Seasonality of food intake in ruminants: recent developments in understanding

S. M. Rhind[1]*, Z. A. Archer[2] and C. L. Adam[2]

[1]*Macaulay Land Use Research Institute, Craigiebuckler, Aberdeen AB15 8QH, UK*
[2]*Rowett Research Institute, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, UK*

Domestic ruminants are used to exploit many vegetation resources that would otherwise be unproductive. For maximal effectiveness, there is a need to understand underlying mechanisms controlling animal performance, including seasonal variations in appetite and food intake. Potentially useful experimental approaches, recent findings and aspects for future study are discussed. Seasonal variation in intake is expressed through changes in the pattern of meals (duration, frequency, inter-meal interval and ingestion rate). These changes are signalled through alterations in both structure and function of the gastrointestinal tract and physiological signals. Studies suggest that multiple, interactive signals are involved, including hormones such as cholecystokinin, insulin, leptin and triiodothyronine. However, baseline concentrations in the peripheral circulation are not appropriate measurements of some of these hormones since there can be seasonal differences in postprandial profiles or changes in rate of dilution in the bloodstream or in the rate of degradation in the liver. Interactions between these circulating signals, liver function and neural signals to the brain need clarification. Systemic nutritional signals also act directly in the brain where they are integrated with seasonal photoperiod (melatonin) signalling within the hypothalamus. Melatonin target sites critical to appetite regulation have still to be identified, but leptin receptors and downstream neuropeptides have been localised within the ovine hypothalamus. These orexigenic and anorexigenic 'compensatory' pathways are sensitive to imposed changes in nutritional status but, with the exception perhaps of cocaine- and amphetamine-regulated transcript, do not appear to drive seasonal 'anticipatory' changes in intake. Mechanisms underlying seasonal changes in hypothalamic sensitivity to nutritional feedback clearly deserve further study.

Photoperiod: Appetite regulation: Hormones: Neuropeptides: Hypothalamus

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Abbreviations: ARC, arcuate nucleus; BBB, blood–brain barrier; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; GH, growth hormone; ICV, intracerebroventricularly; IGF-1, insulin-like growth factor-1; LD, long day; NPY, neuropeptide Y; OB-Rb, signalling form of leptin receptor; POMC, pro-opiomelanocortin; SD, short day; T_3, triiodothyronine; T_4, thyroxine.

*Corresponding author: Dr Stewart Rhind, fax +44 1224 311556, email s.rhind@mluri.sari.ac.uk

Introduction

Ruminants represent a large proportion of the animal species used to exploit areas of land and their associated plant resources that cannot be used more directly by man. The seasonality of food intake of relatively few species or breeds has been studied intensively; most of these are domesticated or semi-domesticated and inhabit relatively high latitudes or altitudes. However, of those that have been studied, most have been found to exhibit marked seasonal variations in appetite and voluntary food intake, which are a function of physiological changes and do not simply reflect a seasonal reduction in food availability (Kay, 1979; Kay & Staines, 1981; Barry *et al*. 1991; Iason *et al*. 2000). This phenomenon is considered to have evolved as an adaptation to regular seasonal reductions in food availability, so that the animal's drive to search for food is reduced when supply is reduced and less energy is expended in foraging (Kay & Staines, 1981). The pattern of variation is subject to modification by many peripheral factors including the energy content of the food (Webster *et al*. 2000), the species or breed under investigation (Semiadi *et al*. 1995; Iason *et al*. 2000) and physiological state (pregnant, lactating, rutting, high or low body condition, etc.) (Barry *et al*. 1991; Sibbald, 1997). In domesticated ruminants, the variation is less marked and seasonal changes in intake may depend on the breed and food type (Iason *et al*. 2000), but it is still a significant determinant of animal performance and therefore an important topic for research.

The purpose of the present review is to address the relative merits of different experimental approaches to the study of seasonality of intake, to summarise some of the most important recent findings concerning seasonality of appetite and intake in ruminants, and also to speculate on potentially important areas for future research.

Patterns of seasonal variation in intake

Patterns of seasonal change in intake have been reported previously for several species of deer (Bandy *et al*. 1970; Milne *et al*. 1978; Loudon *et al*. 1989; Barry *et al.* 1991; Semiadi *et al*. 1995; Rhind *et al*. 1998), Soay sheep (Kay, 1979; Rhind *et al*. 2000) and various conventional sheep breeds (Iason & Mantecon, 1991; Iason *et al*. 1994; 2000) and so they will not be reported in detail here. Briefly, animals of all of the species and breeds studied exhibit higher intakes during periods of long-day photoperiod; the magnitude of the difference with photoperiod or season is more marked in non-domesticated species and is greater in intact males than females (Bandy *et al*. 1970; Kay, 1979). There is little or no information concerning seasonal variation in intake in tropical environments in which photoperiod is relatively constant. The observations of Loudon & Curlewis (1988) indicated the existence of an endogenous rhythm in the body weight of tropical Axis deer (*Axix axis*) maintained at 52°N, but these variations were not entrained to photoperiod.

Efficient livestock production in environments where food supply is abundant depends on relatively high levels of food intake being sustained throughout the production cycle; seasonal reductions in appetite are not consistent with this requirement. Thus, an understanding of the factors controlling this phenomenon is desirable. Furthermore, knowledge of these may lead to an enhanced capacity to ameliorate the adverse effects on animal growth or reproductive performance.

Investigative approaches

Investigations of the pattern and underlying causes of this variation in intake are complicated by the fact that intake is dependent on a large number of interacting factors. Seasonal variation in intake may be a function of an endogenous circannual rhythm (Barry *et al*. 1991), the expression of which is regulated by photoperiod, via the hypothalamic–pituitary system (Lincoln *et al*. 2001).

The mechanisms through which the rhythms are expressed are complex. The central appetite circuits and the peripheral organs, such as liver, pancreas and gastrointestinal tract and adipose tissue are linked by neural and endocrine signals to the brain where the patterns of neuropeptide secretions drive the neural circuits that determine appetite and food intake. However, the sequence of neuroendocrine signals through which a change in photoperiod can alter food intake is poorly understood. Elucidation of the complex mechanisms is likely to require several types of experimental approach:

1. Descriptive studies under controlled conditions, designed to characterise intake patterns and associated metabolic signals, may be required to provide basic data on which hypotheses can be built regarding the underlying control mechanisms. Such experiments frequently involve maintenance of animals indoors and on artificial diets (Rhind *et al*. 1998, 2000). However, care is required in the extrapolation from data obtained in such studies to other circumstances because different breeds or species may exhibit different responses to different conditions (Iason *et al*. 2000).

2. Descriptive studies under field conditions in which the diet and animal behaviours are not constrained may have the disadvantages of seasonal changes in the animal's physiological state which are not directly related to food intake, for example, changes in pelage or in breeding activity. Furthermore, in studies of this type, intake patterns can be affected by seasonal changes in the amount of feed (Heydon *et al*. 1993) or the type of feed (and associated changes in palatability, selection and digestibility) that is available (Kay & Staines, 1981). However, the magnitude of the effects of these factors on intake is generally small when compared with the variation in level of intake associated with season. Studies of this type make an important contribution to the understanding of the ecological and physiological consequences of seasonal variation in intake. Thus, a combination of approaches 1 and 2 is likely to lead to a more complete understanding of the subject than either approach in isolation.

