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Differential temperature effects on photoperiodism in female voles: A possible explanation for declines in vole populations

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Abstract

Many mammalian species use photoperiod as a predictive cue to time seasonal reproduction. In addition, metabolic effects on the reproductive axis may also influence seasonal timing, especially in female small, short-lived mammals. To get a better understanding of how annual cycling environmental cues impact reproductive function and plasticity in small, short-lived herbivores with different geographic origins, we investigated the mechanisms underlying integration of temperature in the photoperiodic-axis regulating female reproduction in a Northern vole species (tundra vole, *Microtus oeconomus*) and in a Southern vole species (common vole, *Microtus arvalis*). We show that photoperiod and temperature interact to determine appropriate physiological responses; there is species-dependent annual variation in the sensitivity to temperature for reproductive organ development. In common voles, temperature can overrule photoperiodical spring-programmed responses, with reproductive organ mass being higher at 10°C than at 21°C, whereas in autumn they are less sensitive to temperature. These findings are in line with our census data, showing an earlier onset of spring reproduction in cold springs, while reproductive offset in autumn is synchronized to photoperiod. The reproductive organs of tundra voles were relatively insensitive to temperature, whereas hypothalamic gene expression was generally upregulated at 10°C. Thus, both vole species use photoperiod, whereas only common voles use temperature as a cue to control spring reproduction, which indicates species-specific reproductive strategies. Due to global warming, spring reproduction in common voles will be delayed, perhaps resulting in shorter breeding seasons and thus declining populations, as observed throughout Europe.

KEYWORDS
ambient temperature, hypothalamic gene expression, photoperiodism, population dynamics, seasonal reproduction, voles

Dedicated to Dr Cor Dijkstra (1950–2017)

1 | INTRODUCTION

In most terrestrial temperate zone regions, winter represents an annual period with short photoperiod, decreased ambient temperature and reduced food availability, which induces increased energetic challenges for nonhibernating mammals. Reproduction under these circumstances is not beneficial for survival of small, short-lived mammals, because pregnancy and lactation are energy-consuming processes (Speakman, 2008), and newly born offspring is vulnerable to harsh environmental conditions. Hence, many temperate species have evolved intrinsic timing mechanisms to predict major seasonal changes and accurately time physiology and reproductive behavior. Because of its absence in interannual variation, many organisms use the purely proximate predictor photoperiod, as reliable signal to prepare metabolically for upcoming seasons. In several species it has been demonstrated that the rate of postnatal maturation is set in utero through transmission of maternal melatonin (van Dalum et al., 2020). In long-day-breeders, prenatal exposure to short photoperiods and postnatal exposure to intermediate photoperiods (i.e., spring programmed) facilitates accelerated postnatal reproductive development in juveniles (Hoffmann, 1973; Horton, 1984, 1985; Horton & Stetson, 1992; Prendergast et al., 2000; Sáenz de Miera et al., 2017; Stetson et al., 1986; Yellon & Goldman, 1984). This phenomenon is named "maternal photoperiodic programming", reviewed in (van Dalum et al., 2020; Horton, 2005; Sáenz De Miera, 2019), and operates through the hypothalamic photoperiodic neuroendocrine system (PNES) for seasonal synchronization (van Rosmalen, van Dalum, et al., 2021; Sáenz de Miera et al., 2017).

The PNES measures photoperiod and subsequently drives annual rhythms in reproduction, and has been described in detail in several mammal and bird species (Baker, 1938; Dardente et al., 2003, 2010, 2018; Hanon et al., 2008; Hut, 2011; Masumoto et al., 2010; Nakane & Yoshimura, 2019; Nakao et al., 2008; Ono et al., 2008; Sáenz De Miera et al., 2014; Wood et al., 2015). In short, photoperiod is reflected in nocturnal melatonin release by the pineal gland. Under long photoperiods in summer, the short period of melatonin release leads to elevated thyroid stimulating hormone β (TSHβ) in the pars tuberalis, where it forms an active dimer (TSH) with alpha-glycoprotein subunit (α-GSU) (Magner, 1990). TSH binds to its receptor (TSHr) in the tanycytes around the third ventricle where it induces iodothyronine deiodinase 2 (DIO2). The balance between DIO2 and DIO3 determines the central availability of active thyroid hormone (T3), which via the pituitary regulates reproductive activation and gonadal growth. This pathway has recently been confirmed in the common (*Microtus arvalis*) and tundra vole (*Microtus oeconomus*) (Król et al., 2012; van Rosmalen, van Dalum, et al., 2021; van Rosmalen et al., 2020).

Energetic demands, such as costs of cellular maintenance, thermoregulation and foraging all compete with reproduction (Bronson, 1989; Ruffino et al., 2014; Schneider, 2004; Speakman, 2008). Ambient temperature largely affects thermoregulatory costs and energy balance in nonhibernating small mammals, due to the large surface-to-volume ratio. It has been demonstrated that ambient temperature influences timing of breeding in birds (Crick et al., 1997; Verhagen et al., 2020), hibernation ending in mammals (Inouye et al., 2000), and gonadal activation in small rodents (Daketse & Martinet, 1977; Kriegsfeld et al., 2000; Larkin et al., 2001; Nelson et al., 1989; Steinlechner et al., 1991). Thermal cues are expected to be involved in modulation of photoperiodic responses to inhibit or accelerate reproductive development (Caro et al., 2013; Hut et al., 2014), but underlying regulatory mechanisms need to be clarified.

This led us to ask how photoperiod and temperature interact to regulate reproductive activation in voles, herbivorous species in which plasticity in onset of spring reproduction has been observed in nature (Ergon et al., 2001; Negus et al., 1986), in which 3-year population cycles have been widely documented (Huntington, 1931; Krebs, 2013; Krebs et al., 1973; Myers, 2018), and in which food and ambient temperature are significant modifiers of female (Baker et al., 1932; Daketse & Martinet, 1977; Simons et al., 2011), and male reproductive activation (Baker et al., 1932; Kriegsfeld et al., 2000; Larkin et al., 2001; Negus & Berger, 1977; Nelson et al., 1983, 1989; Sanders et al., 1981; Steinlechner & Puchalski, 2003). For this reason, an opportunistic dimension (i.e., sensitive to both photic and nonphotic annual cues) to reproductive strategies of voles might be expected.

The neurobiological basis that underlies (thermo) energetic modification of the photoperiodic axis remains to be disclosed. Gonadotropin-releasing hormone (GnRH) neurons are important drivers of reproduction regulating hormonal release (i.e., LH, FSH) from the pituitary gland (Guillemin, 1977; Schally et al., 1970). Long day induced T_3 in the mediobasal hypothalamus (MBH) may control GnRH neurons via hypothalamic areas that are involved in thermo- and metabolic regulation, reviewed in (Hut et al., 2014). The preoptic area (POA) is the primary site for thermoregulation, reviewed in (Morrison & Nakamura, 2019), where both internal and external thermal cues are integrated. Furthermore, the arcuate nucleus (ARC) and the dorso/ventromedial hypothalamus (DMH/VMH) are involved in sensing energy balance. Neurons expressing the RF-amide Kisspeptin (KISS1), are located in the POA and ARC, whereas neurons expressing the RF-amide related peptide (RFRP-3), are located in the DMH/VMH (Henningsen et al., 2016; Oakley et al., 2009; Parhar et al., 2012; Smith et al., 2005; Smith, Dungan, et al., 2005). KISS1 is a neuropeptide known to function as strong activator of GnRH neurons controlling puberty onset and reproduction (De Roux et al., 2003; Hileman et al., 2011; Seminara et al., 2004). Moreover, RFRP3 is controlled by photoperiod, and activates the reproductive axis (Ancel et al., 2012; Henningsen et al., 2016, 2017; Hut et al., 2014; Ubuka et al., 2012). KISS1 and RFRP-3 are therefore possibly involved in integrating thermal cues, regulating reproduction in mammals (Hut et al., 2014; Klosen et al., 2013; Revel et al., 2008; Sáenz De Miera et al., 2014; Simonneaux et al., 2013), albeit that evidence for this concept remains limited. When energetic demands are high (i.e., ambient temperature below or above the thermoneutral zone), it is expected that *Kiss1* expression in the ARC and POA, and *Rfrp* expression in the DMH/VMH is downregulated to

