Predicting Feed Intake of Food-Producing Animals

NATIONAL RESEARCH COUNCIL

Predicting Feed Intake of Food-Producing Animals

Subcommittee on Feed Intake
Committee on Animal Nutrition
Board on Agriculture
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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

In animal production enterprises, profits greatly depend on the ability to successfully maximize feed intake. It is essential, therefore, to understand the large number of physiological, environmental, and management factors that influence feed intake. Although there is still much to learn, scientists and producers have identified many of these factors through research and experience. Data are also available to quantify them.

The twofold purpose of this report is to discuss control mechanisms of feed intake and to quantify intake for each of the animals commonly used for food and fiber in the United States. For each species, a separate chapter provides equations and adjustment factors that can be used to predict dry matter intake, tests these equations and factors using independent data, and identifies areas that need further research.

The widespread use of microcomputers makes diet evaluation and performance projections feasible. Our goal was to assemble the best information available in a usable form to allow accurate predictions of intake under widely varying conditions. The subcommittee chose to present specific applications rather than more complete models because of the rapid evolution of approaches to computerization. However, factors may be easily adjusted to suit the user's particular needs. We hope that a better understanding of factors involved in feed intake will lead to more efficient formulation of animal diets.

The Subcommittee on Feed Intake was appointed in 1982 under the auspices of the Board on Agriculture's Committee on Animal Nutrition (CAN) to develop recommendations for predicting intake of animals. The report includes chapters on all major food-producing animals. The following individuals were responsible for respective sections of the report: Clifton A. Baile, Introduction: Feed Intake Control Mechanisms; Gary L. Rumsey, Fish; Richard Ewan, Swine; Park W. Waldroup, Poultry; H. Russell Conrad, Dairy Cattle; and Danny G. Fox, Beef Cattle and Sheep. Ling-Jung Koong reviewed prediction equations in the species chapters and provided advice on validation procedures.

This report was reviewed by the Committee on Animal Nutrition; the Board on Agriculture; and 13 outside reviewers—David H. Baker, Lane O. Ely, Richard D. Goodrich, Wayne J. Kuenzel, Leo S. Jensen, Santosh P. Lall, David R. Mertens, Donald Polin, Hugh A. Poston, Rodney L. Preston, Nathan E. Smith, Richard G. Shields, and T. S. Stahly. The subcommittee is grateful for the efforts of these individuals and thanks Deena H. Krestel-Rickert for her assistance in preparing the introductory chapter. We especially acknowledge the contributions of Selma P. Baron, who served as staff officer during the early preparation of this report.

DANNY G. FOX
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INTRODUCTION

The control of feed intake and regulation of energy balance are influenced by a number of factors. A regulator of body energy content is apparently interfaced with a controller of feed intake that maintains a balance of energy input and output under normal conditions. However, under certain circumstances, the system can be overridden and result in excessive weight gain or loss (Baile and Forbes, 1974). Subsequently, either condition could lead to metabolic disturbances and inefficient production.

Feeding behavior can be influenced by several external factors such as environmental conditions, sensory cues, and nutrients in the diet. The internal milieu of an animal, including gastrointestinal factors, hormones, and metabolites, also plays a role in feeding behavior.

The primary site responsible for the integrated control of feed intake and energy balance is the central nervous system (CNS), although the specific mechanisms involved are not well understood. Peptides found in the CNS have been shown to have a direct effect on the control of metabolism, feed intake, and reproductive behaviors. For instance, the onset of feeding may be influenced by opioid peptides, and termination of feeding may involve cholecystokinin. A number of CNS and most likely peripheral receptor systems exist that provide information about the animal's metabolic state. A coordinated feeding behavior is established via these receptor systems and CNS centers.

Factors involved in the control of feed intake and energy balance are reviewed in this chapter. A comparison is made between and within species regarding the mechanisms that influence energy balance. The controlling factors considered include those associated with the gut and brain of the animal.

OVERVIEW OF CONTROL SYSTEMS

Several metabolic and sensory factors are known to affect meal size and frequency. While meal size can vary greatly, the total quantity eaten each day, for example, must be controlled to maintain energy balance. The signals of satiety that control individual meal size must have shorter time constants than the signals that regulate long-term energy balance. Feeding behavior is also influenced by certain hormones and metabolites as well as gastrointestinal factors. Understanding the mechanisms involved in signaling the controller of feed intake may lead to improved methods of animal production.

Digestive Tract

In ruminants it has been hypothesized that the amount of forage eaten at a meal might be limited by the capacity of the rumen (Campling, 1970). When cattle were offered feed for about 6 h/day, the weight of the digesta of the rumen compared to that at the beginning of feeding increased by 48 percent and dry matter increased by 96 percent. Regardless of the range of feeds or types of cattle tested, these increases were consistent, supporting the idea that cattle eat until a certain proportional change of ruminal distension is achieved. Recent evidence suggests that the distension may be detected by tension receptors with varying neural adaptation times that are thought to exist in the ruminant stomach. These receptors have not been histologically identified as yet. Grovum (1979) has reported that sheep reduce feed intake in response to distension of the reticulum, and thus, the sheep's reticulum may possess stretch receptors that are sensitive to distension of the gut after a meal.

