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ORIGINAL PAPER

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Effects of season, food deprivation and re-feeding on leptin, ghrelin and growth hormone in arctic foxes (*Alopex lagopus*) on Svalbard, Norway

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Abstract The arctic fox (*Alopex lagopus*) is a medium-sized predator of the high Arctic experiencing extreme seasonal fluctuations in food availability, photoperiod and temperature. In this study, the plasma leptin, ghrelin and growth hormone (GH) concentrations of male arctic foxes were determined during a food deprivation period of 13 days and the subsequent recovery in November and May. Leptin, ghrelin and GH were present in arctic fox plasma in amounts comparable to other carnivores. The plasma leptin concentrations did not react to food deprivation unlike in humans and rodents. However, the leptin levels increased during re-feeding as an indicator of increasing energy reserves. The relatively high ghrelin–leptin ratio, decrease in the plasma ghrelin concentration, an increase in the circulating GH concentrations and the observed negative correlation between plasma ghrelin and free fatty acid levels during fasting suggest that these hormones take part in the weight-regulation and energy metabolism of this species by increasing fat utilisation during food deprivation. The results strengthen the hypothesis that the actions of these weight-regulatory hormones are species–specific and depend on seasonality and the life history of the animals.

Keywords *Alopex lagopus* · Ghrelin · Growth hormone · Leptin · Svalbard

Abbreviations *FFA* free fatty acid · *GH* growth hormone · *RMR* resting metabolic rate

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Introduction

When animals go through periods of limited food availability, they have to rely on their body reserves to provide energy for metabolic functions. Adaptations to periods of food deprivation require adjustments in fat deposition, metabolic rate, hormonal regulation and in the mobilisation of fuel substrates. The adipocyte hormone, leptin, is a peripheral signal involved in the regulation of body adiposity, food intake and metabolic rate in mammals (Caro et al. 1996). It has also been suggested that it is a negative feedback signal to seasonal increases in appetite and body mass gain in arctic ground squirrels (*Spermophilus parryii plesius*; Boyer et al. 1997). Decreased leptin levels have been suggested to be involved in the physiological response to starvation in mammals (Ahima et al. 1996). Food restriction and deprivation reduce circulating leptin levels in both normal and anorexic humans (Dubuc et al. 1998; Eckert et al. 1998), in mice (Ahima et al. 1996) and bats (*Myotis lucifugus*; Widmaier et al. 1997), while re-feeding increases them (Eckert et al. 1998). In other species, however, this correlation is absent with no effects of long-term fasting on the plasma leptin levels of the raccoon dog (*Nyctereutes procyonoides*; Nieminen et al. 2002) and an increase in circulating leptin concentrations during the first 24 h fasting in lactating Antarctic fur seals (*Arctocephalus gazella*; Arnould et al. 2002).

Ghrelin is a newly discovered signal peptide secreted in the hypothalamus and stomach (Kojima et al. 1999) with effects opposite to those of leptin (Shintani et al. 2001). Exogenous ghrelin increases growth hormone (GH) secretion (Kojima et al. 1999). In humans, plasma ghrelin levels decrease with obesity (Tschöp et al. 2001), but increase in fasting rodents (Tschöp et al. 2000). In the canid raccoon dog, however, plasma ghrelin levels are unaffected by 2 months fasting (Nieminen et al. 2002). Exogenous melatonin decreases rat ghrelin levels (Mustonen et al. 2001a) and has an advancing effect on the seasonal rhythms of raccoon dog leptin and GH levels (Nieminen et al. 2002).

The arctic fox (*Alopex lagopus*) is a circumpolar inhabitant of the Arctic, roaming both the Arctic and high-Arctic landmasses and islands, as well as dispersing deep into the pack ice. They are the smallest homeothermic carnivores in the Arctic remaining active throughout the entire winter. On Svalbard, Norway (74–81°N and 10–35°E), the climate is high-Arctic desert, and the sun remains below the horizon from late October to mid February, resulting in complete 24 h darkness from November until the end of January. The temperature is below freezing from September to mid May (Steffensen 1982). In summer, the situation is the opposite with continuous daylight from late April to August.

