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Review

Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms

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ABSTRACT

Undigested food is fermented in the colon by the microbiota and gives rise to various microbial metabolites. Short-chain fatty acids (SCFA), including acetic, propionic and butyric acid, are the principal metabolites produced. However, most of the literature focuses on butyrate and to a lesser extent on acetate; consequently, potential effects of propionic acid (PA) on physiology and pathology have long been underestimated. It has been demonstrated that PA lowers fatty acids content in liver and plasma, reduces food intake, exerts immunosuppressive actions and probably improves tissue insulin sensitivity. Thus increased production of PA by the microbiota might be considered beneficial in the context of prevention of obesity and diabetes type 2. The molecular mechanisms by which PA may exert this plethora of physiological effects are slowly being elucidated and include intestinal cyclooxygenase enzyme, the G-protein coupled receptors 41 and 43 and activation of the peroxisome proliferator-activated receptor γ, in turn inhibiting the sentinel transcription factor NF-κB and thus increasing the threshold for inflammatory responses in general. Taken together, PA emerges as a major mediator in the link between nutrition, gut microbiota and physiology.

1. Introduction

The link between dietary intake and physiology is long-recognized as evident from the age-old adage "you are what you eat" and other colloquial –but not entirely unsupported– expressions like "Feed a cold, starve a fever" highlight the recognition within the general population of the connection between nutrition and pathology [1]. Indeed many investigators now assume that environmental factors, e.g. dietary patterns, are as important as the genetic makeup in the contribution for the phenotypes of individuals, especially the propensity for disease. Especially so-called prebiotic diets in general and long-chain O-linked oligofructoses (fructans) in particular [2], are associated with general better health, and indeed generation of genetically modified crops capable of producing large quantities of fructans has become an industry by itself [3]. Although many of the molecular and immunological aspects by which dietary components could influence physiology [4] or even pathology [5] have been uncovered it is fair to say that the exact mechanism by which nutritional modification of metabolism of the microbiota interacts with the host is still largely obscure at best [6]. Here we argue that propionic acid is an important link in the nutrition, microbiome and physiology triangle.

A large body of research indicates that dietary fiber has a profound effect on general health. These include the increase of post-meal satiety and the decrease of body weight, fat mass and the severity of diabetes [7–12]. These effects may be contributed via the fermentation of dietary fiber by the colonic microbiota and in turn the production of various metabolites, such as SCFA, which are absorbed by the host and influence its energy homeostasis [8,13]. The microbiota also influences the development of obesity and its associated diseases [14]. This influence depends on microbiota composition within an individual, which seems to be defined via a combination of environmental and genetic factors that could favor either obese or lean phenotype [15,16].

Fermentation of dietary fiber by the colonic microbiota is the primary source for the production of SCFA, i.e. acetic, propionic and butyric acid (Fig. 1). SCFA have recently attracted considerable interest, because of their possible importance for host health. Most of the studies (and reviews) on the interaction of SCFA and mammalian physiology, however, concentrate either solely on the role of butyrate alone [17], or on the effects of complex SCFA mixtures, PA mainly being investigated in the context of ruminant physiology in general, and on its role in liver physiology and metabolism in particular. Although in ruminants PA and other SCFA are the major source of energy (PA is the primary precursor for glucose production in ruminants), whereas glucose is the major source for humans, there

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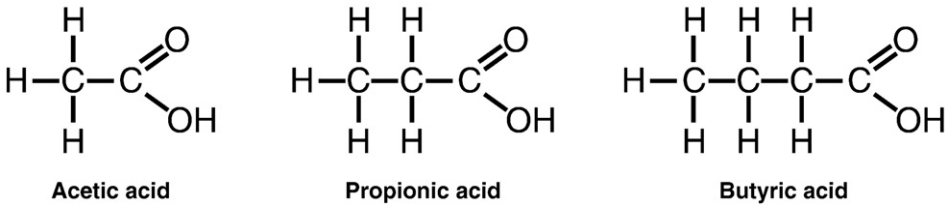

Fig. 1. The molecular structure of the short-chain fatty acids, acetic, propionic and butryric acid.

is good evidence, as we discuss below, that PA is an important factor in human physiology as well.

