Propionate: Hypophagic Effects Observed in Animal Models Might be Transposed to the Human Obesity Management

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Abstract: Volatile fatty acids (VFA) are the main energy source for ruminants, generally accounting for 50-75% of energy digested. They are produced from microbial fermentation of food in the rumen and are known to control food intake. Propionic acid, which is a major VFA produced in the rumen, is responsible of a feeding-induced behavior regulation in ruminants and its absorption results in a down-regulated energy intake in these animals. Although hypophagic effects of propionate have been extensively documented in ruminants and other farm animals, such evidence is almost nonexistent in humans. Interestingly, one human investigation tested the glycemic and insulinemic responses to ingestion of breads enriched with different additives. Amongst tested breads, propionic acid-enriched bread prolonged the duration of satiety compared with other breads tested. Therefore, the current literature survey reviews the physiological understanding of satiety control established in ruminants to bring up novel insights of feeding behavior control in human. Eventually, these challenging hypophagic properties of propionate could be transposed to the field of human obesity management.

Keywords: Feeding behavior, volatile fatty acids, appetite, satiety, food intake.

INTRODUCTION

Ruminants have access to a wide variety of feed to meet their nutritional requirements. The feeding behavior of these animals involves two distinct components: intake and rumination [1]. This latter is highly relevant to the fact that their feed originally consisted primarily of roughage. Fiber of roughage requires to be chewed back and swallowed for a given length of time through the mechanism of rumination in order to reduce fiber length and expose the cellular content of forage to the rumen microbes. The anatomical imposition of rumen fermentation between eosophagia and stomach (abomasum) to ingested feed degradable in the rumen results in a panoply of metabolic end-products. Given that the feeding behavior of ruminants is specific to their anatomy and physiology, some specific digestion end-products of rumination are behind satiety-control mechanisms.

In ruminants, the activity of eating occupies most of the daytime. Changes in feed intake kinetics, such as feed intake rate over time, have been widely studied in investigating satiation mechanisms. Rumen filling is a control of satiation process through a nervous control of rumen distension [2]. Conversely, the removal of rumen digesta boluses during a meal almost doubles the size of that normal meal [3]. Although rumen distension plays a central role in the before satiation process [4], biochemical intermediates produced during ruminal fermentation of feed also regulate short-term control of feed intake. In short-term control of feed intake, some digestion end-products send signals to the central nervous system through various nervous, metabolic or hormonal channels, contributing to the regulation of satiation process during feeding. However, their long-term effect is more complex, since a nutrient may cause premature satiation, without ultimately reducing feed intake. The current survey will focus on short-term control of feeding behavior since it is central to the feeding management of humans attempting to maintain or to reach healthy body weight.

VOLATILE FATTY ACIDS: THEIR ROLE IN FEED INTAKE CONTROL

The rumen forms a very efficient fermenter capable of rapidly digesting carbohydrate compounds found in plant fiber for which ruminants have no specific enzymatic system. The rumen digestion of carbohydrates essentially produces short-chain fatty acids, e.g. volatile fatty acids (VFA), with two to six carbon atoms. These are mainly represented by acetic, propionic and butyric acids, and to a lesser extent valeric and caproic acids with their isomers. The components that are not degraded in the rumen are digested in the abomasum and in the intestine, essentially as single-stomached animals. The relative proportion of VFA produced in the rumen varies according to the composition of the diet.

Volatile fatty acids are quickly metabolized when they pass through the rumen wall. Acetic and butyric acids will mainly be metabolized to ketone and acetoacetate compounds which are delivered into the blood, whereas propionic acid is almost totally converted into lactate in the ruminal epithelium or into glucose by hepatic gluconeogenesis. In ruminants, unless they are given high concentrate diets with

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high proportion of undegradable starch, there is little glucose digested in the intestine. Consequently, in ruminants glucose is primarily endogenously produced by the liver in a fed state, which contrasts with monogastric as human for whom gluconeogenesis is occurring only in a food-deprived state. VFA are the main energy source of ruminants, generally accounting for 50-75% of energy digested. Their production rate through the process of fermentation increases very rapidly as soon as feed enters the rumen. These two characteristics explain why VFA have been suspected to play an important role in satiation.

