

A cross-taxonomic perspective on the integration of temperature cues in vertebrate seasonal neuroendocrine pathways[☆]

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ABSTRACT

The regulation of seasonality has been an area of interest for decades, yet global climate change has created extra urgency in the quest to understand how sensory circuits and neuroendocrine control systems interact to generate flexibility in biological timekeeping. The capacity of temperature to alter endogenous or photoperiod-regulated neuroendocrine mechanisms driving seasonality, either as a direct cue or through temperature-dependent effects on energy and metabolism, is at the heart of this phenological flexibility. However, until relatively recently, little research had been done on the integration of temperature information in canonical seasonal neuroendocrine pathways, particularly in vertebrates. We review recent advances from research in vertebrates that deepens our understanding of how temperature cues are perceived and integrated into seasonal hypothalamic thyroid hormone (TH) signaling, which is a critical regulator of downstream seasonal phenotypic changes such as those regulated by the BPG (brain-pituitary-gonadal) axis. Temperature perception occurs through cutaneous transient receptor potential (TRP) neurons, though sensitivity of these neurons varies markedly across taxa. Although photoperiod is the dominant cue used to trigger seasonal physiology or entrain circannual clocks, across birds, mammals, fish, reptiles and amphibians, seasonality appears to be temperature sensitive and in at least some cases this appears to be related to phylogenetically conserved TH signaling in the hypothalamus. Nevertheless, the exact mechanisms through which temperature modulates seasonal neuroendocrine pathways remains poorly understood.

1. Introduction

Most habitats exhibit seasonal patterns in photoperiod (the length of daylight), temperature, and/or precipitation. These transitions between seasons drive cycles of local resource availability and, accordingly, species have evolved locally adapted patterns of seasonal physiological, behavioral, and morphological change to cope with these predictable annual fluctuations in conditions.

Seasonality has a deep history. It has been proposed that programmed seasonal phenotypic change first evolved in early single cell Eukaryotes, allowing these organisms to transition between alternative phenotypes that switch across successive generations (Lincoln, 2019). Today, seasonal changes in a wide variety of physiological and behavioral traits, including metabolism, movement patterns, and reproductive state, are found in many taxa. An enormous body of literature indicates

that photoperiod plays an important role in regulating seasonal phenotypic transitions in plants (Bäurle and Dean, 2006), fungi (Roenneberg and Merrow, 2001) and animals (Bradshaw and Holzapfel, 2007). In vertebrates, photoperiod can either directly drive seasonal changes in physiology and behavior, or act indirectly, allowing organisms to synchronize endogenous circannual rhythms with the surrounding environment.

The use of photoperiodic cues to time seasonal events is common because these cues are reliable and allow organisms to generate stable annual schedules of change that are synchronized with local seasonality. However, most habitats experience interannual variation in weather, leading to yearly variation in the timing of seasonal resource peaks. Thus, many organisms have evolved the capacity to adjust seasonal timing either directly responding to changes in those resources, or by responding to other biotic and/or abiotic cues that are predictive of

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resource availability (e.g. Ball and Ketterson, 2008; Chmura et al., 2020; Migaud et al., 2010; Tolla and Stevenson, 2020). Given that climate change has no impact on annual cycles of photoperiod, the degree to which organisms are capable of tracking climate-driven changes in resource availability is dependent on their sensitivity to these secondary cues. Cue sensitivity, however, likely differs taxonomically which may lead to phenological mismatches in response to climate change. For example, there are many cases in which the phenological responses of vertebrates has been insufficient to track rapid shifts in the phenology of primary producers (Renner and Zohner, 2018), which are more sensitive to shifts in temperature and precipitation (Piao et al., 2019), both of which are being altered by climate change. This has led to widespread interest in better understanding the mechanisms that underlie phenological plasticity in animals and how they use non-photic environmental cues to align their life-history timing with the environment.

