NEURAL AND HORMONAL CONTROL OF INTAKE: BIOACTIVE PEPTIDES

Mark A. Froetschel
The University of Georgia
Athens, GA

ABSTRACT

Dietary protein in excess of requirements is related positively to intake and digestive function of ruminants. This effect may be traced to the presence of certain biologically active peptides found in specific protein sources and their effects on gastrointestinal motility and endocrine regulation. Exorphins, a particular class of peptides that are released during digestion of certain proteins and absorbed intact, modulate gastrointestinal motility, secretions and endocrine metabolism by binding to specific opioid receptors. Casomorphins are a type of exorphins found in milk protein. Opioid activity of exorphins can be demonstrated by blocking their effects with a pharmacological antagonist such as naltrexone. In mature ruminants, abomasal casein infusion results in naltrexone reversible inhibition of reticular motility and enhanced digesta passage. Feeding a commercially blended protein supplement to ruminants resulted in naltrexone-reversible effects on reticular motility, reticulo-omasal orifice opening and circulating levels of insulin. Bioactive peptides may be responsible for stimulatory effects of certain protein sources on intake and digestive function of ruminants.

INTRODUCTION

A multitude of interrelated factors are involved in regulation of digestive function and intake. These processes are ultimately mediated in the brain via the autonomic nervous system (Miner, 1992). The chemical and physical composition of the feed consumed provides the external stimuli. Nutrient metabolites, hormones and neurotransmitters provide the signals that relay peripheral information to the brain and control intake. Identification of dietary factors that modulate these signals may enhance development of practical methods of increasing intake and productive efficiency of livestock. Proteins may play a more pivotal role in regulation of digestive function and intake than suspected previously. A number of bioactive or regulatory peptides present in dietary proteins influence digestive and metabolic status (Ziouardou et al., 1979). The objective of this paper is to provide rationale that dietary bioactive peptides can influence digestive function and intake in ruminants.

Dietary Protein and Intake

Caloric density is well recognized as the primary dietary determinant associated with feed intake (NRC, 1987). The relationship between caloric density and intake regulation is consequential to the animal maintaining its energy balance. Dietary protein is involved in intake in a more subtle manner. The mechanism for the effect of dietary protein on intake depends upon the level fed relative to both ruminal and metabolic requirements. When protein is fed below the nitrogen requirements of the rumen bacteria, then intake is linked to action of protein stimulating ruminal microbial growth with subsequent changes in digestion and passage (Van Soest, 1982). When protein is fed below the animal's requirements, then intake is often linked to additional protein stimulating anabolism and associated energy requirements. It is more difficult to explain the positive effects of dietary protein on intake when protein is fed at levels that exceed the animal's protein requirement. Ketelaars and Tolkamp (1992) reported a positive quadratic relationship between dietary crude protein supplied and intake ($r^2 = .65$) using a large data set (851 observations) from experiments with sheep fed roughage-based rations. This relationship was a function of organic matter digestibility and the intake response associated with dietary protein was greater when more digestible rations were fed. These researchers noted that the positive effect of dietary crude protein was evident at levels exceeding those that would limit ruminal microbial fermentation (12.5 to 25% CP) and postulated a metabolic mechanism for this result. Wilkerson et al. (1993) amassed a data set consisting of 11 research trials that used 543 growing steers (253 kg) fed roughage-based rations to estimate requirements and efficiency of metabolizable protein. These cattle all were fed incremental levels of supplementary protein above urea-fed controls. A
positive, linear relationship ($r^2 = .63$) between metabolizable protein fed and intake (250 to 550 g/d) can be constructed from their data set. Therefore, it appears that level and source of dietary protein can have a positive effect on intake of growing ruminants fed roughage-based rations. This result is further confirmed by a number of experiments that demonstrate positive effects of undegraded intake protein on intake, digestibility and production responses of lactating dairy cattle (NRC, 1989).

The relationship between dietary protein and intake is not as apparent in research data from feedlot cattle. There are very few feedlot studies that have used a wide range of dietary CP from natural protein sources as experimental treatments. One such experiment compared urea vs. soybean meal supplementation to attain levels of crude protein from 11 to 17% (Braman et al., 1970). These researchers did not detect any effects on intake, but added soybean meal improved gain and feed efficiency of cattle, especially in the early phase of the trial. More recent studies (Eck et al., 1988; Sindic et al., 1993) have demonstrated positive effects of feeding blends of animal and plant protein sources on gain and feed efficiency of feedlot steers, however, these researchers did not detect effects on intake and did not feed levels of crude protein higher than 13.25%. Based on limited data, it appears that the feed intake response to dietary crude protein fed at levels above the animal’s requirement is less in feedlot cattle than in cattle fed forage diets. Nevertheless, considering the results of ruminants fed roughage-based rations, more research is needed to understand why such cattle consume more feed when they are fed certain sources and levels of protein.

