Studies on the bio-regulatory function of polyphenols from the viewpoints of the multiple-organs crosstalk and circadian rhythm.

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Abstract

Recently, much attention has been paid to the prevention of lifestyle-related diseases by food factors. Polyphenols are potent candidates for effective food factors to promote the human health. Among polyphenols, the author focused on flavan-3-ols, in particular procyanidins, which are contained in various plant foods, such as cacao and black soybean. Although bioavailability of procyanidins with a higher degree of polymerization are poor, many evidences have been accumulated to date on the health beneficial functions of procyanidins. For example, procyanidins-rich extracts or foods possess prevention of hyperglycemia, insulin resistance and obesity, and improvement of vascular function. However, there are few data addressing the primary target molecule of procyanidins for metabolic regulation and maintenance of homeostasis in our body. Therefore, the author hypothesized procyanidins firstly affect the digestive tract and build a multiple-organs network. It was found that procyanidins promoted secretion of an intestinal hormone (one of the incretin hormones), glucagon like peptide-1 (GLP-1) from L cells, the enteroendocrine cells. GLP-1 regulates various functions, including promotion of insulin secretion from pancreatic β cells. It is known that certain nutrients such as glucose and glutamate secrete GLP-1, but it is unclear whether non-nutrients secrete this hormone. Recently, the author found that a single oral ingestion of procyanidins prevented postprandial hyperglycemia accompanied by increasing insulin secretion through promoting GLP-1 secretion in mice. As underling molecular mechanism of anti-hyperglycemia, increased insulin by procyanidins promoted translocation of glucose transporter 4 in skeletal muscle. Interestingly, this health beneficial function of procyanidins was dependent on the degree of polymerization, and cinnamtannin A2, one of the tetramer procyanidins, showed the strongest effects. These results indicated that cinnamtannin A2 revealed an insulin-mimetic action *in vivo*, but this action was not observed *in vitro* cell culture study. The author also found that procyanidin-suppressed hyperglycemia had a suitable administration timing in mice, because GLP-1 secretion was regulated by clock gene. Procyanidin also prevented overeating through suppressing the expression of food intake factors in the brain of obese model mice, but not normal mice. This function was also regulated by increased GLP-1 secretion. Moreover, the intake of procyanidins contributed to the improvement of vascular function by promoting nitric oxide (NO) production. As for a putative underlying mechanism, GLP-1 secreted by procyanidins and increased the phosphorylation of endothelial nitric oxide synthase (eNOS) in vascular endothelial cells. In conclusion, these results indicate that procyanidins have various health beneficial functions through GLP-1 secretion from the digestive tract. Thus, bio-regulatory functions of procyanidins are regulated through the crosstalk among multiple-organs and circadian rhythm.