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Dynamics and metabolic effects of intestinal gases in healthy humans

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ABSTRACT

Many living beings use exogenous and/or endogenous gases to attain evolutionary benefits. We make a comprehensive assessment of one of the major gaseous reservoirs in the human body, i.e., the bowel, providing extensive data that may serve as reference for future studies. We assess the intestinal gases in healthy humans, including their volume, composition, source and local distribution in proximal as well as distal gut. We analyse each one of the most abundant intestinal gases including nitrogen, oxygen, nitric oxide, carbon dioxide, methane, hydrogen, hydrogen sulfide, sulfur dioxide and cyanide. For every gas, we describe diffusive patterns, active *trans*-barrier transport dynamics, chemical properties, intra-/extra-intestinal metabolic effects mediated by intracellular, extracellular, paracrine and distant actions. Further, we highlight the local and systemic roles of gasotransmitters, i.e., signalling gaseous molecules that can freely diffuse through the intestinal cellular membranes. Yet, we provide testable hypotheses concerning the still unknown effects of some intestinal gases on the myenteric and submucosal neurons.

Contents

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1. Introduction

Many living beings make use of the mechanical and/or chemical properties of gases to increase their likelihood of survival. For example, planktonic prokaryotes and Haloarchaea [1,2] modify their overall cellular density by inflating and deflating gas-filled cytoplasmatic micro-structures termed gas vesicles [3]. Gases can be actively produced by living organisms. For instance, carbon monoxide is generated by the aeriform cells of the Siphonophore Physalia physalis, which uses an enlarged float filled with gas as a sail to travel by wind on the sea surface [4,5]. Also, exchanges of exogenous gases are crucial to attain aerobic cellular respiration in plants and in animals supplied with circulatory systems.

We focus on an eminent gaseous reservoir in the human body, i.e., the intestine. The first analyses of the intestinal gases date back to the seminal works of Förster [6] and Levitt [7]. On their trail, we aim to update the physiological roles of the gases that can be found in the healthy human intestine, trying to answer the following questions.

1) What kind of exogenous and exogenous gases can be found in the human intestine?
2) How are the endoluminal gases generated and/or dispersed?
3) What are the physiological roles of the intestinal endoluminal gases?

At first, we will analyse volume, composition, local distribution and source of intestinal gas in healthy human individuals. Then, we will describe the intra-/extra-intestinal physiological roles of each one of the most abundant intestinal gases.

2. Intestinal gases: generalities

Quite variable gaseous concentrations can be measured in intestinal lumen, faeces and breath, depending on the quantity and quality of the ingested food, the host/bacterial metabolic processes and the technique used for the assay [8]. The total weight of human intestinal gas amounts to just a few grams, while the total gaseous intestinal volume can be quantified, with a certain approximation, in $\approx$100–500 cm^3 [9–11]. The source of intestinal gas is twofold [12].

1) Exogenous swallowed air.
2) Endogenous gases produced by:
   a) Intraluminal fabrication by the host organism.
   b) Intraluminal fabrication by commensal microorganisms.
   c) *Trans*-membrane diffusion from bloodstream into the intestinal lumen.

The composition of human intestinal gas varies along the gastrointestinal tracts [13]. See the **Table** for quantitative details. Swallowed air is the major source of nitrogen (N_2) and oxygen (O_2), while carbon dioxide (CO_2) comes both from swallowed air and intestinal production [7]. A large amount of intestinal gases is generated by microorganismal fermentation in the human colon [14]. These gases include carbon dioxide (CO_2), hydrogen (H_2), methane (CH_4) [11]. The sum of N_2, O_2, CO_2, H_2 and CH_4 accounts for more than 99% of the expelled intestinal gas [12]. The remaining 1% is composed of odoriferous substances including hydrogen sulfide (H_2S), sulfur dioxide (SO_2), sulfur-containing mercaptans, ammonia (NH_3), indole, skatole, volatile amines, acetic acid, propionic acid, butanoic acid, isobutyric acid, pentanoic acid, etc [11,15].

The gaseous production varies according to the age. To provide an example, the intestinal gases and faecal short-chain fatty acids produced by the gut microbiota of preterm infants increase during the first 4 weeks of life [11]. The dietary uptake deeply affects the amount of some intestinal gases. In particular, the following fermentable foods are known to increase intestinal gas production [16].

a) Non-absorbable carbohydrates such as lactulose and mannitol.
b) Incompletely absorbed carbohydrates such as lactose, fructose, sorbitol.
c) Sulfur-rich foods such as beans, pork, onions, cabbage and cauliflower.

A we shall see later, some gaseous substances can be detected after carbohydrate load using breath tests as markers of colonic carbohydrate fermentation [17–19].

	Atmosphere	Stomach	Colon (Flatus)	Breath
Nitrogen (N_2)	78	$\approx$78 ± 1.0	65 ± 21	$\approx$78 ± 3.5
Oxygen (O_2)	21	$\approx$15 ± 0.7	2.3 ± 1.0	16 ± 1.0
Carbon dioxide (CO_2)	0.04	$\approx$7 ± 2.1	9.9 ± 1.6	4 ± 0.4
Hydrogen (H_2)	Traces	Traces	3 ± 0.7	Traces
Methane (CH_4)	Traces	0	14.4 ± 3.7	Traces
Hydrogen sulfide (H_2S)	Traces	0	Traces	Traces
Sulfur dioxide (SO_2)	Traces	Traces	Traces	0

Table. Approximate percentage of different gases in various human anatomical districts. The values can vary significantly depending on the state of the human body and what is eaten. Intestinal gases may be present in widely different proportions in each bowel region, depending on manifold factors. Data extracted from: [7,12,17–1919].

2.1. Gaseous exchanges between intestinal lumen and blood

Most of the intestinal gases crosses the barrier between the intestinal lumen and the blood by means of passive mechanisms governed by the Fick's law of diffusion [20]. The blood gases are defined as the mixture of gases dissolved in the fluid fraction of blood or transported by carriers such as., e.g., haemoglobin and urea nitrogen. In the human gut, the gradient between the gaseous mixture's partial pressures in the intestinal lumen and in the bloodstream dictates the direction of gases exchanges. The formula provided by Förster [6] summarizes the physiological basis of passive gas exchange in the intestine.

Where V is the total intraluminal gaseous volume, P_L and *Pc* are, respectively, the partial intraluminal and extraluminal gaseous pressures, P_B in the barometric pressure, 47 is the pure pressure of water at 37°. K is a transfer coefficient depending on the type of gas. For instance, N diffuses through the epithelial intestinal barrier slowly than O_2 and CO_2 [18]. Since gases have been traditionally deemed to diffuse freely and passively, previous studies focused mainly on production and reactivity rather than diffusion and transport [21]. Still, the discovery of gas pores has raised the intriguing possibility of active cellular modulation of gas diffusion. Many gases can cross different compartments by means of transmembrane channels [22]. Recent observations suggest that the highly conserved and widely diffused intramembrane channels termed aquaporins (AQPs) transport not just water molecules, but also gases [23]. AQP water channels represent a major transcellular route for water and gas transport in the gastrointestinal tract also during inflammatory processes (Miller et al., 2010; Zhu et al., 2016; Meli et al., 2018) [24–26]. Different AQPs isoforms have been found in the stomach, small and large intestine, everyone preferentially distributed in distinct cell types [27]. For instance, Aquaporin 3 is a water, glycerol and H_2O_2 transporting channel expressed in colonic epithelial cells that is able to affect epithelial tight junction's integrity and permeability [28].

2.2. Patterns of flatus and gaseous volumetry

As the healthy human individual generates 0.6–1.8 L of gas per day, it follows that discard must be continuous. The mechanisms of removal are multiple: microorganismal consumption, host consumption, absorption into the systemic circulation and ensuing expulsion, occurring through the breath, belching, eructation and, above all, flatus [17,29,30]. The data concerning frequency and volume of flatus vary widely, with some subjects passing gas more often than others. The mean total volume of intestinal gases ranges in different studies from ≈260 [31] to ≈705 ml/die, with an upper limit of 1800. On their usual diet, subjects pass gas from ≈7 to ≈10 daytime evacuations, with an upper limit of 20. The record of abdominal symptoms is rare in healthy subjects, corresponding to ≈0.4 discomfort/pain per day [31]. Gender, age, and methane production have no significant influence on frequency and volume of flatus [17]. Flatus is produced also during the sleeping period, but the rate is significantly lower than the daytime (median: 16 and 34 ml/h, respectively) [31]. Larger volumes of flatus are produced after meals. Fiber-free diets decrease the total daily volume, suggesting that fermentable gases make the highest contribution to normal flatus volume. The addition to the diet of 10 g/day of the nonabsorbable disaccharide lactulose increases flatus frequency to ≈19 times/die. On flatulogenic diet, increased gas production leads to increase in number not just of gas evacuations (≈22/day), but also of abdominal symptoms (≈3 mean discomfort/pain per day) [31].

