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Review Article

Review Article

Reassessing the role of nitric oxide in the pathogenesis of sphincter of Oddi dysfunction

Haonan Lin [1,2], Yixuan Liang[2,3], Wangqiang Zhao[2,3], Junwei Cao[2,3], Tianqi Wang[2] and Changmiao Wang[2,*]

[1]Department of General Surgery, Affiliated Hospital of Shaoxing University, Shaoxing, Zhejiang, P. R. China
[2]Department of General Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, P. R. China
[3]School of Integrative Medicine, Dalian Medical University, Dalian, Liaoning, P. R. China

*Corresponding author. Department of General Surgery, The First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Road, Dalian, Liaoning 116011, P. R. China. Tel: +86-18098875919; Email: wangchangmiaodl@sohu.com

Abstract

The pathogenic mechanisms underlying sphincter of Oddi dysfunction (SOD) remain incompletely understood, and it often leads to severe symptoms encompassing nausea, vomiting, and abdominal pain. New evidence now suggests correlations between nitric oxide (NO) and SOD. In this review, we summarized the factors influencing SOD pathogenesis via NO and its derivative, the peroxynitrite anion. NO appears to enhance SOD progression by modulating sphincter of Oddi (SO) contractions via NO-sGC-cGMP signaling or inducing the apoptosis of enteric neurons, interstitial cells of Cajal, smooth muscle cells, and other cellular components via peroxynitrite anion-mediated organelle damage. Thus, a comprehensive understanding of SOD will provide a foundation for the identification of potential drugs and treatment approaches.

Keywords: nitric oxide; NO-sGC-cGMP; sphincter of Oddi dysfunction; peroxynitrite anion; cellular components

Introduction

During the primordial era of Earth, nitrogen underwent lightning-induced conversion to nitric oxide (NO), which facilitated its assimilation by vegetation and bacteria; thus, NO is considered a pivotal factor in the genesis of life [1]. In the modern era (1980), scientists initially characterized NO as an endothelium-derived relaxing factor in endothelial rabbit thoracic aortic vessel ring preparations; however, this factor was not positively identified as NO until 6 years later [2]. Ubiquitously found in different mammalian cells and associated with multiple physiological functions, this ancient messenger has crucial signaling roles in many diverse biological systems, such as the nervous, digestive, and cardiovascular systems, as well as in metabolic pathways and immune responses [3]. As a noncholinergic and mammalian neurotransmitter, NO exerts relaxant effects on smooth muscle in the gastrointestinal tract. Moreover, it regulates cellular DNA synthesis, gene expression, action potential generation, and nerve conduction [4–6]. Nitric oxide synthase (NOS) is crucial for NO synthesis and has vital roles in the fundamental physiological function of the gastrointestinal tract. NO influences gastrointestinal motility via the NO-soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway [1]. Such nitrosative stress responses also induce direct cell death and organelle damage, thereby impacting gastrointestinal motility [7–9].

Sphincter of Oddi dysfunction (SOD) is a series of clinical syndromes caused by impaired mobility function of the sphincter of Oddi (SO). It is often characterized by nausea and vomiting. Currently, there are no better treatment options available, primarily involving medication and surgery [10]. SOD is believed to be a significant cause of postcholecystectomy syndrome; it deserves more attention [11]. SOD is a gastrointestinal motility disorder closely associated with NO levels in the body [12]. Therefore, elucidating its underlying mechanisms will not only enhance our understanding of the physiological processes in the gastrointestinal tract but also facilitate the development of novel therapeutic regimens for SOD.

In this review, we provided a comprehensive overview of the direct regulation of SO by NO and the indirect regulation of SO through the production of superoxide dismutase. These include peroxynitrite anion inhibition of the functional activities of interstitial cells of Cajal (ICC) and enteric neurons via damage to mitochondria, endoplasmic reticulum (ER), and lysosomes. Furthermore, we summarized the effects of NO on ICC, enteric neurons, smooth muscle cells (SMCs), and organelles in the SO to identify new therapeutic targets.

