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Chapter 7

Modulation of Adult Neurogenesis by the Nitric Oxide System

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1. Introduction

Nitric oxide (NO) is a gaseous free radical that acts as a second messenger having an important biological role in intercellular communication and in intracellular signaling in many tissues, including the brain (reviewed by [1]). NO is synthesized by the nitric oxide synthase (NOS) family of enzymes, which convert L-arginine to L-citrulline and NO. There are three different isoforms of NOS: a) neuronal NOS (nNOS or NOS I), b) endothelial NOS (eNOS or NOS III), and c) inducible NOS (iNOS or NOS II) (reviewed by [2]). Different members of the NOS family control different functions of NO (reviewed by [1]).

In the central nervous system (CNS), NO has been linked to the regulation of synaptic plasticity and cognitive functions, and it is also associated with the control of biological functions including sleep-wake cycle, appetite, body temperature, and modulation of hormone release as reviewed by [3]. In the last decade, there has been a growing interest in the study of the role of NO in neurogenesis, the process by which new neurons are formed in the brain. NO regulates neurogenesis in diverse ways, and the different NO synthases are important players in the different effects on neurogenesis. Under physiological conditions NO synthesized from nNOS acts as a negative regulator of neurogenesis [4-9], while in inflammatory conditions, such as neurodegenerative disorders or acute brain insults, a decrease in nNOS and an increase in iNOS expression may act as a mechanism to enhance neurogenesis [8,10-13]. In fact, depending on the source, NO has a pro-neurogenic effect either by promoting neural stem cell (NSC) proliferation, as recently described by our group [13,14], but also by favoring other steps of neurogenesis such as migration [15], differentiation and survival [10,16]. Although the exact molecular mechanisms underlying this dual effect of NO on neurogenesis are not fully clarified, the

modulation of the NO system seems be a good target for the development of strategies to improve endogenous neurogenesis following brain damage.

In this chapter, we describe the use of two different strategies for the enhancement of endogenous neurogenesis using drugs that are linked to the nitrergic system: 1) Nitric oxide-releasing non-steroidal anti-inflammatory drugs (NO-NSAID); 2) Phosphodiesterase type 5 (PDE5) inhibitors. PDE5 inhibitors are suitable to be used in the clinic for the treatment of several pathologies, such as erectile dysfunction [17] and pulmonary arterial hypertension [18], while NO-NSAID are being studied as an alternative to NSAID in the treatment of systemic inflammatory conditions [19]. Although little is known about the use of these drugs for the treatment of CNS disorders, the evidence so far is encouraging. Several reports describe these drugs as a good strategy to promote regeneration of lesioned areas or to be used as an adjuvant approach in cell replacement therapies since they favor neurogenesis [20-22]. Thus, the design of therapeutic strategies using these drugs to efficiently enhance the different steps of neurogenesis, such as a) proliferation, b) migration, c) differentiation, d) integration and, e) survival of NSC in the injured CNS, seems to be a valuable therapeutic approach to improve brain repair.

2. Neurogenesis in the adult mammalian brain

The discovery of NSC in the adult mammalian brain had a strong contribution for the understanding of adult CNS plasticity. Two regions have been classically described as having the characteristics necessary for the maintenance of NSC: a) the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus [23,24], and b) the subventricular zone (SVZ) of the lateral ventricles [25]. NSC can be isolated from the SGZ or SVZ and cultured *in vitro*, since some of the characteristics of these regions can be kept in culture in the presence of growth factors such as the epidermal growth factor (EGF) [26] and/or basic fibroblast growth factor (bFGF) [27].

In vivo, from the SVZ and SGZ, NSC undergo a complex process leading ultimately to the formation of new neurons, a phenomenon referred to as neurogenesis, which enables the continuous production of neuronal cells throughout the adult life of mammals, including humans. Neurogenesis can be summarized into six main stages: 1) proliferation of precursor cells; 2) fate determination; 3) migration; 4) differentiation; 5) integration in the neuronal circuitry, and 6) long-term survival of functional newborn neurons. Each of these stages is tightly regulated locally, and numerous agents have been described to be responsible for the physiological regulation of neurogenesis, such as EGF, bFGF, Numb, Notch, Sox, Sonic hedgehog, Noggin, among others (for review see [28,29]).

When trauma occurs in the CNS, new needs arise for the brain, mainly for repair, and various signals are released from injured areas influencing neurogenic niches and the behavior of NSC, which can migrate to the affected sites. Brain damage may be a) acute, such as traumatic brain injury, ischemic stroke or prolonged brain seizures, or b) chronic, such as slow-progressing neurodegenerative diseases. All these conditions are fol-

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lowed by an inflammatory response [30]. Indeed, several studies have shown that adult neurogenesis is influenced by various pathological conditions, as discussed previously [31]. Models of brain damage were used to demonstrate that neurogenesis may be favored following injury, particularly acute injury, which is generally accepted as an attempt of the brain to repair [31]. On the other hand, the neurogenic capacity is decreased in neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease or Parkinson's disease [32-34].

However, several questions remain unclear about this issue, in particular: a) which factors regulate neurogenesis during inflammation; b) which signaling pathways are involved in the recruitment of NSC for the injured sites; c) how new neurons are integrated and are able to survive long term; d) how can neurogenesis be modulated to improve its efficiency in an inflammatory context. The search for the answers to some of these questions is the challenge of regenerative medicine and a major target by the scientific community nowadays.

3. Neuroinflammation

Neuroinflammation is a biological response to noxious stimuli affecting the CNS, such as stress, injury or infection by external pathogens [35,36]. The main role of the inflammatory response is that of providing an harmful environment for external agents that cause injury and to regain homeostasis, being mediated by the activation of two major groups of cells from the immune system: a) CNS resident cells - microglia and astrocytes, and b) hematopoietic system migrating cells - lymphocytes, monocytes and macrophages [37,38]. The activation of these cells is characterized by the release of different regulatory substances, including chemokines such as stromal derived factor (SDF)-1alpha, complement molecules, monocytes chemoattractant protein-1 (MCP-1), cytokines such as interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, interleukine (IL)-1beta, IL-18 and IL-6, glutamate, reactive oxygen species (ROS) and reactive nitrogen species (RNS) like NO (for review see [31]). Although the main function of neuroinflammation is to protect the brain by promoting the removal of noxious stimuli and committed/dead cells, and thus reestablishing brain tissue homeostasis, neuroinflammation may also become deregulated and contribute to perpetuate secondary tissue damage, as reported previously [39]. In fact, the creation of a positive feedback loop through inflammation itself may result in neuronal loss and/or neuronal damage.

