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Reactive Oxygen Species/Reactive Nitrogen Species as Messengers in the Gut: Impact on Physiology and Metabolic Disorders

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Abstract

Significance: The role of reactive oxygen/nitrogen species as ''friend'' or ''foe'' messengers in the whole body is well characterized. Depending on the concentration in the tissue considered, these molecular actors exert beneficial or deleterious impacts leading to a pathological state, as observed in metabolic disorders such as type 2 diabetes and obesity.

Recent Advances: Among the tissues impacted by oxidation and inflammation in this pathological state, the intestine is a site of dysfunction that can establish diabetic symptoms, such as alterations in the intestinal barrier, gut motility, microbiota composition, and gut/brain axis communication. In the intestine, reactive oxygen/nitrogen species (from the host and/or microbiota) are key factors that modulate the transition from physiological to pathological signaling.

Critical Issues: Controlling the levels of intestinal reactive oxygen/nitrogen species is a complicated balance between positive and negative impacts that is in constant equilibrium. Here, we describe the synthesis and degradation of intestinal reactive oxygen/nitrogen species and their interactions with the host. The development of novel redox-based therapeutics that alter these processes could restore intestinal health in patients with metabolic disorders.

Future Directions: Deciphering the mode of action of reactive oxygen/nitrogen species in the gut of obese/diabetic patients could result in a future therapeutic strategy that combines nutritional and pharmacological approaches. Consequently, preventive and curative treatments must take into account one of the first sites of oxidative and inflammatory dysfunctions in the body, that is, the intestine. *Antioxid. Redox Signal.* 00, 000–000.

Keywords: reactive oxygen species, reactive nitrogen species, metabolic disorders, gut

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Introduction

Within the gastrointestinal (GI) tract, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are by-products of normal cellular metabolism. When maintained at proper cellular concentrations, ROS and RNS act as essential second-messenger molecules to regulate intestinal signaling pathways affecting gene transcription, protein kinase activation, and phosphatase inhibition, thereby regulating cytokine production and coordinating gut motilty (96, 167). These entities are also involved in the maintenance of cell homeostasis and have beneficial effects on several physiological processes and functions, including cell signaling, elimination of invasive pathogens, wound healing, and tissue repair processes, to maintain gut integrity (21).

ROS include radical compounds such as superoxide ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), lipid hydroperoxides, and reactive nonradical compounds, including singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and others (11, 17). Unstable oxygen-centered radicals are highly reactive and can lead to deleterious effects in intestinal cells and tissues. $O_2^{\bullet-}$ can be converted to the more stable and diffusible H_2O_2 by superoxide dismutase (SOD)-mediated catalysis. H_2O_2 is decomposed to water and oxygen or can be converted to HOCl (100 times more toxic than H_2O_2) by peroxidases, such as phagocytic myeloperoxidase, in the presence of chloride ions (Cl^-) (11). H_2O_2 can also react nonenzymically with $O_2^{\bullet-}$ to form $^{\bullet}OH$ in the presence of ferrous iron (Fe^{2+}), a reaction called the Fenton reaction (208).

RNS include radical compounds such as nitric oxide ($^{\bullet}NO$), nitrogen dioxide ($^{\bullet}NO_2$), and nonradical compounds, including peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3). Most of these compounds are unstable because of unpaired electrons in the outer electron orbit (11). ROS and RNS are often linked. For example, $^{\bullet}NO$ is a crucial mediator of GI physiology, and $O_2^{\bullet-}$ rapidly reacts with $^{\bullet}NO$ to form the highly reactive $ONOO^-$. Additional reactions with peroxynitrite give rise to many other NO-derived compounds (147). In this review, we describe the formation and source of ROS/RNS in the gut and the potential deregulation of this process during metabolic disorders such as type 2 diabetes (T2D) and obesity. In addition, we focus on the potential intestinal antioxidant action of dietary supplements and/or antidiabetic drugs available on the market or in development.

ROS/RNS in the Digestive Tract: From Synthesis to Degradation

ROS/RNS synthesis by the host in the GI tract

ROS and RNS are highly reactive. They are continuously produced as by-products of cellular respiration and are also generated by enzymatic reactions. In the GI tract, the main endogenous sources of ROS and RNS are NADPH oxidase (NOX) enzymes, the mitochondrial electron transport chain (mETC), and nitric oxide synthases (NOSs) (11). ROS are also produced in the gut, but in less abundance, by other enzymes, such as myeloperoxidases, lipoxygenases, cyclooxygenases, and the transition metals copper and iron.

Furthermore, exogenous factors can be responsive to ROS and RNS generation. In healthy and pathological states, cross talk between similar or distinct ROS and RNS sources can occur (7, 15, 16). Both exogenous and endogenous sources of ROS contribute to the overall redox state of the GI tract (146).

Membrane-bound multimeric NOX and dual oxidase (DUOX) complexes are the only known enzymes that generate ROS as their primary function, rather than as a by-product (119). The mammalian oxidase family comprises five NOX members (NOX1–5) and two DUOXs (DUOX1–2) (17). The main oxidases expressed along the GI tract are NOX1 and DUOX2, which are found in the epithelium. NOX1 is expressed preferentially in the ileum, cecum, and colon, whereas DUOX2 is expressed in all intestinal segments. NOX2 is expressed by phagocytes (monocytes, macrophages, neutrophils, and eosinophils) and dendritic cells.

NOX4 is present in the epithelium, fibroblasts, and smooth muscle cells. This isoform is constitutively active and preferentially releases H_2O_2 (207). The isoform NOX5 is present in humans, but is not expressed in rodents (17). Another important gut NOX is DUOX2 (thyroid oxidase). In mammals, the expression of the DUOX2/DUOXA2 complex is detected along the GI tract, particularly in the cecum and colon epithelium, and participates in antimicrobial defense in the host mucosa (83). NOXs also produce an important amount of $O_2^{\bullet-}$ in the gut, mainly under conditions of inflammation, such as in a specific pathological context (*e.g., Helicobacter pylori* infection, inflammatory bowel disease [IBD], and tumor development) (21).

Mitochondria are the second-most abundant sources of ROS and RNS under physiological and pathological conditions (13). This organelle produces ROS and organic peroxides as by-products during the mETC. In an elegant review published in 2021, Mailloux (138) described how mitochondria generate ROS and novel methods to quantify production. Evidence suggests that complexes I and III are the most important sources of ROS, and 12 ROS generators have been discovered in the mitochondria (138). The production of mitochondrial ROS during oxidative phosphorylation is tightly controlled.

However, 1%–2% of oxygen consumed during this process is converted to $O_2^{\bullet-}$ when electrons escape from the mETC and are aberrantly transferred to molecular O_2. Thus, generated $O_2^{\bullet-}$ can react with NO radicals to produce $ONOO^-$. $O_2^{\bullet-}$ can also react with Mn-SOD to produce H_2O_2. This process is involved in the regulation of cellular functions by modulating the activity of redox-sensitive transcription factors (nuclear factor erythroid 2-related factor 2 [Nrf-2], hypoxia inducible factor-1 [HIF-1], and nuclear factor-kappa B [NF-κB]), altering kinase activity (MAPK and IκB kinase-β), and inhibiting phosphatases (phosphatase and tensin homologue and protein tyrosine phosphatase 1B) (11, 140, 199).

The third source of ROS and RNS are the NOSs. Three isoforms of NOSs have been identified. Two isoforms are constitutively present in either neuronal NOS (nNOS) or endothelial NOS (eNOS) tissues. A third isoform is expressed by immune, vasculature, and neuronal cells after induction by certain cytokines or microbial products and is named inducible NOS (iNOS). All these isoforms of NOS catalyze the oxidation of L-arginine to produce $^{\bullet}NO$ and L-citrulline. The production of $^{\bullet}NO$ by constitutive nNOS and eNOS is low (nanomolar concentrations), short lasting, and highly controlled by Ca^{2+}-mobilizing agents.

Conversely, iNOS produces high levels of $^{\bullet}NO$ (micromolar concentrations) that can persist for days, which is associated

with oxidative stress and inflammation and eventually leads to loss of protein function and tissue damage (63, 164). ROS are also produced in response to exogenous sources such as ultraviolet radiation, alcohol consumption, cigarette smoking, ingestion of nonsteroidal anti-inflammatory drugs, and many other exogenous agents (32, 62).

ROS/RNS in physiological conditions in the gut

While the overproduction of ROS/RNS and its implication to the development of pathological states are well described, their roles during the physiological state require further investigation. This is probably due to the poor efficacy of current technologies to measure the low levels of ROS associated with cellular and tissue homeostasis (138). Thus, while we know some physiological roles for ROS/RNS, we do not know all of them yet. In the gut, ROS generation *via* NOX2 by phagocytes is associated with relatively high levels of ROS to protect the intestine from pathogens (105).

In the intestinal epithelium, NOX1 and DUOX2 participate in the release of ROS to protect the epithelium from pathogens (14). In addition, it has been hypothesized that ROS production from NOX1 participates in the regulation of numerous signal transduction pathways in epithelial cells. Indeed, NOX1-derived H_2O_2 modulates the redox-sensitive *Wnt* and *Notch* pathways and then controls the proliferation of stem cells and progenitor epithelial cells, the migration of epithelial cells, and the differentiation of enteroendocrine and Paneth cells, as previously described in detail (165).

Numerous articles have shown that direct contact between gut microbiota and host epithelial cells leads to ROS production that requires NOX1. In summary, Jones and Neish (105) precisely described this eukaryotic/prokaryotic interaction that requires ROS production to control cytoskeletal dynamics and immunity. Which molecular actors are involved in this interaction? Aviello and Knaus (12) reviewed the impact of gut microbiota and reported two mechanisms of action. The first is *via* Toll-like receptors and *N*-formyl peptide receptor pathways that are involved in the upregulation of NOX enzyme and its catalytic activity. The second is *via* the regulation of DUOX2 expression by mucosa-associated segmented filamentous bacteria.

