Effects of antibiotics on serum metabolomic profiles in weanling pigs experimentally infected with a pathogenic *E. coli*

Kwangwook Kim[1], Yijie He[1], Cynthia Jinno[1], Seijoo Yang[1], Minho Song[2], Peng Ji[1], Yanhong Liu[1]

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Abstract

Our previous studies have shown that supplementation of low-dose antibiotic growth promoter (**AGP**) exacerbated growth performance and systemic inflammation of weaned pigs infected with pathogenic *Escherichia coli* (***E. coli***). The objective of this experiment, which is extension of our previous report, was to investigate the effect of low-dose AGP on the serum metabolomic profiles of weaned pigs experimentally infected with F18 *E. coli*. Thirty-four pigs (6.88 ± 1.03 kg BW) were individually housed in disease containment rooms and randomly allotted to one of three treatments with 11-12 replicate pigs per treatment. The three dietary treatments were control diet (**control**) and 2 additional diets supplemented with 0.5 or 50 mg/kg of AGP (carbadox), respectively. The experiment lasted 18 d [7 d before and 11 d after first inoculation (d 0)]. The F18 *E. coli* inoculum was orally provided to all pigs with the dose of 10^{10} cfu/3 mL for 3 consecutive days. Blood samples were collected on d 0 before *E. coli* inoculation and on d 5 and 11 post-inoculation (**PI**). Serum metabolomics were analyzed by gas chromatography time of flight-mass spectrometer (**GCTOF-MS**). All processed data were statistically analyzed and evaluated by online MetaboAnalyst tool. No significant differences were observed in the serum metabolites between control and low-dose AGP throughout the experiment. However, further metabolic pathway enrichment analysis showed that the low-dose AGP modified pentose phosphate pathway, DNA synthesis in T and B lymphocytes, pyruvate metabolism and amino acid metabolism compared to high-dose AGP. In conclusion, modification of serum metabolites levels and metabolic pathways by supplementing low-dose AGP may have relevance for pathogenesis, disease activity and clinical manifestations of weaned pigs infected with F18 *E. coli*. These findings may provide a comprehensive understanding of our previous results.

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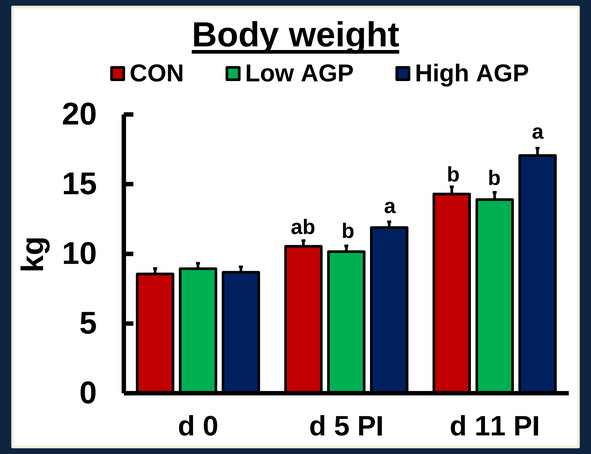
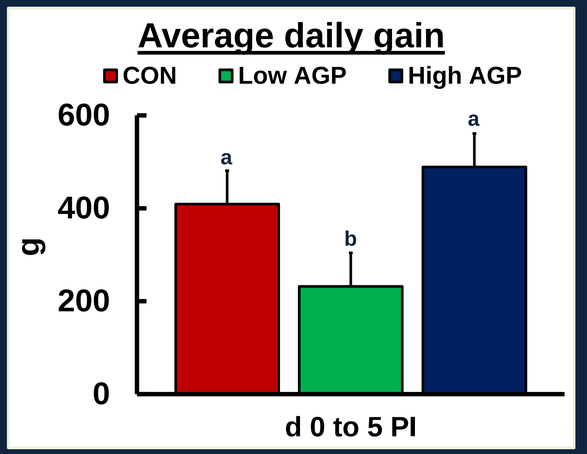
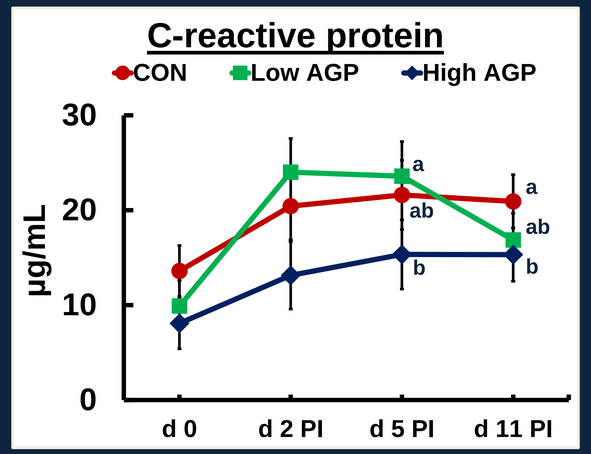
Introduction