In short, neuroinflammation may have a dual effect on the cellular environment, being beneficial or detrimental, depending on the time and state of activation of inflammatory cells [40]. Accordingly, the inflammatory response has been linked to the mechanisms that lead to various CNS diseases, also affecting SVZ and SGZ niches, therefore compromising neurogenesis [41]. Whether this means that inflammation is always detrimental to neurogenesis, or whether it is harmful only when the homeostasis of SVZ and/or SGZ is compromised, will be discussed in the next section.

4. Neuroinflammation and neurogenesis

As mentioned in the previous section, it is now widely accepted that neuroinflammation modulates neurogenesis in different ways, either by increasing or, alternatively, decreasing it [42]. Depending on the severity and complexity of the inflammatory response, which can range from a mild acute to a chronic uncontrolled process, neurogenesis may be dually regulated. Factors such as a) the type of inflammatory stimuli, b) the type of inflammatory cells, c) the type of inflammatory mediator, d) the area of injured tissue and e) for how long the inflammatory cells, particularly microglia, remain activated, are decisive for the shift from a pro-neurogenic to an anti-neurogenic inflammatory status [43].

In this context, the involvement of a particular type of inflammatory cells such as microglia, considered by most authors as the "hallmark of neuroinflammation", seems to be of major importance in the modulation of neurogenesis. The main features of microglial cells are a) the expression of scavenger receptors, b) antigen presentation molecules (Major Histocompatibility Complex (MHC) class II), c) pattern-recognition receptors, and d) production of various cytokines and other inflammatory factors (ROS and RNS) [44]. For a long time, microglial cells were considered as the damaging agents of the inflammatory response, with a default response always leading to detrimental effects on neuronal surrounding environment. However, recent studies describe microglial activity to be plastic (for review see [42]). In fact, the plasticity of microglia seems to be a determining factor in this dual regulation of neurogenesis, since it can assume different morphologies and different phenotypes and subsequently release mediators along an inflammatory response that may influence the physiology of the NSC [45]. Apparently, microglial cells and factors released during inflammatory responses appear to have a dual role in neurogenesis [13,42].

Therefore, numerous studies have reported the involvement of different microglial-derived inflammatory mediators in the regulation of neurogenesis and/or neuroprotection [31,46,47]. Moreover, it has been reported that chronic microglial activation can stimulate one or more stages of neurogenesis, such as NSC proliferation, migration and differentiation, while the long-term survival of newborn neurons seems to be reduced in this context [31].

4.1. Anti-neurogenic role of inflammation

Neuroinflammation, in particular microglial activation, was initially described to be detrimental to neurogenesis [48,49]. Several studies have demonstrated microglia activation by lipopolysaccharide (LPS) to hinder neurogenesis in adult rats [48], by a mechanism mediated through TNF-alpha increased production [50,51]. Other studies have linked this anti-neurogenic effect of inflammation to the increased production of other proinflammatory mediators such as interleukins IL-1 beta and IL-6, or cytokines IFN-gamma and TNF-alpha [52-55]. In addition, ROS and RNS, in particular NO, have also been described as being involved in the detrimental effect of neuroinflammation in the

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formation of new neurons in the adult brain of rodents [49,56,57]. In Table 1 we summarize the main findings concerning the effect of the most important proinflammatory mediators in neurogenesis.

In addition, the deleterious role of inflammation in neurogenesis was corroborated by numerous studies which demonstrated that neurogenesis can be restored when the inflammatory response is controlled by the administration of: a) antibiotics, such as minocycline [48,58,59], or b) non-steroidal anti-inflammatory drugs, such as indomethacin [48,49,60,61].

4.2. Pro-neurogenic role of inflammation

Contrary to initial observations, recent studies indicate that neuroinflammation may also support different stages of neurogenesis, thus favoring the formation of new neurons following injury to the CNS [44]. Thus, the inflammatory microenvironment is responsible for sending "activating signals" to NSC resident in neurogenic niches, such as SVZ or SGZ, that thereafter migrate to the injured areas where they differentiate and integrate the neuronal network [62,63]. In this context, microglial cells are described as central in the regulation of this process, suggesting an ambiguous role of microglia in the regulation of neurogenesis in inflammatory conditions [64].

Apparently, although microglia may be detrimental to neurogenesis in early stages of the inflammatory response after acute insults, prolonged inflammatory response, also referred as chronic inflammation, appears to have a protective effect by directing the replacement of damaged or lost cells [45,65-68]. Thus, it was shown in several studies that inhibition of microglial activation results in continuous production of new neurons from adult NSC [69,70]. Moreover, chronic activation of microglia is concomitant with long-term survival of newly formed neurons [71,72].

Several proinflammatory mediators have been related to the pro-neurogenic effect of inflammation, including: a) cytokines such as IFN-gamma or TNF-alpha, b) chemokines such as SDF-1alpha and its receptor CXCR4 [69,73], or c) trophic factors such as brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) involved in the removal of damaged synapses [72] (see Table 1). In addition to the pro-neurogenic effect, these studies also suggest a neuroprotective role of microglial cells for newborns cells.

4.3. Future studies

Overall, it seems clear that more knowledge about the crosstalk between inflammation and neurogenesis is lacking. For instance, it is necessary to better characterize the genetic and proteomics of the microglial response, as well as more targeted studies are needed to clarify how neuroinflammation modulates each of the neurogenic stages. Identifying which genes are expressed, and subsequently, what kind of proteins are present during an inflammatory response will allow the development of different strategies to control or mitigate the deleterious effects of neuroinflammation on neurogenesis.

