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Melatonin and the Wintering Strategy of the Tundra Vole, *Microtus oeconomus*

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ABSTRACT—Short photoperiod induces physiological changes connected to the wintering of the tundra vole, *Microtus oeconomus*. The aim of the present study was to investigate the effects of continuous melatonin treatment on selected hormones and enzyme activities associated with energy metabolism in the species. Liver, kidney, and muscle glycogen concentrations and glycogen phosphorylase activities, as well as liver and kidney glucose-6-phosphatase and lipase esterase activities were determined. Plasma leptin, ghrelin, thyroxine, testosterone, cortisol, and melatonin concentrations were also measured. Exogenous melatonin stimulated gluconeogenesis, increased glycogen stores, and reduced fat mobilization in kidneys. Melatonin treatment also increased the food intake of the voles. This may have been mediated via elevated ghrelin levels of the melatonin-treated animals, as ghrelin is known to increase appetite of rodents. Winter metabolism of the species does not seem to require accumulation of fat or extra stores of liver or muscle glycogen. On the contrary, successful wintering of the tundra vole presumably depends on continuous food availability.

Key words: ghrelin, glucose-6-phosphatase, glycogen, leptin, lipase esterase

INTRODUCTION

Melatonin regulates seasonal physiological functions such as reproduction (Tamarkin *et al.,* 1985), thermoregulation (Saarela and Reiter, 1994), and moulting (Rust and Meyer, 1969). Photoperiod and melatonin affect body mass (BM), adiposity, and energy intake (Wade and Bartness, 1984; Le Gouic *et al*., 1996) of several seasonal mammalian species. Melatonin also influences liver, kidney, and muscle energy contents of mammals (Mazepa *et al.,* 2000; Nieminen *et al.,* 2001; Mustonen *et al*., unpubl.).

Ghrelin is a newly discovered signal peptide secreted primarily by the stomach (Date *et al.,* 2000). Circulating ghrelin levels are increased by fasting and reduced by refeeding, and exogenous ghrelin increases food intake and BM gain in rodents (Tschöp *et al.,* 2000). We have recently demonstrated suppression of rat ghrelin levels by exogenous melatonin (Mustonen *et al.,* 2001). Leptin, a peptide hormone secreted principally by white adipose tissue (Zhang *et al.,* 1994), has widespread effects on energy homeostasis of vertebrates such as reptiles (Niewiarowski *et al.,* 2000), marsupials (Hope *et al.,* 1999), and eutherian mammals (Pelleymounter *et al.,* 1995). Interactions between melatonin and leptin have been demonstrated in rodents (Ambid *et al.,* 1998; Rasmussen *et al.,* 1999) and in carnivores (Mustonen *et al.,* 2000).

The tundra vole (*Microtus oeconomus*, Pallas, 1776) is a rodent with a circumpolar distribution. In winter the species lives in relatively dry areas on peatland and mineral soils, while in summer it occupies flooded land (Tast, 1966, 1972a). The summer diet of the tundra vole consists of leaves, flowers, seeds, and stalks of sedges and grasses, whereas mainly underground storage organs of these plants are consumed in winter. The tundra vole has high concentrations of muscle carbohydrates compared to more southern rodent species, which may be related to improved cold resistance (Galster and Morrison, 1975). Short photoperiod increases nonshivering thermogenesis of the species as a seasonal thermoregulatory adaptation (Wang *et al.,* 1999).

We investigated short-term effects of continuous melatonin treatment on key enzymes and hormones associated with energy metabolism of the tundra vole. This species is an attractive model for this study, as in nature it experiences harsh winter conditions and extremely short and long photoperiods, including continuous daylight and darkness, due to its northern geographical distribution. Our goal was to discover the most important hormonal and enzymatic targets of melatonin in the seasonal adaptation of the tundra vole.

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MATERIALS AND METHODS

Animals and treatments

Young tundra voles (n=24) were obtained from the laboratory colony of the University of Joensuu (Joensuu, Finland). The animals descended from voles that had been caught in northern Lapland (Pallasjärvi, 68°N) and reared in the laboratory for several generations. The voles were maintained in a dark room with artificial illumination from 0600 to 1800 (12L:12D) at a constant temperature of 20±1°C. They were housed singly in solid-bottomed plastic cages (Makrolon; 42 cm * 22 cm * 15 cm) with wood shavings for bedding and free access to tap water and a pelleted commercial diet (Avelsfoder för råtta och mus R36; 18.5% raw protein, 4.0% raw fat, 1,260 kJ metabolizable energy 100 g^{-1}, Lactamin, Stockholm, Sweden). All procedures were in accordance with institutional guidelines for animal care of the University of Joensuu as well as with the European convention for the protection of vertebrate animals used for experimental and other scientific purposes.

