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REVIEW

Nitric oxide signalling and antidepressant action revisited

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Abstract

Studies about the pathogenesis of mood disorders have consistently shown that multiple factors, including genetic and environmental, play a crucial role on their development and neurobiology. Multiple pathological theories have been proposed, of which several ultimately affects or is a consequence of dysfunction in brain neuroplasticity and homeostatic mechanisms. However, current clinical available pharmacological intervention, which is predominantly monoamine-based, suffers from a partial and lacking response even after weeks of continuous treatment. These issues raise the need for better understanding of aetiologies and brain abnormalities in depression, as well as developing novel treatment strategies. Nitric oxide (NO) is a gaseous unconventional neurotransmitter, which regulates and governs several important physiological functions in the central nervous system, including processes, which can be associated with the development of mood disorders. This review will present general aspects of the NO system in depression, highlighting potential targets that may be utilized and further explored as novel therapeutic targets in the future pharmacotherapy of depression. In particular, the review will link the importance of neuroplasticity mechanisms governed by NO to a possible molecular basis for the antidepressant effects.

Keywords Depression · Nitric oxide · Antidepressants · Neuroplasticity · BDNF

Introduction

Depression is a severe psychiatric condition with a lifetime prevalence of ca. 20% worldwide (Hasin et al. 2018; Kessler and Bromet 2013). Depression is associated to increased risk of all-cause mortality (Lasserre et al. 2016) and a reduced life expectancy of 7–14 years has been reported (Chang et al. 2011; Laursen et al. 2016). Depression is the leading cause of disability worldwide, responsible for 7.5% of years lived with disability and it contributes to 2.5% of the global burden of disease, corresponding to more than 70 million disability-adjusted life years (DALYs) (Vos et al. 2017). Similarly, in a European material, affective disorders are among the most costly diseases (110 billion Euro) and anxiety disorders among the most prevalent (Olesen and Leonardi 2003; Olesen et al. 2008; Wittchen et al. 2011). It has been estimated that the global economy loses about $1 trillion every year in productivity due to depression and anxiety and that the appropriate treatment of depression would result in a large economic productivity gain of $230 billion (Chisholm et al. 2016). Although research indicates that antidepressants are overall effective for treatment of depression (Cipriani et al. 2018), several weeks of treatment are required to achieve a significant mood-improving effect and a significant proportion of patients are partial or non-responders, which limit the success of the therapy for many patients. Since the introduction of the currently marketed antidepressant drugs in the 1950s to the 1980s, which all are based on monoaminergic pharmacological effects, there has been no major breakthrough in finding novel effective drug targets, despite considerable effort (Wegener and Rujescu 2013). Unfortunately, the pathogenesis and neurobiology of affective disorders is not well understood. Based on genetic and environmental factors, multiple hypotheses are proposed involving distinct pathways, for example neurotransmission (Caspi et al. 2003) and neurotrophic factors (Zhao et al. 2018). The present review will focus on the

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role of the atypical neurotransmitter nitric oxide (NO) in depression and (i) address general aspects of the NO system in depression, (ii) focus on drugs affecting NO production as putative therapeutic molecules and finally, (iii) highlight possible molecular mechanisms related to brain neuroplasticity.

Basic principles of nitric oxide signalling in the brain

Initial evidence indicating NO as a possible signalling molecule in the brain came from the seminal work by Garthwaite and colleagues (Garthwaite 2008; Garthwaite et al. 1988), showing that activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate increased the release in a Ca^{2+}- dependent manner of a diffusible messenger, which was later shown to be NO. Today, it is well known that NO is formed on demand during its enzymatic conversion from L-arginine by the enzymes NO synthase (NOS), as reviewed by Guix and co-workers (Guix et al. 2005). Briefly, the three major isoforms of NOS are neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). nNOS and eNOS are Ca^{2}–calmodulin–dependent enzymes constitutively expressed primarily in neurons and endothelial cells. However, iNOS has a high affinity for Ca^{2+}–calmodulin, thus being usually active when expressed in the cell. Under basal conditions, iNOS levels are usually very low, requiring de novo synthesis triggered by immunological or inflammatory stimulation in macrophages, astrocytes, microglia and other cells, to produce significant amounts of NO (Amitai 2010).

Abundant evidence points to the fact that all three NOS isoforms are able to affect cell signalling in the brain, with nNOS representing the major source for NO synthesis, anchored in close proximity to NMDA receptors through postsynaptic proteins (Garthwaite 2008). However, additional stimuli can trigger or inhibit nNOS activation in response to increased intracellular calcium concentration, such as the activation of muscarinic (M1 or M3) (Borda et al. 1998), purinergic (P2R) receptors (Florenzano et al. 2008) and several receptors/transport proteins relevant for serotonergic neurotransmission (Chanrion et al. 2007; Hiroaki-Sato et al. 2014; Marcoli et al. 1997; Raiteri et al. 1991) (Fig. 1).