Many experiments have shown that intraruminal infusions of a VFA mixture (acetic, propionic and butyric acids) with a composition similar to that normally found in the rumen cause a decrease in feed intake during the course of a meal [5-7]. These effects on feed intake appear inversely proportional to the amount of VFA infused, and these responses vary according to individual VFA in the mixture. Among these three fatty acids, propionate likely plays the major and the special role [7-9]. The local administration of anesthetics into the rumen eliminates the hypophagic effects of acetate and butyrate infusions, but not the regulatory effects of propionate infusions [10]. Although reduced stomach or rumen pH are known to decrease feed intake [5-7], administrating these organic acids (propionate) as a salt component (sodium propionate) induced similar responses. An infusion of sodium propionate into the hepatic portal vein depresses intake in sheep, whereas a similar infusion into a jugular vein exerts no regulatory effect on intake [11]. In order to clarify the nervous regulation of feed intake by propionate, lesions of the nerves of the hepatic plexus eliminate the down-regulatory effect of propionate on feed intake in the portal vein [11,12]. This control of feed intake also involves neural receptors in liver sensitive to the availability of oxidizable substrates, including propionate [13]. Thermo- and osmo-receptors in liver appear also involved in this satiety process [14].

In light of these several lines of evidence, there are a great number of receptors in various parts of the digestive tract and associated organs, which are sensitive to several physical and chemical stimuli and which transmit their information to the central nervous system via several routes [2].

MAIN EVIDENCE LINKING PROPIONATE AND FEED INTAKE CONTROL

High rate of ruminal fermentation associated to degradable compounds in the rumen, such as starch, increases the production of VFA with a greater proportion of propionate produced. In lactating dairy cows, a bovine specie requiring a high concentrate diet in early lactation, propionate exerts greater hypophagic effects than acetate [15]. Although hypophagic effects of propionate have been extensively documented in ruminants [8,10,16-20], some evidence did not corroborate its effect on feed intake [21-24]. These inconsistencies are likely explained by a threshold effect of propionate on feed intake control. Unless propionate portal flux exceeds that threshold, feed intake is not negatively regulated by that VFA. This concept agrees with high intake of rumen fermentable grains by lactating dairy cows without reduction of dry matter intake [25].

The dose-response effects of propionate on feed intake were investigated previously in lactating dairy cows [21] and in sheep [8]. These results rely on 3-h infusion periods of propionate and infusion rates represented a propionate mass effect typical to a meal size. Given that cows are capable of compensating smaller meal size by increasing meal frequency [15], 14-h dose-response to intraruminal propionate infusions on feeding behavior were investigated in lactating dairy cows [26]. The results of this study corroborate the central role of propionate in feed intake control which modifies both satiety and hunger. This statement is further sustained by the reductions in dietary energy intake with propionate infusions that were greater than the energy supplied from infusates.

Although the role of propionate in feed intake control is established in ruminants, there is a rarity of such kind of evidence in single-stomached animals. The majority of the studies on this topic had as a goal to better understand feed intake control of farm animals in order to improve growth performances and economic productivity. Accordingly, similar evidence on hypophagic effects of propionate in monogastric animals come from studies using broiler chicks or turkeys. Pinchasov and coworkers [27] showed that the incorporation of propionic acid into a low-energy diet significantly inhibited voluntary feed intake. However, after 10 weeks of *ad libitum* consumption, dietary propionate supplementation was proven less effective in controlling pullet growth than conventional feed restriction [27]. The depression of feed intake and body weight by propionate fed as sodium propionate is induced what ever the route of administration, e.g. in drinking water or through the feeds in hatched turkeys [28]. Similarly, voluntary feed and energy intakes, as well as body weight gain, decreased significantly with the inclusion of propionic acid in the diet of female broiler chicks [29]. Moreover, the relative weight of the abdominal adipose tissue was proven significantly decreased with the dietary inclusion of propionate.

