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Why anti-inflammatory compounds are the solution for the problem with in feed antibiotics

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REVIEW ARTICLE

Abstract

There is increasing pressure to reduce the prophylactic and therapeutic use of antibiotics in animal production based on the fear for inducing bacterial resistance. Antibiotics are very cost effective promoters of growth and health in production animals. Therefore, farmers would only be willing to reduce antibiotics if effective alternatives are available. The search for alternatives is hampered by misconceptions about the exact physiological mechanisms behind growth promotion by antibiotic growth promoters (AGP). Hitherto, they were attributed to their antibiotic properties. This is highly unlikely for various reasons, the main one being the subtherapeutic concentrations used. AGP work much more likely by direct inhibition of the intestinal postprandial inflammatory response. This implies that alternatives to antimicrobial growth promoters should be non-antibiotic anti-inflammatory compounds, which also removes the fear for inducing bacterial resistance. Because of public resistance against the perceived abuse of medicines in animal production, alternatives should preferably not be registered drugs. Most viable options are plants (extracts). Plants are perceived as natural and green, and contain a plethora of candidates. Compounds can easily be selected *in vitro* and subsequently tested *in vivo*. It is expected that these compounds will help to considerably reduce antibiotic use in animal production while maintaining profitability.

Keywords: antibiotics, growth, health, postprandial inflammation

1. Introduction

The increasing concerns about the use of antibiotics in animal production are mainly driven by the fear for inducing bacterial resistance against antibiotics. Whether or not this poses a real risk for humans and whether or not it justifies a whole sale ban (on subtherapeutic use) is still hotly debated (Casewell *et al.*, 2003; Hammerum *et al.*, 2007; Philips, 2007). Some argue the case for allowing certain widely used antibiotics with apparent low risk for humans such as tetracycline (Cox and Popken, 2010). Anyway, one could ask why there is such reluctance in the field to decrease the prophylactic and therapeutic use of antibiotics. The simple answer is that antibiotics are very cost effective promoters of growth and health in production animals. Therefore, farmers would only be willing to reduce dependence on antibiotics if effective alternatives are available. It is argued that in some areas in which antibiotics as growth promoters are prohibited an increase with therapeutic use is seen (Bengtsson and Wierup, 2006; Casewell *et al.*, 2003), and probably for good reasons as we will see below.

2. Alternatives for antibiotics

The search for alternatives is hampered by misconceptions about the exact physiological mechanisms behind the growth promoting effects of antibiotics. Hitherto, the growth promoting effects of antimicrobial growth promoters (AGP) were attributed to their antibiotic properties (Dibner and Richards, 2005). This is highly unlikely for various reasons, the main one being the subtherapeutic concentrations used. Indeed, alternatives based on the antibiotic theory such as probiotics are not very successful, and even adverse effects have been reported (EC, 2000). AGP work much more likely as growth permitters by direct inhibition of the intestinal inflammatory response. Most antibiotics have in common that they accumulate in inflammatory cells (Labro, 1998, 2000; Van den Broek, 1989). What is important here is that many accumulated antibiotics inhibit the innate immune response. The relevant physiological effect of this would be the attenuation of the inflammatory response. This is important for the following reasons. Inflammatory cytokines cause catabolism of muscle tissue and reduced appetite (Gruys *et al.*, 2006), and inflammation is clearly associated with great physiological expenses (Humphrey and Klasing, 2004). Inflammation is most commonly associated with (infectious) diseases. Although the latter is of (episodic) relevance, the much less known postprandial inflammation in the (small) intestines is probably most important in production animals. The degree of this normal physiological response to a meal is strongly related to the dietary energy value (Margioris, 2009), and should be properly regulated to avoid adverse consequences such as muscle catabolism and inappettance. This is normally achieved by the so-called nervous anti-inflammatory reflex (Figure 1) which controls and contains the intestinal inflammatory cells (Tracey, 2002).

It is important to realise that this regulatory mechanism can be overwhelmed by large amounts of (high) energy feed. It is thus easy to see why production animals are at risk, and that a high degree of postprandial inflammation would attenuate growth (Niewold, 2010). It could be argued that reducing the energy density of feed could remedy this, however, this is hardly feasible in the current highly competitive markets, increasing the time to slaughter and associated feeding costs. Instead, antibiotics can inhibit growth reduction by

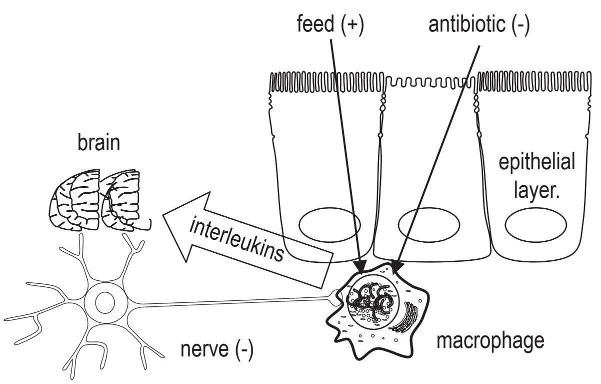

Figure 1. Schematic representation of the intestinal anti-inflammatory reflex. Absorption of high energy feed through the epithelial layer stimulates macrophages to increased (+) production of pro-inflammatory interleukins. The latter reach the brain, and a down-regulatory (-) nervous signal is returned to the macrophages. Antibiotics and other anti-inflammatory compounds can assist in down (-) regulating macrophages, and help attenuate inflammation associated influx of inflammatory cells reducing the thickening of the mucosal wall.