2. Propionic acid metabolism

2.1. Propionic acid occurrence and production

PA occurs naturally in a few food products; for example PA is present in low quantities in milk and relatively higher levels in dairy products such as yogurt and cheese, obviously due to bacterial fermentation, mostly by propionibacteria [18,19]. It is available also as a preservative (E280) in food products, since it has anti-fungal and anti-bacterial effects [20,21]. These food-sources however, do not lead to significant amounts of PA in the human circulation as quantities involved pale in comparison to the primary natural source for PA in humans, which is derived from the fermentation of undigested food by the colonic microbiota [22]. In the colon, PA is produced by fermentation of polysaccharides, oligosaccharides, long-chain fatty acids, protein, peptides and glycoprotein precursors by the anaerobic colonic microbiota (Fig. 2) [23], although in quantitative terms indigested carbohydrates, such as dietary fiber and resistant starch, represent the major source for PA production. These substrates are mainly composed of hexoses and pentoses, which are fermented by the microbiota through a variety of pathways. Hexoses are broken down mainly via the glycolytic pathway or they are converted to 6-phospho-gluconate and then metabolized via the pentose phosphate pathway, the same pathway through which pentoses are metabolized. Pyruvate is the principal metabolite of these fermentation reactions; however very little pyruvate is found in the colon, because it is converted to a series of end products, such as PA and other SCFA. PA is produced from pyruvate via two main pathways: i) Succinate decarboxylation pathway, in which CO_2 is fixed to pyruvate to form

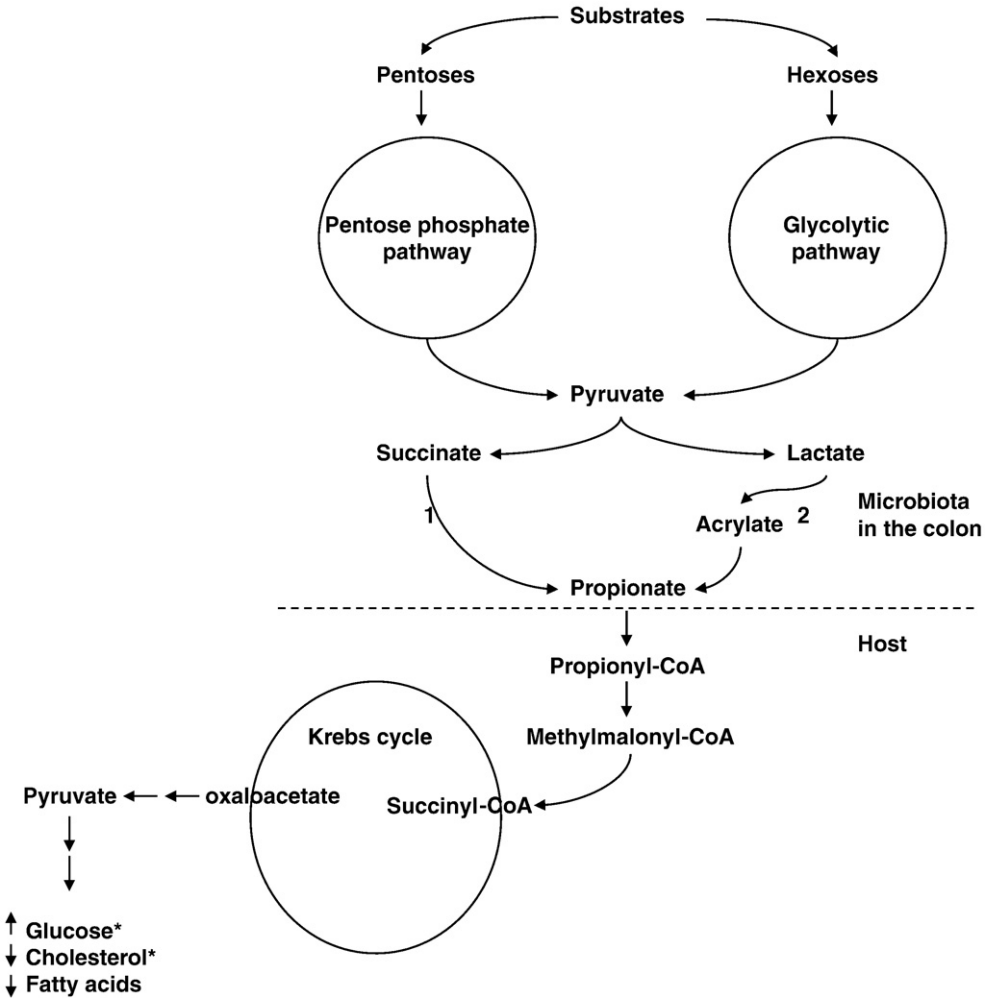

Fig. 2. PA metabolism. Undigested food that reaches the colon is broken down by the microbiota into hexose and pentose molecules, which are further metabolized into pyruvate. Pyruvate is converted into PA via (1) succinate decarboxylation or (2) acrylate pathways. PA is absorbed by the host, where it induces the production of glucose and suppresses the production of fatty acids and cholesterol. *; the effects of PA on the production of glucose and cholesterol in humans are controversial.

succinate, which is subsequently decarboxylated to propionate; and ii) Acrylate pathway, in which PA is produced from acrylate with lactate as a precursor [24,25].