modulate photoperiodic responses, and subsequently suppresses reproductive investment to save energy. Such a mechanism would allow reproduction only when photoperiods are long and voles are subjected to a positive energy balance. Seasonal variation in hypothalamic *Kiss1* and *Rfrp* expression (peaking in summer) have been observed in a wild population of Brandt's voles (Wang et al., 2019). Whether indeed *Kiss1* and *Rfrp* expression in the vole hypothalamus do not only change in response to photoperiod, but also in response to ambient temperature remains to be disclosed.

To understand how thermal cues integrate in the PNES, and subsequently modify female gonadal responses in Northern and Southern species, we investigated photoperiodic responses in both physiology and hypothalamic expression of candidate genes by exposing Northern voles (tundra or root vole, *Microtus oeconomus*) and Southern voles (common vole, *Microtus arvalis*) to different photoperiod and ambient temperature regimes. To compare the balance of integration of photoperiodic-temperature interactions affecting PNES function in Northern and Southern vole species, we present time series of vole population dynamics in relation to ambient temperature, and subsequently investigated the mechanisms underlying integration of thermal cues in the photoperiodic-axis that subsequently regulates female reproduction.

2 | MATERIALS AND METHODS

2.1 | Study area and trapping

The census data set used in this study was previously published elsewhere (Dijkstra et al., 1988). Two-month interval census data were collected from March 1980 to November 1986 at the Lauwersmeer area, the Netherlands (53° 24'N, 6° 16'E). This area is defined as open landscape with grassland, and snap traps were placed in dry habitats. Common voles were snap trapped using fixed locations consisting of 10 traps each. In total 500 traps with carrots were set up for three consecutive nights every other month, and checked at daytime for the three consecutive days, amounting to a constant trapping effort during each census session. Common voles have no protected status according to IUCN red list, and are considered locally as an agricultural pest (Yigit et al., 2016). Reproductive status of trapped voles was determined by several reproductive traits, and animals were classified as sexually active if there was evidence of enlarged testes, pigmented scrotal area, open vulva, pregnancy or enlarged nipples indicating lactation.

2.2 | Meteorological data

Monthly average temperatures between 1980 and 2020 were retrieved from the weather station at Eelde airport, the Netherlands (53.13° N, 6.59° E; https://weerstatistieken.nl/eelde). The deviation from average, average maximum and average minimum temperatures of the previous four months before the peak in proportion sexually active voles (May) were correlated with the proportion of sexually active voles in May (Table S5).

2.3 | Animals and experimental procedures

All experimental procedures were carried out according to the guidelines of the animal welfare body (IvD) of the University of Groningen conform to Directive 2010/63/EU, and approved by the CCD (Centrale Commissie Dierproeven) of the Netherlands (CCD license number: AVD1050020171566). Common voles (*Microtus arvalis*) were obtained from the Lauwersmeer area (Netherlands, 53°24'N, 6°16'E) (Gerkema et al., 1993). Tundra voles (*Microtus oeconomus*) were obtained from four different regions in the Netherlands (van de Zande et al., 2000). Populations have been kept in the laboratory under artificial light conditions since the 1990s as outbred colonies, in which breeding pairs that produced experimental animals had different genetic backgrounds in order to prevent our laboratory colony from inbreeding. All voles used in this study were indoor-bred at the University of Groningen. Periodically, the breeding colonies were enriched with wild caught voles from their original region, to prevent inbreeding. Over the last four years, our breeding colonies have been switched between 8 h light:16 h dark and 16 h light:8 h dark at least twice a year. Mothers and fathers were under a constant photoperiod regime for at least 1-month prior mating. Female pups from litters (34 common voles; 30 tundra voles) were evenly distributed across different photoperiod regimes after weaning. Weaned voles were individually housed in transparent plastic cages (15 × 40 × 24 cm) provided with sawdust, dried hay, an opaque pvc tube and ad libitum water and food (standard rodent chow; Altromin no. 141005).

Female voles (common voles: $N = 92$; tundra voles: $N = 93$) used as experimental animals were conceived, born and raised to weaning under either a short photoperiod (SP, 8 h light:16 h dark: early breeding season, winter/spring programmed) or a long photoperiod (LP, 16 h light:8 h dark: late breeding season, summer/autumn programmed) at 21 ± 1°C and 55 ± 5% relative humidity. At weaning (21 days old), voles were transferred to either 10°C or 21°C under a range of different photoperiods for 29 days, after which animals were killed. Photoperiodic transitions at the day of weaning were abrupt. Photoperiods applied after weaning at 21°C were (hours light: hours dark): 6:18, 10:14, 12:12, 14:10, 16:8, 18:6. Photoperiods applied after weaning at 10°C were: 10:14, 12:12, 14:10, 16:8 (Figure 1). All voles were weighed when 7, 15, 21, 30, 42 and 50 days old.

2.4 | Tissue collections

When 50 days old, voles were killed by decapitation, with short prior CO_2 sedation, 17 ± 1 h after lights OFF (*Tshβ* expression peaks in mouse pars tuberalis (Masumoto et al., 2010)). Thereby, all animals were killed during the light phase, except for animals under 6:18, who were killed just before lights ON, and which were excluded from

molecular analysis. Reproductive organs were dissected and cleaned of fat, and wet masses of paired ovary and uterus were measured (±0.0001 g). Whole brains were removed with special care to visually include the intact proximate pituitary stalk containing the pars tuberalis. Within 5 min after decapitation, brains were slowly frozen on a brass block surrounded by liquid N_2, and stored at −80°C until further dissection. Posterior and anterior hypothalamic areas were dissected on ice as described in (van Rosmalen & Hut, 2021a), and tissues were transferred to tubes containing Trizol immediately after dissection. Subsequently, RNA extractions, reverse transcription and real-time quantitative PCR was performed.

