endogenous estradiol promoted NMDA receptor/PSD-95/nNOS coupling in the hypothalamic preoptic region of adult female rats (d'Anglemont de Tassigny et al., 2007, 2009). Interestingly, another study showed that acute stress increased the expression of nNOS in the hippocampus of female but not male rats (Keser et al., 2011). These evidences indicate that nNOS is an important downstreamer of endogenous estrogen signaling, contributing to the modulation of neural function by the female sex hormones.

nNOS and BPD

BPD, also known as manic-depressive illness, is characterized by recurrent shifted episodes of mania and depression as well as changes in psychovegetative function and cognitive performance, and it is one of the most severely debilitating of affective illnesses (Schloesser et al., 2008). BPD affects more than 1% of the world's population and is one of the leading causes of disability among young people (Grande et al., 2016). According to the longitudinal course, BPD is classified into four basic types including Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and other specified and unspecified bipolar and related disorders. Although depressive symptoms of BPD and MDD are diagnosed by the same HAM-D, certain features are used to discriminate them. More frequent depressive episodes, shorter duration of sadness, abrupt onset and offset and earlier onset age are characterized in BPD

(Grande et al., 2016). Compared with MDD, the key manic symptoms of BPD, including extremely energized, elation, grandiosity, and increased goal activity, is unique.

The understanding of the neurobiological underpinnings of BPD is elucidated by preclinical and clinical researches. The monoamine neurotransmitters are implicated in the etiology of bipolar disorder. Similar abnormalities of the serotonergic and dopamine system in depression have been found in some studies of BPD (Goodwin and Jamison, 2007; Zarate et al., 2006). However, increased noradrenergic function has been observed in mania (Goodwin and Jamison, 2007). Interestingly, significant reductions in cortex GABA levels are only detected in depression, not in BPD (Sanacora et al., 1999; Krystal et al., 2002). Chronic treatment with lithium increases uptake of glutamate at the synaptosome in mice (Dixon and Hokin, 1998) and reduces glutamate-induced and NMDA-mediated excitatory toxicity (Nonaka and Chuang, 1998). Hyperactivity of the HPA axis is also detected in many patients with BPD (Young et al., 2004).

Altered NO signaling has been associated with the pathophysiology of BPD (Baggott and Singh, 2004). Significantly lower level of NOx-including NO_2- and NO_3- levels were observed in peripheral blood of patients suffering from BPD (Kittel-Schneider et al., 2015). Consistently, another clinical study reported that patients with BPD showed reduced NOS activity in platelets compared with health volunteers (Fontoura et al., 2012). Additionally, lithium, a classic medicine for treatment of BPD, increased the level of NO in patients with BPD during depressive episodes (de Sousa et al., 2014). However, contrary results were observed by other groups, reporting that the value of plasma NO levels and total nitrite level in the BPD patients were higher than those of controls (Savas et al., 2002; Yanik et al., 2004). Especially, elevated serum NO was detected in patients with BPD in euthymic phase (Savas et al., 2006). Thus, the correlation between NO in the blood and BPD requires more study. Nevertheless, NO metabolites in the plasma may serve as biomarkers for BPD.

The LC is a nucleus in the brainstem involved in sympathetic effects during stress. The LC comprises the largest group of NA containing neurons in the mammalian brain and the number of NE neurons is reduced in depressed bipolar suicides (Wiste et al., 2008). The LC also harbors a high density of NMDARs (Allgaier et al., 2001; Van Bockstaele and Colago, 1996), activating which result in higher activation of nNOS. It was found that the amounts of NR2C subunit of NMDAR were significantly higher in the LC of patients with BPD, implying a role of nNOS in BPD. Indeed, nNOS locates in norepinephrinergic neurons in the LC, generating NO, suggesting the existence of a glutamate/nitrergic transduction pathway in monoamine neurotransmitter neurons (Bielau et al., 2012a). A postmortem study suggested that nNOS protein level in the LC of depressive subjects is significantly lower than controls (Karolewicz et al., 2004). Similarly, a lower number of nNOS-immunoreactive neurons was detected in the LC of postmortem human suffered from BPD than healthy controls (Bielau et al., 2012a; Bielau et al., 2012b). However, there is lack of correlation between nNOS gene expression and the occurrence of BPD (Silberberg et al., 2010). The nucleotide polymorphism of rs41279104 in nNOS gene had been shown no significant association with BPD (Okumura et al., 2010). These sparked reports indicate that the impairment of nNOS may due to cell loss rather than genetic level alteration. The literature is poor, future research is necessary to elucidate the mechanisms underlying the function of nNOS in the LC in the pathogenesis and etiology of BPD. Collectively, all current data strongly suggest a nNOS-related dysregulation of the nitrergic system in the LC related to the pathology of BPD.

