Mechanisms of Antibiotics: How Do They Really Work

Theo A. Niewold

Nutrition and Health Unit, Faculty of Bioscience Engineering, Katholieke Universiteit Leuven, Kasteelpark Arenberg 30, 3001 Heverlee, BELGIUM; E-mail: theo.niewold@biw.kuleuven.be

Summary

In the absence of immunological challenges, production animals can grow to their full genetic potential. The greatest (immunological) costs for growth are associated with inflammation, because inflammation causes a reduced appetite, muscle catabolism, and predisposes for infections. Whereas most are familiar with systemic inflammation, local intestinal inflammation is more relevant in production animals. Also called metabolic inflammation (MI), it is the normal post-prandial reaction, the level of which is determined by the energy value of feed. Hence, in production animals the normal regulation of MI can be overwhelmed, leading to reduced growth. This imbalance can be remedied by feeding anti-inflammatory compounds. In fact, the antibiotics which have been used as very cost effective promoters of growth and health in production animals are examples of the latter. For years, their growth promoting activity was attributed to their antibiotic properties, which is highly unlikely because sub therapeutic concentrations were used and bacterial resistance is wide spread. Antibiotics used as antimicrobial growth promoters (AGP) work by direct inhibition of MI, as do non-antibiotic anti-inflammatory compounds like acetylsalicylic acid, polyphenols, and certain fatty acids. Alternatives to AGP and antibiotics should therefore be anti-inflammatory compounds, which makes the argument of inducing bacterial resistance irrelevant. Alternatives to antibiotics should preferably not be registered drugs. Plants contain a host of candidates. Pre-selection can be performed by using simple in vitro (anti-) inflammatory assays, followed by in vivo trials. Selected compounds are successful at this moment, and will help maintain profitability while reducing reliance on antibiotics.
Background

Antibiotics do influence the immune system directly in all production animals including pigs. For a good understanding, it is necessary to realise that the immune system does consist of two functionally distinct parts, the systemic part, which is reactive, and the largest part, the mucosal immune system, which should be tolerant. In both parts, there is a pivotal role for the innate response, in other words inflammation. During inflammation, cytokines are released causing catabolism of muscle tissue and reduced appetite (Niewold, 2007), and therefore inflammation clearly has the greatest physiological expenses (Humphrey and Klasing, 2004). For most people, inflammation is mainly associated with (infectious) diseases, and with systemic inflammation. In production animals, the latter is relevant but the much less known metabolic inflammation (MI) in the intestines is much more important. MI is the postprandial inflammatory mucosal response in the (small) intestines. The level of this normal physiological response to a meal is strongly related to the dietary energy value (Margioris, 2009), and is usually properly regulated to avoid adverse consequences such as muscle catabolism and reduced feed intake. Furthermore, if unchecked, MI can lead to intestinal damage, which will offer a niche for certain pathogens. The proper balance is normally maintained by the so-called nervous anti-inflammatory reflex which attenuates the activity of intestinal inflammatory cells (Niewold, 2007).

Feeding large amounts of (high) energy feed, however, can tip the balance towards a higher degree of MI. Therefore, production animals are obviously at risk (Niewold, 2010). From the above, it follows that anti-inflammatory compounds would be able to assist the anti-inflammatory reflex in containing inflammation, and in reducing growth inhibition. Antimicrobial growth promoters (AGP) are prime examples of such compounds. Earlier, the growth promoting effects of AGP were associated with antibiotic properties. There are two main reasons why this is unlikely. First, AGP were used in sub therapeutic concentrations, and second, they are still effective despite the wide spread (pathogen) resistance for instance against tetracycline (Cox and Popken, 2010). This means that only antibiotics with direct anti-inflammatory effects are good growth promoters, and this relationship was indeed demonstrated (Niewold, 2007). Furthermore, it was confirmed in a rodent model that oral sub therapeutic use of a tetracycline down regulated intestinal mucosal immune responses (Costa et al., 2011), and we see the same in pigs (to be published).

Conclusion

The anti-inflammatory action of AGP is their main effect in the sub therapeutic concentrations used, whereas it could be considered a (popular) side effect when the same antibiotic is used in therapeutic concentrations. This may explain the increases in therapeutic use when AGP are banned (Bengtsson
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and Wierup 2006). The theory also predicts non-antibiotic anti-inflammatory compounds like non-steroidal anti-inflammatory drugs (NSAID) to have growth promoting effects, which is indeed the case (e.g. for aspirin (Xu et al., 1990). An important condition for all compounds is that effective concentrations in small intestine should be reached, and therefore, proximal intestinal uptake should be limited (as is the case for tetracyclines), otherwise (stomach resistant) encapsulation is required, which is costly. Furthermore, the effective dose required should be low, in particular for the more expensive compounds.

**Implications**

Alternatives to AGP and antibiotics should be non-antibiotic anti-inflammatory compounds, and not be registered pharmaceuticals, because of societal and political reasons. There are many (potential) feed compounds with anti-inflammatory effects (Niewold, 2010), of which plants and plant extracts are possibly the best option, for economical reasons and because they are rich in bioactive compounds. Plants can contain anti-inflammatory compounds as well as (unwanted) pro-inflammatory ones. Compounds can easily be preselected using in vitro assays with lipopolysaccharide-activated macrophages (Niewold and De Backer, 2010). In this test, the AGP oxytetracycline is used as an anti-inflammatory reference, and non-stimulated macrophages serve to detect pro-inflammatory activity, as well as cytotoxicity. In this test, feed additives with reported growth promoting activity were tested for anti-inflammatory properties. An example of the latter is sanguinarine. Sanguinarine containing extracts were suggested to have growth promoting activity. We demonstrated in vitro anti-inflammatory activity (Niewold, and De Backer, 2010), which is consistent with the in vivo claim. Similarly, polyphenols were described as anti-inflammatory, and indeed anti-inflammatory and growth promoting effects in piglets were demonstrated (Deng et al., 2010). The above implies that both (certain) polyphenols and sanguinarine have limited proximal intestinal uptake, which is indeed the case (Kosina et al., 2004).

The in vitro inflammatory assay is particularly suited for screening large amounts of new (and conventional) components before costly feed experiments are performed. The test limitations lie mainly in the requirement of solubility in the test medium, but this is outweighed by the relative low cost. The method allows also for the identification of pro-inflammatory compounds in feed constituents, and their subsequent removal or reduction in feed.

In conclusion, promotion of growth and health in production animals requires reduction of (metabolic) inflammation. Suitable anti-inflammatory feed compounds can be selected with in vitro assays, and these compounds will help maintain profitability and sustainability of pig production.
- **References**