Of the non-photic cues used to adjust seasonal timing, temperature is perhaps the best studied. It seems intuitive that temperature would be an important regulator of seasonal phenotypic change because it affects both resource availability in the environment and energy expenditure within the organism (Fig. 1). Yet while both observational studies and controlled experiments regularly report a close association between temperature and seasonal timing, Caro et al. (2013) noted that the mechanisms by which temperature cues are perceived and integrated into seasonal programs are not well described. Within ectotherms, growth and development can be modeled as a function of temperature (e.g. Zuo et al., 2012), likely due to Q10 effects (a measure of temperature sensitivity of reaction rates). However, other aspects of ectotherm life history (e.g. timing of brumation, smoltification, and reproduction) are regulated in part by an underlying seasonal program that is also sensitive to temperature, the mechanisms of which are still under investigation (Björnsson et al., 2011; Mayer et al., 1997; Migaud et al., 2010; Wilsterman et al., 2021). Even in endothermic birds and small mammals, which have been the focus of intense research on seasonality for years, it is not clear to what extent ambient temperature exerts timing effects by acting as a cue that is perceived and integrated by the CNS versus a driver of nutritional state that acts as a gatekeeper for seasonal processes. Understanding the interplay between temperature and underlying seasonal neuroendocrine programs is critical and has become an area of tremendous research growth over the past decade.

The purpose of this review is to highlight important findings on how ambient temperature is perceived and integrated into seasonal neuroendocrine pathways and to identify central research questions moving forward. While this review will focus on temperature, we begin with an overview of research on photoperiodism. This will allow us to introduce

important seasonal neuroendocrine timing pathways that may be modulated by temperature and provide important context for interpreting the studies investigating these pathways that follow; additionally, the effects of temperature may be photoperiod-dependent in many taxa (Pankhurst and Porter, 2003 and this review). Next, we describe the importance of temperature cues in permitting flexibility in these seasonal neuroendocrine timing pathways. The subsequent sections detail what is known about taxonomic variation in temperature perception and transduction in vertebrates. Along the way we will highlight important themes, such as the interaction of temperature and photoperiod, metabolic and non-metabolic temperature effects, and differences between temperature perception and signaling in endotherms and ectotherms. To bound the review's scope, we chose to focus on studies that used an experimental paradigm to compare neuroendocrine mechanisms associated with seasonal timing transitions across two or more temperature treatments and also addressed the relatively small body of literature on regulation directly at the gonad. This means that, in general, we do not include common garden studies, field observational studies, or laboratory studies that only include one temperature treatment.

2. Neuroendocrine regulation of seasonality

Much of what we know about neuroendocrine regulation of seasonality in vertebrates comes from studies on the role of changing photoperiod in triggering seasonal phenotypic transitions. While most vertebrates use photoperiod in seasonal timing pathways, there is variation across species in the mechanisms through which photoperiod exerts its effects. Some species generate strong endogenous circannual cycles of phenotypic change that require entrainment with prevailing photoperiod to match internal cycles with local seasonality (Gwinner, 1986), while at the opposite end of the spectrum other species require photoperiodic cues to initiate seasonal changes in physiology, behavior, and morphology (Bradshaw and Holzapfel, 2007). While a detailed discussion of these differences is beyond the scope of this review, what is important is that many elements of timekeeping appear to be conserved: seasonal animals have mechanisms to detect light, translate information about the daily duration of light into a seasonal signal, and integrate this photoperiodic signal with information relayed by other signaling pathways to effect seasonal phenotypic changes.

In mammals, daylight is detected by the retina and this cue is decoded by the suprachiasmatic nucleus (SCN), which regulates and entrains nocturnal melatonin secretion from the pineal gland (reviewed in: Lincoln et al., 2003, Fig. 2). In turn, daily cycles of melatonin secretion affect the daily time course of synthesis and degradation of Eyes Absent 3 (*EYA3*) in thyrotroph cells of the pars tuberalis (PT) (Wood and Loudon, 2018). This cyclic expression of *EYA3* is a component of the putative link between daily and seasonal clocks (Dardente et al., 2010; Wood et al., 2020, 2015).

