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Review

The effects of short-chain fatty acids on the cardiovascular system

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ABSTRACT

The development of cardiovascular diseases is often attributable to loss of endothelial functions of the vascular tissue or to decreased contractile function of the heart muscle. These disturbances are often caused by imbalances in lipid and glucose metabolism. For instance, these imbalances can result in a low-grade inflammatory state of affected endothelial tissue, causing macrophages and fat-rich lipoproteins to accumulate in the subendothelial space. Short-chain fatty acids feature a regulatory function in the cellular metabolism of fatty acids, glucose and cholesterol in various peripheral tissues, both directly as well as at a genetic level. In addition, the strong expression of short-chain fatty acid receptor Ffar2 on various leukocyte populations facilitates a regulatory effect of the fatty acids on various functions of these immune cells. The immunoregulatory effect and influence on lipids, cholesterol and glucose metabolism of short-chain fatty acids can thus contribute to the development of metabolic conditions that promote preservation or recovery of endothelial functions and thereby reduce the risk of development or aggravation of cardiovascular diseases. The current review addresses the effects of short-chain fatty acids on the human cardiovascular system and investigates potential novel interventions for prevention and treatment of cardiovascular disorders using these fatty acids.

Contents

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1. Introduction

Western societies find themselves increasingly confronted with typical nutrition-related diseases, such as obesity and type 2 diabetes mellitus. These diseases often lead to increased risks for the development of several forms of cardiovascular complications [1]. Short-chain fatty acids (SCFAs) are saturated fatty acids featuring an aliphatic chain length of at most eight carbon atoms [2]. The fatty acids are formed by the colonic gut flora from dietary fibres, which manage to escape the host's enzymatic digestive systems in the small intestine. Dietary fibres that manage to reach the large intestine are available for several bacterial fermentative reactions. The fermentation of the different dietary fibres leads to an increase in concentrations of several short-chain fatty acids, especially butyrate, propionate and acetate, in the lumen of the proximal regions of the large intestine [3–5]. The fermentative reactions serve to deliver energy for preservation of the bacterial species and facilitate the excretion of strongly oxidised fatty acids. Thereafter the fatty acids can be absorbed by the enterocytes of the intestines, where they can be further oxidised for the production of energy [6–11].

The beneficial effects of short-chain fatty acids on inflammatory diseases of the intestinal tract and some forms of colon cancer are known for some time. It appears that short-chain fatty acids are able to regulate the inflammatory reactions that contribute to the manifestation of these diseases. They can therefore counteract or even prevent the development of such disorders [12–14]. Short-chain fatty acids can also be absorbed by the enterocytes forming the intestinal wall, whereupon they can be used for the production of energy [9,12,15]. However, a portion of the absorbed fatty acids will not be consumed and can be released via the basolateral membrane to the hepatic portal vein and will reach the systemic circulation after initial liver passage [16,17]. Lesser known are the beneficial effects short-chain fatty acids achieve in the prevention and treatment of various cardiovascular diseases after being absorbed in the circulation [18–20]. In spite of a strong concentration reduction of the fatty acids due to the consumption by enterocytes combined with the ability of the liver to clear large fractions of these acids, even small blood concentrations appear to induce positive effects [21,22]. The *Food and Drug Administration* (FDA) recently acknowledged the claims regarding the use of short-chain fatty acids in the prevention of cardiovascular disease [23,24].

Cardiovascular events are often the result of loss of endothelial function of the blood vessels or reduced contractivity of the cardiac muscle. Disturbance of both functions can often be ascribed to disruptions in lipid and glucose metabolism and generally appear in obese patients or patients who suffer from diabetes [25–27]. After reaching the systemic circulation, short-chain fatty acids prove to be able to regulate the metabolism of various peripheral tissues both directly and on a genetic level. Additionally, butyrate and propionate appear to have anti-inflammatory effects on several immune cells, that could be involved in the development of, for example, atherosclerosis [28–30]. This review illustrates the effects of short-chain fatty acids on the human cardiovascular system and subsequently gives an overview of intervention options in the prevention and treatment of cardiovascular diseases.

2. Synthesis of short-chain fatty acids

In people of Western societies, approximately 20–60 g of the daily intake of carbohydrates evades the digestive and absorptive system of the small intestine and manages to reach the colon [3]. The large intestine houses a large and complex bacterial ecosystem containing around 10^{10} up to 10^{11} cfu per gram wet weight. Having wet weights that vary typically between 250 and 750 g, this implies a total bacterial population close to 10^{13} cfu of the final section of the gastrointestinal tract [31]. The population comprises at least 400 different bacterial species, of which about 99% is anaerobic [3,31,32].