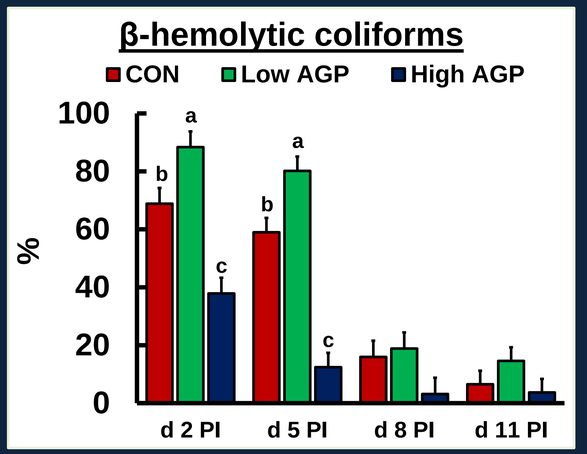
- **Antibiotic resistance is one of the biggest health concerns that lead to tremendous economical losses and increased mortality of both humans and livestock (WHO, 2018).**
- **Low-dose antibiotics application enhanced bacterial selection for antibiotic resistance genes (Davies et al., 2006).**
- **Supplementation of low-dose antibiotic growth promoter (AGP) exacerbated growth performance and systemic inflammation of weaned pigs infected with pathogenic *E. coli* (Kim et al., 2019a,b).**

Preliminary data









(Kim et al., 2019a,b)

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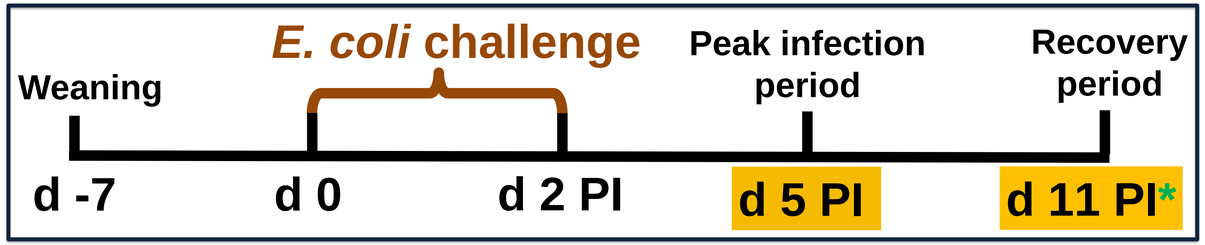
Objective & Methods

Investigate the effect of low-dose AGP on the serum metabolomic profiles of weaned pigs experimentally infected with F18 *E. coli*.



- Experimental design: RCBD (Blocks: BW x Sex)
- 34 weanling pigs (6.88 ± 1.03 kg, 21 d old)
- Treatments: 3 dietary treatments (11-12 pigs/treatment)

Nursery basal diet as control (CON)	*E. coli* challenge
CON + 0.5 mg/kg of AGP (Low dose)	
CON + 50 mg/kg of AGP (High dose)	

- Serum samples were collected on d 0, 5, and 11 PI.
- Serum metabolomics were analyzed by gas chromatography time of flight-mass spectrometer (GCTOF-MS).
- All processed data were analyzed by MetaboAnalyst (http://www.metaboanalyst.ca) (Chong et al., 2018).
  - ✓ Statistical analysis
    - VIP (variable importance projection) > 1
    - Fold change > 2
    - FDR (adjusted *P*-value) < 0.1
  - ✓ Enrichment & pathway analysis
    - *P* < 0.05

