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ORIGINAL ARTICLE

Proanthocyanidin-containing polyphenol extracts from fruits prevent the inhibitory effect of hydrogen sulfide on human colonocyte oxygen consumption

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Abstract

Hydrogen sulfide (H_2S), a metabolic end product synthesized by the microbiota from L-cysteine, has been shown to act at low micromolar concentration as a mineral oxidative substrate in colonocytes while acting as an inhibitor of oxygen consumption at higher luminal concentrations (65 µM and above). From the previous works showing that polyphenols can bind volatile sulfur compounds, we hypothesized that different dietary proanthocyanidin-containing polyphenol (PACs) plant extracts might modulate the inhibitory effect of H_2S on colonocyte respiration. Using the model of human HT-29 Glc–/+ cell colonocytes, we show here that pre-incubation of 65 µM of the H_2S donor NaHS with the different polyphenol extracts markedly reduced the inhibitory effect of NaHS on colonocyte oxygen consumption. Our studies on HT-29 Glc–/+ cell respiration performed in the absence or the presence of PACs reveal rapid binding of H_2S with the sulfide-oxidizing unit and slower binding of H_2S to the cytochrome c oxidase (complex IV of the respiratory chain). Despite acute inhibition of colonocyte respiration, no measurable effect of NaHS on paracellular permeability was recorded after 24 h treatment using the Caco-2 colonocyte monolayer model. The results are discussed in the context of the binding of excessive bacterial metabolites by unabsorbed dietary compounds and of the capacity of colonocytes to adapt to changing luminal environment.

Keywords Hydrogen sulfide · Proanthocyanidins · Polyphenols · Colonocyte · Oxygen consumption

Introduction

Polyphenols are secondary metabolites that are implicated in the protection of plants against different types of stress and aggression. From experimental, clinical, and epidemiological studies, numerous beneficial effects of polyphenols on health have already been proposed (Rodrigo et al. 2014). Among dietary polyphenols, proanthocyanidins (PACs), also known as condensed tannins, are abundant in plant-derived foodstuffs including red wine, green tea, grapes, cranberries, and apples (Gu et al. 2004). Although the dietary intake of polyphenols is rather different between individuals due to different alimentary habits, it has been determined that, for instance, in France, the mean total PAC intake represents 260 mg/day in men and 191 mg/day in women (Perez-Jimenez et al. 2011). In the USA, PACs are the second most abundant dietary phenolic compounds, with an average daily PAC intake representing roughly 220 mg (Gu et al. 2004). Dietary PACs with a degree of polymerization higher than 3 are poorly absorbed in the small intestine, and thus, a vast majority of these compounds are able to reach the colon lumen (Mateos-Martin et al. 2012; Scalbert et al. 2000), where they may interact with the colonic microbiota, the bacterial metabolites, and the epithelium. The concentrations of polyphenols in the fecal water recovered from volunteers with no dietary restriction are in the micromolar range with rather high variability between individuals (Jenner et al. 2005).

In the colonic lumen, the abundant populations of bacteria forming the microbiota are characterized by a complex

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metabolic network, notably regarding nitrogenous compound metabolism (Portune et al. 2016). In fact, although the process of protein digestion in mammals is highly efficient, a significant amount of dietary and endogenous proteins can escape digestion in the small intestine and be transferred to the colon (Blachier et al. 2007). The intestinal microbiota is equipped with proteases and peptidases allowing the hydrolysis of proteins and the release of amino acids. Those latters are metabolized by the bacteria which release various metabolites including hydrogen sulfide (H_2S). Different *S*-containing compounds including notably L-cysteine are substrates for the bacterial production of H_2S (Blachier et al. 2010).

H_2S is now established as the first mineral compound being able to be oxidized at low micromolar concentrations by human cells (Goubern et al. 2007). In colonocytes, although mitochondrial oxidation of H_2S allows ATP synthesis (Lagoutte et al. 2010), it appears that such an oxidation is not meant to increase the cellular ATP levels above a steady-state value, but rather to allow its detoxification (Mimoun et al. 2012). Indeed, when the capacity of colonocytes to metabolize H_2S is overwhelmed, this bacterial metabolite inhibits colonocyte respiration by binding to the mitochondrial cytochrome c oxidase (Li et al. 2009). In fact, we previously shown that 65 µM concentration of the sulfide donor NaHS is able to inhibit colonocyte oxygen consumption (Mimoun et al. 2012). In the human large intestine luminal content and feces, millimolar concentration of total sulfide has been measured, while the free (unbound) fecal sulfide concentration is much lower averaging approximately 60 µM (Blachier et al. 2010).