Digestibility of the foods that ruminants consume can

easily be related to the kinetics of digestion and its passage from the rumen (Waldo, 1969; Mertens, 1973). Forage intake is related to fiber digestion because it is limited by the rate of disappearance of material from the digestive tract (Conrad et al., 1964; Thorter and Minson, 1972; Mertens, 1973). Mertens and Ely (1979, 1982) have proposed a model of fiber disappearance from the digestive tract in ruminants. They have suggested that the ruminant's digestive process is divided into rates of digestion, digestion lag, and potentially digestible fraction. The retention time in the entire digestive tract is influenced by level of intake, physical characteristics of the diet, and rumination time. Specifically, their model suggests that maximum intake of digestible dry matter is affected more by the proportion of indigestible fiber and rate of passage than by the rate of fiber digestion.

In general, increasing the level of feeding to twice maintenance results in a 1 to 2 percent reduction in dry matter digestibility of feed for the ruminant. This reduction can vary with the quality and grind of the feed. In the pig, digestibility decreases with increases in level of feeding but to a lesser extent than in ruminants (McDonald et al., 1973).

Utilization of end products of digestion also differs widely between ruminants and monogastric animals. Nonruminant herbivores, e.g., equines, absorb many products of digestion in the small intestine and utilize them as a source of energy as efficiently as carnivores and omnivores (Roberts, 1975; Hansen et al., 1981). Microbial fermentation of ingesta in the equine cecum and large colon can provide as much as 60 percent of the total digestible energy available from the diet. This energy source is in the form of short-chain volatile fatty acids (VFAs). VFAs are the primary energy source in ruminants, but are provided by fermentation in the rumen, which is anterior to the small intestine. During and after feeding the VFA concentrations in the rumen fluid and blood increase (Chase et al., 1977); these changes are most obvious in sheep and cattle adapted to limited feed access. During limited feed access smaller increases in VFA concentrations occur during smaller spontaneous meals. Large differences in VFA concentrations can exist in various parts of the rumen for several hours after large meals due to slow mixing within the rumen.

In ruminants acetate and propionate appear to play a role in the control of meal size. Intraruminal injections of either metabolite depress feed intake in cattle, sheep, and goats (Baile and Mayer, 1970; Baile and Forbes, 1974). There are similarities that exist between the effects of acetate and propionate in that they can both depress feed intake, but different receptors are thought to exist for each in the ruminal area. It has been demonstrated that there are chemoreceptors present in the wall of the rumen that are sensitive to changes in pH but not specifically to acetate (Harding and Leek, 1972). When infusions were made into the ruminal vein, propionate was most effective in depressing intake, suggesting that propionate receptors are present in the wall of that vein. Anil and Forbes' (1980a) work further substantiated that propionate depresses feed intake more than acetate or butyrate. Sheep receiving a 3-h infusion of sodium propionate into the portal vein ceased eating 30 min after the onset of the infusion until the end of infusion. If the hepatic plexus was denervated, feeding continued during portal propionate infusion, suggesting that the liver is a major site for mediating the effect of this VFA on feeding.

The question has been raised regarding the effects of propionate infusions via the portal vein on blood composition. Results may be hampered by the uncertainty of whether induced blood changes remain within the normal physiological levels. De Jong (1981) showed that the change in VFA levels occurred in animals that were fed once or twice daily. This scheduled feeding regime is associated with large quantities of food eaten in a short period of time and is different from those meals eaten by animals on a free-feeding schedule. De Jong (1981) and De Jong and coworkers (1981) infused isotonic or hypertonic solutions of sodium salts of VFAs (acetate, propionate, *n*-butyrate, isobutyrate, or lactate) at a constant rate for 4 h via portal vein catheters into free-feeding adult goats. The results did not support the contention that VFAs have a function in the control of feed intake, and it was concluded that a role of the VFAs in the control of feed intake did not involve blood concentration changes.

Ruminant feeding behavior can also be influenced by changes in osmolarity of body fluids. Increases in rumen fluid osmolarity from about 250 to 350 mOsM during rapid eating of large meals can produce hypertonicity of body fluids and result in dramatic circulatory and renal changes. For instance, sheep can experience a rise in systolic blood pressure and a reduction in plasma volume within 15 min of the initiation of rapid feeding (Blair-West and Brook, 1969). This is probably due to the transfer of Na^+ and water from body fluid to rumen fluid. These mechanisms may cause ruminants as well as other mammals not to eat if they are severely dehydrated (Utley et al., 1970). Thus, water consumption and changes in body fluids play a role in the control of feed intake. However, in animals not deprived of water or in which feed consumption is slow or feed is taken in small meals, changes in the rumen or body fluid tonicity are unlikely to limit feed intake.