The main cellular target for NO is the enzyme soluble guanylyl cyclase (sGC), which upon activation catalyses the conversion of cyclic guanosine monophosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP activates protein kinase G (PKG)-dependent signalling (Feil and Kleppisch 2008; Kleppisch and Feil 2009). Both nNOS and sGC are co-localized in several limbic brain regions, supporting the idea of an integrated NO-cGMP signalling system (Ding et al. 2004). In addition, NO can also nitrosylate many different proteins affecting their activity, with important consequences for neuronal signalling and neuroplasticity (Jaffrey et al. 2001). A comprehensive overview of NO-mediated mechanisms in the brain is beyond the scope of the present review and can be found elsewhere (Garthwaite 2008).

Nitric oxide and depression

Evidence from humans has not been consistent regarding nNOS expression and/or activity in post-mortem material from patients with major depression. In some studies, a reduced number of nNOS containing neurons in the paraventricular hypothalamic nucleus was observed (Bernstein et al. 2002; Bernstein et al. 1998) and a strong trend ($p < 0.06$) in decreased activity of the constitutive NOS was found in the prefrontal cortex (Xing et al. 2002) and locus coeruleus (Karolewicz et al. 2004) of patients with depression. In the brains from the Stanley Consortium, an increase in the CA1 hippocampal area nNOS immunoreactivity in depression and bipolar disorder has been reported (Oliveira et al. 2008). This highlights the complexity of NO neurochemistry in depression neurobiology, indicating that an imbalance rather than an overall increase or decrease in NOS activity seems to be related to the neurobiology of depression.

To understand the involvement of NO in depression, a number of studies have examined peripheral NO metabolism in major depression, however with rather mixed results. In a study of suicide attempters, increased NO metabolites (NO_2 and NO_3) were observed (Kim et al. 2006; Lee et al. 2006), suggesting a dysfunctional peripheral nitrergic system. A similar finding was reported in drug-naïve depressive patients diagnosed according to DSM-IV (Suzuki et al. 2001) and in the same study, treatment with an antidepressant normalized the nitrite levels, in correlation with the clinical response (Suzuki et al. 2001). In another study of DSM-IV diagnosed depressed patients, there was no correlation between depressive symptoms and levels of nitrate but a significant effect of antidepressant treatment, lowering the nitrate levels was observed (Herken et al. 2007). In addition, there are some studies demonstrating involvement of NO in some but not all forms of IFN-alpha-induced depression (Suzuki et al. 2003). Importantly, measurement of nitrate in serum will only detect the overall nitrate pool and not potential clinically relevant subcompartments. This is exemplified in a study of depressed individuals showing a 73% decrease in nitrite content in the polymorphonuclear leukocytes (Srivastava et al. 2002). Since human polymorphonuclear leukocytes express neuron-like nNOS (Wallerath et al. 1997), this measure may be hypothesized to be more relevant than serum values.

Examinations on polymorphisms of NOS have contributed with mixed findings, although some evidence for a role of NO in depressive disorders seems to be present. In a population-based association study investigating nNOS in unipolar depression, it was tested whether the nNOS C276T