The detoxification of hydrogen sulfide in excess requires the sulfide oxidation unit which has been identified as a mitochondrial enzymatic complex (Bouillaud and Blachier 2011; Jackson et al. 2012). Interestingly, intra-colonic instillation of sulfide at millimolar concentrations increases the expression of genes involved in mucosal inflammation (Beaumont et al. 2016), thus associating energy metabolism perturbation with parameters implicated in intestinal inflammation. In addition, the capacity of the microbiota to produce H_2S has been reported to be higher in subjects with inflammatory bowel disease (IBD) than in healthy control subjects (Carbonero et al. 2012); and H_2S detoxification system appears to be impaired both in Crohn's disease and ulcerative colitis patients (Arijs et al. 2013; De Preter et al. 2012). As presented above, the vast majority of PACs with high degree of polymerization reaches the colon where they interact with the colonic microbiota and epithelium, eventually decreasing the inflammatory and the pro-oxidant processes in the colonic mucosae and contributing to maintain mucosal integrity (Cires et al. 2016; Yoshioka et al. 2008). Moreover, previous works suggested that dietary polyphenols may bind volatile sulfur compounds (Lodhia et al. 2008; Zeng et al. 2010). We then undertake the present study to document the effects of PAC-containing polyphenol extracts from various plants on H_2S-induced alterations of oxygen consumption, energy metabolism and paracellular permeability in human colonic epithelial cells.

Materials and methods

Preparation of the polyphenol extracts from fruits

The preparation and characterization of the polyphenol extracts from cranberries, grapes, apples and avocados have been recently described (Wong et al. 2016a, b). Dried polyphenol-rich extracts were stored at − 70 °C until use.

Cell culture

The human adenocarcinoma cell line HT-29 Glc−/+ cells used in this study was selected by Zweibaum et al. (1985) from the parental cell line. Cells were grown in a glucose-free culture medium for 36 passages, then leaving them to grow at 37 °C under 5% CO_2 atmosphere in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) heat inactivated fetal bovine serum and containing 4 mM glutamine, 25 mM D-glucose. HT29-Glc−/+ cells were used between passages 39 and 57 (one passage every week). Cells were seeded at density of 2×10^4 cells/cm^2 on day 0. The culture medium was changed every day.

Oxygen cell consumption

Six days after seeding, HT-29 Glc−/+ cells were isolated by trypsine/EDTA (0.25 g/L) in phosphate-buffered saline (PBS) containing 1 g/L EDTA. Approximatively 5×10^6 cells in 2 mL of an air saturated respiration medium (20 mM Hepes, 200 mM mannitol, 5 mM KH_2PO_4, 2.5 mM $MgCl_2$, and 0.5 mM EGTA, pH 7.4, enriched with 0.1% bovine serum albumin) were placed in the oxygraph chamber for oxygen consumption measurement rate. Cell respiration at 37 °C was monitored with an "O2k" Oroboros apparatus (Innsbruck, Austria). Oxygen consumption rates were obtained directly from the Datalab 4 software and were calculated as the negative time derivative of oxygen concentration in the closed respirometry chamber. After stabilization of the basal oxygen consumption (state 3, that is in the absence of any exogenous agent and is considered as the 100% reference value), NaHS used as sulfide donor was added alone as a single bolus at 65 µM concentration which inhibits oxygen consumption. NaHS (65 µM) and PACs (1, 10 and 100 µg/mL) were both dissolved in water and mixed for 1 h at 20 °C before adding them in the oxygraph chamber after stabilization of the cell basal oxygen consumption.

The oxygen consumption rates were determined at the basal state, and at 1 and 5 min following the addition of the individual or mixed tested compounds.

Colonic epithelial barrier function

Changes in the colonic epithelial barrier characteristics were determined using human colonic carcinoma Caco-2 cells. Differentiated Caco-2 cells grown as monolayer on porous filters are an established model for the study of intestinal permeability and barrier functions (Grasset et al. 1984; Hidalgo et al. 1989). Transepithelial electrical resistance (TEER), as an indicator of the integrity of the epithelial paracellular pathway, was measured in the Caco-2 cell monolayers grown on 1.12 cm^2 Transwell® filters with an ohm/voltmeter (Word Precision Instrument EVOM, Sarasota, USA). Cell monolayers were used 15 days after seeding when their TEER was stabilized. TEER measurements were carried out up to 24 h of treatment at the apical side with 1.5 and 3.0 mM NaHS or 1 mM sodium deoxycholate used as a positive control to induce epithelial barrier disturbance (Leschelle et al. 2002). Paracellular permeability to FITC-dextran was also determined in the Caco-2 cell monolayers by adding 1 mg/mL FITC-dextran (FD-4) in the culture medium at the apical side. The amount of FD-4 transferred to the basolateral side was determined using the Infinite® 200 Pro spectrofluorimeter (TECAN, Switzerland) with an excitation and emission wavelengths of 490 and 520 nm, respectively. Amounts of FD4 were expressed as final fluorescence units (FU).