3. Exogenous manipulations can be used to develop further the hypotheses generated from approaches 1 and 2 and particularly to investigate the underlying signals that determine seasonal changes in appetite and intake. These signals are generally linked to changes in day length, which is transduced humorally by the daily pattern of melatonin secretion (Morgan *et al*. 1994). The control mechanisms downstream from melatonin involve multiple endocrine and neural systems that are integrated and co-ordinated within the hypothalamus. Further understanding of the mechanisms requires investigation of physiological responses to changes in circulating hormone profiles, neural inputs to the brain and associated changes in the activities of hypothalamic neuronal networks. These changes in endogenous signals can be achieved through controlled changes in food intake, body condition, or photoperiod, but they can also be more precisely manipulated by injection or infusion of selected drugs, hormones or metabolites. The manipulations can be conducted at the level of the digestive tract (Forbes *et al*. 1992), circulating blood (Figlewicz *et al*. 1985), within nerves (Farningham *et al*. 1993) or within precisely defined areas of the brain (Figlewicz *et al*. 1989).

4. Extrapolation from studies of non-ruminant species can offer new insights into potential mechanisms of appetite regulation. For example, studies of selected rodent species which fast completely during hibernation have shown that seasonal changes in glucocorticoids (Kenagy & Place, 2000) and in the permeability of the blood–brain barrier (BBB) to insulin (Florant *et al*. 1991) could be involved in appetite regulation. In addition, hypothalamic appetite control pathways have been studied in some depth in a rodent model exhibiting seasonal appetite–body weight cycles, the Siberian hamster (*Phodopus sungorus*) (Morgan & Mercer, 2001). The potential involvement of these appetite regulatory mechanisms in ruminants has not been widely explored to date.

Control mechanisms: peripheral

The division of appetite control mechanisms into categories is arbitrary, since they clearly inter-act to induce the observed patterns of food intake. For example, long-term (seasonal) changes are a function of short-term changes in expression of the factors that determine total daily food intake. However, they can be divided into two major groups for the purpose of review.

One group of control mechanisms is physical rather than metabolic and includes changes in meal size, number, frequency and speed of food ingestion. There may also be changes in the physical structure of the gastrointestinal tract. The second group of mechanisms controls the first and includes the physiological components, i.e. neural, metabolic and hormonal signals and their behavioural correlates. Investigation of these mechanisms has a long history. The likely involvement of both gut fill and of metabolic signals (Balch & Campling, 1962; de Jong, 1986) has long been recognised but as each new theory concerning appetite regulation has been developed, limitations of those theories have also been identified (Ketelaars & Tolkamp, 1992; Forbes, 1995). However, while each individual concept has provided an inadequate explanation of appetite regulation by itself, it has become clear that at least some components of each of the proposed mechanisms are involved.

Meal patterns and intake rates

Food intake comprises a series of feeding bouts or meals; there is no precise generally agreed definition of a meal and definitions may differ between studies. However, this lack of agreement does not detract from the value of this form of description when studying food intake. In general terms, a meal is a period in which the animal is continuously ingesting food and which is marked at each end by a period in which the animal is not ingesting. In studies of castrated male red deer (*Cervus elaphus*), Rhind *et al*. (1998) found that the higher rates of food intake during the summer were associated with longer meals and shorter inter-meal intervals so that they had larger meals and spent a greater proportion of their time eating (Fig. 1). However,
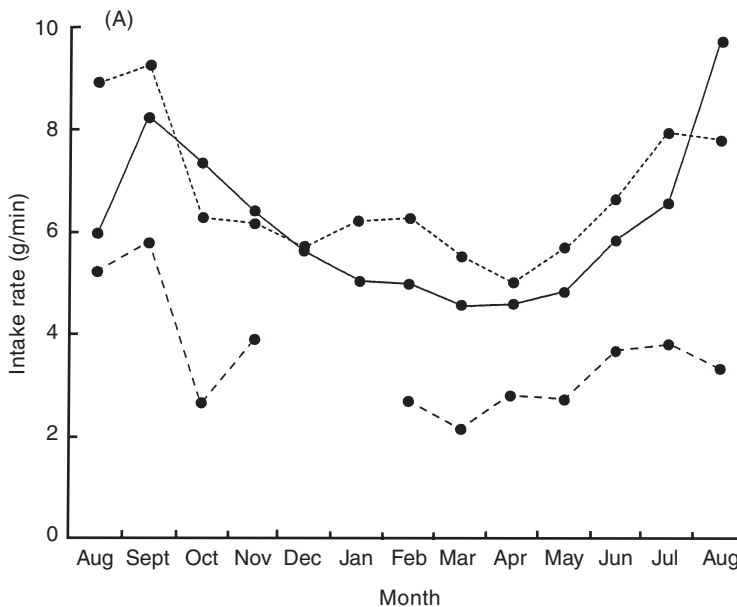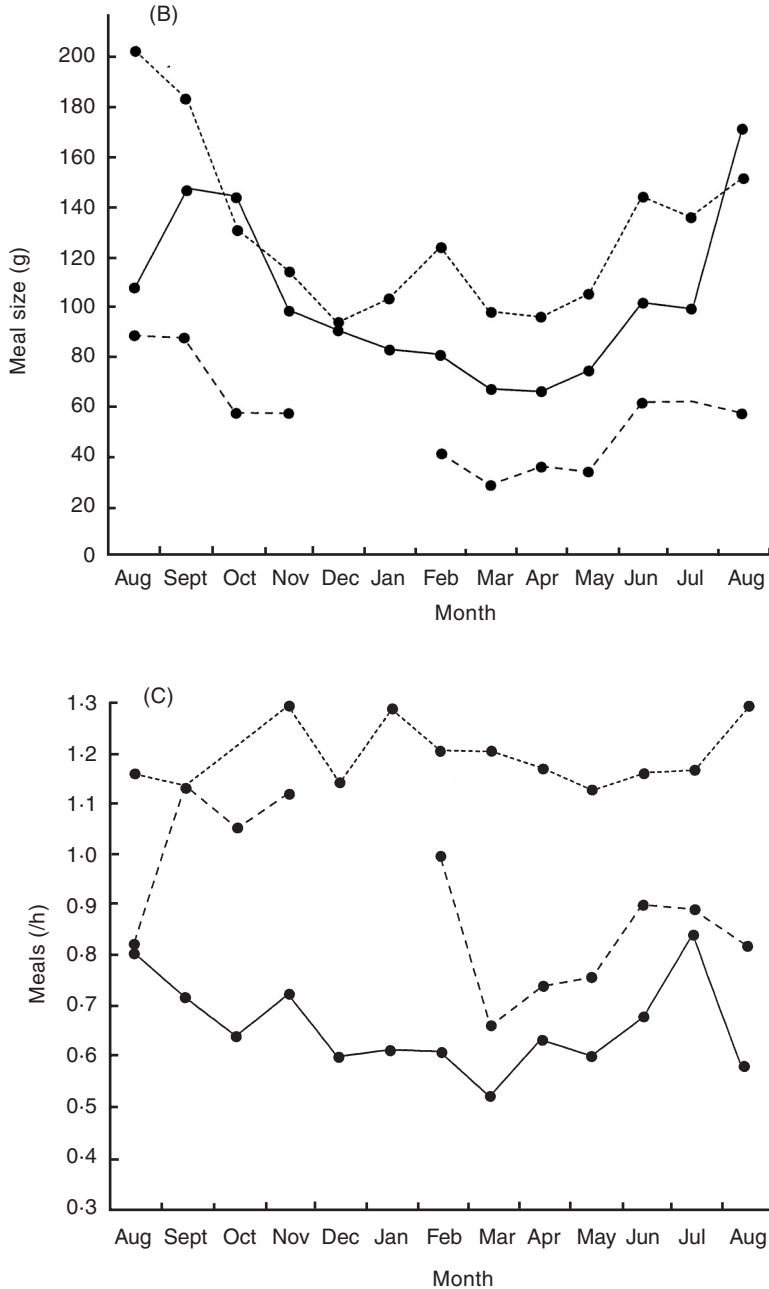
Fig. 1. (A) Mean rates of food ingestion (SED for month 0·58, SED for period 0·27); (B) meal sizes (SED for month 11·81, SED for period 5·80); (C) number of meals/h (SED for month 0·081, SED for period 0·035) at monthly intervals in deer (*Cervus elaphus*) fed *ad libitum*. Results are shown separately for each period of the day: (– – –), early daylight, i.e. the daylight period between dawn and refilling of the feed bins; (——), dark, i.e. the period between dusk and dawn; (……) late daylight, i.e. the daylight period between refilling of the feed bins and dusk. Data are missing from months in which the interval between dawn and refeeding was too short for meaningful measurement. (From Rhind *et al.* 1998.)

