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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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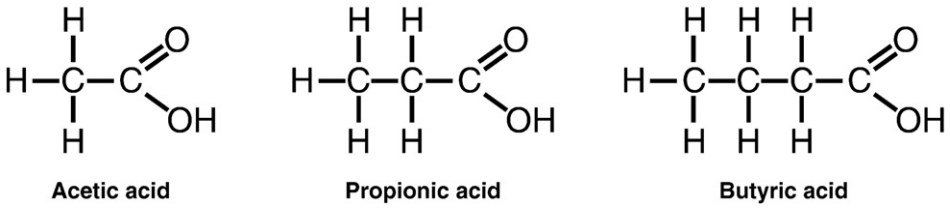

Fig. 1. The molecular structure of the short-chain fatty acids, acetic, propionic and butryric acid.

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

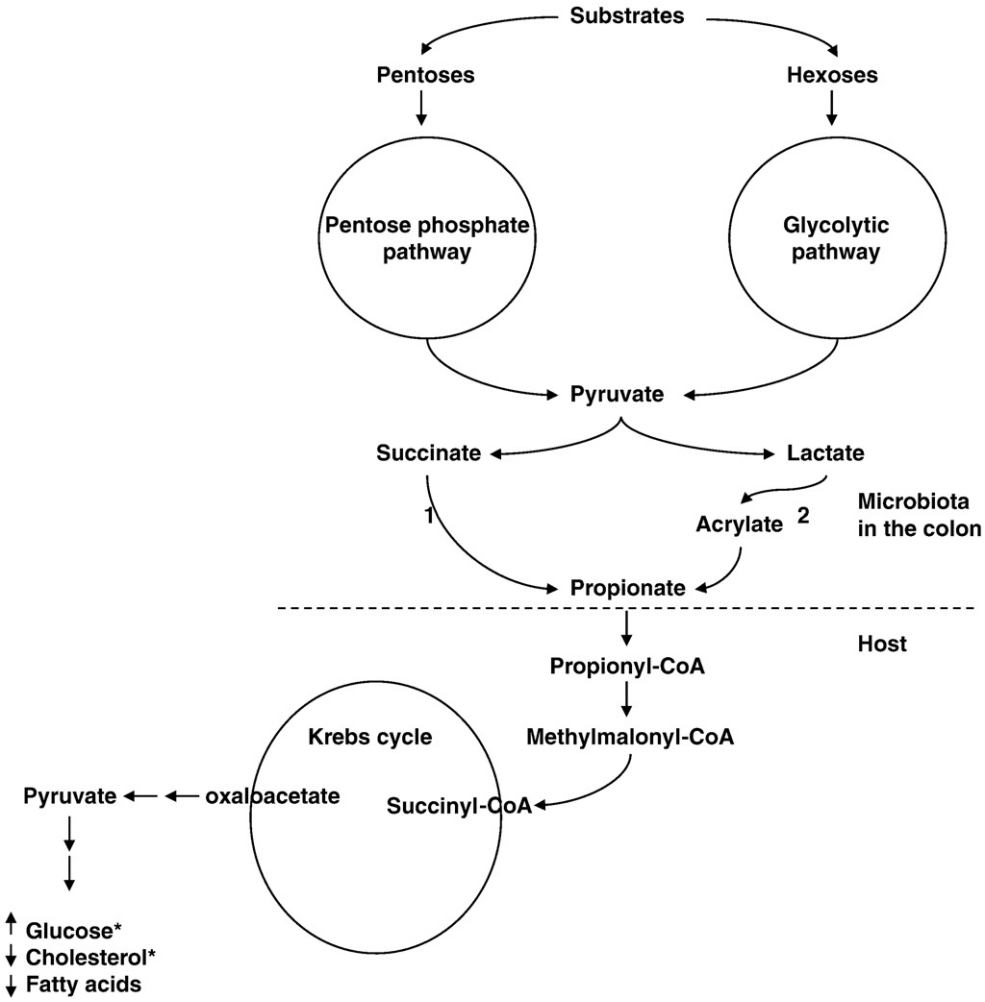

Fig. 2. PA metabolism. Undigested food that reaches the colon is broken down by the microbiota into hexose and pentose molecules, which are further metabolized into pyruvate. Pyruvate is converted into PA via (1) succinate decarboxylation or (2) acrylate pathways. PA is absorbed by the host, where it 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.