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GASOTRANSMITTERS AS MODULATORS OF THE NOCICEPTIVE AND ANTINOCICEPTIVE SYSTEMS

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The article summarizes current data on the roles of nitrogen monoxide, hydrogen sulfide, and carbon monoxide in modulating nociceptive and antinociceptive systems. Currently, gasotransmitters are considered vital endogenous signaling molecules that regulate neuroinflammation, synaptic transmission, and pain sensitivity. For this analysis, contemporary experimental and review studies published in 2021–2026 and indexed in PubMed, Scopus, Web of Science, and Google Scholar were used. It was established that nitrogen monoxide, hydrogen sulfide, and carbon monoxide can exhibit both pronociceptive and antinociceptive effects depending on their concentration, the localization of synthesis, and pathophysiological conditions. Gasotransmitters participate in peripheral and central sensitization, ion channel regulation, glial cell activation, and the development of oxidative stress and inflammatory responses. Concurrently, they can activate endogenous pain-suppression mechanisms via potassium channels, cGMP-dependent signaling pathways, and by restricting neuroinflammation. The accumulated data indicate that pharmacological modulation of gasotransmitter systems is a promising approach for developing novel analgesic agents to manage inflammatory and neuropathic pain syndromes.

Key words: gasotransmitters, nitrogen monoxide, hydrogen sulfide, carbon monoxide, molecular mechanisms, nociception, antinociception, pain modulation, neuroinflammation, neuropathic pain, inflammatory pain.

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ГАЗОТРАНСМІТЕРИ ЯК МОДУЛЯТОРИ НОЦИЦЕПТИВНОЇ ТА АНТИНОЦИЦЕПТИВНОЇ СИСТЕМ

У статті узагальнено сучасні дані щодо ролі нітроген монооксиду, гідроген сульфіду та карбон оксиду у модуляції ноцицептивних та антиноцицептивних систем. На сьогодні газотрансмітери розглядаються як важливі ендогенні сигнальні молекули, що беруть участь у регуляції нейрозапалення, синаптичної передачі та больової чутливості. Для аналізу було використано сучасні експериментальні та оглядові дослідження, опубліковані у 2021–2026 роках і проіндексовані в базах PubMed, Scopus, Web of Science та Google Scholar. Встановлено, що нітроген монооксид, гідроген сульфід і карбон моноксид здатні проявляти як проноцицептивні, так і антиноцицептивні ефекти залежно від концентрації, локалізації синтезу та патофізіологічних умов. Газотрансмітери беруть участь у процесах периферичної та центральної сенситизації, регуляції іонних каналів, активації гліальних клітин, розвитку оксидативного стресу та запальних реакцій. Водночас вони можуть активувати ендогенні механізми пригнічення болю через калієві канали, cGMP-залежні сигнальні шляхи та обмеження нейрозапалення. Отримані дані свідчать про перспективність фармакологічної модуляції систем газотрансмітерів для створення нових анальгетичних засобів при запальних і нейропатичних больових синдромах.

Ключові слова: газотрансмітери, нітроген монооксид, гідроген сульфід, карбон монооксид, молекулярні механізми, ноцицепція, антиноцицепція, модуляція болю, нейрозапалення, нейропатичний біль, запальний біль.

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In recent decades, a substantial rethinking of the role of gaseous molecules in physiological and pathological processes has occurred. While nitrogen monoxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) were previously viewed exclusively as toxic agents, they are nowadays recognized as essential signaling molecules – gasotransmitters – that participate in intercellular communication, the regulation of physiological functions, and pathological processes [12, 13].

Gasotransmitters exhibit significant differences in their chemical nature and biosynthetic pathways; however, they share common features: high lipophilicity, rapid diffusion across biological membranes, the ability to modulate a wide spectrum of cellular functions even at low concentrations, and short half-lives. Unlike classical neurotransmitters, gasotransmitters do not accumulate in synaptic vesicles, are not released via exocytosis, and do not interact with typical membrane receptors. Their biological effects are exerted through the activation of intracellular signaling cascades, alteration of the cellular redox state, protein modification, and the regulation of enzyme activity. To date, their role in regulating inflammation, vascular tone, neuroplasticity, and pain mechanisms has been well established [1, 10, 13]. Regarding the latter, recent studies have demonstrated the active involvement of gasotransmitters in peripheral and central sensitization, regulation of neuroinflammation, activation of glial cells, control of ion channel function, and plasticity of neuronal networks [23, 27]. Particular attention is drawn to the dual nature of their action: depending on the concentration, localization, and pathophysiological context, NO, CO, and H_2S can either enhance nociceptive transmission or exhibit antinociceptive properties [33, 37, 49].

Despite significant progress in the study of gasotransmitters, many aspects of their involvement in pain mechanisms remain controversial. Special

attention needs to be paid to the molecular mechanisms underlying interactions among NO, CO, and H_2S, as well as to the potential of their pharmacological modulation in the development of novel analgesic medicinal products [10, 45].

The purpose of the study was to summarize current data on the roles of nitrogen monoxide, carbon monoxide, and hydrogen sulfide in regulating nociceptive and antinociceptive processes, analyze the mechanisms of their interactions, and evaluate the prospects for the pharmacological application of gasotransmitters in the therapy of pain syndromes.

