Hormones and Behavior 93 (2017) 82–93

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

The importance of hormonal circadian rhythms in daily feeding patterns: An illustration with simulated pigs

Iris J.M.M. Boumans [a,*], Imke J.M. de Boer [a], Gert Jan Hofstede [b], Susanne E. la Fleur [c], Eddie A.M. Bokkers [a]

[a] Animal Production Systems Group, Wageningen University, Wageningen, The Netherlands
[b] Information Technology Group, Wageningen University, Wageningen, The Netherlands
[c] Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands

A R T I C L E I N F O

Article history:
Received 20 October 2016
Revised 10 March 2017
Accepted 10 May 2017
Available online xxxx

Keywords:
Alternans pattern
Feeding behaviour
Motivation
Circadian rhythm
Energy balance
Pig
Melatonin
Cortisol
Decision-making
Modelling

A B S T R A C T

The interaction between hormonal circadian rhythms and feeding behaviour is not well understood. This study aimed to deepen our understanding of mechanisms underlying circadian feeding behaviour in animals, using pigs, *Sus scrofa*, as a case study. Pigs show an alternans feeding pattern, that is, a small peak of feed intake at the beginning of the day and a larger peak at the end of the day. We simulated the feeding behaviour of pigs over a 24 h period. The simulation model contained mechanisms that regulate feeding behaviour of animals, including: processing of feed in the gastrointestinal tract, fluctuation in energy balance, circadian rhythms of melatonin and cortisol and motivational decision-making. From the interactions between these various processes, feeding patterns (e.g. feed intake, meal frequency, feeding rate) emerge. These feeding patterns, as well as patterns for the underlying mechanisms (e.g. energy expenditure), fitted empirical data well, indicating that our model contains relevant mechanisms. The circadian rhythms of cortisol and melatonin explained the alternans pattern of feeding in pigs. Additionally, the timing and amplitude of cortisol peaks affected the diurnal and nocturnal peaks in feed intake. Furthermore, our results suggest that circadian rhythms of other hormones, such as leptin and ghrelin, are less important in circadian regulation of feeding behaviour than previously thought. These results are relevant to animal species with a metabolic and endocrine system similar to that of pigs, such as humans. Moreover, the modelling approach to understand feeding behaviour can be applied to other animal species.

1. Introduction

Regulation of feeding behaviour in animals is controlled by the energy balance (Strubbe and van Dijk, 2002). This control includes processing of feed in the gastrointestinal tract (GIT) and metabolic (hunger and satiation) responses of the body to the energy status. The role of circadian rhythms in metabolic regulation is increasingly evident (Eckel-Mahan and Sassone-Corsi, 2013; Laposky et al., 2008). The sleep-wake cycle, for example, is an important rhythm, because many physiological and behavioural responses depend on whether an animal is awake or asleep (Laposky et al., 2008). In addition, several hormonal responses related to metabolism and involved in the regulation of energy balance show circadian rhythms, such as cortisol, ghrelin and leptin (Kumar Jha et al., 2015). So far, however, it is unclear how the regulation of the energy balance interacts with circadian rhythms and how this interaction affects feeding behaviour during the day (Strubbe and van Dijk, 2002), such as feed intake, meal frequency and meal size.

The feeding behaviour of animals follows recurring daily patterns. These patterns usually coincide with the animals' active periods and commonly consist of two peaks. Two types of activity patterns have been described for feeding: in the bigeminus pattern, the first feeding peak (at the beginning of the active period) is larger than the second one (at the end of the active period); in the alternans pattern, the opposite is true, with the highest peak being the second one (Aschoff, 1957). The bigeminus pattern is found, for example, in the greenfinche, *Chloris chloris*, and meadow vole, *Microtus pennsylvanicus* (Aschoff, 1966), whereas the alternans pattern is found in species such as the capercaillie, *Tetrao urogallus* (Gjerde and Wegge, 1987), and pig, *Sus scrofa* (De Haer and Merks, 1992; Schouten, 1986).