during the course of each meal, the animals were also found to be ingesting the food faster during the summer months than during the winter (Fig. 1). Similar results were obtained in a study of castrated male Soay sheep (Rhind *et al*. 2000).

Additional observations of red deer by Sibbald (1994) and Rhind *et al*. (1998) showed that these components of feeding behaviour differed not only with photoperiod but with periods of daylight and darkness within a 24-h period; thus meals were longer and more frequent during daylight than darkness (Fig. 1). This finding has important implications for experimental design, first because it indicates that measures of food intake should be made throughout 24-h periods, and not only at one part of the day, to ensure that the pattern of meals is determined accurately. Second, it shows that the pattern of food intake is controlled not only by medium- to long-term changes in underlying physiological signals but also by the short-term changes in ambient lighting. Such changes in response to light *per se* (as opposed to physiological changes associated with seasonal changes in photoperiod) may be an important component of the mechanism through which effects of season are expressed.

The observations of Iason *et al*. (2000) showed that, in addition to seasonal differences in meal pattern, sheep also exhibit changes in their bite pattern. The bite rate was found to be lower in summer, when the sheep ate more, than in winter when they ate less. However, the bite size was larger in summer even though sward heights were similar. These observations highlight the complexity of the mechanisms that determine patterns of intake and this in turn may explain why these authors found that breed differences in seasonal patterns of intake and foraging behaviour were poorly related to their inherent differences in voluntary food intake.

These physical, intake-regulating mechanisms may each be subject to different underlying control mechanisms. For example, the physiological signals that control the rate of eating (amount of food consumed per unit of time) or bite size may be different from those that determine the meal length or inter-meal interval. At the same time, the short-term appetite drive may be modified or inhibited altogether by other factors such as daylight or darkness, social factors or climatic conditions, and the expression of each of these factors may involve further mechanisms.

Seasonality of gastrointestinal structure and function

Another group of physical factors that determines the meal pattern pertains to the structure and function of the gastrointestinal tract. While the digestibility does not appear to differ with season in red deer (Barry *et al*. 1991; Sibbald & Milne, 1993; Freudenberger *et al*. 1994) it may be reduced during the summer in goats (Barry *et al*. 1991). The reduction in digestibility in goats, unlike in deer, appears to be a function of increased levels of food intake associated with a lesser seasonal increase in rumen capacity than in deer and an increased rate of outflow from the rumen (Barry *et al*. 1991).

Reports of changes in rumen pool size and retention time in deer are contradictory. Rumen capacity is higher during spring and summer than in winter (Barry *et al*. 1991; Sibbald & Milne, 1993; Freudenberger *et al*. 1994) but reported effects of season on retention times are inconsistent, with Freudenberger *et al*. (1994) reporting an increase in summer while Sibbald & Milne (1993) observed no seasonal difference. Rumen motility in red deer was found not to differ with season (Stafford *et al*. 1993).

Changes with season in the gastrointestinal structure and function and associated patterns of nutrient absorption are likely to contribute to changes in the metabolic and hormonal signals to the appetite centre of the brain. Attempts to relate physical and hormonal signalling mechanisms already have a fairly long history (Tindal *et al*. 1982, 1985) but the mechanisms respon-

sible for the putative translation of a photoperiodic signal into seasonal changes in the capacity of the rumen remain unresolved.

Metabolic signals

Circulating concentrations of metabolites, such as volatile fatty acids, non-esterified fatty acids, ketones and glucose have long been considered to be candidates for the role of signalling agents from the peripheral organs and circulation to the appetite centre in the brain. This led to the formulation of the glucostatic and lipostatic theories, around which much research into appetite has centred (van Itallie, 1990; Forbes, 1995), and to the related ischymetric control theory (Nicolaidis & Even, 1990). This latter concept suggests that circulating concentrations are likely to be modified not only by seasonal changes in the level of food intake and gastrointestinal function, and associated patterns of nutrient absorption, but also by basal metabolic rate and basal energy expenditure rate. Further support for the concept is provided by the observation of liver receptors responsive to propionate (Anil & Forbes, 1980) and receptors responsive to acetate in the rumen wall (Baile, 1971); nutrient supply could be signalled neurally to the brain via these sensors.

It is noteworthy that intrajugular administration of metabolites, such as volatile fatty acids, has been reported to have no obvious effects on food intake, while the effects of infusions into the hepatic portal vein were variable (de Jong, 1986). This observation suggests that metabolites may provide a regulatory signal mediated via neural signals from the liver. Collectively, studies of the effect on meal patterns of manipulations of circulating concentrations have led to the conclusion that volatile fatty acids, non-esterified fatty acids and glucose may have some involvement in the regulation of meals. However, it is unlikely that any of these metabolites has a pivotal role in controlling overall intake (de Jong, 1986; Forbes, 1995) and therefore in the control of seasonal changes in appetite.

Seasonality of metabolic rate

Circulating levels of metabolites are a function of rates of entry and exit from the pool and changes in these factors could be driven by changes in metabolic rate. Some studies have shown that metabolic rate is lower during winter than summer in Soay sheep (Argo *et al.* 1999) and white-tailed deer (*Odocoileus virginianus*) (Silver *et al.* 1969). On the other hand, significant seasonal differences have not been found in red deer (Sibbald *et al.* 1993) and the difference in commercial sheep breeds is minimal (Iason *et al.* 1994).

It has been proposed that seasonal differences in metabolic rate and nutrient requirements may drive the seasonal changes in appetite and intake (Barry *et al.* 1991) but it has also been suggested that the reported seasonal changes in metabolic rate may be a function of changes in temperature and animal activity (Pekins *et al.* 1992). Clearly, the biological significance of such changes is in doubt.