However, the cross talk between microbiota and epithelium, *via* NOXs, could be in the reverse direction, that is, from the epithelium to the bacteria. Inactivation of NOXs is associated with modification of gut microbiota composition and interbacterial communication [for review, Aviello and Knaus (12)].

Regarding RNS, the beneficial effect of $^{\bullet}NO$ is linked to the low concentrations at which it is released by eNOS and nNOS. In contrast to $^{\bullet}NO$ at high concentrations, low levels of $^{\bullet}NO$ favor barrier integrity by affecting tight junction protein expression (150). Moreover, intestinal $^{\bullet}NO$ is a major neurotransmitter that has a strong inhibitory effect on gut motility by acting on intestinal smooth muscle cells (87). Among all microbial-derived neurotransmitters, gaseous $^{\bullet}NO$ from bacteria may influence host physiology and control intestinal immunity, gut motility, and behavior, as we previously described (174).

Endogenous systems of antioxidant defense in the gut

Under physiological conditions, native antioxidant systems are generally sufficient and adapt to protect biological systems from free radical toxicity, including enzymatic/nonenzymatic pathways and repair systems, and protect against oxidative stress (32).

Within the GI tract, the major antioxidant enzymatic defense systems are through SOD, glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT), and these act as detoxification pathways for ROS (165). SODs are metal ion cofactor-requiring enzymes that catalyze the dismutation of $O_2^{\bullet-}$ to H_2O_2 and O_2. In humans, three SOD isoforms have been described: mitochondrial SOD (manganese-requiring), cytosolic SOD, and extracellular SOD (both requiring copper and zinc). Mn^{2+}-SOD has an indispensable role in protecting aerobic life from the deleterious effects of oxygen and may be important in preventing ROS-induced inactivation and GI mucosal injuries (94).

The glutathione redox cycle involves two enzymes: GPx, which uses glutathione to reduce organic peroxides and H_2O_2, and GR, which reduces the oxidized form of glutathione with concomitant oxidation of NADP (21). GPx1 is present in all cell types of the gut, whereas GPx2 is predominantly expressed in epithelial cells. The expression of GPx2 is higher in crypts than in villi, and it exhibits its highest expression in the ileum and cecum. GPx3 is expressed in the GI tract, and plasma GPx3 binds to the basement membranes of intestinal epithelial cells (52). GPx4 is expressed in epithelial cells and the lamina propria (117). These antioxidant enzymes play a key role in GI redox homeostasis.

For example, double-knockout (KO) *Gpx1/Gpx2* mice develop spontaneous colitis, and Cu/Zn-SOD-KO mice develop a severe colitis phenotype in response to dextran sulfate sodium, compared with wild-type mice (68, 100). In a general manner, epithelial cells in the crypts seem to be better protected against oxidative damage than the villi since they exhibit a two- to threefold increase in GPx activity and a three- to fivefold increase in CAT activity *versus* the villi (68).

GR is an NADPH-dependent flavoprotein that reduces oxidized glutathione (GSSG) to reduced glutathione (GSH). Two electrons of reducing power are extracted from NADPH and transferred to GSSG, which is reduced into two molecules of GSH (10). CAT, which is found mainly in peroxisomes, dismutates H_2O_2 to H_2O and O_2. It is present in all human organs and in many pathogens in the GI tract, which utilize it to escape the host response and survive within the host.

The main nonenzymatic antioxidants found in the gut are GSH and the thioredoxin (Trx) system. GSH is a tripeptide formed by L-glutamate, L-cysteine, and L-glycine and is present in millimolar concentrations (2–10 m*M*) in all eukaryotic cells. The oxidation of GSH to disulfide of GSSG and the subsequent decrease in the GSH/GSSG pair are often useful indicators of cellular oxidative stress (184).

The Trx system is composed of Trx and thioredoxin reductases (TrxR). It has many functions in DNA synthesis, defense against oxidative stress, apoptosis, and redox signaling. Trx1 is a cytosolic and extracellular enzyme, whereas Trx2 exists in mitochondria. In addition, three TrxRs are found in cells: cytosolic TrxR1, mitochondrial TrxR2, and a testis-specific thioredoxin glutathione reductase (133, 178). Oxidized Trxs are reactivated by TrxRs through the reducing power of NADPH. Trx expression is markedly elevated in the intestine and has an important role in the gut immune response (95).

Other exogenous antioxidants could also be important for the defense of the host against excessive oxidative damage. Indeed, vitamin C, also known as ascorbic acid, is a hydrosoluble antioxidant found in the cytosol and extracellular fluids. It acts as a free radical scavenger that directly donates electrons to other compounds (including ROS and RNS) to prevent oxidation (107). Vitamin E is a lipophilic antioxidant localized in cell membranes, and α-tocopherol is the most biologically active form of vitamin E. It prevents the lipid peroxidation chain reaction in cellular membranes by scavenging lipid peroxyl radicals (155).

Linking ROS/RNS and gut microbiota

In the intestine, our immune system has a pivotal role in defending against microbial pathogens such as bacteria, viruses, parasites, or fungi by selective recognition without eliminating the entire gut microbiota. Indeed, our intestinal gut microbes are also key in contributing to the host defense against potential pathogens (29). It is commonly accepted that some of our gut microbes will achieve this goal by communicating with our own human cells to stimulate a specific immune response (53).

In addition to the microbes themselves, short-chain fatty acids (SCFAs) (*i.e.,* butyrate, propionate, and acetate) are specific bacterial metabolites shown to activate specific G-protein-coupled receptors (*i.e.,* GPR-43) and thereby trigger the production of antimicrobial molecules by immune cells (169). However, recent evidence also suggests that the balance between the abundance of oxygen and nitrates in the luminal part of the gut is a key contributing factor to the maintenance of a healthy gut microbiota at the epithelium level. Thus, this balance can reduce the risk of intestinal inflammation or alteration of gut barrier function (126, 127).

Indeed, several studies have shown that intestinal inflammation can be triggered by a genetic predisposition, induced by specific chemical compounds or directly stimulated through infection with enteric pathogens. Furthermore, most of the time, intestinal inflammation is linked to uncontrolled luminal expansion of facultative anaerobes such as *Enterobacteriaceae* (phylum Proteobacteria) in mouse models (81, 134, 194). The same observation was made in humans with severe intestinal inflammation; an increased abundance of *Enterobacteriaceae* is observed in cases of IBDs or cancer (38, 149, 185, 189).

How is this balance controlled? What are the factors controlling the availability of O_2 or NO_3^-? How are these factors changing the microbiota? Some of these important questions have been answered and involve very specific mechanisms that are completely (or almost) independent from immune cells. Instead, these mechanisms rely on the oxygen utilization capacity of colonic cells for metabolic activity. In fact, mature colonocytes are characterized by a very high level of energy metabolism and therefore an elevated oxygen consumption. This results in an oxygen partial pressure below 1% oxygen, which is a condition known as epithelial hypoxia (31, 80).

More precisely, under physiological conditions, surface colonocytes are clearly hypoxic because they consume oxygen through mitochondrial β-oxidation of microbiota-derived butyrate to CO_2, a key pathway for producing their own energy (203). Thus, epithelial hypoxia is very limited due to the diffusion of oxygen from the other cells, but this activity of the colonocyte contributes to the maintenance of the mucosal surface and the intestinal lumen in anaerobiosis (125, 181). This activity is physiologically very important since recent data have shown that extremely low quantities of oxygen present in the luminal content of the gut (*i.e.,* anaerobic state) are required to prevent the expansion of putative facultative anaerobic pathogens such as *Escherichia* and *Salmonella* (phylum Proteobacteria) (86, 132, 180, 181).

In addition, maintaining anaerobiosis ensures the survival and growth of obligate anaerobic bacteria, which is generally beneficial to the host. This is the case for bacteria that convert fibers or mucus to fermentation products, including SCFAs (*e.g., Bifidobacterium* spp., *Akkermansia muciniphila*) (163).

The molecular mechanisms able to control beta-oxidation in colonocytes, and therefore the decrease in oxygen, have been recently unveiled. Byndloss *et al.* identified the role of one of the key SCFAs, butyrate. They found that butyrate will instruct the colon to consume oxygen *via* β-oxidation to protect the host against the expansion of potentially pathogenic bacteria (Fig. 1) (28). It is very well known that butyrate is an essential energy source allowing colonic cells to proliferate and contributes to maintaining healthy gut barrier function (38, 82).

A very important and novel mechanism is the consumption of oxygen to β-oxidize butyrate in the mitochondria to limit the diffusion of oxygen from the colonic cell into the luminal compartment and eventually maintain anaerobic conditions. This can also help to better understand why and how the fermentation of specific fibers eventually increases butyrate in the GI tract.

Thus, from a mechanistic point of view, both host-derived RNS (*via* $^{\bullet}NO$ production) and oxygen are key for the proliferation of putative pathogenic facultative anaerobes *Enterobacteriaceae*. Along those lines, recent discoveries suggest that anaerobic bacteria prevent dysbiotic expansion of facultative anaerobic microbes by limiting the production of nitrate and oxygen by the host (191). Unfortunately, the key molecular mechanisms are unknown. Moreover, how anaerobic microbes can control nitrate production by the host is unclear.

Byndloss *et al.* discovered that mice treated with streptomycin have markedly altered microbiota composition but also have decreased butyrate concentrations and increased presence of nitrate and oxygen in the lumen of the gut (28). To understand how and why nitrate increases under antibiotic treatment, genetically modified bacteria and mice have been used. This strategy has not only unequivocally shown that *Escherichia coli* requires nitrate respiration to proliferate but also demonstrates that butyrate elicits a host response important for the control of nitrate production. In fact, they discovered that butyrate activates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) in colonic cells.