Despite the technical and ethical issues involved, a few studies measured the quantities of PA and other SCFA in human colon and portal vein. The PA quantity in the human colon was reported to be 20 mmol/kg and to depend on the balance between production and absorption [22,26], the type of microbiota, the quantity and the type of the substrate and the gut transit time [24]. In contrast to butyrate, the majority of the PA produced in the colon is absorbed, passes the colonocytes and the viscera, and drains into the portal vein. PA can be partially metabolized by colonocytes; however, the quantity that is utilized by visceral tissues, e.g. visceral adipose tissue, has not been examined yet. The quantity of PA in the portal vein in non-fasting humans was demonstrated to be approximately 0.1 mM; while it was 3-fold lower in blood derived from fasting humans [22,27,28]. Around 90% of PA quantity is metabolized by the liver and the rest is transported into the peripheral blood [24], where its quantity in humans was reported to be 6 μM [27,29–31], far in excess of that of butyrate, but lower than acetate. High PA quantities also occurred in certain pathological situations, such as gingival inflammation and propionic acidemia [32,33]. Together, it is fair to say that propionic acid is likely to interact with host physiology.

2.2. Propionic acid and glucose metabolism

PA metabolism was extensively studied in ruminants where it is a major glucose precursor [34–36]. Briefly, PA is converted to propionyl-CoA and enters the Krebs cycle at the level of succinyl-CoA (Fig. 2). This leads to oxaloacetate elevation, from which a large amount, in the liver, is converted to glucose. PA is the main source for glucose production from SCFA, while cellular biochemistry does not allow acetate, butyrate and longer chain fatty acids to contribute to net synthesis of glucose. The only pathway for fatty acids with even numbers of carbon atoms is via acetyl-CoA and Krebs cycle. When acetyl-CoA enters the cycle the 2 carbon atoms are lost as CO_2, so no net gain of oxaloacetate occurs [36]. Biotin and vitamin B12 are essential factors for the anabolic effect [37]. This suggests that reducing biotin and vitamin B12 increases the PA quantity as under these conditions PA is no longer converted to glucose and consequently deficiency in these factors lead to reduced energy uptake of the host organism. Indeed, in severe B12 deficiency in sheep, a reduction in feed intake and an elevation of the PA quantity in blood were found [38]. Much less is known about the effect of PA on glucose production in humans (which anyway rely on other sources to maintain glucose levels), and existing data are inconsistent [24,39,40].

2.3. Propionic acid and cholesterol/fatty acid metabolism

Diets supplemented with PA exhibit hypocholesterolemic effects in animals [41,42]; however, in humans, the effect of PA on cholesterol levels was inconclusive [24]. Recently, evidence has been accumulating that PA has fatty acid-lowering effects. In animals, PA decreased fatty acid production and quantity in the liver [43,44] and in plasma [41,45]. It seems that the effect of PA on fatty acid levels in humans is similar to that in animals. Apart from inhibiting the production of fatty acids in liver, the observed decreases in fatty acid levels by PA probably also are derived from inhibition of lipolysis and the induction of adipogenesis in adipose cells and tissue *in vitro* [46,47] and *in vivo* data showed that PA receptor (GPCR41)-deficient mice exhibited less adiposity compared to the wild type mice [48]. Moreover, leptin, which is an adiposity marker, was induced by PA treatment of human and mouse adipose tissue [49,50]. In view of the established role of circulating fatty acids in vascular pathology, these effects may well contribute to the beneficial effects of diets associated with increased PA production.

3. Propionic acid's physiological roles and potential applications

3.1. Inflammation

It is now well established that the gastrointestinal tract is permanently in a state of low-grade inflammation [51]. Dietary fiber intake, which is the primary substrate for PA production, has been associated with a reduction in low-grade inflammation [8] and in intestinal inflammatory pathogenesis [52–54]. PA, as we mentioned earlier, has anti-fungal and bacterial effects [55]. Moreover, PA has moderate inhibitory activity on cyclooxygenase [56], a major enzyme in the production of pro-inflammatory eicosanoids [57]. *In vitro* studies have provided considerable evidence that PA has anti-inflammatory properties, apart from its influence on eicosanoid metabolism. PA possesses anti-microbial activity against the colonization of the gastrointestinal tract by pathogenic bacteria such as *Salmonella* [21], via, for example, the inhibition of the expression of the invasion genes in *Salmonella typhimurium* [58], which are essential to invade and penetrate the intestinal epithelium. However, it seems that the inhibition of inflammation by PA depends on several factors, such as its concentration, the pH of the extracellular *milieu* and the reason of inflammation, as we describe below.

