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REVIEW ARTICLE

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Unraveling the potential of gasotransmitters as neurogenic and neuroprotective molecules: focus on Alzheimer's and Parkinson's diseases

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ABSTRACT

Alzheimer's disease and Parkinson's disease are the two most prevalent neurodegenerative disorders worldwide, both characterized by progressive neuronal loss. Despite distinct pathophysiological features, they share cellular dysfunctions such as abnormal protein aggregation, oxidative stress, and neuroinflammation, research into which might be beneficial for developing novel therapeutic strategies that could tackle both conditions. This review highlights the emerging role of the gasotransmitters nitric oxide, carbon monoxide and hydrogen sulfide as modulators of adult neurogenesis and neuroprotection in Alzheimer's disease and Parkinson's disease. We have gathered recent evidence demonstrating that these endogenous gases exert anti-inflammatory, antioxidant, and anti-apoptotic effects, and, critically, promote neurogenesis – suggesting a dual neuroprotective and neuroregenerative therapeutic potential. The unique physicochemical features of these gasotransmitters, including their ability to cross the blood–brain barrier and diffuse rapidly throughout the neural tissue, further support their suitability as candidates for innovative neuroregenerative treatments. While clinical translation remains challenging, harnessing the neurogenic and neuroprotective actions of these gasotransmitters may offer transformative avenues for addressing the increasing burden of Alzheimer's disease and Parkinson's disease.

KEYWORDS

Gasotransmitters; nitric oxide; carbon monoxide; hydrogen sulfide; neurogenesis; neuroprotection; Alzheimer's disease; Parkinson's disease

1. Introduction

We live in a time where neurodegenerative diseases significantly prevail among populations, with Alzheimer's disease (AD) and Parkinson's disease (PD) being the two most prevalent worldwide. AD and PD are intricate diseases with distinct pathophysiologies; yet they share hallmark features such as progressive neuronal loss and an associated deterioration of cognitive and/or motor function, which are derived from altered cellular mechanisms, such as abnormalities in protein folding and functioning and significant inflammation and oxidative stress in neuronal cells. These shared features highlight the potential for developing therapeutic strategies that could address both conditions. Despite extensive research efforts, AD and PD persist without a cure, posing numerous challenges for affected individuals and their families, as their daily routines are deeply impacted. Additionally, these diseases place a significant burden on societies due to the high health care and social costs associated with managing these patients. These factors make the search for novel avenues to develop effective treatments for AD and PD urgent. This need is even more critical as global populations have higher average life expectancies, and therefore, the prevalence of these diseases is estimated to increase considerably in the coming years. In this review, we aim to elucidate the potential of the gasotransmitters nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) as modulators of adult neurogenesis, as well as their implications for AD and PD. We summarize and integrate recent evidence concerning the interplay among these gasotransmitters in the brain and

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their influence on key neurogenic processes. By highlighting both shared and distinct mechanisms of action, we propose that targeting gasotransmitter signaling pathways may represent a promising therapeutic strategy for the two most prevalent proteinopathies – Alzheimer's and Parkinson's disease. Despite increasing recognition of their neuromodulatory functions, the roles of gasotransmitters in adult neurogenesis and their therapeutic relevance remain incompletely understood.

2. Literature search methodology

Literature search was performed through PubMed using combinations of the keywords 'gasotransmitters', 'nitric oxide', 'carbon monoxide', 'hydrogen sulfide', 'neurogenesis', 'Alzheimer's disease' and 'Parkinson's disease'. Screening of the reference lists of selected papers was performed to include only experimental studies in *in vivo* mammalian models and humans. We included English-language original studies, reviews, and relevant preclinical or clinical reports addressing the roles of NO, CO, or H_2S in adult neurogenesis and their potential therapeutic relevance in Alzheimer's and Parkinson's diseases. Studies limited to non-neural systems, non-mammalian species, or *in vitro* models were excluded, except when providing mechanistic insights relevant to the topic.

3. Neurogenesis

Neurogenesis is a multistep endogenous process aimed at generating new nerve cells from neural stem cells (NSC) and subsequently integrating them into existing neural circuits. Neural stem cells are quiescent and multipotent cells that can divide into additional undifferentiated neuroepithelial cells and give rise to radial glial cells, the base of neurons, oligodendrocytes, astrocytes and ependymal cells [1]. To be fully successful, the process of neurogenesis involves six sequential main steps, which are interdependent and partially overlap: (1) proliferation of NSCs, (2) fate determination, (3) migration, (4) integration of newborn cells into the pre-existing neuronal circuits, (5) maturation and (6) long-term survival [2]. Each step of the neurogenic process is highly regulated by intrinsic and environmental signals to control cell movement and ensure the correct transition to the next stage. Microglia intervene in neurogenesis by phagocytosing the new neurons that fail to integrate the pre-existing circuits [3]. Newborn neurons are imperative for the proper functioning of vital brain processes, including cognition, learning, and memory, among other functions; and as such, changes in any of the neurogenic steps may compromise these activities, leading to cognitive impairment (reviewed in [4]).

3.1. Adult neurogenesis

Although neurogenesis is most active during embryonic development, being responsible for the formation of all cell types of the nervous system, it also occurs in adulthood, apparently at a basal rate. The discovery of postnatal neurogenesis in mammals, first reported in the 1960s, challenged the long-held belief that the adult brain lacked regenerative capacity [5,6]. Since then, evidence of adult neurogenesis has been confirmed across several species, including humans [7]. Nevertheless, its existence and extent in the adult human brain remain controversial, with conflicting findings sustaining an ongoing debate that continues to attract the neuroscience community. Several authors showed that hippocampal neurogenesis is preserved throughout aging [8–10] while others demonstrated that neurogenesis in the hippocampus is a process that falls drastically in children, being barely detectable in the adult human brain [11,12]. As more data in this area is needed, the evidence gathered so far indicates that in the adult central nervous system (CNS), endogenous neurogenesis occurs due to the existence of NSC in two specific brain regions, called neurogenic niches: the SVZ in the lateral walls of the lateral ventricles [13–17] and the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus [7,18,19]. Nevertheless, as research progresses, neurogenic niches have also been found in other non-canonical areas of the brain, including neocortex [20], striatum [21], amygdala [22] and substantia nigra [23]. To delve further into this thematic regarding the 'novel' neurogenic niches, readers can access two recent reviews [24,25]. The encouraging outcomes observed in experimental models dedicated to test different modulators of neurogenesis demonstrate that enhancement of this process in the adult brain is attainable [26,27]; however, this is not a reality yet

in the context of clinical practice aimed at treating brain diseases. Very inspiring data have appeared in recent years, derived from clinical trials using NSC transplantation for the management of AD and PD, for example (reviewed in [28–31]). Certainly, the replacement of the lost neuronal cells by functional cells that could effectively integrate the neuronal circuits is the ideal goal of neuro-regenerative medicine. Still, another strategy that is also currently being tested is the stimulation of neurogenesis by activation of endogenous NSC [32]. In this regard, some examples include the use of a low-intensity focused ultrasound (LIFUS) apparatus, which activated neurogenesis in Sprague Dawley rats [33] and removed amyloid beta deposits and restored memory in a mouse model of AD [34]. More recently, Chen and colleagues described in a very elegant study the activation of NPCs following the implantation of a biodegradable and biocompatible electrode for electrical stimulation in the brain of C57BL6 mice [35]. These positive effects instill in researchers a continuous challenge and pave the way for exploring further avenues aimed at addressing the question of how to enhance adult neurogenesis in a sustainable and effective fashion. As we will detail subsequently, gasotransmitters might be a potential answer, due to the fascinating intrinsic features that these molecules possess.

4. Gasotransmitters in the brain

In 2002, R. Wang defined five criteria that must be fulfilled in order for a certain molecule to be considered a gasotransmitter. Later in 2014, the same author revised these criteria to six. Based on this, a gasotransmitter should encompass the following features: (1) be a small molecule of gas; (2) be freely permeable across membranes, bypassing the need for specific membrane receptors or other means of transportation; (3) be endogenously produced; (4) have well-defined functions at physiological concentrations; 5) its endogenous functions can be mimicked by exogenously applied equivalents; (6) be involved in signal transduction [36,37]. Presently, nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) completely fulfill these requirements, being well-accepted that these gaseous molecules constitute a recognized group of important gasotransmitters with a great impact on biology. In addition to these three gasotransmitters, other molecules are emerging in this field and have been proposed as new candidates to integrate into the gasotransmitters' family. These new players include ammonia, cyanide, methane, sulphur dioxide and hydrogen gas [38]. Scientific research on the function of these latter molecules as eventual gasotransmitters is still in its infancy, but it is already recognized that while ammonia and methane totally meet all the necessary requirements described by R. Wang, there is still debate regarding the remaining molecules. This review will focus only on NO, CO and H_2S. These gasotransmitters are endogenously produced in cells by means of well-defined enzymatic cascades, but also by non-enzymatic processes. Additionally, biological systems are in constant contact with several external sources that generate these gaseous molecules; therefore we are continuously being subjected to some level of NO, CO and H_2S exposure, which, as we shall see next, will generate diverse effects in cells.

4.1. Nitric oxide

Nitric oxide is a gaseous molecule that was discovered as a secretory product of mammalian cells. The scientific community was intrigued by an endogenous vasodilator known as endothelium-derived relaxing factor (EDRF) up to the discovery of nitroglycerine, a previously known vasoactive medication used to treat angina pectoris, whose research on their mechanism of action helped to identify EDRF as NO [39,40]. Mammalian cells produce NO by enzymatic activity through a specific group of enzymes, the nitric oxide synthases (NOS), which oxidizes L-arginine (L-Arg), producing citrulline and NO [41,42]. This family of enzymes include neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), endothelial NOS (eNOS or NOS3), and mitochondrial NOS (mtNOS), sharing the mechanism of action that requires cofactors for their proper function, such as nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and oxygen for catalyzing the conversion of L-arginine into L-citrulline [43,44]. Dimerization is essential for NOS activity, and heme plays a crucial role in this process [45]. Additional sources of NO include non-enzymatic oxidation of L-Arg [46], xanthine oxidase [47], and other reductases that are able to convert nitrates to nitrites [48,49]. The nNOS is a protein consisting of 1434 amino acids in length with a molecular weight of 161 kDa. In the brain, nNOS is mostly expressed in specific neurons, such as in subpopulations of GABAergic

interneurons of the hippocampus and neocortex and in the spinal cord. Apart from the brain, the skeletal muscle is a main source of nNOS [50–52]. Distinguishing itself from other NOS isoforms, nNOS possesses a PDZ domain at its N-terminal, enabling interactions with proteins also containing PDZ domains [53] thus influencing NOS activity. The eNOS is a 134 kDa protein composed of 1203 amino acids and is constitutively expressed in endothelial cells of the vasculature, including those supplying the brain [54]. The efficient production of NO by eNOS requires precise control of the binding of multiple substrates and cofactors and disruption of this coordinated catalysis, often due to increased oxidative stress, can impair eNOS activity. For instance, ROS can oxidize eNOS cofactors, such as BH4, leading to a shift from the dimeric to the monomeric form of the enzyme, which results in the uncoupling of eNOS, with the consequent production of superoxide anion instead of NO, potentially causing detrimental effects on cells [55]. Inducible NOS is a protein weighing 131 kDa, consisting of 1153 amino acids in length and is the simplest among mammalian NOS enzymes in terms of structure [56]. Expression of iNOS is predominantly observed following oxidative or inflammatory conditions, occurring in various cell types such as macrophages, VSMC, fibroblasts, endothelial cells, cardiomyocytes, leukocytes, and nerve cells [53,57]. Upon induction, iNOS generates substantial amounts of NO in the micromolar range, persisting until the enzyme is degraded, often lasting hours [58]. Nitric oxide is recognized as having either neurotoxic or neuroprotective effects in many diseases' contexts, these effects being highly concentration-dependent, such as in the case of AD, which was recently reviewed by Azargoonjahromi [59]. This author nicely gathered numerous features of NO in AD, and for instance, nitration-modified proteins have been verified in AD patients' postmortem brains which attribute a pathological effect to NO either in the etiology or progression of AD. On the contrary, NO appears to underlie important brain functions such as neuroplasticity and myelination [59]. NO can exert its effects by three different mechanisms: (I) classical NO signaling; (II) less classical NO signaling; and (III) nonclassical NO signaling [60,61]. Briefly, the classical signaling (also known as the canonical pathway) involves the production of NO by NOS with the consequent activation of soluble guanylyl cyclase (sGC) and generation of the second messenger cGMP; the less classical signaling regards the inhibition of cytochrome c oxidase (CcO) in the mitochondria induced by NO; and the nonclassical signaling encompasses a group of post-translational modifications (PTM) induced by the interaction of NO moieties with cysteine residues leading to S-nitrosylation or S-glutathionylation or with tyrosine residues leading to nitration. The work of Martinez-Ruiz and colleagues was a pioneer in this field and is a required reading for a deeper understanding of this issue [60,61]. The NO produced by NOS can target various enzymes and proteins within cells, influencing downstream signaling pathways. Regarding the brain, NO has been associated with the signaling of important processes such as memory and learning, dendritic spine growth, pain transmission and the regulation of presynaptic plasticity in GABAergic and glutamatergic neurons, for example (reviewed in [62]), through various mechanisms, including the regulation of neurotransmitter release and modulation of ion channels. In these scenarios, NO is potentially released from pre – or postsynaptic terminals where it acts as a neurotransmitter with opposing effects, regulating the above-mentioned functions. For instance, when generated post-synaptically, NO is primarily related to NMDAR activation, where it co-localizes with postsynaptic density protein PSD95, acting as a retrograde neurotransmitter. However, the presynaptic terminals of peripheral nitrergic neurons also produce NO, which function as an anterograde neurotransmitter [62]. Beyond the synapse, NO can diffuse to neighboring cells and influence cellular functions more broadly [63].