A comprehensive review of SOD

Normal SO anatomy

The SO refers to the circular sphincter at the distal end of both the common bile and pancreatic ducts and surrounding the ampullary region. The SO consists of three components: the common bile duct sphincter, the pancreatic duct sphincter, and the ampullary sphincter [13]. Bile and pancreatic duct openings create a slight resistance of approximately 5 mmHg, which

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facilitates significant phasic contractions. Contraction at a frequency of 2–6 times per minute progresses forward to promote or inhibit the flow of bile [14]. In approximately 50% of the population, SO is supplied by the arterial arch formed by the posterior superior pancreaticoduodenal artery and the anterior superior artery, while the remaining population is supplied only by the posterior superior pancreaticoduodenal artery [15]. Innervation of SO is supplied by extrinsic and intrinsic nerves. The former is mainly innervated by the sympathetic and parasympathetic nervous systems of the superior mesenteric ganglion after the inferior pancreaticoduodenal artery (Figure 1) [16]. Specifically, nerve impulses in the intestines are transmitted to the ICC for information integration, and then the information is transmitted to the SMC to produce muscle movement [17, 18]. The enteric nervous system (ENS) is a nervous system composed of enteric glial cells (EGCs) and intestinal neurons distributed in the smooth muscle wall, submucosa, and lamina propria [19]. It operates independently of the autonomic nervous system, which operates independently of the brain and spinal cord and plays an important role in the systematic movement of the gastrointestinal tract [20]. ENS can form a network system with ICC and SMC (ENS-ICC-SMC) to jointly regulate gastrointestinal motility. ICC are the pacemaker and signal transduction element of the gastrointestinal tract and enable the integration of neuronal signals into the SMC syncytium, thus stimulating and promoting smooth muscle function [21].

Epidemiological characteristics and pathogenesis of SOD

SOD refers to a group of disorders that affect the biliary tract, pancreas, and liver and are characterized by spasms, stenosis, and abnormal "valve" relaxation at inappropriate times [22]. Abdominal pain or recurrent primary pancreatitis in the absence of gallbladder disease (e.g. gallstones and abnormal bile duct motility) may indicate SOD [23]. It has been reported that destruction of the structure and function of the SO resulting from sphincterotomy can cause a variety of complications, including recurrent cholecystitis (12%), acute cholecystitis (22% of 32 patients with gallstones), and cholangiocarcinoma (eight patients) [24]. Statistically, SOD is more common in women aged 20–50 years, while the general population has a lower incidence of only 1.5% [25, 26]. The incidence of SOD can increase due to factors, including hyperlipidemia [27], alcoholism [22], excessive morphine use [28], and cholecystectomy [29]. Currently, there is no consensus on SOD pathogenesis; however, aberrant ICC counts, impairment of the ENS-ICC-SMC network system, or abnormal Ca^{2+} levels in SMCs may contribute to disease development [18, 27, 30].

Classification and treatment of SOD

To enhance severity assessments, the Rome III Expert Committee has refined and enhanced disease classifications; SOD is categorized into biliary and pancreatic types, with both subclassified into types I, II, and III [23]. Biliary-type SOD often presents as recurrent upper abdominal or right upper quadrant pain; it can last for more than 30 min and is not relieved by antacids or changes in posture, and laboratory data may show elevated liver enzymes [30]. Pancreatic SOD may present as pain similar to pancreatitis and even radiation pain in the posterior back, accompanied by elevated serum amylase and lipase levels [11].

The clinical treatment of SOD includes nondrug and drug treatments. The former includes endoscopic sphincterotomy and endoscopic retrograde cholangiopancreatography, which have an effective percentage of more than 80% in patients with type I and type II biliary SOD and pancreatic SOD [31]. For patients with type III SOD, drug therapy is commonly used, but its efficacy is different [32]. Currently, drug treatments include calcium antagonists, duloxetine, tricyclic antidepressants, botulinum toxin, glyceryl trinitrate, and somatostatin [25, 33]. Oral treatment with nifedipine is clinically effective; in their randomized controlled trial, Khuroo *et al.* reported a reduction in the duration of pain and the number of attacks after treatment [33]. This may be related to the fact that Ca^{2+} blockers inhibit acetylcholine- and potassium chloride-induced SO contractions in a dose-dependent manner [34]. Duloxetine also has good effects on SOD, with reported symptom improvement percentages of up to 90%. Pauls