In turn, the activation of PPARγ represses the expression of the gene encoding iNOS, thereby reducing $^{\bullet}NO$ production and eventually luminal nitrate levels. It is also known that the nuclear receptor PPARγ activates mitochondrial β-oxidation in macrophages (213) and thus consumes oxygen. Strikingly, specific immune cells, such as regulatory T cells (Tregs), are decreased upon antibiotic treatment during intestinal inflammation or when the gut barrier function is altered. Mice

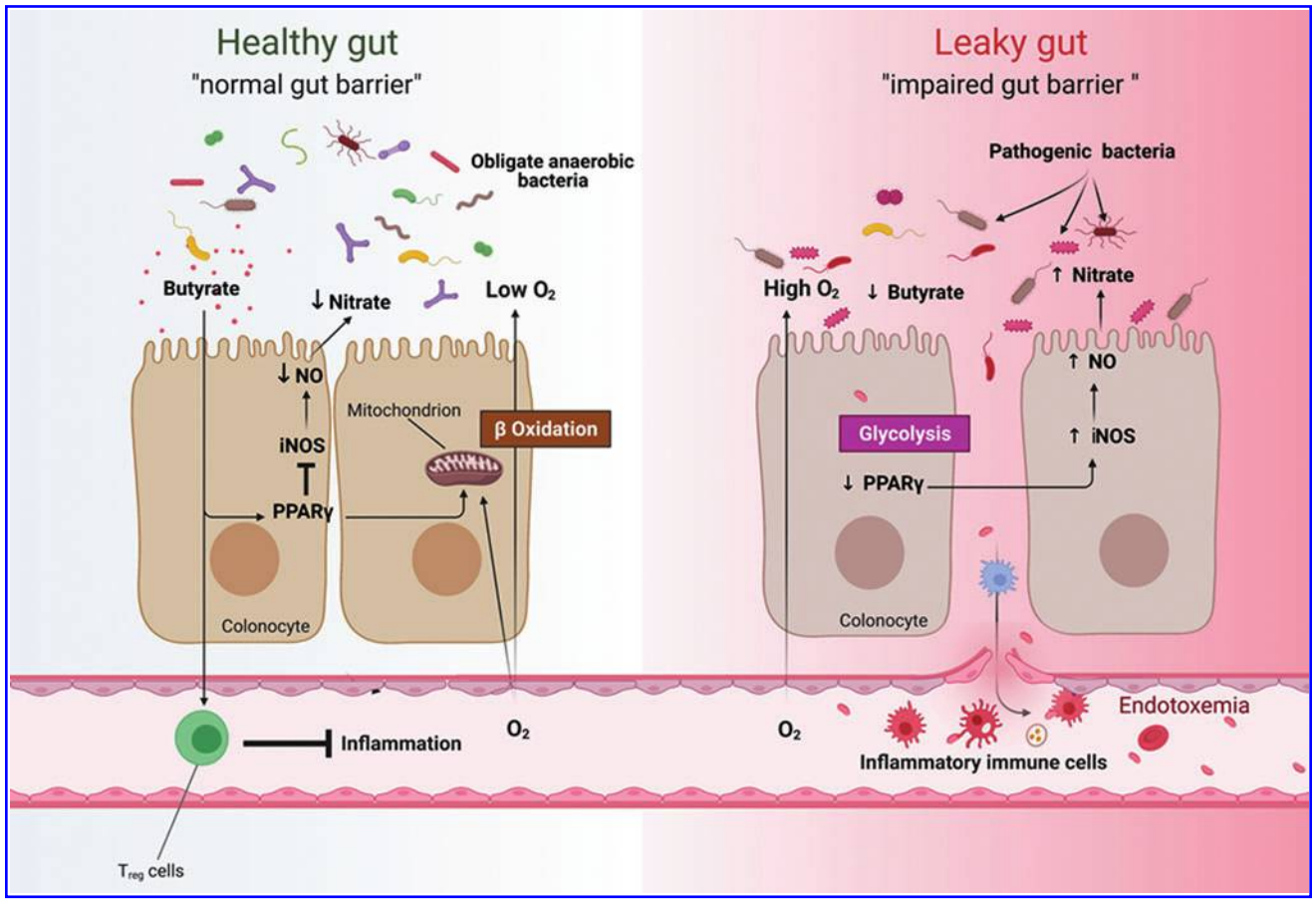

FIG. 1. Colonocytes control the microbiota *via* RNS/ROS balance. Colonocytes utilize butyrate as energy substrate. Butyrate can stimulate immune cells such as Treg to dampen inflammation. Butyrate oxidation by the mitochondria consumes oxygen and directly contributes to maintain anaerobic condition into the lumen. In addition, butyrate activates PPARγ, which in turn represses NOS, NO production, and eventually NO_3^-. Conversely, low butyrate content in the lumen is associated with lower PPARγ activity, higher NOS2 (iNOS) expression, increased NO, and eventually nitrates availability for specific pathogens. Therefore, low butyrate content contributes to both inflammation in the intestine and altered gut barrier function. iNOS, inducible nitric oxide synthase; NO, nitric oxide; NO_3^-, reduced nitrates; PPARγ, peroxisome proliferator-activated receptor gamma; RNS, reactive nitrogen species; ROS, reactive oxygen species; Treg, regulatory T cell. Color images are available online.

lacking PPARγ specifically in intestinal epithelial cells exhibit a reduced number of Tregs, and intestinal PPARγ deletion was associated with higher Nos2 expression and abundance of nitrate in the colon. In addition, mouse intestinal PPARγ does not respond to butyrate or antibiotics and is more sensitive to chemically induced intestinal inflammation (*i.e.,* colitis) (28).

Along the same line and as discussed above, IBD is associated with a profound imbalance in the microbiota composition, including a higher abundance of *Enterobacteriaceae* (phylum Proteobacteria) (149, 179, 185, 189). However, in addition to genetic predisposition, potentially reversible environmental factors are also associated with a higher risk for developing IBD, including antibiotic use, smoking, and a Western-style diet (8, 88, 89, 93, 99, 162). For the latter, a recent study in humans investigated the link between pre-IBD characterized by subjects and low-grade mucosal inflammation (123).

Compared with other subjects, they found that a higher proportion of pre-IBD patients had a history of recent antibiotic exposure, that is, within the past year. However, more importantly, they were also characterized by a higher total fat intake or higher saturated fat intake than healthy subjects (123). Here, again, the microbiota from pre-IBD subjects was characterized by a higher abundance of *Enterobacteriaceae*. To further gain more causality in their approach, they investigated the link between risk factors and signs of disease by developing a mouse model recapitulating all the aspects of the pre-IBD state.

To mimic the risks identified in patients, all the mice were fed a high-fat diet (HFD; 45% fat) or a low-fat diet (10% fat) (as control) and some received a single dose of streptomycin by oral gavage to generate a history of antibiotic usage. Interestingly, the mice exposed to a single shot of antibiotic and an HFD exhibited exacerbated visceral fat mass. They also developed all the signs of pre-IBD, such as a shorter colon length, fewer colonic goblet cells, mild infiltration of inflammatory cells in the intestinal mucosa, and higher markers of inflammation. The microbiota was also characterized by an increase in *E. coli*. Finally, and perfectly in line with the hypothesis of oxygen consumption in the colon, the mice

exposed to the risk factors for pre-IBD exhibited hypoxia in the colonocytes, and also lower PPARγ activation and impaired mitochondrial activity (123).

In conclusion, oxygen availability and the ROS/RNS balance contribute to the maintenance of the gut barrier and depend on a butyrate/PPARγ-dependent mechanism. Thus, this complex mechanism illustrates the fine tuning of the symbiosis existing between host and microbes and highlights how the production of specific SCFAs, such as butyrate, directly interferes with the metabolic capacities of both bacterial cells and host cells (125).

ROS/RNS in the Gut During Metabolic Disorders

The intestine is an organ in dynamic interaction between the host and the luminal environment. It is exposed to nutrients and is responsible for food absorption, digestion, and metabolism, but not exclusively. It is also inevitably an organ exposed to exogenous substances, contaminants, mutagens, and metabolites that originate from the intestinal microbial population. Importantly, alterations in intestinal integrity not only have local consequences but also have a negative impact on the entire body (49).

In this section, we discuss ROS/RNS and oxidative stress in the gut, its impact on gut cells, and its deleterious physiological consequences during metabolic disorders. From a cellular and molecular point of view, an excellent review from Newsholme *et al.* (154) described the deleterious impact of oxidative stress and chronic inflammation, generating lipid peroxidation, protein modifications, DNA damage, and apoptosis during diabetes.

Factors that favor intestinal oxidative stress and inflammation during T2D and obesity

The intestine is the main organ of exposure and absorption for nutrients, drugs, and other contaminants. In addition to its digestive competences, the gut is also a physical and immunological barrier and is extensively subjected to oxidative stress. Here, oxidative stress might be triggered by many factors, including nutritional stress and factors from endogenous sources and exogenous sources (Fig. 2). Nutrition might account for one of the major external causes of oxidative stress occurring in the gut because of the quality, quantity, or ratio of various nutrients. Overnutrition is correlated with high solicitation of the tricarboxylic acid (TCA) cycle. When TCA metabolites exceed the capacity of the mETC, ROS generation is drastically increased (171).

An HFD, corresponding to a diet rich in saturated fats and refined sugar, is associated with body weight increase, fat deposition, and insulin resistance. This diet is usually used to generate an obese and diabetic phenotype in mice similar to that observed in humans (3). Numerous articles from our team and others have shown that an HFD generates a significant increase in inflammation and oxidative stress in the intestine (34, 120, 182). Recently, Wu *et al.* (210) showed that the intestinal injuries induced by lipopolysaccharides (LPS) are aggravated by an HFD *via* an alteration of tight junction integrity and an increase in Nox2 and Nox4 protein expression.