Metabolites

Glucose has long been considered to be an integral component of the feeding control system in monogastric

animals. It has been shown that dramatically reduced rates of glucose utilization associated with administration of glucose analogs or insulin-induced hypoglycemia produce feeding and hunger, whereas increased glucose utilization rates as well as hyperglycemia do not appear to affect feeding (Baile and Mayer, 1969). In the ruminant, blood glucose concentration, arteriovenous differences in glucose concentration, and glucose utilization rates generally decrease rather than increase with feeding (Baile and Forbes, 1974). Thus, there is less evidence that glucose utilization or concentration plays a significant role in controlling feeding in the ruminant (Baile and Della-Fera, 1981); in fact, there has been substantial evidence that supports the contrary.

Meal size was depressed in the pig by duodenal injections of isosmotic solutions of glucose and NaCl via implanted catheters (Houpt et al., 1983a,b). Injections were made after the onset of alternate meals throughout the day. Injections of 5 ml/kg of 5, 20, and 40 percent glucose and 0.9, 3.25, and 6.5 percent NaCl equally depressed the size of an ongoing meal proportionately with respect to their hypertonicity. Neither intermeal interval nor rate of eating changed to account for the reduction of meal size; only meal duration decreased. Such results are indicative of a possible duodenal osmoreceptive system which may be involved in controlling the size of a meal.

In sheep, feeding of concentrate (feed that is more calorically dense than average) can be reduced by high physiological duodenal concentrations of lactate and lactic acid. Receptors in the sheep's duodenum are particularly sensitive to these metabolites (Bueno, 1975). This reduction in feeding may be a result of depressed stomach motility or a feedback effect to the CNS from the duodenal receptors.

Amino acids, e.g., lysine and glycine, may play a role in the control of feeding (Baile and Martin, 1971). In sheep, plasma amino acid levels decline after a single daily feeding but increase a few hours later, reaching their maximum at about 24 h postmeal. Meal size of ruminants is probably unrelated to the absorption of amino acids since they are supplied primarily by the small intestine several hours after ingestion. With respect to amino acid imbalances or protein deficiencies, the suckling (preruminant) lamb will decrease feed intake by one-half in response to a diet low in total protein or void of either isoleucine or threonine (Rogers and Egan, 1975). Therefore, changes in plasma amino acid levels do not appear to directly affect the feed intake of ruminants fed a balanced diet.

The increase in free fatty acids (FFAs) associated with starvation has been suggested to act as a signal to induce feeding, despite the fact that FFAs increase not only with energy depot mobilization but also with feeding in animals adapted to a daily feeding schedule (Chase et al., 1977). Feed intake in sheep was depressed by intraduodenal injections of long-chain fatty acids or fats, but it remains unclear if depression in ruminoreticulum movements or changes in blood fatty acid composition was the cause (Titchen et al., 1966). Thus, there is insufficient evidence as to whether FFAs are a cause rather than an effect of changes in feeding.

Hormones

Hormones considered for their possible role in controlling feed intake include two of pancreatic origin, glucagon and insulin. Experimental work with glucagon was initiated in 1955 by Stunkard et al., in which intravenous infusions of glucagon brought about the sense of satiety in humans. This work has been extended to other species (Penick and Hinkle, 1961; VanderWeele et al., 1979). Glycogenolysis is the major metabolic action of glucagon in the liver and was considered as the mechanism of action for satiety (Geary et al., 1981). But when glucagon was injected intraperitoneally and the expected glycogenolysis occurred, it had no effect on sham feeding (Geary and Smith, 1982a). Langhans et al. (1982a) demonstrated that glucagon doses required to reduce meal size produced changes in hepatic metabolism that are also present at the end of normal meals, e.g., reduced liver glycogen content; but in several instances it has been shown that the hyperglycemic response to glucagon is not sufficient to cause the satiety response (Geary and Smith, 1982b). Some of the most convincing evidence that supports glucagon's role as a satiety factor is provided by Langhans et al. (1982b), who showed that glucagon antibody injections in rats cause increased feeding. Intraperitoneal injections of rabbit antibodies against purified bovine pancreatic glucagon or serum from nonimmunized rabbits were administered at the beginning of the first meal of a dark phase and after a 12-h fast. Feeding increased markedly (63 percent) in these rats versus that in controls, as did meal duration (74 percent). It was concluded that the glucagon released during feeding was sequestered by the antibody and thus removed a proposed essential component for satiety.