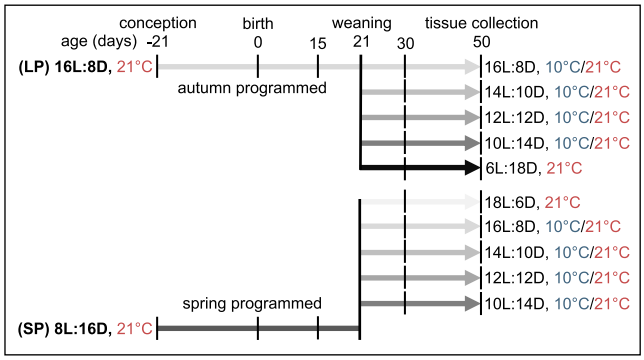

FIGURE 1 Experimental design. Conception, gestation, birth and lactation took place under either LP (i.e., autumn programmed) or SP (i.e., spring programmed) at 21°C. At weaning (21 days old) animals were transferred to either 10 or 21°C at a range of different photoperiods. 6L:18D was only applied in autumn programmed voles, 18L:6D was only applied in spring-programmed voles. Tissues were collected at an age of 50 days [Colour figure can be viewed at wileyonlinelibrary.com]

2.5 | RNA extractions, reverse transcription and real-time quantitative PCR

Total RNA was isolated from the dissected parts of the hypothalamus using TRIzol reagent according to manufacturer's protocol (Invitrogen). In short, frozen pieces of tissue (~0.02 g) were homogenized in 0.5 ml TRIzol reagent in a TissueLyser II (Qiagen) (2 × 2 min at 30 Hz) using tubes containing a 5mm RNase free stainless-steel bead. Subsequently, 0.1 ml chloroform was added for phase separation. Following RNA precipitation by 0.25 ml of 100% isopropanol, the obtained RNA pellet was washed with 0.5 ml of 75% ETOH. Depending on size, RNA pellets were diluted in an adequate volume of RNase-free H_2O and quantified on a Nanodrop 2000 spectrophotometer (Thermoscientific). RNA concentrations were between 222 and 1510 ng/µl, and the ratio of absorbance at 260/280 nm was between 1.80 and 2.03. After DNA removal by DNase I treatment

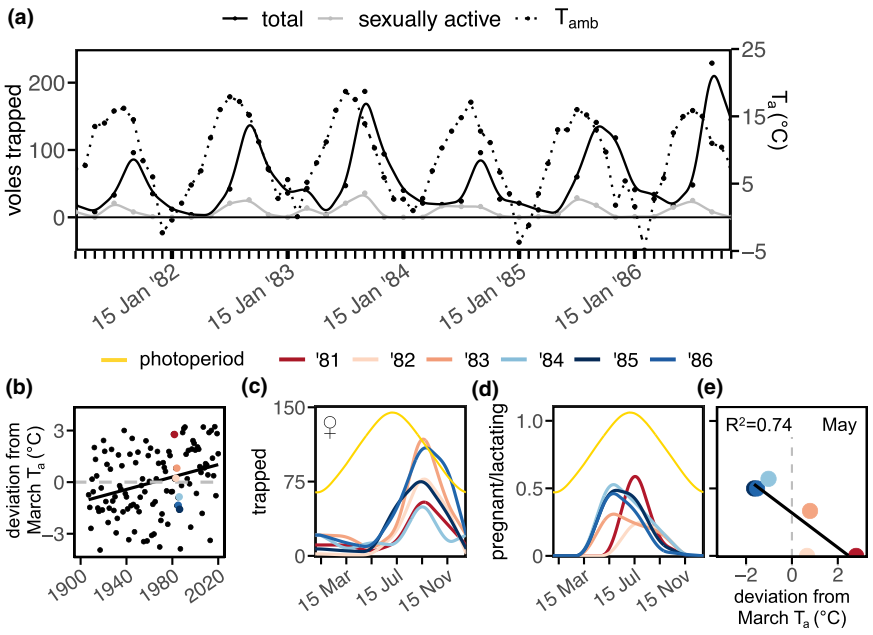

FIGURE 2 Onset of spring reproduction in common voles is associated with ambient temperature. Time series of common vole population dynamics in the Lauwersmeer area, the Netherlands (53.38°N, 6.22°E) between 1981–1986. Analysis of a previously published data set (Dijkstra et al., 1988) (a) Two-month interval census data for the total number of snap-trapped voles /1,500 trap nights (solid, black line), number of sexually active voles (solid, grey line), and monthly average ambient temperature (T_a) (dashed, black line). (b) Deviation from average March T_a is increasing over the years (1907–2020). T_a is retrieved from the Eelde airport weather station, the Netherlands (53.13°N, 6.59°E) (https://weerstatistieken.nl/eeldewileyonlinelibrary.com]). (c) Annual changes in the total number of trapped female voles/ 1500 trap nights related to civil twilight-based photoperiod (yellow), which varies annually between 8.92 h and 18.77 h. (d) Annual changes in the proportion of pregnant or lactating females. (e) Deviation from average March T_a in relation to the proportion of pregnant or lactating females ($F_{1,4} = 11.52$, $p < .03$). Significant linear regression models are indicated with a black line and details can be found in Table S5 [Colour figure can be viewed at wileyonlinelibrary.com]

(Invitrogen), an equal quantity of RNA from each sample was used for cDNA synthesis by using RevertAid H minus first strand cDNA synthesis reagents (Thermoscientific). Then, 20 µl reverse transcription (RT) reactions were prepared using 1 µg RNA, 100 µM Oligo(dT)$_{18}$, 5× reaction buffer, 20 U/µl RiboLock RNase Inhibitor, 10 mM dNTP Mix, RevertAid H Minus reverse transcriptase (200 U/µl). Reagent concentrations used for RT reactions can be found in the Supporting Information (Table S1). RNA was reverse transcribed using a thermal cycler (S1000; Bio-Rad, Hercules). Incubation conditions use for RT were: 45°C for 60 min followed by 70°C for 5 min. Transcript levels were quantified by real-time qPCR using SYBR Green (KAPA SYBR FAST qPCR Master Mix, Kapa Biosystems). Then, 20 µl (2 µl cDNA +18 µl Mastermix) reactions were carried out in duplo for each sample by using 96-well plates in a Real-Time PCR System (StepOnePlus; Applied Biosystems). Primers for genes of interest were designed using Primer-BLAST (NCBI) and optimized annealing temperature (Tm) and primer concentration. All primers (Table S2) used in this study were designed based on the annotated prairie vole (*Microtus ochrogaster*) genome (NCBI:txid79684, GCA_000317375.1), and checked for sequence similarity in shotgun genome sequences of *Microtus arvalis* (NCBI:txid47230, GCA_007455615.1) and *Microtus oeconomus* (NCBI:txid64717, GCA_007455595.1) which were previously sequenced and released on NCBI. Thermal cycling conditions used for RT-qPCR can be found in Supporting Information (Table S3). Relative mRNA expression levels were calculated based on the ΔΔCT method using *Gapdh* as reference (housekeeping) gene (Pfaffl, 2001).

2.6 | Statistical analysis

Effects of photoperiod, temperature and species were determined using type I three-way ANOVAs. Stepwise backwards eliminations were used, and independent variables that were nonsignificant were omitted for final models (Table S4). When interaction terms were significant, underlying single terms were kept in the model even when nonsignificant. Independent samples *t* tests were used for contrast analysis. Statistical significance was determined at $\alpha = .05$. All statistical analyses were performed using RStudio (version 1.2.1335; R Core Team, 2013), and all figures were generated using the R package ggplot2 (Wickham, 2016).

3 | RESULTS

3.1 | Timing of spring reproduction in wild common voles is associated with ambient temperature

Population dynamics of common voles in the Lauwersmeer area, the Netherlands reveal annual cycling patterns with growing populations in spring and summer, and declining populations in autumn and winter (Figure 2a). In each year, population density peaks in September, while interannual variation in vole density levels in September were observed, generating so called population cycles with an enigmatic period of three years (Figure 2a). Furthermore, annual timing of seasonal changes in female and male reproductive traits largely fluctuates between years. (Figure 2d; S2b,e,h). The proportion of sexually active voles peaks in May or in July depending on year (Figure 2d; S2b,e,h). This indicates that vole reproductive status can be modified by nonphotic, unpredictable environmental signals.

