Recent Advances in the Central Control of Intake in Ruminants

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ABSTRACT: Neuropeptide Y (NPY) is a strong stimulant of feed intake in sheep as well as in rodents. The information available indicates that it functions in vivo in the modulation of feeding within the central nervous system, more specifically, within the hypothalamus, and probably within the paraventricular nucleus. Injected NPY can override a variety of satiating factors, including those arising from normal feed intake, artificial distension of the reticulorumen, and intraruminal infusion of sodium propionate. Even so, these satiating factors are able to reduce feeding in the face of at least one dosage of exogenous NPY. Neuropeptide Y has specificity in regard to ingestive behavior in rats. It stimulates feeding and drinking but does not alter grooming behavior. It also preferentially enhances carbohydrate appetite. The possibility that specific appetites are influenced by NPY has not been investigated in ruminants. Finally, further investigations of NPY should enhance our knowledge of feed intake and energy balance regulation and its linkage with reproductive physiology.

Key Words: Cholecystokinin, Feed Intake, Feeding Behavior, Neuropeptides, Norepinephrine, Ruminants

Introduction

The ability to manipulate feed intake may ameliorate the problems associated with shipping stress, disease states, and digestive disturbance caused by changes in diet. Production by livestock under more normal conditions could be enhanced with increased feed intake, or if feedstuffs of lower digestible nutrient content were applied in tandem with increased feed intake, then previous production levels could be maintained at lower cost. Given that a large part of the diet is used for maintenance, even a small adjustment in feed intake could have a large influence on production.

Background

To pragmatically develop a means of manipulating feed intake one must have some understanding of its endogenous regulation. This regulation is linked with an animal's drive to control energy balance. This is evidenced by 1) chickens that reduce their feed intake in response to receiving glucose in drinking water or by other means (Azahan and Forbes, 1989), 2) rats that eat more than normal after being fed less than normal by tube, and vice versa (Harris et al., 1986), and 3) dogs that eat more volume of a diet diluted with cellulose (Cowgill, 1928). This concept applies to ruminants as well. Baile and Della-Fera (1981) reviewed several indications of energy balance control in ruminants. In contrast to energy, dietary insufficiency of other essential nutrients generally reduces feed intake. In some situations feed intake is predominantly influenced by factors unrelated to energy status. These include disease states and low diet digestibility (Conrad et al., 1964).
For an animal to regulate energy balance there must be a mechanism for monitoring energy status that includes signals of 1) body energy content, 2) energy intake, and 3) energy utilization. These signals presumably would be communicated to an integrator that determines hunger or the drive to eat. It is accepted that the integrator is somewhere in the brain, but confusion exists about the identity and importance of individual signals, their means of communication with the brain, and how the brain processes the information. Numerous investigations have focused on roles for digestive end products, peripheral hormones, and physical limitations of the digestive tract as signals influencing relative satiety or hunger. Most of these data have been reviewed several times (Baile and Forbes, 1974; Baile et al., 1983; DeJong, 1986; Forbes, 1987; Grovum, 1987; Theurer and Wanderley, 1987; Carter and Grovum, 1990). Although intake control of ruminants has much in common with that of nonruminants, species variations exist. In rats, the movement of digesta into the duodenum causes release of cholecystokinin (CCK), which apparently by binding receptors on the stomach relays a signal sequentially through the vagus nerve and nucleus of the solitary tract to the paraventricular nucleus of the hypothalamus, an important area in terms of neural influences on feed intake by the central nervous system (CNS). Conversely, CCK in the gut of sheep does not seem to have this function, although it is most likely an important mediator of satiety at the CNS level (Grovum, 1982; Baile and Della-Fera, 1984).