McLaughlin et al. (1984) have demonstrated that female Zucker obese and lean rats decreased daily food intake when immunized against pancreatic glucagon (conjugated to bovine serum albumin). Over a 16-week period, not only did food intake decrease 5.0 percent but weight gains decreased 9.4 percent as well. These results appear contradictory to the hypothesized outcome (Langhans et al., 1982a; McLaughlin et al., 1983a) of increased food intake brought on by immunization against glucagon. However, the observed decreases may well be a consequence of an overcompensatory in-

crease in total (free and antibody-bound) serum glucagon concentrations.

Over the last several decades the hypotheses regarding insulin's involvement in the control of food intake have varied. While hypoinsulinemia does not result in anorexia, feeding can be induced by injections of insulin but only after severe hypoglycemia occurs; yet insulin can also be associated with overeating (Brandes, 1977). Hyperphagia and hyperinsulinemia, but not hypoglycemia, often occur with the development of obesity (Jeanrenaud, 1979). The causes for such associations are not well understood, but insulin resistance is a common factor. Acute and persistent changes in plasma insulin concentration may have opposing effects on feeding. Porte and Woods (1981) proposed that insulin may be a body adiposity signal. Factors that influence the control of food intake may be classified into two categories: (1) factors that cause feeding behavior to change independent of body stores and (2) factors that are sensitive to the size of the adipose mass. The second category involves insulin as the hormone that signals meal feeding to maintain energy balance. This proposal is based on the observations that the plasma insulin concentration increases with the severity of adiposity. Since levels of insulin fluctuate frequently within a 24-h period, it is likely that some means is essential for obtaining an integrated response with a relatively slow time constant. Porte and Woods (1981) hypothesized that insulin in the cerebrospinal fluid (CSF) may possess such a means. Concentrations of CSF insulin change with plasma concentrations but at a much slower rate, with a half-life of hours as opposed to minutes.

Further evidence in support of this hypothesis is provided by continuous lateral ventricular injections of insulin in the baboon over a 14-day period, resulting in a reduction in food intake and body weight (Woods et al., 1979). Similar glucagon injections had no effect, which suggests that the response was caused by a specific peptide. However, many studies have demonstrated that insulin and glucagon have influential roles in controlling feeding behavior and in the regulation of energy balance. Still, much remains to be done toward proving the association of CSF insulin and energy balance regulation and glucagon's role in feeding before these two pancreatic hormones can be considered as satiety signals.

Insulin's effectiveness as a satiety hormone has also been investigated in swine (Anika et al., 1980). Following a 4-h fast, doses of insulin (0.05, 0.13, and 0.25 U/kg) delivered via intrajugular catheters produced a depression of feed intake compared to that in controls. Other doses (0.03, 0.5, and 1.0 U/kg) of insulin did not produce similar effects during the first 10-min feeding period. However, significant depression of feeding did occur in the second 10-min period with the higher doses (0.13, 0.25, and 0.5 U/kg). Anika et al. (1980) suggest that prandially released insulin, whether released by the action of cholecystokinin or glucose absorption, for example, may be influential in bringing a meal to an end.

An interrelationship between insulin and growth hormone (GH) during lipogenesis has been noted by Graham (1967). A high insulin:GH plasma ratio is required for lipogenesis, and this ratio occurs in sheep after meals scheduled at 3-h intervals, whereas lipolysis is stimulated by a low insulin:GH ratio. A decline in the insulin:GH ratio might be expected to occur at the start of a meal if a shortage of absorbed energy triggers lipolysis and feeding. Driver has observed peaks of GH every 2 to 4 h in sheep with free access to food, and he noted that spontaneous feeding did not occur when the GH concentration was high (Driver and Forbes, 1978; Driver et al., 1979). Forbes (1980a,b) suggested that elevated plasma GH levels do not directly inhibit feeding but that this provides evidence for a link between the initiation of feeding and a deficit of energy-yielding metabolites.

Brain

The hypothalamus is directly and indirectly involved in the control of systems and variations of body energy content. The center controlling energy balance in the brain is classically the ventromedial nuclear region of the hypothalamus (VMH). Stimulation of this satiety center inhibits feeding (Hetherington and Ranson, 1939). If complete or partial lesions are made in the entire area, they usually produce an immediate hyperphagia and weight gain that eventually stabilizes at a higher set point and the hyperphagia subsides. Controversy exists over whether VMH lesions induce hyperphagia since some studies have shown that damage to the proximal catecholaminergic pathways can influence feeding. However, these pathways do not synapse in the VMH (Ahlskog and Hoebel, 1973; Gold, 1973).

Much of the early work on the role that the brain plays in controlling feed intake was conducted on rats, but other species, i.e., ruminant and nonruminant domestic animals, have been considered as well. Baile et al. (1968a,b) demonstrated that goats with bilateral lesions of the lateral hypothalamic area became temporarily aphagic and adipsic, and lesions of the ventromedial area produced hyperphagia and substantial weight gain. Aphagia and adipsia can also be induced by lesions of the lateral area of the hypothalamus in swine (Khalaf and Robinson, 1972) and sheep (Tarttelin and Bell, 1968).

