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Weight gain by gut microbiota manipulation in productive animals

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ABSTRACT

Antibiotics, prebiotics and probiotics are widely used as growth promoters in agriculture. In the 1940s, use of *Streptomyces aureofaciens* probiotics resulted in weight gain in animals, which led to the discovery of chlortetracycline. Tetracyclines, macrolides, avoparcin and penicillins have been commonly used in livestock agriculture to promote growth through increased food intake, weight gain, and improved herd health. Prebiotic supplements including oligosaccharides, fructooligosaccharides, and galactosyl-lactose improve the growth performance of animals. Probiotics used in animal feed are mainly bacterial strains of Gram-positive bacteria and have been effectively used for weight gain in chickens, pigs, ruminants and in aquaculture. Antibiotics, prebiotics and probiotics all modify the gut microbiota and the effect of a probiotic species on the digestive flora is probably determined by bacteriocin production. Regulations governing the introduction of novel probiotics and prebiotics vary by geographical region and bias is very common in industry-funded studies. Probiotic and prebiotic foods have been consumed for centuries, either as natural components of food, or as fermented foods and it is possible to cause the same weight gain effects in humans as in animals. This review presents the use of growth promoters in food-producing animals to influence food intake and weight gain.

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1. Introduction

The gut microbiota plays an important part in the harvesting, storage, and expenditure of energy obtained from the diet [1]. Over the last few years, new technologies have been developed that have enabled researchers to attempt more systematic studies on intestinal bacterial flora and have provided more reliable information about its composition [2]. Indeed, an increasing number of studies have connected imbalances in the composition of the gut microbiota with obesity and its associated diseases [3]. Data from agriculture, laboratory animals and humans show that manipulating gut microbiota results in weight modifications and that further investigation of the effects of routinely adding high amounts of bacteria to food is required [4]. The role of digestive microbiota is still largely unknown, but gut flora bacteria do contribute enzymes that are absent for food digestion [5,6].

In the last century, it became obvious that the incorporation of growth promoters into animal feed made it possible to improve animal health conditions and to decrease food production costs significantly [7]. An increase in the growth rate normally reduces the cost of producing meat and a wide range of techniques are now known to be effective in increasing the growth rate and extent of lean deposition in animals. The use of growth promoters is also being enhanced by the shortage of resources, such as animals, feed, water, and land. Animal gut microbiota have been manipulated through diet by means of feed additives, including antibiotics, probiotics and prebiotics. All these agents are typically ingested via feed or water, targeting the gut microbiota, where they initially play an antagonistic or barrier role in reducing the proliferation of pathogenic, opportunistic bacteria, preventing colonization and increasing energy intake [1]. As a result, livestock performance and feed efficiency are closely interrelated with the qualitative and quantitative microbial load of the animal's gut, the intestinal wall's morphological structure and immune system activity.

This review focuses on the use of growth promoters in animals and the possible mechanisms of action of these supplements.

2. Probiotics

Probiotics are live microorganisms, generally bacteria, but also yeasts that, when ingested live in sufficient quantity, have a positive effect on health in addition to the well-known nutritional effects [8]. The word “probiotics” is the antonym of the term “antibiotics”, which was introduced by Lilly and Stillwell in 1965, and indicates the substances produced by microorganisms that encourage the growth of other microorganisms [9]. Microorganisms used in animal feed are mainly bacterial strains of Gram-positive bacteria belonging to the types *Bacillus* (*B. cereus* var. *toyoi, B. licheniformis*, *B. subtilis*), *Enterococcus* (*E. faecium*), *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. farciminis*, *L. plantarum*, *L. rhamnosus*), *Pediococcus* (*P. acidilactici*), *Streptococcus* (*S. infantarius*); other probiotics include microscopic fungi such as strains of yeast belonging to the *Saccharomyces cerevisiae* species [10]. While a substantial number of microbial species have been reported to exhibit potential probiotic properties, established after *in vitro* and preclinical research and/or after full-scale clinical trials, only the most documented and robust strains make it to the market. A good probiotic agent should be nonpathogenic and nontoxic, should tolerate gastric acid, should adhere to gut epithelial tissue, and should produce antibacterial substances. Moreover, it should persist and withstand for short periods in the gastrointestinal tract.

2.1. The history of probiotics

Probiotic foods have been consumed for centuries before microbes were discovered, either as natural components of food or as fermented foods. Scientists in the 1800s mentioned the apparent effect on health of ingesting quantities of fermented milk products, but the reason for these effects on health remained unknown. In 1905, Nobel Prize winner Ilia Metchnikoff was the first to study the addition of lactic acid bacteria in food scientifically [11] (Fig. 1). He proved that it is possible to make edible fermented milk products by using pure cultures of *Lactobacillusbulgaricus,* and suggested that lactobacilli were able to eliminate pathogenic toxin-producing bacteria from the colon. In 1906, Henry Tissier isolated Bifidobacterium from an infant and claimed it could displace pathogenic bacteria in the gut and in 1922, *Lactobacillus acidophilus* was reported to improve chronic constipation, diarrhea and eczema in patients. *L. acidophilus*effects were also confirmed in 1932 in patients with constipation and mental illnesses [11]. In the 1940s, the use of *Streptomyces aureofaciens* probiotics resulted in weight gain in animals, which led to the discovery of chlortetracycline [1].

Between the 1950s and the 1980s, probiotic research focused on screening potential probiotic strains from isolates in nature or from human hosts, and defining the mechanisms of actions for probiotic strains. The term “probiotic” was first used by Lilley and Stillwell in 1965 to describe substances secreted by one microbe that stimulated the growth of another [12]. In 1966 a drug containing bifidobacteria was designed, and its industrial production began in 1972 [13]. The first proposed South African regulations regarding probiotics also appeared in 1972. The term probiotic, meaning food or drugs containing beneficial bacteria for a healthy lifestyle, appeared in world literature much later, in the 80s, following a renewed interest in these beneficial bacteria [14]. In 2001, the U.N. Food and Agriculture Organization redefined probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”. In 2008, it was proposed that probiotics may have the same growth-promoting effects in human as in animals [4]. In 2013, the World Gastroenterology Organization published its global guidelines on probiotics and prebiotics, and confirmed that the efficacy of probiotics is strain-specific and dose-specific, dispelling the myth held by many that any yogurt can be considered a probiotic. To date, there are three broad categories of probiotics: (1) those with no health claims, (2) those which are food supplements with a specific health claim and (3) those considered as a probiotic drug [15]. Moreover, it was proposed that probiotics may have various biological effects and should be treated as medicinal products before they can be approved [1].

2.2. Regulations and biases of probiotics

The regulations governing introduction of novel probiotics and prebiotics vary by geographical region [16]. In the EU, the introduction of novel foods that were not used in the EU before 15 May 1997 is governed by the Novel Food Regulation 285/97/EC. The Novel Food Regulation of 1997 is currently under revision and a proposed new regulation was published in December 2013. For bacteria added to foods, a list of microbes intentionally added to foods is updated annually (QPS, Qualified Presumption of Safety of Microorganisms in Food and Feed) and this list forms the basis of organisms at the species level which are considered safe for foods and feeds in the European Union (EFSA 2013 update). A novel probiotic or prebiotic can be a potential component of conventional foods, food supplements or foods for particular nutritional uses. When designated as a novel food, a safety assessment follows the European Novel Foods Regulation [17], and an evaluation is needed for the EC to make a decision on the safety of the novel component. However, the line between nutrition, pharma and cosmetics is often unclear [18]. While debates and controversies within the scientific community generally stimulate further research, there is a

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