2.3. Gaseous volumetry in gut segments

The intestine has an oro-anal length of ≈5 m, two-third of which refers to the small intestine. The intestinal surface area is ~32 m^2, of which about two refers to the colon [32]. In the undisturbed gut of healthy subjects, extreme volumetric variability can be appreciated in every compartment, due to extra-intestinal pressure, intestinal walls contraction and amount of ingested foods. Alternating two contraction patterns periods (i.e., peristalsis and segmentation), the gut can switch between different flow regimes, optimizing nutrient absorption and minimizing detrimental bacterial overgrowth [33]. Gaseous mixing, transport and *trans*-barrier exchanges are strictly correlated with bowel movements. Gas is moved along the gut independent of solids and liquids, actively propelled by the inner circular and longitudinal musculature [34]. Intestinal transit, and therefore intraluminal pressure, can be also modified by a series of viscero-somatic reflexes triggered by intraluminal lipidic nutrients, mechanical stimulation like rectal distension, intra-abdominal volume load, etc [34]. In presence of foods, liquids and gases, the small bowel, which is empty and closed most of the time, moves more frequently than the colon [35]. With a large degree of approximation [36–38], the ascending colon has a mean volume of ≈200 mL, the transverse colon of ≈185 mL, the descending colon of ≈175 mL and the rectosigmoid colon of ≈200 mL (including the faeces). In the ascending colon, 10% increases occur 90–240 min after feeding as the meal residue enters the cecum [10]. The human mean fluid volume is lower in the fasting colon that in the fasting small bowel (≈13 versus ≈54 mL, respectively). Fluids and gases are not homogeneously distributed, rather are provisionally confined in separated fluid pockets that increase in number after meals (mean number ≈5) [10]. The total colonic fluid volume in almost entirely (~95%) stored in the few fluid pockets (~10%) larger than 1 mL [39]. The intraluminal volume of the partially relaxed colon is mostly filled by gases, since fluids and faeces occupy just a relatively small volume, corresponding to a few dozen mL and ≈200 mL, respectively [39].

After the general description of the intestinal gases provided above, in the next paragraphs we will analyse the physical and biological features of each one of the most prominent intestinal gases.

3. Physiology of individual intestinal gases

The physical/biological features of every intestinal gas will be described. Production, consumption, excretion and disposal in different gut compartments take part in the homeostasis of many physiological processes involving both intestinal and extra-intestinal organs [30]. A few gaseous molecules, namely hydrogen sulfide, nitric oxide, carbon monoxide and sulfur dioxide, have been recently assigned to the mammalian family of gasotransmitters, i.e., signalling molecules freely diffusing through the intestinal cellular membranes ([11] et al., 2021). We will see that they play physiological/pathophysiological roles in processes such as stomach acid release, smooth muscles relaxation, heart contractility control, local blood flow adjusting, inflammation activation, angiogenesis [41].

3.1. Nitrogen (N_2)

Nitrogen supplies the main fraction of intestinal gases. Its concentration varies greatly with the diet, especially in the distal gut [7,18]. It has long been believed that the intestinal N_2 entirely came from swallowed air. However, the gut commensals Klebsiella and Clostridiales strains might produce ~0.01% of the standard nitrogen requirement for humans [42]. Compared with other gases like O_2 and CO_2, N_2 gradient diffusion between lumen and blood is much slower [7]. This means that most of the intestinal N is not absorbed, rather is propelled towards the distal intestinal tracts. While a N_2 partial pressure gradient from the intestinal lumen to the blood does exist in the duodenum and upper small bowel, downhill gradients occur from blood to intestinal lumen in the colon after beans meals. The gradient established by CO_2, CH_4 and H_2 produced by commensal bacteria drives N_2 diffusion from the bloodstream into the colon [7]. Therefore, the gastric N_2 comes entirely from swallowed air, while a certain amount of N_2 in flatus comes from blood diffusion.

3.1.1. Physiological effects of N_2

Contrary to the inert atmospheric nitrogen, the intestinal N_2

plays a role in nitrogenous compound metabolism. In the small intestinal lumen, amino acids from alimentary sources and endogenous proteins are deaminated, hydrolysed, incorporated or degraded by the microbiota, in particular by Bacteroidetes [43,44]. Small intestinal N_2 supply/recycling is crucial for colonic digestion/absorption of endoluminal proteins/amino acids [45]. Nitrogen-derived molecules like nitrated short-chain fatty acids are energy substrates for both colonocytes and peripheral tissues. When the dietary supply of N_2 is deficient, urea nitrogen absorption from the large intestine increases body protein synthesis/deposition [46]. Residual undigested luminal proteins and recovered amino acids act as precursors for the synthesis of numerous metabolic end products that work locally as well as systemically after absorption [47]. Reactive nitrogen oxides such as nitric oxide, nitrite, nitrate, nitrated fatty acids, N-nitrosamines peroxynitrite, S-nitrosothiols are continuously manufactured in the colon [46,47].

3.1.2. Ammonia (NH_3)

The N_2-derived ammonia (NH_3), produced by colonic intestinal bacterial urease, is used not just by the surrounding bacteria as a nitrogen source for amino acid synthesis [48], but also by enterocytes via glutamate, glutamine, citrulline, and urea synthesis. It is noteworthy that *Helicobacter pylori* produces NH_3 using uric acid as a substrate, to locally neutralize gastric acid and improve its survival chances in the highly acid gastric environment [48]. Able to diffuse through the pores of the human Aquaporin 1 [20], NH_3 can be systemically absorbed causing hepatic encephalopathy in patients affected by liver cirrhosis.

Summarizing, intestinal N_2 is crucially involved in the nitrogenous compound metabolism that is mandatory for the survival of both intestinal host cells and microorganismal commensals.

3.2. Oxygen (O_2)

The Oxygen concentration progressively declines throughout the gut. The atmosphere contains about 21% O_2, while the stomach approximately 15–16%, since some of the swallowed O_2 is adsorbed through the intestinal vessels. Most of the O_2 has been removed in the colon, falling to ≈2% of the total gaseous amount [18]. The human Aquaporin 1, abundantly distributed in the endothelial cells of the gastrointestinal tract, facilitates O_2 transport [25]. In the colon, O_2 diffuses from the bloodstream into the lumen, due to its low pressure. However, at very high O_2 intraluminal pressures, mammals can absorb O_2 through their intestines. Experiments in rodent and porcine models, inspired by loaches that use intestinal air breathing to survive under extensive hypoxia, demonstrated that intra-rectal delivery of O_2 attains systemic oxygenation [49,50].

3.2.1. Physiological effects of O_2

While the role of the atmospheric oxygen is correlated with the aerobic respiration, the intestinal oxygen exerts different roles. The scarce amount of intraluminal colonic O_2 favours the proliferation of essential anaerobic commensals [7]. The microbiome, together with genes dependent on hypoxia-inducible factors, maintain the hypoxic environment critical for mucosal cells' nutrient absorption, intestinal barrier function and innate/adaptive immune responses [14]. Further, the hypoxic condition of the large intestine makes various fermenting bacteria able to produce acetic acid, CH_4 and HS_2 as energy sources [48].

Oxygen is a crucial component to build active molecules with intestinal and extra-intestinal effects. Among them, hydrogen peroxide and nitric oxide are of great physiological importance. They will be discussed in the next paragraphs.

3.2.2. Hydrogen peroxide (H_2O_2)

The O_2-derived hydrogen peroxide (H_2O_2) is a major redox signalling molecule with effects on growth and differentiation. Produced by cell-surface NADPH Oxidase enzymes, H_2O_2 shapes both the colonic epithelial surface environment and the colonic bacterial growth, in particular Citrobacter's growth [51]. The process is favoured by the water channel Aquaporin-3 that accelerates H_2O_2 uptake and intracellular accumulation, leading to downstream intracellular signalling [52]. The epithelial release of reactive oxygen species such as H_2O_2 toward the intestinal lumen provides an innate mucosal defensive mechanism after chronic inflammation, as well as after exposure to dysbiotic microbiota [53,54].

3.2.3. Nitric oxide (NO)

Oxygen enters the composition of the endothelial biosynthesis of the gaseous signalling molecule nitric oxide (NO), the first of the gasotransmitters to be discovered. NO is generated from O_2, L-arginine and NADPH by the enzyme nitric oxide synthase (NOS) that reduces organic nitrates [47]. Displaying a half-life time of a few seconds, the extremely active NO freely diffuses across membranes, engendering transient paracrine and autocrine effects [41]. Via intracellular signalling in enteroendocrine cells, NO plays a role in the release of gut peptides such as gastrin, cholecystokinin, etc and is involved in anti-inflammatory processes, feeding behaviour, glucose metabolism [41]. Further, NO promotes CCK-mediated prevention of oesophageal acid reflux during digestion, gastrin release, motilin-mediated contractility of gastric smooth muscles (leading to relaxation of the fundic area after a meal), CCK-mediated neurogenic vasodilatation in mesenteric and cerebral arteries, GLP-1-mediated endothelium-dependent vasodilatation, CCK2Rs-mediated inhibition on motor activity in distal colon, etc [47].

Summarizing, intestinal O_2 contributes to gut homeostasis in a roundabout way. By one side, its shortage in the distal gut promotes the homeostasis of anaerobic commensals essential to host's survival. By another side, O_2 is one of the main constituents of powerful active molecules that affect physiological phenomena well beyond the gut.

3.3. Carbon dioxide (CO_2)

Carbon dioxide is generated in various intestinal segments. The CO_2 content in the stomach is much higher than in the swallowed air (5–9 vs 0.04%), since it is locally produced during the periods of high gastric acid secretion via HCl neutralization by dietary bicarbonates [7,55]. Carbon dioxide partially diffuses from the proximal intestinal lumen into the blood, but its absorption rate is not enough to prevent accumulation in the duodenum and proximal jejuneum. The intestinal CO_2 enters red blood cells and is converted to carbonic acid, which dissociates to hydrogen ion and bicarbonate. Two-thirds of the bicarbonate is converted back to CO_2 in the lungs and expelled by exhalation [7]. Further amounts of jejunal CO_2 are generated by the degradation of dietary triglycerides to fatty acids [56]. CO_2 movements across cellular membranes are not just passive, but also depend to a small extent on active transport performed by aquaporin channels [20]. The amount of CO_2 has increased to ≈10.0% in the colon, with large variations depending on the diet [18]. Colonic CO_2 is a fermentative subproduct of the bicarbonate/acid reaction performed by commensals such as Bifidobacteria and butyrate-producing Clostridial clusters [15,57,58]. Although CO_2 diffuses much more rapidly than H_2, CH_4, N_2, and O_2, a part of the intraluminal gas diffuses into the bloodstream [16]. Therefore, the volume of the intestinal-produced CO_2 is greater than the volume passed in flatus [7].

