

Improving efficiency in meat production

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Abstract

Selective breeding and improved nutritional management over the last 20-30 years has resulted in dramatic improvements in growth efficiency for pigs and poultry, particularly lean tissue growth. However, this has been achieved using high quality feed ingredients, such as wheat and soya, that are also used for human consumption and more recently biofuels production. Ruminants on the other hand are less efficient, but are normally fed poorer quality ingredients that cannot be digested by humans, such as grass or silage. The challenges therefore are to (i) maintain the current efficiency of growth of pigs and poultry, but using more ingredients not needed to feed the increasing human population or for the production of biofuels; (ii) improve the efficiency of growth in ruminants; and (iii) at the same time produce animal products (meat, milk and eggs) of equal or improved quality. This review will describe the use of a) enzyme additives for animal feeds, to improve feed digestibility; b) known growth promoting agents, such as growth hormone, beta-agonists and anabolic steroids, currently banned in the EU but used in other parts of the world; and c) recent transcriptomic studies into molecular mechanisms for improved growth efficiency via low Residual Feed Intake (RFI). In doing so, the use of Genetic Manipulation in animals will also be discussed.

Feed efficiency: Meat: Enzymes: Growth promoters

Introduction

It is widely predicted that the world population will increase to 9 billion by 2050 ⁽¹⁻²⁾. At the same time, economic improvements in developing countries around the world are predicted to result in an increased demand for meat, milk and other animal products, as those societies become more “westernised”. Even though there are calls for people in developed countries to reduce meat consumption for health reasons, particularly processed red meat, the demand for meat is predicted to continue to increase at a similar rate to that seen in the previous 10+ years. Over the last 50 years, tremendous advances in animal genetics and animal nutrition have been made to meet the increasing demand, particularly in pigs and poultry, but this has mainly been achieved using high quality feed

31 ingredients such as wheat, maize and soya. Over recent years these ingredients have become
32 increasingly more expensive, due to a combination of increased demand from the biofuels industry,
33 as well as for animal and human nutrition, along with shortages due to crop failures in some parts of
34 the world. It has been estimated that for many agricultural commodities the rate of production has
35 already reached a peak ⁽³⁾. Hence if we are to continue to meet the demand for animal products, we
36 cannot simply feed more animals the same feed ingredients, as that would require more crops, land
37 and water ⁽¹⁻²⁾.

38 Feed ingredients account for a large proportion of the overall costs of animal production, particularly
39 in non-ruminant species ⁽⁴⁾. Continuing to rely on the same ingredients, in competition with human
40 nutrition and biofuels, mean prices will increase and therefore the cost of meat and animal products
41 will also increase. Therefore the aim of current research is to improve the efficiency with which
42 animals utilise their feeds, giving more product for the same amount of feed or the same amount of
43 product for less feed. This is referred to as Feed Efficiency (FE), which is simply calculated as the
44 change in body weight divided by the change in feed intake (kg gain/ kg feed). Hence increased
45 efficiency would be greater gain per unit feed. Another term used is Feed Conversion Ratio (FCR),
46 which is the kg feed per kg gain, with improved efficiency associated with a lower FCR value (less
47 feed per unit gain). More recently animal scientists refer to Residual Feed Intake (RFI), which
48 compares the feed intake for each individual animal to the average for the herd/ group at the same
49 rate of growth ⁽⁴⁾. Hence an animal with a low RFI (often a negative value) would be eating less for the
50 same growth rate and therefore be more efficient than an animal with a high RFI (a positive value),
51 which would be eating more.