Higher proportions of sexually active female voles (i.e., pregnant or lactating females) in May were detected when average March temperature in that same year was low ($F_{1,4} = 11.52$, $p < .03$, $R^2 = .74$; Figure 2e). A similar negative relationship was found for the proportion of total sexually active voles (females and males) in May ($F_{1,4} = 10.06$, $p < .04$, $R^2 = .72$; Figure S1i). In males, this relationship was nonsignificant ($F_{1,4} = 0.27$, $p = .64$, $R^2 = .06$). Higher proportions of sexually active voles in May led to higher population densities in subsequent months, except for 1984, in which vole density was remarkably low while average March temperature was also low (Figure S1c,f).

3.2 | Temperature overrules photoperiodic spring response in common voles, but not in tundra voles

Spring-programmed common voles at 10°C had a 1.5- to 4-fold higher uterus mass (Figure 3a), 2- to 2.5-fold higher ovary mass (Figure 3e), 1- to 1.3-fold higher body mass (Figure 3i) and 1.2- to 2.3-fold higher gonadosomatic index, GSI (Figure 3m) than common voles at 21°C (Table S4). Contrast analysis revealed that temperature effects on GSI were strongest at 10L:14D and 12L:12D (Figure 3m). Interestingly, temperature effects were stronger in spring-programmed voles ($F_{1,44} = 37.74$, $p < .0001$) than in autumn-programmed voles ($F_{1,30} = 5,77$, $p < .04$).

Common voles at 21°C under long photoperiods showed significantly higher uterus mass ($F_{4,19} = 4.97$, $p = .007$; Figure 3a), ovary mass ($F_{4,19} = 3.29$, $p = .04$; Figure 3e), body mass ($F_{4,19} = 4.99$, $p = .007$; Figure 3i) and GSI ($F_{4,19} = 4.17$, $p = .02$; Figure 3m) than common voles at 21°C under shorter photoperiods. In common voles at 10°C, photoperiodic effects on physiological outputs were small or absent (uterus: $F_{3,25} = 0.76$, $p = .53$; ovary: $F_{3,25} = 1.78$, $p = .18$; body mass: $F_{3,25} = 2.55$, $p = .08$; GSI: $F_{3,25} = 0.55$, $p = .66$), indicating that temperature can overrule photoperiodic signals in this species.

To assess whether female voles programme offspring photoperiodic sensitivity through transfer of maternal photoperiod in utero, voles in this study were either photoperiodical spring-programmed (gestated and raised to weaning under SP) or photoperiodical autumn-programmed (gestated and raised to weaning under LP) (Figure 1). Photoperiodic-history dependent effects were found in common voles, with uterus mass and GSI being slightly higher in spring-programmed voles (uterus: $F_{1,74} = 5.26$, $p < .03$; GSI: $F_{1,74} = 4.81$, $p < .04$; Figure S2a,m,c,o). Although autumn-programmed common voles significantly increased ovary and body mass at 10°C (ovary: $F_{1,30} = 10.08$, $p < .004$; body mass: $F_{1,30} = 10.28$, $p < .004$; Figure 3f,j), this temperature effect was not reflected in GSI ($F_{1,30} = 1.09$, $p = .31$; Figure 3n).

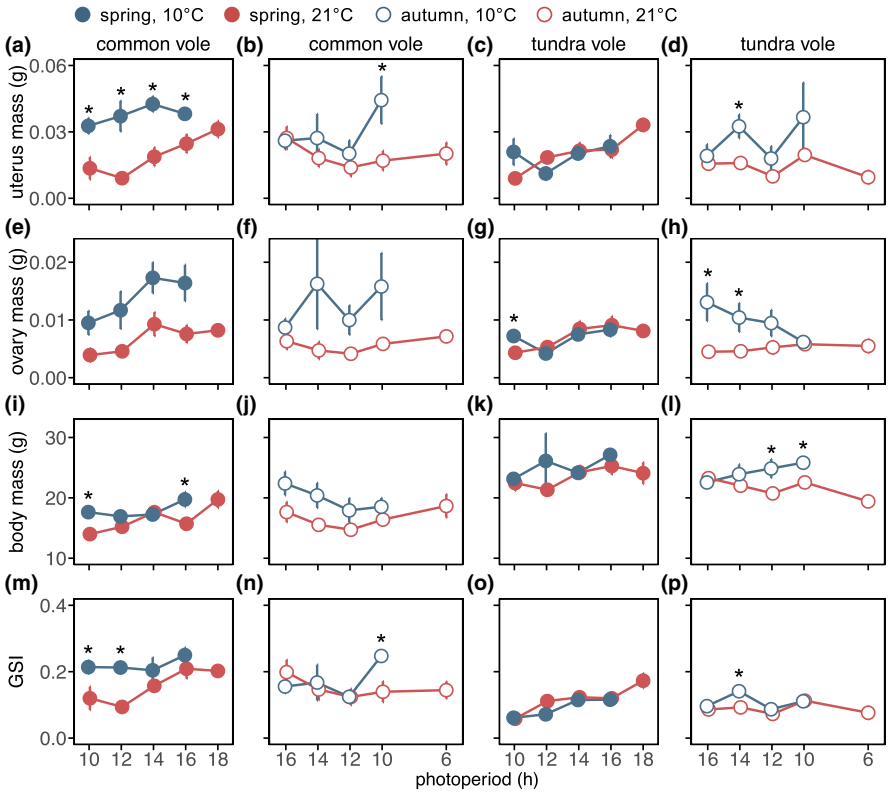

FIGURE 3 Temperature-dependent modulation of photoperiodic responses in physiological outputs of female voles. Responses to photoperiod for (a–d) uterus mass, (e–h) paired ovary mass, (i–l) body mass and (m–p) total reproductive organ mass corrected for body mass (gonadosomatic index, GSI) in 50-day old common and tundra voles respectively, photoperiodical spring programmed (closed symbols; conceived, born and raised to weaning under SP) or photoperiodical autumn programmed (open symbols; conceived, born and raised to weaning under LP) at 10°C (blue) or 21°C (red). The x-axis of autumn-programmed data is plotted in the reversed direction to illustrate annual photoperiodic changes. Data are presented as means ±SEM. Common vole, spring, 10°C: $n = 29$; common vole, spring, 21°C: $n = 24$; common vole, autumn, 10°C: $n = 17$; common vole, autumn, 21°C: $n = 22$; tundra vole, spring, 10°C: $n = 18$; tundra vole, spring, 21°C: $n = 32$; tundra vole, autumn, 10°C: $n = 19$; tundra vole, autumn, 21°C: $n = 24$. Significant effects of contrast analysis are indicated: $^*p < .05$. In summary, significant photoperiodic effects were found in: b, e, g, i, o and p, significant temperature effects were found in a, b, d, e, f, h, i, j, j, m and p (Table S4) [Colour figure can be viewed at wileyonlinelibrary.com]

In tundra voles, ovary mass and GSI were affected by photoperiod, with increased values at long photoperiods (ovary: $F_{4,72} = 2.78$, $p < .04$; GSI: $F_{4,72} = 6.36$, $p < .0002$; Figure 3c,o). In spring-programmed tundra voles, temperature did not affect physiological outputs (Figure 3c,g,k,o; Table S4), while in autumn-programmed tundra voles, low temperature enhances reproductive organ and body mass (uterus: $F_{1,32} = 4.85$, $p < .04$; ovary: $F_{1,32} = 16.05$, $p < .0004$; body mass: $F_{1,33} = 11.17$, $p < .003$; GSI: $F_{1,32} = 4.27$, $p < .05$; Figure 3d,h,l,p). These data indicate that there is species dependent annual variation in the sensitivity to temperature for timing of reproductive onset.