Data analysis

The results are expressed as mean value (± SEM). Statistical analyses were performed using the Student *t* test, ANOVA, and Tukey multiple-comparisons test when appropriate using R software with package lsmeans. Differences with p value < 0.05 were considered as statistically significant.

Results

Characteristics of the oxygen consumption in the presence of H_2S on HT-29 Glc–/+ cells

When NaHS, used as a H_2S donor, was added as a single shot at a concentration of 5 µM with HT-29 Glc–/+ cells, it immediately increased the rate of oxygen consumption up to a maximal value, and then went back to the basal oxygen consumption within approximately 1 min, indicating a rapid and full oxidation of this compound by these cells (Fig. 1a). When higher concentrations of NaHS was tested (i.e., 10 and 20 µM), they increased the oxygen consumption by HT-29 Glc–/+ cells at a similar extent than the increase recorded in the presence of 5 µM (Fig. 1a, b). However, as expected, the time required by the colonocytes for complete sulfide oxidation was proportional to its initial concentration in the incubation medium (Fig. 1a). In presence of 65 µM NaHS in the incubation medium, an immediate short-term stimulation of oxygen consumption was observed, followed by a marked and lasting inhibition of oxygen consumption (Fig. 1c). These results indicate that a part of sulfide is initially rapidly oxidized by the HT-29 Glc–/+ cells, and then the remaining sulfide inhibits O_2 consumption.

Effects of the pre-incubation of polyphenol extracts from different origins with NaHS on subsequent HT-29 Glc–/+ cell oxygen consumption

The cranberry extracts, originating from either cranberries (CR), or grapes (GR), apples (AP), and avocados (AV) when tested alone at the highest concentration tested in the experiments (100 µg/mL), had no effect on the HT-29 Glc–/+ cell basal O_2 consumption (Fig. 2a). As already indicated in Fig. 1c, after 1 min incubation, 65 µM NaHS provoked a rapid and transient stimulation of oxygen consumption. After 5 min, a rate of oxygen consumption largely below that measured in the basal state 3 was observed (Fig. 2b). When NaHS was pre-incubated in the presence of the cranberry polyphenol extract, and then incubated with the HT-29 Glc–/+ cells, a return to the basal state 3 oxygen consumption, which is detectable from the 10 µg/mL concentration, was observed after 5 min (Fig. 2b); suggesting that the polyphenols present in the cranberry extract interact with sulfide, therefore, diminishing markedly its free concentration in the pre-incubation medium, and then allowing cells to largely metabolize the remaining bacterial metabolite within 5 min.

As indicated on Fig. 2c, when NaHS (65 µM) was pre-incubated in the presence of grape PACs extracts tested at increasing concentrations, the rate of oxygen consumption measured 5 min after the beginning of incubation was higher after pre-incubation of sulfide in the presence of the polyphenol extract from 1 µg/mL than in the presence of NaHS alone. Indeed, at the highest concentration tested (100 µg/mL), the polyphenol extract apparently interacts with almost all the sulfide, since in such condition, no inhibitory effect of NaHS on cell oxygen consumption was anymore recorded after 5 min incubation.

When the pre-incubation was performed with 65 µM NaHS and increasing concentrations of apple polyphenol extract, an interaction of sulfide with polyphenols was observed from the 10 µg/mL concentration; resulting in a lower inhibition of O_2 consumption at 5 min than the one recorded without pre-incubation with polyphenols (Fig. 2d). Indeed, at the highest concentration of the apple extract (100 µg/mL), most of the sulfide was presumably bound to polyphenols.