Recently, Rohr *et al.* (182) described that the negative impact of an HFD was also linked to the oxidative stress occurring in epithelial cells, leading to the altered expression

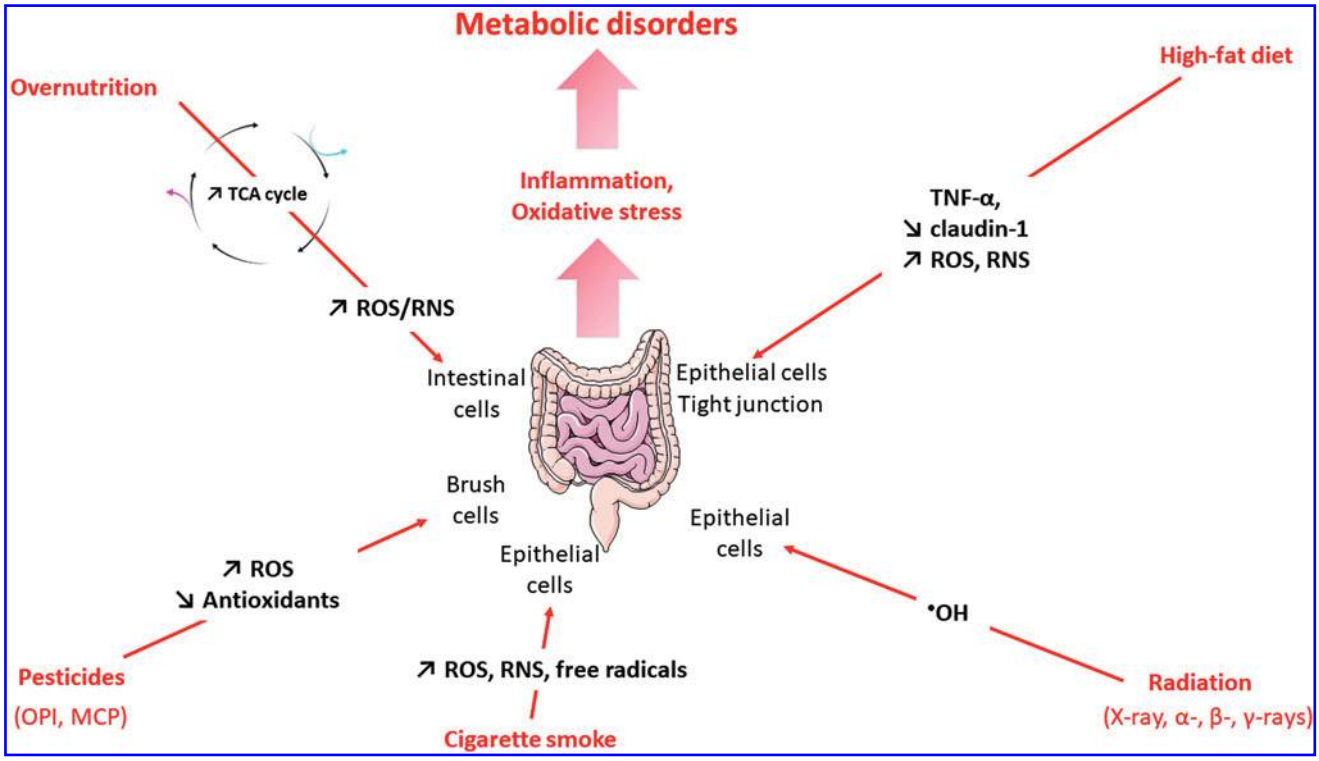

FIG. 2. Origins of intestinal inflammation and oxidative stress during metabolic disorders. Overnutrition, high-fat diet, radiation, cigarette smoke, and pesticides contribute to the generation of ROS and RNS in the gut. These ROS and RNS further lead to inflammation and oxidative stress in metabolic disorders. •OH, hydroxyl radical; MCP, monocrotophos; OPI, organophosphorus insecticide; TCA, tricarboxylic acid; TNF-α, tumor necrosis factor-α. Color images are available online.

of tight junction proteins and stimulation of proinflammatory cytokines and apoptosis. In addition to an HFD, the increase in fructose intake in our diet (*i.e.,* soft drinks) participates in the development of obesity and insulin resistance. In the gut, fructose intake stimulates the nitration of proteins from intestinal tight and adherent junctions (51).

Ingested food contains macronutrients and micronutrients and might contain other molecules, such as pesticides (92) and heavy metals (22, 71) that participate in the development of metabolic disorders. It is clear that organophosphorus insecticides (OPIs), such as monocrotophos [dimethyl (E)-1-methyl-2-(methylcarbamoyl)vinyl phosphate] or MCP, participate in the aggravation of a diabetic state by potentiating hyperglycemia *via* structural, functional, and oxidative damage induced by MCP in border brush cells (206). Very similar proinflammatory and oxidative actions are observed in the intestine of rats in response to phosalone (another OPI) treatment (84).

Regarding heavy metals, cadmium is also known to have a deleterious effect in the development of metabolic disorders (22), particularly in the gut, where it exerts its toxic effect (201). There are multiple actions of cadmium throughout the body, but several studies have shown that cadmium ingestion stimulates the Notch signaling pathway associated with increased ROS production in the intestine (214). The intestinal damage observed includes the alteration of the intestinal barrier, loss of goblet and Paneth cells, and enteropathogen susceptibility.

In addition to junk food or contaminants, excessive alcohol consumption observed in heavy drinkers increases the risk of developing T2D (168). Alcohol is able to promote gut leakiness and oxidative stress in the GI tract (73, 74). Indeed, evidence shows that ethanol activates oxidative pathways, including the upregulation of iNOS (198).

In addition to all factors described above that are linked with food and drink intake, several other participants known to have an impact on metabolic disorders can act on the intestine. This is the case for smoking. Cigarette consumption is associated with hyperglycemia and insulin resistance (136) and has a causal relationship with the development of childhood obesity in response to maternal smoking (18). Cigarette smoke comprises a mixture of different toxic chemicals and has been described as a potential ROS generator.

Experimental models show that cigarette exposure induces intestinal inflammation (19, 204) and hypoxia (77). Little is known regarding its intestinal impact on diabetes, but several studies have shown that smoking is associated with numerous GI-related disorders, such as Crohn's disease (20), IBD (124), and gastroesophageal reflux disease (79). In relation to diabetes, metformin is the first-line drug with hypoglycemic action used to treat T2D. Among all known actions, metformin can inhibit respiratory chain complex I, leading to an increase in the AMP:ATP ratio and a decrease in ROS production (103). In addition, metformin exerts a neuroprotective effect by counterbalancing the mitochondrial dysfunction observed in neurodegenerative disorders associated with T2D (50).

Prasad *et al.* (170) have shown that metformin activates the Nrf-2 pathway to reduce cigarette smoking toxicity in brain endothelial cells that suffer from inflammation and ROS action. Numerous articles summarize the mode of action of metformin in the gut to improve the diabetic state. A recent review from Lee *et al.* (121) described how metformin can (i) modulate gut microbiota (*Bacteroides*) to modulate SCFA release, (ii) strengthen intestinal permeability against different agents such as LPS by increasing *A. muciniphila*, which is known to favor mucin production and stimulate the recovery of tight junction proteins, and (iii) control the immune response by decreasing the release of proinflammatory cytokines. All these data suggest that the use of antidiabetic drugs could decrease ROS and inflammation in the gut of smokers.

Ionizing radiation, such as X-rays and α-, β- and γ-rays, can all produce hydroxyl radicals as a consequence of water radiolysis (58). While each type of radiation differs in energy and penetration parameters, it can exert biological effects upon exposure and, more particularly, in the intestine, where damage and dysfunction are observed (*e.g.,* intestinal inflammation, diarrhea). The origins of ionizing radiation could be multiple and comprise cosmic radiation exposure (195), radiotherapy (158), or irradiation from nuclear bombs (101). Related to this last example, a twofold increase in the incidence of T2D has been observed among survivors of the Hiroshima bombing (101).

Thus, linking the specific production of ROS/RNS by the intestine and the development of metabolic disorders in a case of radiation is difficult since irradiation is not local. Other experiments need to be performed to clearly resolve this question, especially since other articles show controversial data in HFD-fed rats exposed to whole-body gamma irradiation. Here, the authors propose that irradiation exposure could have a dual role with first, induction of prediabetic genes in the gut, and second, induction of intestinal antidiabetic gene expression (108).

Currently, data from the literature attempting to decipher the intestinal molecular mechanism of protection from radiation are controversial and poorly studied. More precisely, activation of Nrf-2 attenuates radiation-mediated crypt injury, whereas intestinal crypts in *Nrf-2* null mice are radiation resistant (30). As radiation can induce diarrhea in patients, some authors propose to treat this side effect by using probiotics to decrease intestinal oxidative stress-induced ROS production (23).

Impact of intestinal oxidative stress on host metabolism and consequences during obesity and T2D: from the cell to the whole body

If we now focus on the gut, the population of intestinal cells is composed of various cell types implicated in the control of metabolism, such as endocrine, epithelial, and neuronal cells (Fig. 3) (110, 174).

Diabetes is characterized by peripheral neuropathy and GI disorders, as reviewed by Yarandi and Srinivasan (218). In this major review, the authors describe how the enteric nervous system (ENS), composed notably of enteric neurons and interstitial cells of Cajal (ICC), is affected by oxidative stress during T2D. To summarize, different factors (hyperglycemia, HFD) generate ROS production that provokes degeneration of ICC and enteric neurons. Myenteric neurons, which constitute one type of motor neuron in the ENS, are particularly sensitive to oxidative stress due to an imbalance between cellular antioxidant defense and free radicals (223). Myenteric neurons are composed of two major types of neurons: choline acetyl transferase (ChAT)-expressing neurons and nNOS-expressing neurons.