Materials and methods. This review included experimental and review studies reporting on the roles of nitrogen monoxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO) in regulating nociceptive and antinociceptive processes, their molecular mechanisms, and pharmacological prospects. Papers that did not contain original data (e.g., commentaries, editorials without new data) and studies focused exclusively on non-clinical toxicological approaches without relevant molecular or functional outcomes were excluded. The included studies were grouped thematically: molecular mechanisms, peripheral and central sensitization, the role of glial cells and inflammation, and pharmacological interventions and therapeutic potential.

Study Selection and Characteristics. The search was conducted across PubMed, Scopus, Web of Science, and Google Scholar; additionally, the reference lists of relevant publications were screened. The final search was performed in April 2026. To identify the maximum number of relevant papers, we combined MeSH terms (in PubMed) and free-text keywords; examples of search queries are provided below.

PubMed: (("gasotransmitters"[MeSH] OR "nitric oxide" OR "carbon monoxide" OR "hydrogen sulfide") AND ("nociception" OR "antinociception" OR "pain" OR "neuroinflammation")) – filters: 2021–2026, English.

Scopus: TITLE-ABS-KEY("gasotransmitters" OR "nitric oxide" OR "carbon monoxide" OR "hydrogen sulfide") AND TITLE-ABS-KEY("nociception" OR "antinociception" OR "pain") – filters: 2021–2026, articles/reviews.

Web of Science: TS=("gasotransmitters" OR "nitric oxide" OR "carbon monoxide" OR "hydrogen sulfide") AND TS=("nociception" OR "antinociception" OR "pain") – filters: 2021–2026.

Google Scholar: "gasotransmitters" AND "nociception" AND "pain" – the first 278 relevant results were screened manually.

Inclusion criteria: publications from 2021–2026, experimental (in vivo, in vitro) and review articles, full-text in English with a DOI. Abstracts without full text and papers unrelated to nociception or pain mechanisms were excluded. The results were collected and summarized in tabular form.

Table 1

Simplified PRISMA Flow

Stage	Description	Number of Records/Studies
1. Identified	Total number of records identified through database searching and other sources	378
2. Duplicates Removed	Number of records removed before screening (e.g., duplicates)	69
3. Screened (Title/Abstract)	Number of records screened after duplicates were removed	309
4. Assessed for Eligibility (Full-text)	Number of full-text articles assessed for eligibility against the inclusion/exclusion criteria	136
5. Included in Review	Total number of primary studies finally included in the systematic review	50

Results of the study and their discussion. According to the literature, investigations into the role of gasotransmitters in nociception are predominantly based on experimental models of inflammatory, neuropathic, and chronic pain [2, 4, 11, 14, 31].

To study inflammatory pain, the formalin test, the carrageenan-induced paw edema model, and CFA-induced arthritis are widely used. In these models, an increased expression of iNOS, CBS, and HO-1, as well as alterations in tissue gasotransmitter levels, have been detected.Neuropathic pain models include chronic constriction injury (CCI), spared nerve injury (SNI), and spinal nerve ligation (SNL). In such models, microglia activation, excessive production of NO, and dysregulation of the H_2S and CO systems are observed.

The evaluation of nociceptive behavior is performed using the von Frey, hot plate, tail flick, and Randall-Selitto tests. The use of selective NOS inhibitors, H_2S donors, and CORMs has enabled confirmation of the involvement of gasotransmitters in the formation of pain responses.

Modern research methods include molecular imaging, electrochemical sensors, and gene expression analysis. Novel technologies for in vivo monitoring of gasotransmitters open up avenues for the detailed study of their dynamics within the nervous system.

The role of nitrogen monoxide (NO) in nociception and antinociception. Nitrogen monoxide (NO) is an essential and one of the most extensively studied gasotransmitters in the mechanisms of pain regulation. It plays a key role in modulating pain signals within both the central and peripheral nervous systems. NO is a low-molecular-weight free radical synthesized from L-arginine by NO synthases (NOS), which are represented by three main isoforms:

neuronal (nNOS), expressed in CNS and PNS neurons; endothelial (eNOS), present in vascular endothelial cells; and inducible (iNOS), which is activated during inflammatory processes. nNOS and eNOS are constitutive enzymes and are activated predominantly in a calcium- and calmodulin-dependent manner, whereas iNOS is activated by pro-inflammatory cytokines and provides prolonged production of substantial amounts of nitrogen monoxide [42]. Associative genetic studies have shown that single nucleotide variants (SNVs) of the NOS1, NOS2, and NOS3 genes encoding nNOS, iNOS, and eNOS, respectively, may be associated with acute and chronic peripheral pain [41].

Animal experiments have demonstrated that one of the primary molecular mechanisms of NO action is the activation of soluble guanylyl cyclase (sGC), which catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). An increase in the intracellular concentration of cGMP activates protein kinase G (PKG), which influences the functioning of various ion channels and intracellular signaling pathways, neuronal excitability, and synaptic transmission [8, 28].