For animals displaying a bigeminus pattern of feed intake, the first and highest peak can be explained by energy deficits following a fasting period, i.e. inactive period. The alternans pattern of feed intake, however, with its higher peak in the second part of the active period, suggests that other mechanisms, besides the energy deficits following fasting, regulate feed intake. Insight into these 'other mechanisms' will enhance our understanding of the ability of animals to adjust their feeding behaviour under various conditions and can provide insight into their growth and health.

* Corresponding author at: Animal Production Systems Group, Wageningen University, P.O. Box 338, 6700, AH, Wageningen, The Netherlands.
E-mail address: iris.boumans@wur.nl (I.J.M.M. Boumans).

http://dx.doi.org/10.1016/j.yhbeh.2017.05.003
0018-506X/

The aim of this study was to gain more understanding of the mechanisms underlying circadian feeding behaviour in animals. We hypothesise that hormones with strong circadian rhythms involved in energy balance can explain feeding patterns, in particular in the regulation of the alternans feeding pattern. We focus in this study on pigs, because they have an alternans feeding pattern and a large amount of empirical data is available on, for example, circadian fluctuations in physiological processes and feeding behaviours (e.g. meal frequency, meal size, meal duration).

1.1. General approach

We used a computer model to mechanistically simulate the regulation of feeding behaviour. Feeding behaviour is very complex, with interactions taking place at many levels (e.g. from molecular, cellular, neurological, to whole animal level). We chose to simulate underlying processes on a physiological and metabolic level, integrating processing of feed in the GIT (intake, digestion and absorption), fluctuation in the energy balance, and hormonal circadian rhythms that affect motivational decision-making on behavioural patterns such as feeding behaviour.

The model allowed us to test the effect of the interaction between energy balance and hormonal circadian rhythms on feeding patterns. Feeding patterns such as feed intake, meal frequency and meal duration emerged when running the model. Furthermore, the model produced patterns for underlying processes, such as energy absorption, metabolic rate and daily energy balance. Model patterns were compared to those observed in empirical studies for validation of the model.

1.2. Energy balance

Animals feed in meals and hence energy intake is episodic, while the need for energy is variable but continuous (Nelson, 2011; Stricker and Verbalis, 1988). The energy balance, therefore, will shift continuously between a positive and a negative balance, which is regulated in the short- and long-term.

1.2.1. Processing of feed

In monogastric animals, such as pigs, ingested feed first enters the stomach, which functions as a temporary storage. From the stomach, digesta is transferred to the intestines where energy is absorbed (Strathe et al., 2008; Wenk, 2001). Woods and D'Alessio (2008) reviewed hormonal and related signals affecting energy intake. Shortly after ingestion, satiation signals from the GIT, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY), and distension signals from the stomach start to operate (Woods and D'Alessio, 2008). These signals contribute to the digestion of feed (e.g. stimulating gut motility and secretions) and are anorexigenic signals that decrease appetite and, subsequently, feed intake. After fasting, orexigenic peptide concentrations of ghrelin increase and stimulate appetite and feed intake.

1.2.2. Energy balance

The energy balance is determined by energy absorption and energy expenditure (see review Schwartz et al., 2003). The balance will shift from positive to negative during the day and affect anabolic and catabolic processes in the body, responsible for storing (e.g. fatty acid and protein synthesis) or releasing energy (e.g. glycolysis and fatty acid oxidation). These processes will affect the amount of body fat (adiposity) stored. As reviewed by Woods and D'Alessio (2008), adiposity affects circulating insulin and leptin levels. The amount of adipose tissue is related to plasma leptin concentrations and a basal amount of plasma insulin is available as a reflection of the amount of fat. While satiation signals from the processing of feed are secreted in phases during meal intake, adiposity signals are more continuously present and affect the energy balance in the longer term. These anorexigenic adiposity signals affect anabolic and catabolic processes and change the sensitivity of the brain to satiation signals.