The proliferation of human and animal lymphocytes activated by a mitogen is inhibited by PA treatment [59,60]. In contrast, Cavaglieri et al. reported that PA did not influence the proliferation of activated lymphocytes [61]. This discrepancy might be a consequence of the PA concentration employed in the various studies; while Cavaglieri et al. used a 2 mM concentration, Wajner et al. [60] demonstrated that PA concentrations above 2.5 mM were required to reduce the proliferation of activated lymphocytes. In addition, Curi et al. [59] found that PA concentrations equal to or more than 3 mM showed a remarkable high inhibition of lymphocyte proliferation, whereas 2 mM produced only a mild reduction in lymphocyte proliferation. Likewise, we have shown [49] that 3 mM PA or higher inhibited the production of the pro-inflammatory cytokine, resistin, by human adipose tissue. Thus at high concentrations PA can directly inhibit the adaptive lymphocyte compartment, but comparison to the PA concentrations present in the portal and peripheral blood makes the physiological relevance of these observations doubtful outside the visceral compartment itself.

Chemically speaking PA is an acid and because of its membrane-permeable nature higher concentrations of PA may directly exert effects on host cell physiology by altering the intracellular pH. At bay with this notion is that the active cellular control of pH is pretty strict and that alternative modes of action seem more likely. It was a concern however in the studies of Brunkhorst et al. [62] and Le Poul et al. [63], who, when trying to demonstrate that PA-induced effects were mediated by activated G-proteins, included controls to show that the effects observed were not due to extracellular or cytoplasmic pH. Furthermore, in our own studies on PA biological activity [49], no evidence of a role for pH-modulation in PA effects was found. Conversely, however, there are good data that environmental pH determines whether or not PA can exert anti-inflammatory actions. Mills et al. [64] demonstrated that PA at pH 5.5 inhibited the oxidative burst and phagocytosis of bovine neutrophils; while, at pH 6.7 it was stimulatory. As most physiological actions of PA can be expected to occur at a more alkaline pH, the physiological relevance of these anti-phagocytotic actions of PA is uncertain. Wajner et al. [60] and Mills et al. [64] indicated that the type of stimulant could influence the concentration of PA that is needed to suppress inflammation. In other words the cause of inflammation, e.g. bacteria, cytokines, adipokines, fatty acids and others can determine whether PA can exert its immunosuppressive properties, or not. This may clarify the inconsistency of neutrophils response to PA. Indeed, Vinolo et al. [65] showed that PA had no effect on phagocytic activity and ROS production in rat neutrophils and thus primary efficacy in the innate immune system is not targeted by PA, although subsequent changes in innate immune cell gene expression might occur: Tedelind et

al. [66] demonstrated that PA inhibited LPS-stimulated TNF-α release by human neutrophils. Moreover, a similar phenomenon was shown in endothelial cells; on the one hand Zapolska-Downar and Naruszewicz [67] demonstrated that PA inhibited the expression of adhesion molecules in cytokine-activated human endothelial cells. On the other hand Miller et al. [68] found no influence of PA on non-activated endothelial cells and *in toto* a picture emerges that direct pathogen clearance by the innate immune system is not majorly influenced by PA (which might be in line with its beneficial rather than its adverse effects on inflammatory bowel disease, e.g. [69]). Effects in these cells are limited to modulation of gene expression.

In vivo, however, results obtained with SCFA effects on inflammatory diseases of the gut are somewhat disappointing, although there is no single study in which PA alone was investigated *in vivo*. Various studies revealed that enemas containing SCFA improved the clinical and inflammatory parameters of ulcerative colitis [70,71]. In contrast, other studies found only trends toward clinical improvement of ulcerative colitis [72,73]. The outcome of the intervention studies for diversion colitis was also inconclusive [74,75]. The equivocal results in human intervention studies may partly be explained by the differences in the setup of these studies, e.g. treatment duration, SCFA concentration and volume, and the small number of patients. Thus a convincing demonstration of efficacy of SCFA in treating these diseases has not been revealed and further studies are necessary to unravel this. Notably, these studies are not reflecting the effects of PA alone, and according to the *in vitro* studies, it is possible that enemas containing PA alone could improve the clinical and inflammatory parameters of gut inflammatory diseases. *In vivo*, the effects of PA on other inflammatory diseases, such as low-grade inflammation, remain also unknown. However, *in vitro* we (unpublished data) demonstrated that PA counteracts the inflammatory reaction in human adipose tissue, which is a primary source for obesity induced low-grade inflammation.