Although much remains unknown about how the brain processes peripheral information, some progress has been made. Early work in sheep and goats suggested that, as in rats, the ventromedial hypothalamus mediates satiety and the lateral hypothalamus mediates hunger (Larsson, 1954; Wyrwicka and Dobrzecka, 1960; Baile et al., 1968). Several endogenous neurochemicals are believed to transmit information between neurons in the feeding circuitry. In ruminants, cholinergic and α- and β-adrenergic agonists elicit feeding when injected at discrete hypothalamic loci (Baile et al., 1973; Driver et al., 1979). Injection of 5-hydroxytryptamine into certain hypothalamic areas stimulates feed intake in sheep (Baile et al., 1979). Agonists of μ- and κ-opiate receptors promote feeding in sheep, whereas the δ-opiate receptor agonist, (D-Ala₂, D-Leu⁵) enkephalin, suppresses feeding (reviewed by Della-Fera and Baile, 1984). Infusion of CCK into a lateral cerebroventricle reduces meal size specifically, whereas infusion of a CCK antibody enhances feed intake in sheep (Della-Fera and Baile, 1979, 1981).

Neuropeptide Y

More recently, CNS modulation of feed intake in sheep has focused on neuropeptide Y (NPY). The NPY story began when Tatemoto (1982) reported its isolation during a search for novel C-terminal, α-amidated peptides in porcine brain. Neuropeptide Y is composed of 36 amino acids. Its name owes to its amino- and C-terminal tyrosine residues and tissue of origin. The sequence of NPY has not been determined in a ruminant, but guinea pig, rabbit, rat, and human forms are identical and differ from the porcine form only by having a methionine instead of leucine at position 17 (Corder et al., 1984, 1988; O'Hare et al., 1988).

Allen et al. (1983) reported that NPY is localized neuronally and in high concentration in rat brain. Antonopoulos et al. (1989) reported the presence of
NPY-like immunoreactivity in several areas of sheep brain, including the hypothalamus. By 1984 two laboratories had published on the feeding-stimulatory action of intracerebroventricularly (i.c.v.) administered NPY in rats (Clark et al., 1984; Levine and Morley, 1984). An appreciable increase in feed consumption by rats and sheep can be detected within 30 min of an i.c.v. injection (Figures 1 and 2). An equal dosage of NPY injected peripherally does not influence feed intake, which supports the theory that this peptide modulates feed intake at the CNS level in both rats and sheep. The influence of NPY on feeding in rats is specific for carbohydrate, and NPY does not alter grooming behavior (Levine and Morley, 1984; Stanley et al., 1985b). Stanley et al. (1985a) injected NPY into seven regions of the brain of rats and produced hyperphagia when they targeted the paraventricular nucleus or the lateral or ventromedial hypothalamic areas but not other brain regions. This suggests that NPY functions in specific hypothalamic loci to modulate hunger. The effect of NPY administered i.c.v. on intake is likely mediated by the paraventricular nucleus and/or ventromedial hypothalamus rather than by more lateral hypothalamic areas because of their proximity to the third ventricle. Further support for this notion is the discovery that the content of NPY in the paraventricular nucleus, and in vivo NPY release from this site, are elevated before feeding and decrease upon feed consumption (Sahu et al., 1988b, 1990). Furthermore, NPY content in this locus is elevated in genetically obese Zucker rats compared with lean controls (Beck et al., 1990). This may indicate that aberrant control of NPY production leads to development of the hyperphagia associated with this genetic obesity. Anorexic humans, conversely, exhibited significantly elevated cerebrospinal fluid NPY concentrations compared with normal humans (Kaye et al., 1989). Perhaps in this situation there is a reduction in sensitivity to NPY.

In sheep, the greatest effect of bolus i.c.v. NPY injections is observed within 30 min. After 2 h of feeding the rate of feed consumption is similar between NPY- and vehicle-treated animals. By delaying access to feed we found that NPY is still a potent feeding stimulant 2 h (or 4 h) after injection (Figure 3). This indicates that the time-dependent diminishing response to a bolus NPY injection (Figure 2) is actually a result of feed consumption and is not due to phenomena such as degradation or dilution of the peptide. Feed consumption would be expected to trigger a peripheral satiety signal that could antagonize a tonic NPY-mediated hunger. Data obtained from parabiotic pairs of mice suggest the existence of a peripheral satiety factor but do not support the theory of a circulating hunger factor (Coleman, 1978). Seoane et al. (1972) found that hungry sheep consume less when cross-circulated with blood from satiated sheep, and vice versa. A potential hunger factor in sheep has not been ruled out, therefore. However, in light of the evidence against a hunger factor in mice, it seems that the increased feeding in satiated sheep when cross-circulated with blood from hungry sheep is due to dilution of a satiety factor. Such a factor could be responsible for diminishing the response to NPY. Two likely satiety factors in the ruminant were tested for their ability to antagonize NPY-induced feed intake in sheep. Feed intake by sheep treated with both NPY and ruminal displacement (the displacement of intraruminal volume by a water-filled balloon) is similar to that of untreated animals (Figure 4). This indicates that reticuloruminimal fill resulting from feed intake could be responsible for the diminished feeding response observed > 2 h after injection (Figure 2). It should