reducing postprandial inflammation. This in turn would mean that only antibiotics that have anti-inflammatory side effects are growth promoters. There is indeed a good relationship between inhibition of inflammatory function and (past) use as AGP (Niewold, 2007). It is unlikely that this relationship is only coincidental. AGP are antibiotics in subtherapeutic dosage, and the anti-inflammatory action is their main effect. Some of the same antibiotics are also popular as therapeutics, in which case the growth promoting anti-inflammation action can be seen as the (welcome) main side effect. It would also explain why the same antibiotics still find therapeutic use despite the wide spread bacterial (pathogen) resistance against for instance tetracycline in the Netherlands (Bengtsson and Wierup, 2006), and in the USA (Cox and Popken, 2010), whereas the same bacterial organisms were the supposed targets according to the antibiotic hypothesis for AGP.

3. Growth promoters should be anti-inflammatory

The anti-inflammatory hypothesis on AGP also explains why non-antibiotic anti-inflammatory compounds like acetylsalicylic acid have a similar growth promoting effect, although they require higher dosages (e.g. aspirin (Xu *et al.*, 1990). In any case, it implies that alternatives to AGP should be non-antibiotic anti-inflammatory compounds. The obvious advantage is that the argument of inducing bacterial resistance will become irrelevant. Aspirin and other non-steroidal anti-inflammatory drugs could be candidates. However, there is public resistance against the perceived abuse of not only antibiotics but also other medicines in animal production. This means that alternatives to antibiotics should preferably not be registered pharmaceuticals, because legislative action can be foreseen. There are many (potential) feed compounds with anti-inflammatory effects, including amino acids and fatty acids (Niewold, 2010). Costs may be prohibitive as yet for the latter. Possibly, most viable options could come from plants and plant extracts. Plants may provide more economically viable alternatives, plants are perceived as 'green', and contain a plethora of candidates. Potential anti-inflammatory compounds can easily be selected by simple *in vitro* assays using lipopolysaccharide-activated macrophages (Niewold and De Backer, 2010; Wu *et al.*, 2003), using the established AGP tetracycline as an anti-inflammatory reference compound (D'Agostino *et al.*, 1998). Promising compounds can subsequently be tested *in vivo*, or existing feed additives with purported growth promoting activity can be tested for anti-inflammatory properties, which would give claims a mechanistic basis.

Tea polyphenols are described as anti-inflammatory (Chen *et al.*, 2006), and feed experiments in pigs demonstrated indeed anti-inflammatory and growth promoting effects in piglets (Deng *et al.*, 2010). Also sanguinarine containing extracts which showed growth promoting activity in broilers (Vieira *et al*., 2008), proved to have *in vitro* anti-inflammatory activity (Niewold and De Backer, 2010).

It should be realised that having *in vitro* anti-inflammatory properties is not sufficient by itself. In order to reach effective concentrations in small intestine, proximal intestinal uptake should be low. This is the case with certain polyphenols (Biasi *et al*., 2011), whereas for instance small chain fatty acids like butyrate are absorbed almost totally in the stomach and stomach resistant encapsulation is required. About 60% of tetracycline (Agwuh, and MacGowan, 2006), and about 1-2% of sanguinarine (Kosina *et al*., 2004) is absorbed in the (rat) stomach, leaving a considerable proportion of both compounds to attenuate small intestinal metabolic inflammation.

4. Conclusions

It is concluded that promotion of growth and health in production animals largely depends on attenuation of (postprandial) inflammation. Alternatives to AGP can be found with relative ease using simple *in vitro* assays. It is argued that plants are most likely the most cost effective source of anti-inflammatory compounds, of which several are already available. It is anticipated that application of these compounds in feed will contribute to reducing antibiotic use in animal production while maintaining profitability.

Conflict of interest

The author declares no conflict of interest.

References

Agwuh, K.N. and MacGowan, A., 2006. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. Journal of Antimicrobial Chemotherapy 58: 256-265.

Bengtsson, B. and Wierup, M., 2006. Antimicrobial resistance in Scandinavia after a ban of antimicrobial growth promoters. Animal Biotechnology 17: 147-156.

Biasi, F., Astegiano, M., Maina, M., Leonarduzzi, G. and Poli, G., 2011. Polyphenol supplementation as a complementary medicinal approach to treating inflammatory bowel disease. Current Medicinal Chemistry 18: 4851-4865.

Casewell, M., Friis, C., Marco, E., McMullin, P. and Phillips, I., 2003. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. Journal of Antimicrobial Chemotherapy 52: 159-161.