Inflammatory mediator	Proliferation of NSC		Differentiation of NCS		Survival of NSC		Signaling pathway	References
	SVZ	DG	SVZ	DG	SVZ	DG		
IL-1 beta	-	-	0	0	+	+	SAPK/JNK	[74,75]
IL-6	-	-	-	-	-	-	JAK/STAT and MAPK	[48,56,67]
IFN-gamma	-	0	+	+	-	0	ERK 1/2 pathway	[52,64,76-78]
	+	0	0	0	=	0	NF-kappaB	[79,80]
TNF-alpha	+	0	0	-	0	-	0	[50]
	0	0	0	0	-	-	TNF-R1 and TNF-R2	[53,76]
	+	0	-	0	=	0	TNF-R1	[81]
	+	+	+	+	+	+	TNF-R2	[82]
	+	0	+	0	+	0	TNF-R1	[83]
	0	-	0	-	+	0	TNR-R1	[54]
	+	+	+	+	+	+	TNF-R2	[43,54]
SDF-1alpha	+	+	+	0	+	0	CXC-R4	[69,73,84]

The effects listed in Table 1 may not be direct. +, Increase; -, decrease; =, not changed; 0, not reported.

Table 1. Modulation of adult neurogenesis by inflammatory mediators.

5. Nitric oxide

NO is a short-lived gaseous free radical synthesized by different members of the nitric oxide synthase family of enzymes. NOS are present in most tissues of the body and convert L-arginine to L-citrulline and NO [2,85]. The NOS family of enzymes is characterized by the existence of three different isoforms in mammalian cells: a) neuronal NOS (nNOS, type I), is constitutively expressed in neurons, where it localizes to synaptic spines, and is activated by calcium/calmodulin following the activation of glutamate receptors; b) endothelial NOS (eNOS, type III), is constitutively expressed in endothelial cells and astrocytes, is regulated by phosphorylation/dephosphorylation and/or by calcium/calmodulin; and c) inducible NOS (iNOS, type II), which regulation is dependent on de novo synthesis of the enzyme, particularly in inflammatory conditions [2,86,87].

Involved in a variety of physiological processes, NO has been described as an important regulator of the activity of systems such as the cardiovascular, immune and nervous systems [88]. There are several biological functions that depend on NO formation, including the regulation of body temperature, appetite and sleep-wake cycle (for review see [3]). The main mechanism regulating NO activity is at the level of its synthesis. In the CNS, NO has a distinct action when compared to classical neurotransmitters, as it is synthesized on demand, diffusing from synaptic terminals, acting not only in NO-releasing cells, but also in neighboring cells [89]. Initially described as an intracellular messenger, NO has also been associated with synaptic plasticity, which is linked to cognitive function, neuronal development and modulation of hormone release [90]. In this context, the role of NO as an intracellular messenger is

mediated by increasing cyclic guanosine 3', 5'-monophosphate (cGMP) levels, following the activation of N-Methyl-D-aspartate (NMDA)-type glutamate receptors [91]. Unlike classical neurotransmitters, which are stored in vesicles or released by exocytosis and further inactivated by re-uptake or enzymatic degradation, NO ends its action after reacting with intracellular substrates [1]. According to the literature, the action of NO in the brain has been associated with two different outcomes: a) regulation of physiological events, by its action as an intracellular messenger [90], or b) regulation of cell death mechanisms, due to its action as a cytotoxic agent [92,93]. This will be explored next in section 5.1.

5.1. Nitric oxide and neuroinflammation

As mentioned in the previous section, the action of NO in the CNS is characterized by the interaction with multiple intracellular targets, activating or inhibiting various signaling pathways. Thus, NO has been described to be involved in the regulation of several physiological functions, but also of various pathophysiological processes [2,85]. This dual action depends on the NOS isoform that catalyzes the formation of NO: a) nNOS and eNOS-derived NO is more involved in the regulation of physiological functions, and b) iNOS-derived NO is more involved in pathophysiological processes. In fact, iNOS is not normally expressed in the healthy brain, but in the presence of pro-inflammatory stimuli such as cytokines, external pathogens, such as bacteria or virus, or stress, such as hypoxia, iNOS may be expressed primarily on macrophages, astrocytes, microglia and endothelial cells [3,86,94,95], but also in neurons [96,97]. However, it should be mentioned that NO overproduction has also been linked to nNOS activation following persistent glutamate excitatory input during an inflammatory response, which has also been linked to iNOS expression [3]. Once expressed, iNOS continuously produces NO, and high levels are reached, in a process that can last for several days, having a cytotoxic effect by inhibiting mitochondrial respiratory chain enzymes, ultimately inducing apoptosis in target cells [95,98-101]. A key factor for the local effect of NO is the concentration achieved. Thus, in physiological conditions, NO concentrations could range from 0.1 to 100 nM, which is lower than those observed in inflammatory conditions, being less reactive. Accordingly, the action of NO is accomplished primarily by binding to the heme group of soluble guanylate cyclase (sGC), whose activation leads to the subsequent production of cGMP [102].

Increased levels of NO have been linked to oxidative and nitrosative stress phenomena, which have been described as involved in the development of several neurodegenerative disorders [2,85]. Thus, a massive release of NO can lead to the production of nitrogen dioxide (NO_2), after the direct reaction between NO and oxygen. NO_2 is a highly reactive nitrosative specie that can react with NO, producing dinitrogen trioxide (N_2O_3). Moreover, NO_2 can also oxidize or nitrate a wide variety of molecules, being the nitration of tyrosine to 3-nitrotyrosine a classical example [103]. N_2O_3, in turn, is involved in other phenomena such as nitrosation/nitrosylation, by reacting with amine or thiol groups, being a good example cysteine, which may be nitrosated to S-nitrosocysteine [103]. Furthermore, NO can also react with superoxide to produce peroxynitrite ($ONOO^-$), another extremely reactive molecule which can oxidize or nitrate other molecules, which has been described to be involved in the pathogenesis of several

neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis [2,104-106]. Likewise, both S-nitrosylation and nitration lead to alterations in the function of proteins, which may be regarded as regulatory phenomena of its activity [103].Thus, understanding the involvement of these phenomena in the pathoetiology of disorders affecting the brain may highlight a potential therapeutic role in modulating these events.