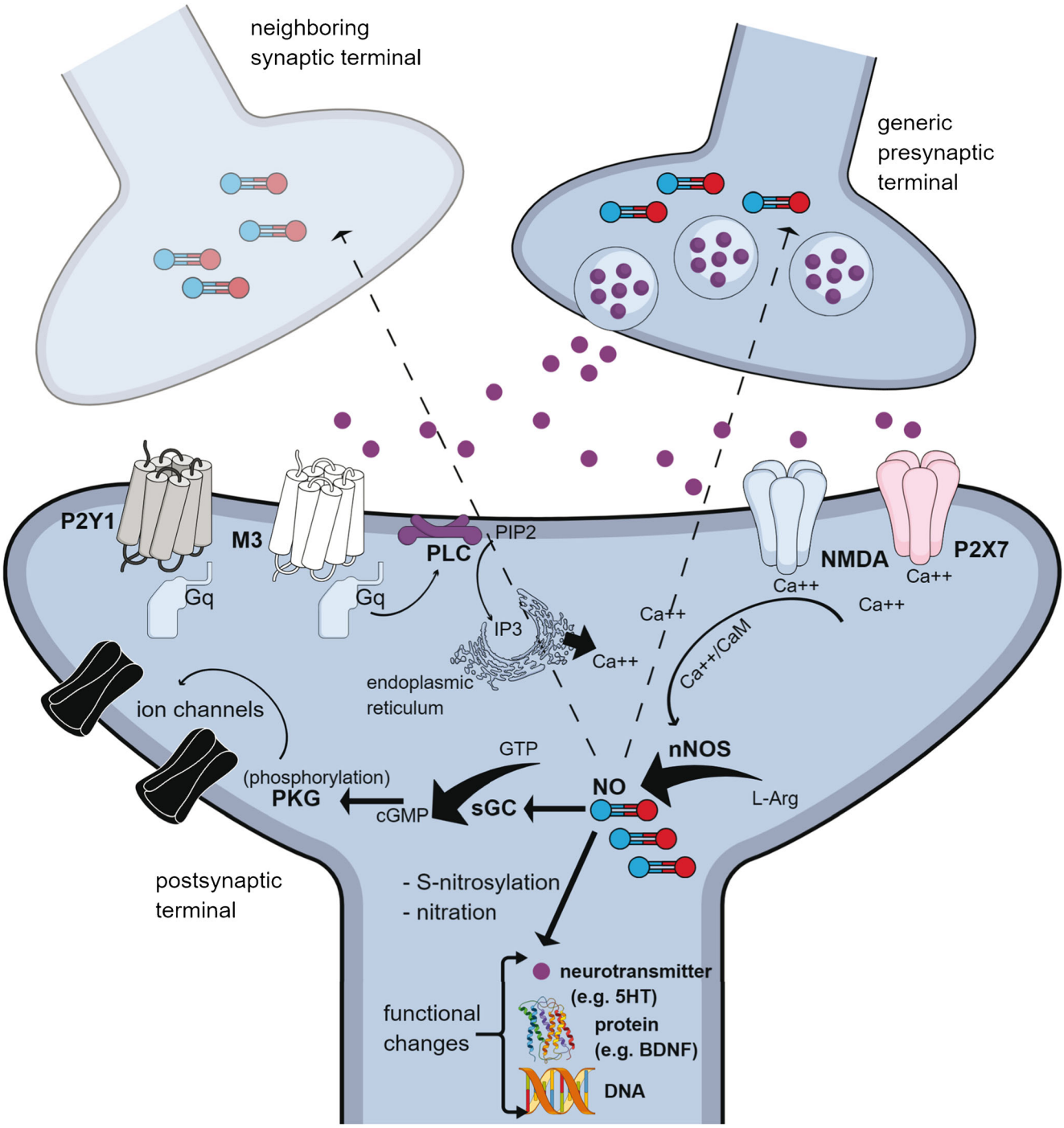

Fig. 1 Role of nNOS-derived NO in synaptic homeostasis. nNOS-derived NO is released following glutamate activation of AMPA and NMDA receptors, with an influx of Ca^{2+} leading to the activation of nNOS. NO exerts various neuromodulatory effects as well as promotes the cellular processes of plasticity and memory either by itself through nitrations and nitrosylations or by the synthesis of its second messenger, cGMP, through soluble Guanylyl Cyclase (sGC), which in turn acts through protein kinase G (PKG) to phosphorylate synaptic proteins. NO can freely cross cellular membranes and act on other cells in a volume-dependent manner, e.g., the presynaptic release machinery. Synthesis of NO can also be stimulated following processes leading to increase in intracellular Ca^{2+} for example through activation of muscarinic M3 or purinergic P2Y1 receptors. During conditions of stress, the synthesis of nNOS may be altered with consequences on synaptic functioning. For further details, please see main text.

polymorphism confers susceptibility to unipolar depression and treatment response to fluoxetine. No association with disease or SSRI treatment response was found in 108 Chinese patients (Yu et al. 2003) but due to the restricted design of the study, it is concluded that other variants of the nNOS gene may play a role. Also, in another genetic association analysis

of case–control samples (325 MDD patients, 154 BP patients and 807 controls) in a Japanese population, using single nucleotide polymorphism (SNP; rs41279104, also called ex1c), no associations between one marker (rs41279104) in nNOS and mood disorder were detected, although the sample sizes were probably too small to allow a meaningful test (Okumura et al. 2010). Moreover, the paper did not perform an association analysis based on linkage disequilibrium and a mutation scan of nNOS (Okumura et al. 2010). In a large genome-wide association study of 435,291 SNPs genotyped in 1738 MDD cases and 1802 controls selected to be at low liability for MDD, it was reported that an association of nNOS with the disease was present, although the size of the NOS-I gene made the authors cautious about the finding (Sullivan et al. 2009). Finally, in a study carried out in a group of 181 depressed patients and 149 control subjects of Polish origin, it was examined whether a single nucleotide polymorphism (SNP) present in the genes encoding iNOS and nNOS could contribute to the risk of developing recurrent depressive disorder (Galecki et al. 2011). It was shown that both investigated polymorphisms could be associated with depression and that the NOS2A and nNOS genes may confer an increased risk of recurrent depressive disorder (Galecki et al. 2011). Recently, a whole-exome sequencing of individuals from an isolated population has identified a significant association in bipolar disorder with NOS1 (missense variant rs79487279) (Lescai et al. 2017). Whether this association could also be relevant for unipolar depressive disorder remains to be established.