Chen, X., Li, W. and Wang, H., 2006. More tea for septic patients? Green tea may reduce endotoxin-induced release of high mobility group box 1 and other pro-inflammatory cytokines. Medical Hypotheses 66: 660-663.

Cox, L.A. and Popken, D.A., 2010. Assessing potential human health hazards and benefits from subtherapeutic antibiotics in the United States: tetracyclines as a case study. Risk Analysis 30: 432-457.

D'Agostino, P., La Rosa, M., Misiano, G., Milano, S., Brai, M., Cammarata, G., Feo, S. and Cillari, E., 1998. Tetracycline inhibits the nitric oxide synthase activity induced by endotoxin in cultured murine macrophages. European Journal of Pharmacology 346: 283-290.

Deng, Q., Xu, J., Yu, B., He, J., Zhang, K., Ding, X. and Chen, D., 2010. Effect of dietary tea polyphenols on growth performance and cell-mediated immune response of post-weaning piglets under oxidative stress. Archives of Animal Nutrition 64: 12-21.

Dibner, J.J. and Richards, J.D., 2005. Antibiotic growth promoters in agriculture: history and mode of action. Poultry Science 84: 634-643.

European Commission (EC), 2000. Report of the Scientific Commission on Animal Nutrition on the assessment under directive 87/153/EEC of the efficacy of micro-organisms used as feed additives. Available at http://ec.europa.eu/food/fs/sc/scan/out40_en.pdf.

Gruys, E., Toussaint, M.J., Niewold, T.A., Koopmans, S.J., Van Dijk, E. and Meloen, R.H., 2006. Monitoring health by values of acute phase proteins. Acta Histochemica 108: 229-232.

Hammerum, A.M., Heuer, O.E., Lester, C.H., Agersø, Y., Seyfarth, A.M., Emborg, H.D., Frimodt-Møller, N. and Monneta, D.L., 2007. Comment on: withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health. International Journal of Antimicrobial Agents 30: 466-468.

Humphrey, B.D. and Klasing, K.C., 2004. Modulation of nutrient metabolism and homeostasis by the immune system. World's Poultry Science Journal 60: 90-100.

Kosina, P., Walterova, D., Ulrichova, J., Lichnovsky, V., Stiborova, M., Rydlova, H., Vicar, J., Krecman, V., Brabec, M.J. and Simanek, V., 2004. Sanguinarine and chelerythrine. Assessment of safety on pigs in ninety days feeding experiment. Food and Chemical Toxicology 42: 85-91.

Labro, M.T., 1998. Antibacterial agents-phagocytes: new concepts for old in immunomodulation. International Journal of Antimicrobial Agents 10: 11-21.

Labro, M.T., 2000. Interference of antibacterial agents with phagocyte function: immunomodulation or immuno-fairy tales? Clinical Microbiology Reviews 13: 615-650.

Margioris, A.N., 2009. Fatty acids and postprandial inflammation. Current Opinion in Clinical Nutrition and Metabolic Care 12: 129-137.

Niewold, T.A., 2007. The non-antibiotic anti-inflammatory effect of antimicrobial growth promoters, the real mode of action? A hypothesis. Poultry Science 86: 605-609.

Niewold, T.A., 2010. The effect of nutrition on stress and immunity. In: Garnsworthy, P.C. and Wiseman, J. (eds) Recent advances in animal nutrition, Nottingham University Press, Nottingham, UK, pp. 191-205.

Niewold, T.A. and De Backer, K., 2010. The *in vitro* anti-inflammatory property of sanguinarine containing extracts is consistent with enhanced *in vivo* performance in production animals. In: Duclos, M. and Nys, Y. (eds.) Proceedings of the XIIIth European Poultry Conference. August 23-27, 2010, Tours, France, pp. 718.

Phillips, I., 2007. Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health. International Journal of Antimicrobial Agents 30: 101-107.

Tracey, K.J., 2002. The inflammatory reflex. Nature 420: 853-859.

Van den Broek, P.J., 1989. Antimicrobial drugs, microorganisms, and phagocytes. Reviews of Infectious Diseases 11: 213-245.

Vieira, S.L., Oyarzabal, O.A., Freitas, D.M., Berres, J., Pena, J.E.M., Torres, C.A. and Coneglian, J.L.B., 2008. Performance of broilers fed diets supplemented with sanguinarine-like alkaloids and organic acids. Journal of Applied Poultry Research 17: 128-133.

Wu, C.H., Chen, T.L., Chen, T.G., Ho, W.P., Chiu, W.T. and Chen, R.M., 2003. Nitricoxide modulates pro- and anti-inflammatory cytokines in lipopolysaccharide-activated macrophages. Journal of Trauma 55: 540-545.

Xu, Z.R., Kornegay, E.T., Sweet, L.A., Lindemann, M.D., Veit, H.P. and Watkins, B.A., 1990. Effects of feeding aspirin and soybean oil to weanling pigs. Journal of Animal Science 68: 1639-1647.