52 There is no doubt that selective breeding and improved diet formulations over the last 20-30 years
53 have improved the feed efficiency of pigs ⁽⁴⁾ and chickens ⁽⁵⁾, with FCR values of 2.0 or less currently
54 achievable (i.e. >50% efficiency). Indeed it is predicted that FCR values of 1.5 and less will be seen
55 relatively soon for both pigs and chickens (note that the lowest value theoretically possible would be
56 1.0, meaning 100% efficiency). In contrast, ruminants are a lot less efficient ⁽⁶⁾, with FCR values of 5.0
57 or more being normal (i.e. <20% efficiency). However we must remember that ruminants can utilise
58 ingredients not used for human consumption (e.g. grass and silage) and are therefore not competing
59 with humans, non-ruminants and biofuels for the high quality ingredients. Feed efficiency can be
60 improved in ruminants by feeding higher quality ingredients as concentrates ⁽⁷⁾, but that is not the

61 solution for the future. What we need is to maintain or improve the efficiency of livestock, while at the
62 same time maintaining or improving the quality of the animal products, but using alternative (human
63 inedible) feed ingredients as much as possible. In that way we will be converting human inedible
64 ingredients into high quality, human edible foods. This review will highlight a few ways in which this is
65 being achieved or might be achieved in the future.

66

67 **Use of enzymes as feed additives**

68 A number of enzymes are already used commercially as feed additives, particularly in non-ruminant
69 (pig and poultry) feeds, to increase the digestion and subsequent absorption of nutrients ⁽⁸⁻¹⁰⁾. They
70 are mainly used to improve the digestion of feed components that the animals cannot normally digest
71 or are only able to digest fairly poorly, such as complex carbohydrates and phytate. By increasing the
72 digestibility of the feed, more nutrients enter the body and less pass through in the faeces, resulting in
73 increased growth for the same level of feed intake, hence improving feed efficiency.

74 A number of enzyme feed additives are commercially available to improve the digestibility of cereal
75 carbohydrates, particularly targeting xylans and arabinoxylans present in the cell walls ⁽⁹⁾. By digesting
76 these important structural carbohydrates in the cell wall, that then allows the animals' own
77 carbohydrate-digesting enzymes (e.g. α -amylase) better access to the main starch stores within the
78 plant cells. Secondly, the digestion reduces the viscosity problems associated with arabinoxylans and
79 β -glucans ⁽⁹⁾. A number of studies have shown improved feed efficiency/ FCR of pigs and chickens
80 when these enzymes are added to the feed. For example, Xylanase supplementation of feed was
81 shown to improve FCR (1.41 vs 1.56 in controls) in broiler chickens by increasing weight gain, but not
82 affecting feed intake ⁽¹¹⁾. As well as increasing the digestibility of the carbohydrate component of the
83 feed and reducing the viscosity, there are suggestions that these carbohydrate-degrading enzymes
84 might have prebiotic actions on the gut microflora via the oligosaccharides they produce ⁽⁹⁾. This could
85 be another potential mechanism for their effects on feed efficiency. The absorption of nutrients across
86 the gut is also known to affect production of gut peptides, which can subsequently alter gut motility
87 and feed intake. Indeed Xylanase supplementation of feed has been shown to increase plasma PYY
88 levels in broiler chickens ⁽¹²⁾ and we have recent data showing effects of Xylanase supplementation
89 on plasma peptide YY, gastric inhibitory polypeptide and glucagon-like peptide-1 concentrations in
90 young pigs ⁽¹³⁾. Hence the regulation of gut peptides and their subsequent effects on gut motility, feed

91 intake and/or nutrient utilisation might be additional, alternative mechanisms for the effects of these
92 carbohydrate-degrading enzymes on feed efficiency.

93 Phytase is another enzyme used commercially in non-ruminant (pig and poultry) feeds ⁽¹⁰⁾. Phytase
94 digests Phytate (also called Phytic acid or inositol hexakisphosphate, IP6), the main storage form for
95 Phosphorus (P) in plants. Phytate (IP6) is inositol with 6 phosphate groups attached and phytase is
96 able to cleave individual phosphate groups, thereby releasing them for absorption and use by the
97 animal. Phytase supplementation results in greater absorption of P and calcium (Ca) from the feed in
98 broiler chickens and pigs ⁽¹⁴⁾, resulting in increased growth and reduced FCR. However, the increased
99 growth may not simply be due to increased absorption of these important micronutrients. Chicken
100 studies ⁽¹⁵⁾ have shown that high levels of Phytate in the diet inhibit pepsin and trypsin activities and
101 therefore inhibit protein digestion and amino acid absorption, resulting in increased FCR. Inclusion of
102 Phytase as well as high Phytate in the diet reduced the inhibitory effect on proteolysis, resulting in
103 improved (reduced) FCR ⁽¹⁵⁾.