Putative hormonal signals

Hormonal signals can serve to integrate effects of changes in photoperiod, nutritional state and other aspects of physiological state (pregnancy, lactation, thermal status, etc.), thereby providing

a signal to the brain which is appropriate to both season and physiological state. Thus, an appropriate appetite response can be triggered, which takes account of both long- and short-term signals. Rodent studies indicate that these are likely to involve different physiological mechanisms (Weigle, 1994).

It might appear that in order to be a candidate for the role of controlling seasonal changes in intake, the profile of a hormone should also exhibit a seasonal pattern of change. However, this view is arguably simplistic as it is possible that hormones can have a role in the mediation of seasonal changes in intake without large changes in circulating concentrations. This may be possible through changes in (a) the rate of delivery of the hormone to the target tissue or (b) the pattern of secretion at particular periods of the day, for example, postprandially. In addition, changes in the expression of receptors for the hormone or in expression of downstream intracellular signalling could also result in seasonal changes in response. Each of these phenomena is likely to be influenced by the actions of other hormones acting in concert.

Changes of season are associated with photoperiod-driven changes in physiological signals. However, the physiological signals are also determined indirectly by the changes in nutritional state associated with seasonal changes in food intake. Thus the signals that provide feedback to the appetite centre not only regulate the pattern of intake but are inevitably also a function of the pattern of intake. The observed changes with season in hormone profiles may therefore be interpreted either as a secondary consequence or as playing a primary role in driving seasonal intake. Careful experimental design is therefore necessary to tease apart these two components.

Studies of several species have shown the elevated food intake levels of summer to be closely associated with higher circulating concentrations of prolactin, insulin-like growth factor-1 (IGF-1) and leptin (Rhind & McMillen, 1995; Bocquier *et al.* 1998; Rhind *et al.* 1998, 2000; Marie *et al.* 2001). The thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), also exhibit seasonal changes with highest concentrations generally occurring in spring and lowest in early autumn (Loudon *et al.* 1989; Rhind & McMillen, 1995; Rhind *et al.* 1998, 2000). Thus, the timings of maximum and minimum concentrations of these hormones are less closely linked to the times of the solstices than for the other hormones. In the seasonal Siberian hamster, circulating T_4 concentrations are higher during long days (LD), but peripheral T_4 administration during short days (SD) does not prevent the seasonal decrease in food intake (O'Jile & Bartness, 1992).

While this observation might seem to be at odds with a role for the thyroid hormones in seasonal changes in intake, it is noteworthy that Nicholls *et al.* (1988) have reported evidence to support a unifying theory suggesting the involvement of the thyroid hormones in the expression of seasonal changes in reproductive function in groups as diverse as birds and ruminants. It is possible that they are similarly involved in the expression of seasonal changes in food intake.

Other metabolic hormones such as insulin (Rhind & McMillen, 1995; Rhind *et al.* 1998, 2000) and cortisol (Rhind & McMillen, 1995; Rhind *et al.* 1998, 2000) generally do not show large seasonal variation in circulating concentrations. There is limited evidence that growth hormone (GH) concentrations may be slightly elevated during the summer (Rhind & McMillen, 1995; Rhind *et al.* 2000).

In order to dissociate the effects of photoperiod and intake on hormone profiles, year-round studies have been conducted with red deer (Rhind *et al.* 1998) and Soay sheep (Rhind *et al.* 2000) fed *ad libitum* or fed a ration equivalent to their mid-winter level of intake. Prolactin profiles exhibited large seasonal variations that were independent of food intake. However, thyroid hormone profiles were affected by increases in nutrient intake during the summer so that photoperiod-induced changes were evident only when the food intake was held constant.

Although the patterns of secretion of the hormones that exhibit seasonal changes are in the same direction as the seasonal patterns of food intake, daily food intakes and profiles of GH, insulin, T_3 and T_4 have all been found to be poorly correlated in both sheep and red deer and whereas prolactin and IGF-1 were significantly positively correlated with intake in deer, there was no such relationship in Soay sheep (Rhind *et al*. 1998, 2000). Collectively, these observations suggest that there may not be a direct link between these hormones and food intake. Furthermore the hypothalamo–pituitary disconnected rams of Lincoln *et al*. (2001) showed clear photoperiod-driven prolactin cycles but showed no corresponding changes in appetite.

The absence of a clear, direct hormonal effect has led to some more detailed studies of selected hormone profiles and in particular of the within-day profiles of hormones such as insulin and GH that exhibit substantial postprandial changes in secretion. While circulating levels of insulin in ruminants are apparently not affected by photoperiod (Rhind *et al*. 1998, 2000), this hormone is secreted in response to the postprandial increase in supply of energy-providing substrates such as glucose, propionate and amino acids, and it favours their assimilation into tissue (Trenkle, 1981). The role of insulin as an appetite-regulating mechanism merits further research not only because it is involved in the regulation of energy metabolism, but also because it has recently been shown that the pattern of postprandial change in insulin concentrations changes with season in Soay sheep maintained on a constant level of food intake. The peak postprandial values were significantly greater in long or declining daylength (June and September) than at the time of the vernal equinox (March) (Rhind *et al*. 2000). It is postulated that such changes with season could be a function of the seasonal changes in circulating levels of prolactin which, in studies with rats, has been shown to stimulate insulin production (Moldrup *et al*. 1993; Petryk *et al*. 2000). Furthermore, insulin is known to influence activity in hypothalamic appetitive pathways (Schwartz *et al*. 1992). In contrast to the differences observed in insulin profiles, postprandial GH profiles exhibited no such differences with season (Rhind *et al*. 2000).

Do hormones act directly on the brain?

The low level of correlation between circulating hormone profiles and food intake suggests that intake is not regulated simply by these hormones acting directly on the appetite centres of the brain. Although the ventromedial hypothalamic region where many of the appetite regulatory neurones reside may be exposed directly to circulating blood (i.e. hormones would not have to cross the BBB), it is assumed that signalling hormones require transportation across the BBB to reach other hypothalamic nuclei and brain regions. Studies of rodents and other species have shown that some hormones are actively transported across the BBB, including insulin (Baura *et al*. 1993), leptin (Banks *et al*. 1996) and prolactin (Martensz & Herbert, 1982). These active transport processes represent a potential mechanism for the control of hormone delivery to the brain and therefore for control of peripheral feedback and of the intake response. Such regulatory mechanisms could explain the absence of a clear relationship between circulating hormone profiles and seasonal changes in appetite because they could determine the supply of hormone to the appetite centre, irrespective of circulating profiles. Such mechanisms have the advantage of allowing regulation of the peripheral metabolism according to short-term need while not allowing the associated short-term changes in hormone profiles to perturb the long-term regulation of appetite. The factors that control the rate of transfer across the BBB are unknown but may include seasonal changes in circulating hormone profiles and changes in membrane permeability induced by hormonal changes or as a result of endogenous rhythms within the cells of the barrier membranes.

Work on yellow-bellied marmots (*Marmota flaviventris*) (Florant *et al*. 1991), rodents that exhibit extreme seasonal changes in food intake, has shown that the rate of transfer of insulin across the BBB into the cerebrospinal fluid is lower during winter than summer. While Rhind *et al*. (2000) were unable to demonstrate any such seasonal change in the efficiency of insulin transfer across the BBB in Soay sheep, the potential involvement of such a mechanism in the seasonal regulation of intake in ruminants deserves further study.