1.3. Circadian rhythms

Circadian rhythms that underlie behavioural patterns are regulated by internal body clocks (endogenous oscillators) (Aschoff, 1963, 1966). These body clocks can adjust the physiological and behavioural responses of an animal to stimulate or inhibit feeding behaviour at certain times (Strubbe and van Dijk, 2002). Periodic environmental factors, known as *zeitgebers*, synchronise animal responses to a 24 h period (Aschoff, 1966). The light-dark cycle is an important *zeitgeber* in circadian rhythms. Light synchronises the suprachiasmatic nuclei (SCN) in the anterior hypothalamus of the brain (the master clock), which regulates circadian rhythms in the body such as the sleep-wake cycle and behavioural activity (Johnston, 2014). Under normal conditions, with ad libitum feed access and a normal light-dark cycle, the master clock synchronises with peripheral oscillators (outside the SCN), to synchronise processes such as fasting and feeding behaviour (Kumar Jha et al., 2015). While the light-dark cycle is an important *zeitgeber* for the circadian clock, feed availability is an important *zeitgeber* for peripheral oscillators involved in the regulation of circadian feeding behaviour (Kriegsfeld et al., 2002).

Some hormones involved in the regulation of energy balance show strong circadian rhythms. In mammals, these hormones include melatonin, leptin, ghrelin, and glucocorticoids (see review Kumar Jha et al., 2015). Melatonin concentrations fluctuate during the day following the light-dark cycle, with higher secretion at night in both diurnal and nocturnal animals (Claustrat et al., 2005; Kumar Jha et al., 2015). Melatonin causes sleep in diurnal mammals, but not in nocturnal mammals. Nocturnal animals are active when melatonin levels are high (Kumar Jha et al., 2015). Melatonin is involved in the regulation of energy flow and expenditure; insulin synthesis, secretion and action; and in the synchronisation of metabolic processes with insulin-sensitive and -resistant phases over the day (Cipolla-Neto et al., 2014). Leptin stimulates energy expenditure and inhibits feed intake, while ghrelin has the opposite effect and counterbalances the effects of leptin (Kumar Jha et al., 2015). Glucocorticoids are light-entrainable and peak shortly before the onset of activity, which means shortly before light in diurnal animals or shortly before dark in nocturnal animals (Dallman et al., 2004). In addition, glucocorticoids can also be entrained to feed availability under feed-restricted conditions (Dallman et al., 2004). Glucocorticoids are involved in several biological functions, in addition to their well known function as stress hormone. They influence metabolic mechanisms by, for example, stimulating gluconeogenesis and fat breakdown by lipolysis to maintain blood glucose levels (De Guia et al., 2014). The effects of glucocorticoids on feeding behaviour are complex because glucocorticoids interact with other systems involved in feeding behaviour. For example, corticosterone increases food intake but also stimulates insulin secretion, which inhibits food intake, thus masking the effects of corticosterone on feeding behaviour (La Fleur et al., 2004; Peckett et al., 2011; Vera et al., 2017).

Since feed availability is an important *zeitgeber* in metabolism, fluctuations in many circulating hormone concentrations are related to feed intake patterns. In a study with pigs that were feed-deprived for 72 h, serum concentrations of insulin-like growth factor 1 (IGF-1, a hormone with anabolic effects), leptin, ghrelin and cortisol were collected every 12 h. While the circadian patterns of IGF-1, leptin and ghrelin disappeared with feed deprivation, cortisol levels increased but retained a comparable circadian rhythm to non-feed-deprived pigs (Salfen et al., 2003). This suggests that cortisol rhythms are feed-independent and might be important in the causation of an alternans feeding pattern. Besides cortisol, melatonin patterns are also known to be less affected by feed intake (Kriegsfeld et al., 2002). This suggests that melatonin and cortisol might be important in the causation of the circadian feeding pattern under ad libitum feeding conditions. They might function as