Arctic foxes on Svalbard are top predators and scavengers and prey on food from both the marine and terrestrial food webs (Prestrud 1992; Frafjord 1993). They are opportunistic feeders, prospering on a wide variety of foods that show extensive seasonal variation. Except for a small and extremely range-restricted population of introduced sibling voles (*Microtus rossiameridionalis*), no other small mammals are present in the archipelago (Henttonen et al. 2001). Thus, arctic foxes have to rely on migrating and resident bird species as prey. In spring and summer, food is in excess when hundreds of thousands of seabirds arrive to the numerous bird cliffs together with waterfowl. However, access to food becomes limited during autumn and winter because most birds leave Svalbard by October. Carcasses of Svalbard reindeer (*Rangifer tarandus platyrhynchus*), other arctic fox individuals and seals (*Phocidae*), together with Svalbard ptarmigan (*Lagopus mutus hyperboerus*) and food stored during spring and summer, are potential food items during the dark winter, but their occurrence is low (Prestrud 1992; Frafjord 1993).

The magnitude of the seasonal variation in body fat and body weight is very high in the arctic fox. Deposition of subcutaneous and visceral fat takes place in August–September reaching a maximum in November–December, when the body lipid stores may constitute more than 20% of the total body weight. Body fat is rapidly mobilised from March through May and is lowest in June–July (6%; Prestrud and Nilssen 1992). However, autopsies of arctic fox carcasses trapped between November and March show large individual variations in subcutaneous and visceral fat. Many foxes are in good body condition, while others have depleted almost all visible fat (E. Fuglei, personal communication). This indicates periods (days–weeks) of fasting due to food shortage during winter (Prestrud and Nilssen 1992; Fuglei and Øritsland 1999).

There is seasonal variation in voluntary diurnal food intake in arctic foxes in captivity, with high food intake in summer and decreased food intake in winter (Underwood 1971; Prestrud 1982; Haga 1993; Fuglei and Øritsland 1999). However, the seasonal cycles in body fat reserves and body weight do not only depend on changes in food availability. Previous studies have found a seasonal variation in body mass of ad libitum-fed arctic foxes in captivity with the lowest body mass in the summer season and the highest in winter (Haga 1993; Korhonen and Alasuutari 1995; Fuglei and Øritsland 1999), which probably reflects the normal pattern of fat deposition observed in these species (Prestrud and Nilssen 1992). Wild arctic foxes kept in captivity on Svalbard also showed seasonal variation in resting metabolic rate (RMR), with the lowest values in October–December and the highest in May–July (Fuglei and Øritsland 1999). Furthermore, food deprivation induced reductions in RMR, also called metabolic depression, in arctic foxes both in May and November. The mechanisms responsible for the alterations in metabolism, body mass and food intake are poorly understood.

In the present study, plasma concentrations of leptin, ghrelin and GH were measured from wild arctic foxes before and during food restriction and during re-feeding in May and November. Values of free fatty acid (FFA) concentrations from the same individual animals from Fuglei et al. (2000) were used in the present study. As a small carnivore living in a habitat with extreme fluctuations in food availability, photoperiod and temperature, the arctic fox is a very attractive model to study these novel hormones of weight-regulation and their possible interactions in seasonal body mass regulation.

Materials and methods

Eight wild male arctic foxes were caught near Ny-Ålesund (78°55′N, 11°56′E), Svalbard, Norway, and kept for a period of 3 months–3 years in the same area as they were captured between 1993 and 1995. Due to this, we considered the foxes as wild foxes with intact physiological adaptations to the environment. They were captured in baited live-traps that consisted of a wooden frame covered with wire mesh netting on all sides (1 m long×0.32 m wide×0.30 m high). The foxes triggered a trapdoor by pulling on a baited stick causing the attached bar to release. Different baits such as eggs, sausages, Svalbard ptarmigan, Svalbard reindeer and seal blubber were used. All traps were checked once every day. The foxes were kept year round in separate, adjacent, outdoor steel cages (2.5×2×2 m) at the Norwegian Polar Institute Research Station in Ny-Ålesund, exposed to natural temperature and photoperiod. Each cage was furnished with a wooden sleeping box (0.5×0.5×1 m). The foxes were fed ad libitum with a commercial fox dry food (FK-Revepellets, Felleskjøpet, Norway) softened in water. The metabolizable energy of the food was 33% from protein, 43% from fat and 24% from carbohydrates (Ahlstrøm et al. 2003). Water was always provided ad libitum. Heating elements in the feed-cups prevented freezing of the food and water.