The role of NO in pain mechanisms is dual in nature, as this molecule can exhibit both pronociceptive and antinociceptive effects depending on its concentration, site of synthesis, cell type, and the signaling mechanisms activated. Under physiological conditions, NO participates in the regulation of normal neuronal transmission; however, under pathological conditions, its overproduction can contribute to the development of hyperalgesia and central sensitization.

One of the key mechanisms of NO involvement in pain development is its capacity to modulate synaptic transmission within both the central and peripheral nervous systems. At the peripheral level, in response to tissue injury or the action of pro-inflammatory mediators, NO is synthesized by endothelial cells, macrophages, other immunocompetent cells, and sensory neurons. During the inflammatory process, iNOS activation increases its concentration, accompanied by enhanced release of pro-inflammatory mediators, notably prostaglandins, interleukins, and tumor necrosis factor alpha (TNF-α). This contributes to lowering the activation threshold of nociceptors and the development of their peripheral sensitization [13].

NO has been established to increase the sensitivity of TRPV1 and ASIC channels in peripheral sensory neurons, amplifying the generation of pain impulses [41]. Furthermore, it stimulates vasodilation and increased vascular permeability, contributing to the development of edema and neurogenic inflammation. A significant role in this process is played by the interaction of NO with prostaglandins and cytokines.

In inflammatory processes, iNOS can produce large amounts of NO for prolonged periods. Under conditions of elevated reactive oxygen species generation, NO interacts with the superoxide anion ($O_2^{\bullet -}$) to form peroxynitrite ($ONOO^-$), which exhibits pronounced cytotoxic properties and contributes to the development of oxidative and nitrosative stress.

Within the CNS, NO plays an important role in the mechanisms of synaptic plasticity and pain signaling. At the spinal cord level, it participates in the phenomenon of central sensitization. The activation of NMDA receptors in the neurons of the spinal cord dorsal horns causes an increase in the intracellular calcium concentration, which activates nNOS and stimulates NO synthesis. This molecule, in turn, can act as a retrograde signaling mediator, modulating synaptic transmission and promoting the enhanced release of excitatory neurotransmitters, notably substance P, CGRP, and glutamate. Furthermore, NO can attenuate the inhibitory mechanisms of GABA- and glycinergic transmission, contributing to the development of allodynia, hyperalgesia, and the maintenance of chronic pain [4, 8, 41, 44].

An important direction of current research is the study of the role of NO in neuroinflammation. The activation of microglia and astrocytes is accompanied by iNOS induction and the production of substantial amounts of NO, contributing to the maintenance of chronic inflammation and neuronal damage. In neuropathic pain models, iNOS inhibition is accompanied by reduced glial activation and the attenuation of the pain syndrome. For instance, Rasmussen RH et al., using a mouse model of migraine-related tactile hypersensitivity induced by the KATP channel activator levcromakalim, found that the non-selective NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME) effectively prevented hypersensitivity [32, 37].

On the other hand, NO also plays an important role in the mechanisms of pain inhibition. The activation of the NO–sGC–cGMP system can stimulate the opening of ATP-dependent potassium channels (KATP), leading to neuronal membrane hyperpolarization and reduced excitability [32, 41, 44]. The dual nature of NO action is confirmed by numerous experimental data. For instance, NOS inhibitors frequently reduce the manifestations of inflammatory and neuropathic pain; however, in certain models, the suppression of NO synthesis can, conversely, enhance pain sensitivity. This indicates a physiological antinociceptive role for basal NO levels.

Of particular significance is the role of nitric oxide in the function of descending antinociceptive systems. Within the brainstem structures, NO modulates the activity of serotonergic and noradrenergic neurons that control the transmission of pain signals at the spinal cord level [41].

Furthermore, NO contributes to the analgesic effect of opioids and non-steroidal anti-inflammatory drugs. In peripheral tissues, NO enhances the action

of morphine via the NO-cGMP-K_{ATP} pathways, whereas NOS inhibitors reduce pain and diminish the development of opioid tolerance [7, 26].

The activation of eNOS and the moderate production of NO promote vasodilation, improved microcirculation, and suppression of neuroinflammation. Certain NO donors exhibit an analgesic effect in models of ischemic and neuropathic pain. Within the spinal cord, NO can activate the cGMP-PKG pathway, leading to the opening of K_{ATP} channels and neuronal hyperpolarization, thereby decreasing neuronal excitability and pain transmission [2, 44].

Understanding the role of NO in pain modulation opens up new opportunities for therapy. Thus, the use of NOS inhibitors or NO donors could help reduce pain, particularly in inflammatory and neuropathic pain. However, it is essential to consider the potential side effects of prolonged use of these medicinal products, as well as the need for further studies to optimize their use.

Hydrogen sulfide in pain regulation. Hydrogen sulfide is one of the most recently discovered gasotransmitters; however, in recent years, substantial data have accumulated on its involvement in nervous system function and the regulation of pain sensitivity. The endogenous synthesis of H_2S is predominantly carried out by three enzymes: cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MPST). The localization of these enzymes depends on the tissue type: CBS is predominantly expressed in the central nervous system, CSE in peripheral tissues and the vascular system, whereas 3-MPST is widely present within the mitochondria of various cells [12]. Like other gaseous mediators, H_2S can penetrate cell membranes, modulating neuronal electrophysiological properties and inflammatory processes.