4.2. Carbon monoxide

The first time that CO was detected in the human body dates to 1894 [64]. However, the knowledge that it was endogenously produced took more than fifty years to be established [65]. Twenty years later, Tenhunen and colleagues described heme oxygenase (HO) as responsible for the cleavage of heme to form biliverdin, generating CO and free iron (Fe^{2+}) [66,67]. One of the most well-known aspects of CO in biological systems is its effects as a toxic agent when inhaled at high doses from external sources. Upon competing with oxygen for the same binding site on hemoglobin, it will form carboxyhemoglobin, which reduces the oxygen delivery to the tissues and organs, leading to lethal poisoning. Presently, CO is well accepted as a relevant endogenous signaling molecule and has been considered a gasotransmitter since 1990 [68]. The interest in the physiological role of CO emerged not only with the observation of its colocalization with sGC in the olfactory processes in the brain, but also with the discovery of NO as a gasotransmitter, which

opened a new research field on membrane/receptor-independent signaling gas molecules. There are three genetically distinct isoforms of HO, all present in the nervous system and differently regulated. HO-1, the inducible isoform, is a heat-shock protein (HSP-32) with 288 amino acids and approximately 33 kDa and its expression is stress-responsive to hyperoxia, hypoxia, lipopolysaccharide (LPS), or oxidative stress. In the brain, the expression of HO-1 protein is present in a small group of neurons and glial cells [69]. Levels of HO-1 protein were detected in rat hippocampus at different ages, while HO-1 mRNA was physiologically detectable in the hippocampus and cerebellum [70,71]. HO-2, a protein composed of 316 amino acids and 36 kDa, was found to be constitutively expressed on the endoplasmic reticulum of cortical neurons and type I astrocytes, with a closely related localization to the sGC. HO-3 was described in 1997 as a pseudogene and Scapagnini and colleagues found its mRNA expression mainly in astrocytes of the hippocampus, cerebellum, and cortex [68,71,72]. Of the three heme oxygenase, HO-3 is the less understood so far and in fact, the investigation of the structure of the rat HO-3 gene failed to prove any function, suggesting that HO-3 might not be catalytically active and as such HO-3 gene might be confirmed as a pseudogene derived from the HO-2 transcript [73]. The oxidative catabolism of heme has been estimated to account for 86% of endogenous CO production [67]. In mammals, in addition to these enzymatic pathways, CO can also be produced through many other routes, such as lipid peroxidation, for example. Carbon monoxide production was observed upon peroxidation of isolated phospholipids [74] and is a result of cytochrome P450 activation during iron-dependent lipid peroxidation [75] and is also a product of microbiome activation [76], among other sources. A very well-designed chronology on the discovery of the biological and physiological importance of endogenous CO can be read in Wu and Wang's review [77]. CO has several targets, mostly related to the activation of protective-signalsing pathways. The primary molecular target of CO is the heme-iron center of haemoproteins, competing with the O_2-binding sites of hsemoglobin when in high levels and in this scope, sGC is one of the most widely recognized molecular targets of CO. The activation of MAPKs is also a very important target for CO and in this signaling pathway, CO is especially relevant for the cytoprotective, anti-inflammatory, anti-apoptotic, and anti-proliferative effects that follow p38 MAPK activation (reviewed in [78]). CO is also involved in the regulation of ion channels, mostly K^+ channels, and was observed to stimulate alternative signaling pathways in the brain leading to activation of cyclooxygenase [79,80]. Most of the effects described for CO are due to HO modulation, especially inducible HO-1. The signaling function of HO proteins has been extensively studied in the last decade, showing that HO plays an important role in the defense mechanism against oxidative stress, since biliverdin and its reduced form, bilirubin, may work as potent physiological antioxidants [81,82]. Also related to cellular protection against oxidative stress, the induction of HO-1 expression by Nrf2, which results from the binding of the latest to the antioxidant response element in the promoter region of the HO-1 gene, was described by several authors and pointed as a potential pharmacological target for neurodegenerative diseases [83,84]. Similarly, as demonstrated for NO, there is a common sense that CO participate in the regulation of neuronal function and communication, particularly the CO-HO-1 axis [85–87]. CO has been implicated in several neuronal signaling pathways with emphasis on its role in olfactory neurotransmission, mostly mediated by cGMP [78]. Additionally, others have shown that CO can act as a neurotransmitter and is involved in long-term potentiation (LTP), namely, it is important to initiate the LTP, but it does not seem to be so relevant regarding the maintenance phase in the hippocampus of rodent models [88,89]. CO has been described as neuroprotective, especially by overexpression of HO-1, considered an effective antioxidant in the CNS. In a study conducted by Cousar et al., it was shown that there is an increased level of HO-1 after severe traumatic brain injury in the CSF of infants and children [90]. The synthesis of the HO-1 subtype was shown to be activated during cerebral ischemia – reperfusion injury and was highly concentrated in the border of the infarcted tissue and glial cells [91]. An increase in HO-1 following normobaric hypoxia was also detected in astrocytes, and the consecutive increase in intracellular cGMP in neurons led to a reduced activity of caspase-3 and therefore protected against apoptosis and cell death [92]. Moreover, a neuroprotective role for HO-2 has been recognized in a brain hypoxia context, as reviewed by Muñoz-Sánchez and Chánez-Cárdenas [93]. However, HO-1 up-regulation has also been widely implicated in neuronal damage and degeneration. The deregulation of HO system has been associated with the pathogenesis of AD, where HO-1-overexpression was mainly observed in the hippocampus and cerebral cortex, and co-localizes to neurons, neurofibrillary tangles, GFAP-positive astrocytes, choroid plexus epithelial cells, ependyma, corpora amylacea and senile plaques [94,95]. Hence, HO-1 protein was pointed as a significant candidate for serum biomarker for initial assessment of AD because this protein increases in patients

with AD and also with mild cognitive impairment [96,97]. The strong expression of HO-1 in nigral astroglia and in dopaminergic neuronal Lewy bodies was also associated with the neuropathology of PD [98,99]. Brain ageing was also pointed out as a result of HO-1 deregulation, as it was demonstrated that HO-1 expression increases with ageing in the human normal brain, both in neurons and neuroglia and in the cerebral cortex and hippocampus [100].

4.3. Hydrogen sulfide

Hydrogen sulfide is a gaseous molecule with a very characteristic odor of rotten eggs and at the time of its discovery it was classified as a hazardous toxic gas. However, as the interest in this molecule increased within the scientific community, the categorization of H_2S has changed from a harmful entity to a molecule with a very important role at the physiological level, as reviewed by Vandiver and Snyder [101]. A timeline of this historical change can be found in Szabo's paper, where there are the key discoveries related to H_2S over the last three centuries, but also a compilation of the most frequently cited papers in the field [102]. In the human body, tissues such as the liver, the gut, and the kidneys are the main producers of H_2S, which occurs mostly by an enzymatic process named transsulfuration [103]. This is a series of events that uses methionine as a sulfur donor to subsequently convert this amino acid into cysteine through the generation of homocysteine and cystathionine as intermediates. Additionally, the catabolism of cysteine also produces H_2S [104,105]. These pathways are regulated mainly by three enzymes: cystathionine gamma-lyase (CSE, CTH or CGL), cystathionine beta-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST, 3MST, MST, or MPST) (reviewed in [106]). Non-enzymatic processes, mostly from bound sulfane sulfur such as persulfides, thiosulfates or polysulfides, in the presence of NAD(P)H, may also be implicated in H_2S production, as well as additional exogenous sources [107], but they will not be discussed in this review. Cystathionine gamma-lyase, a 405 amino acid protein with a 45 kDa, is considered the main enzyme that generates H_2S, and it is an intermediary in the transsulfuration pathway. It appears to be found mostly in the cytoplasm of cells and, in certain cases, in mitochondria. This enzyme is extensively expressed in a variety of systems, including the vascular and respiratory systems and to a lesser extent in the CNS [108–111]. CBS is a cytosolic protein with 551 amino acids in length and 61 kDa. As part of the transsulfuration pathway, it is responsible for the production of cystathionine through the condensation of serine and homocysteine. In contrast to the CSE enzyme, CBS is highly expressed in the CNS and is also found in other systems, such as cardiovascular or respiratory [109–111]. In the brain, the hippocampus, cerebellum, and cerebral cortex contain the largest amounts of this enzyme [112,113]. It has been demonstrated that CBS expression influences differentiation and proliferation of neuronal stem cells [114]. 3-mercaptopyruvate sulfurtransferase, with 297 amino acids and 33 kDa, is highly expressed throughout all mammalian cells and tissues and it is involved in cysteine catabolism. L-cysteine and homocysteine are direct substrates of CSE and CBS. However, the production of H_2S by 3MST needs a first step conducted by cysteineaminotransferase (CAT) to metabolize L-cysteine to 3-mercaptopyruvate. Then, as the name says, 3-MST converts 3-mercaptopyruvate to pyruvate and creates persulfides, by transferring sulfur to free acceptors, which release H_2S. The cellular localization of 3-MST has been reported has be mainly mitochondrial, but recent research has shown that this enzyme can also be found in the cytoplasm of several types of cells [109–111]. H_2S seems to interact with DNA, proteins, and reactive species and given this wide range of targets, H_2S can easily be involved in a variety of pathways that may be directly or indirectly related to physiology or pathology in biological systems. Having proteins as targets, H_2S can react through a PTM called S-sulfhydration (or S-persulfidation), leading to the formation of persulfides (RSSH) upon binding to thiol (RSH) groups present in cysteine residues. Like other PTMs, protein S-sulfhydration is a reversible modification that can increase or decrease protein function and the number of proteins modified by endogenous H_2S is emerging, pointing to its importance in biological processes. Interestingly, H_2S does not react directly with free cysteines; this modification requires a reactive thiol that can already be nitrosylated (R-SNO), glutathionylated (R-SSG), or sulfenylated (R-SOH) [115,116]. Another mechanism by which H_2S acts is by binding metallic centers of proteins, a process recognized as a way of H_2S-inducing toxicity and the first described biological effect of H_2S. For further details on this, the mechanism of action of H_2S was extensively reviewed by Filipovic and colleagues, covering a wide range of topics not only related to chemical properties and biology of H_2S but also their biogenesis, regulation and physiological and pharmacological effects of H_2S [117]. Additionally, an extensive

and complete review addressing the physiological role of H_2S has been published recently by Cirino and colleagues [118]. Like the other mentioned gasotransmitters, H_2S can regulate several cellular processes, such as oxidative stress, mitochondrial bioenergetics, inflammation, apoptosis, cell differentiation, vasodilation, cell metabolism, ER stress, and DNA damage repair. Within the scope of this review, we will focus mainly on the biological processes that occur or are related to the CNS. Increasing evidence shows that H_2S exerts antioxidant, anti-inflammatory, and anti-apoptotic effects in the brain (reviewed in [119]). H_2S has been correlated with the regulation of oxidate stress in the brain by acting directly with molecules that are involved in cellular antioxidant pathways, such as glutathione (GSH). Kimura and colleagues showed that H_2S increases and redistributes de GSH levels inside the mitochondria through the reduction of cystine to cysteine, and this protects neurons from oxidative stress [120,121]. Furthermore, H_2S has been proven to exert neuroprotection via inhibition of microglia activation following inflammatory effects, counteracting neurotoxicity, through the inhibition of iNOS, NF-kB, ERK, and p38 MAPK signaling pathways [122]. H_2S has also been shown to significantly reduce brain edema and behavioral symptoms by anti-apoptosis and anti-autophagy effects in a TBI model by reverting TBI-induced caspase-3 cleavage and Bcl-2 decline [123,124]. In the central nervous system, a dual role for H_2S was also observed, for instance, it was found to ameliorate ischemic lesions, but it was also described to aggravate stroke (reviewed in [118,125,126]). The concept that H_2S plays a role in synaptic neurotransmission had emerged already in the mid-90s/early 2000s and a very well-described role for H_2S in the CNS is its impact on LTP, which is a common form of synaptic plasticity, thought to be the neural basis of learning and memory. The production of H_2S by CBS in the brain seems to control LTP in an NMDA-dependent manner [112,127]. Moreover, sodium hydrogen sulfide (NaHS), a H_2S donor, increased the levels of NR2B, a subunit of the NMDA receptor, as well as improved cognitive function in a model of hepatic ischemia/reperfusion injury [128]. In the midbrain, the major enzymes involved in endogenous H_2S biosynthesis are CBS and CTE, and, as this brain region is the dominating region affected in the pathogenesis of PD, H_2S has been suggested to be beneficial in attenuating PD-like neural damage [129,130]. Nevertheless, the relationship between protective mechanisms of H_2S and the pathogenesis of PD remains largely elusive.