5.2. Nitric oxide and neurogenesis

The involvement of NO in the regulation of neurogenesis is a matter of debate given the range of different observations reported in the literature. In fact, the role of NO in neurogenesis only recently has been identified [4,5,107]. Depending on the source and concentration attained locally in the brain, NO has a dual influence in the neurogenic process both by inhibiting or stimulating neurogenesis.

Based on the distribution of NO-producing cells in stem cell niches, several works have proposed to study the involvement of NO produced at the perivascular niche - which includes pericytes and smooth muscle fibroblasts, endothelial cells, microglia, glial progenitors and astrocytic endfeet – in the regulation of neurogenesis, thus reinforcing the involvement of NO signaling in angiogenesis and neurogenesis [4,108,109]. Indeed, the discovery of blood vessels expressing eNOS and neurons expressing nNOS, close to SVZ and SGZ neurogenic niches, was essential for the establishment of a causal relationship between NO and the formation of new neurons. Moreover, it was also shown that nNOS-derived NO is involved in the regulation of neurogenesis, particularly by regulating NSC function, so that a cytostatic function can be assigned to NO in the CNS [4,5,107]. Thus, NO production occurs in close proximity to the NSC. Other authors have shown that nitrergic neurons expressing nNOS are arranged in close relationship throughout the rostral migratory stream (RMS), also describing a regulatory action of NO in the migration of SVZ-derived progenitor cells along the RMS [110].

Although most studies initially performed reported NO as an anti-neurogenic agent in the normal adult brain, in hypoxic ischemic stress conditions its effect can be radically different favoring stem cell proliferation, as demonstrated in recent studies [4,12,13,108,111,112]. In fact, the oxygen tension environment appears to modulate the effect of perivascular NO in neurogenesis [112,113], which may vary from: a) pro-neurogenic action, dependent on the expression of eNOS and nNOS, in physiological condition [108]; b) to anti-neurogenic action, dependent on the expression of iNOS, in extreme environments such as hypoxic and ischemic tissue and/or tumors [12,13,114,115]. However, more studies should be conducted to clearly understand how NO produced by different cell types from the perivascular niche regulate neurogenesis. In fact, it still remains to clarify the limit of oxidative stress and other redox states that lead to the differential production of NO by each NOS isoforms - nNOS, eNOS and iNOS - so that one can describe its perivascular action for neurogenesis.

During development, NO is differentially and transiently produced in the brain [116-118]. Moreover, the differential cellular and subcellular localization of nNOS in the CNS may explain different functions of NO produced by nNOS [119]. In fact, in the cortex, there are two types of NOS neurons whose distribution is of particular interest due to the relationship between

the sites of NO production and the sites of development of particular pathologies [119]. Furthermore, its pre- or postsynaptical expression influences nNOS functions [120,121]. In the adult olfactory bulb (OB), nNOS is highly expressed in developing neurons of the olfactory epithelium during embryogenesis [120,122] and in the periglomerular cells and granule cells in the OB in the adult [120,123], being necessary for the early postnatal development and for the glomerular OB organization, respectively [123,124]. Furthermore, following a lesion in the OB, nNOS expression is upregulated causing repopulation of this region [117,122,123]. Moreover, developing ependymal cells, which are in close association with SVZ-derived progenitor cells, also transiently express nNOS after birth, but its activity decreases with the maturation of the central canal [125], thus suggesting a role of NO synthesized by nNOS in the development of ependymal cells [125]. Ependymal cells, together with astrocytes, create an appropriate environment for neurogenesis [126].

NO production may be induced by neurotrophic factors, which results in an antiproliferative effect on target cells by inducing cell cycle arrest/exit favoring cell differentiation [127-129]. Most of the studies on the involvement of NO in adult neurogenesis characterized its effect on cell proliferation. However, the evaluation of survival and integration of newly-generated neurons in the neuronal circuitry is also important, since NO is known to be an important regulator of apoptosis [130]. In this context, different studies have shown that NO increases short-term survival of progenitor cell progeny in the DG of adult rats by inhibiting apoptosis after SE [131], and further preventing increases in the activity of caspase-3 [132].

5.2.1. Anti-neurogenic role of nitric oxide

The anti-neurogenic effect of NO has been attributed to its production via nNOS, as demonstrated in several studies using *in vitro* and *in vivo* experimental models. Thus, it was reported that nNOS-derived NO has an antiproliferative effect, and may be also involved in neuronal differentiation, survival and synaptic plasticity [4-6,133,134]. The antiproliferative effect of NO was confirmed by several authors, which showed that the inhibition of NO production by intra-ventricular infusion of a NOS inhibitor or by the knockout of nNOS increase cell proliferation in the DG or in the olfactory subependymal zone of rodents [4,6,7,108]. Indeed, other studies were performed where the selective inhibition of nNOS with 7-nitroindazole (7-NI) was shown to greatly increase cell proliferation in the SVZ, RMS and OB of adult rats, but not in the DG [5]. Moreover, the inhibition of nNOS was also shown to increase neurogenesis and to reduce infarct size, following a stroke [135]. The presence of differentiated nitrergic neurons in the periphery of the neurogenic areas, mainly surrounding the SVZ, and its anatomical organization, contributes to this physiological downregulation of neurogenesis [5,110]. However, the inhibitory role of nNOS-derived NO in neurogenesis was also demonstrated in the DG, after cerebral ischemia [135]. In the DG, the neural precursors of the SGZ are in close proximity with the nitrergic neurons of the hilus, also suggesting a role for NO in the control of adult neurogenesis in this region [136]. These studies showed that chronic inhibition of nNOS increases neurogenesis, supporting the idea that, physiologically, NO produced by nNOS has an anti-neurogenic effect. Recently, several studies have suggest-

ed a mechanism for the negative effect of NO on neurogenesis in the SVZ. These authors suggested the inhibition of the EGF receptor [134] by a mechanism dependent on the nitrosylation of specific cysteine residues and the activation of the phosphoinositide 3-kinase (PI3-K)/Akt signaling pathway [9] as the main mechanisms by which NO negatively regulates neurogenesis in the SVZ (Table II). Furthermore, these authors described the antimitotic effect of NO as being related to the nuclear presence of the cyclin-dependent kinase inhibitor $p27^{Kip1}$ [9].