The reception and transduction of light into a photoperiodic signal is more complicated in non-mammalian vertebrates (Fig. 2). For example, while retinal photoreception is common across vertebrates, additional extra-retinal photodetection occurs in most non-mammalian vertebrate lineages (Pérez et al., 2019). Additionally, the circadian systems of non-mammalian vertebrates are organized into networks comprised of multiple master circadian clocks that, in combination, synchronize daily rhythms of physiology and behavior (Bertolucci et al., 2017; Cassone et al., 2017; Falcón et al., 2010). It appears that in many non-mammalian species, the pineal gland has direct light input channels and acts as one of several self-sustained master circadian clocks. In some of these taxa, for example the green anole (*Anolis carolinensis*), the pineal may be one component of seasonal signaling as at certain times of year pinealectomy increases male testis size (Underwood, 1981). However, in non-mammalian taxa other organs are also important. In many fishes, amphibians, and reptiles, for example, the parapineal organ is photoreceptive and, in some cases forms a parietal eye (Mayer et al., 1997; Smith et al., 2018); birds and mammals have lost the parapineal gland

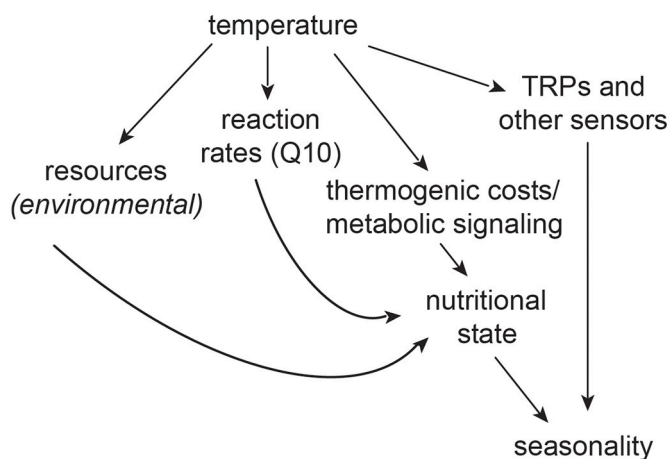


Fig. 1. Conceptual diagram showing the different ways the environmental temperature could be perceived and/or affect other biological processes that influence seasonal phenotypes. TRP: transient receptor potential channel. Q10: a measure of the temperature sensitivity of reaction rates.