Initially, H_2S was viewed primarily as a toxic substance; however, contemporary studies have proven its essential physiological role. It has been demonstrated that within the nervous system, it modulates synaptic transmission, regulates ion channel function, maintains mitochondrial homeostasis, and participates in neuroprotection mechanisms [33].

The role of H_2S in pain regulation is complex and characterized by a dual effect. The results of experimental studies indicate that the action of H_2S depends significantly on its concentration, site of generation, and exposure duration. At low concentrations, H_2S can exhibit neuroprotective and antinociceptive properties, whereas excessive production can stimulate the development of pain responses [17, 41].

One of the most important mechanisms of the pronociceptive action of H_2S is its effect on transient receptor potential (TRP) channels. In studies by Roa-Coria et al., H_2S was shown to activate TRPV1, TRPC6, and TRPA1 receptors, which play key roles in the generation of pain signals and the development of inflammation. Their activation is accompanied by an increase in membrane permeability to calcium and sodium ions, which promotes depolarization of sensory neurons, enhances nociceptive transmission, and leads to hyperalgesia. These receptors play a particularly crucial role in pain signaling during inflammation and tissue injury. Special attention in pain regulation mechanisms is paid to the effect of H_2S on T-type calcium channels (Cav3.2). Studies have demonstrated that the activation of these channels also contributes to the development of hyperalgesia and neuropathic pain. Their stimulation is considered to be one of the primary mechanisms underlying the pronociceptive action of H_2S [16, 34, 39].

Under the influence of H_2S, the expression of NMDA and ATP-dependent P2X3 receptors in the spinal cord increases, amplifying pain conduction and promoting central sensitization. Furthermore, H_2S increases the release of substance P and calcitonin gene-related peptide (CGRP), thereby promoting neurogenic inflammation [18].

Another experimental confirmation of the pronociceptive activity of hydrogen sulfide was the reduction of nociceptive responses in models of inflammatory and neuropathic pain following administration of CSE and CBS enzyme inhibitors, resulting in a subsequent decrease in H_2S formation [22].

Concurrently, numerous studies confirm the presence of antinociceptive properties of H_2S. Low concentrations of hydrogen sulfide have been shown to reduce the production of reactive oxygen species, suppress pro-inflammatory signaling cascades, and attenuate neuroinflammation [5, 12].

One of the essential mechanisms underlying the antinociceptive action of H_2S is the activation of ATP-dependent potassium channels, whose opening promotes neuronal membrane hyperpolarization and suppresses the transmission of pain signals [23].

An important factor in reducing neuroinflammation is the experimentally proven capacity of H_2S to inhibit NF-κB activation, decrease the production of TNF-α, IL-1β, and IL-6, and limit microglia activation. Owing to this, H_2S attenuates central sensitization and pain chronification [33, 35]. It has also been demonstrated to reduce neuroinflammation via the suppression of the NLRP3/caspase-1/GSDMD signaling pathway [48].

H_2S exhibits pronounced antioxidant properties by neutralizing reactive oxygen species, enhancing the activity of superoxide dismutase, and boosting the glutathione system. This is of critical importance in chronic pain, where oxidative stress represents one of the leading pathogenetic mechanisms [38].

In experimental models of neuropathic pain, H_2S donors have been shown to reduce allodynia and hyperalgesia. Slow-releasing H_2S donors, which maintain physiological concentrations of the

gasotransmitter for prolonged periods without inducing toxic effects, are particularly promising [15, 23, 33].

The effect of H_2S on mitochondrial function has also attracted researchers' attention: at low concentrations, it supports electron transport chain activity and ATP synthesis, whereas at high concentrations, it inhibits cellular respiration, thereby regulating neuronal energy metabolism [43].

H_2S participates in the regulation of apoptosis and autophagy. It has been established to suppress caspase-dependent neuronal death and support cell survival during ischemic and inflammatory injury to nervous tissue [1, 19, 34].

Contemporary studies also indicate an essential role of H_2S in the interaction between the nervous and immune systems. H_2S influences the function of macrophages, T lymphocytes, and microglia, modulating the intensity of the inflammatory response; this makes H_2S a promising therapeutic target for not only pain syndromes but also neurodegenerative diseases [34, 35].

Carbon monoxide and the HO system in pain mechanisms. Carbon monoxide was long considered exclusively as a toxic agent capable of binding hemoglobin and disrupting oxygen transport. However, the discovery of endogenous CO synthesis became a major milestone in the development of modern neuropharmacology and the biochemistry of signaling systems [6, 21]. Today, CO is recognized as a fully fledged gasotransmitter that participates in the regulation of vascular tone, thermoregulation, emotional behavior, inflammatory processes, cellular metabolism, and nociceptive transmission [6, 9, 50].