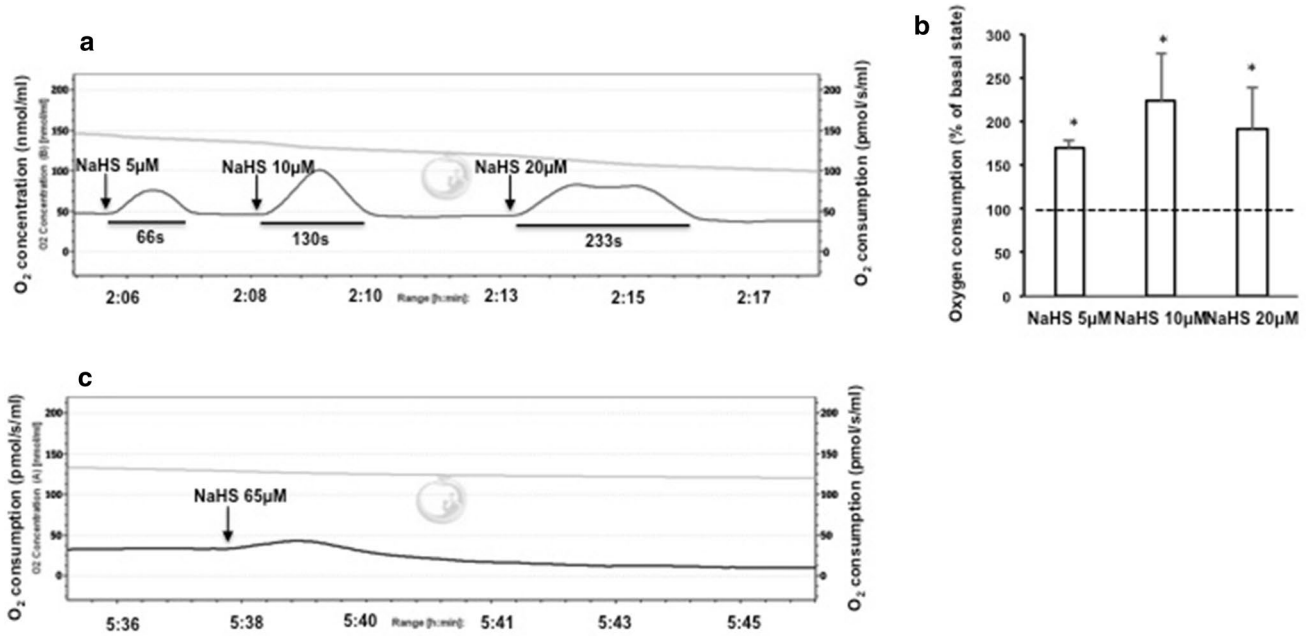

Fig. 1 Typical effect of NaHS on HT-29 Glc−/+ cell oxygen consumption. After the stabilization of the basal oxygen consumption rate, NaHS was added as a single shot at the time indicated by an arrow and oxygen consumption was measured using an "O2K" Oroboros apparatus (**a**). Bottom curve (black line) represents rate of oxygen consumption (pmol/s mL) and upper curve (grey line) represents oxygen concentration (nmol/mL). Time needed for complete NaHS oxidation is noted below the horizontal line. **b** oxygen consumption in the presence of 5, 10 or 20 µM NaHS expressed as % of basal state measured without any agent measured after 1 min. **c** Typical effect of 65 µM NaHS on HT-29 Glc−/+ cell oxygen consumption. The results are mean ± SEM obtained from six independent experiments. $^*p < 0.05$ vs. basal oxygen consumption (100%, measured without any agent)

As indicated on Fig. 2e, when the pre-incubation was performed with 65 µM NaHS and increasing concentrations of the avogado extract, an interaction with sulfide was detected from the 10 µg/mL concentration, resulting in an inhibition of O_2 consumption at 5 min which was lower than the one recorded without pre-incubation (NaHS 65 µM). Indeed, at the highest concentration of the extract (100 µg/mL), most of the sulfide was presumably bound to polyphenols. The duration of the pre-incubation period (10, 30, 60 min) between the polyphenol extract (100 µg/mL), whatever their origin, and NaHS (65 µM) similarly affect the oxygen consumption rate by the colonic cells (data not shown).

Effects of millimolar concentrations of NaHS on the epithelial paracellular permeability

Since H_2S at excessive concentrations inhibits colonocyte respiration, a phenomenon that can likely impact the colonocyte mitochondrial ATP synthesis, we then tested for up to 24 h the effect of millimolar concentrations of NaHS on the epithelial barrier integrity using Caco-2 cell monolayers grown on transwell filters, which represent an established in vitro model of colonocyte monolayer for permeability measurement. As indicated in Fig. 3a, although NaHS tended to increase the transfer of FITC-dextran from the luminal to the basolateral side of the monolayer, this paracellular transfer appears modest when compared to the effect of 1 mM deoxycholic acid used as a positive control. In addition, the measurement of the transepithelial electrical resistance (TEER), used also as a marker of the integrity of the paracellular pathway, revealed no significant effect of NaHS on this parameter, compared with that of deoxycholic acid (Fig. 3b). Accordingly, the potential protective effect of the polyphenol extracts initially planned was not tested in this model.