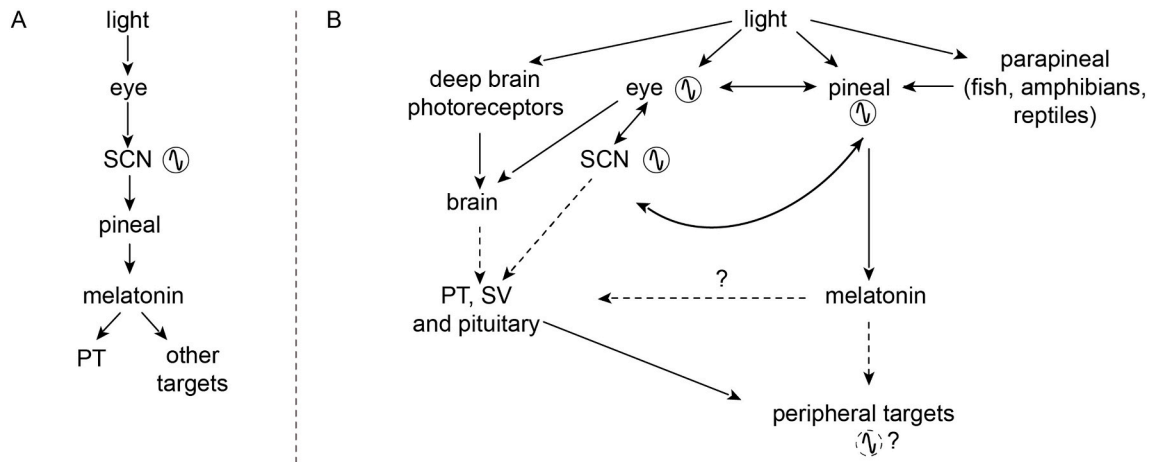


Fig. 2. Light perception and transduction in (A) mammals and (B) non-mammalian vertebrates. The sinusoidal curve in a circle shows that light exposure entrains circadian molecular cycles in the SCN. SCN: suprachiasmatic nucleus, PT: pars tuberalis, SV: saccus vasculosus.

over the course of their evolutionary history though the pineal gland of birds is itself photosensitive (Benoit et al., 2016). Non-mammalian vertebrates also possess deep brain photoreceptors to detect light (Bertolucci et al., 2017; Li et al., 2004; Silver et al., 1988). Deep brain photoreceptors have been located in numerous brain regions in birds, fishes, and reptiles (reviewed in: Bertolucci et al., 2017; Hang et al., 2016; Kuenzel et al., 2015; Pérez et al., 2019), however the link between light detection and translation into a seasonal photoperiodic signal is still being established. For example, fish lack an anatomically distinct PT and instead a region called the saccus vasculosus may be the site of opsin-mediated photodetection and transduction into a seasonal photoperiodic cue (Nakane et al., 2013), however melatonin may not bind in the saccus vasculosus (Chi et al., 2019). In taxa studied to date, what is clear is that while non-mammalian vertebrates generate circadian rhythms in circulating levels of plasma melatonin, melatonin is not always required for the translation of light cues into a reading of seasonal photoperiod, suggesting functional redundancy in at least some groups within these taxa (Dawson et al., 2001; Mayer et al., 1997; Migaud et al., 2010; Wilson, 1991). However, there are alternative

pathways by which melatonin could influence seasonal timing: melatonin, for example, can also act directly on gonadotropin-inhibiting hormone (GnIH) neurons to induce GnIH expression (Ubuka et al., 2016a). GnIH can activate or inhibit reproduction in a taxon-specific manner (Ubuka et al., 2016b). Melatonin has also been shown to alter GnIH expression and control seasonal neuroplasticity of song control systems in Indian weaver birds (*Ploceus philippinus*) (Kumari et al., 2015). Thus, more work is needed to determine the role of melatonin in seasonal circuits of non-mammalian vertebrates.

Despite taxonomic differences in light reception and signal transduction, there appears to be downstream convergence in seasonal signaling via hypothalamic thyroid hormone (TH). In mammals and birds, long day conditions and increases in *EYA3* expression increase the expression of the beta subunit of thyroid stimulating hormone (TSH β) in the PT (Dardente et al., 2010; Nakao et al., 2008). It is notable that in birds elevated transcription of PT *EYA3* and activation may occur absent upstream melatonin signaling (Appenroth et al., 2020). TSH β combines with α GSU (α -glycoprotein subunit) to form thyroid stimulating hormone (TSH) which binds to ependymal tanycytes lining the third