A total of eight adult male foxes were used for the whole study (for details see Table 1). In May, food deprivation experiments were conducted on three foxes (1993), two foxes (1994) and six foxes (1995), while in November two foxes (1993) and five foxes (1994) were used. Experiments were carried out according to the following protocol: food was withdrawn from the foxes for 13 days, after which they were re-fed ad libitum. Twenty hours after food was withdrawn, called day 1, the first blood sample was taken and used as the post-absorptive level. Thereafter blood was sampled on day 7 and day 13 after food deprivation, and again on day 5 and day 9 of re-feeding, with the same protocol in May and in November. The arctic fox encounters long periods of food deprivation in winter in its natural habitat and is quite well adapted to withstand periods of food deprivation (Fuglei and Øritsland

Table 1 Schedule showing when the blood samples were taken from the eight foxes from 1993 to 1995

Fox no.	1993		1994		1995
	May	Nov	May	Nov	May
1	X	X	X	X	X
2	-	X	X	X	X
3	-	-	-	X	X
4	-	-	-	-	X
5	-	-	-	X	X
6	-	-	-	X	X
7	X	Dead	-	-	-
8	X	Released	-	-	-

1999; Fuglei 2000; Fuglei et al. 2000; Nieminen et al. 2001). The blood samples were obtained from the cephalic vein using a syringe (needle 1.2×40 mm); heparin was used as an anticoagulant. To reduce the influence of possible circadian variation in plasma hormones, blood was always sampled in the afternoon. Blood was centrifuged (10 min at 3,000 rpm) immediately after the samples were collected. Plasma was separated and stored at −20 °C. When blood samples were taken from one animal in the same season, May or November, in more than 1 year the mean value was calculated for that animal.

Leptin concentrations were measured with the Multi-species Leptin RIA kit (intra-assay variation 2.8–3.6% CV, interassay variation 6.5–8.7%; Linco Research, St. Charles, Mo., USA) and the plasma ghrelin levels with the ghrelin (human) RIA kit (< 5% and < 14%; Phoenix Pharmaceuticals, Belmont, Calif., USA). GH concentrations were determined with the hGH human growth hormone double antibody kit (1.5–5.9% and 1.8–8.3%; DPC, Los Angeles, Calif., USA). All these assays were validated such that serial dilutions of the arctic fox plasma showed linear and parallel changes with the standard curve produced with human standards (data not shown). The leptin and GH assays have also previously been used in the blue fox (*Alopex lagopus*), a variant of the arctic fox reared in the fur industry (Mustonen et al. 2001b; Nieminen et al. 2001).

The Wilcoxon test for related samples was used to compare the results of consecutive measurements. No statistical analyses were performed when the number of cases was two or less due to an insufficient amount of sampled plasma to perform the hormonal analyses. Comparisons between measurements from different seasons were performed using the Student's *t*-test for independent samples (e.g. all leptin measurements from November vs. all measurements from May). Correlations were calculated using the Spearman correlation coefficient (r_s). A p value of less than 0.05 was considered to be statistically significant.

Results

There was an expected fall in the body mass of the animals during food deprivation followed by an immediate recovery of body mass after re-feeding (Fig. 1). The body mass at day 1 was 3.4 ± 0.4 kg ($n = 7$) in May and 3.6 ± 0.6 kg ($n = 5$) in November. After 13 days food deprivation, the body mass decreased significantly to 2.4 ± 0.2 kg in May ($n = 6$) and 2.8 ± 0.6 kg in November ($n = 5$; *t*-test, $p < 0.001$). Body mass loss during 13-days food deprivation was 28% in May and 22% in November.

Leptin, ghrelin and GH could all be detected from arctic fox plasma using RIA methods with clear parallelism and linearity with human standards. The plasma

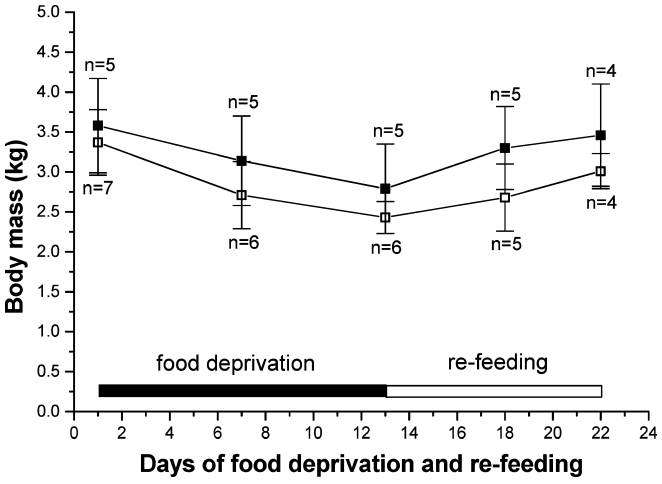

Fig. 1 Average body mass during food deprivation and re-feeding in May (*unfilled symbols*) and November (*filled symbols*), in arctic foxes on Svalbard presented as the mean ± SD