Additional features of NO, CO and H_2S in the context of brain diseases can be found in a recent and mandatory review for all researchers dedicated to the study of gasotransmitters' biology, conducted by Siracusa and colleagues [131].

4.4. Interplay between the gasotransmitters in the brain

In recent years, compelling evidence has emerged in the literature regarding the interplay between NO, CO and H_2S in several tissues [131–133]. The aim of this review is not to present an extensive list of these but rather to put the focus on what is known regarding the interplay between these gasotransmitters in the brain. Most of the interactions relating these gasotransmitters to each other regard their effects upon the regulation of the different enzymes that synthesize these gaseous molecules, with these effects being either at the expression or activity levels. Subsequently, several studies are presented demonstrating the synergistic effects found so far between these signaling molecules in neuronal cell lines or tissues. In *in vitro* models of neuroinflammation (primary cultures of astrocytes or microglia and a microglial cell line exposed to LPS), it was shown that H_2S influences NO production by regulating the NO-producing enzymes. It was found that H_2S (by exposing cells to NaHS), modulated the production of NO in a way inversely proportional to H_2S concentration: high levels of H_2S decreased LPS-induced NO while low levels of H_2S resulted in high NO production. The NO isoform which appears to be involved in this process, regards iNOS, and due to the above-described effects, H_2S was pointed by these authors as having anti-inflammatory effects upon microglia and astrocytes [134] (Figure 1(A)). The association between H_2S and iNOS reported in these *in vitro* experiments was later confirmed in studies using *in vivo* models, such as in the studies of Wang et al. [135] and Kumar et al. [136]. Wang and colleagues established a model of brain ischemia by inducing middle cerebral artery occlusion in ICR mice. After this procedure, mice were injected either with NaHS or 5-(4-Hydroxyphenyl)−3H-1,2-dithiole-3-thione (ADT), a slowly releasing H_2S donor described as having neuroprotective effects [137]. The authors found that both H_2S donors protected the blood–brain barrier (BBB) integrity following the experimental stroke and, in addition, ADT was also able to inhibit the levels of iNOS as well as the levels of pro-inflammatory molecules [135]. Kumar et al. demonstrated how H_2S

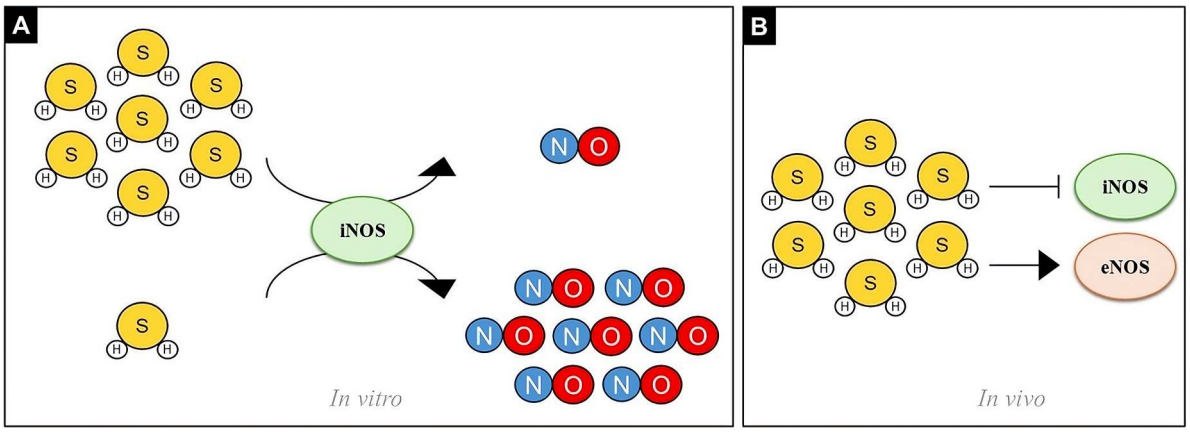

Figure 1. Interplay between H_2S and NO in neuronal cells. (A) In *in vitro* models of neuroinflammation (primary cultures of astrocytes or microglia, and a microglial cell line exposed to LPS),: it was found that H_2S (by exposing cells to NaHS) modulated the production of NO in a manner inversely proportional to H_2S concentration: high levels of H_2S decreased LPS-induced NO, while low levels of H_2S resulted in high NO production through the iNOS isoform [134]. (B) In an *in vivo* model of brain ischemia (induction of middle cerebral artery occlusion in ICR mice), it was found that ADT (5-(4-Hydroxyphenyl)−3H-1,2-dithiole-3-thione, a slowly releasing H_2S donor) inhibited the levels of iNOS [135]. In addition, in an *in vivo* model of hyperhomocysteinemia (Sprague Dawley rats injected with homocysteine) exposed to NaHS, decreased iNOS and increased eNOS protein levels were found in the cortex and hippocampus [136].

influences two NO-producing enzymes in the brain of an *in vivo* model of hyperhomocysteinemia (HHcy; 8–10 weeks old Sprague Dawley rats injected with homocysteine (Hcy)) [136]. These authors have shown that both iNOS mRNA and protein were elevated in the cortex and hippocampus of Hcy-treated animals, compared to the untreated group. Exposure of HHcy animals to H_2S (in the form of NaHS supplementation) decreased iNOS, at the mRNA and protein level, in the cortex and hippocampus. Regarding eNOS mRNA and protein, a decrease was found in the cortex of the HHcy group, with no changes in the hippocampus compared to the control group. When Hcy-treated animals were exposed to H_2S, an increase in eNOS mRNA was observed in the cortex. At the protein level, it was found that H_2S supplementation increased eNOS both in the cortex and hippocampus of the HHcy group [136] (Figure 1(B)). These data point to a causative effect of H_2S upon the levels of NO-producing enzymes in the brain, especially in the cortex and hippocampus regions. Collectively, either the *in vitro* or the *in vivo* neuronal models indicate an association between H_2S and NO, by demonstrating that H_2S modulates mainly the iNOS and eNOS isoforms. Additionally, a very interesting synergistic effect between H_2S and NO was described in the work of Ohno et al., which demonstrated that the way H_2S acts will dictate how NO acts afterward [138]. These authors have shown that H_2S endogenously produced modifies PTEN protein by means of S-sulfhydration, and this modification confers protection against NO in SH-SY5Y neuronal cells. The fact that PTEN is targeted by H_2S impedes the modification of PTEN by NO through S-nitrosylation and, consequently, this will keep PTEN in its active form [138].

In a study from 2006, it was investigated the interaction between H_2S and CO in hippocampal neurons in an *in vivo* model of febrile seizures [139]. Febrile seizures were experimentally induced in Sprague–Dawley rats with 21 days of age, and several groups were established afterward by injecting animals with an H_2S donor (NaHS), a CBS inhibitor (hydroxylamine), a CO activator (hemin), or a HO-1 inhibitor (ZnPP-IX). The authors found that when CBS was inhibited, the levels of HO-1 were reduced, along with the levels of CO. Additionally, when H_2S levels were potentiated, this resulted in higher levels of CO, with concomitant upregulation of HO-1. In a similar way, when HO-1 was inhibited,tthis led to a decrease in both H_2S production and CBS protein levels. The opposite was observed when the levels of endogenous CO were stimulated, which translated into an increased production of H_2S and higher CBS levels (Figure 2(A)) [139]. The role of each of these gasotransmitters alone upon febrile seizures has already been described [140,141], but now, the above-presented data show that H_2S and CO work in a synergistic manner, protecting neurons from the damage imposed by febrile seizures. It was also demonstrated by others, not a direct interaction between H_2S and CO, but a mechanism by which CO regulates the levels of H_2S, by interfering with

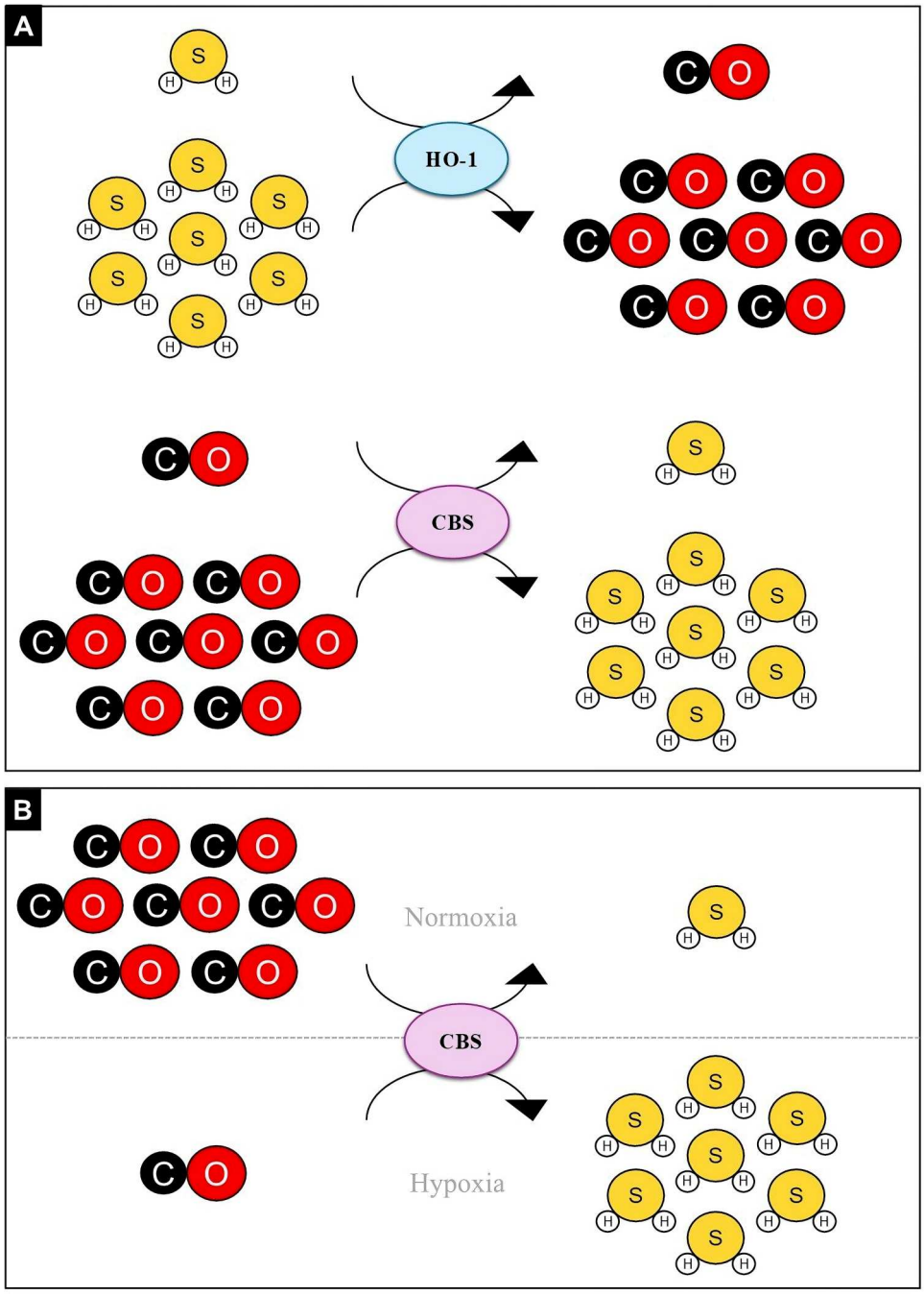

Figure 2. Interplay between H2S and CO in neuronal cells. (A) In an *in vivo* rat model of febrile seizures, reduced HO-1 and CO levels were found following inhibition of CBS with hydroxylamine, and increased HO-1 and CO levels were observed following stimulation with NaHS. Additionally, reduced CBS and H_2S levels were found following inhibition of HO-1 with ZnPP-IX, and increased CBS and H_2S levels were observed following CO stimulation with hemin [139]. (B) In the brains of HO-2 deficient mice, it was found that under normoxic conditions, CBS activity was inhibited when constitutive CO levels bound this enzyme, resulting in reduced H_2S levels. On the contrary, under hypoxic conditions, CO levels were reduced, and CBS was activated, leading to increased production of H_2S in the brains of these mice [142,143].

