Formyl Peptide Receptor-1 Activation is Crucial for the Spontaneous and Salt-Induced Hypertension in Dahl Salt Sensitive Rats: Mitochondria vs. Microbiota

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INTRODUCTION

- Chronic activation of the immune system contributes to vascular injury in hypertension. The formyl peptide receptor (FPR) is a pattern recognition receptor which plays a crucial role in the function of the innate immune system.
- FPR is a G-protein-coupled receptor that can bind N-formyl peptides such as N-formylmethionine-leucyl-phenylalanine (fMLP), produced by bacterial degradation.
- Mitochondria carry hallmarks of their bacterial ancestry including the usage of N-formyl-methionyl-tRNA as an initiator of protein synthesis.
- Literature has established that there is increased gut permeability in several models of hypertension, which could be the source of bacterial NFPs.
- N-formyl peptides (NFPs), regardless of origin, are recognized by FPR as pathogens and thus play a role in the initiation of inflammation.
- Functionally, the activation of FPR induces a slow and sustained contraction in airways and/or vascular leakage. Systemic FPR-1 activation leads to systemic inflammation.

HYPOTHESIS

We hypothesized that mitochondria-derived NFPs and FPR-1 activation would lead to vascular remodeling and the genesis of high BP. A high-salt (HS) diet would further exacerbate this response by causing gut barrier disruption.

METHODS

- Male Dahl S (salt-sensitive) and R (salt-resistant) rats (6-week-old) were given a LS (0.3% NaCl) or HS diet (2% NaCl).
- Blood pressure (BP) was measured by telemetry.
- After 3 weeks on LS or HS diets, rats were treated (osmotic mini-pump) with FPR-1 antagonist [Cyclosporin H (CsH), 0.3 mg/kg/day, 14 days].
- In another group, rats received water with amoxicillin (AMO, 5 mg/kg/day) for 3 weeks to deplete bacteria.
- Blood samples were collected to measure zonulin, a leaky gut biomarker via Elisa.
- Mesenteric resistance arteries (MRA) were collected to assess vascular function via wire myograph. Vascular remodeling in mesenteric resistance arteries (MRA) was evaluated using pressure and culture myograph.
- Calculation of structural and mechanical parameters:
  - Wall thickness (WT) = (De0Ca − Di0Ca)/2
  - Cross sectional area (CSA)= (π/4) X (De0Ca 2 − Di0Ca 2)
- Statistical analysis: Results are expressed as mean ± SEM. Student's t-test, non-linear regression, or two-way ANOVA was used to compared differences between groups. When ANOVA was used, the Bonferroni correction was performed. Significance was set at P<0.05.

RESULTS

Mitochondrial NFPs are increased in the circulation of Dahl S rats, independent of salt intake

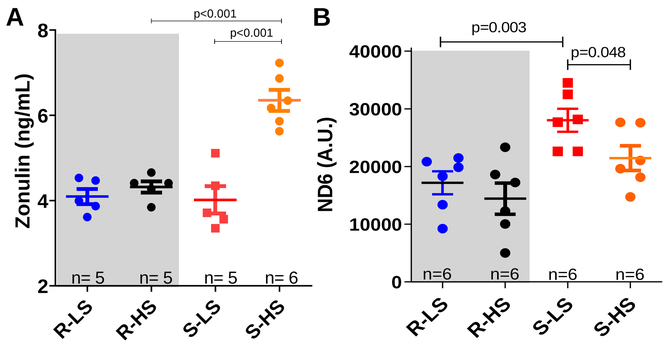


Fig. 1: Serum zonulin levels (A) and mitochondrial ND6 (NADH dehydrogenase 6) expression in plasma analysis (B) from male Dahl salt-resistant (R) and Dahl salt-sensitive (S) rats on low-salt (LS; 0.3%) and high-salt (HS; 2%) diet. Data presented in mean±SEM. Statistics: t test or 1-way ANOVA: number of animals and P are indicated on graphs. FPR indicates formyl peptide receptor. AU indicates arbitrary units;