3.3 | Temperature affects hypothalamic gene expression in tundra voles, but not in common voles

To assess at what level of the reproductive axis thermal cues act to modify photoperiodic output signals, we measured gene expression levels in posterior and anterior hypothalamus in a subset of experimental groups in which temperature and photoperiod largely affected reproductive organ mass: spring-programmed 10L:14D and 16L:8D at 10 and 21°C.

Our results show that *Tshβ* expression in the pars tuberalis is higher in voles at long photoperiod (16L:8D) than in voles at short photoperiod (10L:14D) ($F_{1,42} = 21.52$, $p < .0001$), and was not affected by temperature ($F_{1,42} = 0.42$, $p < .53$; Figure 4a,h). Under 16L:8D, *Tshβ* levels were approximately 2-fold higher in common voles than in tundra voles ($F_{1,19} = 5.23$, $p < .05$).

Although in common voles, *Tshr* levels were relatively low, a small reduction was observed at 16L:8D ($F_{1,17} = 8.51$, $p < .01$; Figure 4b), but *Tshr* was not affected by temperature ($F_{1,42} = 0.09$, $p = .77$). In tundra voles, photoperiod did not affect *Tshr* ($F_{1,21} = 0.11$, $p = .75$; Figure 4i), while *Tshr* expression was enhanced at 10°C ($F_{1,9} = 6.01$, $p < .05$; Figure 4i). Furthermore, overall *Tshr* levels were approximately 3-fold higher in tundra voles than in common voles ($F_{1,44} = 103.2$, $p < .001$).

Indeed, *Dio2* follows similar responses to photoperiod as observed in *Tshβ* ($F_{1,42} = 21.52$, $p < .0001$; Figure 4c,j). In tundra voles,

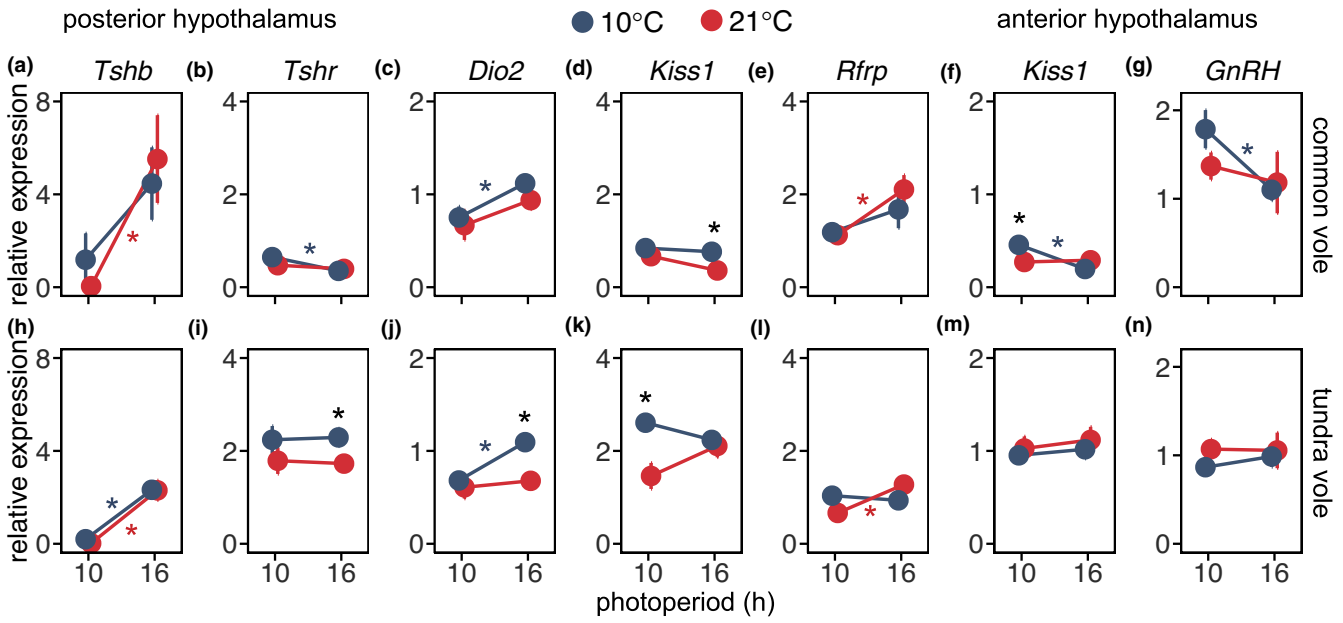

FIGURE 4 Temperature-dependent modulation of photoperiodic spring responses in hypothalamic gene expression. Spring-programmed responses to photoperiod for relative gene expression levels in the posterior hypothalamus (a, h) *Tshβ*, (b,i) *Tshr*, (c, j) *Dio2*, (d, k) *Kiss1*, (e, l) *Rfrp3*, and anterior hypothalamus: (f, m) *Kiss1*, (g, n) *GnRH* in 50-day old common and tundra voles, respectively, at 10°C (blue) or 21°C (red). Data are presented as means ±SEM. Common vole, 10L:14D, 10°C, $n = 8$; common vole, 10L:14D, 21°C, $n = 5$; common vole, 16L:8D, 10°C, $n = 6$; common vole, 16L:8D, 21°C, $n = 4$; tundra vole, 10L:14D, 10°C, $n = 7$; tundra vole, 10L:14D, 21°C, $n = 8$; tundra vole, 16L:8D, 10°C, $n = 4$; tundra vole, 16L:8D, 21°C, $n = 7$. Significant effects of contrast analysis are indicated: *$p < .05$. In summary, significant photoperiodic effects were found in: a, b, c, e, f, g, h, j, l, significant temperature effects were found in: d, j, k, and significant interactions between photoperiod and temperature were found in: f, k, l (Table S4) [Colour figure can be viewed at wileyonlinelibrary.com]

Dio2 was further enhanced at 10°C ($F_{1,20} = 6.83$, $p < .03$), while in common voles, temperature did not affect *Dio2* ($F_{1,18} = 1.14$, $p = .32$; Figure 4c).

In both vole species, *Kiss1* expression in the ARC (posterior hypothalamus) was affected by temperature (common vole: $F_{1,18} = 8.79$, $p < .009$; tundra vole: $F_{1,20} = 9.59$, $p < .006$; Figure 4d,k). In common voles, ARC *Kiss1* was elevated at 10°C under 16L:8D ($F_{1,8} = 22.32$, $p < .002$), indicating that temperature affects *Kiss1* only at long photoperiods. In tundra voles, ARC *Kiss1* was elevated at 10°C under 10L:14D ($F_{1,11} = 15.09$, $p < .003$), indicating that temperature affects *Kiss1* only at short photoperiods. Furthermore, general *Kiss1* levels in the ARC were >2-fold higher in tundra voles than in common voles ($F_{1,38} = 141.46$, $p < .0001$).

In common voles, *Rfrp* levels were higher at long photoperiod independent of temperature ($F_{1,18} = 6.56$, $p < .02$; Figure 4e). In tundra voles, a significant photoperiod-temperature interaction was found, with increased *Rfrp* levels at 10°C under 10L:14D, and decreased *Rfrp* levels at 21°C under 16L:8D ($F_{1,20} = 7.27$, $p < .02$; Figure 4l).