H_2S-producing enzymes [142,143]. In these studies, CBS was identified as a CO-responsive protein with important cellular regulatory functions. For instance, it was reported that in normoxic conditions, CBS activity was inhibited when constitutive levels of CO bind this enzyme, resulting in reduced levels of H_2S, in the brain of HO-2 deficient mice. On the contrary, in hypoxia, the levels of CO were reduced, and CBS was activated, leading to an increased production of H_2S in the brain of this model (Figure 2(B)). It was described that CO

was able to bind to the CBS heme prosthetic group, therefore preventing the normal functioning of the enzyme. Very interestingly, *in vitro* studies have shown that NO binds to CBS in a quick and tight manner, and compared to CO, CBS has a stronger and preferred affinity for NO [144]. This data led us to theorize that CBS might be also a NO-responsive protein; however, this has not yet been investigated in neuronal cells or experimental models of brain diseases. Surprisingly, in a study from 2002, it was described that sodium nitroprusside, a NO donor, increased the activity of CBS and the production of H_2S in rat brain cell suspensions, by modifying cysteine residues in the CBS enzyme [145]. However, these authors reported that the enhancement of CBS activity was independent of NO production (as other NO donors were not able to increase CBS activity), but instead, was dependent on the presence of Ca^{2+} and calmodulin, which appeared to be the modulators of CBS structure, having the ability of changing the enzyme conformation between an active and inactive form [145].

Studies relating the three gasotransmitters to each other are very limited, especially in the brain, as most of the data concern the effects of one gasotransmitter on another. The study of Coletti and colleagues investigated the potential interactions between NO, CO, and H_2S in neuronal samples exposed to inhibitors of the three main gasotransmitter-producing enzymes [146]. By using explants from hypothalamic and neurohypophyseal regions, collected from 6-7-week-old Wistar rats, these authors demonstrated that LNMMA (a NOS inhibitor) reverted NOS activity, increased CBS in the hypothalamus and neurohypophysis, and increased HO activity in the hypothalamus of this model. Additionally, AOAA (a CBS inhibitor) decreased CBS activity, whereas ZnDPBG (a HO inhibitor) inhibited HO activity. These two drugs had no effect on either NOS and HO activity or on NOS and CBS activity, respectively. This data suggests that NO interacts with the H_2S-producing enzymes in the hypothalamus and neurohypophysis and with the CO-producing enzymes in the hypothalamus [146] (Figure 3).

It is well established that the Keap1/Nrf2/ARE cascade is a fundamental pathway that regulates the antioxidant activity of a cell. This signaling controls the expression of genes encoding critical proteins in the elimination of reactive species. Under oxidative/nitrosative stress, Nrf2 (which is constitutively under the control of Keap1) translocates to the nucleus where it activates a myriad of antioxidant genes. Several authors have proposed this pathway as the common mechanism underlying the action of the three gasotransmitters [131,147]. Recently, Siracusa et al. nicely gathered information regarding the role of each of the three gasotransmitters upon this signaling pathway [131]. These authors found that, in different experimental conditions, each of these gaseous molecules activates, *per se*, the Keap1/Nrf2/ARE cascade, most of the presented studies being conducted in experimental models of brain diseases [131]. Paul and Snyder also compiled evidence for the role of H_2S upon the activation of the Keap1/Nrf2/ARE cascade, in different cellular contexts, namely the sulfhydration of Keap1, which is one of the main modes of action of H_2S within a cell

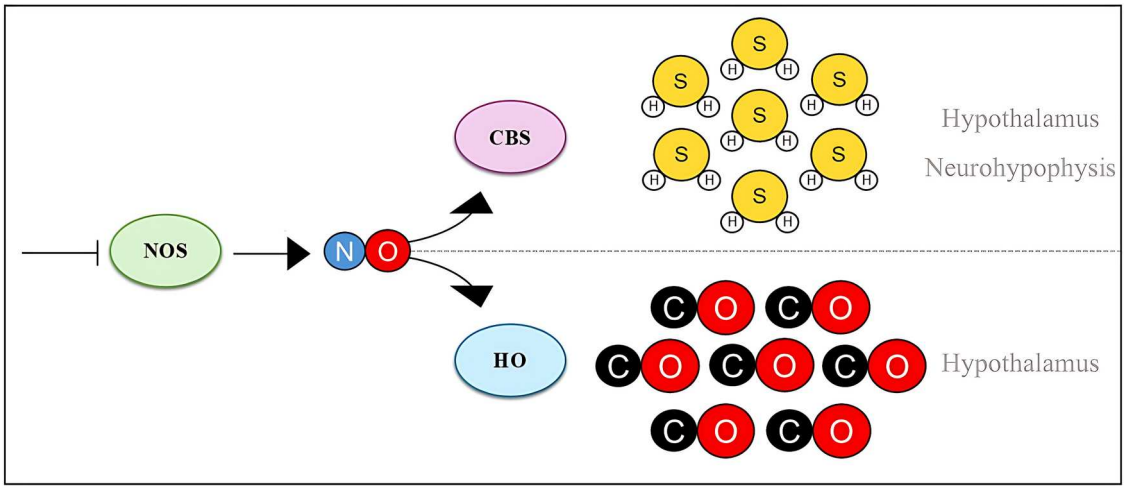

Figure 3. Interplay between NO, CO, and H_2S in neuronal cells. Treatment with L-NMMA (a NOS inhibitor) decreased NOS activity but increased CBS activity in hypothalamic and neurohypophyseal explants collected from Wistar rats, while also increasing HO activity in the hypothalamic samples, suggesting an interconnection between these three gasotransmitters in the brain [146].

[148]. Additionally, it has been described that the activation of Nrf2 signaling induced by H_2S confers protection in experimental models of PD (reviewed in [149]) as well as protects from cellular damage in an *in vitro* model of traumatic brain injury [150]. Also, CO has been shown to protect from cerebral ischemia in a mouse model of cerebral artery occlusion, and one of the underlying mechanisms for this effect regards the activation of the Nrf2 pathway [151]. Collectively, these data show that the regulation of Nrf2 pathway is a shared mechanism underlying the action of the three gasotransmitters in neuronal cells, thus reinforcing the interplay between these molecules (Figure 4). As in other tissues and organs, it is now clear that the brain is a place where interactions between NO, CO, and H_2S also occur. It is evident that these gasotransmitters may influence each other's cellular effects at different levels, such as in terms of their production or in terms of the signaling pathways they regulate. This new perspective on the interaction between these gases in the brain is quite important and must be considered if we seek to develop novel therapies for brain diseases based on these endogenously produced molecules.

4.5. How do gasotransmitters influence adult neurogenesis?

The identification of gasotransmitters as intervening players in neurogenesis will aid in clarifying the occurrence of this process in the adult mammalian brain and will certainly shed light on the conception of gasotransmitter-based strategies for brain diseases characterized by massive neuronal death as it occurs in AD and PD. The literature concerning the effects of NO upon neurogenesis is vast and many studies report a dual role for this gasotransmitter upon this process in the adult brain. It is well described that the effects of NO on adult neurogenesis differ when comparing studies performed in healthy brains to those performed on lesioned brains, as reviewed by Estrada and Murillo-Carretero [152]. In a healthy brain, NO synthetized by nNOS acts as a negative modulator of cell proliferation in neurogenic niches. For instance, Moreno-Lopez et al. found that pharmacological inhibition of NOS promotes neurogenesis in the brains of adult mice, concluding that physiological NO levels negatively impact adult neurogenesis, specifically in the subventricular

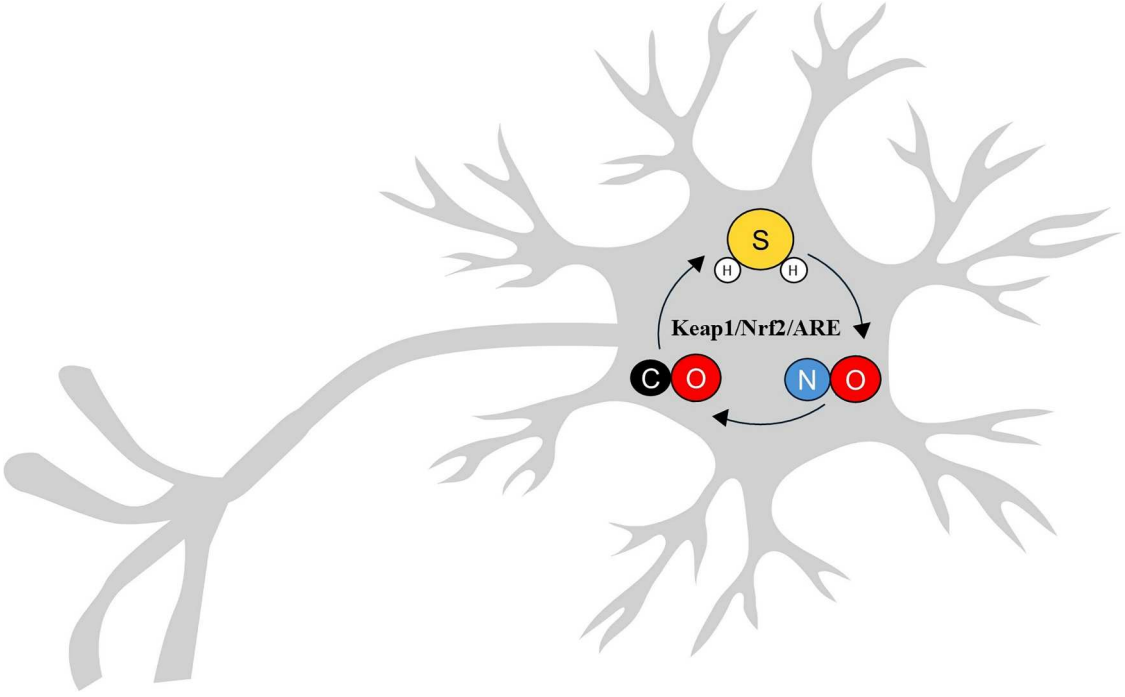

Figure 4. The Keap1/Nrf2/ARE signaling as the central point in NO, CO, and H_2S interplay. The role of each of the three gasotransmitters in the Keap1/Nrf2/ARE signaling pathway is well established in several experimental models of brain diseases. Based on this, the Keap1/Nrf2/ARE cascade is proposed as the common mechanism underlying the interconnection between NO, CO, and H_2S [131,147–151].