Discussion

The fruit polyphenol extracts used in the present work are exactly the same than those characterized and tested in two recently published studies. In one of them, we reported that these extracts protected human colonic epithelial cells against the deleterious effect of another amino acid-derived bacterial metabolite, namely *p*-cresol (Wong et al. 2016a), while in the other, we observed that they were able to interfere with bacterial LPS in vitro and even more importantly,

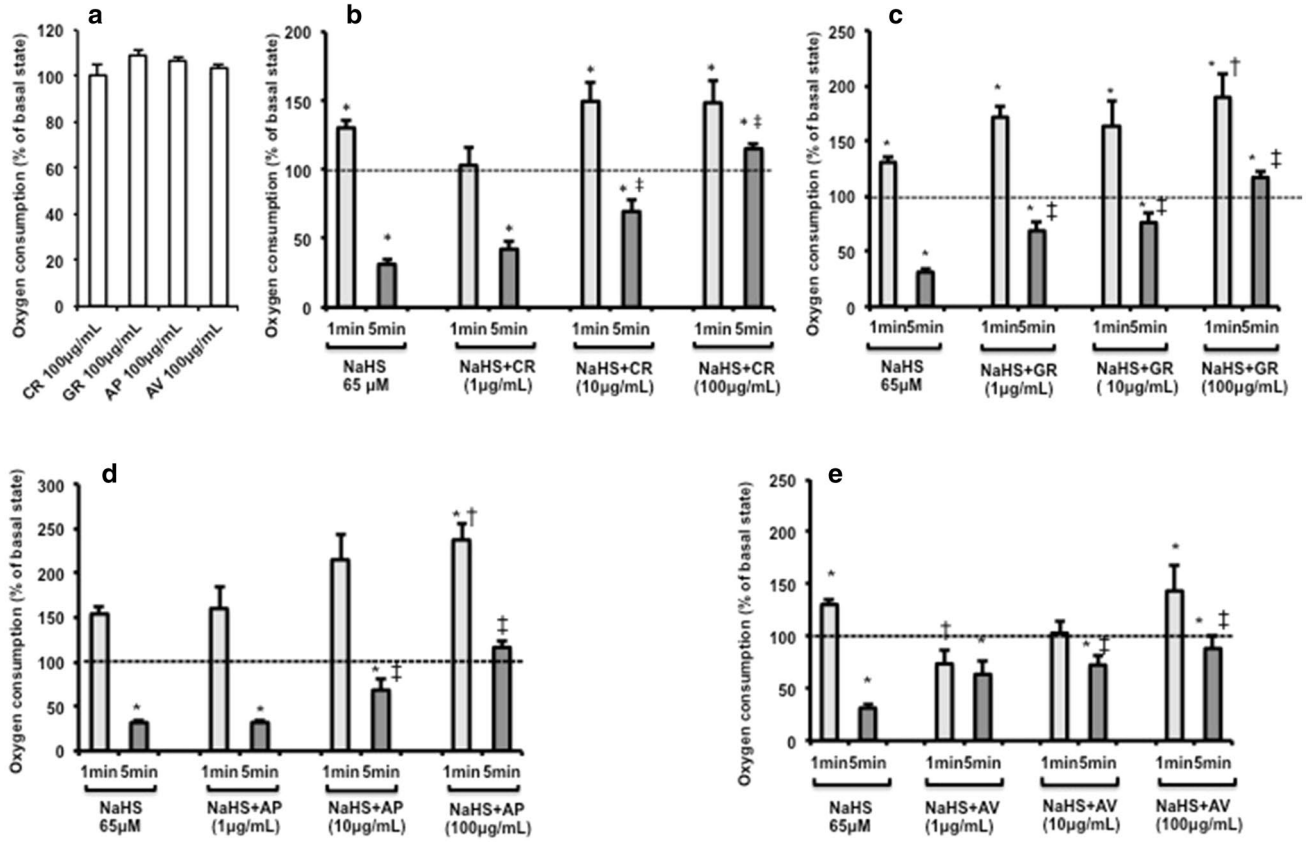

Fig. 2 Effects of proanthocyanidin-containing polyphenol extracts from various origins and of pre-incubation of the proanthocyanidin-containing polyphenol extracts with NaHS on HT-29 Glc−/+ cell oxygen consumption. **a** Effects of proanthocyanidin-containing polyphenol extracts from cranberries (CR), grapes (GR), apple (AP), and avocados (AV) on HT-29 Gl−/+ cell oxygen consumption. After stabilization of the basal oxygen consumption rate, polyphenol extracts from various origins were added at a concentration of 100 µg/mL, and HT-29 Glc−/+ cell oxygen consumption was measured. The dotted line corresponds to the basal oxygen consumption (100%). To test the effect of pre-incubation of NaHS 65 µM with the proanthocyanidin-containing polyphenol extracts on subsequent cell oxygen consumption, NaHS was first pre-incubated 1 h with various concentrations (1.0, 10.0, and 100 µg/mL) of the different polyphenol extracts, and then the mixtures were incubated with the HT-29 Glc−/+ cells, and oxygen consumption was measured after 1 and 5 min incubation. Pre-incubation of NaHS was performed with either the cranberry extract (**b**) (NaHS + CR), or with the grape extract (**c**) (NaHS + GR), or with the apple extract (**d**) (NaHS + AP) or with the avocado extract (**e**) (NaHS + AV). The results are mean ± SEM obtained from six independent experiments. $^{*}p < 0.05$ vs. basal oxygen consumption (100%, measured without any agent); $^{\dagger}p < 0.05$ vs. oxygen consumption measured with NaHS alone at 1 min after the beginning of incubation; $^{\ddagger}p < 0.05$ vs. oxygen consumption measured with NaHS alone at 5 min after the beginning of incubation

that the grape extract decreased the post-prandial increased of LPS absorption associated with the intake of a high-fat meal in human volunteers (Wong et al. 2016b).

The present study indicates that polyphenols in the different fruit extracts can largely reduce the inhibitory effect of 65 µM NaHS on colonocyte respiration. This concentration of NaHS was chosen as it represents a concentration of NaHS that significantly inhibits oxygen consumption in colonocyte (Mimoun et al. 2012). At this concentration of NaHS, the extracts obtained from grapes was found to be the most efficient among the different extracts tested, as the concentration of 1 µg extract per mL, at difference with the other mixtures, was already efficient in diminishing the inhibitory effect of NaHS on cell respiration.

Based on the results obtained in previous studies (Lodhia et al. 2008; Zeng et al. 2010) the protective effect of PACs on colonocyte respiration is most likely related to a chemical interaction between sulfide and polyphenols in the extracts. The putative binding between H_2S and the polyphenols was apparently maximal after 10 min pre-incubation at 20 °C, since the effects of the extracts were similar after longer time pre-incubation. Further works outside the aim of this study are necessary for characterizing the interactions between these compounds.

Since the same polyphenol extracts than those used in the present study were found to protect against the deleterious effects of the bacterial metabolite *p*-cresol on the epithelial barrier function (Wong et al. 2016a, b), and since