nNOS and Anxiety

Anxiety is a crucial and adaptive behavioral response to dangerous situations. Transient anxiety elicits appropriate responses to protect the body (Millan, 2003). Anxiety disorders are a common group of mental disorders, characterized by long-lasting anxiety, which is accompanied by a characteristic series of physiological and behavioral responses including vigilance, avoidance and arousal (Gross and Hen, 2004). According to the Diagnostic and Statistical Manual of the American Psychiatric Association, anxiety disorders are divided into six discrete categories including generalized anxiety disorder (GAD), social phobia, simple phobia, panic disorder, post-traumatic stress disorder, and obsessive compulsive disorder, among which GAD is the most highly prevalent. Cognitive behavioral therapy, benzodiazepines, buspirone, and antidepressants are common treatment of anxiety disorders in clinic.

A variety of molecular targets, including neurotransmitters and transcript factors, involved in anxiety, have been revealed (Gross and Hen, 2004). Benzodiazepines (BZPs), a type of classic medicine for treatment of anxiety enhance the effect of GABA at the $GABA_A$ receptor, resulting in anxiolytic properties (Millan, 2003). The serotonergic system is extensively implicated in anxiety. Knockout of $5-HT_{1A}$ receptor leads to an anxiogenic phenotype and selective serotonin reuptake inhibitors (SSRIs) are used as the first-line compounds for clinical treatment of anxiety (Gross and Hen, 2004; Heisler et al., 1998; Ramboz et al., 1998; Gross et al., 2002). Decreased level of CREB and neuropeptide Y system (NPY) are also implicated in anxiety-related behaviors (Valverde et al., 2004; Pandey, 2003). Moreover, a perturbation of glutamatergic transmission is implicated in affective disorders including anxious states (Moghaddam, 2002).

The implication of NO in anxiety has been proposed by a series of studies (Situmorang et al., 2018; Kumar and Chanana, 2017; Gulati et al., 2017). The distribution of neurons expressing NOS in brain areas such as the medial amygdala (MeA), the dorsolateral periaqueductal grey (dlPAG), the hypothalamus, and the hippocampus indicate potential function of NO in anxiety (Vincent and Kimura, 1992; Dun et al., 1994). Benzodiazepines (BZDs), such as diazepam, are a type of early found and classic anxiolytic drug (Gross and Hen, 2004; Tan et al., 2010). Acute administration of 7-NI, a typical nNOS inhibitor, resulted in anxiolysis similar to diazepam (Dunn et al., 1998). Indeed, inhibition of nNOS activity by 7-NI treatment reduced anxiety-like responses to social stimuli in rodents (Workman et al., 2008; Volke et al., 1997). Mice lacking gene that encodes nNOS expressed abnormal anxiety levels compared to WT mice (Workman et al., 2008; Bilbo et al., 2003; Wultsch et al., 2007). It was demonstrated that the anxiolytic effect of nNOS inhibition was mediated by reduced production of NO in the brain (Joung et al., 2012). However, a serial of studies found that NO donor including sodium nitroprusside and molsidomine induced anxiolytic-like behavior (Kalouda and Pitsikas, 2015; Trevlopoulou et al., 2016). But it was not well demonstrated the effect was attributed to the generation of NO or the chemicals themselves. The interaction between NO and classic anxiolytic drugs also support an anxiolytic property of NO reduction. In our lab, Zhang et al found that repression of nNOS-NO pathway in the hippocampus accounts for the regulatory role of $5-HT_{1A}$ receptor by fluoxetine, producing anxiolytic effect (Zhang et al., 2010). The neurosteroid dehydroepiandrosterone sulphate (DHEAS) exerted anxiolytic effect, which was potentiated by NO precursor L-arginine (Ovsiukova et al., 2003; Chakraborti et al., 2011). In contrast, the anxiolytic effects of DHEAS were abolished by a type of NOS inhibitor, L-NAME, pretreatment [Chakraborti et al., 2011]. Moreover, the anxiolytic effects of morphine were partially modulated by NO [Dun et al., 1994; Joshi et al., 2015). These evidences suggest suppression of NO generation exert anxiolytic-like effect. But it is not clear whether and how over-activity of nNOS-NO signaling plays an important role in the pathogenesis of anxiety, which will be discussed in the following paragraph.