zone and the olfactory bulb [153]. Packer and colleagues also described increased neurogenesis in the olfactory subependyma and the dentate gyrus when NO levels were reduced, either by pharmacological inhibition of NOS or by knocking down nNOS in adult mice [154]. On the contrary, compelling evidence has shown that high levels of NO are produced in neuronal cells after brain lesions and, among other functions, it has been demonstrated that this neuromodulator can positively regulate adult neurogenesis. Several studies, including those from our group, have consistently confirmed a positive correlation between high NO levels produced after brain damage, such as ischemia, traumatic brain injury, or epileptic seizures, and adult neurogenesis in multiple brain regions [155–163]. Zhang et al. established a brain ischemic model in young-adult Wistar rats using embolic middle cerebral artery occlusion and then administered DETA/NONOate (a NO donor). Compared to the untreated group, rats subjected to NO exposure exhibited increased cell proliferation and migration in the subventricular zone and the dentate gyrus. In parallel, the experimental group exposed to NO also demonstrated a much better performance concerning the functional recovery from ischemic stroke [163]. In the study of Zhu et al., 4-month-old Sprague Dawley rats were subjected to focal cerebral ischemia. It was observed the presence of newly divided cells in the DG in the ischemic group, contrasting with that of the control group. Interestingly, this effect was not verified in rats treated with an iNOS (aminoguanidine) inhibitor or in iNOS−/− animals, indicating a role for iNOS-derived NO in this neurogenic response [155]. The study of Luo et al. also supports a role for iNOS-induced neurogenesis in the hippocampus [157]. By using adult Sprague–Dawley rats subjected to focal cerebral ischemia, these authors found that the expression of nNOS was reduced in the hippocampus of these animals. In addition, the ischemic condition increased the proliferation of cells in the DG and upregulated the iNOS expression [157]. Lu et al. described a broad range of effects concerning NO on several neurogenic steps in adult Wistar rats subjected to TBI and then injected with DETA/NONOate. These authors observed increased proliferation, survival, migration, and differentiation of neural progenitor cells in multiple brain regions, including the hippocampus and subventricular zone. The NO donor also improved several parameters related to neurological function [162]. The involvement of NO in different neurogenic stages in the adult brain has also been demonstrated in several epileptic seizure models. For example, NO produced from nNOS and iNOS appears to contribute to the increased number of proliferative cells found in the dentate gyrus of adult Sprague-Dawley rats injected with pentylenetrazol, as demonstrated by the work of Jiang and colleagues [158]. Additionally, our group has consistently shown a role for NO in adult neurogenesis in a kainic acid-induced seizure model in 12-week-old C57BL/6J mice. We demonstrated that iNOS-derived NO promotes cell proliferation in the hippocampus of injured mice. With the aim to unveil the cellular processes underlying this NO-mediated enhancement of adult neurogenesis, we found that overexpression of iNOS or S-nitrosylation of proteins associated with the Ras/ERK1/2 pathway works as key contributors [156,159–161].

Similar to NO, CO appears to influence adult neurogenesis and encouraging data involving this gasotransmitter arise from studies conducted either in NSC lines or in *in vivo* models of brain injury (reviewed in [164]). In 2014, Nada et al. reported the first evidence that CO might have a role in adult neurogenesis [165]. These authors established a permanent middle cerebral artery occlusion model in 8–10 weeks old C57BL/6 mice, to which were afterwards administered Ginkgo biloba/EGb 761 extracts. It was found that the extracts protected mice from brain injury and increased proliferation of NSC. Interestingly, when HO-1 was silenced in this model, neurogenesis decreased significantly compared to the control group, suggesting that CO might underlie the effects of Ginkgo biloba/EGb 761-induced increase in neurogenesis in mice with ischemic stroke [165]. The studies of Choi et al. also support a role for CO as a modulator of adult neurogenesis [166]. These authors established a model of TBI in 3-months old C57Bl/6 mice and afterwards exposed them to the CO-releasing molecule (CORM)−3. They found that CORM-3 decreased pericyte death, increased the differentiation of NSCs into mature neurons, and in general improved the progression of neurological damage in the treated mice. Very interestingly, these authors also found that the effect of CO on NSC differentiation was accompanied by elevated phosphorylated nNOS levels, suggesting crosstalk and synergistic effect between CO and NO in regulating adult neurogenesis in the TBI model [166]. The studies of Almeida and colleagues are very supportive of a role for CO in adult neurogenesis. In these studies, three different *in vitro* neuronal models were used, SH-S5Y5 and NT2 human cell lines and organotypic hippocampal slice cultures (OHSC), and all were exposed to a CO-releasing molecule A1 (CORM-A1) [167]. The authors reported an enhancement in both cell proliferation and neuronal differentiation in all the established models. Although these data

regard *in vitro* models, they are very encouraging, especially those obtained with the OHSC, as this is described as an important model of adult neurogenesis since it reproduces neural stem cell proliferation, differentiation, and migration within an intact neuronal circuitry [168]. Later, the same authors described that part of the mechanism underlying the increased differentiation found in SH-S5Y5 cells after CORM-A1 exposure regards the stimulation of the pentose-phosphate pathway and the glutathione system [169]. The same group also described that exposure of human NSC to CO, generated following the combination of methyldiphenylsilacarboxylic acid ($MePh_2SiCO_2H$) with potassium fluoride and dimethyl sulfoxide, resulted in improved survival and dopaminergic differentiation of these cells [170]. More recently, it was demonstrated that neural precursor cells, oligodendrocyte precursor cells, and microglial cells were diminished in the hippocampus of the delayed CO encephalopathy rat model [171]. These authors established a model of delayed CO encephalopathy, a condition that can arise up to 4-weeks after recovery from acute CO poisoning, by exposing 6-weeks old Wistar rats to high concentrations of CO. Aiming to elucidate the mechanisms underlying this condition, they investigated the effects of CO exposure on neural precursor cells and glial cells in the granular and subgranular zone of the DG 21 days after CO exposure. The authors found that CO reduced adult hippocampal neurogenesis and correlated this with the cognitive impairment typical in this disease [171]. This apparently contradictory data regarding CO's effect on the different stages and players of adult neurogenesis may regard different CO concentrations across studies: this latter study used high CO levels whereas the first mentioned studies used low CO doses.

More recently, studies focused on the effect of H_2S on adult neurogenesis have started to emerge and the first ones concern work conducted on neuronal cell lines as described in [172,173] and reviewed in [174,175]. For example, H_2S has been described as a promoter of neuronal differentiation in NG108-15 cells, following exposure of cells to NaHS. Later, studies performed in animal models have also shown a role for H_2S in different steps of neurogenesis. For instance, it was demonstrated that H_2S (either by exposure to L-cysteine or NaSH) increased proliferation and differentiation of neural stem cells isolated from the brains of mouse embryos at E13.5. To confirm the involvement of H_2S, the authors modulated the levels of CBS protein by knocking down the CBS gene or pharmacologically inhibiting CBS with AOAA [114,176]. Additionally, the same authors also showed that H_2S promoted proliferation of NSC in the dentate gyrus of the hippocampus of neonatal C57BL/6 mice previously subjected to hypoxia [176]. The benefits of H_2S upon neurogenesis were also demonstrated more recently by Mohseni et al. [177]. These authors established a model that mimics fetal alcohol spectrum disorders (FASD) and subdivided part of the animals to be supplemented with NaHS from postnatal day 2 until postnatal day 10. The group exposed to NaHS presented a higher percentage of proliferative cells in the dentate gyrus of the hippocampus when compared to the untreated group [177]. Additionally, the authors found that H_2S also increased spatial memory and decreased the number of apoptotic cells in the NaHS-treated group [177]. Collectively, despite the above-mentioned studies respecting the embryonic/neonatal neurogenesis, they are encouraging and show a beneficial effect for H_2S on specific neurogenic steps. More recently, Wang et al. notably showed that H_2S increased adult neurogenesis in an *in vivo* experimental model of PD [129]. These authors established the 1-methyl-4-phenyl1,2,3,6-tetrahydropyridine (MPTP) model of PD in C57BL/6J mice aged 12–16 weeks and evaluated the effect of NaHS intraperitoneally injected. It was observed that the H_2S donor prevented the loss of dopaminergic neurons in the PD model. The beneficial effects of H_2S supplementation went even further, by promoting proliferation of NSC in the SVZ. In an attempt to detail the underlying mechanisms, these authors demonstrated that the effects of H_2S-induced adult neurogenesis in the PD model were mediated by the Akt/glycogen synthase kinase-3β/β-catenin pathway [129].

In general, NO, CO, and H_2S are described as having positive effects on stimulating neurogenesis in the adult mammalian brain (Figure 5). Most of the effects reported here concern the enhancement of the proliferative phase in the cascade of events of a neurogenic response. This does not imply that other neurogenic stages are unaffected by these gasotransmitters, but rather that they remain understudied, which stresses the importance of further investigation into this area. Nevertheless, the beneficial effects reported here suggest that these molecules are promising candidates to integrate new therapies directed at brain diseases that would benefit from the repopulation of functional and integrated neurons.

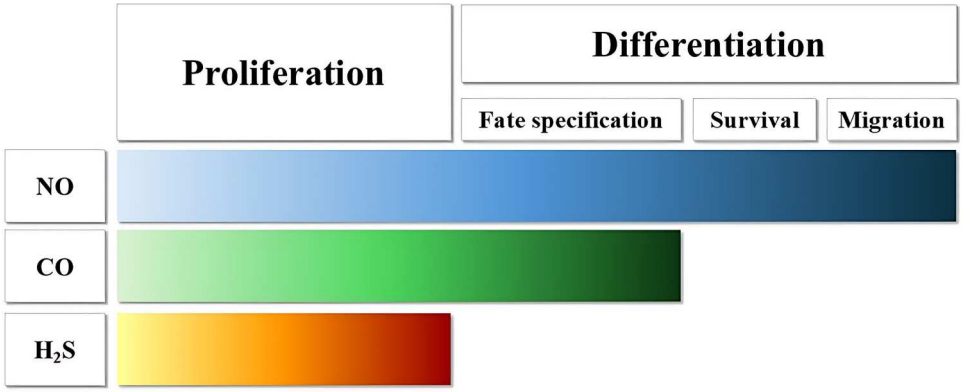

Figure 5. Identification of the neurogenic stage where NO, CO, and H_2S act in the adult mammalian brain. NO has been described as acting on the proliferation, fate specification, survival, and migration of neural stem cells; CO has been described as acting on the proliferation and fate specification of neural stem cells; H_2S has been described as acting on the proliferation of neural stem cells.

4.6. The therapeutic potential of gasotransmitters for neurodegenerative diseases

4.6.1. Intracellular significance of gasotransmitters in Alzheimer's disease and Parkinson's disease

The study of gasotransmitters' biology in health and disease is currently a hot topic of research, as evidenced by the number of recent publications in this area. The notion that imbalanced production or defects in the signaling of NO, CO or H_2S might contribute to the mechanisms underlying AD and PD is not a novel concept. In this regard, numerous studies have emerged in recent years aiming to uncover the role of these gaseous molecules in the development and progression of these diseases [131–133,178–181]. In this section, we will summarize the current knowledge regarding the intracellular significance of NO, CO, and H_2S in the context of AD and PD. Still, studies using human biological samples to assess the levels of these gasotransmitters and decipher their effects on the state and progression of the disease remain limited and contradictory to some extent.

4.6.1.1. The significance of intracellular NO in Alzheimer's disease and Parkinson's disease. Relevant information concerning the presence and potential effects of NO in AD patients comes from studies using indirect approaches to assess this gas, such as those focusing on the evaluation of the activity and/or expression of NO-synthesizing enzymes or from studies detecting NO markers, such as nitrotyrosines. For example, it was found that there was increased NOS activity in brain microvessels [182] and elevated expression of all NOS isoforms in astrocytes and neurons in postmortem brains of AD individuals, compared to the control group [183]. Good and colleagues demonstrated the colocalization of nitrotyrosines with neurofibrillary tangles in AD patients' postmortem brains, compared to the control subjects [184]. A study from the early 2000s measured the NO levels, indicated by the presence of nitrate and nitrite in the plasma, and found a marked reduction in the amount of NO in the AD group [185]. More recently, Venturelli et al. published a very elegant study aiming to assess a set of different parameters related to NO functioning in a cohort of AD patients (including patients with different levels of AD severity) *versus* healthy controls (including young and old individuals) [186]. The authors measured NO bioavailability (by measuring NO metabolites in plasma), systemic vascular function and cerebral and peripheral blood flow, among other parameters. These parameters were diminished in older subjects compared to the younger ones, and this difference was more pronounced in the AD individuals as the severity of the disease increased. The authors hypothesized that the circulatory damage present in the AD patients was related to the reduced NO levels found in this group [186]. Through untargeted metabolomic studies using blood-derived samples, Hurtado and colleagues reported that the L-arginine/NO pathway is among the metabolic pathways altered in AD [187]. Later, in line with Hurtado et al.'s findings, the group of Fleszar analyzed blood samples collected from dementia and non-dementia patients using targeted metabolomic analysis to measure the arginine-to-asymmetric dimethyl arginine (Arg/ADMA) ratio. These authors found a decreased

Arg/ADMA ratio, which indicates decreased NO bioavailability, in vascular dementia patients, which showed a tendency to correlate with the degree of cognitive impairment [188].