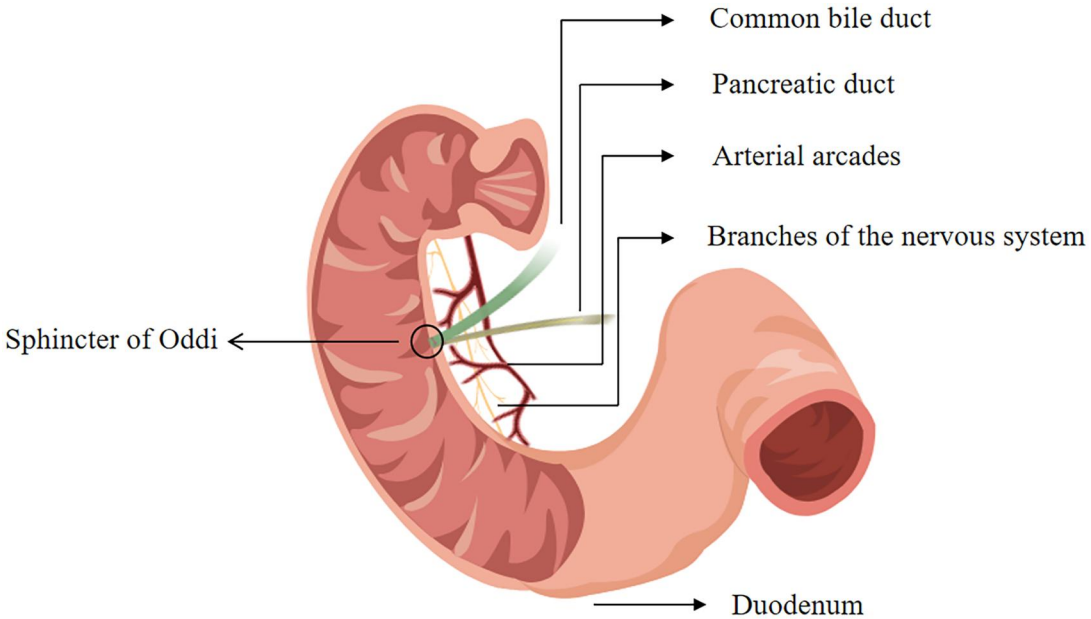

Figure 1. Blood vessels and nerves innervating the SO. Schematic representation of the blood supply and extrinsic innervation of SO. Arterial arcades are composed of the posterior superior pancreaticoduodenal artery and the anterior superior pancreaticoduodenal artery. Branches of the nervous system consist of the nervous and parasympathetic nervous systems.

et al. found that duloxetine reduced pain symptoms by affecting visceral pain signal transduction mediated by 5-HT (It is an indole derivative.) and norepinephrine [35]. For the treatment of SOD with tricyclic antidepressants, 35.6% of patients' symptoms improved or disappeared when using low-dose treatment, but once the drug dose was too high, adverse reactions occurred, and the drug had to be discontinued [36, 37]. In another SOD study, Wehrmann *et al.* reported a 57% improvement in symptoms after a single injection of botulinum toxin (100 mouse units) into the Vater papilla [38]. The toxin can bind precisely to SO cholinergic preganglionic fibers, inhibit acetylcholine release, relax muscles at the injection site, and relieve symptoms [39]. After taking nitroglycerin, the patient's SO pressure and contraction amplitude decreased [40]. The use of somatostatin as a therapeutic agent for SOD is controversial; a study reported that a moderate dose of stilamin (somatostatin analogs) (250 μg/h) promoted SO exercise, whereas a high dose (500 μg/h) inhibited this effect [41]. However, scientists found that another somatostatin analog (octreotide) increased basal SO pressure in all subjects, suggesting stimulating effects in SO [42]. Current research has shown that remission rates for drug and nondrug treatments are similar, but clinical trials investigating SOD drugs are insufficient, and a consensus on drug treatment effects remains elusive [30, 43].

A comprehensive review of NO

NO production pathway in the human body

NO production is attributed to nonenzymatic and enzymatic sources. Nonenzymatic NO is generated through skin photolysis or chemical decomposition and transformation of ingested inorganic nitrogen [44–46]. Enzymatic NO is a byproduct of the synthesis of L-citrulline catalyzed by NOS from acidic L-arginine. Three types of NOS involved in this synthetic reaction have been identified, namely, neuronal nitric oxide synthase (nNOS or NOS1), inducible nitric oxide synthase (iNOS or NOS2), and endothelial nitric oxide synthase (eNOS or NOS3) [3, 47]. nNOS is normally found in neurons on both sides of the synaptic cleft in the brain [48]. eNOS is often expressed in endothelial cells within blood vessels [49]. nNOS and eNOS are characterized by Ca^{2+} dependence and can synthesize only a small amount of NO [48, 49]. iNOS is expressed in immune cells and epithelial cells, and its participation in synthesis reactions does not require Ca^{2+}. When inflammation occurs, iNOS is overexpressed, and a large amount of NO is produced (Figure 2A) [1]. When excessive NO accumulates in epithelial cells, it reacts with superoxide free radicals to generate reactive nitrogen species (RNS), causing DNA damage to the cells [50].