At the beginning of the experiment, half of the voles received subcutaneous melatonin implants, the other half was sham-operated. Constant-release melatonin capsules are known to provide e.g. ewes with a short day signal rather than a functional pinealectomy (O´Callaghan *et al.,* 1991). We used halved PRIME-X® melatonin implants containing 6 mg melatonin in a silastic matrix manufactured by Wildlife Pharmaceuticals, Inc. (Fort Collins, CO, USA). The capsules were implanted surgically into the interscapular subcutaneous tissue of the voles, which were anaesthesized with subcutaneous Ketamine (Ketalar, 50 mg ml^{-1}, Parke-Davis Scandinavia AB, Solna, Sweden). A 0.5 cm incision was cut with a sterile scalpel along the spine between the scapulae and the capsule was inserted into this pouch with sterile forceps. The wound was sutured with 3–0 plain gut with a single knot. The control group was sham-operated with identical anaesthesia, incisions, and sutures but without the insertion of melatonin-filled capsules.

The voles were 1–5 months of age and weighed 16–29 g at the beginning of the experiment. Animals of different age and BM were evenly distributed among two study groups of 12 individuals each: Group 1 (controls) consisted of 8 males and 4 females whereas group 2 (melatonin-treated voles) consisted of 5 males and 7 females.

Data collection

BM gain (g) and relative food intake (g food consumed g BM^{-1} wk^{-1}) of the voles were recorded weekly at 1200–1300 hr throughout the study. After 29 days, the voles were sacrificed at 1100–1300 hr by an overdose of diethyl ether. Blood samples were obtained by cardiac puncture with aseptic needles into test tubes containing EDTA and centrifuged at 1000 x g to obtain 50–200 µl of plasma. Livers, kidneys, and muscle samples from the quadriceps muscle of the left thigh were dissected and immediately frozen in liquid nitrogen and stored at –40°C. The presence of implants in the interscapular subcutaneous tissue of the melatonin-treated voles was verified after sampling.

Biochemical determinations

The activities of different enzymes were determined spectrophotometrically. Liver and kidney samples were weighed to the nearest 0.001 g and homogenized in cold citrate buffer for the glucose-6-phosphatase (G-6-Pase; pH 6.5) and glycogen phosphorylase measurements (pH 6.1). The activity of G-6-Pase was measured using glucose-6-phosphate as substrate in the presence of EDTA after an incubation time of 30 minutes at 37.5 °C (Hers and van Hoof, 1966). Glycogen phosphorylase activity was measured in the presence of glucose-1-phosphate, glycogen, sodium fluoride, and AMP (Hers and van Hoof, 1966).

Homogenization was carried out in cold 0.85 % NaCl for the lipase esterase measurement. Lipase esterase activities were measured according to the method of Seligman and Nachlas (1962) using 2-naphtyl-laurate without taurocholate as substrate. Glycogen concentrations were measured spectrophotometrically according to the method of Lo *et al.* (1970).

Hormone determinations

Plasma testosterone and thyroxine (T4) concentrations were measured with the Spectria [^{125}I] Coated Tube Radioimmunoassay kits of Orion Diagnostica (Espoo, Finland). Testosterone and T4 levels were determined from each individual due to the small sample volume these measurements required (20–25 µl of plasma). Plasma leptin concentrations were measured with the Multi-species Leptin RIA kit from Linco Research Inc. (St. Charles, MO, USA). Plasma ghrelin levels were determined with the Ghrelin (Human) RIA kit from Phoenix Pharmaceuticals Inc. (Belmont, CA, USA). The crossreactivities of the kits to rat leptin and ghrelin are 61 and 100%, respectively. These kits have been previously used to measure leptin and ghrelin levels of microtinae plasma (Nieminen *et al.*, 2002). Plasma melatonin concentrations were determined with the Melatonin RIA kit manufactured by DLD Diagnostika GmbH (Hamburg, Germany). Plasma cortisol levels were determined with the Cortisol [^{125}I] Radioimmunoassay kit of Orion Diagnostica. Plasma leptin, ghrelin, melatonin and cortisol concentrations were determined by pooling the plasma samples of voles from a particular treatment due to the high sample volume requirements (100 µl of plasma) of the analyses. Equal amount of blood was added from each animal to obtain 100 µl of plasma required.