Bioactive Peptides

A number of regulatory peptides have been reported to be present in both exocrine secretions (Young et al., 1987; Rao, 1991) and as components of dietary proteins (Meisel and Schlimme, 1990; Koldovsky, 1989; Daniel et al., 1990). Their function is dependent on the ability of these peptides to pass through the small intestine and to be absorbed with their biological activity intact. These peptides can then serve as communication signals that relay information regarding nutrient supply and digestive efficiency to the central nervous system. These compounds are known as bioactive peptides and one particular class, exorphins (Zioumdrou et al., 1979), exert opioid activity that can influence physiological parameters associated with regulation of digestive function and intake (Meisel and Schlimme, 1990; Daniel et al., 1990). Although the relationship of bioactive peptides to intake regulation remains to be demonstrated, their absorption would relate temporarily to feed termination. In a review of intestinal absorption of protein, Webb (1990) discussed several experiments that demonstrate the capability of the ruminant small intestine to absorb intact peptides (mostly di- and tripeptides). Peptides as small as 3-4 amino acids have been identified as having opioid activity (Daniel et al., 1990).

Milk protein and specifically casein has been studied in great detail as a source of opioid peptides, especially in regard to nutrition of human neonates. Although the effects of casein as a source of biologically active peptides has not been studied extensively in ruminants, several experiments have used casein as a post-ruminal infusion. Studies involving post-ruminal infusion of casein have set the groundwork for developing the concept of a ruminally non-degradable protein requirement for high-producing, lactating dairy cattle (Spiers et al., 1975). The positive production response to post-ruminal casein infusion has been largely attributed to the supplementation of limiting amino acids; however, other factors may be involved.

The biologically active peptides in casein that have received the most attention are referred to as β-casomorphins. The apparent resistance of these peptides to proteolytic attack is attributed to their relatively high content of proline residues. Daniel et al. (1990) demonstrated that gastric emptying rate, as well as gastrointestinal transit time, were significantly longer when young rats were given a casein suspension than when they were given a whey protein suspension via gastric tube. In addition, these effects were eliminated with an intraperitoneal injection of naloxone administered prior to the protein suspensions. Opioid antagonists such as naloxone or naltrexone block receptors and reverse opioid effects and thus are used to identify these peptides. The potential for β-casomorphins to have a similar effect on gastrointestinal motility and passage rate in adult ruminants is intriguing. Ruckebusch (1983) states that there are two major central inhibitory pathways that influence ruminal motility. The first involves adrenergic modulators and influences ruminal intrinsic motility (tone). The second involves an opioid inhibitory system that influences extrinsic contractions (frequency). Opioid peptides reportedly exist in protein sources besides casein and include
such plant proteins as gluten, gliadin, zein, hordein and soy α-protein (Meisel and Schlimme, 1990). Presence in a variety of proteins suggests these peptides may play a general role in feedback regulation of digestive efficiency of dietary proteins. In addition, differences in the relative opiate activity of hydrolysates of various protein sources (Zioukdou, 1979) have been identified and may be responsible for effects of specific protein sources on intake and digestive function in cattle.

Kil and Froetschel (1994) demonstrated that casein infused into the abomasum has a “casomorphin-like effect” on reticu-culoruminal motility and digesta passage. Casein solutions were infused at 0, 1.25, 2.5 and 5.0% (w/v) for 3 h at 16.7 ml/min. Each treatment was administered to one of four ruminally and abomasally cannulated steers (603 ± 22.7 kg) during one of four infusion periods. Steers were fed foraged-based rations (58% sorghum silage), at maintenance, in 12 equal meals at 2-h intervals. Motility was measured manometrically and detailed descriptions of physiographic tracings were accomplished using a digitizing tablet (Landel Scientific). During the 3-h infusion period, the frequency, duration, amplitude and area (amplitude .5 duration) of reticular contractions decreased linearly with infusion by 3.1 to 5.1%, 2.0 to 4.0%, 5.8 to 15.5%, and 11.3 to 18.5%, respectively. Ruminal volume was reduced linearly with infusion by 5.6 to 8.2% after the 3-h infusion period. The duration of the second phase of the reticular contraction, which corresponds with the opening of the reticulo-omasal orifice (Kelley et al., 1991) was reduced by 1.0 to 3.9%. These results show that although abomasal casein infusion results in a casomorphin-like effect on reticular motility, it may stimulate passage.