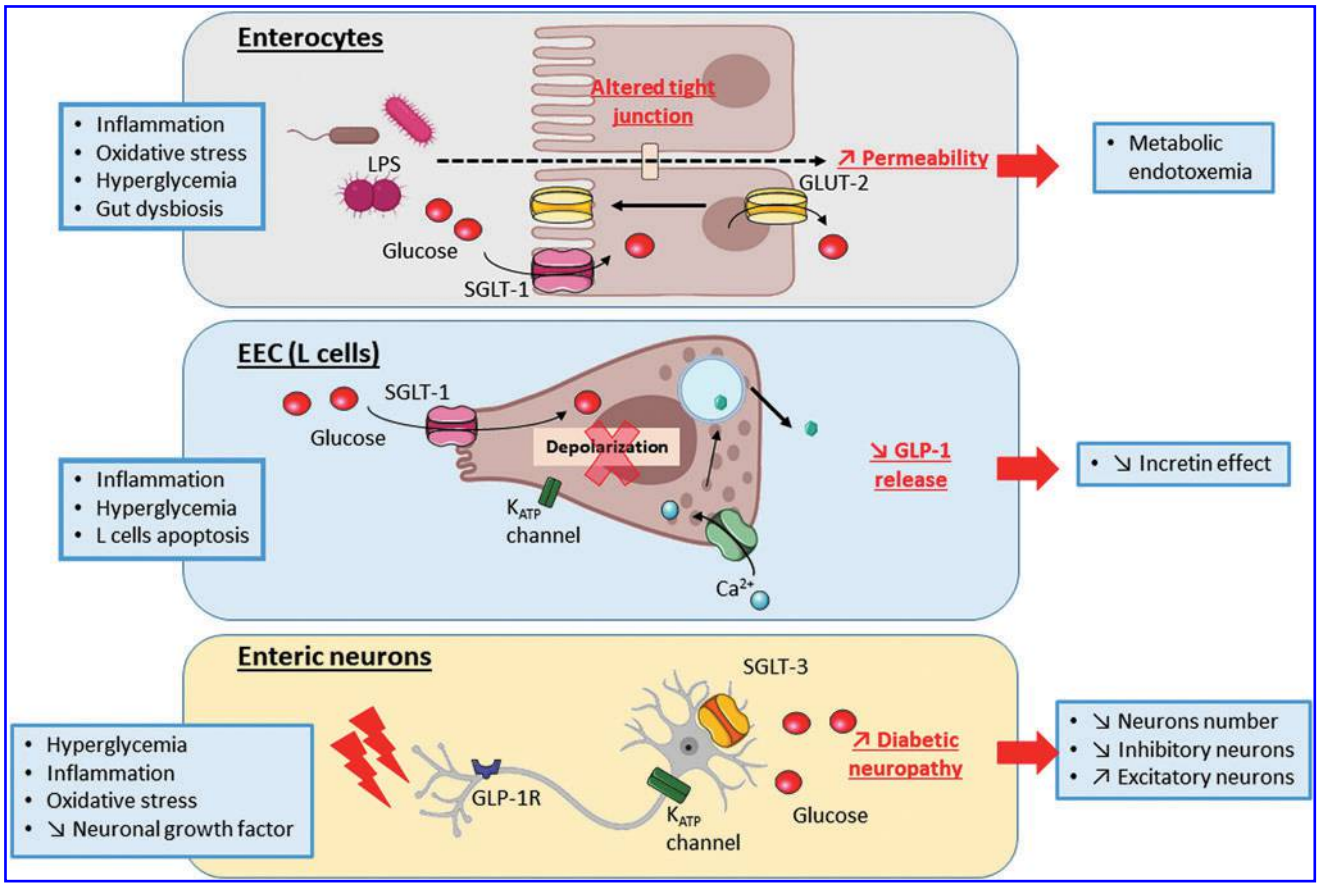

FIG. 3. From health to diabetes: Potential cellular dysfunctions. In addition to an increase of GLUT2 expression at the apical membrane of enterocytes, intestinal inflammation and oxidative stress (observed during diabetes) are characterized by (i) an altered gut barrier that participates in the LPS-induced low-grade inflammation, that is, metabolic endotoxemia; (ii) a drastic decrease of GLP-1 release by L cells; and (iii) diabetic neuropathy that alters the neuronal response to nutrients such as glucose and GLP-1. EEC, enteroendocrine cells; GLP-1, glucagon-like peptide-1; GLP-1-R, glucagon-like peptide-1 receptor; GLUT2, glucose transporter 2; K_{ATP}, ATP sensitive potassium channel; LPS, lipopolysaccharide; SGLT, sodium-dependent glucose cotransporters. Color images are available online.

Consequently, acetylcholine synthetized by ChAT neurons exerts a stimulatory effect on intestinal smooth muscle cells, and $^{\bullet}$NO release by nNOS neurons exerts an inhibitory effect (110). During T2D, the deleterious action of oxidative stress on enteric neurons favors an increase in the ChAT/nNOS ratio (Fig. 3), leading to gut hypermotility in the proximal part of the intestine, that is, the duodenum (Fig. 4) (110). Therapeutic strategies (based on antioxidants and anti-inflammatory approaches) could counterbalance this effect on enteric neuronal loss (72). In fact, we have demonstrated that the alteration of ENS function observed in the diabetic state is associated with duodenal hypermotility and generates an insulin-resistant state *via* the gut/brain axis (2, 3, 75, 110).

Under fed conditions, duodenal hypermotility observed in T2D is in favor of glucose absorption participating in the deleterious effect of hyperglycemia in the whole body (75, 110). Also, we discovered that duodenal contractions could be sensed by the brain, particularly the hypothalamus, an important region implicated in the control of glucose metabolism (2, 3, 75, 113). In a diabetic context, duodenal hypermotility generates the synthesis of an aberrant afferent nervous message to the brain, leading to the absence of $^{\bullet}$NO release in the hypothalamus. In fact, hypothalamic $^{\bullet}$NO is known to stimulate the efferent nervous system to increase glucose utilization in metabolic tissue (adipose tissue, liver, and muscles) (1, 2).

Restoring a normal duodenal contraction by acting on ENS neurons and then restoring the gut/brain axis to improve insulin sensitivity are now considered novel therapeutic pathways (110). Currently, we have developed the concept of ''enterosynes'' that correspond to different molecules present in the gut and are able to target enteric neurons. This is the case for factors released by enterocytes such as apelin (75), intestinal neurotransmitters such as galanin (2), bioactive lipids (3), and gut microbiota (78). Of course, all molecules that have potential anti-inflammatory and/or antioxidative action that favors ENS function could be considered enterosynes. In addition to this mechanosensing, another mechanism of detection is altered in the gut during T2D.

We have published that different cell types in the gut (enterocytes, neurons, enteroendocrine cells) can detect glucose (76). These cells are considered ''glucose sensors,'' and activation of these intestinal and enteric glucose sensors has repercussions on the gut/brain axis controlling glycemia

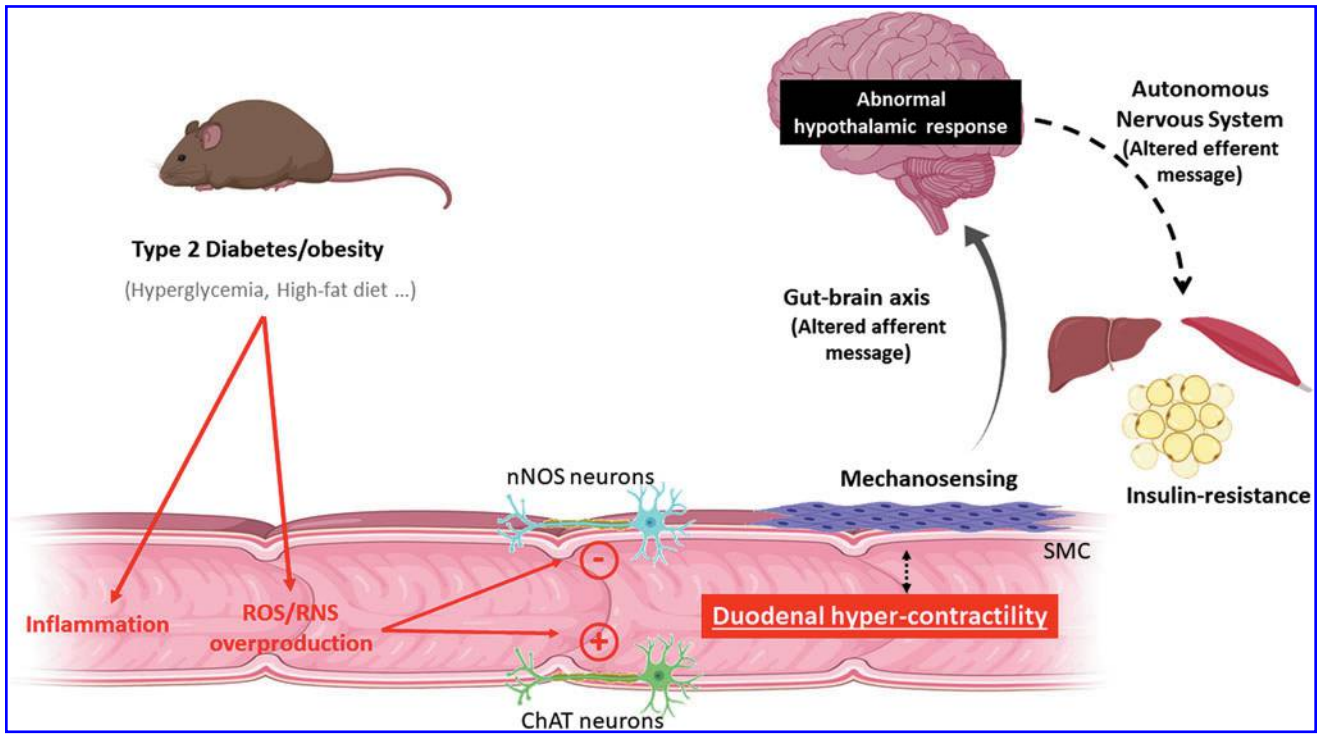

FIG. 4. T2D alters the mechanosensing system and the gut brain axis. T2D is associated with intestinal ROS/RNS overproduction and inflammation. These pathological responses generate an increased ratio of ChAT/nNOS expressing-neurons in the myenteric network. This ChAT/nNOS ratio triggers a duodenal hypercontractility, which in turn disturbs the mechanosensing system and generates an aberrant gut signal to the brain. In response to this abnormal stimulation, the hypothalamus sends back an aberrant efferent signal, participating in the establishment of insulin resistance in different tissues (muscle, liver, adipocytes), as observed in T2D. ChAT, choline acetyl transferase; nNOS, neuronal nitric oxide synthase; SMC, smooth muscle cells; T2D, type 2 diabetes. Color images are available online.