FPR-1 antagonist decreases hypercontractility in Dahl S rat arteries on low salt

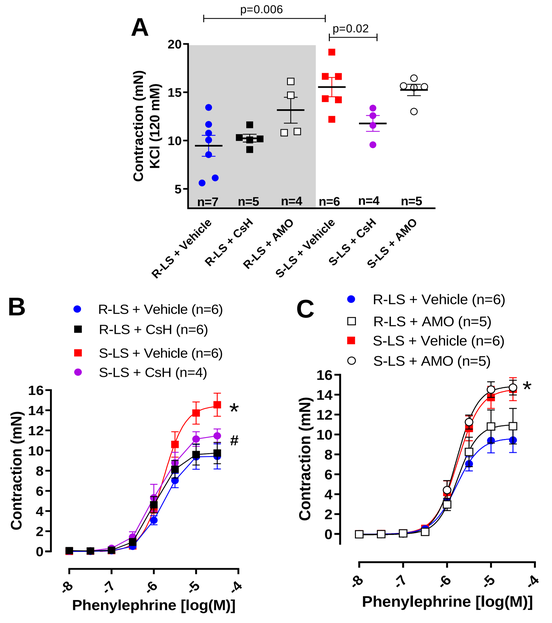


Fig. 3: KCl (120 mmol/L; A) and phenylephrine (B and C)-induced contraction in mesenteric resistance arteries from male Dahl salt-resistant (R) and Dahl salt-sensitive (S) rats on low salt (LS; 0.3%) treated with cyclosporin H (CsH) or amoxicillin (AMO) for 14 d. Data presented in mean±SEM. Number of animals and P are indicated on graphs, otherwise P<0.05. Statistics: 1- or 2-way ANOVA; * vs R-LS; # vs S-LS.

Dahl S rats have spontaneous elevation in blood pressure that is prevented with CsH treatment

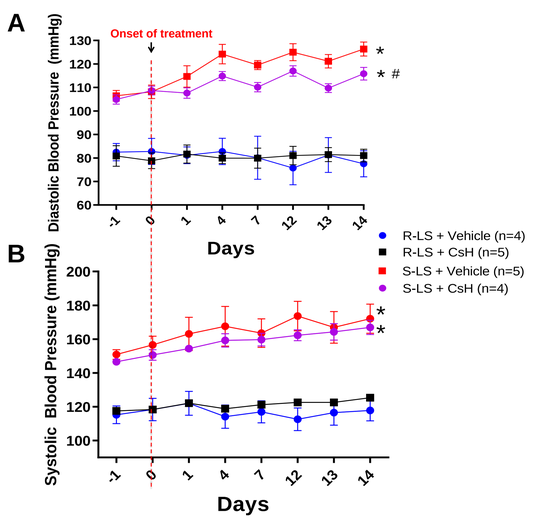


Fig. 2: Diastolic and systolic blood pressure, measured by telemetry, from male Dahl salt-resistant (R) and Dahl salt-sensitive (S) rats on low-salt (LS; 0.3%) diet treated with cyclosporin H (CsH; A and B) for 14 d. The first point (−1) on the graph is the baseline average of BP for 14 d. Arrows indicate the start of the treatment. Data presented in mean±SEM. Number of animals are indicated on graphs. P<0.05. Statistics: 2-way ANOVA; * vs R-LS and R-LS+CsH; # vs S-LS.

FPR-1 antagonist and antibiotic treatment decrease CSA in Dahl S rats

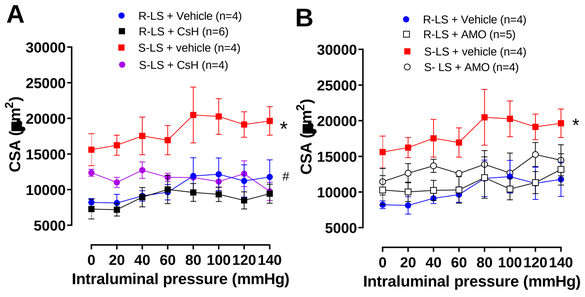
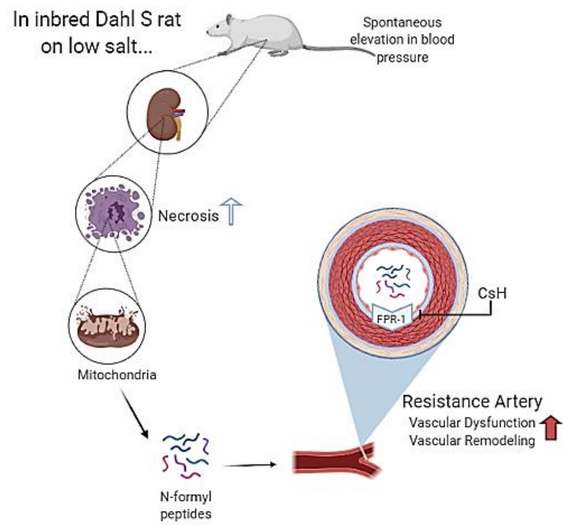


Fig. 4: Cross-sectional area (CSA) measured with increasing intraluminal pressure in mesenteric resistance arteries from male Dahl salt-resistant (R) and Dahl salt-sensitive (S) rats on low salt (LS; 0.3%) treated with Cyclosporin H (CsH; A) or amoxicillin (AMO; B) for 14 d. Data presented in mean±SEM. Number of animals and P are indicated on graphs, otherwise P<0.05. Statistics: 1- or 2-way ANOVA; * vs R-LS; # vs S-LS.

CONCLUSIONS



- Mitochondrial N-formyl peptides and FPR-1 (formyl peptide receptor-1) activation promote vascular injury and premature, spontaneous blood pressure elevation in Dahl salt-sensitive rats independent of high-salt diet.
- Activation of FPR-1 induces vascular hypercontractility and hypertrophy in Dahl salt-sensitive rats independent of high salt.
- Blockade of FPR-1 ameliorates vascular injury and prevents the increase of blood pressure.

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