The three types of NOS contain two domains for catalytic proteins and two domains for regulatory proteins, and they require prosthetic groups to bind to form dimers for catalytic activity [51]. In terms of the composition of the domain, they all have reductase, oxygenase, and calmodulin, but eNOS also has an autoinhibitory loop, and nNOS has a unique postsynaptic density protein-95/disk-large/zonula occludens-1 (PDZ) structure [52]. nNOS and eNOS are involved mainly in the physiological processes of vasodilation and information transmission. iNOS also plays a role in mediating cysteine S-nitrosylation of target proteins in the cytoplasm [52]. Gao *et al.* reported that botulinum toxin stimulates the synthesis of iNOS, which can cause S-nitrosylation of a variety of proteins from mouse macrophages [53]. Information on the shared and distinct characteristics of the three nNOS subtypes is shown in Table 1.

The physiological role of NO

NO plays an important role in the body. One study showed that NO can maintain vascular homeostasis by regulating tissue blood flow and preventing platelet and white blood cell adhesion [54]. It can also regulate insulin secretion and glucose uptake through pathways, such as carbohydrate and lipid metabolism [55]. NO even has a small anti-inflammatory effect, and Singh *et al.* reported that NO directly inhibits the growth of nonreplicating *Mycobacterium tuberculosis*, thereby preventing subsequent pathological inflammation [56]. NO is also involved in the signaling pathways of motor control, energy homeostasis, and learning [57]. The NO-sGC-cGMP pathway involves NO diffusion into adjacent SMCs, where it binds to and activates its receptor, sGC. This activation leads to GTP (serves as the provider of guanine nucleotide during DNA replication and during transcription) catalysis by sGC, resulting in the production of the second messenger cGMP, whose effects are mediated via its downstream effector-regulated protein kinase (PKG). PKG and cGMP can modify the activity of these channels, thereby influencing the direction and rate of ion movement across the cell membrane. This regulation maintains the balance of ions inside and outside the cell, ultimately impacting cell function and signal transduction (Figure 2B) [58].

Nitrosative stress caused by excess NO

Excessive NO occurs when the body is stimulated, such as inflammation and diseases. Inflammation stimulates iNOS to catalyze the excessive production of NO, which enhances the physiological response to RNS and results in oxidative damage [7]. Excessive NO can have negative effects by generating nitrosative stress and affecting the calcium channel. Nitrosative stress manifests as excessive production of peroxynitrite ($ONOO^-$) to oxidize proteins, lipids, and DNA, eventually leading to cell death [7, 59]. $ONOO^-$ is the combinative production of NO radical (generated at various NO-binding sites in NOS) and superoxide anion radical (produced within mitochondria) (Figure 2C). It is used to induce cell death by targeting different organelles (mitochondria, ER, Golgi apparatus, and lysosomes) [7]. For instance, $ONOO^-$ impacts the activity of enzymes in the mitochondrial respiratory chain, including NADH dehydrogenase, complex cytochrome c reductase, cytochrome C oxidase, and ATP synthase, which ultimately promotes mitochondrial apoptosis [60]. Yang *et al.* reported that the increased production of $ONOO^-$ in the ER was related to injury in the ER [61]. A study also revealed that $ONOO^-$ serves as a mediator of oxidative damage to Golgi-related protein components, ultimately resulting in Golgi apparatus disruption in an ischemic animal model [62].

Moreover, NO reduces the activity of L-type Ca^{2+}, activates sGC, initiates the NO-sGC-cGMP pathway, reduces myofilament contraction interactions, and causes smooth muscle relaxation [63, 64]. When NO is overproduced, this effect will continue to enhance and inhibit gastrointestinal peristalsis [65, 66].