Are there indirect hormonal effects on the brain?

An alternative mechanism through which seasonal changes in peripheral circulating hormone profiles could impinge on the appetite centre is via neural feedback from the liver or alimentary tract. The function of these organs could be altered by hormonal signals thereby resulting in altered neural feedback. The potential importance of such neural feedback from the liver has been demonstrated through denervation studies in sheep (Anil & Forbes, 1988).

An example of a possible hormonal–liver–neural interaction can be deduced from the findings of a number of studies. T_3 concentrations are higher in spring and early summer and lowest in late summer and early autumn (Rhind & McMillen, 1995; Rhind *et al*. 1998, 2000). A reduction in T_3 concentrations in ruminants can induce an increase in insulin secretion and a reduction in the rate of degradation (Achmadi & Terashima, 1995). This may increase insulin concentrations in the hepatic-portal vein, into which the insulin is secreted (Harmon, 1992), without necessarily altering concentrations in the peripheral circulation where portal blood is significantly diluted. Thus, the rate of delivery of insulin to the liver may be increased in response to a seasonal decline in T_3 concentrations. Similarly, IGF-1 inhibits insulin secretion (Leahy & Vandekerkhove, 1990) and so a seasonal reduction in concentrations of this hormone could also affect insulin secretion. Since studies of rodents have shown that small amounts of insulin infused into the portal vein can act, via a vagus nerve signal to the brain, to induce a reduction in meal size (Vanderweele, 1994), it is postulated that the seasonal changes in circulating T_3 could be one of the factors driving seasonal changes in the eating pattern; this could operate through a combination of an altered insulin signal to the liver and associated change in the neural feedback from the liver.

Neural signals from the rumen or other parts of the alimentary tract could also be altered by hormonal signals. A direct influence on appetite of the seasonally-variable hormone, prolactin, has been ruled out (Lincoln *et al*. 2001). However, there is evidence from rodent studies that it can induce gut hypertrophy (Bates *et al*. 1963) and both prolactin and GH receptors have been shown to be present in parts of the intestine and in the pancreatic islets of Langerhans (Lobie *et al*. 1993; Moldrup *et al*. 1993); IGF-1 receptors are also present in the gut (Laburthe *et al*. 1988; Termanini *et al*. 1990). These observations suggest that a number of hormones are likely to exert effects on both the gut and on the organ producing insulin. Thus, there is potential for interaction and feedback between the gastrointestinal tract, the peripheral circulation and the appetite centre of the brain, via both neural and endocrine routes. Consequently, seasonal changes in any or all of these hormones could affect appetite and food intake through changes in gut function, hormone secretion and neural feedback to the brain. At present, much of the information pertaining to the roles of hormones in appetite regulation is derived from studies of non-ruminant species but these studies can be used to identify potentially important mechanisms to be studied in ruminants.

One potential effect on gut function of hormonal or other signals is altered synthesis and secretion of hormones secreted by the gut, such as cholecystokinin (CCK), somatostatin, bombesin and galanin and others (Baile *et al*. 1986; Morley, 1987; Walsh, 1987). These hormones

have been implicated in the processes of satiety and therefore could be involved in the regulation of meal pattern and intake. However, they probably do not act in isolation but in concert with other hormones such as insulin which can enhance CCK activity within the brain (Riedy *et al*. 1995). Similarly, leptin, for which there are receptors on neurones of the vagus nerve (Buyse *et al*. 2001), acts synergistically with CCK to induce short-term inhibition of food intake (Barrachina *et al*. 1997) and long-term reduction in body weight in rodents (Matson & Ritter, 1999).

While there is virtually no information concerning the roles of these hormones in the expression of seasonality of intake in ruminants, CCK, which is secreted in response to ingestion of food and interacts with sensors in the gut wall (Praissman *et al*. 1983) and pancreas (Steigerwalt & Williams, 1981), was found to act as a satiety factor in ruminants (Farningham *et al*. 1993), with its effects being potentiated by central administration of insulin (Riedy *et al*. 1995; Woods *et al*. 1996). Thus, CCK may be involved in the determination of meal pattern and therefore level of intake. Although it has been suggested (Stricker & Verbalis, 1990) that the observed effects of peripheral CCK administration may simply be a response to CCK-induced nausea, there is strong evidence from CCK immunisation studies of pigs (Pekas & Trout, 1990; Pekas, 1991) that this hormone is directly involved in the control of food intake. The evidence of its involvement in ruminants is less convincing since immunisation is not associated with an increased level of intake (Trout *et al*. 1989; Rhind *et al*. 2001). Nevertheless, a small, indirect role in the seasonal regulation of intake is suggested by a recent immunisation study in red deer, which showed that the amplitude of the seasonal cycle was reduced by CCK immunisation (Rhind *et al*. 2001). This finding is consistent with observations of seasonal variation in sensitivity to the satiety effects of CCK in hamsters (Mercer, 1998).

Regulation of hormone action

Plasma hormone concentrations do not necessarily equate with the observed biological response, not only because the response may depend on the action of multiple hormones acting in concert but also because the action of the hormones depends on the numbers and activity of their receptors and on downstream changes in cell function. In addition, binding proteins may modify the action of hormones. Receptor activities are known to vary in response to hormonal signals (Bick *et al*. 1992) and may be subject to seasonal variation but this has not been studied. When interpreting the effects of thyroid hormone profiles it is also important to note that the majority of the biologically active form, T_3, is derived from T_4 and the conversion process, which involves deiodinase enzymes, occurs in many tissues, including the brain (Beckett & Arthur, 1994). Consequently, tissue concentrations are not necessarily directly related to circulating concentrations and the signal provided to the target tissue is not necessarily the same as that indicated by circulating concentrations. The potential for seasonal variation in the activity of deiodinase enzymes has been demonstrated in ruminants but so far only in goat skin (SM Rhind and CE Kyle, unpublished results).

Control mechanisms: central

Hypothalamic regulation of seasonal appetite cycles

Systemic signals such as those discussed earlier exert their effects on appetite and feed intake through action on the so-called 'appetite centre(s)' of the brain. The critical role of the hypo-

thalamus in mammalian appetite regulation was recognised from lesion experiments as long ago as the 1940s and 1950s which led to the concept of hypothalamic 'hunger' and 'satiety' centres (Stellar, 1954). More recent work has begun to elucidate the hypothalamic neural pathways involved in orexigenic and anorexigenic drives. Such research, largely based on non-seasonal rodent models, has been stimulated by the accelerated impetus to understand the molecular basis of impaired body-weight regulation in obesity (Kalra *et al*. 1999). Theoretically, nutritional status must be signalled from the periphery to the brain, and the discovery of the adipose tissue product, leptin, was seen as a major breakthrough in this regard. Leptin was found to impact directly on many hypothalamic pathways, particularly on neurons of the arcuate nucleus (ARC) in the mediobasal hypothalamus (Ahima *et al*. 2000).