5.2.2. Neurogenic role of nitric oxide

The pro-neurogenic effect of NO has been reported in several studies using genetic or pharmacological approaches, showing that increased levels of iNOS after an insult to the brain are related to increased neurogenesis in the hippocampus, an event correlated with concurrent decreases in nNOS levels [8,137-139] (Table 2). However, in a study regarding the effect of NO on cell proliferation it was described the involvement of NO derived from both iNOS and nNOS in the enhancement of neurogenesis in the DG of adult rats, following seizures [140]. Other studies also showed that NO synthesized by iNOS following ischemia or by eNOS stimulates neurogenesis in the SVZ or DG, respectively [12,111]. Furthermore, we recently showed that the iNOS-derived NO promotes the proliferation of NSC in the hippocampus of adult rats following SE [13]. Following an injury, the concomitant neuroinflammation results in the activation of microglial cells, which continuously express iNOS [141]. This event leads to the production of large amounts of NO that was shown to be favorable to increasing neurogenesis following acute brain injuries.

Although some questions remain to be assessed, several studies have sought to explore the signaling pathways by which NO from inflammatory origin exerts its pro-neurogenic effect, namely in the regulation of proliferation. Recently, we have shown that supraphysiological concentrations of NO induce the proliferation of SVZ-derived NSC through the activation of at least two signaling pathways, in a biphasic manner: a) the mitogen-activated protein (MAP) kinase ERK 1/2 pathway, and/or b) the cGMP/cGMP-dependent kinase (protein kinase G; PKG) pathway. Thus, the proliferative effect of NO seems to be initially mediated by the direct activation of ERK1/2 signaling pathway [13]. The increased activation of the ERK 1/2 signaling pathway after exposure to NO, leads to the activation of several downstream targets, namely the kinase p90RSK, subsequently leading to decreased nuclear levels of its target $p27^{Kip1}$, allowing cell cycle progression and cell division [13]. Moreover, the activation of cGMP/cGMP-dependent kinase (PKG) pathway appears to be involved following longer periods of exposure to supraphysiological levels of NO [14]. NO involvement in the regulation of other stages of neurogenesis has also been investigated. NO released in inflammatory conditions is also involved in NSC differentiation into astrocytes, a process also referred to as astrogliogenesis, by a mechanism dependent on the activation of JAK/STAT-1 signal transduction pathway [142].

Taken together, these findings show that NO is an important regulator of neurogenesis. The effect of NO on neurogenesis seems to be dependent on the developmental period and of the source of NO. Furthermore, depending on the local concentration and surrounding molecular

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environment NO may regulate neurogenesis in various ways, either favoring it, or impairing it [136,143,144]. As discussed above, NO has concentration-dependent effects. Thus, under physiological conditions NO acts as a negative regulator of neurogenesis [4,5,107], whereas in inflammatory conditions a decrease in nNOS and an increase in iNOS can act as a mechanism to enhance neurogenesis [12,13,134,145,146]. However, the exact molecular mechanisms underlying this dual effect are not fully understood and more studies are needed to determine the downstream targets of NO, particularly to identify potential therapeutic targets and to assess whether modulation of these players is possible to improve the outcome of neurogenesis. Most of the drugs used in studies for the characterization of NO involvement in neurogenesis are therapeutically used with other purposes unrelated to brain injury recovery. So, its implementation as a therapeutic strategy to modulate neurogenesis should be explored. Next, some of the most promising pharmacological approaches intended to modulate signaling pathways dependent on NO will be discussed.

NO source	Proliferation of NSC		Differentiation of NCS		Survival of NSC		Signaling pathway	References
	SVZ	DG	SVZ	DG	SVZ	DG		
nNOS	-	0	=	0	=	0	Nitrosylation of EGF receptor	[9]
	-	0	=	0	0	0	(PI3-K)/Akt pathway	[9,134]
	0	-	0	-	0	0	PSA-NCAM and CREB	[147]
	0	-	0	-	0	-	cAMP phosphorylation	[6]
eNOS	+	0	+	0	0	0	BDNF and VEGF	[148]
	0	+	0	+	0	=	VEGF	[111]
iNOS	+	0	0	0	=	0	ERK 1/2 pathway	[13]
							cGMP/PKG pathway	[14]
	+	+	+	+	0	=	NMDA receptor	[62,149,150]
	+	+	+	+	0	0	L-VGCC	[151]
	+	0	+*	0	=	0	JAK/STAT-1 pathway	[142]

The effects listed in Table II may not be direct. +, increase; -, decrease; =, not changed; 0, not reported; Polysialylated-neuronal cell adhesion molecule, PSA-NCAM; cAMP response element-binding, CREB; Brain-derived neurotrophic factor, BDNF; Vascular endothelial growth factor, VEGF; L-type voltage-gated Ca2+ channel, L-VGCC. * - astrogliogenesis.

Table 2. NO-dependent modulation of adult neurogenesis.

6. The nitric oxide system as a target to enhance endogenous neurogenesis

In physiological conditions, damaged cells and tissues are continuously being repaired in order to maintain homeostasis and normal function of the organism. A deregulation or malfunction of self-repair mechanisms could lead to the emergence of several pathologies as referred in sections 3 and 4. In the adult CNS, the major limitation that researchers face is the restricted

ability for regeneration. Moreover, this process is even more limited during an inflammatory process as the surrounding environment is detrimental to the survival of newborn cells [43]. Acute brain lesions, such as stroke, spinal cord injury, trauma and seizures, which are accompanied by an inflammatory response, have a strong participation on neuronal loss [43]. Neuroinflammation is also a hallmark of chronic pathologies, such as Alzheimer's disease, Huntington's disease and Parkinson's disease [31]. Thus, to overcome the limited ability for brain repair and as an attempt to revert the loss of neurons following inflammation, some strategies have been studied. The most promising strategies include a) stimulation of endogenous neurogenesis, or b) transplantation of exogenous neural precursors/stem cells. Transplantation of exogenous stem cells is a complex approach with several disadvantages including ethical concerns. Furthermore, the risk of rejection and uncontrolled proliferation of grafted cells, which may lead to tumor formation, raises some concerns about its therapeutic applicability. However, although the potentiation of endogenous neurogenesis appears to be a better approach, with higher possibility for therapeutic application, some disadvantages/limitations should be taken into account, such as: a) low yield in the formation of new neurons, b) low rate of long-term survival of new neurons, and c) poor specificity for increasing neurogenesis in the target/lesioned tissue. Here we focus on the stimulation of endogenous neurogenesis by targeting the pre-existing pools of NSC, particularly in SVZ and SGZ niches, mainly by modulating the nitrergic pathways.