The primary source of endogenous CO is the enzymatic degradation of heme mediated by heme oxygenase (HO). Two main isoforms of the enzyme are distinguished: inducible HO-1 and constitutive HO-2 [6, 36]. The latter is predominantly expressed in neurons and glial cells of the spinal cord and brain, trigeminal nerve cells, superior cervical ganglia, as well as in large and small cerebral vessels, providing a basal level of CO production. Meanwhile, HO-1 is activated by oxidative stress, hypoxia, heat shock, endotoxins, inflammation, and tissue injury. In various experimental pain models in rats and mice, HO-2 has been demonstrated to influence primarily central nociceptive signaling [46].

Similar to NO, one of the primary mechanisms of CO action is activation of soluble guanylyl cyclase, increasing intracellular cyclic guanosine monophosphate [10]. The elevated cGMP concentration activates a series of signaling cascades that alter the functional state of neurons and their electrical activity. The HO–CO–cGMP system has been established to participate in the regulation of synaptic transmission and neuronal plasticity processes [45, 49]. Although the efficiency of guanylyl cyclase activation by CO is lower than that of NO, this mechanism plays an important role in pain development.

Within the CNS, CO also influences the release of glutamate, adenosine diphosphate, γ-aminobutyric acid, and other neurotransmitters that directly determine the intensity of nociceptive signal transmission [49]. Concurrently, numerous studies demonstrate the antinociceptive potential of the heme oxygenase system. For instance, in mice with peripheral inflammation induced by complete Freund's adjuvant, the administration of cobalt protoporphyrin IX (CoPP), an HO-1 inducer, and tricarbonyldichlororuthenium(II) dimer (CORM-2), a CO-releasing molecule, resulted in the suppression of nociceptive and apoptotic responses [10, 24]. In another study involving opioid-induced hyperalgesia, an increase in heme oxygenase activity and CO production within the spinal cord was established, and the capacity of CO to enhance the analgesic effect of opioids in chronic pain via the modulation of peripheral μ- and δ-opioid receptor expression was demonstrated [5, 30]. The genetic deletion of HO-2 or its pharmacological blockade in mouse experiments also reduces nociceptive activity and pain severity.

The induction of HO-1 represents a vital adaptive mechanism of cellular defense. Heme degradation products – CO, biliverdin, and bilirubin – possess antioxidant and cytoprotective properties. Consequently, the HO-1/CO system is viewed as one of the key mechanisms for limiting inflammation and tissue damage [5, 6].

In addition, CO influences mitochondrial function, inflammatory processes, and apoptosis. In peripheral tissues, the HO-1/CO system can suppress the development of inflammatory responses: CO downregulates the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, and inhibits neutrophil migration into the injury zone. This is accompanied by a reduction in the peripheral sensitization of nociceptors. Furthermore, CO stimulates the expression of antioxidant enzymes and reduces oxidative stress [3, 25, 36, 45].

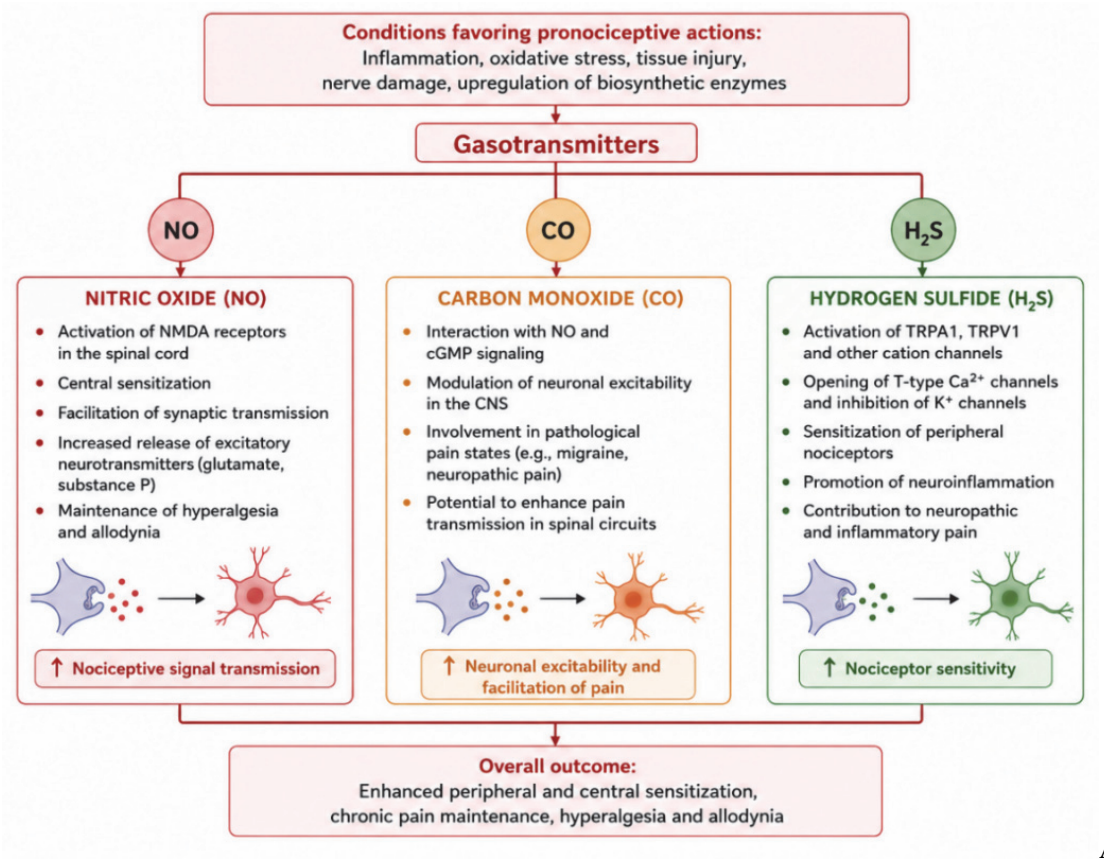
The HO-1/CO system plays an important role in interacting with the NLRP3 inflammasome, whose levels increase significantly in the spinal cord, hippocampus, and prefrontal cortex during the development of neuropathy. Its activation is accompanied by the production of IL-1β and IL-18, representing one of the key mechanisms underlying the maintenance of neuroinflammation in chronic pain. In experimental settings, CO has been shown to inhibit NLRP3 activation, limit the development of the inflammatory response, and alleviate nerve injury-induced allodynia [40, 45]. In animal models of neuropathic pain, the activation of HO-1 is accompanied by reductions in allodynia and hyperalgesia, restriction of microglial and astrocytic activation within the spinal cord, and attenuation of central sensitization [30, 45].