3.3.1. Physiological effects of CO_2

Short-chain fatty acids (acetate, propionate and butyrate) are the dominant fermentation acids that accumulate to high concentrations in the colon and produce large amounts of CO_2 [58]. The extreme acid load associated with high colonic pCO_2 is partially counteracted by the proximal colon epithelium's apical membrane that provides resistance towards CO_2 diffusion and confers cellular protection [59]. Apart from the role in peripheral chemoreceptors' activation during hypoxia [60,61], CO_2 is involved in manifold metabolic reactions. For instance, CO_2 enters the composition of carbon monoxide and lactate, discussed in the next paragraphs.

3.3.2. Carbon monoxide

(CO) is one of the known gasostransmitters. Contrary to the very short-lived and labile NO, H_2S and SO_2, the hemoglobin-binded CO is a relatively stable molecule with half-life time up to 4 h [41]. Its biological functions are mainly related to the activation of soluble guanylyl cyclase and, to a less extent, cytochrome P450 inhibition. Synthesized by two enzymes, the produced CO acts on intestinal bacteria to cause release of adenosine triphosphate, which in turn activates inflammasome response and interlukin-1β production [41,48].

3.3.3. Lactate

A crucial intermediate of carbon metabolism is the lactate, that, produced in anaerobic conditions, stands for a readily combusted fuel shuttled throughout the body as energy source [62]. A relatively small number of lactate-utilizing colonic species produce short-chain fatty acids, butyrate, acetate and propionate [58]. The lactate produced in anaerobic conditions by Bifidobacterium and Lactobacillus spp. contributes to the intestinal epithelial development by increasing the expansion of Paneth and goblet cells [63]. It is noteworthy that Bacteroides and Firmicutes isolates are susceptible to growth inhibition by relevant concentrations of lactate and acetate, whereas the lactate-producer Bifidobacterium adolescentis are resistant [64]. Lactate may work as a whole-body metabolite acting as a potent signalling molecule in the central nervous system, impacting neuron/astrocyte activity in brain areas well beyond the neuronal diffusion zone [62].

Summarizing, intestinal CO_2 is produced in different ways in various intestinal segments. Carbon dioxide's metabolites play direct roles in pH homeostasis, energy production and intestinal anti-inflammatory responses.

3.4. Methane (CH_4)

Methane is produced by the human enteric microflora through anaerobic fermentation of both endogenous and exogenous carbohydrates [17]. The human colonic concentration of methane is ≈ 14% [18], with differences observed according to the amount of ingested fermentable dietary residues, time of the day and individual variations [48]. To make a comparison, cattle produce ≈250–500 Lt of methane every day, with an estimated emission rate of 95–150 g/animal/day [7]. Just one/two third of healthy human adults produce methane, especially the population of middle east and Africa [12]. There is no methane production below the age of 3 years, while a rise is recorded from 14 to 18 years. Contrary to H_2, the colonic CH_4 production is relatively constant throughout the day. Human CH_4 is produced in anaerobic conditions not by bacteria, but by methanogenic microorganisms of the Archea domain [65]. Methanobrevibacter smithii is able to reduce CO_2, methanol, or acetate to CH_4, using H_2 as an electron donor [66,67]. Tiny amounts of CH_4 can be produced under hypoxic conditions to counteract intracellular oxygen radical production not just by microorganisms, but also by host structures such as, e.g., rat mitochondrial subfractions and bovine endothelial cell cultures [68]. In this case, CH_4 is generated from phosphatidylcholine metabolites containing both electron donor and acceptor groups [69]. Like H_2, the intraluminal colonic CH_4 diffuses to the blood for gradient concentration, enters the splanchnic circulation and is excreted through the breath) [48,70–72].

3.4.1. Physiological effects of CH_4

Methane is not inert as previously thought. Recent studies have provided evidence for methane bioactivity in various in vivo settings [73]. It influences the enteric nervous system's cholinergic pathway, increasing contraction amplitudes [74]. In guinea pig ileum, CH_4 delayed ileal peristaltic conduction velocity by increasing contractility [75]. In radiolabelling experiments of small intestinal infusion, CH_4 slowed dogs' and guinea pigs' small intestinal transit, by increasing bowel contractions oral and aboral to the stimulus [76,77]. The increases in contractile activity correlated with CH_4 production have been associated with slowed intestinal transit time and constipation-predominant irritable bowel syndrome [76,78,79]. Further, abundance in methanogenic bacteria has been positively correlated with chronic intestinal pseudo-obstruction [17,80]. Rifaximin has been shown to improve chronic constipation by altering methane production [81]. Patients with irritable bowel syndrome are characterized not just by reduction of methane producing microorganisms, but also by reduction of butyrate producing bacteria, known to improve intestinal barrier function [78,82].

High levels of exhaled CH_4 can be detected in haemorrhagic shock, since internal haemorrhage's bleeding causes reactive changes of the mesenteric circulation [83]. During these hypoxic events, CH_4 production and subsequent mitochondrial redox regulation/oxidative phosphorylation has the positive effect to improve basal respiration [68]. Mitochondria themselves can be sources of endogenous CH_4 under oxido-reductive stress conditions [84]. Further, various colonic bacteria produce chemical compounds during hypoxic condition that can be used as energy source, such as acetic acid, CH_4 and HS_2 [48]. Exogenous CH_4 exerts also anti-inflammatory and anti-apoptotic beneficial effects [72]. Methane modulates leukocyte activation and plays shielding roles in hepatitis [85], acute lung injury [86], diabetic retinopathy, spinal cord ischemia/reperfusion injury and sepsis [87].

Summarizing, intestinal CH_4 is produced by intestinal commensal anaerobia in approximately one-two third of healthy humans. Methane delays intestinal transit and compensates oxido-reductive stress conditions. Its extra-intestinal effects are so extended, that a few researchers are starting to suggest that CH_4 could stand for a fifth gasotransmitter apart from NO, CO, H_2S and SO_2.

3.5. Hydrogen (H_2)

H_2, which accounts for ≈3% of the colonic gases, in healthy individuals is almost entirely produced by the dietary fiber's intraluminal fermentation performed by anaerobic commensals in the large intestine [18]. H_2 production requires ingested, fermentable substrates. Nine/tenth consists of non-absorbable oligosaccharides such as beans and lactulose, the last one tenth consists of poorly absorbed proteins, short chain fatty acids and alcohols [88]. To provide an example, the amount of lactose in a glass of milk generates 500–1000 ml of H_2 after bacterial fermentation. The intraluminal fermentation of dietary fibers leads also to the production of short-chain fatty acids such as butyrate. Hydrogen-producer species are abundant in the gut microbiota and include not just the two major colonic phyla, i.e., Firmicutes and Bacteroidetes, but also members of the genera Roseburia, Ruminococcus,

Eubacterium [67]. It is remarkable that a large number of hydrogen cross-feeding microbes have evolved, the three main hydrogenotrophic colonic groups consisting of sulfate-reducing bacteria (such as Desulfovibrio), methanogenic archaea and reductive acetogens [16,89,90]. Luminal colonic H_2 freely diffuses between the lumen and the blood, the net movement depending on the pressure gradient. Colonic H_2 absorption is highly effective at low colonic hydrogen accumulation rates, but not at higher accumulation rates [91]. About 15% of H_2 diffuses back into the bloodstream, with the rest passing as flatus. The colonic H_2 absorbed by the blood is cleared by the lungs during breathing, where its presence can be easily quantified. The time taken for H_2 to appear in the breath after ingestion of a standard load of glucose or lactose is used to determine whether the upper gastrointestinal tract has been colonized by H_2 producing bacteria [90,92].

3.5.1. Physiological effects of CH_4

H_2 displays antioxidant properties. Physiological H_2 concentrations might protect the healthy colonic mucosa from oxidative insults, preventing inflammation or carcinogenesis [89]. Using hydrogen molecules generated by fermentation reactions, various bacteria are able to produce in the hypoxic condition of the large intestine chemical compounds that can be used as energy source, such as acetic acid, CH_4 and HS_2 [48]. When H_2 is not fully metabolized, fermentation may be incomplete and intermediates such as lactate, succinate, and ethanol accumulate [16]. Also, roles on local intestinal motility have been suggested for H_2. Indeed, it was able to shorten the colonic transit of guinea pigs in the proximal colon by 47%, but just by 10% in the distal colon [75].

Summarizing, intestinal H_2 is major byproduct of colonic fermentative metabolism. Hydrogen preserves the healthy colonic mucosa from oxidative insults and might have a role in shortening colonic transit.