Restraint stress can induce psychological and physical changes including anxiogenic-like behavior, endocrine dysfunction, and autonomic alterations in rodents (Resstel et al., 2009; Busnardo et al., 2013, 2010). Increased nNOS expression in the PFC and hippocampus is associated with stress-triggered anxiety states (Vila-Verde et al., 2016). Besides the expression level changes, interestingly, Zhu et al found that
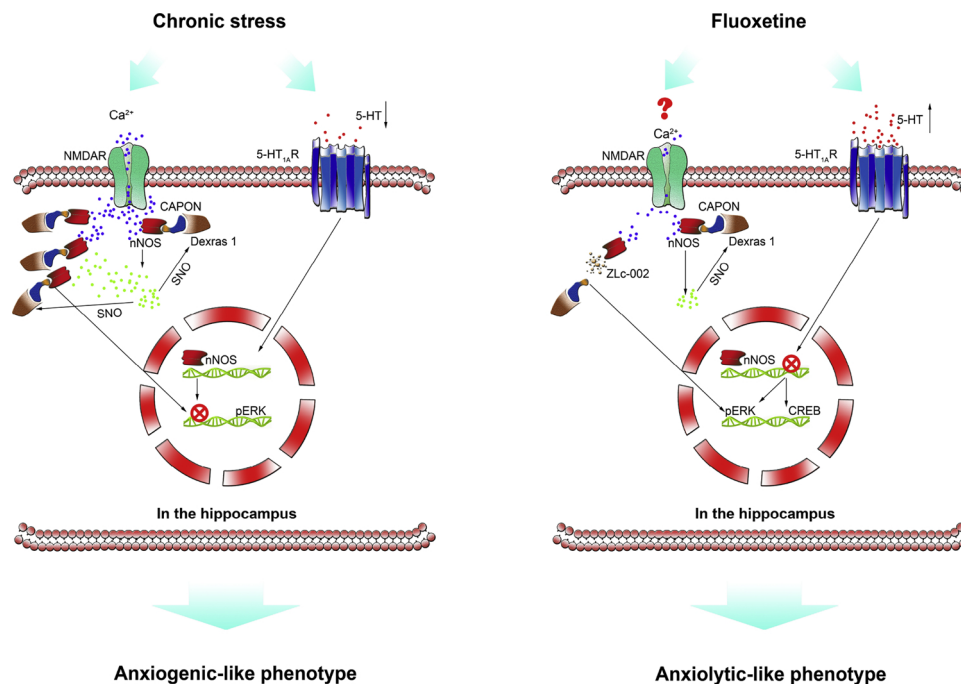
Fig. 4. Novel target for treatment of anxiety: nNOS-CAPON.

chronic mild stress caused augment of nNOS-CAPON-Dexras 1 complex in the hippocampus (Zhu et al., 2014b). Consequently, the nNOS-CAPON association led to a large amount of NO generation, resulting in a high level of S-ntriosyation of Dexras 1 binding to CAPON (Fig. 4). After S-nitrosylation, Dexras 1 down-regulated ERK phosphorylation, thereby causing anxiogenic-like phenotype (Zhu et al., 2014b). Recently, we found that this mechanism mediated the effect of NF-κB in stress-induced anxiety behaviors (Zhu et al., 2018). Decreased 5-HT in the hippocampus after stress contributes to the etiology of anxiety. Silencing of 5-HTR1 A signaling up-regulated the expression of nNOS in the hippocampus, regulating anxiety-related behaviors (Zhang et al., 2010). The nNOS-NO pathway have strong suppressive effect on ERK phosphorylation (Cai et al., 2017). Collectively, the dysfunction of 5-HTR1 A and the excessive coupling of nNOS with CAPON have similar biological end mediating the pathology of anxiety behavior (Fig. 4). However, ERK has common and wide biological effects, rendering it not a satisfactory target for drug discovery. The disruption of nNOS : CAPON interaction only modulate ERK in certain pathway in specific cells, might representing a suitable drug target for anxiety treatment and other neuronal diseases (Li et al., 2015).

Chronic mild stress augments the nNOS-CAPON-Dexras 1 complex, repressing the phosphorylation of ERK. Disruption of the association of nNOS and CAPON reverses this process and exerts an anxiolytic effect. Fluoxetine produces anxiolytic function through down-regulating the expression of nNOS and CREB activity.

Conclusions and perspectives

In summary, nNOS is closely implicated in a wide range of pathologies and molecular mechanisms of affective disorders. The expression of nNOS in the CNS is widely distributed. In the hippocampus, nNOS tightly correlates with MDD and anxiety while the function of nNOS in the LC in the pathology of BPD attracts more attention. Besides, the role of nNOS in other places such as the cortex, hypothalamus, and dorsal raphe, *etc.* in the pathophysiology of affective disorders is also very important. Thus, we are still at the starting line for understanding the full roles of nNOS in modulating motion and mood. Due to the impairment of memory formation after nNOS activity inhibition, the development of drugs for curing affective disorders is limited.

Fortunately, uncoupling nNOS–PSD95 and nNOS-CAPON interactions did not cause this severe side effect. We believe that after further understanding of nNOS and its signaling mechanism and the expected development of new technologies, nNOS will be an important target for treatment and cure of affective disorders.

Conflict of interest

The Authors declare they have no conflict of interest.

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