Relationship between NO and SOD

Impact of NO on SOD

NO was observed to inhibit ICC excitability or reduce the density of neurons [67, 68]. In addition, our previous experiments found that the occurrence of SOD is related to the ENS-ICC-SMC network system [18]. Therefore, we focused on the potential effects of NO on the key cells of SOD (ICC, intestinal neurons, and SMCs) and summarized its damage to related key cells (Figure 3). When immune cells are stimulated (by inflammation or disease), excess

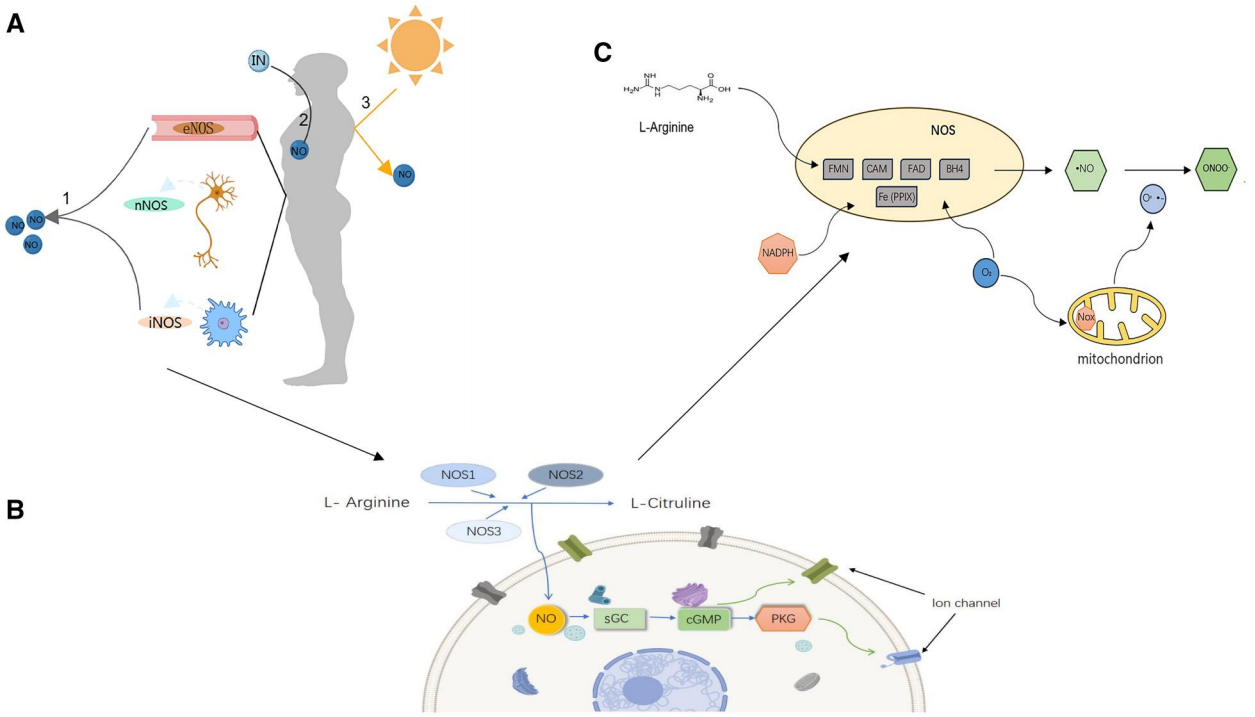

Figure 2. NO is synthesized *in vivo* and participates in signaling pathways. (A) Brief description of the main ways of nitric oxide synthesis. (B) Effects of the NO-sGC-cGMP pathway on SO motility and on cellular ion channels. (C) Schematic representation of $ONOO^-$ generation. IN = inorganic nitrogen, FMN = flavin mononucleotide, CaM = calmodulin, FAD = flavin adenine dinucleotide, BH4 = tetrahydrobiopterin, Fe (PPIX) = iron protoporphyrin IX, NADPH = nicotinamide adenine dinucleotide phosphate, NOX = NADPH oxidases, •NO = nitric oxide radical, $O2•^-$ = superoxide anion radical.

Table 1. Similarities and differences among the three types of NOS

Characteristics	nNOS	iNOS	eNOS
Site of expression [49–51]	Neurons on both sides of the synaptic cleft	Immune cells, epithelial cells	Vascular endothelial cell
Production of NO [1]	Several	A significant quantity	Several
Domain [109]	Reductase, oxygenase, and calmodulin and PDZ structure	Reductase, oxygenase, and calmodulin	Reductase, oxygenase, and calmodulin and autoinhibitory ring
Form of catalysis [52]	Dimer	Dimer	Dimer

NOS = nitric oxide synthase, nNOS = neuronal nitric oxide synthase, iNOS = inducible nitric oxide synthase, eNOS = endothelial nitric oxide synthase, PDZ = postsynaptic density protein-95/disk-large/zonula occludens-1.