Statistical analyses

Body mass indices (BMIs) that reflect the amount of fat in the body were calculated by the formula: weight (g) $length^3$ $(cm)^{-1}$. Length from the nose to the anus was measured to the nearest mm after sacrification. Paired comparisons were performed with the Student's t-test for unpaired data. For nonparametric data, the Mann-Whitney U test was performed. $P<0.05$ was considered to be statistically significant.

RESULTS

BM of the voles increased during the study, but exoge-

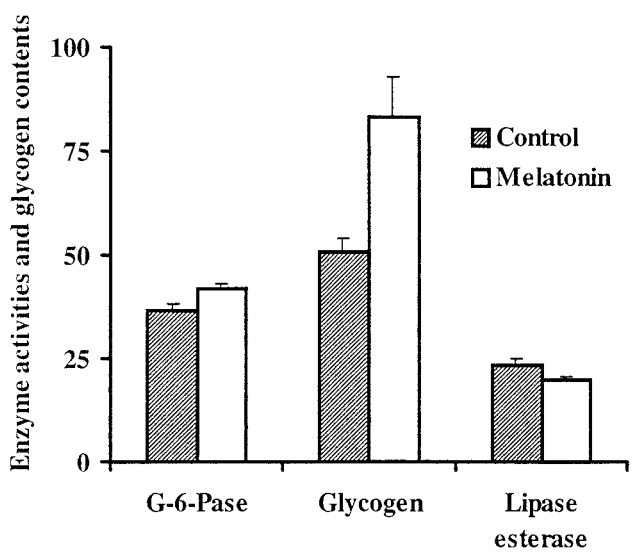

Fig. 1. Kidney glucose-6-phosphatase activities (µ g P mg $tissue^{-1}$ h^{-1}), glycogen contents (µ g glycogen mg $tissue^{-1}$), and lipase esterase activity levels (µ g 2-naphtol 0.1g $tissue^{-1}$ h^{-1}) of control and melatonin-treated tundra voles (mean+SE).

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Table 1. Effects of 29 days of melatonin implants on selected enzymatic and hormonal parameters of energy metabolism in the tundra vole liver, kidney, muscle, and plasma (mean±SE). * differs significantly from the control group of the same sex † all the melatonin-treated voles differ from all the controls (Mann-Whitney U test, p<0.05).

		Control males	Control females	Melatonin males	Melatonin females
Glycogen	liver	18.3 ± 3.97	29.7 ± 7.37	11.3 ± 3.16	18.0 ± 4.13
μg mg tissue^{-1}	kidney	0.49 ± 0.036	0.55 ± 0.044	0.67 ± 0.052*	0.94 ± 0.150*
	muscle	1.32 ± 0.228	0.38 ± 0.025	0.53 ± 0.117*	0.97 ± 0.156*
Glycogen phosphorylase,	liver	24.5 ± 2.71	26.1 ± 2.46	23.5 ± 2.93	24.3 ± 1.24
μg P mg tissue^{-1} h^{-1}	kidney	6.2 ± 0.49	6.6 ± 0.38	6.8 ± 0.75	7.2 ± 0.62
	muscle	130.6 ± 22.55	126.3 ± 10.98	120.3 ± 6.72	143.7 ± 13.00
Glucose-6-phosphatase	liver	59.9 ± 1.59	61.0 ± 1.42	63.5 ± 2.83	56.0 ± 0.65*
μg P mg tissue^{-1} h^{-1}	kidney	36.7 ± 1.98	37.2 ± 1.86	40.5 ± 1.44†	42.8 ± 1.80†
Lipase esterase	liver	34.5 ± 1.97	33.0 ± 0.94	37.1 ± 2.03	34.8 ± 1.29
μg 2-naphtol mg tissue^{-1} h^{-1}	kidney	25.0 ± 2.02	20.4 ± 1.23	21.3 ± 1.17†	18.7 ± 0.61†
Testosterone nmol l^{-1}	plasma	0.35 ± 0.182	0.04 ± 0.014	0.07 ± 0.034	0.07 ± 0.020
Thyroxine nmol l^{-1}	plasma	31.4 ± 3.55	31.3 ± 2.16	32.4 ± 4.80	23.6 ± 1.77*