In the chicken the hypothalamus is also the site of many food-regulatory effector functions. Several physi-

ological changes have been noted to occur in the chicken when electrolytic lesions are made, but only those relevant to feed intake will be considered here. Some hypothalamic lesions produce aphagia (Feldman et al., 1957), and hyperphagia accompanies functional castration, but no hyperphagia has occurred in permanently castrated males and females (Snapir et al., 1969). Properly placed lesions normally produced increases in body weight as a result of the production and accumulation of excess fat. However, occasionally no effect results. A typical hypothalamic obesity can be demonstrated in the chicken with basomedial hypothalamic (BMH) lesions (Robinzon et al., 1977a). Placement of bilateral septal lesions by intracranial injection of 6-hydroxydopamine in geese produced a significant increase in feed intake (Snapir et al., 1976). In contrast to the hypothalamic obesity brought about by BMH lesions, septally lesioned geese and cocks did not develop obesity but were hyperphagic (Snapir et al., 1976; Robinzon et al., 1978). These results with geese are similar to those obtained from bulbectomized chickens, in which a marked increase in feed intake occurred without obesity (Robinzon et al., 1977b).

Thus, lesions of the hypothalamus produce a number of effects related to the control of feed intake in both ruminant and monogastric animals. However, there are probably differences in the feedback and receptor systems involved in energy balance for each type.

The route via which information travels from the sensor of energy balance to the hypothalamus is not clear, although the bloodstream has been suggested as a possible pathway for such communication. Hervey (1959) noted metabolic adaptations that occurred in parabiotic pairs of rats. When the VMH of one partner of a pair was lesioned, it became obese while the other partner became thin and died apparently from inanition. It has been suggested that the nonlesioned hypothalamus of the one partner responded to the total positive energy balance of both rats by reducing its food intake. Subsequently, only its own body weight was affected and not that of the obese rat. More recently, parabiotic rats have been used to demonstrate the existence of endogenous factors that separately control feed intake and metabolism of body fat. Kasser et al. (1984) have shown that the hypothalamic tissue pentose phosphate pathway can be uniquely altered, supporting the concept of an eminent role for CNS metabolism in controlling feed intake. It is clear that the hypothalamus plays a primary and critical function in the regulation of energy balance in animals.

Other Factors

Factors other than those previously mentioned can affect feeding behavior. Sensory cues of olfaction and taste can influence the selection and consumption of various foods for most species. Ruminant animals are capable of utilizing a variety of waste products as feedstuffs. However, many of these products are unpalatable and not utilized to their fullest extent. Olfactory cues can influence whether or not a meal will be initiated, and taste may affect the length of that meal. It appears that species variability does exist with regard to taste preferences. However, most species exhibit a preference for sweet tastes (Hellenkant, 1978). Although palatable flavors can increase feed intake in many species (Baldwin, 1978), only a few flavors have been tested systematically (Zivkovic, 1978; McLaughlin et al., 1983a).

Ammonium ions, i.e., urea, whether injected or used as a diet supplement, are also effective in controlling feeding. Baile (cited in Conrad et al., 1977) demonstrated that ammonium infusions into the rumen failed to reduce rumen motility until lethal levels had been added. Conrad et al. (1977) found that an intraruminal injection of an ammonium load in goats during spontaneous meals reduced meal length, rate of eating, and meal frequency. They also reported that when urea was added to the diets of cows, the first meal length, as well as meal size, was decreased, but total feed intake was unaffected since the number of spontaneous meals increased. Thus, those physiological factors that limit meal length with urea in the rations are undefined, yet they are important considerations in the successful feeding of cows in situations where eating time is limited.

Other factors that can affect feed intake are temperature and environmental conditions. Growth or lactation in an animal can be reduced by heat stress in some species, but the critical temperatures at which effects become noticeable vary within and between species. Feeding can be inhibited by extreme heat loads, but it has been postulated that this may be a stress-related response as opposed to a normal satiety signal. However, most species do have a uniform milk production rate and feed efficiency over a relatively wide range of conditions.

Sex hormones are also influential in determining amounts of feed eaten by animals. When weight gain is induced in rats by progesterone, the increase in feed intake is more variable than the weight gain. In fact, when feed is restricted to the control intake, progesterone treatment produces two-thirds of the additional energy storage that occurs in free-fed rats (Hervey and Hervey, 1967), thus indicating a decreased energy expenditure.