leptin concentrations (Fig. 2) were not affected by fasting; nor were there any clear seasonal changes in the leptin concentrations. However, during the recovery phase in November, the plasma leptin concentrations increased significantly until day 5 of re-feeding ($n = 5$; Wilcoxon test, $p < 0.035$) followed by a nonsignificant decrease, while the slight feeding-induced increase in May was statistically nonsignificant (Wilcoxon test, $p < 0.08$).

The plasma ghrelin concentrations (Fig. 3) decreased during the first week of food deprivation, and the decrease was significant in May ($n = 4$; Wilcoxon test, $p < 0.025$) and nearly significant in November ($n = 5$; Wilcoxon test, $p < 0.075$). Generally, the plasma ghrelin concentrations were higher in May than in November (*t*-test, $p < 0.05$). The plasma ghrelin concentrations were analysed against values of FFA concentrations of the same individuals from Fuglei et al. (2000). The plasma ghrelin concentrations correlated negatively with the

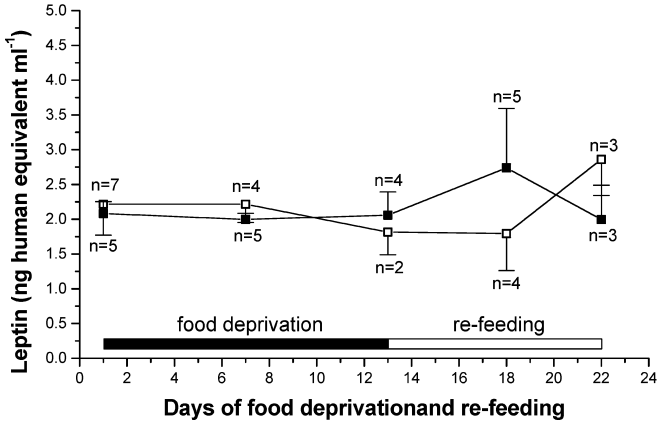

Fig. 2 Average plasma concentrations of leptin (ng human equivalent ml^{-1}) during food deprivation and re-feeding in May (*unfilled symbols*) and November (*filled symbols*), in arctic foxes on Svalbard presented as the mean ± SD

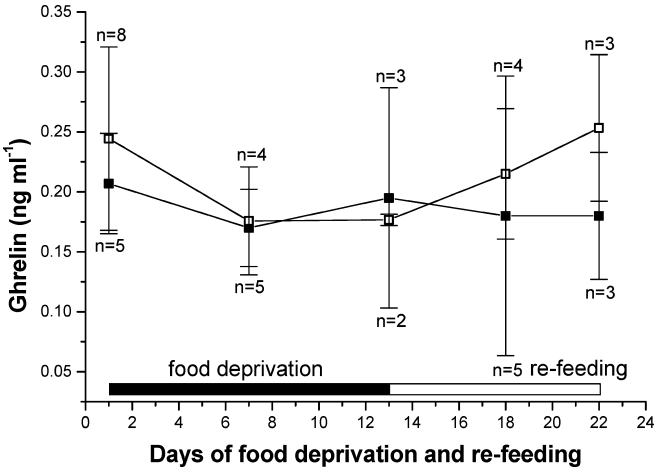

Fig. 3 Average plasma concentrations of ghrelin (ng ml^{-1}) during food deprivation and re-feeding in May (*unfilled symbols*) and November (*filled symbols*), in arctic foxes on Svalbard presented as the mean ± SD