nous melatonin did not significantly affect the mass gain (1.5±0.82 (group 1) vs. 0.8±0.32 g (group 2) mass gain during the study). Relative food intake of the melatonin-treated animals increased significantly during the experiment (1.2±0.04 vs. 1.4±0.03 g food consumed g BM^{-1} wk^{-1} at the beginning and at the end of the study, respectively, *t*-test, p<0.014), which was not observed in the controls (1.2±0.07 vs. 1.3±0.03 g food consumed g BM^{-1} wk^{-1}). Body lengths, BMIs, and weights of livers, kidneys, and testes were not significantly influenced by melatonin treatment.

Liver glycogen content was not significantly affected by exogenous melatonin, but kidney glycogen concentrations were significantly elevated in the melatonin-treated voles (Mann-Whitney U test, p<0.0004, Table 1, Fig. 1). Kidney glycogen content was significantly higher in the female voles (Mann-Whitney U test, p<0.015). Muscle glycogen concentrations were significantly decreased by melatonin in the males (Mann-Whitney U test, p<0.008), but significantly increased in the females (Mann-Whitney U test, p<0.042).

Liver, kidney, and muscle glycogen phosphorylase activities were not significantly influenced by melatonin treatment (Table 1). Phosphorylase activities were significantly higher in muscle than in livers and kidneys (Mann-Whitney U test, p<0.0004). Hepatic G-6-Pase activities were significantly suppressed in the melatonin-treated females (Mann-Whitney U test, p<0.008). G-6-Pase activities in kidneys were significantly increased by exogenous melatonin in both sexes (t-test, p<0.014, Fig. 1). Liver lipase esterase activities were not significantly affected by melatonin treatment, but in kidneys the activities were significantly suppressed by exogenous melatonin (Mann-Whitney U test, p<0.026, Fig. 1). Kidney lipase esterase activities were significantly higher in the male voles (Mann-Whitney U test, p<0.003).

Daytime plasma melatonin levels were higher in the melatonin-treated voles than in the controls (580.9 vs 55.4 pg ml^{-1}, respectively). Also ghrelin concentrations were over two-fold higher in the melatonin-treated voles (1.7 vs 0.7 ng ml^{-1}). Plasma testosterone (Table 1), leptin (1.9 vs 1.8 ng ml^{-1}) and cortisol concentrations (73.1 vs 79.2 nmol l^{-1}) were not affected by melatonin. The T4 concentrations in the female voles were decreased due to treatment (Mann-Whitney U test, p < 0.023).

DISCUSSION

Tundra voles are nonhibernating herbivores, which winter under the snow cover. Body size and foraging activity levels of the species decrease in winter leading to reduced energy expenditure (Wang and Wang, 1996). Finnish tundra voles, however, have to forage throughout the cold season, as they do not collect large stores of plant material unlike Siberian tundra voles (Tast, 1972a). Food availability is known to be an important factor controlling BM and wintering success of tundra voles (Tast, 1972b). BM of our voles increased during the experiment, as they were young and growing animals. Their BM was not affected by melatonin treatment, but exogenous melatonin significantly increased their energy intake. This response to high circulating melatonin levels (short photoperiod) may be of fundamental importance in nature during the seasonal scarcity of food.

Rat ghrelin concentrations have decreased due to exogenous melatonin (Mustonen *et al.,* 2001). Our results indicate to increased ghrelin levels in the melatonin-treated voles. As the measurement could not be carried out in individual voles, the results will need conformation in further studies concentrating on ghrelin. Our ghrelin data, however, are in concordance with the higher energy intake of the melatonin-treated animals, as ghrelin is known to increase food intake of rodents (Tschöp *et al.,* 2000). In autumn, increasing melatonin secretion could be a signal that enhances ghrelin secretion of the voles. High ghrelin levels could stimulate the appetite of the animals and thus maintain a sufficient foraging activity level to ensure their survival

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through the cold season. The increase in food intake caused by ghrelin is probably mediated by an increased production of neuropeptide Y (NPY) (Shintani *et al.,* 2001), the hypothalamic concentrations of which are augmented by prenatal melatonin exposure (Díaz *et al.,* 2000).