Contemporary studies also demonstrate CO's involvement in the regulation of apoptosis.

Furthermore, it can suppress caspase activation and support neuronal survival under conditions of ischemia, trauma, or chronic inflammation [10].

However, the clinical application of CO and its donors remains limited due to the risk of toxic effects upon their excessive accumulation. Consequently, the development of safe CO delivery systems and selective HO-1 inducers represents a highly relevant direction in modern pharmacology.

In summary, gasotransmitters exert a dual effect on pain regulation mechanisms and, depending on specific factors, can exhibit both pronociceptive properties (Fig. 1A) and antinociceptive properties (Fig. 1B).



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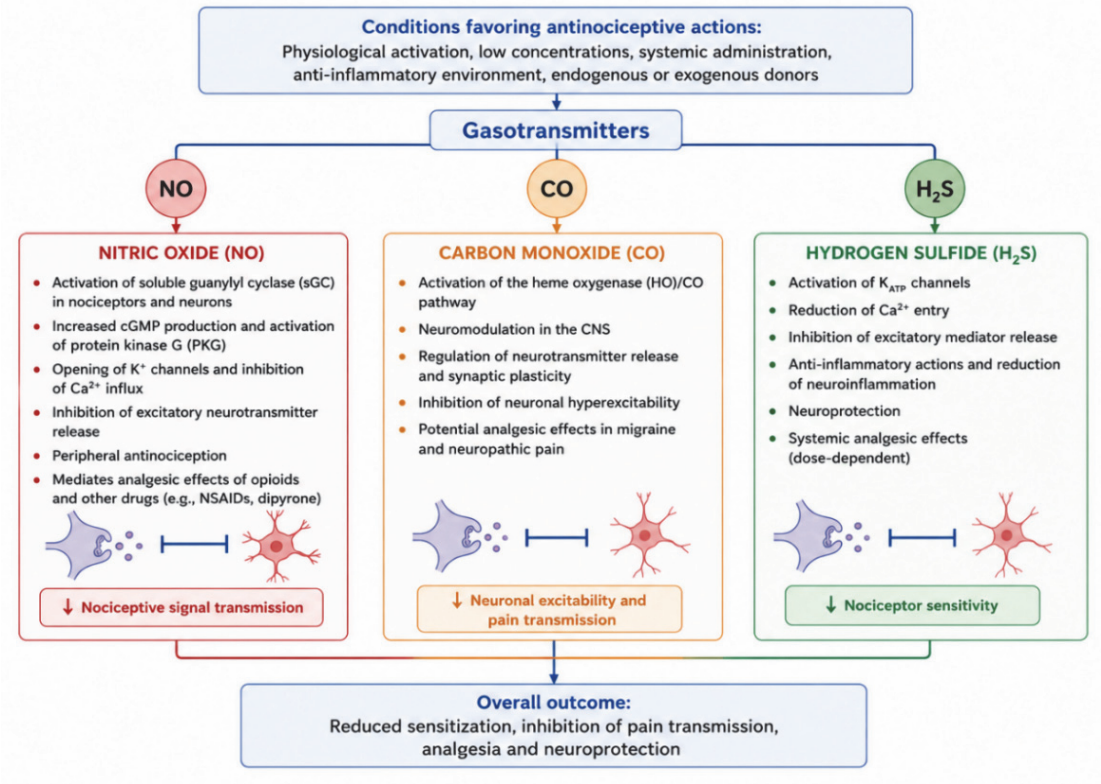

B

Fig. 1. Pronociceptive (A) and antinociceptive (B) effects of nitric oxide, carbon monoxide, and hydrogen sulfide.