However, the brains of seasonal animals must receive and respond to photoperiodic as well as nutritional feedback, and the area of the brain in which these inputs are integrated and the extent to which they both influence the same neural pathways have yet to be determined. Changes in photoperiod are transduced humorally through changes in the diurnal pattern of pineal melatonin secretion (Morgan *et al*. 1994). However, sites of melatonin action on the appetite-body-weight axis have yet to be fully elucidated (Morgan & Mercer, 2001).

Early lesion experiments in seasonal ruminants demonstrated the involvement of the ventromedial hypothalamus and lateral hypothalamus in appetite and energy balance regulation (Baile & Forbes, 1974). More recently, it was elegantly demonstrated that sheep with complete lesions of the basal hypothalamus, including at least the ARC and median eminence, show no photoperiod-induced alterations in food intake and body weight (Lincoln *et al*. 2001). This contrasts with findings based on seasonal Siberian hamsters which showed normal appetite and body-weight responses to photoperiod despite monosodium glutamate-induced lesions of at least 80 % of ARC neurones (Ebling *et al*. 1998). On the basis of these studies, it appears that the ARC is a key site for appetite control, but other hypothalamic nuclei are also involved in seasonal appetite regulation.

The extent to which photoperiod entrains an endogenous circannual rhythm or provides independent appetite drive remains open to conjecture. Long-term cycles of intake and body weight persist in seasonal ruminants that are pinealectomised (Lincoln *et al*. 1989) or kept in constant conditions (Forbes, 1982), but not in the ARC- and median eminence-lesioned rams of Lincoln *et al*. (2001). However, a critical concept associated with photoperiodic entrainment is the provision of anticipatory regulation or drive (i.e. induction of changes in physiology before they are required) to the appetite–body-weight axis, as distinct from the compensatory regulation (i.e. induction of changes after they are required), which occurs as a result of nutritional feedback. It can be theorised that photoperiod, via melatonin, sets a seasonally appropriate body weight, perhaps encoded within the hypothalamus or higher brain centre, against which nutritional feedback is assessed and appropriate afferent adjustments are made to intake and/or metabolism. This is the basis of the sliding set point of seasonal body-weight regulation, a concept which was originally propounded by Steinlechner *et al*. (1983) and has been reviewed elsewhere (Mercer *et al*. 2000*a*; Adam & Mercer, 2001). Although based on the Siberian hamster model, many features are likely to be relevant to the seasonal ruminant, with both animals showing hypophagia and weight loss in response to SD and hyperphagia and weight gain in response to LD. Briefly, if food restriction is imposed on hamsters undergoing SD weight loss, the rate of weight loss accelerates; then, when allowed to feed freely again, the hamsters regain weight only to match that of controls kept in SD throughout (Mercer *et al*. 2001). In other words the seasonal mammal defends a body weight appropriate to its photoperiod experience.

Melatonin target sites

Using ligand binding and gene expression studies, melatonin receptors have been shown to be localised in the ventromedial hypothalamus and premamillary area of the ovine hypothalamus (Chabot *et al*. 1998; Malpaux *et al*. 1998), and in the suprachiasmatic and dorsomedial hypothalamic nuclei of Siberian hamsters (Morgan *et al*. 1994; Ellis *et al*. 2000). The importance of each of these target areas with regard to melatonin actions on seasonal intake and body weight awaits clarification. The latter two sites, in particular, deserve further study since they are known to project afferents to the paraventricular hypothalamic nucleus, which also receives afferent input from the ARC and is an important integrative site for energy balance regulation (Morgan & Mercer, 2001). Identification of the phenotype(s) of melatonin receptor-expressing neurones in these nuclei will clearly represent a major step towards the elucidation of seasonal intake regulation. While this approach will increase our understanding of transduction of photoperiodic information within the hypothalamus, it is pertinent also to address mechanisms of nutritional feedback to this region of the brain.

Leptin and leptin receptors

The activities of known hypothalamic orexigenic and anorexigenic receptors and neuropeptide pathways have been the subject of recent studies in seasonal animals. Many of these neuropeptides are known to be leptin-sensitive (Ahima *et al*. 2000) and circulating leptin profiles appear to be photoperiod-dependent. As in Siberian hamsters (Atcha *et al*. 2000; Klingenspor *et al*. 2000; Mercer *et al*. 2001), plasma leptin concentrations in sheep are higher in LD, reflecting the higher food intake and adiposity in this photoperiod, than in SD when intake and adiposity are low (Marie *et al*. 2001). In addition, as in all species studied to date, plasma leptin concentrations in sheep decline during periods of food restriction (Marie *et al*. 2001) and fasting (Adam *et al*. 2000*a,* 2002).

The signalling form of the leptin receptor (OB-Rb) has been localised in the ovine hypothalamus, with gene expression being detected, notably, in the ARC, ventromedial hypothalamus and paraventricular hypothalamic nucleus (Dyer *et al*. 1997; Williams *et al*. 1999). Leptin generally has clear anorexigenic actions and, as in laboratory rodents, leptin administered intracerebroventricularly (ICV) decreases appetite in sheep (Henry *et al*. 1999). Thus seasonal changes in circulating leptin concentrations are unlikely to be driving photoperiod-induced changes in food intake since these concentrations are high when appetite is high in LD and low when appetite is low in SD. Indeed it is paradoxical that the high levels of leptin in LD do not act to depress appetite, and the low levels of leptin in SD do not stimulate appetite, thereby counteracting the seasonal cycle. It therefore appears unlikely that leptin plays a role in regulating the central operation of 'anticipatory' sliding body-weight set point in seasonal animals (Klingenspor *et al*. 2000). However, seasonal animals retain the ability to exhibit 'compensatory' responses to seasonally inappropriate amounts of circulating leptin. There is growing evidence of seasonal adjustments in hypothalamic sensitivity to leptin feedback that may be fundamental to the seasonal intake cycle. In the Siberian hamster model, down-regulation of ARC OB-Rb gene expression accompanies the decline in circulating leptin concentrations during SD weight loss. This contributes to the 'anticipatory' regulation and contrasts with the elevated OB-Rb gene expression seen during 'compensatory' regulation when circulating leptin is reduced by imposed food restriction (Mercer *et al*. 2001). However, no difference in ARC OB-Rb gene expression has been seen in LD *v*. SD sheep (Archer *et al*. 1999), although it is elevated in sheep with reduced circulating leptin during food restriction or fasting (Archer *et al*. 1999; Adam *et al*. 2000*a,* 2002).