As discussed in section 5.2, NO has been widely described as a dual regulator of adult neurogenesis, being involved in the regulation of proliferation, migration, neuronal differentiation and survival of NSC (see Table II). The great majority of studies in the literature characterized the involvement of NO in the regulation of NSC proliferation. In fact, as reported by our group, NO from inflammatory origin has a proliferative effect in the SVZ and SGZ [13]. However, more studies about the involvement of NO in the regulation of migration, differentiation in functional neurons that must correctly integrate neuronal circuits and survival of the newly formed neurons must be performed in order to understand how these neurogenic steps are regulated in an inflammatory context. Although little is known about the *in vivo* applicability of this strategy, recent encouraging evidences are already in the literature where the pharmacological modulation of different players in the nitrergic system has been proved to promote neurogenesis. However, we believe that this approach in a regenerative context should not be considered as an isolated approach, but instead, it could be adjuvant to other strategies in order to ensure an efficacious therapy. Therefore, two different strategies should be considered to enhance neurogenesis: a) controlled increase in NO levels by using NO donors, particularly NO-NSAID and, b) prevention of cGMP degradation by the use of PDE5 inhibitors. Next, these therapeutic approaches for brain repair will be discussed.

6.1. Nitric oxide-releasing non-steroidal anti-inflammatory drugs

NO-releasing drugs have been widely used in several studies for the characterization of the involvement of NO in the regulation of different steps of endogenous neurogenesis. These pharmacological tools were essential to understand that NO-mediated effects on neurogenesis are time and concentration-dependent [14,142]. A wide variety of NO-releasing compounds

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are available, being the most common the diazeniumdiolates, also referred as NONOates (such as DEA/NO, SPER/NO or DETA/NO), that spontaneously release NO under physiological conditions [152]. NONOates were also used in numerous studies to investigate the effect of supraphysiological concentrations of NO on neurogenesis, thus mimicking high NO concentration achieved in the brain in inflammatory conditions [13,142]. However, NO-releasing drugs are chemically distinct, having different half-life times, releasing different amounts of NO *in vitro*. The major disadvantages of the use of these drugs lie in the inability to control the amount of NO released *in vivo*, and the incapacity to specifically release NO in the target tissue/cells. Moreover, factors such as pH, temperature, some co-factors and light, are able to alter the release of NO by these compounds [152,153]. As described above, given that different amounts of NO have different effects on neurogenesis, it is essential to control the release of NO in order to keep it in levels that are beneficial to neurogenesis. Thus, it arises the need to develop new NO-releasing drugs in order to overcome these disadvantages.

More recently, a new class of NO-releasing compounds has been developed, NO-NSAID. These drugs are synthesized by adding a nitric oxide donating group to classical NSAID. Conventional NSAID are broad-spectrum compounds used worldwide due to their properties as analgesics, antipyretics and, at higher doses, anti-inflammatory. However, chronic use of NSAID is limited, mainly due to increased side effects in the gastrointestinal (GI) tract, cardiovascular system and kidneys (extensively reviewed by [154-156]). Traditional NSAID exert their effect by inhibiting both isoforms of cyclooxygenase enzyme (COX-1 and COX-2), thus blocking the synthesis of prostaglandins. The great majority of side effects associated to the use of these drugs are associated with the inhibition of COX-1 pathway, and subsequent decrease in gastroprotective prostaglandins.

To overcome these side effects and improve safety of NSAID, new drugs were designed a) coxibs, selective COX-2 inhibitors, and b) hybrid prodrugs, which include NO-NSAID. The latter drugs take advantage of some characteristics of NO such as its potent vasodilator effect, inhibition of leukocyte adherence to the gastric vascular endothelium and inhibition of caspase activity, thus mimicking the biological effects of prostaglandins in the GI tract [19,157,158]. Several *in vivo* studies have shown that NO released by NO-NSAID has a reduced GI toxicity profile compared to NSAID alone, without affecting the anti-inflammatory effectiveness [159-161]. In fact, low levels of conventional NO donors were shown to inhibit cell apoptosis *in vivo* by inhibiting caspase activity and, thus, sparing the gastric mucosa from the pro-apoptotic effect induced by TNF-alpha, an effect that seems to be dependent on cGMP formation [161-164]. In addition, NO released by NO-NSAID inactivates caspases, contributing to the gastric-sparing effect of these drugs. Moreover, these NO-donating drugs release NO in amounts that mimics *in vivo* NO production by constitutive NOS, which seems to be linked to a reduced toxicity when compared to the parent NSAID [19,165]. In addition, the relatively slow rate of NO release by NO-NSAID when compared to classic NO donors, such as sodium nitroprusside (SNP) [166], allows a more controlled release of NO and a long-lasting protective effect, which should be considered a major advantage in the use of these drugs. Since there is no massive burst in NO levels, excitotoxic events are prevented when compared to classical drugs.