Cross-talk between NO, CO, and H_2S. The investigation of interactions between different gasotransmitter systems is of great interest. For a long time, nitrogen monoxide, carbon monoxide, and hydrogen sulfide were considered as separate signaling molecules with distinct mechanisms of action. However, the contemporary concept of gasotransmitter regulation is based on the idea of an integrated signaling network in which they interact closely with one another. This interaction is dynamic and complex, and is mediated by modifications in enzyme activity, shared signaling cascades, redox regulation, and gene expression control [9, 20]. It participates in maintaining cellular homeostasis, regulating neuroinflammation, and mediating pain responses. A disruption of the balance within this system can play a key role in the development of chronic pain, neurodegenerative processes, and inflammatory diseases.

One of the mechanisms underlying crosstalk between gasotransmitters is the mutual regulation of the activities of their biosynthetic enzymes. For instance, H_2S influences NOS activity via protein sulfhydration. Studies have also demonstrated that H_2S increases NO production in endothelial cells by activating eNOS [34]. In turn, NO modifies H_2S-synthesizing enzymes (CSE and CBS) via S-nitrosylation and influences heme oxygenase activity, thereby stimulating CO production, which in turn modulates NOS activity and regulates NO levels [10].

Gasotransmitters share common target mechanisms. For instance, one of the key crosstalk pathways is regulation of the cGMP system – a crucial second messenger that mediates antinociceptive effects via activation of protein kinases and ion channels. NO and CO can bind to the heme group of sGC and activate it, leading to increased cGMP levels. Concurrently, the efficiency of NO in this process is significantly higher [9]. Competition between NO and CO for binding to heme structures influences the intensity of the signaling response. H_2S is also capable of interacting with the cGMP system by modulating the activity of phosphodieesterases. Thus, all three gasotransmitters form a single redox-sensitive signaling network.

Another common feature is their effect on ion channels: they all modulate the activity of calcium, potassium, and sodium channels, thereby influencing the excitability of nociceptors and spinal cord neurons. For example, H_2S activates T-type calcium channels (Cav3.2), TRPV1, and TRPA1 channels; NO modulates the activity of K^+ channels and NMDA receptors; while CO alters the functional activity of calcium channels [16, 23, 34]. The cumulative effect of these influences determines the excitability of nociceptive neurons and the intensity of pain signal transmission.

Gasotransmitters also interact at the level of neuroinflammation regulation. They regulate the production of pro-inflammatory cytokines, notably tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), chemokines, and other inflammatory mediators [13, 43]. A vital aspect is the involvement of gasotransmitters in regulating the NLRP3 inflammasome. H_2S and CO have been established to inhibit inflammasome activation, whereas the excessive production of NO can maintain the inflammatory process via the formation of peroxynitrite [29].

The activation of microglia and astrocytes plays an important role in the development of chronic pain. Gasotransmitters can both stimulate and suppress the activity of these cells, thereby influencing central sensitization processes.

The interaction of NO, CO, and H_2S in their effect on oxidative stress is of particular significance. For instance, NO at high concentrations can promote the formation of reactive nitrogen species and the development of oxidative damage. Concurrently, H_2S and CO predominantly exhibit antioxidant properties and can limit excessive free radical production, thereby enhancing antinociceptive effects [5]. The simultaneous administration of H_2S and CO donors in experimental settings demonstrated an antiallodynic effect that was more pronounced than when they were administered individually [5].

The interaction of gasotransmitters also plays a substantial role in mitochondrial functioning. NO, CO, and H_2S can influence the activity of electron transport chain components, regulate ATP production, and control apoptosis. These mechanisms are of crucial importance in the pathogenesis of neuropathic pain and neurodegenerative diseases.

Recent studies also indicate the possibility of the formation of new signaling molecules resulting from direct chemical interactions between gasotransmitters. For instance, the interaction between NO and H_2S generates nitrosothiols, thionitrites, and ferro-nitrosyls, which possess their own biological activity. Frequently, these compounds exhibit greater stability, ensuring their impact on target areas that the gasotransmitters themselves cannot reach due to rapid diffusion. They play an important role in vasodilation, neuromodulation, and antioxidant processes.

Each of these can both promote the onset of pain and reduce pain sensations. The final effect depends on the compound's concentration, the site of action, and the organism's physiological state. Contemporary data suggest that it is the balance between individual gasotransmitters, rather than the absolute concentration of each, that determines the character of the ultimate biological outcome.

Thus, the NO, CO, and H_2S systems do not function in isolation. They form a complex integrated network that provides fine-tuned regulation of nociceptive processes, inflammation, and cellular homeostasis. A disruption of the balance between

gasotransmitter systems may represent one of the key mechanisms underlying the development of chronic pain.

Prospects for the application of gasotransmitters in pain management. Given the complex roles of NO, CO, and H_2S in modulating pain signals, they have attracted significant attention as potential targets for pharmacological pain therapy. This is also highlighted by the fact that contemporary pharmacotherapy of pain syndromes is predominantly based on the administration of NSAIDs, opioid analgesics, anticonvulsants, and antidepressants. However, their long-term use is frequently accompanied by the development of side effects, the formation of tolerance, and insufficient efficacy, particularly in chronic and neuropathic pain [45]. Therefore, the pharmacological modulation of gasotransmitter systems is considered a promising approach for treating chronic pain. The primary directions include the use of gasotransmitter donors, synthetic enzyme inhibitors, and combination drugs.