Further evidence of seasonal changes in sensitivity to leptin comes from studies of Siberian hamsters. Adult males and females given leptin continuously for 2 weeks had accelerated weight loss in SD compared with LD, with no effect on food intake (Atcha *et al*. 2000). However, adult males given a slightly larger dose of leptin daily for 2 weeks showed increased intake in SD but not in LD, leading these authors to conclude that leptin given to SD hamsters caused them to respond like LD hamsters (Drazen *et al*. 2001). In contrast, single intraperitoneal injections of a much larger, pharmacological dose of leptin decreased intake in adult males in both SD and LD (Reddy *et al*. 1999). Thus responses to leptin appear both season- and dose-dependent in Siberian hamsters. Data from sheep suggest an additional influence of gender. Evidence from one sheep study involving castrated males with steroid replacement suggested that a pharmacological dose of leptin ICV in a single injection decreased food intake in autumn but not in spring (Miller *et al*. 2000). However pharmacological ICV leptin infusions into gonadectomised sheep (i.e. with minimal steroid influence) for 12 d did not reduce intake in autumn but did reduce intake in early spring, with the reduction being greater in females than males (Clarke *et al*. 2001). To date, the physiological relevance of many leptin administration experiments has been doubtful since dose rates have clearly been in the pharmacological range. However, use of physiological dosing regimens is now more likely since sensitive assays for leptin concentrations in blood and cerebrospinal fluid have been developed for sheep (Crabtree *et al*. 2001; Marie *et al*. 2001). Further elucidation will come from experiments that address the effects of direction of photoperiod change and duration of photoperiod exposure. In view of the preliminary evidence of seasonal changes in hypothalamic sensitivity to nutritional (leptin) feedback, which is probably important for the maintenance of seasonal appetite–body-weight cycles, it is critical to elucidate the underlying mechanisms. These are likely to involve changes in the activities and/or nutritional responses of known hypothalamic appetite-related neuropeptides and the following section considers the evidence for seasonal changes in their expression.

Orexigenic neuropeptides

Neuropeptide Y (NPY) is one of the most potent orexigenic neuropeptides known; it stimulates appetite when administered ICV to sheep (Miner, 1992). Also, as observed in laboratory rodents, NPY gene expression in the ovine ARC is increased by negative energy balance induced by food restriction (McShane *et al*. 1993; Adam *et al*. 1997) or fasting (Adam *et al*. 2000*a*; 2002). ARC NPY gene expression is similar between LD and SD Siberian hamsters, despite large differences in voluntary food intake and body weight; however, it is up-regulated in either photoperiod by an imposed food restriction producing similarly large differences in intake and body weight (Reddy *et al*. 1999; Mercer *et al*. 2000*b*, 2001). Furthermore Siberian hamsters exhibit no seasonal changes in the appetite response to ICV-administered NPY (Boss-Williams & Bartness, 1996). These findings suggest that animals undergoing photoperiodically-induced weight change, as opposed to an imposed weight loss regimen, remain in energy homeostasis; in other words, they remain at a body weight that is perceived centrally as appropriate to their photoperiodic experience (Mercer *et al*. 2000*b*). Equivalent data for sheep are equivocal at present. Although levels of ARC NPY mRNA were increased in both photoperiods in food-restricted castrated males with steroid replacement, relative to *ad libitum*-fed animals, there was no difference in expression between artificial SD and LD (Archer *et al*. 1999; Fig. 2). However, others have reported seasonal alterations in NPY activity in freely-grazing ovariectomised ewes. In these animals, the
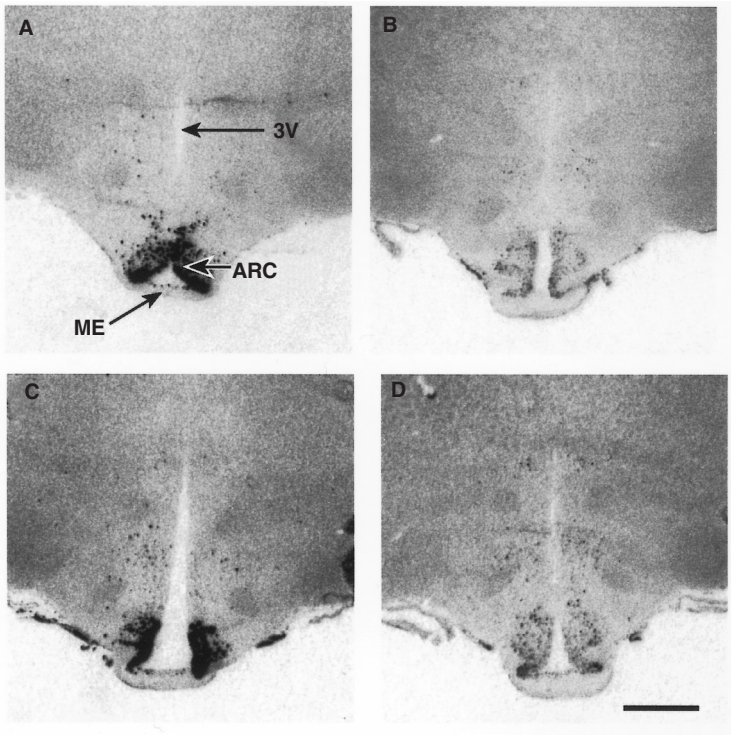
Fig. 2. Coronal hypothalamic sections showing neuropeptide Y gene expression in the arcuate nucleus (ARC) of sheep with low (A, C) or high (B, D) food intake and kept in short day (A, B) or long day (C, D) photoperiod. 3V, third ventricle; ME, median eminence; —, scale bar, 3 mm. (From ZA Archer, SM Rhind, PA Findlay, S McMillen and CL Adam, unpublished results.)

number of ARC cells expressing NPY immunoreactivity and NPY mRNA was higher in late summer, when voluntary food intake is usually high, than in spring, when intake is usually low (Barker-Gibb & Clarke, 2000; Clarke *et al*. 2000). However, these experiments were conducted in natural photoperiod in field conditions; body fatness and satiety of the ewes and food availability were not recorded. Since ARC NPY gene expression is increased in both food-restricted sheep and those on similar levels of food intake but in low body condition (Adam *et al*. 1997; Archer *et al*. 2000), it is clear that more highly controlled testing is required to elucidate the potential involvement of NPY in the seasonal intake cycle of sheep.

Agouti-related peptide co-localises with NPY in the ARC of rodents and exhibits similar distribution in sheep (Archer *et al*. 2000; Mercer *et al*. 2000*b*). Its orexigenic effects are mediated through its antagonism to the anorexigenic melanocortin pathway by actions at the hypothalamic melanocortin-3 and -4 receptors (Ollmann *et al*. 1997). There is no convincing evidence that it is significantly modulated by photoperiod, although gene expression is highly up-regulated by food restriction, in both sheep (Archer *et al*. 1999) and Siberian hamsters (Mercer *et al*. 2001).

Gene expression for the leptin-sensitive orexins (or hypocretins) exhibits similar lateral hypothalamic localisation in sheep (Archer *et al*. 2002) and rodents (Mercer *et al*. 2000*b*). ICV

administration clearly stimulates appetite in rodents (Sakurai *et al*. 1998) and sheep (Sartin *et al*. 2001) and yet there are no differences in gene expression between Siberian hamsters in SD (low appetite) and LD (high appetite) (Reddy *et al*. 1999; Mercer *et al*. 2000*b*). Moreover, pre-pro-orexin gene expression has been shown to be up-regulated in SD relative to LD in sheep (Archer *et al*. 2002). Although initially this finding appears counterintuitive, appetite control may not be the primary role of this neuropeptide. Apart from their involvement in arousal behaviour (Samson & Resch, 2000), orexins also impact on the reproductive–neuroendocrine axis, notably stimulating gonadotrophin-releasing hormone–luteinising hormone surge release in steroid-primed rats (Pu *et al*. 1998; Kohsaka *et al*. 2001). The up-regulation of orexin expression in sheep during SD could therefore be related to the reproductive stimulation in this photoperiod (Archer *et al*. 2000). Indeed, evidence is accumulating for an involvement of orexins in nutritional modulation of reproductive neuroendocrine output (Blache *et al*. 2002).