NO produced by the iNOS enzyme-catalyzed reaction circulates through the bloodstream and directly penetrates the cell membrane, leading to cell hypoxia and progressive damage to mitochondrial oxidative phosphorylation. This triggers excessive reactive oxygen species (ROS) release from mitochondria, which infiltrates the nucleus to inflict DNA damage and ultimately promote apoptosis [69]. Specifically, NO promotes smooth muscle relaxation by activating the NO-sGC-cGMP pathway and reducing the activity of L-type Ca^{2+} in SMCs [64, 70]. Ueshima *et al.* reported that FK409 (a spontaneous NO releaser) can reduce the number of ICC [71]. Venkataramana *et al.* suggested that chemical donors of NO or activated immune cells selectively kill intestinal neurons by producing NO [72].

The relationship between NO-sGC-cGMP and SOD

Downstream cGMP-regulated phosphodiesterases, cGMP, and cGMP-PKG were shown to modulate cellular ion channel functionality, alter ion flow directions, and regulate muscle contraction and relaxation [73]. cGMP regulates smooth muscle movement by opening large Ca^{2+}-activated K^+ channels [74]. PKG regulates calcium levels by regulating intracellular calcium inflow and outflow, thereby causing smooth muscle relaxation [75]. When too much NO is released upstream, it will continue to produce downstream substances, resulting in decreased shrinkage ability. Bagcivan *et al.* used YC-1, a novel sGC activator, to immerse isolated SO from experimental sheep and observed reduced SO contractile ability [76]. In an endoscopic examination of 20 patients with suspected SOD, a solution containing vardenafil (a phosphodiesterase type 5 inhibitor) was administered to the duodenum (1 mg/mL) to effectively reduce basal sphincter pressure [77].

Relationship between $ONOO^-$ and SOD

$ONOO^-$ is the combinative production of NO and superoxide anion radicals. One study revealed that $ONOO^-$ impairs ICC functions during inflammation [78]. It also affects Rho kinase II, troponin, and actin expression to regulate SMC contraction [79, 80]. $ONOO^-$ directly destroys intestinal neurons via nitrosylated proteins, causing signal transmission disorders and indirectly promoting smooth muscle dyskinesia [81, 82]. It reduces aquaporin-3 and occludin, destroys the ENS-ICC-SMC network,

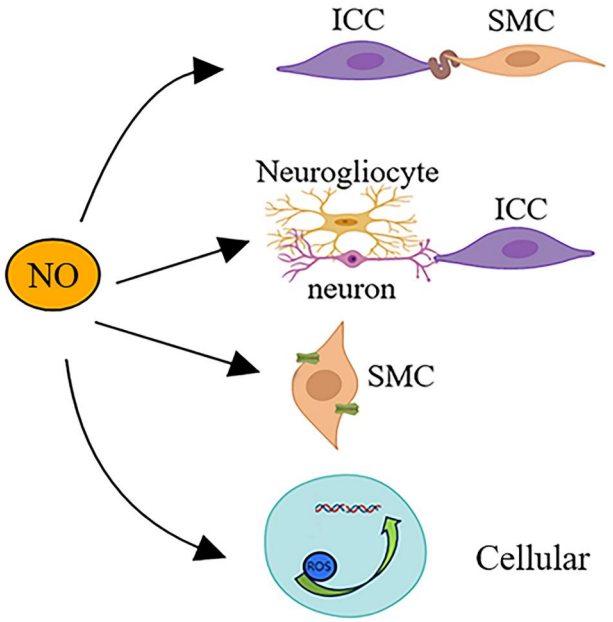

Figure 3. The potential effects of NO on cells. The potential role of NO on SO, which can regulate the movement of SO by inhibiting the activity of cells, such as ICC, SMC, neurogliocyte, and neuron, is briefly described. SMC = smooth muscle cell, ICC = interstitial cells of Cajal, ROS = reactive oxygen species.

and promotes disease occurrence [83]. Researchers have reported that antioxidant enzymes can be used to treat SOD by scavenging superoxide radicals and reducing peroxynitrite production [84]. Researchers have also reported that water-soluble vitamin E (Trolox), tea polyphenols, and quercetin can directly remove $ONOO^-$, but these agents have not yet been tested in clinical trials investigating SOD [85, 86]. Overall, these observations generally promote SOD drug development and provide a foundation for new drug development in the future.