Estrogen has been suggested as a factor that can affect feed intake by acting on an area of known sensitivity in the anterior hypothalamus (AH) which sends projections to the VMH (Kennedy and Mitra, 1963;

Kennedy, 1964). More recently, Wade and Zucker (1970a,b) have demonstrated that estradiol can act directly on the VMH. The result was a depression of feed intake, which was apparently an estrogen-induced action; however, this depression was not observed in weanling rats under 40 days of age unless they were hypophysectomized.

They concluded that before puberty pituitary hormones blocked the VMH restraint on intake. There must be other sites of action involved in estrogen's effects on feed intake since estrogens are capable of stimulating eating in rats that have access to exercise wheels. This occurs indirectly by stimulating locomotive activity, hence increasing energy expenditure, and lesions of the AH block this locomotor action of estrogen. High levels of estrogens are generally considered to inhibit growth which in turn can depress feed intake. Tarttelin (1968) has also reported depressed feed intake coinciding with estrus in the ewe. Growth and intake do not appear to be affected by estrogens in the prepubertal rat, but after puberty estrogens do have an effect on intake (Wade and Zucker, 1970a,b).

Diethylstilbestrol (DES) has been used as a feed additive or as an ear implant for stimulating weight gains and improving feed efficiency of growing and finishing ruminants (Riggs, 1958; National Research Council, 1963). It has also been reported by Trenkle (1969) that estrogenic compounds, e.g., DES, produce only a slight increase in feed intake.

Other steriods, e.g., dehydroepiandrosterone (DHEA), a 17-ketosteroid, can produce a decrease in weight gain without affecting feed intake in lean mice and yellow obese mice that have hypertrophic adipose tissue (Yen et al., 1977; Cleary et al., 1982). Not only was body weight reduced but the feed efficiency ratio, fat cell number, and size of the fat cell were significantly decreased (Cleary et al., 1984).

In the Leghorn cock testosterone propionate (TP) is effective in inducing hypophagia and, in turn, reducing carcass fat content, while DES increased adiposity markedly through hyperphagia. Injections of the combined steroids (TP and DES) produced only moderate obesity (Snapir et al., 1983). The results suggest that TP may decrease feed intake and lipogenesis, whereas DES has the opposite effect.

REGULATORY PEPTIDES

Other hormones are involved in the regulation of energy balance and control of feeding behavior, including peptides of the gastrointestinal (GI) tract and brain. For years knowledge of GI hormones was limited to the existence of three or four, but now many GI peptides are known to exist. Many of their actions remain undefined, however. While advances have been made in the area of regulatory peptides within the last decade, much remains to be discovered with respect to synthesis, release, and actions of the various forms of the peptides. One GI hormone for which there is evidence for a role in controlling feed intake is cholecystokinin (CCK).

Cholecystokinin

Gibbs et al. (1973) showed that CCK is capable of inhibiting feed intake. Studies have revealed that sham-fed fistulated rats decreased feed intake following intraperitoneal or intravenous (IV) injections of CCK, and the observed percentage of inhibition of feed intake was dose dependent (Lorenz et al., 1979).

The specificity of CCK has been clearly demonstrated by comparing the effects of closely related peptides. A sulfate group present on the seventh amino acid, tyrosine, can influence the actions and receptor-binding affinities of CCK-active peptides (Steigerwalt and Williams, 1981) and is necessary for the satiety effect (Ondetti et al., 1970). The desulfated CCK is far less active than the sulfated form; for example, Lorenz et al. (1979) reported the potency of desulfated CCK-8 to be 10 times less than that of the sulfated form in inhibiting feeding.

Over the last decade the effects of CCK on the feeding behavior of food-producing animals have been studied. Intraportal injections of CCK in pigs proved to be more effective in inhibiting intake than intrajugular injections, whereas intraperitoneal injections were significantly less effective than injection at either intravenous site (Anika et al., 1981). In comparison, peripherally administered CCK produced very little or no effect on feed intake in sheep (Baile and Grovum, 1974; Anil and Forbes, 1980b). However, if a small dose of an impure CCK-33 preparation was injected intrajugularly over a 296-min period, a decrease of 40 percent in intake occurred within the first 10 min of injection. This decrease did not persist over subsequent time periods, despite the continuation of the injection (Grovum, 1981). In chickens intravenous injections of CCK-8 or caerulein decreased feeding within the first 10 min of injection and then normal feed intake resumed (Savory and Gentle, 1980). Feeding was also shown to decrease after administration of a CCK-33 preparation in a different test system (Snapir and Glick, 1978).

There are variations in the effects of CCK between species. Effects of CCK may vary due to interspecies rate of digestion. In chickens, for instance, feed first passes through the crop and gizzard, delaying the arrival of the ingesta to the intestines and, in turn, delaying the release and effect of intestinal CCK. Savory and

Gentle (1980) proposed that meals that were greater than 6 min in length could be influenced by CCK released from the duodenum as a result of the newly ingested food reaching that part of the intestinal tract. In sheep there is also a delay of intestinal digestion since food is held in the rumen, subjected to microbial digestion, and then slowly passed to the intestines. Therefore, GI CCK may not work as a satiety agent in sheep and chickens by the same route as in other animals, such as pigs. These characteristics should be considered when evaluating the effectiveness of gut hormones on feeding behavior.