3.6. Hydrogen sulfide (H_2S)

In healthy humans, the most of H_2S is a by-product of colonic bacterial metabolism [93]. Intraluminal and faecal colonic H_2S concentrations are rather variable [8]. Cysteine catabolic bacteria and, to a lower extent, sulfate-reducing bacteria generate H_2 using as substrates both dietary and endogenous compounds of organic and inorganic nature [8,94]. Two enzymatic *trans*-sulfuration pathways are involved in H_2S production, i.e., the cystathionine gamma-lyase in the vascular system's smooth muscles, and the cystathionine beta-synthase in both central and intestinal nervous systems (Verbeure et al., 2021) [41]. To generate H_2S in an anaerobic watery environment like the human colon, some requirements must be satisfied, e.g., high-concentration of sulfate ions and organic substances as carbon source and sulfate-reducing bacteria like Desulfovibrio bacteria [48]. Sulfate reduction and methanogenesis are mutually exclusive in the colon because of the sulfate availability, which favours the production of H_2S instead of CH_4 [16]. Hydrogen sulfide is produced also by endogenous cellular enzymes expressed in intestine, liver, kidney and brain. H_2S is synthetized by specific enzymatic pathways in different intestinal cells, including neurons and smooth muscle [95]. Vegetables like garlic and onions contain the natural H_2S donor allicin, that contributes to generate large amounts of colonic H_2S provided with beneficial vasoactivity [96].

3.6.1. Physiological effects of H_2S

H_2S is an important energy substrate in colonocytes because its mitochondrial oxidization results in ATP synthesis [8]. However, when the intracellular H_2S concentration locally exceeds the colonocyte capacity for its oxidation, the mitochondrial respiratory chain is inhibited and the energy metabolism is impaired [8]. Therefore, too high luminal H_2S concentration affects the integrity of the mucosal layer, leading to inflammation.

H_2S is regarded as an endogenous gasotransmitter, acting as a signalling molecule immediately after release [97]. It affects intestinal motility, promoting colonic transit. Exogenous H_2S might exert an excitatory effect on colonic motility, through Substance P release from afferent nerves together with activation/deactivation of different Ca2+ channels in smooth muscle cells [98]. Inhibition of H_2S biosynthesis increases motility, while H_2S donors cause smooth muscle relaxation and inhibition of propulsive motor patterns [95]. Crosstalk does occur between NO and H_2S in colonic smooth muscle. H_2S and its oxidation product polysulfide can activate nociceptors expressed in sensory nerves, causing visceral nerve hypersensitivity. After high protein meals, the H_2S donor amino acid L-cysteine suppresses ghrelin release from the rat stomach, reducing appetite for a long time [41]. Colonic H_2S stimulates GLP-1 release, improving glycemia in male mice. Considering its short half-life time, H_2S could stimulate nearby colonic cells instead of ileal cells after plasmatic transport [99]. High concentrations of hydrogen sulfide produced by bysulfate-reducing bacteria produce gut inflammation, leading to pH lowering and inhibition of the beneficial lactic acid bacteria [100].

H_2S also modulates colonic compliance and nociception, inflammatory bowel disease and colorectal cancer. H_2S and its oxidation product polysulfide can activate nociceptors expressed in sensory nerves, leading to visceral nerve hypersensitivity. Recent findings suggest that endogenous H_2S might play roles in angiogenesis and smooth muscle vascular relaxation [97]. Abnormal H_2S metabolism is associated with heart failure, hypertension, atherosclerosis, asthma, diabetes and neurodegenerative diseases [93,97]. Increased expression of various H_2S-producing enzymes could be correlated with ulcerative colitis and human colonic cancer development [94,101]. H_2S displays a bell-shaped pharmacology, whereby lower (endogenous) H_2S production promotes, while higher (generated from exogenous H_2S donors) inhibits colorectal cell tumoral proliferation.

Summarizing, H_2S is an endogenous gasotransmitter produced almost exclusively in the colon as a by-product of colonic bacterial metabolism. Hydrogen sulfide produces ambivalent physiological effects, depending on its intracellular concentration.

3.7. Sulfur dioxide (SO_2)

A highly toxic gas detectable in atmospheric pollutants, sulfur dioxide is not harmful if ingested in low concentration with food. One of the main sources of SO_2 in the human body comes from the addition of sulfites to food products because of their bacteriostatic, bactericidal and antioxidant properties. Sulfites are regarded as safe for consumption at concentrations up to 5000 parts per million [102]. Sulfur dioxide is used as a preservative termed E220 for dried fruits, food starches, wine/beer fermentation and medications to prevent oxidation and changes in pigment. Also, SO_2 or its conjugate base bisulfite is endogenously produced during intestinal fermentation. Generated through cysteine metabolism and ingested sulfur's conversion, SO_2 is an intermediate product of sulfur-oxidizing bacteria and sulfate-reducing organisms, in particular Desulfovibrio genus. Variation in the distribution of sulfate-reducing microbial communities have been detected in healthy mice [103]. Usually, the healthy individuals' colonocytes are able to absorb and detoxify the gas. Sulfur dioxide is generated also in mammalian cardiovascular tissues from sulfur-containing amino acids. Interactions occur between SO_2 and the other gasotransmitter H_2S, the latter regulating some SO_2 pathways [40].

3.7.1. Physiological effects of SO_2

Although its biological role in mammalian biology is not well understood, SO_2 is regarded as the fourth gasotransmitter. Very small amounts of SO_2 display cytoprotective, antioxidant and anti-inflammatory properties that ameliorate colitis in rats, reversing inflammatory features like oxidative stress, NF-κ B and inflammasome activation, endoplasmic reticulum autophagy, p53 activation and apoptosis [104]. Endogenous sulfur dioxide in low concentrations regulates cardiac and blood vessel function, triggering endothelium-dependent vasodilation and myocardial antioxidant defense reserve [105]. Recent studies showed that SO_2 ameliorates systemic and pulmonary hypertension, prevents atherosclerosis development and protects against myocardial ischemia-reperfusion injury [40].

However, SO_2 at high concentrations displays harmful effects, especially on the colonocytes. High SO_2 levels cause colonocyte's cell death, goblet cell loss, crypt architectural distortion and superficial mucosal ulceration, leading to permeability and barrier function shortfall [106]. A key deleterious SO_2 effect consists of impairment of short chain fatty acids metabolism [107]. Competition for the available intestinal hydrogen occurs between sulfur-reducing bacteria and short chain fatty acids-producing bacteria, causing reversible inhibition of butyrate oxidation [100]. This leads to decreases in butyrate acid, that is vital in providing up to 70% of the energy metabolism required by the colonocytes. High SO_2 concentrations cause endothelium-independent vasodilation mediated via calcium channels, leading to harmful inotropic effects on cardiac output function [108]. An association has been found between sulfur dioxide and increase in ischemic heart disease, heart failure and arrhythmia, mainly due to mitochondrial dysfunction in cardiac muscles [109].

Summarizing, intestinal SO_2 is both ingested with food and produced by intestinal bacteria via sulfur conversion. Like a two-faces Janus, sulfur dioxide is a beneficial antioxidant/anti-inflammatory molecule at low doses and an extremely dangerous poison at high doses.

In conclusion, the intestinal gaseous mixture is composed by a large number of gases, each one characterized by its own sources, dynamics, metabolism, biological effects.

4. Conclusions

We discussed the production and storage mechanisms of intestinal gases, emphasizing their biological roles and growing importance in human physiology and pathology. Rather than waste material discarded by host's and microbiome's biological reactions, the intestinal gaseous mixture affects energy metabolism, gut transit regulation, immunity, paracrine and eccrine regulation, bacterial proliferation, blood musculature control, gut metabolic exchanges with blood and breath, etc. Being intestinal gas' volume and composition important factors for the experimental assessment of gut microbiome, functional disorders, bowel perforation diagnostics, etc [18], the quantitative data provided in this review may be helpful in basic research and translational medicine. An important operational feature of intestinal gases is that some of them are detectable in exhaled breath, such as hydrogen and methane after ingestion of test-carbohydrates [92,110]. Breath test is useful in the diagnosis of carbohydrate maldigestion syndromes, small intestinal bacterial overgrowth, methane-associated constipation, evaluation of bloating/gas, etc [111,112]. Orally administered urea containing isotopically labelled CO_2 is hydrolysed by the urease produced in large quantities by *Helicobacter pylori*. Urea is then hydrolysed to ammonia and carbon dioxide, which diffuses into the blood and is excreted by the lungs [113]. Ingestible electronic capsules are starting to be fabricated that can accurately sense intestinal gases like oxygen, hydrogen and carbon dioxide. For instance, a recently introduced telemetric gas-sensing capsule displays performances in the measurement of hydrogen production that are comparable with indirect measurement through breath testing [114]. Indeed, direct intestinal gaseous measurement permits the definition of regional fermentation patterns via hydrogen gas profiles [115]. The new technology has the potential to assess not just the effects of various diets on healthy individuals, but also the effects of diseases like small intestinal bacterial overgrowth and carbohydrate malabsorption.

Hydrogen sulfide, nitric oxide, carbon monoxide and sulfur dioxide are classified as gasotrasmitters, i.e., endogenously generated molecules that exert regulatory effects [116]. These molecules are either produced by mitochondrial enzymes and/or display significant effects on mitochondria, suggesting ancient regulatory roles in bacteria [117]. Another molecule could be counted as gasotransmitter, namely, **cyanide**. Its effects on the gastrointestinal tract are still unknown. Exposure to cyanide occurs via cigarette smoking, inhalation during plastics combustion, large ingestion of apricot kernel, flaxseed, cassava, almonds, radish [118]. Hydrogen cyanide is readily soluble in biological fluids in the volatile undissociated form. While cyanide at high concentrations is a cytotoxic agent exerting damage via mitochondrial inhibition, cyanide at low concentrations promotes ATP production, resulting in cell proliferation [119,120]. Cyanide could be involved in the physiology of the intestinal tract. Indeed, it has been suggested that the stomach accounts for 18% of the total injected radioactivity [121]. Most of the cyanide is excreted in the urine and only small amounts are found in the faeces, indicating intestinal absorption into the body fluid [122].

