

Akkermansia muciniphila induces sex specific blood pressure changes and RAS activation

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Background: Akkermansia muciniphila (Akk), an intestinal mucin degrading bacterium has been associated with hypertension, a key risk factor for cardiovascular disease. Still, there's no clear evidence showing how Akk directly affects blood pressure. Renin-angiotensin- system (RAS) is a well-known blood pressure regulator, activation of which leads to oxidative stress. Previous studies have reported that Akk is more prevalent in females comparing to males and blood pressure exhibits sexually dimorphic traits. Therefore, we hypothesize that Akk regulates both RAS and blood pressure in a sex-dependent manner.

Methods: Spontaneously hypertensive rats (SHR) of both sexes (10-13-week-old, N=5-6 rats/group) were maintained on a normal chow (Harlan Teklad, TD 7034). These rats were gavaged with either 108 CFU/ml of Akk or PBS as control every other day for four weeks. Blood pressure was continuously monitored for 24 hours every week by radiotelemetry. After four weeks, kidney tissues were collected for the analysis of RAS associated receptors and oxidative stress related genes by real time PCR.

Results: Oral administration of Akk significantly decreased systolic BP (176.7 vs. 170.6 mmHg, $p<0.0001$) and mean BP (148.0 vs. 144.7 mmHg, $p=0.0004$) in male SHR rats. In contrast, in female SHR rats, systolic BP (161.2 vs. 164.5 mmHg, $p=0.01$) and mean BP (137.3 vs. 139.6 mmHg, $p=0.0032$) was increased.

following oral ingestion of Akk. Treatment with Akk showed higher expression of angiotensin II type 1 receptor a (AT1Ra) ($p=0.0315$) in females, a receptor for vasoconstrictive angiotensin II. However, this difference in AT1Ra was not observed in males. No significant differences were observed for angiotensin II type 2 receptor (AT2R), which has opposing effects and protective function. Oral administration of Akk resulted in a trend toward reduced expression of the vasodilatory receptor mas1 in females compared to males ($p=0.0680$). In male SHR rats, Akk significantly increased the mRNA expression levels of the antioxidant enzyme superoxide dismutase 1 (sod1), which protects against oxidative stress.

Conclusion: We report sex specific effects of Akk, a promising next generation probiotic, on blood pressure, that is, Akk increases blood pressure in females and decreases it in males. These are associated with corresponding changes in the renal RAS of both sexes, suggesting that Akk may regulate blood pressure via its impacts on renal RAS and oxidative stress. Our study provides evidence supporting Akk-mediated precision medicine for hypertension based on sex. Protein and enzymatic activity of renal RAS component will be studied in the future.

Keywords: Akkermansia muciniphila, Renin-angiotensin- system (RAS), Hypertension