PIG AS A GOOD MODEL FOR STUDYING OBESITY IN HUMANS

As mentioned above, there is no evidence in the literature pertaining to propionate and feed intake in single-stomached animals such as cats, dogs or monkeys, particularly because of the fact that these animals are not bred in term of productivity. However, the domestic pig has many similarities with humans, making it an excellent research model to study the metabolism on several aspects [30]. Interestingly, current developments in the farming of fast-growing pig lines have created new perspectives for the study of human obesity, which for decades has been a major public health problem in economically developed countries and which has recently become a serious concern in economically underdeveloped countries [31]. In fact, the increased proportion of obese individuals in the world's population has led to epidemics of type 2 diabetes, which has lost its connotation of adult-onset disease and is turning into the world's leading public-health threat [32]. This simultaneous raise of obesity and type 2 diabetes prevalence

supports James Neels' "thrifty gene" theory [33], which hypothesized that there exist metabolically thrifty genes that permit a more efficient use of food, fat accumulation, and rapid weight gain during periods characterized by food abundance and subsequent famine. It is argued that before these genes that resulted in high levels of insulin and leptin and that were advantageous under the conditions of unpredictably alternating feast and famine typical of past centuries have become a disadvantage in the modern affluent world, causing both obesity and diabetes [32].

The mechanisms of genetic selection for a better utilization of food are active in feral pigs, as well as in humans. This has been demonstrated in wild pigs from Ossabaw Island (Georgia, USA), which were well adapted to feast and famine but which, when put on a high-fat diet and exercise restrictions, shortly developed traits preceding diabetes and heart disease, such as increased sugar and fat levels, hypertension, and arteriosclerosis [34]. However, this is only a confirmation of previous reports that pointed out similarities between pigs and humans in the genetic control of growth and fat-accumulation traits, suggesting that pigs are likely a representative model for studying human obesity [35]. It appears that pigs mimic the health problems of obese humans so well that they could be much more useful in studying diabetes and heart disease [34] than other animal models, such as rodents or fatty worms [36]. In addition, this animal model offers the advantages of low genetic variance, homogeneous feeding regime, the absence of confounding factors typical of humans, such as smoking and alcohol consumption, and the availability of body fluids and tissues. Moreover, the known anatomical and physiological similarities between pigs and humans suggest that pig is preferable to other more common animal models for studying human obesity and cardiovascular pathologies [30].

With regard to propionate in this model, a study of Giesting and Easter [37] was conducted to assess the effects of organic acid supplementation on performance of starter and finisher pigs. Results showed that the addition of each acid (fumaric and citric acids) improved the efficiency of gain, while propionate depressed feed intake. Similar results were found by Castell and coworkers [38] who observed reduced average daily weight gains and feed intake when propionate was present in pig starter and grower diets. Accordingly, this evidence showed the hypophagic effects of propionate in an animal model that is similar to human on many aspects.

PROPIONATE AND FOOD INTAKE CONTROL IN HUMANS

Two studies from Liljeberg *et al*. [39,40] assessed glycemic and insulinemic responses in addition to satiety scores after ingestion of barley bread enriched with different additives in healthy human subjects. Results showed that consumption of bread baked with sodium propionate significantly lowered the postprandial blood glucose and insulin responses, and significantly prolonged the duration of satiety compared with all other breads. Other studies also observed that postprandial glucose and insulin responses were lower after ingestion of a bread with added sodium propionate than after ingestion of a reference bread [41,42]. As shown in Table **1**, when calculating the areas under the satiety curve (0-180 min), a significant higher value was found with the bread baked with the high concentration of sodium propionate than with whole-meal bread (reference product) [39].