Some of the gases found in the intestine may exert effects on both the peripheral intestinal neurons and the central neurons. For instance, NO is synthetized “on demand” in the brain from post-synaptic terminals and is involved in neuronal signalling and volume transmission [21,123]. Hydrogen sulfide is a neuromodulator that enhances NMDA-induced currents in hippocampal neurons [124] and mediates brain interactions between glial calcium waves and neuronal activity [94]. Ammonia, due to the NH_3 -permeable channels, can be systemically absorbed causing hepatic encephalopathy in patients with liver cirrhosis [21]. A role of H_2O_2 as intercellular signalling molecule/neuromodulator in the brain is becoming increasingly apparent (Ledo et al., 2022) [125]. Further, N_2 hyperbaric exposure induces narcosis by targeting the striatum and the substantia nigra compacta [126]. In this respect, we suggest a testable hypothesis, i.e., that the intestinal submucosal/myenteric neurons might be as sensitive to NH_3 and H_2O_2 as the central neurons. Indeed, gut-generated ammonia and hydrogen peroxide could well have metabolic effects on the intestinal neurons, considering that cell-produced volatile substances often regulate neighbouring cells in a paracrine fashion. This notion is supported by the ability of H_2O_2 to diffuse in the extracellular space of the living rodent brain over 100 μm within its 2.2 s average half-life [125]. The in vivo H_2O_2 brain diffusion coefficient of about 2.5×10^{-5} cm^2/s makes it theoretically possible for intraluminal-generated H_2O_2 to reach the intestinal nervous system and exert effects on the intestinal neurons. Further, the fact that H_2O_2 can be transported through Aquaporin 3 in colonic epithelial cells [28] suggests the possibility that hydrogen peroxide might be able to reach at least the neurons of the submucosal plexus. In sum, we suggest that still unknown effects of intestinal gases and their by-products on the myenteric and submucosal neurons are (possibly) waiting to be discovered.

In conclusion, intestinal gases display physiological as well as pathological effects not just on various intestinal segments, but also on extra-intestinal organs. Viewed as toxic gases and/or

environmental toxins until a few years ago, many gaseous molecules have been recently "promoted" to the role of biologic mediators [116]. The capability to metabolically interact with the intestinal wall and to cross the barrier between the lumen and the bloodstream makes intestinal gases a versatile tool to achieve intracellular, extracellular, paracellular, paracrine as well as distant actions, both in a state of well-being and in response to manifold noxae.

References

[1] A. Oren, The function of gas vesicles in halophilic archaea and bacteria: theories and experimental evidence, Life 3 (1) (2013) 20, https://doi.org/10.3390/life3010001, 2012.

[2] K. Völkner, A. Jost, F. Pfeifer, Accessory gvp proteins form a complex during gas vesicle formation of Haloarchaea, Front. Microbiol. (2020), https://doi.org/10.3389/fmicb.2020.610179.

[3] F. Pfeifer, Distribution, formation and regulation of gas vesicles, Nat. Rev. Microbiol. 10 (2012) 705–715, https://doi.org/10.1038/nrmicro2834.

[4] J.L. Larimer, E.A. Ashby, Float gases, gas secretion and tissue respiration in the Portuguese man-of-war, Physalia, J. Cell. Comp. Physiol. 60 (1962) 41–47, https://doi.org/10.1002/jcp.1030600106.

[5] C. Munro, Z. Vue, R.B. Behringer, C.W. Dunn, Morphology and development of the Portuguese man of war, Physalia physalis, Sci. Rep. 9 (1) (2019) 15522, https://doi.org/10.1038/s41598-019-51842-1.

[6] R.E. Forster, Physiological basis of gas exchange in the gut, Ann. N. Y. Acad. Sci. 150 (1968) 4–12, https://doi.org/10.1111/j.1749-6632.1968.tb19024.x, 1.

[7] M. D Levitt, Volume and composition of human intestinal gas determined by means of an intestinal washout technic, N. Engl. J. Med. 284 (1971) 1394–1398, https://doi.org/10.1056/NEJM197106242842502.

[8] F. Blachier, M. Andriamihaja, P. Larraufie, E. Ahn, A. Lan, E. Kim, Production of hydrogen sulfide by the intestinal microbiota and epithelial cells and consequences for the colonic and rectal mucosa, Am. J. Physiol. Gastrointest. Liver Physiol. 320 (2) (2021) G125–G135, https://doi.org/10.1152/ajpgi.00261.2020.

[9] A.D. Badley, M. Camilleri, M.K. O'Connor, Noninvasive measurement of human ascending colon volume, Nucl. Med. Commun. 14 (6) (1993) 485–489.

[10] C. Schiller, C.P. Fröhlich, T. Giessmann, S.W. Mönnikes, et al., Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment. Pharmacol. Ther. 22 (10) (2005) 971–979, https://doi.org/10.1111/j.1365-2036.2005.02683.x.

[11] X. Wang, J. Li, N. Li, K. Guan, D. Yin, et al., Evolution of intestinal gases and fecal short-chain fatty acids produced in vitro by preterm infant gut microbiota during the first 4 Weeks of life, Front. Pediatr, Sec. Pediatric Gastroenterology, Hepatology and Nutrition (2021), https://doi.org/10.3389/fped.2021.726193.

[12] D. Roccarina, E.C. Lauritano, M. Gabrielli, F. Franceschi, V. Ojetti, A. Gasbarrini, The role of methane in intestinal diseases, Am. J. Gastroenterol. 105 (6) (2010) 1250–1256, https://doi.org/10.1038/ajg.2009.744.

[13] K. Kalantar-Zadeh, K.J. Berean, R.E. Burgell, J.G. Muir, P.R. Gibson, Intestinal gases: influence on gut disorders and the role of dietary manipulations, Nat. Rev. Gastroenterol. Hepatol. 16 (12) (2019) 733–747, https://doi.org/10.1038/s41575-019-0193-z.

[14] R. Singhal, Y.M. Shah, Oxygen battle in the gut: hypoxia and hypoxia-inducible factors in metabolic and inflammatory responses in the intestine, J. Biol. Chem. 295 (30) (2020) 10493–10505, https://doi.org/10.1074/jbc.REV120.011188.

[15] D. Heresbach, B. Flouríe, F. Briet, L. Achour, J.C. Rambaud, B. Messing, Effect of colonic fermentation on respiratory gas exchanges measured in the post-absorptive state, Am. J. Clin. Nutr. 62 (5) (1995) 973–978, https://doi.org/10.1093/ajcn/62.5.973.

[16] F. Scaldaferri, O. Nardone, L.-R. Lopetuso, V. Petito, S. Bibbò, et al., Intestinal gas production and gastrointestinal symptoms: from pathogenesis to clinical implication, Eur. Rev. Med. Pharmacol. Sci. 17 (2) (2013) 2–10.

[17] A.B. Sahakian, S.-R. Jee, M. Pimentel, Methane and the gastrointestinal tract, Dig. Dis. Sci. 55 (8) (2010) 2135–2143, https://doi.org/10.1007/s10620-009-1012-0.

[18] A. Modesto, N.R. Cameron, C. Varghese, N. Peters N, B. Stokes, et al., Meta-Analysis of the composition of human intestinal gases, Dig. Dis. Sci. 67 (2022) 3842–3859, https://doi.org/10.1007/s10620-021-07254-1.

[19] R. Freire, M. Mego, L. Fontes Oliveira, S. Mas, F. Azpiroz, et al., Quantitative GC–TCD measurements of major flatus components: a preliminary analysis of the diet effect, Sensors 22 (3) (2022) 838, https://doi.org/10.3390/s22030838.

[20] M. Michenkova, S. Taki, M.C. Blosser, H.J. Hwang, T. Kowatz, Carbon dioxide transport across membranes, Interface Focus 11 (2) (2021) 20200090, https://doi.org/10.1098/rsfs.2020.0090, 10.1098/rsfs.2020.0090.

[21] B. Rodriguez-Grande, J. P- Konsman, Gas diffusion in the CNS, J. Neurosci. Res. 96 (2) (2018) 207–218, https://doi.org/10.1002/jnr.24077.

[22] M. Herrera, J.L. Garvin, Aquaporins as gas channels, Pflügers Archiv 462 (4) (2011) 623–630, https://doi.org/10.1007/s00424-011-1002-x.

[23] Y. Zhang, K. Xu, Y. Liu, B.O. Erokwu, P. Zhao, et al., Increased cerebral vascularization and decreased water exchange across the blood-brain barrier in aquaporin-4 knockout mice, PLoS One 14 (6) (2019) e0218415, https://doi.org/10.1371/journal.pone.0218415.

[24] E.W. Miller, B.C. Dickinson, C. J Chang, Aquaporin-3 mediates hydrogen peroxide uptake to regulate downstream intracellular signaling, Proc. Natl. Acad. Sci. USA 107 (36) (2010) 15681–15686, https://doi.org/10.1073/pnas.1005776107.

[25] C. Zhu, Z. Chen, Z. Jiang, Expression, distribution and role of aquaporin water channels in human and animal stomach and intestines, Int. J. Mol. Sci. 17 (9) (2016) 1399, https://doi.org/10.3390/ijms17091399.