Since stressful life events have been considered a crucial environmental triggering factor for depressive episodes (Kendler et al. 2000), a majority of the basic characterization of the involvement of NO in depression has been carried out in animal models involving exposure to stressful situations. Interestingly, nNOS is found expressed in different brain regions related to stress (Arevalo et al. 1992; Bhat et al. 1996; Ceccatelli et al. 1996; Nylén et al. 2001), suggesting NO to be an important modulator of the behavioural and physiological stress response. In addition, the expression of nNOS, along with NO levels, is significantly increased in the brain of animals that have been exposed to stressful stimuli (Harvey et al. 2005; Harvey et al. 2004; Madrigal et al. 2001; Madrigal et al. 2002; Wegener et al. 2010; Zhou et al. 2011). Basal levels of functional iNOS, although in lower levels than nNOS, are also present in the brains of normal healthy adult animals (Amitai 2010), showing significantly higher expression upon stress exposure in different limbic brain regions (Bollinger et al. 2017; Gądek-Michalska et al. 2016; Harvey et al. 2004; Tang et al. 2018). Consistent with the elevated nNOS and/or iNOS expression, increased NO levels can be observed in the hypothalamus, hippocampus and prefrontal cortex of animals exposed to stress in models of depression, such as forced swimming and the chronic mild stress (Gilhotra and Dhingra 2009; Harvey et al. 2005; Harvey et al. 2004; Krass et al. 2010). Simultaneously, neuroendocrine responses to stress, including increased hypothalamus–pituitary adrenal (HPA) axis activity, which is often disrupted in mood disorders (Badenhorst et al. 2017; Brand and Harvey 2017a; Brand and Harvey 2017b; Swaab et al. 2005), can be observed. In fact, a direct relationship between HPA axis activity and NO has been observed, in that endogenously NO inhibits the release of corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and corticosterone (Costa et al. 1993; Rivier and Shen 1994a). Studies using systemic injection of different NOS inhibitors suggest that NO may exert a tonic negative influence on the HPA axis activity in the presence or absence of circulating glucocorticoids (Givalois et al. 2002; Rivier and Shen 1994b; Tsuchiya et al. 1997). In contrast, microinjection of an NO donor in the brain ventricles or into brain regions controlling the HPA activity show that NO may increase HPA axis activity (Okada et al. 2002; Seo and Rivier 2001). Such discrepancies can be explained based on the brain region studied, the type and intensity of stimuli triggering HPA axis activation and on the species under investigation (Bugajski et al. 2004; Mancuso et al. 2010; Rivier 2001; Rivier 2003). Nevertheless, there is profound evidence suggesting that NO might be an important messenger in regulating neuroendocrine responses to stress.

Experiments performed with mice with targeted disruption of the nNOS or iNOS genes have suggested a clear involvement of NO on depression neurobiology. Thus, transgenic mice lacking nNOS show hyper locomotor activity in a novel environment, increased social interaction in their home cage and decreased depression-related behaviour, with impaired spatial memory retention (Tanda et al. 2009). Mice lacking nNOS (nNOS−/−) are also more aggressive than wild-type (WT) mice in standard testing paradigms (Nelson et al. 2006). Moreover, nNOS null mutant mice are resistant to stress effects and show a less depressive-like phenotype in the forced swimming and tail suspension tests (Zhou et al. 2007). More importantly, nNOS deletion or intrahippocampal nNOS inhibition blocked the corticosterone-induced behavioural modifications in the chronic mild stress model, thus indicating that hippocampal nNOS is necessary for the role of glucocorticoids in mediating depressive behaviours (Zhou et al. 2011). Since iNOS-mediated NO production is more prominent in response to inflammation and disease, an iNOS −/− phenotype is the increased susceptibility to some infections (Zaragoza et al. 1998; Zaragoza et al. 1999). In addition, the sickness behaviour induced by LPS administration is decreased in iNOS null mice, supporting a prominent role of iNOS in the development of behavioural changes associated to neuroimmunoactivation. However, evidence also supports that iNOS null mice express increased reactivity to stress, in the absence of immunological stimuli, such as increased anxiety in response to predator scent (Abu et al. 2008). On the other hand, iNOS−/− mice also evidenced normal locomotor

activity and increased resilience in the forced swimming test (Montezuma et al. 2012) and impaired extinction of fear memories (Lisboa et al. 2015). However, with these results, it may be difficult to translate the involvement of iNOS-mediated NO levels to a clinical situation, since the iNOS-deficient animals present compensatory elevated cortical and decreased hippocampal NO levels in response to stress (Abu et al. 2008; Buskila et al. 2007).

In conclusion, both nNOS- and iNOS-derived NO levels are altered in depression and in limbic brain regions of stressed animals. These alterations may contribute to the development of behavioural and endocrine abnormalities that compromise adaptation to stress and increase vulnerability to depression.

No signalling and antidepressant intervention

The effect of clinically used antidepressants on nitrergic signalling has been shown in a few studies, thus supporting NO involvement in depression and antidepressant action. The first clinical study reported results from a study with patients suffering from ischemic heart disease and depression, 17 received paroxetine and 14 patients nortriptyline and it was observed that serum nitrite and nitrate levels were significantly decreased following paroxetine treatment but not nortriptyline (Finkel et al. 1996). Paroxetine was also shown to be significantly more a potent inhibitor of the NOS enzyme activity than nortriptyline (Finkel et al. 1996). Similarly, several established antidepressants of distinct chemical classes, including imipramine, paroxetine, citalopram and tianeptine, have all been shown to inhibit hippocampal NOS activity in vivo when applied locally in the brain in therapeutically relevant concentrations (Wegener et al. 2003). In another preclinical study, pre-treatment with the main precursor of NO, L-arginine, counteracted the antidepressant-like effect of imipramine and venlafaxine but not the effects of bupropion or fluoxetine, effects being associated with decrease in brain NO metabolism (Krass et al. 2011). Similarly, it has been shown L-arginine antagonizes the effects of the classic tricyclic antidepressant, imipramine (Harkin et al. 1999). Supporting these findings, a decrease in NMDA stimulated NO synthesis was observed in cultured neurons incubated with antidepressants of different classes (Li et al. 2006). However, a more recent study reported that treatment with 7-nitroindazole (7-NI), venlafaxine and fluoxetine attenuated stress-induced neuronal activation in overlapping brain regions, suggesting that nNOS inhibitors and monoaminergic antidepressants may share common neurobiological substrates (Silva et al. 2012). Supporting that hypothesis, it has been demonstrated that low and ineffective doses of L-NAME were able to potentiate the behavioural effects of imipramine and fluoxetine but not reboxetine, a noradrenaline reuptake inhibitor, in the FST (Harkin et al. 2004; Harkin et al. 2003). Altogether, this evidence suggests that attenuation of NO levels might contribute to the behavioural effect of conventional monoaminergic antidepressants.