The initial studies attempting to assess the NO profile in the context of PD originated from post-mortem analyses of different brain regions in PD patients and their respective controls. For example, Hunot et al. found elevated expression of iNOS in the substantia nigra of PD patients [189], while Eve and colleagues described elevated nNOS expression at the mRNA level in the subthalamic nucleus and reduced expression in the putamen of PD patients compared to controls [190]. These studies were pioneers in showing a link between NO and PD and provided valuable contributions to this field. However, it is important to note that these findings are limited to a small sample size (< 11 PD patients and < 16 control individuals) and lacked appropriate quantification methods, which may impact the interpretation of the results. Later, Shukla and coworkers reported no significant differences in nitrite levels in the cerebrospinal fluid of PD patients compared to healthy controls, nor did they find any association between these levels and disease severity as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [191]. In contrast, elevated levels of NO were found in the serum of PD patients compared to healthy individuals, and this was positively correlated with disease severity according to UPDRS [192]. However, these findings were contradicted by studies from Tuncel et al. and Cubukcu et al., which reported significantly lower NO levels in the serum of PD patients compared to the control group. Cubukcu et al. further observed that this finding showed a negative correlation with disease severity as measured by the UPDRS [193,194]. A more recent study, analyzing a cohort of PD patients with varying disease durations and age-matched controls, found reduced NO derivative levels in PD patients' serum regardless of diagnosis duration (< 1 year, 1–3 years, or > 3 years). Interestingly, the most pronounced difference occurred in patients with the earliest diagnosis. Based on these findings, the authors proposed that derivatives of NO could serve as potential biomarkers for PD progression, in combination with other inflammatory molecules such as IFNγ and IL-10 [195].

4.6.1.2. The significance of intracellular CO in Alzheimer's disease and Parkinson's disease. The literature shows ambiguity regarding the presence and role of CO/HO-1 in the brain and body fluids of patients with neurodegenerative diseases. For example, Si et al. recently compiled much of the evidence on HO-1's effects in AD. Regarding neuroprotective mechanisms, they reported that HO-1 stimulation in brain cells, via CO (and other effectors such as MAPK, AMPK and Nrf2), contributes to suppressing Tau aggregation and amyloid β deposition while improving neuronal survival in AD patients [196]. This data apparently contrasts with earlier work by Schipper et al., who found variable HO-1 expression, depending on the sample type. On one hand, Schipper and colleagues consistently described elevated HO-1 expression in several brain regions, such as neurons and astrocytes of the hippocampus and temporal cortex of AD patients compared to age-matched controls [94,197]. These results align with recent work by Fernandez-Mendivil et al., who demonstrated elevated HO-1 in microglia from postmortem AD brains [198]. On the other hand, Schipper's group found decreased HO-1 protein and mRNA levels in the choroid plexus epithelium, CSF, and plasma from AD patients [199,200].

In PD, elevated HO-1 has been observed in the substantia nigra [98,99], serum/plasma [201,202], and saliva of patients compared to age-matched controls [203,204]. In this regard, Schipper's lab proposed salivary HO-1 measurement as a biomarker for early PD detection.

4.6.1.3. The significance of intracellular H_2S in Alzheimer's disease and Parkinson's disease. In the early 2000s, decreased levels of H_2S and CBS were reported in plasma and brain samples of patients with AD and vascular dementia [205,206]. Concerning another H_2S-synthesizing enzyme, Zhang et al. demonstrated diminished CTH expression in the hippocampus and frontal lobe samples (cortex) of AD patients compared to controls [207]. More recently, very exciting studies have been conducted on this research topic, in a challenging attempt to have a broader and detailed view of the role of H_2S in the context of brain disease. Disbrow et al. found elevated H_2S and related metabolites in AD and related dementias patients, compared to controls [208]. The authors showed that the increase in H_2S was attributed to elevations in both acid-labile and bound sulfide pools rather than in free sulfide. Additionally, the authors correlated dysregulated H_2S levels with the poor cognition indices presented by the diseased group. Based on these findings, Disbrow and colleagues proposed plasma H_2S as a biomarker for Alzheimer's disease and related dementias [208]. Later, the same authors went even further and, by assessing plasma sulfide and performing magnetic

resonance imaging in a group of AD and related dementias patients, they showed a positive correlation between dysfunctions in sulfide metabolism and brain atrophy (decreased gray matter volume and decreased white matter integrity) in the diseased group [209]. Greco et al. developed an innovative methodology aiming to explore H_2S levels in cerebrospinal fluid of patients with different neurological disorders. Based on a technique joining selective electrochemical detection with ion chromatography, these authors were able to measure both free and bound sulfur forms of H_2S [210]. In general, the levels of either free or bound sulphur forms of H_2S measured on CSF were constantly higher in AD and PD patients when compared to the control group [210]. Concerning PD, Vandiver and coworkers analyzed postmortem brain samples and looked at nitrosylation and sulfhydration, two posttranslational modifications by which NO and H_2S signal, respectively. These authors found increased nitrosylation and decreased sulfhydration of parkin in the striatum of PD patients. They proposed that reduced sulfhydration impairs parkin's catalytic activity, contributing to pathology [211].

The apparent conflicting data between some of the above-mentioned studies involving human samples, regarding the effect of NO, CO, and H_2S on the brain, reflect aspects associated with the complexity involved in this topic, such as the specificity and accuracy of gasotransmitter measurements. For instance, given the labile and reactive nature of these gases, they can be rapidly interconverted into other chemical species, which could act as a confounding factor during measurement. Methodologies used to detect these gaseous molecules often vary between studies; different methods differ in sensitivity and may detect gasotransmitter-related molecules or derivatives rather than the gasotransmitters themselves, thereby influencing the data. Further variability may arise from differences in diagnostic criteria for AD/PD, cohort sizes (AD/PD patients vs. controls), or disease stages (early vs. late-stage) at the time of study.

In general, the compiled data presented here suggest that both low and high levels of these gasotransmitters lead to deleterious imbalances and pathological scenarios. Thus, using circulating NO, CO or H_2S levels in plasma or other biological fluids as potential biomarkers for early AD/PD detection and diagnosis is highly promising and warrants further investigation.

4.6.2. Effects of exposure to sources containing NO, CO or H_2S in preclinical models of Alzheimer's disease and Parkinson's disease.

In recent years, data obtained from studies using rodent models of AD and PD exposed to different sources of NO, CO, or H_2S has highlighted the positive effects these gaseous species exert on the progression of these diseases. In general, these three gasotransmitters display neuroprotective features in rodent models of AD and PD, with main effects including improvements in cognition and motor function, as well as a reduction in oxidative stress, inflammation, and Aβ accumulation (Table 1).

Regardless of the model studied or the route of administration of the gasotransmitter under investigation, their application in preclinical models produced protective effects at the neuronal level. Furthermore, the compilation of these studies identified several cellular mechanisms and events underlying the effects of gasotransmitters, allowing for a better understanding and potential modulation of these pathways, to promote neuroprotection in the context of AD and PD (Table 2).

In addition to the gasotransmitter sources mentioned in Table 1, several recent studies raise an important question about the potential of certain nutraceuticals, whose mechanism of action increases the levels of a specific gasotransmitter, to influence the course of various diseases, including AD and PD [212–217]. For instance, McCarty and colleagues compiled extensive information on the protective effects of a diet enriched with taurine, cysteine, folate, B12, or betaine on AD patients, due to the boost that these compounds have on H_2S levels in the brain [212]. Other studies in experimental models have shown that exposure to vanillic acid, genistein, quercetin, or, resveratrol, among others, upregulates HO-1 and protects against AD-related features [218–220]. Additionally, pharmacological induction of HO-1 through bioactive compounds such as caffeic acid, resveratrol, and curcumin has shown positive therapeutic effects in chemically induced PD models [221]. Further beneficial effects were observed in studies assessing cognitive and motor function in inhabitants subjected to chronic H_2S inhalation, emitted from geothermal vents in Rotorua city in New Zealand, for example [222]. In these residents who live in a high and chronic H_2S environment, it was noticed a tendency for a faster performance on a classical motor test used to assist in the diagnosis of PD, without any negative impact on their cognitive function [222]. Overall, the above-mentioned studies notably demonstrate that exposure to these gasotransmitters reduces disease progression while improving

Table 1. Summary of the neuroprotective effects of NO, CO and H_2S exposure on preclinical models of Alzheimer's disease and Parkinson's disease.

Alzheimer's disease	*NO source*	*Experimental model*	*Key cellular effects*	*References*
	GSNO	Wistar rats	Improved cognition Reduced oxidative stress Reduced Aβ Reduced neuronal loss	[248,249]
		APP/PS1 mice	Neuroprotective	[250]
	GSNO + L-arginine	Wistar rats	Improved cognition Reduced Aβ	[251,252]
	L-arginine	Wistar rats	Improved cognition	[253,254]
	DNIC	Wistar rats	Improved cognition	[255]
Parkinson's disease	*NO source*	*Experimental model*	*Key cellular effects*	*References*
	SNP	Wistar rats	Improved motor function	[256,257]
Alzheimer's disease	*CO source*	*Experimental model*	*Key cellular effects*	*References*
	CORM-3	3xTg-AD mice	Improved cognition Reduced Aβ	[258]
Parkinson's disease	*CO source*	*Experimental model*	*Key cellular effects*	*References*
	HBI-002	C57BL/6 mice	Neuroprotective	[259]
	CoPPIX	C57BL/6 mice	Neuroprotective	[260]
Alzheimer's disease	*H_2S source*	*Experimental model*	*Key cellular effects*	*References*
	NaHS	Wistar rats	Improved cognition Antioxidant Anti-inflammatory Anti-apoptotic Neuroprotective	[261–264]
		APP/PS1 mice	Improved cognition Reduced Aβ	[265]
	Tabianos water NaHS	3xTg-AD mice	Improved cognition Reduced Aβ	[266]
		Wistar rats 3xTg-AD mice	Improved cognition Antioxidant Anti-inflammatory Anti-apoptotic	[267]
	AP39	APP/PS1 mice	Improved memory Reduced Aβ	[268]
	NaGYY	3xTg-AD mice	Improved cognition Improved motor function Reduced tau	[269]
	Tacrine-ACS81	Kunming mice	Improved cognition Improved motor function Anti-inflammatory	[270]
	ATB-346 Diallyl trisulfide	Wistar rats	Improved behavior Antioxidant Anti-inflammatory	[271]
	Naringin	Wistar rats	Improved cognition Neuroprotective	[272]
	Sulfanegen	APP/PS1 mice	Antioxidant Anti-inflammatory Neuroprotective	[273]
	Methionine restriction	APP/PS1 mice	Improved cognition Reduced Aβ	[274]
Parkinson's disease	*H_2S source*	*Experimental model*	*Key cellular effects*	*References*
	NaHS	Sprague-Dawley rats	Improved cognition Improved plasticity Improved motor function Decreased depression Antioxidant Anti-inflammatory Anti-apoptotic Neuroprotective	[275–279]
		C57BL/6J mice	Enhanced neurogenesis Improved survival and weight Antioxidant Anti-apoptotic Neuroprotective	[129,280,281]

(*Continued*)

Table 1. Continued.

Parkinson's disease	*H_2S source*	*Experimental model*	*Key cellular effects*	*References*
		Wistar rats	Improved motor function Neuroprotective	[282]
	GYY4137	C57BL/6J mice	Improved motor function Anti-nitrosative Neuroprotective	[283]
	Inhaled H_2S	C57BL/6J mice	Improved motor function Antioxidant Anti-inflammatory Neuroprotective	[284]

Note: APP/PS1: amyloid precursor protein/presenilin 1, ATB-346: hydrogen sulfide-releasing non-steroidal anti-inflammatory drug derived from naproxen, CoPPIX: Cobalt protoporphyrin IX chloride (a potent and effective inducer of HO-1), CORM-3: carbon monoxide releasing molecule-3, DNIC: dinitrosyl iron complex; GSNO: S-nitrosoglutathione, HBI-002: oral formulation of carbon monoxide, NaHS: sodium hydrosulfide, SNP: sodium nitroprusside.

Table 2. Cellular mechanisms and events underlying the neuroprotective effects of NO, CO and H_2S exposure on preclinical models of Alzheimer's disease and Parkinson's disease.