[26] R. Meli, C. Pirozzi, A. Pelagalli, New perspectives on the potential role of aquaporins (AQPs) in the physiology of inflammation, Front. Physiol., Sec. Integrative Physiology. (2018), https://doi.org/10.3389/fphys.2018.00101.

[27] S. Liao, G. Li, L. Lv, Z. Mei, The regulatory roles of aquaporins in the digestive system, Genes & Diseases 8 (3) (2021) 250–258, https://doi.org/10.1016/j.gendis.2019.12.011.

[28] J. Yde, S.J. Keely, H.B. Moeller, Expression, regulation and function of Aquaporin-3 in colonic epithelial cells, Biochim. Biophys. Acta Biomembr. 1863 (7) (2021) 183619, https://doi.org/10.1016/j.bbamem.2021.183619.

[29] W.L. Hasler, Gas and bloating, Gastroenterol. Hepatol. 2 (9) (2006) 654–662. PMID: 28316536.

[30] M. Montalto M, M. Di Stefano, A. Gasbarrini, G.R. Corazza, Intestinal gas metabolism, Digestive and Liver Disease Supplements 3 (2) (2009) 27–29, https://doi.org/10.1016/S1594-5804(09)60015-2.

[31] C. Manichanh, A. Eck, E. Varela, J. Roca, J.C. Clemente, et al., Anal gas evacuation and colonic microbiota in patients with flatulence: effect of diet, Gut 63 (3) (2014) 401–408, https://doi.org/10.1136/gutjnl-2012-303013.

[32] H.F. Helander, L. Fändriks, Surface area of the digestive tract – revisited, Scand. J. Gastroenterol. 49 (6) (2014) 681–689, https://doi.org/10.3109/00365521.2014.898326.

[33] A. Codutti, J. Cremer, K. Alim, Changing flows balance nutrient absorption and bacterial growth along the gut, Phys. Rev. Lett. 129 (2022) 138101.

[34] F. Azpiroz, Intestinal gas dynamics: mechanisms and clinical relevance, Gut 54 (7) (2005) 893–895, https://doi.org/10.1136/gut.2004.048868.

[35] Y.H. Fang, C.X. Chen, B.L. Zhang, Effect of small bowel preparation with simethicone on capsule endoscopy, J. Zhejiang Univ. - Sci. B 10 (1) (2009) 46–51, https://doi.org/10.1631/jzus.B0820148.

[36] S.E. Pritchard, L. Marciani, K.C. Garsed, C.L. Hoad, W. Thongborisute, et al., Fasting and postprandial volumes of the undisturbed colon: normal values and changes in diarrhea-predominant irritable bowel syndrome measured using serial MRI, Neuro Gastroenterol. Motil. 26 (1) (2014) 124–130, https://doi.org/10.1111/nmo.12243.

[37] M. Nilsson, T. H Sandberg, J.L. Poulsen, M. Gram, J.B. Frøkjaer, et al., Quantification and variability in colonic volume with a novel magnetic resonance imaging method, Neuro Gastroenterol. Motil. 27 (12) (2015) 1755–1763, https://doi.org/10.1111/nmo.12673.

[38] M.M. van Meegdenburg, E. Heineman, P.M. A Broens, Dyssynergic defecation may aggravate constipation: results of mostly pediatric cases with congenital anorectal malformation, Am. J. Surg. 210 (2) (2015) 357–364, https://doi.org/10.1016/j.amjsurg.2014.09.038.

[39] J. Goelen, B. Alexander, H.E. Wijesinghe, E. Evans, G. Pawar, et al., Quantification of fluid volume and distribution in the paediatric colon via magnetic resonance imaging, Pharmaceutics 13 (10) (2021) 1729, https://doi.org/10.3390/pharmaceutics13101729.

[40] Y.Q. Huang, H.F. Jin, H. Zhang, C.S. Thang, J.B. Du, Interaction among Hydrogen sulfide and other gasotransmitters in mammalian Physiology and Pathophysiology, Adv. Exp. Med. Biol. 1315 (2021) 978–981.

[41] W. Verbeure, H. van Goor, H. Mori, A.P. van Beek, J. Tack, P.R. van Dijk, The role of gasotransmitters in gut peptide actions, Front. Pharmacol. 12 (2021) 720703, https://doi.org/10.3389/fphar.2021.720703.

[42] K. Igai, M. Itakura, S. Nishijima, H. Tsurumaru, W. Suda, et al., Nitrogen fixation and nifH diversity in human gut microbiota, Sci. Rep. 6 (2016) 31942.

[43] A.M. Davila, F. Blachier, M. Gotteland, M. Andriamihaja, P.H. Benetti, et al., Intestinal luminal nitrogen metabolism: role of the gut microbiota and consequences for the host, Pharmacol. Res. 68 (1) (2013) 95–107, https://doi.org/10.1016/j.phrs.2012.11.005.

[44] W.G. Bergen, G. Wu, Intestinal nitrogen recycling and utilization in health and disease, J. Nutr. 139 (5) (2009) 821–825, https://doi.org/10.3945/jn.109.104497.

[45] A.T. Reese, F.C. Pereira, A. Schintlmeister, D. Berry, M. Wagner, et al., Microbial nitrogen limitation in the mammalian large intestine, Nat. Microbial. 3 (12) (2018) 1441–1450, https://doi.org/10.1038/s41564-018-0267-7.

[46] J.O. Lundberg, E. Weitzberg, Biology of nitrogen oxides in the gastrointestinal tract, Gut 62 (4) (2013) 616–629, https://doi.org/10.1136/gutjnl-2011-301649.

[47] M. Carlström, C.H. Moretti, E. Weitzberg, J.O. Lundberg, Microbiota, diet and the generation of reactive nitrogen compounds, Free Radic. Biol. Med. 161 (2020) 321–325, https://doi.org/10.1016/j.freeradbiomed.2020.10.025.

[48] Y. Naito, K. Uchiyama, T. Takagi, Redox-related gaseous mediators in the gastrointestinal tract, J. Clin. Biochem. Nutr. 63 (1) (2018) 1–4, https://doi.org/10.3164/jcbn.18-56.

[49] R. Okabe, T.F. Chen-Yoshikawa, Y. Yoneyama, E. Kobayashi, H. Date, T. Takebe, Mammalian enteral ventilation ameliorates respiratory failure,