Common voles under 10L:14D showed slightly increased *Kiss1* levels in the POA (anterior hypothalamus) at 10°C ($F_{1,11} = 5.82$, $p < .05$; Figure 4f). However, in tundra voles, temperature and photoperiod did not affect *Kiss1* in the POA (PP: $F_{1,21} = 0.62$, $p = .44$; temp: $F_{1,21} = 0.52$, $p = 0.48$; Figure 4m). As observed in the ARC, also general POA *Kiss1* levels were higher in tundra voles than in common voles ($F_{1,44} = 109.39$, $p < .0001$).

GnRH expressing neurons are located in the POA and act on the pituitary gland where the release of gonadotropins is regulated to drive reproduction. For this reason, it was unexpected that in common voles, *Gnrh* was reduced under long photoperiods ($F_{1,16} = 5.07$, $p < .04$; Figure 4g), and unaffected by temperature ($F_{1,16} = 1.34$, $p = .27$). In tundra voles, *Gnrh* was rather stable and not affected by photoperiod ($F_{1,16} = 0.12$, $p = 0.73$; Figure 4n) or temperature ($F_{1,16} = 0.34$, $p = .57$).

4 | DISCUSSION

Our results confirm the importance of thermal cues for female reproduction in small mammals. Lowering ambient temperature caused accelerated reproductive organ maturation in spring-programmed common voles, while temperature effects were not reflected in hypothalamic gene expression (Figure 5d). In contrast, temperature in tundra voles did not influence physiological spring responses, while expression of several hypothalamic genes was affected by temperature (Figure 5e).

Annual population cycle dynamics in common vole populations revealed that cold springs are associated with advanced onset of spring reproduction (Figure 2e; S2i). This eventually may lead to higher vole densities in subsequent months (Figure S1c,f). These data confirm that seasonal reproductive cycles in common voles are plastic, and are therefore not exclusively controlled by photoperiod, but also depend on ambient temperature. This is in agreement with

previous studies reporting large interannual variation in the ratio of reproductive females in spring, which has been shown to be positively or negatively related to temperature depending on ecological context (Giraudoux et al., 2019; McLean & Guralnick, 2020). Field transplant experiments revealed that the immediate environment drives the onset of spring reproduction in field voles, *Microtus agrestis* (Ergon et al., 2001). Thus, annual variation in cycle dynamics within vole populations may be attributed to local environmental breeding cues, such as food, temperature, rain, predators and parasites (Huntington, 1931).

Our laboratory experiments confirmed our observation that cold springs advance reproductive onset, since lowering ambient temperature caused accelerated reproductive organ development in spring-programmed female common voles (Figure 3). In Syrian hamsters (*Mesocricetus auratus*) at low temperatures, ovary mass was not affected, while fewer follicles and corpora lutea were observed (Reiter, 1968). For this reason, ovary mass may be an unreliable indicator for hormonal secretion. Histological analyses were not performed in our study; therefore, this data should be interpreted with caution. In contrast, uterine size is positively related to thickness of secretory epithelium and the number of endometrial glands (Reiter, 1968). Therefore, low uterus mass observed at high temperature is presumably related to incomplete maturation of uterine glands, indicating infertility, because uterine glands are crucial for pregnancy (Cooke et al., 2013).

In addition, common vole males also accelerated gonadal growth at 10°C (van Rosmalen, van Dalum, et al., 2021), confirming that in nature, female and male voles may be synchronized in their reproductive status. Similar findings have been reported in an earlier study, showing that the largest and most fertile female and male common voles were those raised at 5°C under 15L:9D, while the smallest and least fertile animals were raised at 33°C under 10L:14D (Daketse & Martinet, 1977). In contrast, hamsters and other vole species show decreased gonadal size, and decreased reproductive output at low temperatures (Nelson et al., 1989; Steinlechner et al., 1991). Opposite temperature effects may be explained by species differences in optimal ambient temperature for reproduction and different photoperiodic histories of the animals. Here we show that maternal photoperiod affects postnatal growth of reproductive organs in female voles, as was previously demonstrated in male long-day breeders (Hoffmann, 1973; Horton, 1984, 1985; Horton & Stetson, 1992; Prendergast et al., 2000; Sáenz de Miera et al., 2017; Stetson et al., 1986; Yellon & Goldman, 1984), including common voles (van Rosmalen, van Dalum, et al., 2021).

Although large variation in the onset of the breeding season could be observed between years, the offset of the breeding season in autumn was rather synchronized with photoperiod (Figure 2d; Figure S2b,e,h). It is therefore possible, that temperature sensitivity changes throughout the season. Although, in autumn-programmed common voles, ovary and body mass were also elevated at 10°C (Figure 3f,j), GSI was unaffected by temperature (Figure 3n). These results demonstrate that in common vole females, photoperiodical spring-programmed responses can be modulated by temperature, whereas photoperiodical autumn-programmed responses are relatively insensitive to modulation by temperature.

Because grass growth is initiated when temperatures are rising, it is counterintuitive that voles, an herbivorous species, accelerate reproductive development when spring temperatures are low. However, grass growth is initiated at 5–10°C (Cooper, 1964; Peacock, 1975, 1976), and at 53°N latitude (from where our common voles originate) an average ambient temperature of 10°C occurs in spring (Hut et al., 2013). It is therefore likely that when food is abundant, common voles perceive 10°C as an additional environmental cue indicating spring, which therefore further facilitates reproductive activation. Given a specific photoperiod, autumn, is generally warmer than spring (Hut et al., 2013), and 21°C may therefore be perceived as an additional environmental cue indicative of autumn, causing a reduced reproductive sensitivity to photoperiod. It has previously been shown that there is an optimal ambient temperature for breeding performance in deer mice, *Peromyscus maniculatus borealis* (Bronson & Pryor, 1983). Our data set did not contain extremely cold springs (Figure 2b); therefore, we may only have data for the right side of the parabolic relationship between ambient temperature and reproductive status. Extremely cold and extremely warm springs are both expected to delay reproductive onset, since under these circumstances all energy is needed for thermoregulatory functions and tissue maintenance. This hypothesis is in line with the heat dissipation limit theory, which suggests that heat generated during metabolism limits energy intake, and therefore decreases reproductive output when temperatures are high (Simons et al., 2011; Speakman & Król, 2010; Zhao et al., 2020). This effect has been confirmed in common voles (Simons et al., 2011). Endotherms can maintain their body temperature under a large range of ambient temperatures, and many mammalian species can reduce their energy expenditure by entering daily torpor when food is scarce or temperatures are low (Heldmaier et al., 2004; Hut et al., 2011; van der Vinne et al., 2015). In contrast, voles do not enter torpor when energetically challenged (Nieminen et al., 2013; van Rosmalen & Hut, 2021b), yielding limited energy savings. For this reason, the vole reproductive strategies and the underlying PNES may be more sensitive to temperature.