A second experiment (Kil and Froetschel, 1994) was conducted to determine whether the effects of abomasal casein infusion on reticulo-ruminal motility were mediated by opioid peptides. Four steers were infused abomasally (4 h) with either a 5% (w/v) solution of casein or its hydrolysate with or without a preload of naltrexone as an opioid antagonist (.5 mg/kg BW) in a 2 x 2 factorial designed experiment. The hydrolysate decreased contraction frequency within 30 min of infusion and 60 min prior to effects of intact casein. Naltrexone reversed the motility effects of casein and accentuated the effects of the hydrolysate. Ruminal liquid outflow, as measured by the disappearance of a pulse dose of cobalt-EDTA was decreased by 17.9% with the hydrolysate. Naltrexone had an effect on contraction duration that was independent of abomasal infusates, indicating that it blocked basal activity of endogenous opioid peptides or interacted with other neurotransmitters that influence gut motility. These results demonstrate that casein exerts naltrexone reversible inhibition of gastrointestinal motility in the ruminant. The hydrolysate exerted inhibitory effects sooner than did the intact protein, and these effects were amplified by naltrexone. Overall, the negative effects of the hydrolysate on reticular motility were less than those caused by intact casein. These responses are consistent with β-casomorphins plus a dual excitatory-inhibitory, gut motility response to antagonists as have been reported previously (Kroner, 1989). These results indicate that casein and its hydrolysate differ in their opioid activity, probably due to differences in their peptide availability.

A recent study was completed with abomasal and ruminally fistulated steers to determine if a commercially blended protein supplement (Wayne Feeds Div., Continental Grain Co., Chicago, IL) would exert opioid-mediated effects on reticulo-ruminal motility and on circulating levels of plasma insulin (Froetschel et al., 1994). The supplement, consisting of a mixture of blood meal (30%), fish meal (30%), corn gluten meal (24.5%) and meat and bone meal (12.0%), was estimated (NRC, 1989) to contain 47% undegraded intake protein (UIDP). Four steers were fed isonitrogenous diets containing either 30% UIP with urea (.18 lb./head/d) or 40% UIP with the supplement (1.4 lb./head/d) in a 2 x 2 factorial designed experiment. The diets were forage based (57% wheat silage:43% concentrate) and fed at a maintenance level of intake. After 10 d of being fed the experimental diets, steers received either saline or .5 mg/kg of naltrexone as an opioid antagonist, at feeding, via their abomasal cannulae. Thereafter, reticular motility was measured and jugular blood samples were collected for 8 hours. Reticular contractions were 11.3% less frequent and 8.0% shorter in duration with the 40% UIP vs. the 30% UIP diet. With naltrexone, reticular contraction frequency was 6.8% faster when cattle were fed 40% UIP but 16.5% slower with 30% UIP. The reticulo-omasal orifice opening time was 11.5% longer in duration when cattle were fed 40% UIP vs. 30% UIP. The pattern of motility response observed indicates that the protein supplement exerted an opioid-mediated effect. Reticular contractions, needed primarily for mixing digesta, were reduced. In contrast, the reticulo-omasal orifice contractions needed for passage were increased.
when steers were fed the protein supplement. These effects were reversed with administration of the opioid antagonist naltrexone. The effects of opioid peptides on the opening of the reticulo-omasal orifice may be responsible for enhanced digesta passage and increased intake by cattle fed certain protein supplements. This also may explain the observation that dairy cattle fed greater levels of protein excrete feces of greater liquid consistency (Ireland-Perry and Stallings, 1993).

There was a characteristic post-prandial rise in insulin that occurred 1 to 3 h post feeding. The basal level of insulin and the post-prandial rise was 20.9% and 42.2% higher when steers were fed 40% UIP vs. 30% UIP. After naltrexone administration, basal levels of insulin did not differ, and the post-prandial rise was 41.4% less. These results indicate that insulin secretion may be regulated partly by the presence of dietary opioid peptides. Both post-prandial and basal levels of insulin were influenced by the UIP protein supplement but effects were reversed with naltrexone administration. More research is needed to assess the impact of protein sources that may contain opioid peptides on insulin because of its role in intake regulation (Deetz and Wangness, 1980; Deetz et al., 1980; NRC, 1987).

CONCLUSION

Certain sources of dietary protein fed at levels that exceed the animal’s requirement stimulate intake by ruminants. The mechanism responsible for this effect remains to be elucidated. A potential mechanism may be the bioactive peptides present that can influence digestive function and hormonal profiles associated with intake. In addition to bioactive peptides, certain amino acids and polyamines also may be responsible for intake responses associated with dietary protein. Understanding the role of protein metabolites on intake regulation could lead to both dietary and pharmacological methods of increasing feed intake by livestock.

LITERATURE CITED