Clinical And Translational Resource And Technology Insights| 2 (6) (2021) 773–783, https://doi.org/10.1016/j.medj.2021.04.004. E5.
[50] P.A. Mountford, P.D. Leiphrakpam, H.R. Weber, A. McCain, R. M Scribner, et al., Colonic oxygen microbubbles augment systemic oxygenation and CO2 removal in a porcine smoke inhalation model of severe hypoxia, bioRxiv (2021), https://doi.org/10.1101/2021.12.08.466665.
[51] B.M. Miller, M.J. Liou, L.F. Zhang, H. Nguyen, Y. Litvak, et al., Anaerobic respiration of NOX1-derived hydrogen peroxide licenses bacterial growth at the colonic surface, Cell Host Microbe 28 (6) (2020) 789–797.e5, https://doi.org/10.1016/j.chom.2020.10.009.
[52] J.J. Zwiazek, H. Xu, X. Tan, A. Navarro-Ródenas, A. Morte, Significance of oxygen transport through aquaporins, Sci. Rep. 7 (2017) 40411, https://doi.org/10.1038/srep40411.
[53] A.K. Singh, R.Y. Hertzberger, U.G. Knausa, Hydrogen peroxide production by lactobacilli promotes epithelial restitution during colitis, Redox Biol. 16 (2018) 11–20, https://doi.org/10.1016/j.redox.2018.02.003.
[54] J.F. Burgueño, J. Fritsch, A.M. Santander, N. Brito, I. Fernández, et al., Intestinal epithelial cells respond to chronic inflammation and dysbiosis by synthesizing H2O2, Front. Physiol. 10 (2019) 1484, https://doi.org/10.3389/fphys.2019.01484.
[55] M.A. McIver, A. C Redfield, E.B. Benedict, Gaseous exchange between the blood and the lumen of the stomach and intestines. https://doi.org/10.1152/ajplegacy.1926.76.1.92, 1926.
[56] P. Ritz, D. Cloarec, M. Beylot, M. Champ, B. Charbonnel, et al., Effects of colonic fermentation on respiratory gas exchanges following a glucose load in man, Metabolism 42 (3) (1993) 347–352, https://doi.org/10.1016/0026-0495(93)90085-3.
[57] A. Rivière, M. Selak, D. Lantin, F. Leroy, L. De Vuyst, Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut, Front. Microbiol., Sec. Microbial Symbioses (2016), https://doi.org/10.3389/fmicb.2016.00979.
[58] P. Louis, S.H. Duncan, P.O. Sheridan, A.W. Walker, H. Flint, Microbial lactate utilisation and the stability of the gut microbiome, Gut Microb. 3 (2022) E3, https://doi.org/10.1017/gmb.2022.3.
[59] V. Endeward, G. Gros, Low carbon dioxide permeability of the apical epithelial membrane of Guinea-pig colon, J. Physiol. 567 (Pt 1) (2005) 253–265, https://doi.org/10.1113/jphysiol.2005.085761.
[60] S. Oikawa, H. Hirakawa, T. Kusakabe, Y. Hayashida, Effect of CO2 on cardiovascular regulation in conscious rats, in: J.M. Pequignotì, C. Gonzalez, C.A. Nurse, N.R. Prabhakar, Y. Dalmaz (Eds.), Chemoreception. Advances in Experimental Medicine and Biology, Springer, Boston, MA, 2003, p. 536, https://doi.org/10.1007/978-1-4419-9280-2_60.
[61] T. Akaishi, E. Onish, M. Abe, H. Toyama, K. Ishizawa, et al., The human central nervous system discharges carbon dioxide and lactic acid into the cerebrospinal fluid, Fluids Barriers CNS 16 (1) (2019) 8, https://doi.org/10.1186/s12987-019-0128-7.
[62] V.L. Mahan, Effects of lactate and carbon monoxide interactions on neuroprotection and neuropreservation, Med. Gas Res. 11 (4) (2021) 158–173, https://doi.org/10.4103/2045-9912.318862.
[63] Y.-S. Lee, T.Y. Kim, Y. Kim, S.H. Lee, S. Kim, et al., Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development, Cell Host Microbe 24 (6) (2018) 833–846.e6, https://doi.org/10.1016/j.chom.2018.11.002.
[64] S.P. Wang, L.A. Rubio, S.H. Duncan, G.E. Donachie, G. Holtrop, et al., Pivotal roles for pH, lactate, and lactate-utilizing bacteria in the stability of a human colonic microbial ecosystem, mSystems 5 (5) (2020) e00645, https://doi.org/10.1128/mSystems.00645-20, 20.
[65] A. Gandhi, A. Shah, M.P. Jones, N. Koloski, N.J. Talley, et al., Methane positive small intestinal bacterial overgrowth in inflammatory bowel disease and irritable bowel syndrome: a systematic review and meta-analysis, Gut Microb. 13 (1) (2021) 1933313, https://doi.org/10.1080/19490976.2021.1933313.
[66] T.L. Miller, M. J Wolin, E.C. de Macario, A.J. Macario, Isolation of Methanobrevibacter smithii from human feces, Appl. Environ. Microbiol. 43 (1) (1982) 227–232, https://doi.org/10.1128/aem.43.1.227-232.1982.
[67] P.B. Hylemon, S.C. Harris, J. M Ridlon, Metabolism of hydrogen gases and bile acids in the gut microbiome, FEBS Lett. 592 (12) (2018) 2070–2082, https://doi.org/10.1002/1873-3468.13064.
[68] M. Boros, E. Tuboly, A. Mészáros, A. Amann, The role of methane in mammalian physiology-is it a gasotransmitter? J. Breath Res. 9 (1) (2015) 014001 https://doi.org/10.1088/1752-7155/9/1/014001.
[69] M. Ghyczy, C. Torday, J. Kaszaki, A. Szabó M. Czóbel, M. Boros, Hypoxia-induced generation of methane in mitochondria and eukaryotic cells: an alternative approach to methanogenesis, Cell. Physiol. Biochem. 21 (1–3) (2008) 251–258, https://doi.org/10.1159/000113766.
[70] J.H. Bond Jr., R.R. Engel, M.D. Levitt, Factors influencing pulmonary methane excretion in man. An indirect method of studying the in situ metabolism of the methane-producing colonic bacteria, J. Exp. Med. 133 (1971) 572–588.
[71] C. Schneider, K.D. Wutzke, J. Däbritz, Methane breath tests and blood sugar tests in children with suspected carbohydrate malabsorption, Sci. Rep. 10 (2020) 18972, https://doi.org/10.1038/s41598-020-75987-6.
[72] E. Zaorska, M. Gawryś-Kopczyńska, R. Ostaszewski, D. Koszelewski, Methane, a gut bacteria-produced gas, does not affect arterial blood pressure in normotensive anaesthetized rats, bioRxiv (2021), https://doi.org/10.1101/2021.03.31.437828.
[73] M.Z. Poles, L. Juhász, M. Boros, Methane and inflammation - a review (fight fire with fire), ICMx 7 (2019) 68, https://doi.org/10.1186/s40635-019-0278-6.
[74] Y.M. Park, Y.J. Lee, Z. Hussain, Y.H. Lee, H. Park H, The effects and mechanism of action of methane on ileal motor function, Neuro Gastroenterol. Motil. 29 (9) (2017), https://doi.org/10.1111/nmo.13077.
[75] J. Jahng, I.S. Jung, E.J. Choi, J.L. Conklin, H. Park, The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time, Neuro Gastroenterol. Motil. 24 (2) (2012) 185–190, e92, https://doi.org/10.1111/j.1365-2982.2011.01819.x.
[76] M. Pimentel, H.C. Lin, P. Enayati, B. van den Burg, H.R. Lee, et al., Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity, Gastrointstinal and Liver Physiology 290 (6) (2006) G1089–G1095, https://doi.org/10.1152/ajpgi.00574.2004.
[77] K. N Lee, O.Y. Lee, D.H. Koh, W. Sohn, S.P. Lee, S. P, et al., Association between symptoms of irritable bowel syndrome and methane and hydrogen on lactulose breath test, J. Kor. Med. Sci. 28 (2013) 901–907.
[78] A. Attaluri, M. Jackson, J. Valestin, S.S. Rao, Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS, Am. J. Gastroenterol. 105 (2010) 1407–1411.
[79] K. Triantafyllou, C. Chang, M. Pimentel, Methanogens, methane and gastrointestinal motility, J Neurogastroenterol Motil 20 (1) (2014) 31–40, https://doi.org/10.5056/jnm.2014.20.1.31.
[80] M.Z. Khan, R. Lyu, J. McMichael, S. Gabbard, Chronic intestinal pseudo-obstruction is associated with intestinal methanogen overgrowth, Dig. Dis. Sci. 67 (10) (2022) 4834–4840, https://doi.org/10.1007/s10620-021-07343-1.
[81] U. Ghoshal, D. Srivastava, A. Misra, A randomized double-blind placebo-controlled trial showing rifaximin to improve constipation by reducing methane production and accelerating colon transit: a pilot study, Indian J. Gastroenterol. 37 (5) (2018) 416–423, https://doi.org/10.1007/s12664-018-0901-6.
[82] M. Pozuelo, S. Panda, A. Santiago, S. Mendez, A. Accarino, et al., Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome, Sci. Rep. 5 (2015) 12693, https://doi.org/10.1038/srep12693.
[83] A. Bársony, N. Vida, A. Gajda, A. Rutai, A. Mohácsi, et al., Methane exhalation can monitor the microcirculatory changes of the intestinal mucosa in a large animal model of hemorrhage and fluid resuscitation, Front. Med., Sec. Intensive Care Medicine and Anesthesiology (2020), https://doi.org/10.3389/fmed.2020.567260.
[84] A.T. Mészáros, A.L. Szilágyi, L. Juhász, E. Tuboly, D. Érces, et al., Mitochondria as sources and targets of methane, Front. Med.,Sec. Intensive Care Medicine and Anesthesiology (2017), https://doi.org/10.3389/fmed.2017.00195.
[85] R. He, L.P. Wang, J.L. Zhu, et al., Methane-rich saline protects against concanavalin A-induced autoimmune hepatitis in mice through anti-inflammatory and anti-oxidative pathways, Biochem. Biophys. Res. Commun. 470 (2016) 22–28.
[86] A.J. Sun, W.H. Wang, X.J. Ye, et al., Protective effects of methane-rich saline on rats with lipopolysaccharide-induced acute lung injury, Oxid. Med. Cell. Longev. (2017) 7430193.
[87] Z.Y. Li, Y.F. Jia, Y. Feng, et al., Methane alleviates sepsis-induced injury by inhibiting pyroptosis and apoptosis: in vivo and in vitro experiments, Aging 11 (2019) 1226–1239.
[88] M.D. Levitt, S. Olsson, Pneumatosis cystoides intestinalis and high breath H2 excretion: insights into the role of H2 in this condition, Gastroenterology 108 (5) (1995) 1560–1565, https://doi.org/10.1016/0016-5085(95)90707-6.
[89] F. Carbonero, A. Benefiel, H. Gaskins, Contributions of the microbial hydrogen economy to colonic homeostasis, Nat. Rev. Gastroenterol. Hepatol. 9 (2012) 504–518, https://doi.org/10.1038/nrgastro.2012.85.
[90] N.W. Smith, P.R. Shorten, E. Altermann, et al., Examination of hydrogen cross-feeders using a colonic microbiota model, BMC Bioinf. 22 (2021) 3, https://doi.org/10.1186/s12859-020-03923-6.
[91] H.F. Hammer, Colonic hydrogen absorption: quantification of its effect on hydrogen accumulation caused by bacterial fermentation of carbohydrates, Gut 34 (6) (1993) 818–822, https://doi.org/10.1136/gut.34.6.818.
[92] C.H. Wilder-Smith, S.S. Olesen, A. Materna, A.M. Drewes, Fermentable sugar ingestion, gas production, and gastrointestinal and central nervous system symptoms in patients with functional disorders, Gastroenterology 155 (4) (2018) 1034–1044, https://doi.org/10.1053/j.gastro.2018.07.013, e6.
[93] D.R. Linden, Hydrogen sulfide signaling in the gastrointestinal tract, Antioxidants Redox Signal. 20 (5) (2014) 818–830, https://doi.org/10.1089/ars.2013.5312.
[94] F.F. Guo, T.C. Yu, J. Hong, J.-Y. Fang, Emerging roles of hydrogen sulfide in inflammatory and neoplastic colonic diseases, Front. Physiol., Sec. Gastrointestinal Sciences (2016), https://doi.org/10.3389/fphys.2016.00156.
[95] M. Jimenez, V. Gil, M. Martinez-Cutillas, N. Mañé, D. Gallego, Hydrogen sulphide as a signalling molecule regulating physiopathological processes in gastrointestinal motility, Br. J. Pharmacol. 174 (17) (2017) 2805–2817, https://doi.org/10.1111/bph.13918.
[96] G.A. Benavides, G.L. Squadrito, R.W. Mills, H.D. Patel, T.S. Isbell, et al., Hydrogen sulfide mediates the vasoactivity of garlic, Proc. Natl. Acad. Sci. U.S.A. 104 (46) (2007) 17977–17982, https://doi.org/10.1073/pnas.0705710104.
[97] D. Wu, M. Li, W. Tian, et al., Hydrogen sulfide acts as a double-edged sword