Ambient temperatures that belong to a certain photoperiod can be deduced from the ellipse-like relationships between photoperiod and monthly average temperatures at specific locations (Figure 5c). Assuming that genetic adaptation of the PNES is optimal in the center of the species geographical distribution, it is expected that common voles are better adapted to the local seasonal environment of Groningen, the Netherlands (Figure 5a; 53°N, current latitudinal center of distribution) while tundra voles are better adapted to the local seasonal environment of Oslo, Norway (Figure 5b; 60°N, current latitudinal center of distribution). Groningen and Oslo differ in the ellipse-like relationship between photoperiod and ambient temperature, leading to different ambient temperatures that belong to specific photoperiods in spring (Figure 5c). Our data demonstrated that spring-programmed common voles are sensitive to temperature, whereas tundra voles are

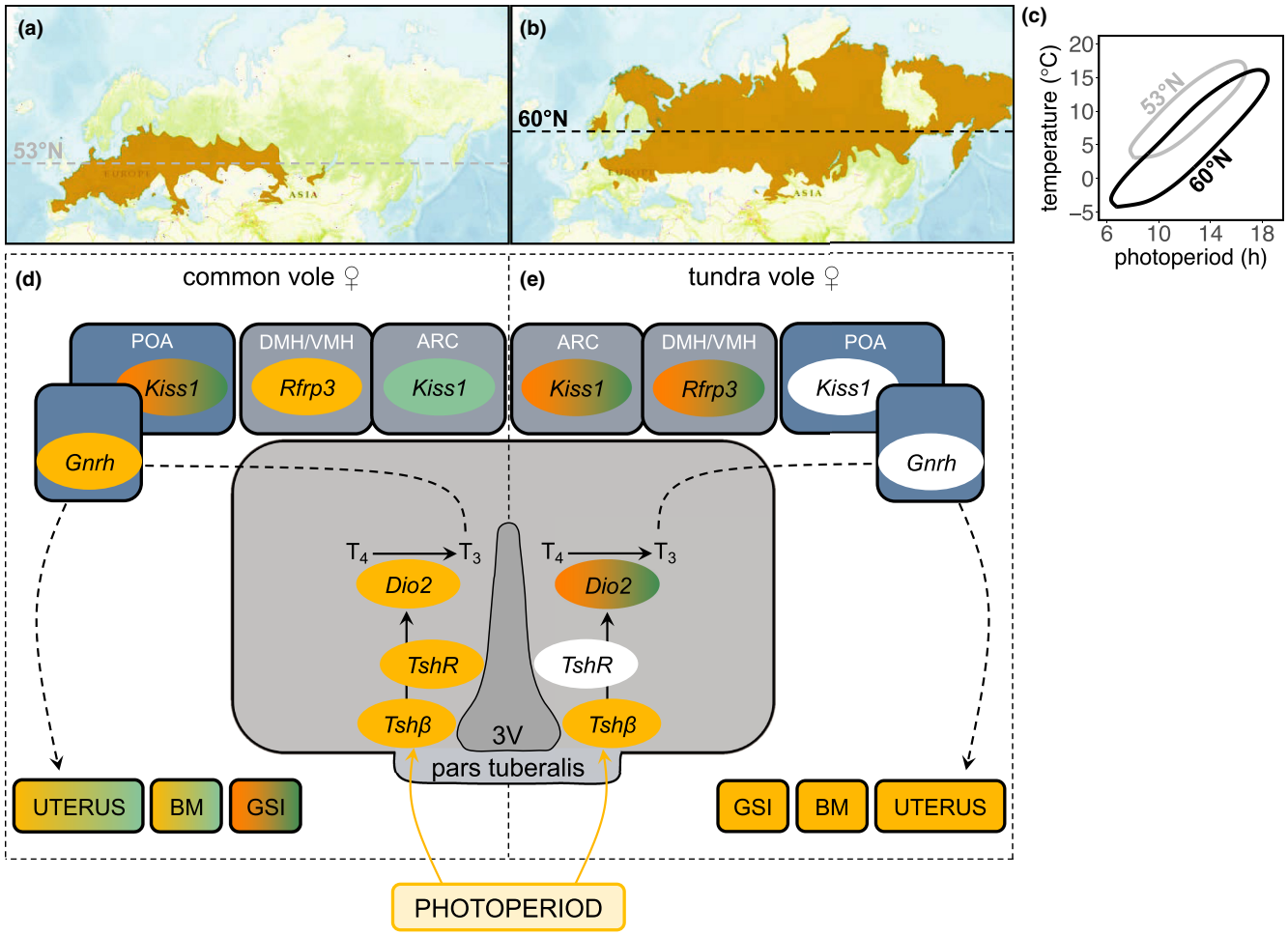

FIGURE 5 Graphical summary showing the effects of photoperiod and ambient temperature on the photoperiodical spring-programmed PNES in 50-day old female common and tundra voles. Geographic range in orange for (a) common voles and (b) tundra voles (obtained from: https://IUCNredlist.orgwileyonlinelibrary.com]). (c) Ellipse-like annual relationship between photoperiod and ambient temperature for Eelde (53°N; grey) and Oslo (60°N; black). Ambient temperature is retrieved from the Eelde airport weather station, the Netherlands (53.13°N, 6.59°E) and Oslo airport weather station, Norway (60.19°N, 11.10°E) (obtained from: https://weerstatistieken.nl/eeldewileyonlinelibrary.com]and https://wunderground.comwileyonlinelibrary.com]). Effects of photoperiod (yellow) and ambient temperature (green) on the PNES in photoperiodical spring-programmed (d) common and (e) tundra voles. Components of the PNES affected by both temperature and photoperiod or by interactions between temperature and photoperiod are marked yellow + green [Colour figure can be viewed at wileyonlinelibrary.com]

insensitive to temperature (Figure 3). However, broader temperature ranges under different photoperiodic conditions need to be applied in order to confirm whether tundra voles are also insensitive to more extreme temperatures as was shown for deer mice living at different latitudes (Bronson & Pryor, 1983). In that study, reproductive output in house mice was insensitive to temperature, whereas deer mice showed narrow temperature ranges at which breeding took place, with high temperatures leading to reproductive success at 56°N and low temperatures leading to reproductive success at 31°N. In 1988, Bronson proposed that the use of photoperiod and ambient temperature as a cue to time breeding might depend on local habitats which change with latitude (Bronson, 1988). Natural selection might either inhibit or promote the use of photoperiod, nutritional and thermal cues to control seasonal reproduction, which will result in species-specific reproductive strategies (Hut et al., 2014).

Local variation in annual food patterns depends on annual photoperiod-temperature patterns, and might be a driving force in the evolution of breeding seasons in small mammals. The sensitivity to photoperiod and ambient temperature as a breeding cue can differ depending on the predictability of the environment, which varies with latitude (Bronson, 1989). On one hand, temperate latitudes are highly predictable environments that allow photoperiod to be the main driver for seasonal variation in reproductive success. On the other hand, latitudes further away from the equator may display unpredictable snowfall which leads to unpredictable changes in food availability, predation risk and thermoregulatory costs. Therefore, opportunistic reproductive strategies may have evolved in short-lived mammals living at extreme latitudes.

Although we did not find major species differences in photoperiodic responsiveness, only common voles are sensitive to temperature in spring (Figure 3). The latitudinal distribution range of tundra

voles is far up North, where they live under isolating snow covers for a large part of the year. The rather stable ambient temperatures under snow covers in winter and early spring, may make temperature an unreliable seasonal cue for tundra voles. Furthermore, timing of spring reproduction in wild tundra vole populations may still correlate with temperature, but this does not necessarily mean that temperature has a direct effect on reproductive responses. However, there can be an indirect effect of temperature on vegetation growth, and voles may use an opportunistic reproductive strategy in which the use of food availability as a cue is driving reproductive onset (van Rosmalen & Hut, 2021a). Given that common voles have at least three nonbiotic cues (photoperiod, temperature and food) to time reproduction, and tundra voles only two (photoperiod and food), the effects of rising temperatures may be worse for tundra voles because they may get more out of phase with plant growth than common voles. Comparisons between these two vole species may be used as models to investigate temperature modification of neurobiological mechanisms underlying photoperiodic responses.