(112, 113). Therefore, it was established that intestinal inflammation/oxidative stress in the jejunum disturbs glucose sensing by intestinal cells (67). Thus, afferent nervous messages from the gut reach the brain and give an aberrant message to the hypothalamus. This phenomenon participates in the gut/brain axis dysfunction observed during metabolic disorders (Fig. 5) (67, 76). Again, intestinal inflammation and oxidative stress are crucial targets to treat T2D.

Glucagon-like peptide-1 (GLP-1) is a hormone released by enteroendocrine L cells that exerts antidiabetic effects by stimulating insulin release and sensitivity (37, 40, 111, 113). Diabetes is associated with a lack of GLP-1 release by the gut (Fig. 3), and therapeutic strategies use GLP-1 agonists or drugs that inhibit GLP-1 degradation (211). Evidence underlines inflammation-associated GLP-1 reduction during T2D. A recent work from Wongkrasant *et al.* (209) showed that proinflammatory tumor necrosis factor-α provokes L cell apoptosis during T2D. In addition, using a GLP-1-secreting cell line model, researchers have discovered that GLP-1 cells themselves can release ROS in response to hyperlipidemia (106), a characteristic of T2D.

The intestinal barrier limits the action of harmful substances and pathogens. Classically, it is composed of a mucus layer (163), epithelial layer, and lamina propria. Disruption of this barrier is associated with gut pathologies such as infection, intestinal bowel disease, and metabolic disorders (114, 176). To summarize, disruption of the intestinal barrier observed during obesity and T2D is associated with metabolic endotoxemia (Fig. 4) and impairment of GLP-1 production leading to whole-body inflammation (176).

Which factor could initiate this deleterious phenomenon? One possibility could be chronic hyperglycemia itself. Hyperglycemia generates an increase in ROS production in epithelial Caco-2 cells in correlation with a decrease in *occludin, zonula occludens-1*, and *claudin-1* mRNA expression (188). An HFD induced gut inflammation (59) and ROS release (118) from the intestine in rodents. Similar effects on tight junction proteins are observed in prediabetic mice, where disruption of the intestinal barrier is considered an early event in the development of the T2D phenotype (151). To give a general view of ''gut barrier disruption and HFD,'' Rohr *et al.* recently proposed a review showing the role of an HFD on barrier integrity, microbiota, and proinflammatory cytokines (182). What happens after gut barrier disruption during T2D?

In the middle of the 2000s, we discovered that HFD-fed mice present a significant increase in LPS absorption, leading to an increase in plasma LPS (also called metabolic endotoxemia) and low-grade inflammation at the origin of metabolic syndrome (41). In fact, in some situations LPS exerts a negative effect in the intestine that has a large impact on the whole body. As described above, the first site of action of LPS could be the intestinal epithelium, where LPS generates an oxidative stress state in the intestine. In addition to its implication of inflammatory processes observed in

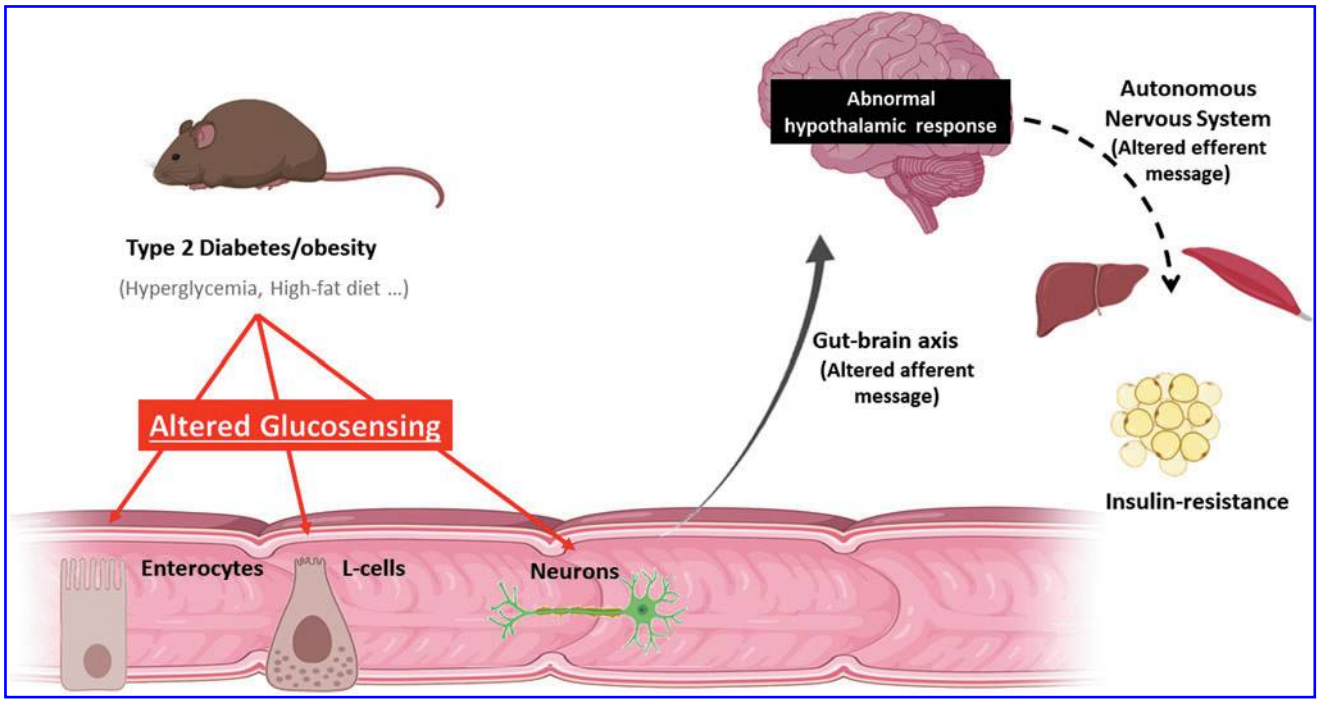

FIG. 5. T2D alters both the glucosensing system and gut/brain axis. During T2D and obesity, glucose detection is altered in numerous intestinal cells (enterocytes, L cells, neurons). Therefore, the communication between the gut and the brain is disturbed and leads to an abnormal hypothalamic response. In turn, the autonomic nervous system sends an aberrant nervous signal that generates insulin resistance. Color images are available online.

metabolic tissue (adipose tissue, liver, and muscles) (33), LPS is associated with microvascular (neuropathy, retinopathy) and macrovascular (peripheral arterial disease [PAD], stroke, myocardial infarction) complications observed during advanced T2D (139).

Several researchers have shown a positive correlation between serum LPS and zonulin, a marker of epithelial permeability (196), in patients with myocardial infarction (46) and in PAD patients (131). These results show that LPS could participate in the enhancement of platelet aggregation and atherosclerosis. In addition, researchers have shown a close correlation between plasma LPS and soluble NOX2-derived peptide, a marker of NOX2 activation. Thus, this is another reason for targeting intestinal oxidative stress to limit gut barrier dysfunction and associated pathologies.

Oral microbiota and T2D: a potential link with the enterosalivary cycle

In addition to gut microbiota, it is now well established that oral microbiota participates in the establishment of a diabetic state. In 2017, Blasco-Baque *et al.* (24) discovered that periodontitis generates periodontal microbiota dysbiosis without affecting the gut microbiota. In addition, the authors have clearly demonstrated that insulin resistance in HFD-fed mice is enhanced by *Porphyromonas gingivalis*-induced periodontitis. In fact, patients with periodontitis present a high probability of developing T2D (144).

Therefore, targeting the oral microbiota could represent a novel method to improve the diabetic phenotype (144). A recent article has shown that microbiota in saliva could be considered a feeding signature (145). Several pathologies, such as hypertension and T2D, are associated with the impairment of $^{\bullet}$NO production and bioavailability. The enterosalivary cycle permits the transformation of nitrate to nitrite in the mouth, and the second modification of nitrite to $^{\bullet}$NO occurs in the stomach and by nitrate reductases in different tissues, as previously described in detail (159). This physiological pathway leads to increased systemic $^{\bullet}$NO levels, which are beneficial to health.

In this case, evidence suggests that the reduction of nitrate in saliva by oral bacteria contributes to the increase in systemic $^{\bullet}$NO and could then be considered a probiotic to treat metabolic disorders (183). The identification of probiotics, particularly nitrate-reducing bacteria, is of substantial importance, as is the case with *Rothia* species (183), and could be used with other antidiabetics.

Redox-Based Therapeutics, Impact on Digestive Health Care, and Host Metabolism

In a recent elegant review, Diaz de Barboza *et al.* (62) described the antioxidant defense system in the gut, and some have been described above. In the gut, this system is represented by (i) endogenous antioxidant enzymes (SOD, CAT, GPx) that transform ROS into nonreactive molecules; (ii) endogenously produced free radical scavengers (*e.g.,* GSH, ubiquinol); (iii) food-derived factors with antioxidant activity (polyunsaturated fatty acids [PUFAs], vitamins C and E, selenium, *etc.*), or (iv) factors released by bacteria such as pigments (200).

Targeting oxidative stress and inflammation of the gut during metabolic disorders has been recently proposed. Here, we focus our attention on these recent approaches using the antioxidant system of defense coupled with or without well-known prescribed antidiabetics.

Prevention and nutraceutical approaches via *functional foods*

Numerous studies have clearly shown the importance of dietary supplements in the control of metabolic parameters such glycemia and body weight (128). Regarding the thematic of this review (*i.e.,* intestinal ROS/RNS and metabolism), we focused on recent advances proposed by researchers. It is worth noting that we are dealing with few examples, but we have to acknowledge that there are many other possibilities described in the literature.