G-6-Pase activity indicates the ability of the tissue to release free glucose from glucose-6-phosphate into the blood stream (Harris, 1986). Glycogen phosphorylase, on the other hand, is the regulatory enzyme of glycogenolysis. Liver G-6-Pase and glycogen phosphorylase activities as well as muscle phosphorylase activities of the bank vole (*Clethrionomys glareolus*) and the field vole (*Microtus agrestis*) are highest in winter (Hyvärinen, 1984). Exogenous melatonin caused only slight effects on these enzyme activities in tundra vole liver and muscle. The only effect observed occurred in G-6-Pase activity levels in livers of the females. Melatonin has previously increased liver and muscle glycogen stores in nonexercised and exercised rats (Mazepa *et al.,* 2000), but in our experiment it did not affect these glycogen stores in the voles.

Liver lipase esterase activities of bank voles are highest in autumn and early winter (Hyvärinen, 1984). In our experiment, melatonin did not affect hepatic lipase esterase activity levels. Neither were leptin levels affected. In humans and laboratory rodents, leptin levels correlate positively with body adiposity (Maffei *et al.,* 1995). Melatonin and photoperiod have affected leptin concentrations, and leptin gene and receptor gene expression of rodents and mustelids (Ambid *et al.,* 1998; Mercer *et al.,* 2000; Mustonen *et al.,* 2000). Carbohydrate metabolism seems to be more important for energy production by voles than lipid utilization during winter months (Hyvärinen, 1984). Microtinae rodents derive energy from endogenous carbohydrates during starvation (Mosin 1984). After a total fast of only 20–26 hr, they die due to deep hypoglycemia. Voles can die after starvation still having adipose tissue in their bodies, because utilization of fat is relatively small.

Exogenous melatonin influences water consumption, urine production and electrolyte concentration, circulating antidiuretic hormone levels (Richardson *et al.,* 1992), blood pressure (Kawashima *et al.,* 1987), as well as glomerular filtration rates (Tsuda *et al.,* 1995) of mammals. Renal actions of melatonin are supposed to be mediated through Mel1a subtype receptor localized in the basolateral membrane of proximal tubules (Song *et al.,* 1997). Effects of melatonin treatment on glycogen content and enzyme activities of tundra vole kidneys were clear. This phenomenon has also previously been observed in the laboratory rat in a similar study (Mustonen *et al.*, unpubl). Responses of vole kidneys to exogenous melatonin were nearly opposite to those of rats, indicating that the renal effects of melatonin are species-specific. In tundra voles, melatonin increased glycogen stores and gluconeogenesis and reduced fat mobilization in kidneys. This energy is probably used as a metabolic fuel for the kidney itself. It is also possible that kidneys contribute to general energy metabolism of microtines in winter. Extra capacity for glycogen storing and gluconeogenesis may be crucial, when cold temperatures increase thermoregulatory needs and food deprivation poses a threat to survival.

T4 concentrations in the female voles decreased due to melatonin treatment. The inhibitory effect of the pineal gland on thyroid function has also been observed in other rodents (Vriend, 1983). In nature, thyroid activity of small mammals is often suppressed in winter (Hyvärinen, 1984). This may function as an energy-sparing adaptation to winter metabolism of voles by slowing metabolic rate and retarding somatic growth. Testosterone levels of the voles were not affected by exogenous melatonin. This was understandable, as most of our voles were immature. In the wild, tundra voles reach sexual maturity in the summer of birth or in the spring after wintering. Increasing daylength is considered to be the principal determinant for the onset of breeding season (Tast, 1966).

In summary, a short-term continuous melatonin treatment stimulates gluconeogenesis, increases glycogen stores, and reduces fat mobilization in kidneys of the tundra vole. It also stimulates appetite of the voles, possibly via increasing ghrelin concentrations. Winter metabolism of this species does not depend on the accumulation of fat or extra storage of liver or muscle glycogen. In fact, costs of deposition of energy can be several times more expensive to small mammals than the energy gain from the utilization of such stores (Miernikiewicz *et al.,* 1996). The successful wintering of tundra voles probably depends on continuous food availability.

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