Anorexigenic neuropeptides

Gene expression in the ARC for pro-opiomelanocortin (POMC), the precursor for a variety of peptides including the anorexigenic melanocortins, is consistently elevated in Siberian hamsters kept in LD *v*. SD (Adam *et al*. 2000*b*; Mercer *et al*. 2000*b*, 2001). Again, this appears counterintuitive with regard to the seasonal pattern of appetite drive. The apparent anomaly may reflect the fact that the difference is a secondary consequence of the increased appetite and adiposity in this photoperiod. However, there is an alternative explanation based on seasonal reproductive activity and the equivocal data from sheep add weight to this argument. No difference was found in hypothalamic POMC mRNA expression in castrated males with a constant level of oestradiol replacement kept in LD and SD (Archer *et al*. 1999). However, another study has shown that POMC gene expression was similar in LD and SD in castrated males with no steroid replacement, but higher in SD than LD in castrated males treated with testosterone (Hileman *et al*. 1998). Conversely, POMC gene expression in ovariectomised ewes in natural photoperiod was higher in spring and summer (increasing daylength and LD, respectively) than in autumn (decreasing daylength) (Clarke *et al*. 2000). Similarly, immunoreactivity for β-endorphin (another POMC product) was increased in entire ewes in LD (Skinner & Herbison, 1997). Clearly there are insufficient data to indicate that changes in POMC gene expression either parallel or drive seasonal changes in intake. However, POMC appears to be highly sensitive to gonadal steroid feedback in a species- and gender-dependent manner. Thus, in the LD breeding season of Siberian hamsters, sex steroids in males and females putatively stimulate POMC expression (Adam *et al*. 2000*b*; Mercer *et al*. 2001) while the opposite appears to be the case in the SD breeding sheep. POMC expression is similar in SD and LD in castrated males with no steroid replacement or with constant oestradiol concentrations (Hileman *et al*. 1998; Archer *et al*. 1999) but is decreased in SDs in castrated females with no steroid replacement and in entire females with their seasonally-increased circulating progesterone and oestradiol (Skinner & Herbison, 1997; Clarke *et al*. 2000). Furthermore, testosterone inhibits POMC gene expression in castrated males (Hileman *et al*. 1998), but this effect is seen only in LD and not in SD. Clearly, further studies are required to elucidate seasonal alterations in steroid feedback modulation of POMC. The available evidence indicates that POMC expression does not play a role in seasonal appetite regulation but illustrates the interplay between seasonal reproductive cycles and hypothalamic energy balance circuitry.

   Another anorexigenic neuropeptide which exhibits similar patterns of hypothalamic localisation and sensitivity (down-regulation) in response to negative energy balance in sheep and

laboratory rodents is cocaine- and amphetamine-regulated transcript (CART) (Adam *et al*. 2000*a*, 2002). There are no data for sheep kept in different photoperiods, but CART gene expression in the ARC of Siberian hamsters is consistently up-regulated in SD in both genders (Adam *et al*. 2000*b*; Mercer *et al*. 2001). The importance of this finding lies in the timing of the up-regulation, which occurs within 2 weeks of photoperiod change, before divergence of body-weight trajectories and unlike any other energy balance neuropeptides studied (Adam *et al*. 2000*b*). CART may therefore have a role in driving seasonal appetite change. Interestingly, since CART mRNA co-localises extensively with POMC mRNA in the ARC (Elias *et al*. 1998), the opposite responses to photoperiod of these mRNA in Siberian hamsters provides evidence of transcript-specific regulation within individual neurones (Adam *et al*. 2000*b*; Mercer *et al*. 2001). Unlike the changes in POMC, the photoperiod-induced changes in CART precede significant reproductive responses and are unlikely to be attributable to changes in gonadal steroid concentration.

Conclusion

Current understanding of seasonality of appetite in ruminants is based primarily on descriptive observations, but in the future it will be based increasingly on more complex experimental paradigms involving perturbations or challenges to the normal physiology.

Historically, in ruminants, certain types of food intake regulatory mechanisms have been considered to be more important than others. For example, rumen fill and blood metabolites have each been considered to be the key signal. However it is now clear that multiple signals contribute to the integrated mechanism of seasonal appetite control, including hormonal signals from the circulation, neural signals originating in the gut, liver and fat depots and neural cross-talk between different brain regions. It is also apparent that it is likely that there are many signalling factors that have yet to be discovered and investigated. For example, the role in ruminants of the recently discovered appetite-stimulating hormone ghrelin (Hayashida *et al*. 2001) and the suggestion that a neural pathway exists which signals body mass to the appetite centre (Adams *et al*. 2001) both merit investigation.

Most investigations of the physiological mechanisms that determine the pattern of food intake focus on only one or two components of a highly complex, integrated system. While there is clearly an ongoing requirement for experiments of this type, there is also a need for experimental designs that enable many systems to be studied together and the results to be integrated. In the investigation of the roles of circulating hormones in the pattern of food intake, most studies to date have involved relatively infrequent sampling intervals (say once every 7 or 14 d). While these data provide a measure of gross seasonal changes, the sampling frequency is insufficient for the assessment of changes with season in postprandial or circadian profiles and 24-h hormone profiles may be necessary for the proper characterisation of seasonal changes in their actions.

There is a need to investigate seasonal changes in hormone receptor activities both peripherally and within the brain. There are seasonal changes in hypothalamic sensitivity to nutritional feedback, and it remains to be established whether this is a causal factor in seasonal intake regulation or a secondary phenomenon. Thus, LD photoperiod increases appetite drive and food intake, body weight and adiposity resulting in increased nutritional feedback from the periphery to the hypothalamus (via leptin and insulin, for example). Conversely, SD photoperiod depresses food intake, body weight and adiposity resulting in reduced feedback. Importantly, these gradual and sustained changes in nutritional feedback do not trigger the com-

pensatory alterations in hypothalamic appetite-related neuropeptide activity that occur in response to acute changes in nutritional feedback of similar magnitude imposed experimentally.

The physiological signals that stimulate appetite in LD and depress it in SD remain open to conjecture, although a role for hypothalamic CART in SD appetite suppression cannot be ruled out. To date, there is no convincing evidence for the involvement of other ARC neuropeptides that are classically implicated in appetite control in non-seasonal rodents. Nonetheless it appears fundamental to the maintenance of seasonal appetite cycles that these neuropeptides are resistant to photoperiod-induced changes in nutritional feedback. In other words, the improved nutritional feedback in LD (summer) does not act to suppress appetite, and the reduced nutritional feedback in SD (winter) does not stimulate appetite, thereby counteracting the seasonal changes in intake. The key to elucidating these mechanisms lies in determining the site(s) and mode(s) of action of melatonin in both driving changes in appetite and disengaging or altering hypothalamic sensitivity to changing nutritional feedback. An additional factor that must be considered when addressing central seasonal intake regulation is the steroid sensitivity of many of the hypothalamic pathways involved and the close relationship between appetite and reproductive cycles.

Finally, it is clear that there are many different and equally valid experimental approaches to the study of seasonality of intake in ruminants, ranging from the whole animal down to the cellular level. These diverse methodologies will also provide the basis for much future research to elucidate further this complex regulatory system.

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