Chronic inflammatory events were linked to Alzheimer's disease, where several pro-inflammatory mediators are released, such as the cytokines IL-1beta and TNF-alpha [167], and caspase enzymes are activated [168]. Chronic administration of NSAID appears to reduce the risk for developing Alzheimer's disease [169-172], also ameliorating impairment of cognitive functions in patients (reviewed in [173]). Other studies have been performed to study the effect of anti-inflammatory drugs in the treatment of acute brain lesions, such as *status epilepticus* and ischemia. In this context, anti-inflammatory drugs, such as indomethacin, have been described to reduce microglial activation and to promote NSC proliferation and improve migration and survival of newborn cells, thus restoring neurogenesis following cranial irradiation or focal ischemia [49,174]. Therefore, although the neuroprotective effects of NSAID in models of chronic brain inflammation have been recently described in the literature, the side effects of NSAID in other biological systems should not be ignored. Given the advantages of NO-NSAID, and given their ability to rapidly cross the blood-brain barrier (BBB) [175], NO-NSAID have been considered for the treatment of CNS disorders, particularly for the control of neuroinflammation that, as already discussed, may affect neurogenesis [165]. However, to date, little is known about the effect of NO-NSAID on neurogenesis following acute or chronic brain injury. Nevertheless, studies in models of chronic brain inflammation showed that chronic administration of NO-flurbiprofen significantly attenuated brain inflammation by decreasing the density and reactive state of microglial cells [176,177]. In this study, treatment with NO-flurbiprofen reduced brain inflammation and attenuated the effects of LPS-activated microglia in young and adult rats, but not in aged rats, which suggested this drug to be a possible therapeutic tool to be used in the onset of Alzheimer's disease, before the development of chronic inflammatory events associated with age [178]. Besides the reports that NSAID decrease the expression of iNOS in inflammatory cells, NO-flurbiprofen appears to upregulate the expression of this enzyme in LPS-activated microglial cells [179]. This effect leads to an even higher increase in NO production, which has been attributed to NO released from NO-flurbiprofen, since traditional NO donors lead to similar results. Interestingly, the activation of microglial iNOS following a brain insult enhances NSC proliferation in the SGZ following epileptic seizures, thus promoting neurogenesis [13].

Overall, the beneficial effects of NO-NSAID observed in experimental models of neurodegenerative diseases are encouraging for the development of strategies to control neuroinflammation and target endogenous neurogenesis by using these drugs [165]. However, further studies need to be conducted in order to understand the mechanisms and within which concentrations NO-derived from NO-NSAID may promote neurogenesis.

6.2. Phosphodiesterase 5 inhibitors

The main intracellular target of NO is the heme-containing enzyme sGC. Activation of sGC leads to an increased production of cGMP [102,180], which subsequently activates cGMP-dependent PKG [181,182]. PKG regulates various physiological events, such as synaptic plasticity or synthesis and release of neurotransmitters (reviewed by [183]). In physiological conditions, intracellular cGMP levels are controlled through cyclic nucleotide phosphodiesterases (PDE), enzymes that hydrolyze the 3'-phosphodiester bound of cyclic AMP (cAMP) or

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cGMP, originating their respective inactive monophosphates, 5'-AMP or 5'-GMP. PDE are ubiquitous enzymes classified in 11 families by their different substrate specificity, kinetic properties and cellular and subcellular distribution (extensively reviewed in [184]). As different PDE families present such a wide distribution among the tissues, including the brain, inhibition of one or more PDE has been studied as an approach for the treatment of several diseases, mainly by controlling the levels of the respective second messengers cAMP and/or cGMP.

cGMP-dependent physiological functions, may be regulated by controlling PDE type 5 isoenzyme activity, which specifically hydrolyzes cGMP. Thus, a good strategy to increase intracellular levels of cGMP may be through inhibition of this enzyme [185]. PDE5 is a widely expressed cytosolic enzyme, whose protein activity was found in the lung, vascular and tracheal smooth muscle, spleen, platelets, corpus cavernosum [186-188], being also highly present in several brain regions, including Purkinje cells and SVZ [189-191]. PDE5 and PDE5 inhibition have been extensively studied in the last decades and several PDE5 inhibitors have been developed. The most characterized PDE5 inhibitor is sildenafil, commercially available as Viagra, a drug used for the treatment of erectile dysfunction and pulmonary arterial hypertension. However, besides PDE5, sildenafil also inhibits PDE 1 and 6 with lower potency [192]. In order to overcome this issue, more selective PDE5 inhibitors were developed for the treatment of erectile dysfunction: vardenafil (Levitra), tadalafil (Cialis) and, more recently, avanafil (Stendra). In addition, a new compound with even higher selectivity for PDE5 was also developed, T0156 [193].

The decrease in cGMP levels appears to be one of the causes for the decreased neurogenesis in aging, which normally correlates with the development of neurodegenerative diseases [194]. Although neurogenesis is increased in early stages of neurodegenerative diseases, as a compensatory mechanism, the more advanced or severe stages are characterized by impairment of neurogenesis [195]. In the aged brain, there is a decrease in NO levels with a concomitant decline in cGMP levels, ultimately resulting in the abolishment of cell proliferation and impairments in learning and memory [194]. Targeting an enzyme specific for the hydrolysis of cGMP, such as PDE5, has been proven to be a good strategy to reverse this process and, thus, enhance neurogenesis following acute or chronic brain insults. In fact, PDE5 inhibitors are known to modulate several functions in the adult brain. Several reports showed that PDE5 inhibitors, such as sildenafil, have a neuroprotective role, by improving memory and learning [20,196-201]. Beyond the important role in memory and cognition, PDE5 inhibitors could also be used to target endogenous neurogenesis in the adult brain. In neurodegenerative diseases such as Alzheimer's disease, the progressive neurodegeneration results in cognitive dysfunction, with memory loss and motoneural impairment. The administration of PDE5 inhibitors has been studied as a possible therapy for this disease, due to their ability to reverse long-term memory deficits [202,203]. Sildenafil has also been described to improve symptoms of multiple sclerosis [22], while chronic administration of sildenafil or tadalafil appears to have an anxiolytic effect [204]. Moreover, following an acute injury, PDE5 inhibitors are described to enhance endogenous neurogenesis and neuronal function recovery in models of ischemic injury or stroke [205-208]. In addition, sildenafil was shown to stimulate SVZ-derived NSC proliferation, an effect that appears to be dependent on the activation of the PI3-K/Akt pathway [191].