In the posterior hypothalamus, where the pars tuberalis is localized, PNES genes (i.e., *Tshβ*, *Tshr* and *Dio2*) all respond to photoperiod (Figure 4), which has previously been shown in mammals (Dardente et al., 2010; Masumoto et al., 2010; Sáenz de Miera et al., 2017; Wang et al., 2019), and in captive vole populations (Król et al., 2012; van Rosmalen et al., 2020). Increased *Rfrp* under long photoperiods as observed in common voles and in tundra voles at 21°C (Figure 4e,l), has previously been observed in both short and long-day breeders, and is believed to be important in controlling seasonal reproduction (Henningsen et al., 2016).

Although common voles strongly respond to temperature in physiological outputs (Figure 3a,e,i,m), hypothalamic gene expression was mostly insensitive to temperature (Figure 4a–g). The posterior hypothalamus contains kisspeptin neurons localized in the ARC controlling daily timing of food intake (Padilla et al., 2019), and is involved in sensing fat reserves and may subsequently be involved in decreasing fertility when food is scarce (Fu & van den Pol, 2010; Harter et al., 2018). The anterior hypothalamus contains kisspeptin neurons localized in the POA, which receives projections from thermoreceptors in the skin and also contains thermosensitive neurons (Morrison & Nakamura, 2019). Therefore, it was rather unexpected that *Kiss1* in common voles was only slightly upregulated by low temperature. On one hand, this suggests that other factors more downstream or outside the PNES are responsible for temperature modulations of photoperiodic responses. In mammals, cold exposure leads to upregulation of DIO2 in brown adipose tissue (BAT), leading to elevated peripheral T_3 levels (De Jesus et al., 2001; Lowell & Spiegelman, 2000; Silva & Larsen, 1985). Whether, circulating T_3 can act on the hypothalamus to activate GnRH neurons and subsequently control uterine growth remains unclear. In addition, uterine nuclei contain receptors for T_3, and may therefore be a target organ for low temperature-induced circulating T_3 affecting seasonal uterine growth (Evans et al., 1983). Furthermore, cold exposure increases metabolism by activating BAT which mediates nonshivering thermogenesis. Perhaps, these changes in energy expenditure may contribute in driving modulations of photoperiodic responses in response to cold exposure.

Downstream *GnRH* expression in the anterior hypothalamus does not reflect gonadal weight (Figure 4g,n). Steroid feedback mechanisms on hypothalamic areas and the phase of the estrous cycle are highly involved in initiating the GnRH surge and may play an important role in our observations. However, this data has to be interpreted with caution as the current study only considered gene expression and did not assess protein release at the median eminence. Furthermore, negative sex steroid feedback on ARC kisspeptin neurons (Greives et al., 2008; Rasri-Klosen et al., 2017; Sáenz De Miera et al., 2014), may explain similar *Kiss1* and *GnRH* levels observed in different experimental groups. This is an important issue for future studies, and may be solved by shortening the interval between changing environmental conditions and tissue collection.

Interestingly, tundra voles have increased hypothalamic *Tshr*, *Dio2* and *Kiss1* levels at low temperature (Figure 4i–k), however this is not reflected in reproductive organs. Therefore, it is conceivable that spring-programmed tundra voles are also sensitive to temperature, but later in development than common voles. Because of the substantial delay between gene expression and physiological responses, cold exposure experiments for extended periods with time-series sampling is necessary to reveal whether indeed upregulated *Tshr*, *Dio2* and *Kiss1* are responsible for the accelerated reproductive organ maturation at 10°C. In agreement with a previous study, *Rfrp* was not affected by temperature under LP when food was available ad libitum, while *Rfrp* was downregulated at low temperature when food was scarce (van Rosmalen & Hut, 2021a). In the experiments described here, food was available ad libitum. Thus, animals could increase their food intake to compensate for increased thermoregulatory costs at low temperatures. Previous experiments revealed that temperature has different effects on the photoperiodic axis when food is scarce (van Rosmalen & Hut, 2021a). In contrast, in house mice, hypothalamic *Rfrp* is a biomarker of ambient temperature independent of adiposity or food intake (Jaroslawska et al., 2015).

Our findings show that reproductive responses of both vole species are sensitive to photoperiod, whereas particularly the spring response of the common vole is determined by temperature. This is in line with our common vole census data, which reveals that warm springs are associated with later reproductive onset. Accelerating reproductive organ maturation when born in a relatively cold spring, but with abundant food available, is an adaptive response that facilitates reproduction and increases fitness. Due to a cold temperature in spring, reproductive onset is advanced, and pups will be born early in spring under increasing photoperiod, resulting in juveniles being programmed to accelerate reproductive organ development. This will lead to additional generations of pups within the same season, leading to exponential growth. This is because early born pups can produce litters within the same season as they were born in. Furthermore, common voles have extreme reproductive potential when the seasonal environment is favorable that allows particularly flexible adjustment of population growth (Tkadlec & Zejda, 1995). All else being equal, a larger population at the end of reproduction leads to a higher absolute number of animals that survive winter, which may in turn lead to a larger population producing early in the season when winter remain relatively cold.

Due to increased vole density, more animals will advance their spring reproduction, and therefore these animals can produce an additional generation of pups, leading to a peak in vole density in the subsequent summer. This cycle will continue until vole density is extremely high, and therefore food resources are getting scarce and mortality increases. Food scarcity in winter/spring results in slower reproductive organ development (van Rosmalen & Hut, 2021a). This might result in a population collapse and might be an explanation for the three-year population cycles documented in voles. Given that very complex ecological interactions lead to highly variable population dynamics, it is not excluded that factors other than photoperiod and temperature contribute to the genetic control of reproduction.

Furthermore, warmer springs due to global warming (Figure 2b) may cause delayed onset of spring reproduction, while the offset of the breeding season appears to be relatively unaffected by temperature (Figures 2 and 3, S2), leading to a dramatic shortening of the breeding season. This observation provides a possible explanation for recent decline in vole populations and population cycles observed in Europe (Cornulier et al., 2013; Ims et al., 2008). However, in our analysis we did not control for possible other factors (e.g., agricultural practices) that may contribute to declining vole populations.

Defining the molecular mechanisms through which thermal cues modify maternally photoperiodical-programmed responses to adaptively adjust timing of reproductive organ development will be important for a better understanding of how seasonal cycling environmental breeding cues shape female reproductive function and plasticity.

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AUTHOR CONTRIBUTIONS

Laura van Rosmalen, Cor Dijkstra, Roelof A. Hut conceived and designed the experiments, Laura van Rosmalen, Bernd Riedstra, Nico Beemster, Cor Dijkstra conducted the experiments, Laura van Rosmalen analysed the data, Laura van Rosmalen and Roelof A. Hut wrote the manuscript, and Laura van Rosmalen, Bernd Riedstra, Nico Beemster, Roelof A. Hut read and commented on the manuscript.

OPEN RESEARCH BADGES

This article has earned an Open Data Badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available at https://doi.org/10.6084/m9.figshare.14798337.v3.

DATA AVAILABILITY STATEMENT

All data used has been published in a public repository (Figshare) (https://doi.org/10.6084/m9.figshare.14798337.v1) (van Rosmalen, Riedstra et al., 2021).

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