NO	*Alzheimer's disease*	*Effects of gasotransmitter*	*References*
		GSNO treatment in streptozotocin-exposed Wistar rats ameliorated cognitive function. The underlying mechanism involved the restoration of BDNF and NRF-2 levels, improvement of the oxidative stress profile and reduction of Aβ levels and neuronal loss.	[248]
		GSNO and L-arginine treatment in streptozotocin-exposed Wistar rats was neuroprotective by improving cognitive function (improvement of spatial learning tasks). The associated mechanisms include epigenetic modification via HDAC2 inhibition, decreased Aβ levels and increased BDNF in the hippocampus.	[251,252]
		Wistar rats injected with $AlCl_3$, exhibited increased Aβ levels, impaired performance in novelty-seeking tasks, reduced CA1 neurons, and decreased nNOS and β-secretase. Treatment with L-arginine demonstrated protective effects by increasing hippocampal NO levels.	[253,254]
		GSNO treatment in APPSw/PS1(dE9) mice was neuroprotective by reducing calpain-mediated p35 proteolysis, Cdk5/GSK-3β activities and Tau hyperphosphorylation.	[250]
		GSNO treatment in BCCAO rats improved performance in learning and memory tasks. The associated mechanisms include reduced Aβ levels and decreased ICAM-1/VCAM-1 expression in the rats' brains.	[249]
		The NO-donor dinitrosyl iron complex protected against memory disorders in Wistar rats injected with toxic Aβ fragments.	[255]
NO	*Parkinson's disease*	*Effects of gasotransmitter*	*References*
		SNP improved stepping test performance in 6-OHDA-injected rats. It also enhanced the responsiveness of putative striatal medium spiny neurons (MSNs) in the dyskinetic striatum.	[257]
		SNP decreased the abnormal involuntary movements (AIMs) in 6-OHDA-lesioned Wistar rats.	[256]
CO	*Alzheimer's disease*	*Effects of gasotransmitter*	*References*
		CORM-3 treatment in 3xTg-AD mice reduced Aβ levels and improved memory deficits. The associated mechanism includes decreased BACE1 expression, which was dependent on NF-κB.	[258]
CO	*Parkinson's disease*	*Effects of gasotransmitter*	*References*
		Oral CO (HBI-002, a drug containing CO currently under development by Hillhurst Biopharmaceuticals) treatment in MPTP-exposed C57BL/6 mice decreased neurodegeneration and reduced αSyn pathology.	[259]
		CoPPIX (a potent and effective inducer of HO-1) treatment in MPTP-exposed C57BL/6 mice was neuroprotective by increasing the number of dopaminergic neurons and TH levels in the SNpc.	[260]
H_2S	*Alzheimer's disease*	*Effects of gasotransmitter*	*References*
		Naringin and/or exercise improved spatial learning and memory in Wistar rats injected with Aβ. Concomitantly prevented neuronal cell death and increased H_2S levels and CBS protein in the AD model.	[272]
		Methionine restriction reduced Aβ accumulation and improved cognitive performance and mitochondrial dysfunction in the APP/PS1 mice. The underlying mechanism was related to the activation of CBS/H2S signaling.	[274]
		Sulfanegen treatment in APP/PS1 and in Aβ1-42-injected mice demonstrated antioxidant and anti-inflammatory properties by restoring impaired 3MST function. Sulfanegen was shown to mitigate neurodegeneration in these AD models.	[273]
		Sodium GYY4137 (NaGYY) treatment in 3xTg-AD mice improved motor and cognitive functions by preventing Tau hyperphosphorylation through GSK3β sulfhydration.	[269]

(*Continued*)

Table 2. Continued.

H_2S	Alzheimer's disease	Effects of gasotransmitter	References
		NaHS treatment in LPS-induced AD in Wistar rats exhibited anti-inflammatory, anti-apoptotic, and antioxidant effects, and improved neuronal alterations.	[261]
		Treatment with the tacrine-H_2S donor hybrid compound in $AlCl_3$-induced AD mice ameliorated cognitive and motor functions. Additionally, the H_2S donor increased hippocampal H_2S levels and reduced inflammatory markers.	[270]
		Sulphur-containing water (Tabianos water) and NaHS treatment in 3xTg-AD mice improved learning and memory and reduced Aβ plaques in the cortex and hippocampus. The underlying mechanism involves decreased activities of JNK, ERK and p38 kinases.	[266]
		NaHS treatment in APP/PS1 mice increased hippocampal H_2S levels, reverted impaired LTP, and improved cognitive function and synaptic plasticity by restoring GluN2B expression and GluN2B-dependent NMDARs function.	[285]
		NaHS treatment in APP/PS1 mice enhanced learning and memory, reduced Aβ plaques and neuronal loss, increased H_2S-sinthetizing enzymes (CBS and 3MST) and antioxidant defences.	[286]
		NaHS treatment in APP/PS1 mice reduced Aβ levels and rescued cognitive function by decreasing BACE1 and PS1 and increasing ADAM17 and the PI3K/Akt signaling.	[287]
		Treatment with H_2S-releasing compounds (ATB-346 and diallyl trisulfide) in streptozotocin-exposed Wistar rats improved behavioral performance, prevented neuroinflammation and oxidative stress, and positively modulated cholinergic function. The associated mechanism involves reducing asymmetric dimethylarginine (ADMA) levels.	[271]
		AP39 treatment in APP/PS1 mice ameliorated spatial memory deficits, prevented brain atrophy, and reduced Aβ levels by preserving mitochondrial function.	[268]
		NaHS treatment in 3xTg-AD mice subjected to foot shock with situational reminders improved cognitive function, reduced Aβ deposition, oxidative stress, and inflammation.	[288]
		NaHS treatment in Aβ1-42-induced AD rats ameliorated cognitive impairment and neuroinflammation by decreasing TNFa, IL-1B and COX-2 expression. Additionally, NaHS prevented the degradation of IκB-α and inhibited the activation of NF-κB, ERK1/2 and p38 MAPK.	[262]
		NaHS treatment in APP/PS1 mice ameliorated spatial learning and memory acquisition. The underlying mechanism involves reduced Aβ40 and Aβ42 levels, decreased BACE1 and PS1 expression and increased ADAM17 expression. Additionally, NaHS treatment induced a shift from the plaque-forming beta pathway to the non-plaque forming alpha pathway of APP cleavage.	[265]
		NaHS treatment in Aβ1-40-induced AD rats rescued neuronal cell death and reduced the release of TNF-α, IL-1β and IL-6 in the hippocampus. The anti-inflammatory effects of H_2S were mediated by suppressing COX-2 upregulation and inhibiting NF-κB activation in the hippocampus.	[263]
		Tabiano's spa water (rich in H_2S) and NaHS treatment in AD models (Wistar rats injected with streptozotocin or Aβ1-40, and 3xTg-AD mice) protected against learning and memory deficits and reduced protein markers of AD, oxidative stress, inflammation, and apoptosis.	[267]
		NaHS treatment in Aβ1-40-injected Wistar rats improved learning and memory performance, prevented apoptosis in the CA1 region, and reduced inflammation, astrogliosis, and microgliosis. The underlying mechanism involves reduced phosphorylation of p38 MAPK and p65 NF-κB.	[264]
H_2S	Parkinson's disease	Effects of gasotransmitter	References
		NaHS treatment in rotenone-induced Sprague-Dawley PD rats improved hippocampal synaptic plasticity and reduced the PD-related depression symptoms.	[275]
		NaHS treatment in MPTP-induced C57BL/6 PD mice improved motor behavior test performance and ameliorated cellular damage. The underlying mechanism involves activation of the BDNF-TrkB pathway.	[289]
		NaHS treatment in rotenone-induced PD rats alleviated cognitive impairment through microglia M2 polarization.	[276]
		NaHS treatment in 6-OHDA-injected rats reduced neuronal apoptosis in the substantia nigra by improving autophagic flux.	[277]
		NaHS treatment in 6-OHDA-injected Wistar rats ameliorated PD symptoms and reduced the death of TH-positive neurons. The underlying mechanism involves activation of K-ATP channels and suppression of endoplasmic reticulum stress markers.	[290]
		NaHS treatment in MPTP-exposed C57BL/6J mice reduced neuronal loss and enhanced neurogenesis by modulating the Akt/glycogen synthase kinase-3β/β-catenin signaling pathway.	[129]
		NaHS treatment in 6-OHDA-injected Sprague-Dawley rats ameliorated PD symptoms and reduced the loss of dopaminergic neurons. Additionally, NaHS increased the Warburg effect and leptin levels.	[278]
		NaHS treatment in 6-OHDA-injected Wistar rats improved behavioral test performance, increased dopaminergic neuron survival and decreased oxidative stress.	[291]

(*Continued*)

Table 2. Continued.

H_2S	Parkinson's disease	Effects of gasotransmitter	References
		NaHS treatment in 6-OHDA-injected Wistar rats improved the motor function test performance and increased dopaminergic neuron survival. These effects were dependent on ATP-sensitive potassium channels.	[282]
		GYY4137 treatment in MPTP-injected C57BL/6J mice improved behavioral test performance, reduced dopaminergic neuron loss in the substantia nigra and striatum, and decreased nitrative stress, resulting in reduced nitrated modification of α-synuclein.	[283]
		Striatal CBS overexpression in MPTP-exposed C57BL6 mice increased H_2S levels, improved motor function, and reduced dopaminergic neuron loss. Additionally, NO and 3-nitrotyrosine levels, as well as nitrated α-synuclein levels, were reduced.	[292]
		Overexpression of CBS in 6-OHDA rats increased CBS protein and H_2S levels, improved motor function, reduced dopaminergic neuron loss, decreased α-synuclein levels, and attenuated oxidative stress. Pharmacological modulation of H_2S with NaHS replicated these protective effects, whereas AOAA showed the opposite.	[293]
		NaHS treatment in MPTP-exposed C57BL/6J mice prevented astrocytic activation in the striatum and dopaminergic neurons loss, and ameliorated motor function. The underlying mechanism involves decreased miR-135a-5p levels and inhibition of ROCK2 activation.	[294]
		NaHS treatment in MPTP-exposed C57BL/6J mice improved survival rate and weight loss and reduced neuronal damage. Additionally, NaHS increased serotonin levels and restored the glutamate/γ-aminobutyric acid balance.	[280]
		ACS84 (a hydrogen sulfide-releasing L-Dopa derivative compound) treatment in 6-OHDA-injected Sprague-Dawley rats improved motor function, reduced dopaminergic neuron degeneration in the subtantia nigra, and attenuated oxidative stress.	[295]
		NaHS treatment in MPTP-exposed C57BL/6J mice ameliorated dopaminergic neuron loss. The underlying mechanism involves UCP2 and antioxidant and anti-apoptotic effects.	[281]
		Inhaled H_2S treatment in MPTP-exposed C57BL/6J mice restored motor function and prevented TH-positive neuronal damage. Additionally, H_2S exhibited antioxidant and anti-inflammatory effects.	[284]
		NaHS treatment in PD models (6-OHDA-injected and rotenone-exposed Sprague–Dawley rats) prevented movement loss, TH-positive neuron loss, and protected against oxidative stress and inflammation.	[279]

Note: 3MST: 3-mercaptopyruvate sulfurtransferase, 6-OHDA: 6-hydroxydopamine, AD: Alzheimer's disease, ADAM17: a disintegrin and metalloprotease domain 17, ADMA: asymmetric dimethylarginine, $AlCl_3$: aluminium chloride, AOAA: aminooxyacetic acid, APP: amyloid precursor protein, APP/PS1: amyloid precursor protein/presenilin 1, Aβ: amyloid beta, BACE1: beta-secretase 1, BCCAO: bilateral common carotid artery occlusion, BDNF: brain-derived neurotrophic factor, CBS: cystathionine-β-synthase, CO: carbon monoxide, CORM-3: carbon monoxide releasing molecule-3, COX-2: cyclooxygenase-2, ERK: extracellular signal-regulated kinase, GluN2B: subunit of the NMDA receptor, GSK3β: glycogen synthase kinase-3β, GSNO: S-nitrosoglutathione, H_2S: hydrogen sulfide, HDAC2: histone deacetylase 2, HO: heme oxygenase, ICAM-1: intercellular adhesion molecule 1, IL-1β: interleukin 1β, IL-6: interleukin 6, JNK: c-Jun N-terminal kinase, LPS: lipopolysaccharide, MAPK: mitogen-activated protein kinase, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NaHS: sodium hydrosulfide, NF-κB: nuclear factor kappa B, NMDARs: N-methyl-D-aspartate receptors, nNOS: neuronal nitric oxide synthase, NO: nitric oxide, NRF-2: nuclear factor erythroid 2-related factor 2, PD: Parkinson's disease, PI3K/Akt: phosphatidylinositol 3' -kinase/Akt, PS1: presenilin 1, ROCK2: Rho-associated coiled-coil kinase 2, SNP: sodium nitroprusside, TH: tyrosine hydroxylase, TNF-α: tumor necrosis factor alfa, UCP2: uncoupling protein 2, VCAM-1: vascular cell adhesion molecule 1.

learning and memory capacity as well as motor function in preclinical models of AD and PD. These encouraging preclinical data suggest that NO, CO, and H_2S positively modulate a number of symptomatic and molecular features of AD and PD and generally exert significant neuroprotective effects.