NO has also been implicated in the antidepressant role of several other substances, like tramadol (Jesse et al. 2008), bupropion (Dhir and Kulkarni 2007) and lithium (Ghasemi et al. 2008). The effects of the fast-acting antidepressant ketamine also seem to involve modulation of NO levels, since L-arginine pre-treatment can counteract its effects (Liebenberg et al. 2015; Zhang et al. 2013). More recent evidence suggest that the effects of ketamine could be related to NMDA receptor blockade with subsequent reduced NO-mediated S-nitrosylation of a downstream signalling cascade, which disinhibits rapid protein synthesis (Harraz et al. 2016).

In addition to the clinical used antidepressants, specific drugs affecting NO synthesis have been tested for antidepressant efficacy, further corroborating NO involvement in depression neurobiology. A comprehensive review of these compounds lies beyond the scope of this text and can be found elsewhere (Wegener and Volke 2010). Briefly, acute systemic administration of both iNOS and nNOS inhibitors, such as 7-NI, 1-(2-trifluoromethylphenyl)-imidazole (TRIM) or 1400W, has antidepressant-like effects but does not affect locomotion (Harkin et al. 2003; Heiberg et al. 2002; Montezuma et al. 2012; Spiacci Jr et al. 2008; Volke et al. 2003; Yildiz et al. 2000). Both 7-NI and TRIM have proven to be effective in other animal models with better face validity, such as the chronic mild stress model of depression (Mutlu et al. 2009; Yazir et al. 2012) and the learned helplessness paradigm (Stanquini et al. 2018). The behavioural effect is centrally based, since inhibition of nNOS into the hippocampus or in the medial prefrontal cortex causes a dose-dependent antidepressant-like effect in the FST (Diniz et al. 2016; Joca and Guimaraes 2006; Pereira et al. 2015; Sales et al. 2017). These findings further support the association of increased stress-induced NO signalling in relevant brain regions with the development of depressive psychopathology.

Interestingly, the importance of intact serotonin signalling has been shown, in that serotonergic depletion abolished the antidepressant-like effect of some NOS inhibitors in the FST (Harkin et al. 2003). This effect seems to have important centrally based neurobiology, since the antidepressant-like effect induced by intrahippocampal administration of a selective nNOS inhibitor could be prevented by co-administering a serotonin 1A receptor (5-HT_{1a}) antagonist (Hiroaki-Sato et al. 2014). However, not all inhibitors seem to possess this profile, as it was also demonstrated that the effect of agmatine, which is decarboxylated L-arginine, was independent of the serotonin 5-HT depletion (Krass et al. 2008).

Methylene blue (MB), although not exclusively selective for the NOS, is potentially of special relevance since it is so far

the only compound proven to be effective in patients (Bodini 1899; Naylor et al. 1986; Naylor et al. 1987; Naylor et al. 1988). Unfortunately, these pioneer studies were not fully randomized but a recent randomized crossover study confirmed efficacy of MB for treatment for residual symptoms of bipolar disorder (Alda et al. 2017). MB does not only inhibit NOS in the brain in vivo (Volke et al. 1999) but also several other haeme-containing enzymes, like monoamine oxidase (MAO) (Ehringer et al. 1961; Gillman 2008; Jakubovic and Necina 1963) and various cytochromes, which may partly account for the clinical efficacy and for the case reports suggesting a hyper serotonergic state following use of MB (Gillman 2008; Stanford et al. 2009). New analogues of MB are being developed (Petzer et al. 2012), which preclinically maintain the antidepressant efficacy without a major effect on MAO (Delport et al. 2017; Delport et al. 2018).