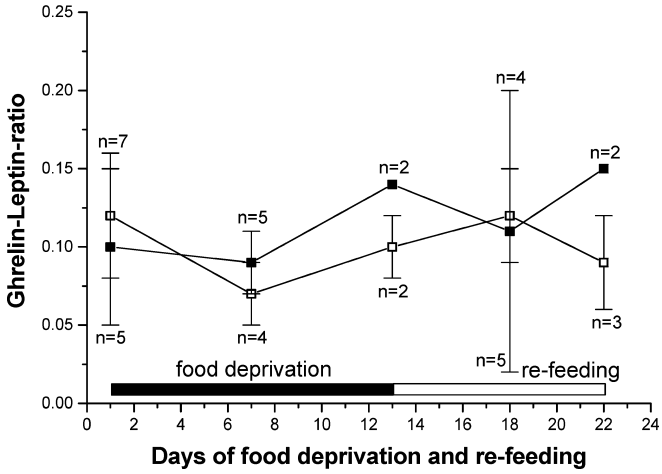

Fig. 5 Leptin–ghrelin ratios during food deprivation and re-feeding in May (*unfilled symbols*) and November (*filled symbols*), in arctic foxes on Svalbard presented as the mean ± SD

plasma FFA concentrations when all the measurements from both seasons were analysed together ($r_s = -0.364$, $p < 0.01$).

The plasma GH concentrations (Fig. 4) showed an initial increase during the first week of food deprivation in May ($n = 3$) (Wilcoxon test, $p < 0.043$). There were no other significant effects of seasonality or food deprivation on the GH concentrations. The GH concentrations correlated negatively with the body mass change of the animals when all the material was analysed as a whole ($r_s = -0.454$, $p < 0.05$).

The ratio of ghrelin to leptin (Fig. 5) decreased initially during the first week of food deprivation in May ($n = 4$; Wilcoxon test, $p < 0.043$). The ratio showed no other changes according to food deprivation or seasonality.

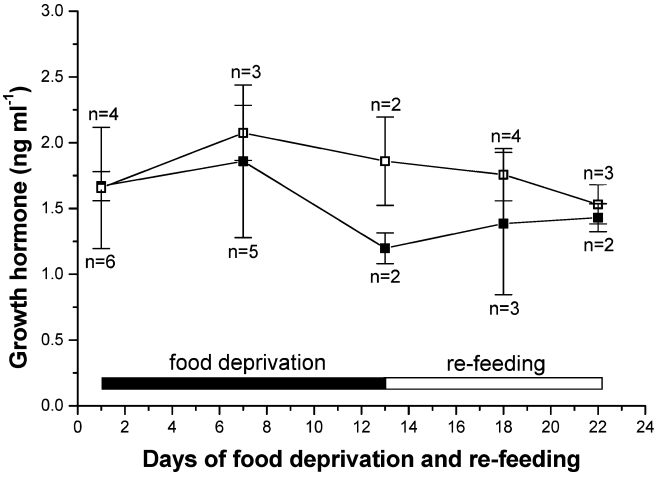

Fig. 4 Average plasma concentrations of growth hormone (ng ml^{-1}) during food deprivation and re-feeding in May (*unfilled symbols*) and November (*filled symbols*), in arctic foxes at Svalbard, in arctic foxes on Svalbard presented as the mean ± SD

Discussion

The arctic fox experiences extreme challenges in its natural habitat due to huge seasonal fluctuations in food availability, ambient temperature and photoperiod. It has to be able to preserve its energy stores in winter, make effective use of the transient abundance in summer and gather energy stores for the next period of cold, dark and starvation.

The adipocyte hormone leptin is suggested to be involved in the hypothalamic control of energy expenditure, body mass, fattening and food intake (Caro et al. 1996; Boyer et al. 1997). However, in the present study there were no significant differences in the pre-experimental post-absorptive (day 1) concentrations of leptin between May and November (Fig. 2), suggesting that there was no relationship between leptin concentrations and seasonal variations in body mass and food intake found in arctic foxes during these times of the year (Fuglei and Øritsland 1999). The well-documented, seasonal fattening of wild arctic foxes on Svalbard, with the highest levels of body fat in November–December (20%) and the lowest in June–July (6%; Prestrud and Nilssen 1992), does not correlate with plasma leptin levels, either. This observation is similar to another canid, the raccoon dog, with plasma leptin levels decoupled from body adiposity during the winter with the highest seasonal leptin levels and falling body mass during winter sleep (Nieminen et al. 2002).

Food deprivation is reported to acutely decrease plasma leptin concentrations (Ahima et al. 1996; Dubuc et al. 1998; Eckert et al. 1998). The plasma leptin concentrations of arctic foxes showed no acute effects of fasting. However, during the re-feeding phase between day 13 and day 18, the plasma leptin concentrations increased significantly in November and a slight increase could also be observed in May. This fits to the earlier observations in the farmed blue fox with a similar

increase in circulating leptin concentrations during the recovery period from food deprivation (Nieminen et al. 2002) as the energy reserves (adipose tissue) are replenished. The results of the present study further enforce the hypothesis of leptin not always being an indicator of body adiposity in carnivores (Nieminen et al. 2001, 2002; Arnould et al. 2002).