For instance, NO donors are used to enhance pain inhibition by activating the NO–cGMP–K_{ATP} pathway. Among the potential NO donors under consideration are organic nitrates, S-nitrosothiols, and nitrosyl complexes. For example, nitroglycerin is added to analgesic therapy for cancer pain to enhance the effect of opioids. Cyclooxygenase-inhibiting NO donors (CINODs), which combine anti-inflammatory and analgesic properties with a lower incidence of certain NSAID-related side effects, have attracted special attention. For instance, they exhibit a gastroprotective effect: NO stimulates the production of protective gastric mucus and improves microcirculation. Examples include NO-naproxen (naproxcinod), NO-diclofenac, and NO-aspirin.

Significant interest is generated by CO-releasing molecules (CORMs) – compounds capable of releasing CO in a controlled manner into tissues – and HO-1 inducers, such as cobalt protoporphyrin IX (CoPP). In preclinical studies, CORMs demonstrate pronounced anti-inflammatory and analgesic properties in experimental models of arthritis, postoperative pain, and neuropathic pain. One of the advantages of CORMs is the ability to achieve localized, dosed CO release, which minimizes systemic toxicity. The most extensively studied are CORM-2, CORM-3, and photoactivated CORMs. Furthermore, their administration induced a reduction in allodynia and pain aversion – the emotional component of pain associated with an increase in opioid receptor expression within the hippocampus resulting from the activation of the HO–CO pathway [9]. Both HO inhibitors and inducers are being developed to regulate CO levels for balancing pronociceptive and antinociceptive actions.

In the H_2S system, slow-releasing H_2S donors are being actively investigated [33]. The most thoroughly studied are sodium hydrosulfide (NaHS), sodium sulfide (Na_2S), GYY4137, AP39, and the ATB series of H_2S-releasing drugs (e.g., H_2S-naproxen). They are used to activate antinociceptive pathways, particularly by opening potassium channels, thereby altering neuronal excitability and reducing pain. Such compounds can provide an analgesic effect with lower gastrotoxicity compared to traditional NSAIDs. Novel σ_1 receptor antagonists coupled with H_2S donors have been developed [15]. Inhibitors of H_2S synthesis (CSE and CBS inhibitors) reduce increased pain sensitivity in inflammatory and neuropathic pain by decreasing endogenous H_2S production.

Given the interconnectedness of NO, CO, and H_2S, the development of combined or hybrid drugs that simultaneously target multiple gas pathways is highly promising. For instance, NOSH-acetylsalicylic acid – a hybrid compound that releases both NO and H_2S – demonstrates an enhanced analgesic effect with fewer side effects [34].

A separate direction involves controlled-release delivery systems for gasotransmitters, particularly hydrogels and nanomaterials, which provide localized release of NO, CO, or H_2S, as well as their targeted delivery and prolonged action [33, 37].

However, certain risks limit their application, including the need for precise dosing due to the dual action of these gases and the risk of toxicity with uncontrolled use, particularly for CO [27, 47]. Another difficulty in their application is their short half-life. Furthermore, there is currently a need for deeper investigations into their mechanisms of action and interaction, as well as for clinical trials. On the other hand, the positive role of gasotransmitters in nociception opens new opportunities for personalized pain therapy, especially for chronic pain, which remains a challenge in modern medicine.

Conclusion

Gasotransmitters are crucial endogenous signaling molecules involved in the regulation of numerous physiological and pathological processes, including the mechanisms of pain sensitivity. Their unique ability to rapidly diffuse and interact with cellular receptors and ion channels ensures the effective transmission and modulation of pain signals in both the periphery and the central nervous system.

An analysis of current experimental data indicates a dual nature of gasotransmitter action in the nociceptive and antinociceptive systems: they can either amplify nociceptive signaling or activate pain inhibition mechanisms. This duality depends on gas concentration, the localization of synthesis, tissue conditions, and the phase of the pain process.

An important aspect of modern concepts regarding pain regulation mechanisms is the understanding that NO, CO, and H_2S do not function in isolation; instead, they form a single integrated signaling network. The

interaction between gasotransmitter systems occurs through the regulation of intracellular signaling pathways, ion channels, neuroinflammation, and oxidative stress.

The use of experimental pain models has significantly expanded our understanding of the role of gasotransmitters in the development of acute, inflammatory, and neuropathic pain. The accumulated results establish a solid foundation for pursuing novel therapeutic approaches.

Prospects for further research. Promising directions in modern pharmacology include the development of drugs based on gasotransmitter donors, molecules with controlled release of NO, CO, and H_2S, as well as the formulation of combined therapeutic strategies aimed at the simultaneous modification of multiple signaling pathways. Thus, further investigation into the biological role of gasotransmitters may facilitate the creation of new, effective treatments for pain syndrome and advance current approaches to pain pharmacotherapy.

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