Besides the well-established interaction between NMDA and NO synthesis, alternative pathways, which have also been suggested to be involved in the psychopathology of depression, display convergent mechanisms to NO formation (Fig. *1*). Among those, purinergic and muscarinic mechanisms are the most studied. Under stressful conditions, ATP release is increased, leading to the activation of the purinergic P2X7 receptors (P2X7R), which is highly expressed on neuronal and non-neuronal cells (microglia and astrocytes) (Volonte et al. 2012). Following activation, the P2X7 receptors allow the influx of Ca^{2+}, formation of the Ca–calmodulin complex and production of NO (Vorherr et al. 1993). This mechanism seems to be involved in some antidepressant-like effect of P2XR antagonists, since the systemic administration of a P2X antagonist displays antidepressant properties, which were associated with a decrease in the nitrite/nitrate levels in the prefrontal cortex (Pereira et al. 2013). In the same study, a co-localization of nNOS and P2R in the frontal cortex was present and the coupling of these two proteins could be hypothesized to modulate behavioural consequences of stress exposure and the observed antidepressant-like effects following P2XR antagonism (Pereira et al. 2013). Similarly, activation of muscarinic cholinergic receptor (mAchR) subtypes 1, 2 and 3 increases the intracellular Ca^{2+} following their activation by acetylcholine. In fact, studies have shown that stimulation of muscarinic receptors induces NO synthesis and cGMP formation in vitro (Bauer et al. 1994) and in vivo (Fassini et al. 2015). Additionally, it was shown that the activation of mAchR by carbachol has a dose-dependent relationship on nNOS activity, with low doses leading to activation of nNOS, while higher doses inhibited the enzymatic activity (Borda et al. 1998). Surprisingly, it has not yet been investigated if the antidepressant-like effect induced by scopolamine (Dulawa and Janowsky 2018), a muscarinic antagonist, involves modulation of NO levels in the brain.

Finally, since nNOS is anchored to the membrane by the scaffolding protein PSD-95, enabling downstream signalling via the carboxy-terminal PDZ ligand of nNOS (Jaffrey et al. 1998; Jaffrey and Snyder 1996), disruption of this complex specifically prevents NMDA-R signalling coupled to nNOS, while leaving other functions of both the NMDA-R and nNOS intact (Zhou et al. 2010). The antidepressant-like and effects on NO levels of this approach have been demonstrated in a number of studies (Doucet et al. 2013; Doucet et al. 2015), although the results are not always consistent (Tillmann et al. 2017).

No signalling and neuroplasticity in depression

Neuroplasticity is an important property of neuronal adaptation, which may be disrupted in depression (Manji et al. 2001; Manji et al. 2000). Neuroplasticity changes induced by external environmental factors, such as stress and other negative stimuli, have been demonstrated to play a significant role in both the onset and precipitation of depression (Pittenger and Duman 2008). Conversely, antidepressant intervention has been suggested to exert an important part of the antidepressant effects through regulation of neuroplasticity (Duman and Aghajanian 2012; Duman et al. 2016). It is believed that various neurotrophins, a family of small peptide growth factors, regulate neuroplasticity, which include proliferation, differentiation, survival and death of neuronal cells and supporting tissue (Levy et al. 2018). Brain-derived neurotrophic factor (BDNF), the predominant neurotrophin in the brain, binds to the tropomyosin receptor kinase B (TrkB) receptor and subsequently activates intracellular signalling pathways governing transcription and dendritic translation of proteins necessary for cellular survival, differentiation and learning/memory formation in the hippocampus (Leal et al. 2017). Importantly, dysfunctional signalling through BDNF and TrkB has been implicated in a number of psychiatric disorders, including depression (Autry and Monteggia 2012). In support of that, stress decreases whereas chronic treatment with antidepressants increases BDNF levels in the prefrontal cortex and in the hippocampus and intact BDNF signalling in the brain is shown to be necessary for the behavioural effects of conventional antidepressants (Adachi et al. 2008; Autry and Monteggia 2012).

Interestingly, NO seems to be also able to modulate BDNF levels, since it was demonstrated that NO donors (SNP, NOR3) decrease BDNF release in hippocampal cell culture, whereas the inhibition of NO production increases these levels (Canossa et al. 2002). Accordingly, in vivo experiments showed that chronic treatment with L-NAME increased BDNF mRNA and protein levels in the hippocampus and in the prefrontal cortex of rats (Pinnock and Herbert 2008; Salehpour et al. 2017). In line with this observation, the antidepressant-like effect induced by chronic treatment with

the selective nNOS inhibitor 7-NI or with the sGC inhibitor ODQ was associated with increased expression of hippocampal BDNF protein levels (Stanquini et al. 2018). Similarly, increased levels of BDNF have also been observed after treatment with other NOS inhibitors, either in cultured or in vivo neocortex (Xiong et al. 1999). However, in another study, the antidepressant effect induced by aminoguanidine, a preferential iNOS inhibitor, was not correlated with increased BDNF signalling in the prefrontal cortex of FSL rats (Silva Pereira et al. 2017). Mice with deficient iNOS expression, however, present increased BDNF levels in the PFC and hippocampus associated to antidepressant-like phenotype (Joca et al. 2012). It is, therefore, likely that both iNOS- and nNOS-derived NO can modulate BDNF signalling in stress adaptation. Although NO has usually been shown to downregulate BDNF levels, peroxynitrite formation derived from NO and O^{2-} was observed to trigger TrkB signalling (Yuen et al. 2000), suggesting BDNF signalling to be affected. Evidence from cultured hippocampal neurons indicates that inhibition of BDNF secretions is more pronounced in response to exogenous NO levels or under exacerbated NO concentrations, whereas endogenous low levels of NO would facilitate BDNF–TrkB signalling (Kolarow et al. 2014). A bioinformatic analysis predicted a direct action of NO on the amino acid residues of BDNF or TrkB, suggesting protein S-nitrosylation or tyrosine nitration in both rodents and humans quoted molecules (Biojone et al. 2015). These direct actions of NO on BDNF or TrkB proteins could trigger functional negative feedback to control protein function, or it could drive a reinforcement of downstream BDNF/trkB signalling.