*PI= post-inoculation

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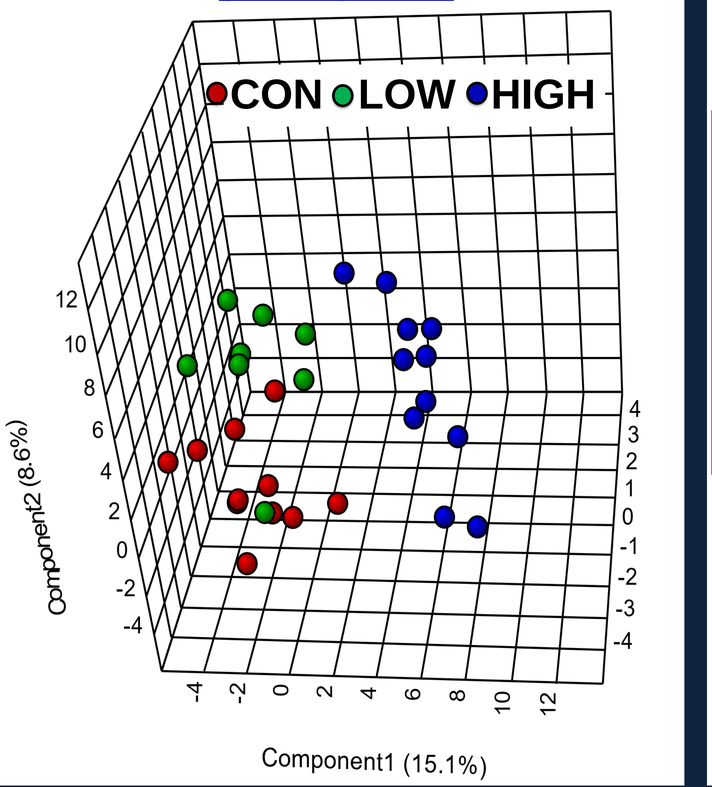
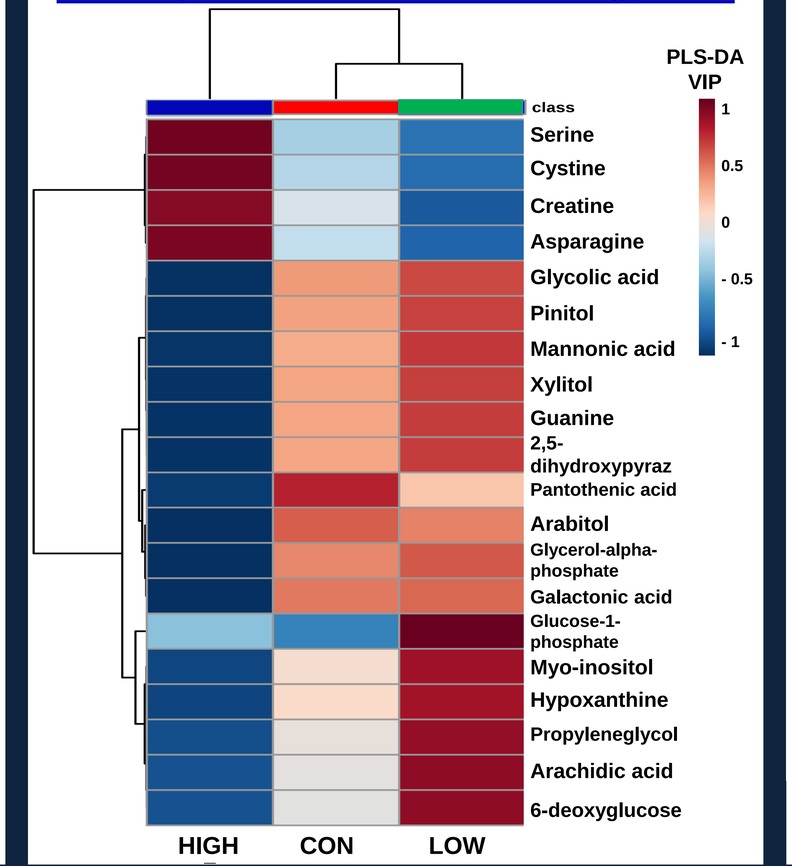
Results