3.2. Insulin sensitivity

Inhibitory effects of PA on free fatty acids metabolism and inflammation, which we mentioned earlier, suggest that PA could be a potential therapeutic agent to improve insulin sensitivity; since free fatty acid-elevation has been demonstrated to cause inflammation [76,77] and vice versa [78,79] and both lead to insulin resistance [79–83]. We observed a PA-dependent increase in GLUT-4 in primary human adipose explants, which also point in this direction. Moreover, evidence has been described for induction of lipogenesis and adipogenesis and inhibition of lypolysis [46,47]. Furthermore, butyrate prevents and reverses diet-induced insulin resistance in mice [84]. Taken together, good evidence exists that systemically relevant concentrations of PA might exert a beneficial effect on insulin sensitivity in the adipose compartment and thus PA may well form the elusive link between pre- and pro-biotic supplementation and its beneficial effects on obesity-related diseases.

3.3. Food intake and satiety

A substantial amount of evidence has shown that absorbed PA causes satiety and reduces food intake in ruminants [85–87]. So far, in humans only two studies investigated the role of PA on satiety and both demonstrated that dietary supplementation of PA caused satiety [88,89]. The underlying mechanism remains under debate. Studies in ruminants revealed that the mechanism by which PA conveys its effect on satiety is not simple and integrates neuronal, endocrine, paracrine and autocrine pathways between and within organs and tissues. One of the suggested mechanisms was hypertonia [90]; however, further work [91] disproved that by showing that PA reduced feed intake more than equimolar acetate, mannitol, or saline. Anil and Forbes [86] reported in animal studies that receptors existed in the liver that were sensitive to PA and that surgical sectioning of the hepatic nerve plexus around the wall of the hepatic artery abolished the satiety effect of PA. Further splanchnic blockade with anaesthetic, splanchnotomy and hepatic vagotomy, as well as total liver denervation, were shown to abolish the reduction in feed intake by portal infusion of PA, although as these procedures target innervation of the viscera *in toto*, other organs/tissues apart from the liver may be involved as well [92]. Indeed vagal-innervated visceral adipose tissue is a primary endocrine tissue that produces adipokines, which regulate satiety and energy homeostasis. It was shown that PA induced the production of the satiety hormone leptin by human, mouse and ruminant adipose tissue [46,49,50]. *In vivo*, in mice, PA administered via gavage induced leptin but did not reduce food intake. The latter was suggested to be due to gavage-induced stress [46], since in the same study, food intake was reduced in mice fed chow containing 3% of sodium propionate in diet as compared to controls fed equimolar sodium chloride. Leptin is a potent anorexigenic hormone that suppresses food intake through the central nervous system [93] and vagal neurons [94]. This suggests that visceral adipose tissue is another potential mechanism to regulate the satiety induced by PA infusion and this notion would fit well with the direct effects of PA on the adipose tissues physiology, in particular with respect to release of adipokinetic hormones. Finally, food intake could be inhibited by adverse internal cues. For example, it was shown that the ingestion of a high quantity of PA by ruminants induced strong food aversions apparently due to nausea and discomfort [95–97].

4. Potential adverse effects

4.1. Propionic acidemia

High quantity of PA could also have potential adverse effects. This has been described in the metabolic disorder propionic acidemia, which is caused by defects in propionyl-CoA carboxylase enzyme [98]. It is a biotin-dependent mitochondrial enzyme involved in the metabolism of odd-chain fatty acids and the amino acids methionine, threonine, isoleucine and valine by converting propionyl-CoA to methylmalonyl-CoA. This defect of the enzyme leads to increased amounts of PA and other acids and toxins such as ammonia, which causes food refusal, vomiting, immunosuppression, mental retardation, predisposition for infections and sepsis [99,100]. However, [101] succeeded to improve these symptoms by liver transplantation, while minimal effects were shown on PA quantity. This suggests that these symptoms are not due to high PA quantity per sé, but rather due to accumulation of various metabolites. Another evidence to support this notion is derived from the fact that another organic acidemia (branched chain academia; [99]) causes the same symptoms, however without propionic acid accumulation [102,103].

4.2. Autism spectrum disorders and effects on neurobehavioral development

Autism is a disorder of neural development including development deficiencies of language and social interaction skills, appearance of repetitive and disordered movements [104], hyperactivity, sensory disturbances, restricted interests and sometimes self injury [105,106]. Very recently and interestingly, it was demonstrated that intraventricular infusions of PA caused behavioral and brain abnormalities in rats similar to those seen in humans suffering from autism via probably altering brain fatty acid metabolism [107–110]. Rather large amounts have been used to induce the symptoms (e.g. 4 μl of 0.26 M solution). It therefore remains to be seen that the concentrations that are produced by the microbiota lead to similar effects. There is also some evidence that high levels of PA can induce oxidative stress in various brain regions: some brain regions (neocortex, hippocampus, thalamus, and striatum) of rats treated with PA (intraventricular infusions of 4 μl 0.26 M PA per animal) showed increased lipid and protein oxidation accompanied by decreased total GSH in the

neocortex. Catalase activity was decreased in most brain regions suggestive of a reduced antioxidant enzymatic activity [111].