Conversely, neurotrophins are also able to modulate NO or NOS levels, since BDNF has been found to upregulate NO signals, in either hippocampal or neocortical neurons (Kolarow et al. 2014; Xiong et al. 1999). Similarly, the ratio of nNOS-positive neural progenitor cells (NPCs) is increased following treatment with BDNF (Cheng et al. 2003). On the other hand, BDNF can suppress NO production in microglia, thus counteracting inflammatory processes in the brain (Mizoguchi et al. 2014).

More recent evidence indicated that the interplay between NO and BDNF-TrkB signalling is more complex and involves more signalling cascades. Both NMDA and TrkB can be associated to PSD-95 and induce downstream signalling mechanisms that regulate synaptic plasticity (Cai et al. 2018). In this scenario, PSD-95–nNOS interaction may downregulate BDNF expression via inhibiting ERK activation. On the other hand, NMDA–PSD-95 uncoupling would increase BDNF levels and facilitate BDNF–TrkB–PSD-95 signalling mechanisms related to neuroplasticity, which could contribute to the behavioural effect of these drugs. These results could help explain the effect of NOS inhibitors on BDNF expression.

In humans, a recent study conducted with patients presenting elevated depressive symptoms revealed decreased serum BDNF levels associated to increase NO levels and impaired antioxidant capacity (Eraldemir et al. 2015). Although it is not possible to infer about brain NO and BDNF levels in these patients, studies conducted with brain tissue from animal's have given further support for a putative role of NO in regulating BDNF levels under stressful situations and depression.

Despite the aforementioned evidence that NO might regulate BDNF levels in stress and depression, evidence about the effects of NOS inhibitors in promoting recovery of impaired synaptogenesis and dendritic branching in stressed animals is scarce. It is known, however, that NO is critically involved in the establishment and activity-dependent refinement of axonal projections during the later stages of development (Manucha 2017). Under physiological concentrations, NO signals downstream, either through sGC activation or through nitrosylation to promote the growth of presynaptic filopodia, which rapidly leads to the formation of new synaptic contacts in in vitro experiments (Sunico et al. 2005). Conversely, high levels of NO, as in nerve injuries, can produce the opposite effect, with reduced synaptogenesis through cGMP-dependent and S-nitrosylation-mediated mechanisms (Sunico et al. 2005). Although this can be blocked by treatment with NOS inhibitors (Sunico et al. 2005) and since inhibition of NO synthesis in adult rats increases hippocampal expression of synaptophysin (Joca et al. 2007), it is not known whether blocking NO synthesis may prevent a stress-induced decrease in synaptogenesis and dendritic arboring. However, this seems likely, since PSD-95 promotes synaptogenesis and multi-innervated spine formation through nitric oxide signalling (Nikonenko et al. 2008). However, further research is needed and the question is open for investigation. A proper answer would contribute for a better understanding on the role of NO on stress-induced neuroplasticity related to neuropsychiatric disorders.

Another important neuroplasticy factor affected by NOS inhibitors is neurogenesis, which has been exhaustively reviewed elsewhere (Chong et al. 2018; Gray and Cheung 2014). Only a brief overview is presented here. Neurogenesis is the process of neural stem cells (NSCs) to foster newborn neurons in replacement for damaged neurons or maintaining the function. Neurogenesis has attracted significant interest and although somewhat controversial in humans, it has been suggested that neurogenesis may be linked to recovery from clinical depression (Duman et al. 2001a; Duman et al. 2001b; Spalding et al. 2013) and even in a controversial paper that it may be a prerequisite for an antidepressant response (Santarelli et al. 2003). In the brain, neurogenesis has been observed in the subventricular zone (SVZ) and the subgranular zone of the dentate gyrus (DG) (Ehninger and Kempermann 2008; Spalding et al. 2013). Interestingly, it has also been demonstrated that the subventricular zone is surrounded by nNOS positive neurons (Romero-Grimaldi et al. 2008) and cells expressing nNOS