104 Both of these feed additive enzymes have positive effects on feed efficiency in pigs and chickens fed
105 cereal-based diets. They do so by different mechanisms, meaning their benefits are likely to be
106 additive, but importantly they may allow the use of poorer quality (i.e. human inedible) feed
107 ingredients, an important consideration for future sustainability and food security. These and other
108 enzymes are also being investigated for use in ruminants ⁽¹⁶⁾.

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110 **Use of growth promoters/ metabolic modifiers/ anabolic agents**

111 There are 3 main classes of growth promoters ⁽¹⁷⁾ – beta-adrenergic agonists (BA), anabolic steroids
112 and growth hormone (GH, also called somatotropin, ST). They all improve feed efficiency in livestock
113 to some extent and this is associated with increased lean mass (particularly skeletal muscle) and
114 reduced fat mass ⁽¹⁷⁾. Indeed they have all been in the news at different times in relation to their illegal
115 use as performance enhancing drugs in sportsmen and women. Their effects on muscle and fat mass
116 were first discovered in the 1950s (anabolic steroids) or 1980s (BA and GH) and a number of
117 commercial products are currently licenced for livestock production around the world ⁽¹⁷⁾, although
118 they are all banned in the EU. For example, Ractopamine and Zilpaterol (both BA) are licenced for
119 use in pigs and/or cattle in North and South America, South Africa, India and Australia, but not China.
120 Similarly, the anabolic steroid mix of Trenbolone Acetate and Oestradiol (TBA & E2) is licenced for

121 use in beef cattle in North and South America, South Africa, India, Australia and China and GH (either
122 bovine or porcine ST) is licenced for use in dairy cattle or pigs in the same areas. We were unable to
123 find information for other parts of the world (e.g. Northern Africa and other parts of Asia), so to our
124 knowledge only the EU has a total ban on the use of these agents in livestock production. This is
125 despite much of the early research work being carried out in the EU, especially the UK, and the
126 original scientific reports suggesting their use was safe ⁽¹⁸⁾, as long as appropriate guidelines were
127 followed (e.g. a withdrawal period prior to slaughter).

128 At Nottingham, we have been comparing the molecular modes of action of BA and GH in both
129 sheep⁽¹⁹⁻²¹⁾ and pigs⁽²²⁻²⁴⁾ combining transcriptomic and metabolomics technologies in a systems
130 biology approach to identify novel mechanisms to achieve the same effects. Ultimately the aim is to
131 identify novel target genes/ proteins to develop more acceptable drugs or for targeted breeding or
132 nutritional manipulations. We have made good progress and have identified upregulation of the serine
133 biosynthesis pathway ^(19; 21; 23) and a number of other novel changes in response to BA and/or GH
134 treatments. We are currently performing proof-of-principle studies to determine whether the novel
135 genes we have identified really do regulate growth, body composition and/or feed efficiency. If
136 successful, the next stage will be to use this information to develop breeding strategies, new dietary
137 regimens or drugs that result in improved feed efficiency in livestock.

138 For proof-of-principle studies we often utilise transgenic animals (mainly mice) where the gene of
139 interest is either over-expressed or knocked out/ down (i.e. genetic manipulation or GM), often in a
140 tissue-specific manner. This is done to investigate whether manipulation of the specific gene results in
141 the predicted changes in tissue growth and/or metabolism, as well as changes in feed efficiency or
142 whole body energy expenditure. Such studies cannot be performed in cultured cells, so must be done
143 in animals. Although technically challenging, GM can now be achieved in livestock ⁽²⁵⁾, so that it will
144 theoretically be possible to produce herds of transgenic livestock. Indeed the Chinese government is
145 funding work using GM aimed at developing new breeds of livestock for agricultural use in the future,
146 including research into their safety ⁽²⁶⁾. One of the main advantages of GM over conventional animal
147 breeding is that GM speeds up the process and is more gene specific; whereas conventional
148 breeding, while very successful over the last 50 years, can result in unwanted side effects, both on
149 animal welfare but also product quality. The halothane pig ⁽²⁷⁾ and Callipyge sheep ⁽²⁸⁾ are prime

150 examples of this. Both have increased growth rates, particularly muscle, but one (halothane) results in
151 highly stressed pigs and both result in poorer meat quality.