![Figure 2. Feed intake by sheep after intracerebral ventricular (icv; upper panel) or intravenous (iv) injection of neuropeptide Y (NPY). Bars represent SEM calculated from error mean square of analysis of variance. After i.c.v. injection, 2.35 and 11.8 nmol NPY-treated sheep exhibited greater (P < .05) feed intake than vehicle-treated sheep. No differences were detected after i.v. injection of NPY. Feed intake after 24 h was not influenced by treatment (Miner et al., 1989).](https://example.com/figure2.jpg)
be noted that although the experimental technique displaced ruminal contents, the resulting distension may have been sensed in the reticulum if digesta were forced in that direction (Grovum, 1987). The level of displacement used in this study was estimated to be twice that which normally occurred in these sheep after 1 h of feeding during a control treatment. In other words, the balloon volume was twice the measured volume of feed wetted to ruminal moisture content that control sheep consumed in 1 h. Balloon volume was only 16% of ruminal capacity (Miner et al., 1990b). In this study, ruminal fill in sheep with ad libitum access to feed was less than half of ruminal capacity. We observed similar results with intraruminal propionate infusion. A 2-h infusion of sodium propionate (8 mmol/min) reduced feed intake of NPY-injected sheep to a level similar to that of control animals not injected with NPY and infused with isoosmotic NaCl solution. Thus, in these studies it seems that intake level depended on a balance between the effects of ruminal displacement (or propionate infusion) and NPY administration. It remains to be seen whether increasing the dosage of one factor can completely block the effect of NPY, or vice versa, indicating sequential processing in the CNS.

Neuropeptide Y can now be added to the list of neurochemicals involved in modulating feed intake at the CNS level. It would be helpful to know more about how these neurochemicals interact. One potential interaction, which we have recently examined in sheep, is that of NPY with norepinephrine (NE). Several pieces of information make this interaction seem likely. Both factors will stimulate feeding when injected i.c.v. or into specific hypothalamic areas, especially into the paraventricular nucleus. Both NPY and NE specifically enhance appetite for carbohydrate in rats (Leibowitz, 1978; Leibowitz et al., 1985; Stanley et al., 1985a,b; Morley et al., 1987). In the rat, NPY-containing fibers project from the brainstem to the paraventricular nucleus (Sawchenko et al., 1985). Severance of these fibers reduces the content of both NPY and NE in the paraventricular nucleus and causes hypersensitivity to the feeding-stimulatory effect of exogenous NPY (Sahu et al., 1988a). In vivo release of both NPY and NE at the paraventricular nucleus coincides with meal initiation (Leibowitz et al., 1984; Leibowitz, 1986). Adrenalectomy, which attenuates the orexigenic effect of centrally injected NE, has been shown also to attenuate NPY-induced feeding in one study, although not in another (Morley et al., 1987; Kalra et al., 1988b). In vitro, NPY increased the number of α2-adrenergic binding sites in the medulla oblongata (Agnati et al., 1983). It also enhanced α2-mediated presynaptic inhibition of NE release from this tissue as well as from the hypothalamus, brainstem, midbrain, and hippocampus (Fuxe et al., 1984; Vallejo et al., 1987). As a precedent, NPY and NE seem to interact in the control of gonadotropins (Kalra et al., 1988a).
Clark et al. (1988) reported that stimulation of feed intake with CNS-NPY in rats can be blocked by prior administration of the specific \( \alpha_2 \)-adrenergic receptor antagonist, yohimbine. This indicates that NPY mediates its feeding effect through an adrenergic mechanism. In contrast, experiments in sheep reveal that yohimbine pre- or co-treatment will not block NPY-induced feed intake (Miner et al., 1990a). However, at that time the pharmacology of adrenergically mediated feeding in ruminants was not completely described. Baile et al. (1973) had reported that an alpha component was important but specific drugs for the receptor subtypes did not yet exist.