The number of animals in this study was too small ($n = 2$) in some cases to perform any statistical analyses (especially on day 13 of food deprivation). Due to this, some significant effects during the later stages of fasting could have been masked. Another major drawback is the fact that we did not study acute effects of food withdrawal and can therefore not exclude the possibility that fed animals could have had higher leptin levels during the first days of food deprivation. However, it has previously been observed in captive blue foxes that the plasma leptin levels remain almost unaffected during a 3-week total fast, thus supporting the results of this study (Nieminen et al. 2001).

In humans and rodents, plasma ghrelin concentrations increase rapidly in fasting, but decrease with refeeding or obesity (Tschöp et al. 2000, 2001). In the case of the arctic fox, however, the ghrelin levels decreased during the first week of fasting (Fig. 3). At high concentrations ghrelin reduces lipolysis and thus contributes to the accumulation of fat (Tschöp et al. 2000). On the other hand, in humans, GH contributes to the response of fasting by increasing lipolysis (Brück 1983). The initial decrease in circulating ghrelin levels and the simultaneous slight increase in GH concentrations could both contribute to the arctic fox's adaptation to food restriction by enhancing the utilisation of subcutaneous fat—the energy used during fasting (Fig. 4). This is also supported by the negative correlation between the concentrations of plasma ghrelin and FFA, indicating the degradation of triglycerides during food deprivation. This has also previously been shown in the arctic fox by Fuglei et al. (2000); further evidence comes from the negative correlation between body mass and plasma GH levels, inducing lipolysis. GH also prevents protein wasting. The preservation of muscle mass would be of importance to the arctic fox, as it forages actively during the winter, and a decrease in the availability of food could require higher levels of locomotor activity (Fuglei 2000). Fuglei et al. (2000) found that food deprivation induced an increase of ß-hydroxybutyrate levels in arctic foxes, which are important in the conservation of body protein. This could be further enhanced by the relatively high ghrelin–leptin ratio (Fig. 5) in the present work shifting the balance from satiety into active foraging.

In the high-Arctic environment, where periodic limitations of food availability are common, the ability to adapt to food deprivation is fundamentally important for survival. Metabolic depression during starvation is known to have a profound weight-saving effect and may be an important adaptation for animals living in the Arctic (Øritsland 1990). Fuglei and Øritsland (1999) found that food deprivation reduced RMR in arctic foxes both in winter and summer; Prestrud (1982) previously found the same in arctic foxes that were only studied in winter. This adaptation is essential for extending survival time and increasing the possibility of an animal finding food. An average sized arctic fox is estimated to have an average fat reserve of 15,640 kJ in November–December (Prestrud and Nilssen 1992), which gives enough energy to survive in the resting state for 25 days with metabolic depression, compared to 19 days without RMR being reduced (Fuglei 2000). Fat stores have a primary role in energy supply during food deprivation in the arctic fox and increased lipolysis results in conservation of muscle proteins (Fuglei et al. 2000). The observed decrease in the plasma ghrelin levels and an increase in the GH concentrations during the first week of food deprivation fit to this pattern of increased fat utilisation.

The present study is the first to report plasma levels of leptin, ghrelin and GH in the wild arctic fox. Leptin protein could be measured in arctic fox plasma at concentrations comparable to leptin levels of other carnivores measured with the same method (Nieminen et al. 2001, 2002; Arnould et al. 2002). Similar to the raccoon dog, plasma leptin concentrations were unaffected by fasting (Nieminen et al. 2002), but increased during refeeding supporting the model of leptin being, at least at some points of the animal's seasonal cycles, an indicator of increasing adipose tissue mass. Further studies will be needed to ascertain whether the small number of cases could have masked a clearer correlation between body mass and plasma leptin levels. Ghrelin protein could also be detected in the plasma of arctic foxes, but changes produced by fasting were opposite to those observed in humans and laboratory rodents. Yet it could, together with GH, contribute to the response of fasting by enhancing lipolysis. In agreement with other recent studies (Nieminen et al. 2002), there was no direct correlation between plasma ghrelin and GH concentrations. These results further emphasise that the responses to fasting are species-specific and depend on the ecology and life history of the species studied.

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