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153 **Molecular studies of low Residual Feed Intake (RFI) animals**

154 The concept of low and high RFI has progressed rapidly over recent years ⁽²⁹⁻³⁰⁾. Studies are being
155 carried out around the world aimed at identifying specific genes (or markers) for improved feed
156 efficiency in virtually all livestock species (cattle, pigs, sheep, poultry). The genetic approach has
157 been to identify markers (Quantitative Trait Loci, QTL, or Single Nucleotide Polymorphisms, SNPs) of
158 low RFI for subsequent use in selective breeding programmes. For example, a Chinese group ⁽³¹⁾
159 recently identified a SNP in a microRNA (miR-1596) gene in chickens that resulted in reduced
160 expression of miR-1596 in livers and was associated with low RFI. Interestingly, they suggested there
161 were more than 70 target genes for miR-1596 ⁽³¹⁾, which were mainly involved in energy metabolism,
162 apoptosis and immune responses, with some being important proteins for assembling mitochondria.

163 We collaborated with another Chinese group ⁽³²⁾, to investigate differential gene expression in skeletal
164 muscle from pigs with low vs high RFI using a deep sequencing (RNAseq and miRNAseq) approach.
165 A number of mRNA (IGF2, FABP3 and PGC1a) and miRNA (miR1, miR30, miR10b, miR145) were
166 found to be differentially expressed, but importantly the majority of mitochondrial genes were down-
167 regulated. The data suggested that low RFI was linked with changes in expression of mRNA and
168 miRNA associated with increased muscle growth and reduced mitochondrial activity in skeletal
169 muscle ⁽³²⁾.

170 Effects on mRNA or miRNA associated with mitochondria appear to be a recurring theme in the low
171 RFI studies ⁽³³⁻³⁴⁾ and this agrees with some of our growth promoter studies, where we also see down-
172 regulation of a number of genes associated with mitochondria, including both Tricarboxylic Acid cycle
173 and oxidative phosphorylation genes (unpublished data).

174 Once again the genes being identified in these various RFI studies could be potential targets for novel
175 drugs, dietary regimens or GM in animals, as well as being used for conventional breeding strategies
176 to improve feed efficiency in livestock.

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180 **Conclusions**

181 There are tools already available to improve feed efficiency in meat production, including the use of
182 enzyme feed additives and growth promoters. Recent molecular studies are starting to identify other
183 mechanisms that might be utilised in the future, including manipulation of gut microflora or gut
184 peptides and targeting of gene expression in skeletal muscle or other tissues using drugs or GM
185 technologies. Whether the use of drugs or GM technologies will be acceptable to the EU general
186 public in the future remains to be seen, but we cannot simply wait until food and meat availability
187 becomes limited (or very expensive) before starting research on these more controversial topics. At
188 present, food and meat are readily accessible and reasonably affordable throughout most of the EU,
189 so the current ban on the use of growth promoters does not really affect the consumer. However this
190 might change if feed ingredients continue to increase in price and there are issues with crop failures
191 around the world limiting their availability for animal feeds. The EU might then have to reconsider the
192 ban or accept that meat and animal products will become more expensive and less accessible, as
193 well as potentially limiting the countries we import meat from. We should emphasise that safety and
194 quality of the products will always be a primary concern and must not be ignored in the drive to
195 improve feed efficiency for meat production. Indeed we would suggest that research into the safety
196 aspects must be carried out alongside the research into the manipulation of feed efficiency, as is
197 currently happening in China. Finally, we suggest that greater emphasis is needed on the use of
198 “poorer quality” ingredients in animal feeds in future, to reduce the competition with human nutrition
199 and biofuels for the high quality ingredients, such as wheat, maize and soya.

200

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205

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209

210

211 **Conflicts of Interest**

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214

215 **Authorship**

216 Both authors contributed equally to the planning and writing of this manuscript.

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