High levels of subcutaneously added PA in rats (around 1.5–2 μmol/g body weight) caused slight but significant delays in the day of appearance of hair coat and eye opening, indicating an effect of PPA on the development of physical parameters [112]. In behavioral tests PA-treated rats did not habituate to open fields, and presented a lack of retention of the shuttle-avoidance task. The levels of PA used were comparable to those of human propionic acidemia (blood concentrations 1–5 mmol/l, brain concentrations 1 μmol/g). The results suggest that early postnatal PA administration to rats alters normal development and induces long-term behavioral deficits.

4.3. Gingival inflammation

Gingival inflammation is an inflammatory process in the gum tissue of the mouth, which is caused by the release of short-chain fatty acids in millimolar concentrations by periodontal bacteria. It was shown that PA is the major metabolite produced *in vitro* (by *Prevotella loescheii*) [113] and *in vivo* [114]. In the *in vivo* study it was further shown that the subgingival concentration of PA was more than 10-fold higher (9.5 mM) in severely diseased patients than in mildly diseased patients (0.8 mM), while it was undetectable in the healthy sites of the mouth of the same patients. The same group demonstrated in a different study [115] that applying PA mixed with other short-chain fatty acids into gingival margins of designated teeth induced gingival inflammation. The PA effect on gum tissue seems contradictory to the pronounced anti-inflammatory effects of PA that we discussed earlier; this suggests that PA effect on inflammation depends on the target tissue or type of inflammation.

5. Molecular mechanisms

5.1. Cyclooxygenase inhibition

As mentioned, PA has moderate inhibitory activity on cyclooxygenase [56], a major enzyme in the production of pro-inflammatory eicosanoids [57] and indeed several non-steroidal anti-inflammatory drugs (NSAIDs), such as fenoprofen, flurbiprofen, ibuprofen and naproxen, are PA analogues [116]. In view of the concentrations of PA in the colonic intestine, a direct anti-inflammatory effect of PA via cyclooxygenase is to be expected and this is a likely mechanism for the down-regulation of low-grade mucosal inflammation by prebiotic diets. Furthermore, both prebiotic diets [2] and cyclooxygenase inhibition [117] are associated with reduced incidence of colorectal cancer and thus PA-dependent inhibition of cyclooxygenase may well be implicated in this effect as well. This notion is strongly supported by the observation of Comalada et al. [118] that bacterium-derived SCFA seem directly responsible for anti-carcinogenic effects of pre/pro-biotic supplementation in preclinical models of colon cancer. Thus, direct modulation of the colonic production