Some PUFAs from the diet are well known to have antioxidant properties in the whole body, and their role as functional foods to improve metabolic syndrome is well described in the literature (137, 190). The n-3 PUFA family and a group of conjugated linoleic acids exert pleiotropic actions with antioxidant and anti-inflammatory consequences. In a recent review, Abrescia *et al.* described that PUFAs could act *via* two processes (5). The first describes the ability of some PUFAs to interact with PPARs, leading to modification of cellular functions. The second requires the capacity of PUFAs to modify plasma membrane lipid composition, which has consequences on cell signaling. Here, PUFAs can modulate the activity of plasma membrane enzymes such NOS and NOX, controlling the production of ROS/RNS.

The authors propose that PUFAs may modulate the Nrf-2 pathway, which controls antioxidant enzyme transcription (165). Little is known about the implication of Nrf-2 signaling in the intestine and its implication in metabolic disorders, but some articles describe that its beneficial antidiabetic effect acts on the liver (226) and pancreas (65). In addition, metformin (the most prescribed antidiabetic drug) exerts actions to increase the life span *via* Nrf-2 signaling in *Caenorhabditis elegans* (160). In fact, in this nematode, the Nrf proteins are represented by their ortholog SKN-1.

Onken and Driscoll (160) have shown that Nrf-2/SKN-1 signaling in the intestine is required to activate antioxidant defenses to extend the life span in response to metformin. Activation of Nrf-2 by metformin or natural products (142) could be considered a potential preventive or therapeutic approach. Thus, regarding the importance of the gut/brain axis in the control of glucose metabolism *via* a neuronal pathway (1, 110), utilization of PUFA/Nrf-2 signaling to prevent the onset and progression of diabetic neuropathy (142) (including enteric neurons) could be an opportunity to improve hyperglycemia and insulin resistance during T2D.

This assumption is confirmed by the effect of supplementation of dietary omega-6 long-chain PUFAs in zebrafish and the stimulation of transcription of *interleukin (IL)-10* (an anti-inflammatory cytokine) and antioxidant enzymes (*CAT, GPx*) in the intestine (153).

The Mediterranean diet represents one of most studied approaches to metabolic disorders (42, 156). This beneficial action in humans is correlated with changes in the gut microbiome in older (85) patients and those with obesity/diabetes (143). From a molecular point of view, extra virgin olive oil added to a Mediterranean diet has the capacity to decrease postprandial oxidative stress in humans by decreasing NOX2 activity (43, 45), leading to an improvement in postprandial glycemia (205). The postprandial glycemia observed during T2D could be counterbalanced by extra virgin olive oil.

In fact, a recent article from Carnevale *et al.* (44) demonstrated that this oil mitigates the coupled ''LPS-oxidative stress'' related to postprandial glycemia. A large majority of the positive effects reported are due to the presence of a phytochemical compound present in olive oil, that is, oleuropein. In humans, treatment with oleuropein before lunch prevents the postprandial glycemic profile by hampering NOX2-derived oxidative stress (47). In a diabetic context, oleuropein-containing chocolate enriched with extra virgin olive oil has an antidiabetic effect by stimulating GLP-1 and insulin release and decreasing postprandial glycemia (60).

Of course, in addition to this action of oleuropein, dark chocolate alone could exert antidiabetic action *via* the inhibition of NOX2 by cocoa polyphenol as previously described (129, 130). The utilization of prebiotics (such as polyphenols) (202), probiotics (such as *A. muciniphila*) (35, 176), symbiotics (36), and postbiotics (39) to prevent metabolic disorders is well described in the literature. Again, some of their positive effects *via* antioxidant and anti-inflammatory properties are detailed in excellent reviews (6, 26, 70).

Coenzyme Q (ubiquinone, 2-methyl-5,6-dimethoxy-1,4-benzoquinone) is crucial for optimal biological activity. Its antioxidant property is due to a reduction in ubiquinol. Evidence suggests that coenzyme Q10 can have clinical implications for the treatment of chronic diseases such as cancer and neurodegenerative, cardiac, and metabolic disorders (61, 90). No safety concerns were observed after oral administration of ubiquinol (97) or coenzyme Q10 (141) to healthy volunteers.

Recently, Martucci *et al.* developed a technology based on microcapsules that can release coenzyme Q10 ''to allow high constant blood concentrations without a sharp decrease'' (141), and this could bring new antioxidant therapy to treat chronic diseases in humans. At the molecular level, Korkina *et al.* tested an antioxidant formulation based on ubiquinol in a model of dextran sulfate sodium-induced colitis (116). Pretreatment (but not simultaneous or post-treatment) of rats with ubiquinol improves gut inflammation and intestinal electrical/mechanical impairment associated with a decrease in parameters associated with oxidative stress. The link between gut inflammation and oxidative stress observed in patients with T2D and the potential positive impact of coenzyme Q10 are evident.

Unfortunately, to date, little is known about the use of coenzyme Q10 as an ''antidiabetic'' agent and further studies are required, as explained by Arenas-Jal *et al.* in a recent review (9). A systematic review and meta-analysis from Zhang *et al.* (224) highlighted that coenzyme Q10 supplementation in type 2 diabetic patients improves fasting glycemia. Ubiquinol could be used in combination with antidiabetic agents similar to those used with statins in hypercholesterolemic patients with heart failure (109).

Resveratrol is one of the most studied polyphenols from the stilbene class and is present in some fruits (grapes, blackberries) and peanuts. Resveratrol is known to have antioxidant properties that have healthy effects on gut dysfunctions observed during colitis (221) or metabolic disorders (192). After oral administration, resveratrol is absorbed by enterocytes, and its biotransformation (especially sulfation and glucuronidation) leads to the synthesis of metabolites that reach the portal vein and different targeted metabolic tissues (192). In patients with diabetes, a 2-week

oral treatment with resveratrol increased the expression of Nrf-2 and SOD in peripheral mononuclear blood cells and was associated with a significant reduction in weight and body mass index (187).

Metabolic disorders (obesity and T2D) are characterized by both inflammatory and oxidative states of the gut that participate in the establishment of intestinal barrier injury and alterations to the gut/brain axis. Consequently, restoring the gut barrier and gut/brain axis represents an innovative approach to treat hyperglycemia and insulin resistance, as described above (176). Related to its impact in the gut, evidence shows that resveratrol attenuates oxidative stress-induced intestinal barrier injury through the PI3K/Akt-mediated Nrf-2 signaling pathway (227).

In detail, resveratrol exerts a beneficial action in epithelial cells by improving the activities of antioxidant enzymes (SOD, CAT, and GPx) and by decreasing intracellular ROS levels and apoptosis induced by H_2O_2. In addition to this antioxidant action, the same authors showed that resveratrol increased the expression levels of tight junction proteins (claudin-1, occludin, and ZO-1). Furthermore, resveratrol targets the duodenum to improve insulin sensitivity *via* the brain (56). Modulation of the gut/brain axis by resveratrol implicates numerous molecular actors (SIRT-1, serotonin), including GLP-1 (54), a gut hormone with antioxidant and antidiabetic properties (48, 173) as described below.

Drugs on the market

Medication for metabolic disorders is in perpetual progress, and the identification of novel molecular targets remains a strong point of medical research. There are multiple targets, including central agents (neurotransmitters), incretin hormones (GLP-1), and pharmacological drugs (metformin) (27, 55, 193). In this review, we have focused on two main antidiabetic drugs, that is, GLP-1 and metformin, which exert anti-inflammatory and antioxidant actions in the gut.

GLP-1 is secreted by intestinal enteroendocrine L cells in response to nutrients such as glucose, lipids, and amino acids (27). GLP-1 is known as an incretin hormone that improves insulin secretion by the pancreas and insulin sensitivity in metabolic organs such as the muscle. In addition to this well-known action on peripheral tissue, GLP-1 can also modulate the gut/brain axis to favor glucose entry in the liver and muscle (112, 113). GLP-1 can also act directly in the brain to control food intake and glucose flux in the whole body (111).

Prebiotics and probiotics that are used to improve energy balance and glucose homeostasis exert their action *via* a GLP-1 signaling pathway (69). Therapeutic strategies based on GLP-1 signaling require the utilization of a GLP-1 agonist (152) or inhibitor of dipeptidyl peptidase IV (98), the enzyme involved in GLP-1 degradation. The powerful role of GLP-1 as an antioxidant is well described in the literature. Petersen *et al.* wrote a review that deciphered the impact of GLP-1 on oxidative stress during diabetes in various experimental models (166).

To summarize this impressive work, GLP-1 has the capacity to decrease ROS production and increase the expression and/or activity of antioxidative enzymes such as SOD and CAT in different models, including obese/diabetic models, to counterbalance the damage induced by ROS overproduction. For example, the GLP-1 receptor agonist liraglutide confers cardioprotective effects from ROS in the hearts of diabetic mice by activating the Nrf-2 pathway (157). A similar effect is observed in the pancreas of diabetic rodents pretreated with recombinant human GLP-1, which prevents the deleterious action of streptozotocin (STZ) on SOD expression (212).

A very similar action is observed in the gut of diabetic rodents. It was demonstrated that the administration of STZ reduced the expression of CAT and SOD, whereas treatment with liraglutide could partially reverse the STZ-induced effects (222). In addition, T2D is associated with mitochondrial stress in enterocytes, leading to ATP and ROS overproduction.

Berberine, an alkaloid product produced by plants, stimulates the release of intestinal GLP-1 in diabetic rodents (197). Consequently, in this study, GLP-1 restored the basal physiology of mitochondria from enterocytes to decrease this stress induced by an HFD. It is worth noting that the anti-inflammatory action of resveratrol in the colon may require a GLP-1 pathway (57). Thus, future therapeutic strategies may take into account the possible use of a combination of drugs and dietary supplements to improve antioxidant and/or anti-inflammatory action to manage T2D (Fig. 6).