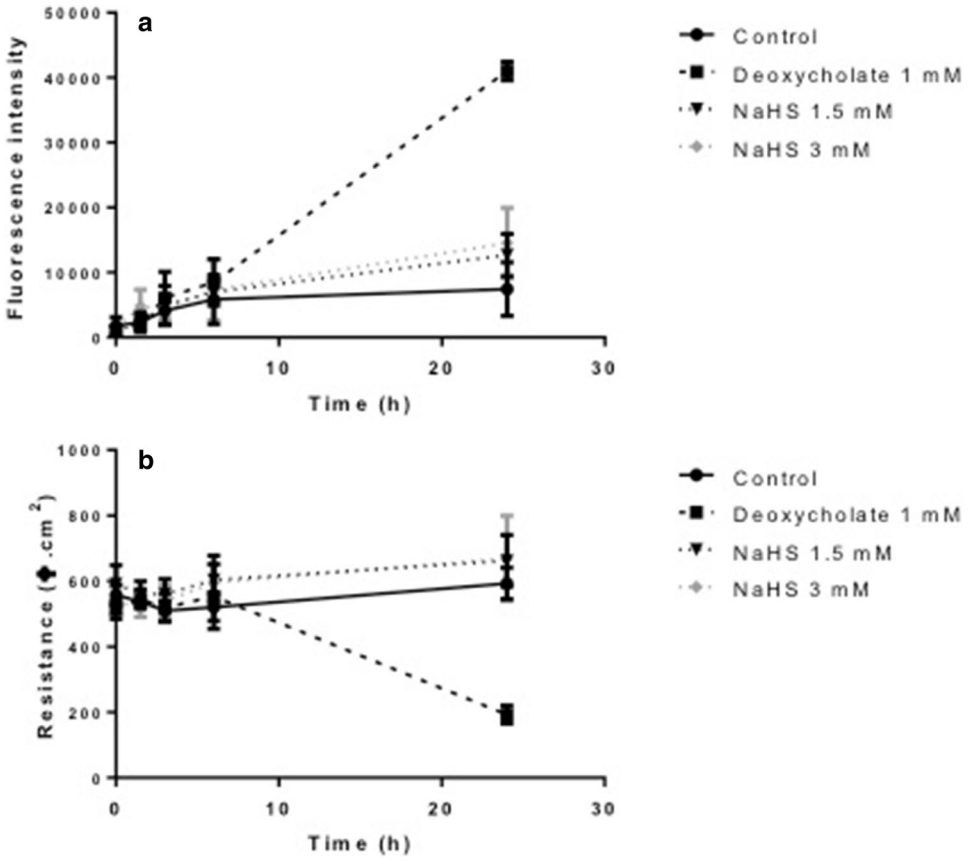

Fig. 3 Effects of incubation of NaHS with Caco-2 cell monolayers on the epithelial paracellular permeability. **a** Caco-2 cell monolayers were cultured for up to 24 h without (control) or with NaHS (1.5 or 3.0 mM) or deoxycholate (1 mM) used as a positive control, and the transfer of FITC-dextran from the luminal to the basolateral side was measured. **b** Caco-2 cell monolayers were cultured for up to 24 h without (control) or with NaHS (1.5 or 3.0 mM) or deoxycholic acid (1 mM) used as a positive control, and the transepithelial resistance was measured. The results are mean ± SEM obtained from four independent experiments

millimolar concentrations of H_2S inhibit largely oxygen consumption in colonocytes (Beaumont et al. 2016), we decided to test the effect of millimolar concentrations of NaHS on the paracellular permeability using the model of Caco-2 cell monolayers grown in a transwell filter. Unexpectedly, even at those millimolar concentrations, no significant effect of NaHS was recorded after 24 h treatment, indicating that no major adverse effects of sulfide on epithelial paracellular permeability were associated with the energy metabolism alterations in these experimental conditions. This latter result may be linked, at least partly, to the fact that hydrogen sulfide is volatile in culture media, and to the adaptive capacities of colonocytes that allow these cells to deal with prolonged sharp increase of the H_2S luminal concentration (Beaumont et al. 2016; Leschelle et al. 2005).

The present study with experiments performed both in the presence and absence of PACs reveals new interesting characteristics of the interactions of sulfide with the colonocyte mitochondria. Firstly, the initial rapid stimulating effect of 65 µM NaHS on O_2 consumption by colonocytes strongly suggests a rapid diffusion of H_2S through the colonocyte peripheral membranes followed by rapid binding with the first and rate-limiting enzyme of the sulfide-oxidizing unit, namely sulfide quinone reductase (SQR) (see Fig. 4). However, most importantly, this very short-term stimulation observed with 65 µM NaHS was always of lesser extent than the one observed with 20 µM NaHS (Fig. 1), suggesting also a slower binding of the unmetabolised H_2S to the mitochondrial cytochrome c oxidase and partial inhibition of cell respiration. In such condition, even after 5 min incubation, the O_2 consumption remained at only 30% of the normal O_2 consumption, indicating uncomplete hydrogen sulfide oxidation because of cytochrome c oxidase activity inhibition (Fig. 4). Then, knowing that the inhibition of the cytochrome c oxidase activity is reversible (Cooper and Brown 2008), we can reason that in the presence of a fixed luminal concentration of H_2S, the oxygen consumption by colonocytes would remain inhibited as long as the sulfide concentration in the cells is maintained above the one that poisons cell respiration. From that point of view, any luminal compounds which neutralize sulfide will decrease the free luminal concentration of this gas below deleterious concentrations, thus possibly protecting colonocytes from an "acute metabolic assault" (Fig. 4). Zinc chloride has already been reported as able to bind sulfide thus protecting colonocytes from inhibition of respiration (Mimoun et al. 2012).

