**ABSTRACT**

Routine use of antibiotics in animal feed at sub-therapeutic dose for growth promotion and disease prevention is suspected to be a major driving force for rapid emergence of antibiotic-resistant pathogens, which have become a serious threat to public health worldwide. To ensure public health and safe supply of food products, alternative approaches to disease control are urgently needed. Through a comprehensive screening process, we discovered several dietary supplements to be highly effective in enhancing host innate immunity and disease resistance without triggering proinflammatory responses. Of particular interest are short-chain fatty acids (SCFAs) produced naturally by intestinal commensal bacteria. We found that SCFAs strongly induce the expressions of multiple genes for endogenous antimicrobial host defense peptides (HDPs), which possess potent immunomodulatory and broad-spectrum antimicrobial activities. In addition, dietary supplementation of SCFAs reduced the load of Salmonella enteritidis in the chicken cecum following experimental infection, providing further evidence that the induction of HDP gene expression is inversely correlated with the length of the aliphatic carbon chain of fatty acids. Chicken HD11 macrophages and primary monocytes, with SCFAs being the most potent, medium-chain fatty acids moderate and long-chain fatty acids largely ineffective. Moreover, we observed a strong synergy in inducing HDP synthesis among SCFAs and between SCFAs and a botanical extract. Therefore, dietary supplementation of immune-boosting SCFAs or SCFA-botanical extracts may have potential for further development as a promising anti-bacterial alternative approach to disease control and prevention. In addition to poultry, such an immunomodulatory approach is expected to be broadly applicable to all other animal species including humans, offering great potential of enhancing production efficiency, and food safety, while minimizing the use of antibiotics and emergence of drug-resistant pathogens.

**INTRODUCTION**

Widespread use of antibiotics as growth promoters is suspected to be a major source for the development of antibiotic-resistant pathogens, which have become a major public health concern worldwide. Enhanced disease resistance by specifically boosting the synthesis of endogenous host defense peptides (HDPs) may represent a promising alternative strategy. HDPs have been found in nearly all forms of life and play an important role in the first line of defense. HDPs kill a broad range of pathogens by causing a breach in the first line of defense, disrupting cellular membrane permeability, and inducing an influx of ions and water, thus leading to cellular lysis and death. As an important source of energy, fatty acids are represented by a large group of carboxylic acids with an aliphatic hydrocarbon chain that are either saturated or unsaturated. Based on the number of carbon atoms in the aliphatic chain, fatty acids are broadly classified into three groups, namely SCFAs (C1-C3), medium-chain fatty acids (MCFAs) (C4-C10), and long-chain fatty acids (LCFAs) (C12-C). Butyrate, acetate, and propionate are the major species of SCFAs produced by bacterial fermentation of carbohydrates in the intestine. The concentrations of acetate, propionate, and butyrate vary in molar ratios from 48:29:23 to 70:15:15 in human feces and cecal contents in chicken. As an important energy source, SCFAs also possess many other biological roles, such as regulating gut microbiota, controlling insulin secretion, increasing gut transit, and preventing and reversing colonization of endogenous and exogenous pathogens for disease control and prevention.

**CONCLUSIONS**

- Butyrate selectively induces HDP gene expression both in vitro and in vivo and enhances pathogen clearance with a minimal impact on the proinflammatory response.
- HDP gene expression is inversely correlated with the aliphatic carbon chain length of fatty acids, with SCFAs being most potent inducers, MCFAs moderate, and LCFAs largely ineffective.
- SCFAs induce an anti-inflammatory response and reduce the eukaryotic colonization of chicken in a synergistic manner.
- SCFAs and their analogs may have potential for further development as a cost-effective, antibiotic-alternative approach in disease control and prevention.

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