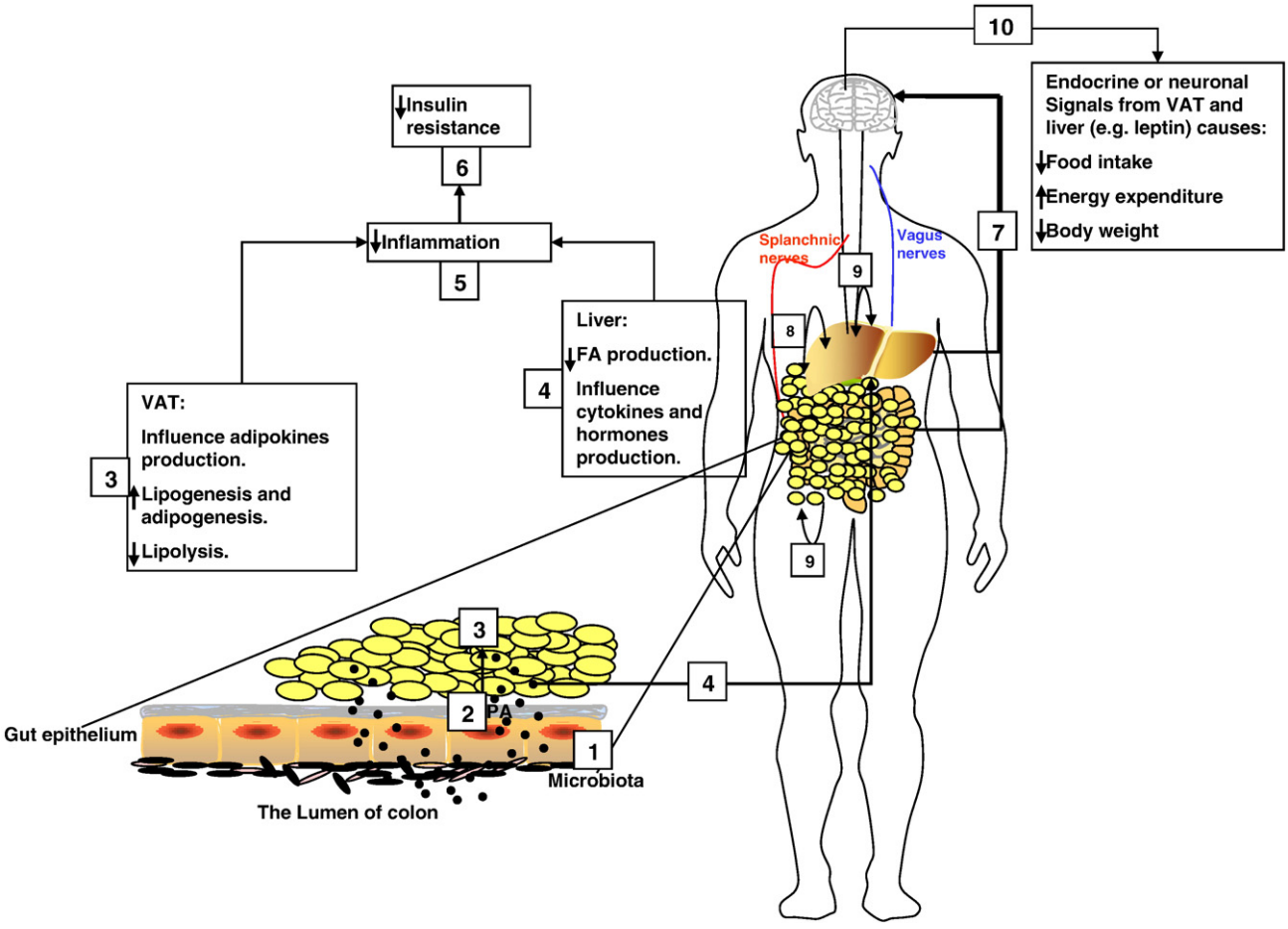

Fig. 3. Schematic representation of a hypothetical model to explain the effects of PA. PA is produced by the fermentation of undigested food by the colonic microbiota (1). PA passes the gut epithelium (2) and reduces the production and the release of FA from VAT (3) and liver (4). This might lead to inhibition of inflammation (5) and consequently to insulin sensitivity (6). In addition, PA influences the production of hormones by VAT (3) and liver (4), which in turn initiates endo- (7), para- (8) and auto-crine (9) and neuronal pathways (via vagus and splanchnic nerves) to reduce food intake and to influence other metabolic effects (10).

of pro-inflammatory cyclooxygenase-derived eicosanoids may be an important factor by which PA suppresses intestinal immunology.

5.2. G-protein coupled receptors (GPCR)

In 2003, three independent studies found that PA was the most potent and efficacious ligand for GPCR41, and equipotent with acetate for GPCR43 [63,119,120]. GPCR41 and GPCR43, like other GPCRs, are linked to GTP-binding proteins (G-proteins). G-proteins are attached to the cytoplasmic face of the receptor, where they serve as relay molecules functionally coupling the receptors to their downstream targets. G-proteins are classified into four major classes, namely Gs, Gi/o, Gq/11 and G12/13. Each of them is specific for a particular set of GPCRs and a particular set of downstream targets. GPCR41 was shown to initiate its signaling through coupling with the Gi/o family of G-proteins, as evident from the absence of a response when transfected cells were treated with a Gi/o-protein-inhibitor [63,119]. On the other hand, GPCR43 was shown to be coupled to both Gi/o and Gq families of G-proteins [63,119,120]. Notably, neither GCR41 nor GPCR43 has been tested for its ability to interact with a full panel of G-proteins and families. GPCR43 was found to be expressed at high levels and GPCR41 was expressed to a lesser extent in various immune cells [119], providing an obvious link between the immune system and microbial PA production. Very recently Maslowski et al. generated GPCR43 knockout mice and established the importance of GPCR43 as an anti-inflammatory chemoattractant receptor [121]. In this study, GPCR43 knockout mice showed exacerbated inflammation in models of inflammatory diseases, i.e. colitis, arthritis and asthma. Wild type germ-free mice, which are devoid of bacteria and therefore produce little or no SCFA, showed a similar dysregulation of certain inflammatory responses. Furthermore, acetate supplementation in drinking water for germ-free wild type mice produced a reduction in inflammation in the same disease models. As propionic acid is one of the two SCFA to reach significant concentrations in the circulation under normal conditions, these experiments strongly support the role of propionic acid production by the microbiota as an important anti-inflammatory mechanism.