in human hepatocellular carcinoma cells through EGFR/ERK/MMP-2 and PTEN/AKT signaling pathways, Sci. Rep. 7 (2017) 5134, https://doi.org/10.1038/s41598-017-05457-z.
[98] X. Quan, W. Chen, B. Qin, J. Wang, H. Luo, F. Dai, The excitatory effect of hydrogen sulfide on rat colonic muscle contraction and the underlying mechanism, J. Pharmacol. Sci. 149 (3) (2022) 100–107, https://doi.org/10.1016/j.jphs.2022.04.004.
[99] J. Pichette, N. Fynn-Sackey, J. Gagnon, Hydrogen sulfide and sulfate prebiotic stimulates the secretion of GLP-1 and improves glycemia in male mice, Endocrinology 158 (10) (2017) 3416–3425, https://doi.org/10.1210/en.2017-00391.
[100] D. Dordević, S. Jančíková, M. Vítězová, I. Kushkevych, Hydrogen sulfide toxicity in the gut environment: meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes, J. Adv. Res. 27 (2021) 55–69, https://doi.org/10.1016/j.jare.2020.03.003.
[101] W.J. Cai, M.J. Wang, L.H. Ju, C. Wang, Y.C. Zhu, Hydrogen sulfide induces human colon cancer cell proliferation: role of Akt, ERK and p21, Cell Biol. Int. 34 (6) (2014) 565–572, https://doi.org/10.1042/CBI20090368.
[102] S.V. Irwin, P. Fisher, E. Graham, A. Malek, A. Robidoux, Sulfites inhibit the growth of four species of beneficial gut bacteria at concentrations regarded as safe for food, PLoS One 12 (10) (2017) e0186629, https://doi.org/10.1371/journal.pone.0186629. Published online 2017 Oct 18.
[103] I. Kushkevych, O. Leščanová, D. Dordević, S. Jančíková, J. Hošek, et al., The sulfate-reducing microbial communities and meta-analysis of their occurrence during diseases of small–large intestine Axis, J. Clin. Med. 8 (10) (2019) 1656, https://doi.org/10.3390/jcm8101656.
[104] S. Banerjee, S. Ghosh, K. Sinha, S. Chowdhury, P.C. Sil, Sulphur dioxide ameliorates colitis related pathophysiology and inflammation, Toxicology 412 (2019) 63–78, https://doi.org/10.1016/j.tox.2018.11.010.
[105] Y. Liang, D. Liu, T. Ochs, et al., Endogenous sulfur dioxide protects against isoproterenol-induced myocardial injury and increases myocardial antioxidant capacity in rats, Lab. Invest. 91 (2011) 12–23, https://doi.org/10.1038/labinvest.2010.156.
[106] M. Beaumont, M. Andriamihaja, A. Lan, N. Khodorova, M. Audebert, et al., Detrimental effects for colonocytes of an increased exposure to luminal hydrogen sulfide: the adaptive response, Free Radic. Biol. Med. 93 (2016) 155–164, https://doi.org/10.1016/j.freeradbiomed.2016.01.028.
[107] L.M. Teigen, Z. Geng, M.J. Sadowsky, B.P. Vaughn, M.J. Hamilton, A. Khoruts, Dietary factors in sulfur metabolism and pathogenesis of ulcerative colitis, Nutrients 11 (4) (2019) 931, https://doi.org/10.3390/nu11040931.
[108] Z. Meng, J. Li, Q. Zhang, W. Bai, Z. Yang, et al., Vasodilator effect of gaseous sulfur dioxide and regulation of its level by Ach in rat vascular tissues, Inhal. Toxicol. 21 (14) (2009) 1223–1228, https://doi.org/10.3109/08958370902798463.
[109] G. Qin, M. Wu, J. Wang, Z. Xu, J. Xia, N. Sang, Sulfur dioxide contributes to the cardiac and mitochondrial dysfunction in rats, Toxicol. Sci. 151 (2) (2016) 334–346, https://doi.org/10.1093/toxsci/kfw048.
[110] H.F. Hammer, M.R. Fox, J. Keller, S. Salvatore, G. Basilisco, et al., European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and pediatric patients: European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Neurogastroenterology and Motility, and European Society for Paediatric Gastroenterology Hepatology and Nutrition consensus, United European Gastroenterol J 10 (1) (2022) 15–40, https://doi.org/10.1002/ueg2.12133.
[111] A. Rezaie, M. Buresi, A. Lembo, H. Lin, R. McCallum, et al., Hydrogen and methane-based breath testing in gastrointestinal disorders: the north American consensus, Am. J. Gastroenterol. 112 (5) (2017) 775–784, https://doi.org/10.1038/ajg.2017.46.
[112] J. Keller, H.F. Hammer, P.R. Afolabi, M. Benninga, O. Borrelli, European guideline on indications, performance and clinical impact of 13C-breath tests in adult and pediatric patients: an EAGEN, ESNM, and ESPGHAN consensus, supported by EPC, United European Gastroenterol J 9 (5) (2021) 598–625, https://doi.org/10.1002/ueg2.12099.
[113] A. O'Connor, The urea breath test for the noninvasive detection of Helicobacter pylori, Methods Mol. Biol. 2283 (2021) 15–20, https://doi.org/10.1007/978-1-0716-1302-3_2.
[114] K.J. Berean, N. Ha, J.Z. Ou, A.F. Chrimes, D. Grando, et al., The safety and sensitivity of a telemetric capsule to monitor gastrointestinal hydrogen production in vivo in healthy subjects: a pilot trial comparison to concurrent breath analysis, Aliment. Pharmacol. Ther. 48 (6) (2018) 646–654, https://doi.org/10.1111/apt.14923.
[115] K. Kalantar-Zadeh, K.J. Berean, N. Ha, et al., A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut, Nat Electron 1 (2018) 79–87, https://doi.org/10.1038/s41928-017-0004-x.
[116] P. Pacher, Cyanide emerges as an endogenous mammalian gasotransmitter, Proc. Natl. Acad. Sci. U.S.A. 118 (25) (2021) e2108040118, https://doi.org/10.1073/pnas.2108040118.
[117] L.K. Wareham, H.M. Southam, R.K. Poole, Do nitric oxide, carbon monoxide and hydrogen sulfide really qualify as 'gasotransmitters' in bacteria? Biochem. Soc. Trans. 46 (2018) 1107–1118.
[118] S. Maherni, A. Amanlou, G. kiaee, M. Amanlou, Determination of hydrogen cyanide concentration in mainstream smoke of tobacco products by polarography, J Environ Health Sci Eng 13 (2015) 57, https://doi.org/10.1186/s40201-015-0211-1.
[119] T.B. Hendry-Hofer, P.C. Ng, A.E. Witeof, S.B. Mahon, M. Brenner, et al., A review on ingested cyanide: risks, clinical presentation, diagnostics, and treatment challenges, J. Med. Toxicol. 15 (2) (2019) 128–133, https://doi.org/10.1007/s13181-018-0688-y.
[120] E. Randi, K. Zuhra, L. Pecze, T. Panagaki, C. Szabo, Physiological concentrations of cyanide stimulate mitochondrial Complex IV and enhance cellular bioenergetics, Proc. Natl. Acad. Sci. USA 118 (20) (2021) e2026245118, https://doi.org/10.1073/pnas.2026245118, 18.
[121] P.N. Okoh, Excretion of 14C-labeled cyanide in rats exposed to chronic intake of potassium cyanide, Toxicol. Appl. Pharmacol. 70 (1983) 335–339.
[122] E. Jaszczak, S. Narkowicz, J. Namieśnik, Ż. Polkowska, Determination of cyanide in urine and saliva samples by ion chromatography with pulsed amperometric detection, Monatsh. Chem. 148 (9) (2017) 1645–1649, https://doi.org/10.1007/s00706-017-1977-x.
[123] E. Del-Bel, F.F. De-Miguel, Extrasynaptic neurotransmission mediated by exocytosis and diffusive release of transmitter substances, Front. Synaptic Neurosci. 10 (2018) 13, https://doi.org/10.3389/fnsyn.2018.00013.
[124] A.V. Yakovlev, E.D. Kurmasheva, Y. Ishchenko, R. Giniatullin, G.F. Sitdikova, Age-dependent, subunit specific action of hydrogen sulfide on GluN1/2A and GluN1/2B NMDA receptors, Front. Cell. Neurosci. 11 (2017) 375, https://doi.org/10.3389/fncel.2017.00375.
[125] A. Ledo, E. Fernandes, A. Salvador, J. Laranjinha, R.M. Barbosa, In vivo hydrogen peroxide diffusivity in brain tissue supports volume signaling activity, Redox Biol. 50 (2022) 102250.
[126] J.C. Rostain, C. Lavoute, Neurochemistry of pressure-induced nitrogen and metabolically inert gas narcosis in the central nervous system, Compr. Physiol. 6 (3) (2016) 1579–1590, https://doi.org/10.1002/cphy.c150024.