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tytuł rozprawy

Wpływ kwasu masłowego oraz kwasu walerianowego na regulację ciśnienia tętniczego.

The effect of butyric acid and valeric acid on the regulation of arterial blood pressure.

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Background

Increasing evidence suggests that molecules produced by gut bacteria affect the health of the host. Short chain fatty acids (SCFAs) such as butyric acid (BA) and valeric acid (VA) are produced by bacterial fermentation of dietary fiber in colon. SCFAs exert local effects on intestines as well as systemic effects after crossing the gut-blood barrier. Several studies suggest that BA affects the circulatory system, however, the mechanisms are not clear. To the best of my knowledge, hemodynamic effects of VA, have not yet been reported. The aim of the study was to assess the effect of two metabolites of gut bacteria i.e. butyric acid and valeric acid on the circulatory system.

Publication No. 1

This paper reviews research on the cardiovascular effects of microbiota-produced short chain fatty acids and methylamines. Short chain fatty acids such as acetic, propionic, butyric and valeric acids are mainly produced during bacterial fermentation of dietary fiber. SCFAs have been found to dilate blood vessels and lower blood pressure. Changes in plasma levels of gut microbiota-derived products may result from alterations in bacterial metabolism and changes in gut-to-blood penetration of the molecules. Gut microbiota-derived products may serve as mediators and markers in cardiovascular diseases.

Publication No. 2

BA is one of several short chain fatty acids produced by gut microbiota. The study showed that the concentration of BA in the colon was approximately three orders of magnitude higher than the concentration of BA in the systemic blood. BA administered into the colon (IC) produced a prolonged decrease in arterial blood pressure (BP) and heart rate (HR). Subphrenic vagotomy and IC pretreatment with the antagonist of GPR41/43 receptors (ANT) significantly reduced the hypotensive effect of IC BA. The hypotensive effect was also reduced by IV administered hexamethonium but not by atropine. In *ex vivo* conditions, BA dilated mesenteric (MA) and gracilis muscle (GMA) arteries. Furthermore, I performed analogical series of experiments using intravenous administration. BA administered IV produced shorter decrease in BP than BA administered IC and did not affect HR. In conclusion, the colon appears the most likely site of BA action at physiological

concentrations. A 2-3-fold increase in the concentration of colonic BA lowers BP which seems to be mediated by GPR41/43 and afferent vagal signaling.

Publication No. 3

Valeric acid (VA) is a short chain fatty acid which is produced by gut bacteria during fermentation of dietary fiber. The acid also can be found in herbs such as *Valeriana officinalis*. Furthermore, VA is released from medicines such as estradiol valerate by esterases. The present study showed that the concentration of VA in the colon was approximately four orders of magnitude higher than the concentration of VA in the systemic blood. VA-D9 was detected in the brain, the liver, the kidneys and the heart, 5 min after its administration into the colon (IC). VA administered IC produced a decrease in arterial blood pressure (BP) which was accompanied by a decrease in heart rate (HR). The hypotensive effect of VA was inhibited by the antagonist of GPR41/43 receptors (ANT) but not by the subphrenic vagotomy. Hexamethonium prolonged the hypotensive effect of VA while atropine did not influence the hypotensive effect. In *ex vivo* conditions VA dilated GMA and MA. Furthermore, I performed analogical series of experiments using intravenous administrations of VA. Intravenous bolus of VA produced a short-lasting hypotensive effect with no significant change in HR. The hypotensive effect was significantly prolonged if VA was administered in the continuous intravenous infusion. In conclusion, the study for the first time shows that VA rapidly penetrates from the colon to tissues involved in the control of BP and produces a significant hypotensive effect.

Conclusions

Results of my studies show that the highest concentrations of VA and BA are present in the colon, a major habitat of gut bacteria. BA and VA penetrate from the colon to the systemic circulation and exert a hypotensive effect. The hypotensive effect is mediated via the nervous system and via a direct action of the acids on blood vessels.

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