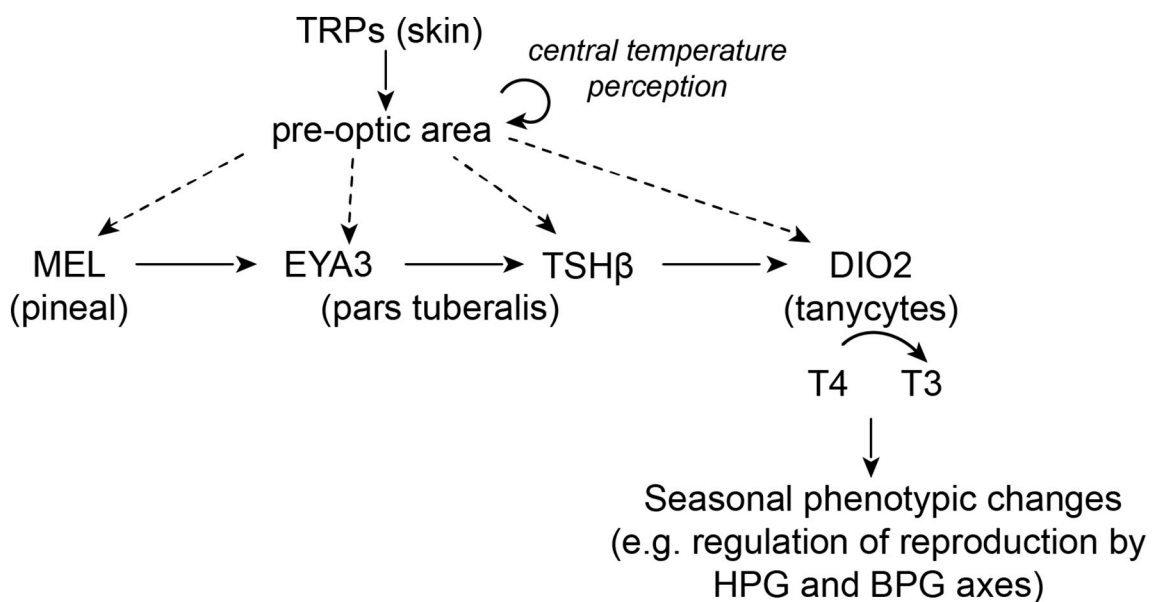


Fig. 3. Schematic showing potential routes by which temperature cues could be integrated directly into seasonal timekeeping mechanisms. Solid lines represent established pathways for mammals (see text for details) and dashed lines represent hypothesized pathways by which temperature could exert an effect on seasonal phenotypes. TRPs: transient receptor potential ion channels, MEL: melatonin, HPG: hypothalamic-pituitary-gonadal axis, BPG: brain-pituitary-gonadal axis.

ventricle causing a reciprocal switch in the expression of type 2 and type 3 deiodinases (DIO2 and DIO3) (Fig. 3; reviewed in: Wood and Loudon, 2014). The increase in DIO2 converts the prohormone thyroxine (T4) to triiodothyronine (T3), the most bioactive form of thyroid hormone (TH), while the decrease in DIO3 lessens the rate of degradation of T3 into inactive metabolites (Hanon et al., 2008; Nakao et al., 2008; Wood et al., 2015; Yasuo et al., 2005). Although amphibians and most reptiles, excluding snakes, possess a distinct PT (Fitzgerald, 1979), research examining PT TSH signaling in these taxa is limited (West and Wood, 2018). One recent study has investigated TSH signaling in the pituitary infundibulum in snakes (Winters et al., 2022).

Fish lineages have multiple paralogs for key timekeeping genes along the TH signaling pathway, which may have distinct functions (Lorgen et al., 2015; Maugars et al., 2014). However, TH signaling pathways are likely important for fish seasonality. Coronet cells in the saccus vasculosus may have important endocrine functions, including photoperiod-dependent DIO2b signaling, which was seen in masu salmon (*Oncorhynchus masou masou*; Nakane et al., 2013). However this was not observed in Atlantic salmon (*Salmo salar*) where instead, TSH expression in the pituitary may be driving changes in brain TH signaling (Irachi et al., 2021). Seasonal expression of the DIO2b gene in fishes has also been described in additional brain regions including the pituitary, thalamus, hypothalamus, and optic tectum (Irachi et al., 2021; Lorgen et al., 2015). Fish studies examining seasonal changes in TSH β gene expression across brain regions, and their potential to act as a photoperiod-responsive upstream regulator of seasonal DIO2b, have yielded mixed results (Doyle et al., 2021; Fleming et al., 2019; Irachi et al., 2021; Larsen et al., 2011; Lorgen et al., 2015; Nakane et al., 2013; O'Brien et al., 2012). One study suggests that EYA3 may be important for seasonal regulation in the absence of changes in TH signaling downstream (Doyle et al., 2021).

