

Antihypertensive effect of pork immersed in sake lees through nitric oxide synthesis

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Objectives: Hypertension is a condition in which blood pressure is high at rest and is caused by lifestyle disorders. It is called a silent killer because of fatal complications such as cerebral apoplexy, heart disease and chronic renal failure. Because inhibiting angiotensin-converting enzyme (ACE) can reduce the elevated blood pressure, ACE becomes a target for hypertension therapy. It requires more than 4 hours to develop an antihypertensive therapeutic effect of ACE inhibitors after administration. Therefore, to shorten the time lag of their therapeutic effect by daily consumption of meat products becomes more helpful for hypertension therapy. The objective of the present study was to elucidate the antihypertensive mechanism of water-soluble extract derived from pork immersed in sake lees using an animal model of hypertension, in which an antihypertensive effect was not induced by ACE inhibition.

Materials and Methods:

- i) Verification of an antihypertensive effect of water-soluble extract derived from pork immersed in sake lees. Angiotensin II (0.1 mg/kg) was intraperitoneally administered 55 minutes after the oral administration of water-soluble extract or distilled water (10 ml/kg), and the blood pressure was measured within 10 minutes. The dosage of water-soluble extract was adjusted for protein concentration (50 mg/kg).
- ii) Elucidation of the mechanism for the antihypertensive effect of water-soluble extract derived from pork immersed in sake lees. Angiotensin II (0.1 mg/kg) and L-NAME (5.0 mg/kg), which is a nitric oxide synthase (NOS) inhibitor, were intraperitoneally administered 55 minutes after the oral administration of water-soluble extract (50 mg/kg) to clarify the involvement of nitric oxide synthesis in the hypotensive effect of water-soluble extract. Next, the free L-arginine concentration in the dosed sample was measured by reversed-phase high performance liquid chromatography. After oral administration of the same (0.8 mg/kg) or 2 times concentration (1.6 mg/kg) of L-arginine solution compared with dosed sample of water-soluble extract, Angiotensin II (0.1 mg/kg) was intraperitoneally administered to measure blood pressure.

Results and Discussion:

- i) Verification of an antihypertensive effect of water-soluble extract derived from pork immersed in sake lees. Dietary water-soluble extract significantly decreased the systolic and diastolic blood pressure in the animal model of hypertension. Since this model does not improve the hypertensive symptom by ACE inhibitors, the present result indicates that the antihypertensive effect of water-soluble extract was induced by the other mechanism except for ACE inhibition.
- ii) Elucidation of the mechanism of antihypertensive effect of water-soluble extract derived from pork immersed in sake lees. We hypothesized that the antihypertensive effect of water-soluble extract was due to the enhancement of NOS in the vascular wall. The present result revealed that simultaneous administration of Angiotensin II and L-NAME in the animal model of hypertension abolished the antihypertensive effect of water-soluble extract. Based on this result, we hypothesized that water-soluble extract exhibits the antihypertensive effect through the following pathways. Nitric Oxide is synthesized in vascular endothelial cells as a byproduct of the conversion of L-arginine to L-citrulline by NOS. It migrates into the vascular smooth muscle and activates guanylate cyclase, which it converts guanosine triphosphate to cyclic GMP. It stimulates the uptake of calcium ions in the sarcoplasmic reticulum, leading to a decrease in the concentration of calcium ions in the cytoplasm, and the associated relaxation of vascular smooth muscle leads to a decrease in blood pressure. However, it is unclear whether the promotion of NOS is due to the activation of NOS or free L-arginine in the sample. However, orally administration of same and double concentration of L-arginine solution could not improve the symptom of hypertension. These results indicate that NOS is activated not L-arginine but the other components in water-soluble extract, resulting hypotensive action.

Conclusions: The present results demonstrate that water-soluble extract derived from pork immersed in sake lees shows antihypertensive effect through NOS activation. Therefore, dietary pork immersed in sake lees may cover for time lag until ACE inhibitors exert their therapeutic effect.

Key words: NOS, Pork immersed in sake lees, Antihypertensive effect