Despite the finding that exogenous administration of CCK results in decreased feed intake in several species, little conclusive evidence exists that supports the fact that CCK is essential for satiety to occur. Recently, McLaughlin et al. (1985) used antibodies (AB) to CCK to sequester endogenous CCK to determine the effect on feed intake. Zucker lean rats were autoimmunized using a conjugated CCK-8. Both average daily feed intake and weight gain increased in immunized rats versus controls. Sequestering of CCK released during a meal increased meal size, and in those animals that developed significant endogenous CCK-AB titers daily feed intake and weight gain increased. These data provide strong evidence that CCK may play a role in satiety.

Several other experimental approaches have been used to demonstrate that endogenous CCK might mediate intestinal satiety. Some amino acids, in particular *l*-phenylalanine, in the lumen of the small intestine causes CCK to be released. If infused intragastrically in monkeys, *l*-phenylalanine decreased feed intake, whereas *d*-phenylalanine was ineffective (Gibbs et al., 1976). Evidence exists for a negative feedback control of CCK release by trypsin in the lumen (Brande and Morgan, 1981). Oral administration of a trypsin inhibitor causes a decrease in trypsin activity and decreases CCK content in the intestinal mucosa (implying CCK release). This inhibitor also increases the secretion of pancreatic enzymes, a known effect of CCK. Brande and Morgan (1981) suggest that by changing the level of trypsin activity in the gut it is possible to alter the amount of CCK released. Other work indicates that trypsin inhibitors decrease feed intake in rats and that trypsin supplements can increase intake (McLaughlin et al., 1983b,c).

Numerous studies have demonstrated the presence of CCK peptides in the brain of both mammalian and nonmammalian species. At least five forms of CCK are known to exist: a component larger than CCK-39, a component similar to CCK-39, CCK-12, CCK-8, and CCK-4. Of these forms CCK-8 is the predominant form in the brain (Rehfeld, 1978; Rehfeld et. al., 1979; Goltermann et al., 1980). There appears to be a specificity of regional distribution of CCK peptides and receptors in the brain. The highest concentration of CCK and its receptors occurs in the cortex; however, significant quantities of CCK-8 have been located in the hippocampus, periaqueductal gray, and dorsomedial hypothalamus as well (Rehfeld, 1978; Saito et al., 1980; Beinfeld et al., 1981).

Evidence that supports the role of brain CCK peptides in satiety has been obtained from experiments in which lateral ventricular (LV) injections of CCK were made in sheep (Della-Fera and Baile, 1979; Della-Fera et al., 1981) and pigs (Parrott and Baldwin, 1981). Significant decreases in feeding occurred when fasted sheep were administered as little as 0.01 pmol of CCK-8/min. Larger doses of 2.5 pmol of CCK-8/min or greater suppressed all feed intake during 3-h injection periods (Della-Fera and Baile, 1979). With respect to fasted pigs, feed intake also decreased in a dose-dependent manner. In both species CCK-8 affected only feed intake without affecting water intake or body temperature (Della-Fera and Baile, 1980a; Parrott and Baldwin, 1981). Amounts of CCK-8 required to induce this response were similar between species.

Experiments in which CCK antiserum was injected into the LV of sheep provide the strongest evidence for CCK's involvement in satiety (Della-Fera et al., 1981). Significant increases in feed intake occurred during injection of antiserum versus injection of normal control serum. The pattern of increased feed intake may have been related to an inhibition of satiety as opposed to the stimulation of hunger, since typical postmeal intervals did not occur during injection of CCK antiserum but did occur with the control. The early onset of increased feeding in association with injections of CCK antiserum indicated that CCK antibody may have been effective by sequestering CCK in the CSF. CCK may have been released into the CSF prior to interaction with the receptors that mediate the satiety effect; thus, it is possible that CCK is transported via CSF to its sites of uptake or action (Della-Fera et al., 1981).

In experiments with chickens, in which 4-week-old broilers were injected intracerebroventricularly with doses of 100 and 150 ng, CCK-8 reduced feed intake over a period of 60 and 105 min, respectively. Feed intake was reduced by 87 percent for the first 15 min postinjection of 150 ng of CCK-8 (Denbow and Myers, 1982). This decrease was nearly fourfold greater with less than one-third the amount injected intravenously by Savory and Gentle (1980). In the latter studies subjects were 12- to 17-week-old hens and thus larger in body mass. When injected with 40 times the amount of CCK-8 used by Denbow and Myers (1982), feed intake was only reduced by approximately 45 percent.