5. Clinical translation

While clinical translation remains a long-term goal for neurodegenerative diseases such as AD and PD, gasotransmitter-based therapies are already a reality in some non-neurological conditions. The main scenarios include the treatment of persistent pulmonary hypertension in newborns, where inhaled NO is a main therapeutic option [223] or the treatment of pulmonary arterial hypertension in adults, where the prescribed drugs act on the stimulation of the NO pathway [224]. Additionally, it is interesting to see that several clinical trials have been designed in recent years to test the safety of gasotransmitters. Many of these have been compiled in recent reviews by Siracusa and Gomperts [225,226], putting the idea of a gasotransmitter-based therapy closer to being reached. Most of the available studies focus on CO administration, for example, low-dose inhaled CO in the context of sepsis-induced acute respiratory distress syndrome [227] and idiopathic pulmonary fibrosis [228]. The phase I clinical trial conducted by Fredenburgh and colleagues demonstrated that CO administration was well-tolerated and appeared to be safe in the tested cohort [227].

Similarly, the phase II trial led by Rosas and coworkers confirmed the safety of inhaled CO, but failed to show amelioration in the studied endpoints in the patients enrolled in the study [228]. More recently, the safety, efficacy, and pharmacokinetics of an oral CO-releasing compound, HBI-002, were evaluated in a phase I clinical trial involving healthy volunteers, which concluded that the drug was generally well tolerated [229]. Building on these findings, the same compound was subsequently tested in phase IIa clinical trials involving patients with sickle cell disease [230] and patients with Parkinson's disease (Hillhurst Biopharmaceuticals, 2025). These studies are still ongoing, and therefore no results are yet available. However, they raise the possibility of a rationale for gasotransmitter-based therapy in neurodegenerative diseases.

6. Future perspectives

To deepen our knowledge on this topic, scientific efforts are being directed toward improving our understanding of gasotransmitters' biology. In recent years, researchers have dedicated significant time to (1) developing improved methods for detecting gasotransmitters to precisely determine their levels in cells and tissues from experimental models and human biological samples and (2) discovering novel means of administering gasotransmitters to achieve tissue – and cell-specific delivery. Very recently, Gan and colleagues compiled an extensive review highlighting the latest advancements in the synthesis of specialized probes for the detection and imaging of NO and CO [231]. Among the studies presented by Gan and colleagues, the work of Zhang et al. deserves special mention as it describes the synthesis of a new fluorescent NO probe with several interesting features in the neuronal context. For instance, this NO sensor can detect and image NO under neuroinflammatory conditions in both cell lines (BV-2 cells exposed to high NO levels via NOC-9 treatment) and in *in vivo* models (BALB/c mice subjected to ischemic brain damage), where it successfully permeates the BBB [232]. Additionally, the work of Xu and colleagues is equally inspiring as they describe the synthesis of a new NIR fluorescent NO probe capable of penetrating the BBB, enabling the real-time monitoring of NO in the brain of an AD mouse model [233]. Concerning novel CO probes with potential neuronal applications, Morstein and his team conducted promising work by defining a ligand-directed activity-based sensing fluorescent approach, able to detect and image CO release from both live cells (HEK293 T) and brain tissue (Drosophila) [234]. Several interesting findings are also emerging regarding H_2S, as highlighted in recent reviews by Quan et al. [235] and Jia et al. [236]. The H_2S probes developed in recent years show fast responses, low detection limits and easier handling, as confirmed by the work of Feg et al. [237], Wang et al. [238], and Hong et al. [239]. In the neuronal context, the NIR fluorescent probe designed by Hong and coworkers successfully detected H_2S in different experimental models, including SH-SY5Y living cells and hippocampal tissue sections from mice. Interestingly, this probe detected reduced levels of H_2S in the hippocampus of AD mice compared to control mice [239]. The recent work of Marwah et al. [240] and Zhao et al. [241] is particularly encouraging by showing that chemically diverse H_2S probes can penetrate the BBB and provide neuroprotection in different PD models. For instance, Marwah et al. describe that transdermal delivery of the mitochondrial-targeted hydrogen sulfide donor AP39 successfully protects against 6-OHDA-induced mitochondrial dysfunction in SH-SY5Y cells. Using excised murine skin and an *in vitro* BBB model, the authors confirmed AP39's permeation and observed improvements in mitochondrial bioenergetics and reductions in mitochondrial-associated ROS caused by 6-OHDA exposure [240]. Similarly, Zhao and colleagues design a novel nanomotor-based H_2S donor with the ability to penetrate the BBB in an *in vivo* PD model. The H_2S donor was injected into MPTP-induced PD mice through the tail vein, a procedure that significantly prevented the damage of neurons in mice. This effect was achieved following the reduction of neuroinflammation and the reduction of ROS as well as α-syn aggregates [241].

Another promising research avenue involves developing gasotransmitter-donor hybrids with therapeutic potential for neurodegenerative diseases. In this respect, the work of Sestito et al. has demonstrated significant findings in recent years. In 2019, these authors combined memantine, a drug prescribed for moderate-to-severe Alzheimer's disease, with an isothiocyanate moiety capable of releasing H_2S. Testing this hybrid compound in neuronal cell lines revealed that, in addition to maintaining the memantine's beneficial effects, it acted as an H_2S source accessible to neurons. This hybrid compound proved to be effective against neuronal inflammation and oxidative stress while reducing Aβ (1-42) aggregation [242]. Later, the same group combined rivastigmine, a cholinesterase inhibitor for Alzheimer's and Parkinson's dementia,

with sulforaphane and erucin, natural H_2S-releasing compounds extracted from broccoli and rocket, to create a novel H_2S hybrid with very interesting features. These authors found that this new slow releasing H_2S complex presented anti-inflammatory, antioxidant and neuroprotective features in an *in vitro* neuronal model [243].

Hydrogel-based gasotransmitter delivery represents another active research area. In this respect, Sarkar and colleagues recently published a comprehensive review detailing current NO-, CO-, and H_2S-based hydrogel formulations, though most applications focus on NO for wound healing [244]. In fact, hydrogels are emerging as very attractive drug carriers (either loaded with therapeutic agents or cells), for the treatment of AD and PD, and are considered an effective alternative to the current pharmacological formulations [245–247]. However, to the best of our knowledge, no gasotransmitter-based hydrogels have yet been tested for AD or PD, leaving open an exciting opportunity for researchers. The above-presented findings emphasize that the search for refined and innovative solutions to measure the precise levels of intracellular gasotransmitters, as well as the ideal method to deliver these molecules to specific tissue targets, is a rapidly growing research topic. Only by clarifying the exact amount of NO, CO and H_2S that cells experience, in health and disease, alongside understanding the effects of potential interactions between these three molecules, will it be possible to develop neuroregenerative therapies based on these endogenous gases.

7. Conclusion

Alzheimer's disease and Parkinson's disease are complex, multifactorial brain diseases whose etiology remains poorly understood. Despite intensive research in this area, current treatments only ameliorate symptoms rather than curing these diseases. These limitations underscore the need to pursue novel avenues for identifying new players and targets so innovative treatments can be defined. This review compiles extensive evidence demonstrating the neuroprotective effects of the main gasotransmitters (NO, CO, and H_2S) in AD and PD. Collectively, the data reported here demonstrate that these gases ameliorate or prevent key hallmarks of brain injury, including neuroinflammation, oxidative stress, blood–brain barrier dysfunction, and neuronal cell death. Importantly, low levels of NO, CO, and H_2S exhibit anti-inflammatory, antioxidant, and anti-apoptotic effects in several tissues, including the brain. Beyond these established roles, we expand on these features going one level higher by defining these gasotransmitters as pro-neurogenic molecules. The neurogenic features reported here for NO, CO and H_2S make these molecules even more attractive than previously assumed, highlighting the potential of these gases as candidates to integrate new therapies directed to neurodegenerative diseases like AD and PD. Enhancing neurogenesis to repopulate damaged neuronal regions could offer a transformative therapeutic solution for AD and PD patients (Figure 6). The neurogenic and neuroprotective

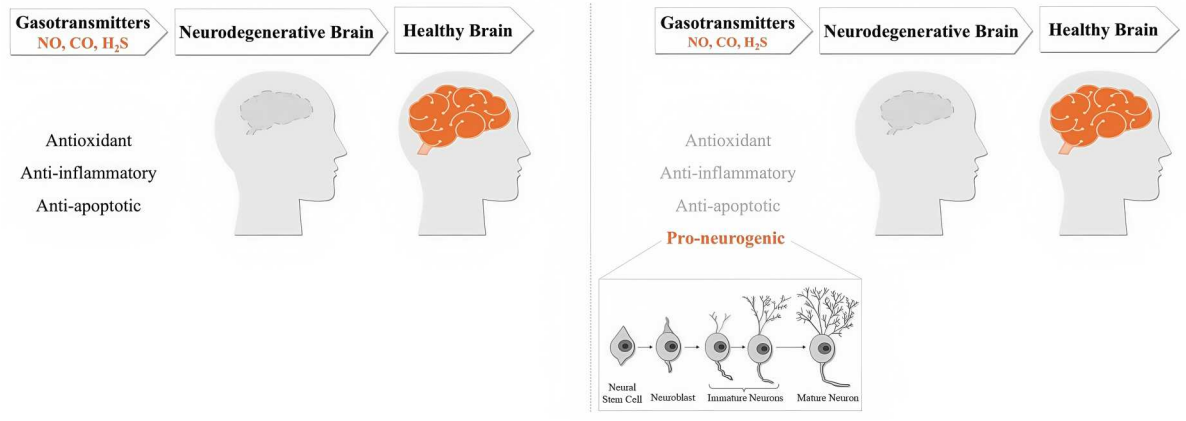

Figure 6. NO, CO, and H_2S as potential candidates to integrate new therapies directed at neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. These gasotransmitters ameliorate or prevent key hallmarks of brain injury, including neuroinflammation, oxidative stress, blood-brain barrier dysfunction, and neuronal cell death. Beyond these established classical roles, we present convincing evidence that NO, CO, and H_2S can act as pro-neurogenic molecules, acting at different stages of the neurogenic process and thus having the potential to transform a neurodegenerative brain into a healthy brain.

features of NO, CO and H_2S add to the unique intrinsic physicochemical features that gasotransmitters own. These gaseous molecules are endogenously produced within cells and can easily cross biological membranes without the need for a specific receptor or transporter. Being small molecules confers on them the great advantage of easily crossing the blood–brain barrier and diffusing rapidly throughout neuronal tissue. Gasotransmitters act in a biphasic way, meaning that low concentrations induce physiological effects as signaling molecules, while high concentrations can be toxic, contributing to the onset of several ill conditions. One of the critical challenges lies in defining the threshold between beneficial and toxic concentrations, which is essential for translating gasotransmitter-based therapies into clinical practice for neurodegenerative diseases. Interestingly, several of the mechanisms discussed here are not exclusive to AD and PD, and many of the identified pathways likely extend to other neurodegenerative diseases, such as amyotrophic lateral sclerosis, frontotemporal dementia, and multiple sclerosis. Future research should therefore explore the effects of these gasotransmitters on the progression of additional neurodegenerative conditions so that novel therapeutic strategies may also be rationalized.

Declaration of generative AI

During the preparation of this work, the authors used Perplexity.ai to detect typing errors. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Author contributions

CRediT: **Sónia Simão:** Conceptualization, Writing – original draft, Writing – review & editing; **Daniela F. Santos:** Writing – original draft, Writing – review & editing; **Mariana Teixeira:** Writing – original draft; **Rafaela R. Agostinho:** Writing – original draft; **Joana Rodrigues:** Writing – original draft; **Marta Vitorino:** Writing – original draft; **Inês M. Araújo:** Funding acquisition, Project administration, Supervision, Writing – review & editing.

Disclosure statement

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