Despite the dramatic phenotype of the GPRC43 KO, also GPCR41 might still turn out to be an important contributor to PA effects in physiology. Both receptors are expressed by human adipose tissue [46,49,50,63,119] leading to adipogenesis and inhibition of lipolysis in mouse adipocytes via GPCR43 [46,47] while induction of leptin production, a marker for adiposity, occurs through GPCR41 [50]. *In vivo*, GPCR41 was responsible for gut microbiota induced-adiposity in mice [48]. Thus the exact contribution of these two receptors to total PA functionality in the body requires further investigation.

5.3. PPARγ and NF-κB

The nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) is a ligand activated transcription factor, in turn inhibiting the sentinel transcription factor, nuclear factor-kappa B (NF-κB) and thus increasing the threshold for inflammatory responses in general. Like chemically-related molecules (other fatty acids and anti-diabetic drugs, e.g. thiazolidinediones [122]), PA can activate PPARγ (our own unpublished results). PPARγ agonists were shown to inhibit the expression of genes regulated via NF-κB; this was through PPARγ-dependent and independent mechanisms [123–126]. PA down-regulated the activity of NF-κB in human colon adenocarcinoma cell line and endothelial cells [66,67,127], and direct interaction with PPARγ is thus a likely mechanism, providing yet another level in which immunity and PA may interact.

6. Conclusions and perspectives

PA has long been underestimated in terms of its physiological impact, most studies addressing the effects of butyrate and to a lesser extent acetate. Although the latter two are probably of principal importance in intestinal physiology, systemically they are less likely to have significant effects. PA is mainly produced by the fermentation of indigested food by the microbiota in the colon, but can reach the blood compartment and the adipose tissue, where it reduces fatty acid levels in plasma via inhibition of lipolysis and induction of lipogenesis in adipose tissue and suppression of fatty acid production in liver. We speculate that this is a major mechanism by which prebiotics exert their effects on obesity-related disease. Lowering plasma fatty acids may be especially important, since it is known that high plasma fatty acids cause inflammation. In addition, it is known that fatty acids and inflammatory factors cause insulin resistance [79–83], so the PA-lowering effects on fatty acids and inflammation might lead to the observed improvement in insulin sensitivity. These beneficial effects are usually associated with a reduction of body weight and indeed it has been demonstrated that PA inhibits food intake and increases the duration of satiety via the integrations of neuronal, endocrine, paracrine and autocrine pathways between and within organs and tissues. As depicted in Fig. 3, both adipose tissue and liver have been shown to be targets for PA. For example, PA influences the production of hormones by adipose tissue, such as the induction of leptin. This might contribute to the suppression of food intake, since leptin is a potent anorexigenic hormone that suppresses food intake through receptors expressed in the central nervous system [93] and vagal neurons, which innervates visceral adipose tissue. PA as mechanism for the interaction between microbiota and adipose tissue would provide a new paradigm in our view of humans as metaorganisms, and further research into this notion is certainly called for.

PA mediates its effects via various molecular mechanisms, which are now emerging. Directly, it influences pathogen physiology and down modulates intestinal cyclooxygenase activity, via the circulation it can stimulate its receptors GPCR41 and GPCR43 and anti-inflammatory effects via the associated signal transduction pathways. A last level is the inhibition of NF-κB through PPARγ. However, many questions remain. For example, why are there several molecular targets for PA and how do they interact with each other to convey PA signaling? Also the reason why a lipophilic membrane-permeable compound should have any membrane receptors at all remains unclear [128,129], but this holds true for many other lipids as well. Why does PA have two GPCRs? Is the function of GPCR41 different from that of GPCR43, and if not, then why are these two receptors expressed, in some cases, in the same cell type (e.g. adipocytes)? Finally, the affinity for PA is low and PA receptors need supraphysiological concentration of PA to mediate its effects. This raises the question whether GPCR41 and GPCR43 are the effective receptors for PA under normal physiological conditions. It is possible that PA as well as other SCFA act as surrogate agonists rather than endogenous agonists for GPCR41 and GPCR43, or it is possible, but less likely, that these receptors are activated in certain pathological situations when the PA concentration is unusually high, such as gingival inflammation and propionic acidemia. Disregarding these open questions, it is clear that PA is an important part of the communication between the microbiota and the physiology of the host and more recognition of this notion may prove useful for designing improved functional foods.

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