Therefore, studies were conducted to determine the pharmacology of NE-stimulated feed intake in sheep (Miner et al., 1990a). As shown in Figure 5, i.c.v. administration of NE promotes feeding in a dose-dependent manner. The feeding effect of NE can be blocked by i.c.v. pretreatment with the nonspecific \( \alpha \)-adrenergic receptor antagonist, phentolamine, and with the specific \( \alpha_1 \)-antagonist, prazosin. The specific \( \alpha_2 \)-antagonist, yohimbine, does not diminish NE-induced feeding in sheep. Neuropeptide Y-induced feed intake, in contrast to NE, is not attenuated by prazosin. These preliminary data are interpreted to indicate that an \( \alpha_1 \) adrenergic pathway may be more important in sheep than in rats, in which the \( \alpha_2 \) adrenergic pathway mediates NE-induced feeding. Furthermore, NPY in sheep may modulate feeding independently of an adrenergic mechanism. The dependence of NPY on an adrenergic mechanism in rats is not certain, either. Phentolamine failed to attenuate NPY-induced feed intake in several laboratories, and the specific \( \alpha_2 \) adrenergic receptor antagonist, rauwolscine, also failed to block NPY-induced feeding even though it does block the effect of NE (Levine and Morley, 1984; Stanley and Leibowitz, 1985; Clark et al., 1988; Kyrkouli, 1989). Morley et al. (1987) additionally reported that neither vagotomy nor adrenalectomy influenced NPY-induced feeding, but that both blocked NE-induced feeding.

In addition to the putative role for NPY in energy balance regulation is its link with gonadotropin secretion. Neuropeptide Y-containing axons contact GnRH-containing cells in rat brain (Tsuruo et al., 1990). Intraventricular administration of NPY inhibits LH secretion in ovariectomized rats. McDonald et al. (1989) concluded that NPY inhibited GnRH neurons in the hypothalamus. McShane et al. (1990) found that NPY administered i.c.v. inhibits pulsatile LH secretion in intact ewes but does not influence GnRH-induced LH secretion, indicating also that in sheep NPY inhibits GnRH neurons. Malven et al. (1990) corroborated this finding in ovariectomized ewes.

Figure 5. Influence of adrenergic receptor antagonists on norepinephrine (NE) and neuropeptide Y (NPY)-induced feed intake in sheep. Antagonists were injected 20 min before NE or NPY. Dosages were (B) 600 nmol NE and 600 nmol phentolamine; (C) 600 nmol NE and 600 nmol yohimbine; (D) 1,200 nmol NE and 60 nmol prazosin; and (E) 3 nmol NPY and 60 nmol prazosin. Each panel letter (A–E) represents a separate experiment. Within experiment, bars with different superscripts represent differences \( P < .05 \) and error bars represent SEM calculated from error mean square of analysis of variance. Taken from Miner et al. (1990a,c) and unpublished data (J. L. Miner).
and further showed that ventromedial, but not lateral, dorsolateral, or posterior, hypothalamic areas are sensitive sites for injection. As discussed above, the concentration of NPY in certain hypothalamic areas is correlated with hunger on a meal-to-meal basis. Whether long-term undernutrition can elevate NPY to the point of effectively inhibiting gonadotropin release is open to question. Anorexic women are characterized as having significantly increased NPY levels in cerebrospinal fluid and display abnormal neuroendocrine function (Kaye et al., 1989).

Implications

Recent evidence that neuropeptide Y is a neurotransmitter involved in central nervous system regulation of feed intake improves our understanding of how ruminants control intake. As the endogenous regulation is more completely understood it becomes increasingly possible to design methods of manipulating feed intake for the betterment of animal husbandry.

Literature Cited


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