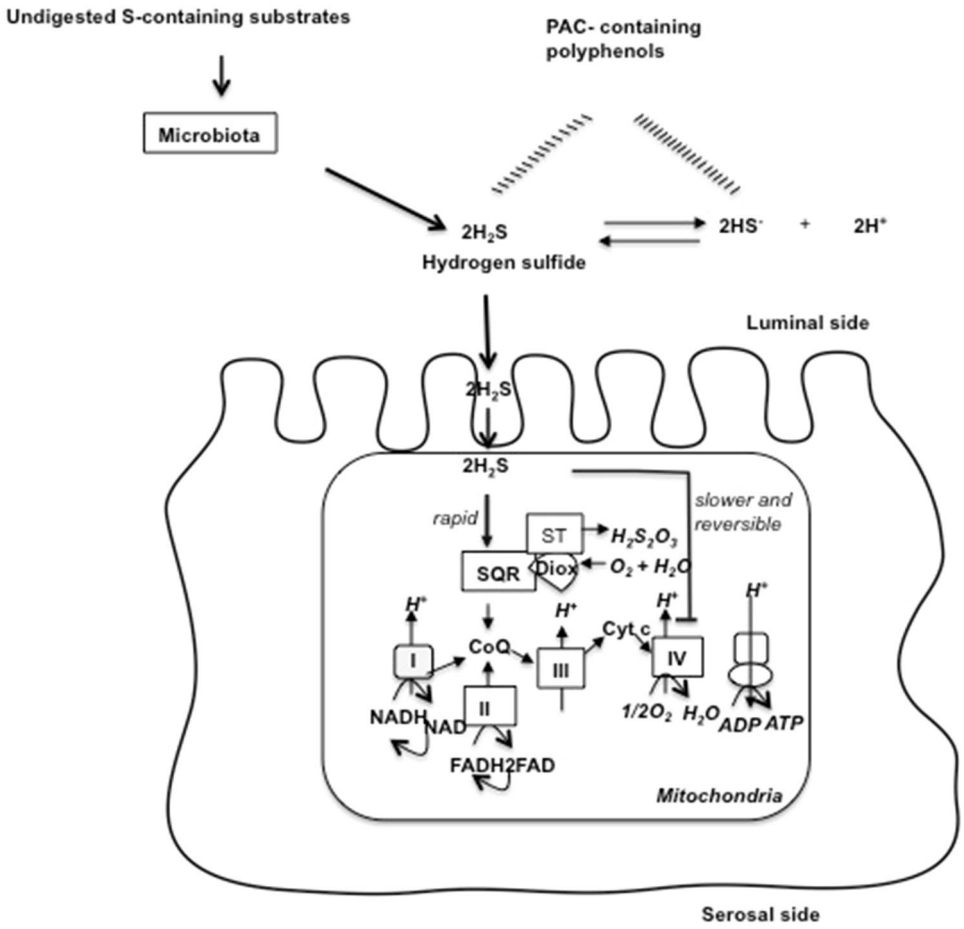

Fig. 4 Schematic representation of the impact of proanthocyanidin-containing polyphenol extract on the effect of hydrogen sulfide on colonocytes. Hydrogen sulfide (H_2S) is produced by the microbiota from several dietary and endogenous sulfur containing compounds, notably L-cysteine released from undigested or partially digested dietary and endogenous proteins. H_2S diffuses through the colonocyte apical membranes. In colonocytes, at low concentrations, H_2S binds rapidly to sulfide quinone reductase (SQR), the first enzyme of the mitochondrial sulfide-oxidizing unit which allows the rapid oxidation of H_2S into thiosulfate ($H_2S_2O_3$) with concomitant oxygen consumption and ATP production. At higher concentration, part of H_2S binds rapidly to SQR, while the remaining compound binds slower and reversibly to the cytochrome c oxidase (complex IV), leading to decreased oxygen consumption and thus ATP production. By interacting with extracellular H_2S, proanthocyanidin (PAC)-containing polyphenol decreases the concentration of bioactive H_2S, thus facilitating its detoxification by the sulfide oxidation unit and limiting its inhibiting effect on cell respiration. This scheme is adapted from Blachier et al. (2017)

Conclusion

To the best of our knowledge, our study is the first one which reports capacity of PAC-containing polyphenol extracts for decreasing sulfide deleterious effect on colonocyte respiration, notwithstanding there are some limitations of our study which are worth detailing. Firstly, all these experiments were performed in vitro and thus, the proof of concept presented here requires validation in an in vivo design. Secondly, it is known that polyphenols can be partially metabolized by the colonic microbiota (Appeldoorn et al. 2009), and thus it would be desirable to also test, in future experiments, the capacity of bacterial metabolites derived from polyphenols to bind sulfide and prevent their deleterious effects.

With these reservations in mind, our study should encourage further studies on phytochemicals which are transferred from the small to the large intestine and possess capacity for binding to deleterious compounds produced in excess by the colonic microbiota. Such binding may proof to be useful for participating in the maintenance of the colonic epithelium health in an unfavorable luminal environment (Blachier et al. 2017).

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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