have also been identified in neuronal precursors in DG (Islam et al. 2003), suggesting that nNOS could participate in the regulation of neurogenesis. Indeed, it has been demonstrated that the nNOS-mediated suppressing on neurogenesis effect may be caused by NO generated from neurons, not from NSCs (Luo et al. 2010). In addition, evidence that the subcellular localizations of nNOS in neurons and in NSCs seems to be distinct, implying that the role of nNOS in neurons and NSCs is different (Luo et al. 2010). It has also been demonstrated that inhibition of NO synthesis with 7-NI increases proliferation of neural precursors isolated from the postnatal mouse subventricular zone (Matarredona et al. 2004). However, another report has demonstrated that nNOS inhibition with 7-NI enhanced the proliferation of progenitor cells in the dentate gyrus and that the antidepressant-like effect of this drug was dependent on this neurogenic effect (Zhu et al. 2006). These results are in line with findings using a nNOS knockout mouse line, where the number of new cells, generated in neurogenic areas of the adult brain, the olfactory subependyma and the dentate gyrus, was strongly augmented, indicating that division of neural stem cells in the adult brain can be negatively controlled by NO (Packer et al. 2003). It has also been reported that the nNOS inhibitor L-VNIO or deletion of the nNOS gene could affect the differentiation of NSCs into neurons and astrocytes (Luo et al. 2010). Specifically, it was found that nNOS could facilitate differentiation of hippocampal neural progenitor cells (Park et al. 2017), suggesting that nNOS in NSCs is essential for neurogenesis. In the DG of the hippocampus, NSC forms granule neurons contributing to neuroplasticity, learning and memory. Impairments in these cognitive functions have been observed in nNOS transgenic mice, suggesting that nNOS affects differentiation of NSCs in the DG (Weitzdoerfer et al. 2004). High levels of the nNOS are found in granule neurons in the DG (Islam et al. 2003) and NO generated from nNOS in these neurons may therefore be speculated to negatively govern granule neuronal precursor proliferation and further reduces differentiation of granule neuronal precursors. Given these observations, it is possible to speculate that the behavioural effects of NOS inhibitors observed in animals under exposure to chronic stress might involve positive regulation of hippocampal neurogenesis.

One of the special physiological properties of NO is the function as a retrograde messenger, influencing synaptic properties, such as LTP and LTD (Izumi and Zorumski 1993; Zorumski and Izumi 1993). Such processes are crucial in synaptic homeostasis and, conversely, affecting NO levels may virtually affect the plasticity and homeostasis of all known synapses (Hardingham et al. 2013; Hölscher 1997). In diseases where synaptic dysfunction, such as depression, is important, NO is likely to play a major role. In fact, NO has been shown to mediate local activity-dependent excitatory synapse development and spine dynamics (Nikonenko et al. 2013) and a change in NO levels during development has been shown to promote axon pruning in a cGMP-independent mechanism and to enable a switch between phases of neuronal degeneration and regrowth (Rabinovich et al. 2016).

Changes in synaptic function are similarly reflected in the observed levels of neurotransmitters. Several in vivo studies have demonstrated that NO can modulate the extracellular level of neurotransmitters in the central nervous system, e.g., 5-HT, DA, GABA and glutamate (Kaehler et al. 1999; Lorrain and Hull 1993; Segovia et al. 1997; Segovia et al. 1999; Segovia et al. 1994; Strasser et al. 1994; Wegener et al. 2000). In addition, NO can inactivate the rate limiting enzyme in the synthesis of 5-HT, tryptophan hydroxylase (Kuhn and Arthur Jr. 1996, 1997) and it has been suggested to stimulate synaptic vesicle release from hippocampal synaptosomes (Meffert et al. 1996; Meffert et al. 1994). Furthermore, NO regulates 5-HT reuptake (Pogun et al. 1994a; Pogun et al. 1994b; Pogun and Kuhar 1994), inhibits uptake of [3H] DA by striatal synaptosomes (Lonart et al. 1993; Lonart and Johnson 1994) and transforms 5-HT into an inactive form (Fossier et al. 1999). It has also been demonstrated that a physical interaction between the serotonin transporter and neuronal nitric oxide synthase, via PDZ-PDZ interactions, may underlie reciprocal modulation of their activity (Chanrion et al. 2007). The connection between NO and 5-HT is substantiated by observations showing that NO as well as 5-HT are involved in the pathophysiology of migraine (Lassen et al. 1998; Lassen et al. 1997; Thomsen 1997; Thomsen and Olesen 1998), as well as the inverse relationship between NO and 5-HT in peripheral tissue. These neurochemical studies could provide evidence for the observation that the antidepressant-like effect induced by NOS inhibitors is dependent on brain serotonin levels.

Conclusion and perspectives

Evidence from preclinical models has consistently shown that inhibiting NO synthesis can lead to antidepressant-like effects. These effects can be achieved through different pharmacological mechanisms, including direct nNOS and/or iNOS inhibition, blockade of P2 receptors or muscarinic receptors. As a result, reduced NO levels could allow appropriate monoaminergic signalling during stress to promote behavioural adaptation. In this scenario, it is likely that upon chronic exposure to stress, continuous inhibition of NO synthesis could facilitate neuroplastic mechanisms related to the antidepressant effect, such as increased BDNF-TrkB signalling and neurogenesis.

Despite significant advances in this field, challenges remain in developing compounds that may differentially inhibit the ‘right’ NOS isoform at the right place. However, the NO system continues to be an interesting approach in the future development of antidepressants.

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Compliance with ethical standards

Conflict of interest GW declares having received research support/lecture/consultancy fees from H. Lundbeck A/S, Servier SA, Astra Zeneca AB, Eli Lilly A/S, Sun Pharma Pty Ltd., Pfizer Inc., Shire A/S, HB Pharma A/S, Arla Foods A.m.b.A., Alkermes Inc., Johnson & Johnson Inc. and Mundipharma International Ltd. All other authors declare no conflict of interest.

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