This is the case with the combination of ''metformin/genistein'' (genistein is a natural molecule belonging to the class of isoflavones), which stimulates the release of GLP-1 and downregulates the inflammatory and oxidative response in the plasma, pancreas, and intestine (177). Obviously, the oral administration of drugs represents an alternative for patient compliance and an easier method of treatment. A recent review from Xu *et al.* (216) described the different types of transport of drugs through the intestinal barrier. In fact, oral drugs often present poor bioavailability, and therapeutic strategies have focused on novel systems of transport to target specific intestinal cells (215). This is the case for the development of nanocarriers or the oral delivery of peptides using lipid-based nanocapsules (217).

Here, the authors have clearly demonstrated how the oral GLP-1 analogue liraglutide encapsulated in nanoparticles prevents hepatic steatosis and body weight gain in HFD-fed mice. This system of nanoparticles, as an innovative system of carrier resistance to low pH, is ready for human use and could be tested with the combination of drugs and dietary supplements (Fig. 6).

Metformin is the first-line therapeutic option to treat T2D (121). In addition to its antihyperglycemic action, metformin could induce weight loss during obesity by modulating the gut microbiota population and hypothalamic neuronal response, controlling food intake (121, 220).

Metformin has a global impact in the whole body, but several effects are linked with its action on ROS/RNS signaling. First, metformin downregulates the mRNA expression of various proinflammatory markers in the intestinal epithelium of diabetic mice and is associated with an improvement in the diabetic state (225). This effect may be linked to the capacity of metformin to (i) decrease intracellular ROS levels, as described in endothelial cells (161), (ii) increase antioxidant enzyme activity (102), and (iii) scavenge hydroxyl radicals but not superoxide radicals and H_2O_2 (25).

In contrast, a recent article from Rajendran *et al.* showed that oral treatment with metformin fails to demonstrate an antioxidant action of this drug on the jejunum of pigs (172). Thus, although metformin improves the duodenum/brain axis of HFD-fed rats (66), its precise site of action in the intestine

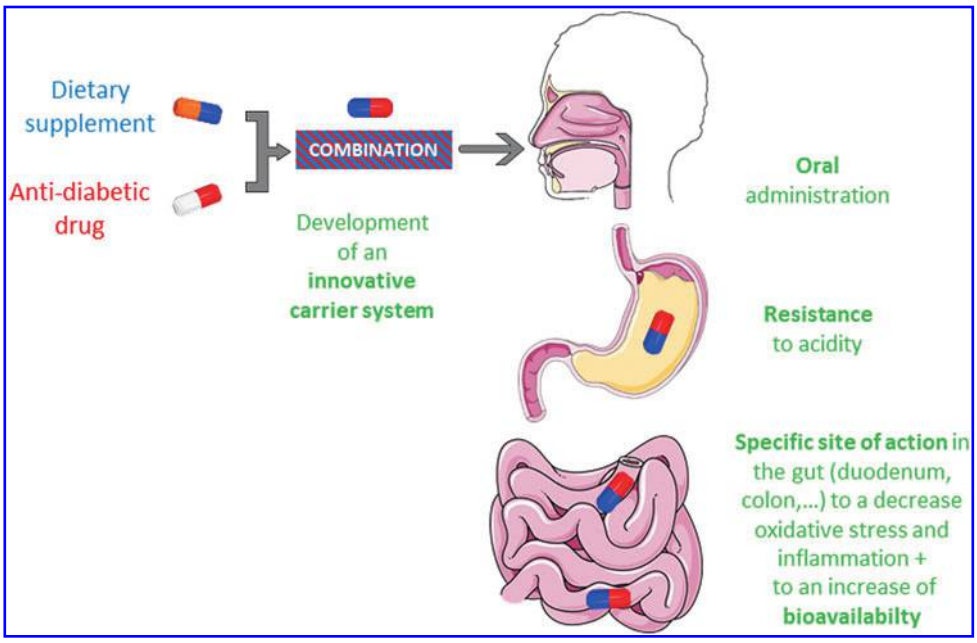

FIG. 6. Potential future therapeutic approaches. The use of a combination of dietary supplement and anti-diabetic drug in addition to an innovative carrier system represents a real novelty to treat metabolic disorders. A potential safety approach with (i) oral administration, (ii) resistance to stomach acidity, and (iii) a specific site of action represents the next scientific challenge to improve the quality of life of patients. Color images are available online.

(from duodenum to colon) and its impact on ROS/RNS signaling remain to be determined. In addition to its potential direct effect on the gut, metformin could have an ''indirect'' anti-inflammatory role, which acts by modifying the gut microbiota population (*Akkermansia*, *Bacteroides*, *Butyricimonas*), which is known to downregulate the expression of the inflammatory cytokine IL-18 (122).

An innovative molecule that is being investigated to treat T2D is imeglimin; it is a phase 3-ready drug that is administered orally. Several reviews have clearly described the mode of action of imeglimin (91, 115, 219). This therapeutic molecule has the capacity to reduce ROS formation and oxidative stress by rebalancing the respiratory chain activity, but investigations into its role in ROS signaling in the gut are required. This potential novel antidiabetic drug has a powerful effect on hyperglycemia since it increases insulin sensitivity in the liver and muscle and insulin release by the pancreas. Imeglimin is absorbed by the intestine and reaches target tissue *via* circulation.

Perspectives: relevant new technologies for future therapies

Of course, other antioxidant molecules (not presented in this review), such as flavonoids (64) or a combination of dietary supplementation with antidiabetic drugs, as described above (177), represent multiple possibilities to improve the quality of life of patients who are obese and/or have diabetes. As described above, oral GLP-1-based therapy with nanoparticles is cutting edge technology that is ready for human use to treat patients with T2D (217).

Targeting a specific site of intestinal action for a precise drug (duodenum or colon as example) or improving its absorption (and then bioavailability) is crucial to treat metabolic syndrome. Again, the possibilities are increasing, and Ma *et al.* have clearly described the different existing methods to deliver the antioxidant/anti-inflammatory curcumin *via* an oral route (135). These methods include solid dispersions, nano/microparticles, polymeric micelles, nanosuspensions, lipid-based nanocarriers, cyclodextrins, conjugates, and polymorphs. This is also the case for coenzyme Q10, which is poorly water soluble and presents important interindividual variation after oral administration. Therefore, microencapsulation of coenzyme Q10 could be proposed to increase its efficacy and bioavailability (104).

To conclude, therapeutic strategies for metabolic disorders must first take into consideration the route of administration for patients. Of course, the oral route is the preferred route for patients and the most optimal route for targeting the gut. Second, antidiabetic drugs and/or dietary supplements can be administered *via* innovative systems of transport to specifically target a cell type in the gut. Third, therapeutic molecules could have anti-inflammatory and antioxidative actions to restore the global physiology of the gut and consequently modify the pathological state of the whole body.

Among the potential therapeutic molecules, oral administration of the bioactive peptide apelin had antidiabetic effects in HFD-fed mice (75) Also, apelin can be carried in nanosystems (186) and has anti-inflammatory and antioxidative properties (148). Numerous other molecular candidates with better efficacy could be discovered in the future, which represents a scientific challenge.

Authors' Contributions

A.A., S.F., P.D.C., and C.K. wrote the article.

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P.D.C. is the inventor on patent applications dealing with the use of *A. muciniphila* and its components in the treatment of metabolic disorders. P.D.C. is cofounder of A-Mansia

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Abbreviations Used

CAT = catalase
ChAT = choline acetyl transferase
Cl^- = chloride ion
DUOX = dual oxidase
EEC = enteroendocrine cells
eNOS = endothelial nitric oxide synthase
ENS = enteric nervous system
GI = gastrointestinal
GLP-1 = glucagon-like peptide-1
GLP-1-R = glucagon-like peptide-1 receptor
GLUT2 = glucose transporter 2
GPR = G-protein-coupled receptors
GPx = glutathione peroxidase
GR = glutathione reductase
GSH = reduced glutathione
GSSG = oxidized glutathione
H_2O_2 = hydrogen peroxide
HFD = high-fat diet
HIF-1 = hypoxia inducible factor-1
HOCl = hypochlorous acid
IBD = inflammatory bowel disease
ICC = interstitial cells of Cajal
IL = interleukin
iNOS = inducible nitric oxide synthase
K_{ATP} = ATP sensitive potassium channel
KO = knockout
LPS = lipopolysaccharide
MAPK = mitogen-activated protein kinase
MCP = monocrotophos
mETC = mitochondrial electron transport chain
N_2O_3 = dinitrogen trioxide
NADP = nicotinamide adenine dinucleotide phosphate
NADPH = reduced nicotinamide adenine dinucleotide phosphate
NF-κB = nuclear factor-kappa B
nNOS = neuronal nitric oxide synthase

Abbreviations Used (Cont.)

NO = nitric oxide
$^{\bullet}NO_2$ = nitrogen dioxide
NO_3^- = reduced nitrates
NOS = nitric oxide synthase
NOX = NADPH oxidase
Nrf-2 = nuclear factor erythroid 2-related factor
$O_2^{\bullet-}$ = superoxide
$^1O_2$ = singlet oxygen
$^{\bullet}OH$ = hydroxyl radical
$ONOO^-$ = peroxynitrite
OPI = organophosphorus insecticide
PAD = peripheral arterial disease
PPARγ = peroxisome proliferator-activated receptor gamma
PUFA = polyunsaturated fatty acid
RNS = reactive nitrogen species
ROS = reactive oxygen species
SCFA = short-chain fatty acid
SGLT = sodium-dependent glucose cotransporters
SIRT-1 = sirutin 1
SMC = smooth muscle cells
SOD = superoxide dismutase
STZ = streptozotocin
T2D = type 2 diabetes
TCA = tricarboxylic acid
TNF-α = tumor necrosis factor-α
Treg = regulatory T cells
Trx = thioredoxin
TrxR = thioredoxin reductase