The mechanism of action of CCK's central effect on

feeding behavior is not yet clearly defined. The problem is complex in that centrally administered CCK can produce changes in GI function (Della-Fera and Baile, 1980a,b; Bueno et al., 1983) and secretion of specific hormones (Della-Fera and Baile, 1981). The possibility exists that the effects of brain CCK may be mediated through the release of other brain peptides such as calcitonin (Care et al., 1971) or neurotransmitters such as norepinephrine (McCaleb and Myers, 1980). Clearly, much more information is required to propose a unifying hypothesis for these actions of CCK.

Opioid Peptides

Recently, evidence has been generated that indicates a role for certain brain peptides such as neurohormones or neurotransmitters in hunger and satiety. Opioid peptides have been implicated in several bodily functions and processes (Terenius, 1978; Margules et al., 1979; Amir et al., 1980), including feeding and ingestive behavior (Morley, 1980). An opiate receptor system has been suggested as a component in initiation of hunger in the ruminant (Baile et al., 1981).

A broad spectrum of opiate agonists and antagonists have been tested to determine the mechanisms involved and the class(es) of opiate receptors responsible for opiate-induced feeding. Feeding can be stimulated in sheep receiving injections ICV of opioid peptides; e.g., an enkephalin analog can stimulate satiated sheep to eat (Baile et al., 1981). Opiate antagonists, such as naloxone, can suppress feeding in sheep (Baile et al., 1981; Bueno et al., 1983), guinea pigs (Schulz et al., 1980), rabbits (Sanger and McCarthy, 1981), and mice (Holtzman, 1974). Naloxone-injected IV in combination with an LV injection of enkephalamide eliminates the feeding responses of enkephalamide (Bueno et al., 1983).

In yet another series of experiments, IV injections of a similar enkephalin analog (Tyr-D-Ala-Gly-Phe-N[CH^3]-L-PheNH_2-HOAc) stimulated feeding in satiated sheep (approximately 50-kg body weight). An approximate 14-fold increase of peptide was required for this response versus the amount of analog used in the LV study (12.25 versus 0.92 mg) (Baile et al., 1981). The findings from these LV studies are indicative of the fact that CNS is a likely site of action for opioid peptides, but it remains to be shown where the IV-injected peptides act.

Another opioid peptide associated with the hunger component of feed intake is β-endorphin. Increased plasma β-endorphin concentrations have been shown to be related to hunger (McLaughlin and Baile, 1985). They postulated that if rats were immunized against β-endorphin, antibodies would sequester β-endorphin and produce a decrease in feed intake and body weight. In fact, rats autoimmunized against β-endorphin increased feed intake and body weight. It is not clear if these responses are due to a decreased free concentration or an increased total concentration of plasma β-endorphin. Increased production of other proopicorticotropin cleavage products, e.g., adrenocorticotropic hormone, in these rats may contribute to the observed increases in feed intake, body weight, and pituitary size.

On the basis of various studies showing that different opiate agonists bind different classes of receptors with varying affinities, some tentative conclusions concerning specific receptor systems involved in feeding can be drawn. It appears that kappa- and mu-opiate receptors may be particularly important in the hyperphagic response since opiates that are relatively specific for either of these types of receptors are highly effective in inducing feeding (Larrson and Rehfeld, 1979; Yim et al., 1980; Morley and Levine, 1981).

In an effort to test the differential roles that opiate receptor subtypes play in feed intake, Della-Fera et al. (1983) tested D-alanine ($2_{D\text{-}Ala}$) dynorphin (dyn)-17 and dyn-13, and dyn-17. Feed intake was increased during a 60-min LV injection in sheep. Dyn-β had no effect, whereas ($2_{D\text{-}Ala}$ 5_{Leu}) enkephalin (DADL) decreased feed intake. Della-Fera et al. (1983) suggested that since dyn-A and DADL act on receptors other than kappa and delta, that exclusivity may not exist for their action at the receptor level.

The specific sites of opiate receptors involved in the feeding responses and the mechanism of opiate action responsible for eliciting feeding remain unknown. Some evidence does exist, however, for an interaction between opiates and dopamine in the nigrostriatal pathway (Urwyler and Tabakoff, 1981). It has also been suggested that glucose levels are important in regulating the sensitivity of the opiate receptors involved in feeding (Morley et al., 1983). Thus, opiate peptides may contribute to the onset of feeding under certain conditions.

THE ROLE OF FEED INTAKE IN THE REGULATION OF ENERGY BALANCE

The mechanisms involved in receiving information from the periphery and then processing it centrally to produce an appropriate response are not adequately defined. Factors such as GI conditions, hormones, and metabolites act on receptor systems which essentially transduce analog information (e.g., concentration) into neuronal units. Due to the changes in individual neuronal firing that interface with a detector cell and spike a potential generator, e.g., temperature receptor (Edinger and Eisenman, 1970), as well as the number of