Table 1. Areas Under the Satiety Curve (AUC) for the Bread Products

	AUC (unitless)*
Whole-meal bread	316.2 ± 76.7^{a}
Plus sourdough	317.2 ± 42.5^{ab}
Plus lactic acid	393.9 ± 62.5^{ab}
Plus Ca-lactate	425.9 ± 75.4^{ab}
Plus Na-propionate	409.7 ± 72.9^{ab}
Plus Na-propionate, high concentration	510.7 ± 89.8^{b}

Values are means ± SEM, $n = 11$. Values not sharing the same letters are significantly different ($p < 0.05$). Table adapted from Liljeberg *et al*. [39]. * Satiety was measured with a unitless scale [45].

Darwiche and coworkers [42] showed that the gastric emptying rate of the barley bread decreased markedly after the addition of sodium propionate [see Fig. (**1**)] and was accompanied by lowered glycemic and insulinemic responses. Thereby, prolonged postmeal satiety usually occurs concomitant with low gastric emptying rate because the extension of the stomach is potentially a factor that promotes a feeling of satiety. As previously discussed by Liljeberg and Björck [40], different theories have been presented regarding the effects of salts of organic acids on gastric emptying. A nonspecific acid or pH receptor situated in the proximal part of the small intestine is responsible for the inhibition of gastric emptying [43]. The mechanisms by which sodium propionate affects gastric emptying have not been clarified to

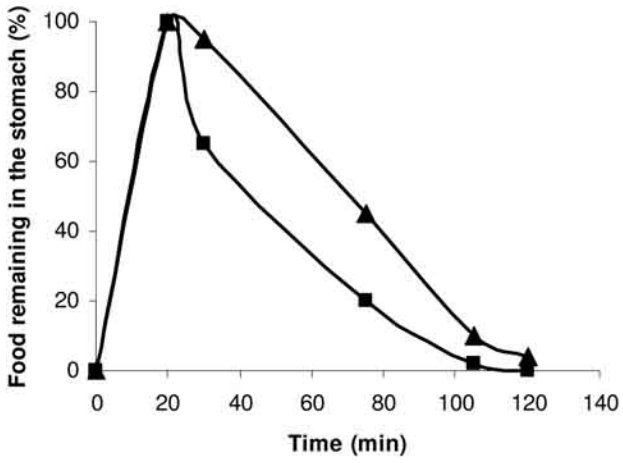

Fig. (1). Median amount of food remaining in the stomach in healthy subjects after ingestion of a whole-meal barley bread (■) and an identical bread with added sodium propionate (▲). $n = 9$. Figure adapted from Darwiche *et al*. [42].

date. However, an influence of sodium propionate on gastric secretion is a possible mechanism [42].

PROPIONATE: COULD THE HYPOPHAGIC PROPERTIES OBSERVED BE TRANSPOSED IN TERMS OF OBESITY MANAGEMENT?

Worldwide, the prevalence of obesity and overweight in industrialized countries and in a substantial number of developing countries is estimated to range from 40-60% [44]. This problem represents an enormous burden on health care systems and, most importantly, the quality of life of the affected individuals is substantially lowered. Even though extensive research and public awareness efforts have been made over the previous decades, the proportion of people affected is still rising.

Obesity is a result of a higher energy intake compared to the quantity of energy expended. Our modern lifestyle has made available more energy-dense food while many physical activities have become facultative in daily life. Both of these factors contribute to the disequilibrium in energy balance, resulting in a positive energy balance. Thereby, overweight and obesity are associated with a large variety of health consequences and the increase in obesity prevalence is occurring despite the growing public awareness about this issue.

With respect to this alarming state, the beneficial potential of propionate on energy balance is likely a sound aspect of feed intake control to be investigated in future experimental studies. It is innovative and might be an interesting opportunity to relate animals and humans in the field of obesity management.

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