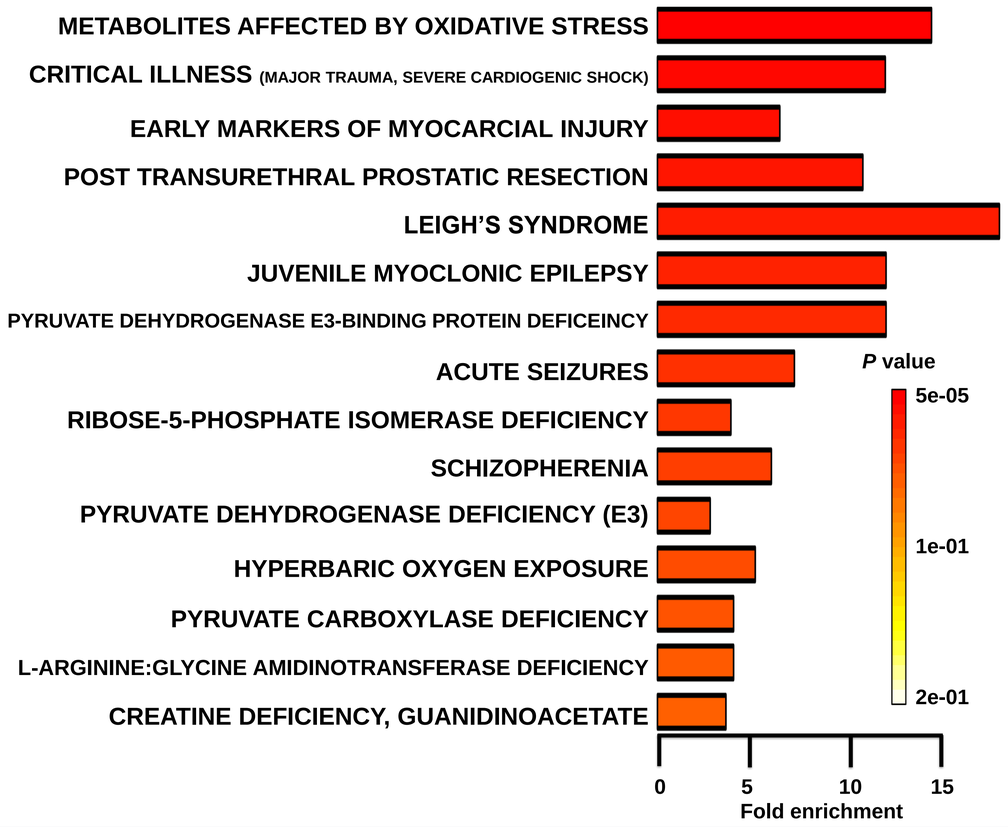
Synchronized 3D plots: Partial least squares – discriminant analysis (PLSDA), d 5 PI



Heatmap and hierarchical clustering, d 5 PI



Metabolite sets enrichment, d 5 PI



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Results

Most affected metabolic pathways

- Supplementation of low-dose AGP modified
  - ✓ Pentose phosphate pathway (RNA synthesis)
  - ✓ DNA synthesis in lymphocytes
  - ✓ Pyruvate metabolism
  - ✓ Amino acid metabolism
  - ✓ Galactose metabolism
  - ✓ Glycolysis/gluconeogenesis

  compared with high-dose AGP on d 5 PI.
- No differences were observed in serum metabolites among dietary treatments on d 0 and 11 PI.

Conclusions

- Supplementation of low-dose AGP modified serum metabolites and associated metabolic pathways of weaned pigs infected with F18 *E. coli* during the peak infection period.
- The most affected metabolic pathways include nucleic acid synthesis and major nutrient metabolism, which may account for the lower growth rate and worse diarrhea of pigs fed low-dose AGP.

References

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