On the other hand, $ONOO^-$ can destroy organelles (mitochondria, ER, and lysosomes), leading to cell death of ICC, intestinal nerves, and smooth muscle, and indirectly leading to the occurrence of SOD [9, 87, 88]. $ONOO^-$ prevents mitochondrial respiration by inhibiting cytochrome C oxidase in mitochondria [60]. Mitochondrial sensitivity to various injuries is widely acknowledged, and alterations in the quantity, structure, and dimensions of mitochondria can serve as damage indicators [89]. Among such injuries, hypoxia exerts the most pronounced impact by inducing swelling and rupture [90]. Wei *et al.* showed that the ultrastructure of the sphincter inside the bile duct showed significant mitochondrial expansion under conditions of biliary muscle spasm [91]. Viader *et al.* confirmed that mitochondrial damage was critical for enteric ENS degeneration; their animal models exhibited abnormal mitochondrial metabolism in intestinal neurons and glial cells [87]. When inflammatory factors stimulate ICC and enteric neurons, mitochondrial ROS levels are significantly increased, leading to mitochondrial hypoxia. This positive feedback loop elevates RNS production and causes further mitochondrial damage [92]. However, researchers have discovered that pharmacological interventions, such as Xiangsha Liujunzi decoction and hesperidin, can ameliorate mitochondrial damage by stabilizing mitochondrial architecture [93, 94]. This study provides new ideas for the prevention and treatment of mitochondrial damage caused by SOD.

$ONOO^-$ can also induce endoplasmic reticulum stress (ERS), further disrupting the normal function of protein folding and transport and glycosylation [95]. It is now accepted that intracellular Ca^{2+} release from the smooth ER regulates slow-wave currents and pacemaker activity in the ICC and controls smooth muscle motility [96]. This release also damages enteric neurons via dysregulation of the CXCR3 pathway, interruption of nerve impulse transmission, and inhibition of smooth muscle movement [97, 98]. All of these factors are considered potential ER damage factors in SOD. Inflammation is associated with ERS in that it stimulates the ER and exacerbates inflammatory responses through the JNK, IRE1, and other pathways [99]. In light of these findings, researchers have discovered that NF-κB/HIF-1α inflammatory pathway inhibition effectively mitigates ERS responses and safeguards cellular integrity [100].

It was found that NO was closely related to the integrity of lysosomes [101]. Lysosome impairment is a crucial mechanism underlying cellular demise, exerting a significant influence on infection, inflammation, and tumorigenesis [102]. The mechanism of action is as follows: under oxidative stress, photodamage, or pro-apoptotic protein conditions, increased lysosomal membrane permeability occurs, which allows intracellular proteases and hydrolases to enter cells and subsequently cause cellular damage [103–105]. Lysosomal autophagy dysfunction impairs autophagic flux in ICC and promotes reduced smooth muscle peristalsis [88]. Additionally, Wen *et al.* suggested that autophagosomes and autolysosomes damage neurons and reduce nerve impulse transmission under ischemic conditions [106]. However, a small amount of lysosomal autophagy cannot induce disease. Researchers have reported that a moderate amount of lysosomal autophagy can be repaired by lysosomal regeneration to avoid excessive loss and disease occurrence [107]. Wang *et al.* reported that pulsatilla saponin D and camptothecin inhibited autophagic flow and reduced autolysosome formation [108].

Summary and prospects

With improved living standards, alcoholism has become common, which has contributed to an increase in the incidence of SOD. NO may be a key factor potentially affecting SOD, and an in-depth understanding of its NO pathogenic mechanisms can be used to explore new therapeutic drugs and help improve SOD prognosis. In this review, we provided evidence showing that NO not only induces pathogenesis via nitrosative stress or NO-sGC-cGMP signaling but also destroys key cells (ICC, enteric neurons, and SMCs) and cellular organelles (mitochondria, ER, and lysosomes) during SOD. Therefore, as a future research direction, we will explore cellular and molecular mechanisms that will provide new drug treatment options for patients who seek nonsurgical treatments or who are intolerant to surgery.

Authors' Contributions

H.L., Y.L., and W.Z. performed the literature research and wrote the manuscript. C.W., J.C., and T.W. corrected the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

We declare that we have no conflicts of interest.

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