Overall, apart from small differences in the selectivity for PDE5, the majority of PDE5 inhibitors present similar effects in increasing cGMP levels and subsequent activation of nitrergic pathways. In spite of the fact that inhibition of PDE5 does not have an anti-inflammatory effect as NO-NSAID, the neuroprotective effect of PDE5 inhibitors appears to be consensual. However, in the CNS, the effect of PDE5 inhibitors is highly dependent on their permeability to the BBB, and more studies need to be conducted in order to correctly characterize the kinetics on PDE5 inhibitors permeabilization into the CNS. Within this background, the modulation of PDE5 activity could be a good approach to control the levels of cGMP, which could be used in the treatment of several pathologies in which the levels of cGMP are altered. Although there are some studies focused on the stimulation of neurogenesis, the use of inhibitors for PDE5 deserves further investigation in order to clarify their role in controlling different stages of neurogenesis, including migration, differentiation, functionality and survival of newborn neurons, and further understand the mechanisms underlying these effects.

6.3. Other strategies

The involvement of NO in a wide-range of physiological processes and cell function makes it a desirable molecule to use in the clinics, being a major target of pharmaceutical industry. Besides the strategies mentioned above, many synthetic compounds with various chemical and biological modifications have been developed in order to overcome some limiting factors of NO such as its short half-life, the instability during storage and its potential toxicity. Thus, recent innovations in the field of nanotechnology of the profile of NO-donating drugs are being tested to increase the utility and the safety of these compounds in order to be used in biomedical applications, as described below.

There is a wide variety of NO donors that are capable of releasing NO spontaneously or in a controlled way to certain target tissues. The great challenge is how to release NO and to achieve an optimal concentration locally in the brain, thus promoting a therapeutic effect with minimum toxicity [209]. Recent investigations aim at incorporating NO donors into biopolymers mimicking endogenous production of NO at target sites [202]. Nanomaterials are delivery systems with many advantages and a promising therapeutic applicability. These new systems are advantageous due to their: a) small size; b) ability to target specific tissues or cells, having the capacity to cross several biological barriers, such as BBB, reaching tissues that are inaccessible to classic drugs; c) ability to accumulate high drug concentrations; d) enhancement of bioavailability and drug solubility; e) facilitation of drug administration; f) increase of drug circulation in the blood; g) reduction of the dose required to exert an efficient therapeutic effect; and e) decreased local toxicity and reduction of side effects (reviewed by [203]).

The application of nanomaterials to classic NO donors may be an alternative to improve their stability and to therapeutically deliver NO. Among the most studied nanosystems are liposomes and polymeric nanocarriers, such as micelles and hydrogels. Overall, this emergent field of study is of great interest since it allows the development of compounds that release NO in a controlled and sustained way. However, there is a lack of studies concerning the application of these strategies to the CNS. To date, none of these nanosystems is commercially available to target/improve endogenous neurogenesis and further studies are needed in order

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to develop effective NO-releasing drugs. By these strategies, NO levels in certain targets can be regulated overcoming the traditional limitations of classical NO donors, thus allowing the control of NO levels in specific regions of adult brain in an attempt to repair the lesioned brain.

7. Future directions

Most brain disorders have common features such as neurodegeneration and neuroinflammation. Understanding the mechanisms underlying the evolution of these pathologies, the factors that lead to their onset and the biology of neuronal injury is of extreme importance for the development of efficient therapies, thus allowing to act on risk groups in order to prevent their occurrence. Neurogenesis is an important mechanism of repair in the adult brain, being considered as a critical target to counteract the loss of neurons. As discussed above, two promising strategies could be considered to improve neurogenesis, which include a) transplantation of exogenous neural precursors/stem cells, or b) stimulation of endogenous neurogenesis. However, both strategies for increasing neurogenesis have been linked to an inflammatory response.

Transplantation of exogenous stem cells is a complex and invasive approach with several disadvantages, raising questions about its therapeutic applicability, such as: a) uncontrolled proliferation of grafted cells that may lead to tumor formation, b) the risk of rejection, and c) ethical concerns. However, potentiation of endogenous neurogenesis appears to be a better approach, although with some disadvantages/limitations, such as: a) low yield in the formation of new brain cells, b) low rate of long-term survival of newly generated neurons, and c) poor specificity for increasing local neurogenesis in the target/lesioned tissue. Overall, stimulation of endogenous neurogenesis appears to have higher possibilities for a therapeutic application although it is a less efficient strategy, it has been considered a safer approach when compared to the invasive transplantation of exogenous precursor/stem cells.

Knowing how the inflammatory response affects neurogenesis and the factors that are altered following brain lesion will allow the modulation of certain signaling pathways involved in the regulation of neurogenesis. In fact, the modulation of the nitrergic system could be beneficial for controlling neurogenesis following brain inflammation.

Nitric oxide, by its importance as a regulator of neurogenesis, appears as potential target for the enhancement of endogenous neurogenesis, thus, the development of selective drugs for modulation of the nitrergic signaling pathways is an increasing challenge to pharmaceutical companies. Currently, many strategies are under study for the treatment of CNS disorders, some of them targeting the nitrergic system. The development of NO-NSAID is of great interest as it combines the anti-inflammatory effect to the release of NO, thus reducing the deleterious effects of neuroinflammation and, simultaneously, taking advantage of the pro-neurogenic effect of NO [165]. Moreover, PDE5 inhibitors also seem to be a good strategy to improve neurogenesis, although they lack an anti-inflammatory effect when compared to NO-NSAID [210]. Although little is known about the applicability of this strategy in a regenerative context,

recent encouraging evidences support that NO-NSAID and PDE5 inhibitors should be considered as therapeutic strategies to enhance neurogenesis as discussed in this chapter.

In spite of all the evidences showing the important role of the nitrergic system in the modulation of neurogenesis, further studies are needed. In fact, more studies regarding the regulation of migration, differentiation in functional neurons and survival of the newly generated cells must be performed in order to fully understand how these neurogenic events are regulated in an inflammatory context, given the large number of molecular players involved besides NO. Modulation of the nitrergic pathways in a regenerative context should be considered, not as an isolated approach, but instead, as an adjuvant strategy in order to ensure an efficacious therapy.

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