Seasonal changes in TH signaling regulate diverse downstream neuroendocrine processes associated with specific seasonal phenotypic changes (Fig. 3). Changes in hypothalamic T3 availability affect the activity of the hypothalamic-pituitary-gonadal (HPG) axis in birds (Nakao et al., 2008; Yamamura et al., 2006; Yoshimura et al., 2003 but see Bentley et al., 2013) and mammals (Freeman et al., 2007; Prendergast et al., 2002; Watanabe et al., 2004), just as brain T3 affects the brain-pituitary-gonadal axis (BPG) in fish (Ogawa et al., 2013; Parhar et al., 2000). Though the precise mechanism linking elevated T3 to activation of the reproductive axis has not been established, two populations of hypothalamic neurons which produce the RF-amides kisspeptin (KISS) and gonadotropin-inhibiting hormone (GnIH; or the mammalian ortholog RFRP-3), are likely relays between T3 and gonadotropin releasing hormone (GnRH) (Dardente et al., 2019). Many non-placental vertebrates possess two forms of KISS (KISS-1 and KISS-2), whereas birds lack KISS altogether (Felip et al., 2009). Changes in T3 are also correlated with structural changes in tanycyte-neuronal interactions at the median eminence, which may affect seasonal reproduction and other processes (Yamamura et al., 2006). Seasonal changes in T3/T4 have also been implicated in seasonal metabolic remodeling (Barrett et al., 2007; Murphy et al., 2012), avian migration (Sharma et al., 2018) and fish smoltification (Larsen et al., 2011). Thus, hypothalamic/brain TH is considered a key player in the regulation of vertebrate seasonality, with strong evidence coming from birds, mammals, and teleost fish, although other taxa remain under-investigated.

3. Flexibility in seasonal systems - the importance of temperature

While photoperiod and endogenous circannual rhythms interact to create a timekeeping system that is quite stable year to year, animals also need flexibility to cope with interannual variation in conditions. Interest in understanding exactly how cues like temperature, food, and precipitation are perceived and integrated into physiological systems has increased as concern over the potential impacts of global climate

change have magnified.

It is generally assumed that animals with greater ability to adjust timing of seasonal phenotypic changes in response to temperature cues will fare better in a rapidly changing world. Ecological studies in diverse systems have documented the extent of phenological (seasonal) shifts and evaluated how closely they track local and global changes in temperature. In general, taxa vary in the degree to which they shift phenology (e.g. Parmesan, 2007; Poloczanska et al., 2016; Thackeray et al., 2016, 2010). While ecological factors may explain some of this variation, for example heterogeneity in exposure to climatic shifts, it is likely that taxonomic differences in temperature sensitivity and signal transduction are also important. This has inspired physiologists to identify the mechanisms that generate variation in temperature sensitivity.

Temperature may affect seasonal timing either directly, through temperature perception and transduction by the nervous system, or indirectly, through effects on metabolism and body condition. A third possibility is that temperature may influence seasonal timing via its impact on food or other resources that an organism requires (Fig. 1). Since in these cases it is the resources that animals are responding to, we will not review this literature, however given that temperature and resource availability are often correlated in field studies it remains critical for the field to be cautious and avoid attributing causal mechanisms to correlational patterns.

In some cases, there is strong evidence that temperature acting as a metabolic driver has the potential to impact seasonal timing. For example, anadromous fish species that must achieve a specific threshold body condition to undergo seaward migration are a prime case where temperature impacts on metabolic state could regulate seasonality (Dodson et al., 2013). Additionally, marine turtles have been found to seek out warmer microhabitats in order to speed up egg maturation allowing females to nest earlier (Fossette et al., 2012). However whether temperature-induced changes to metabolic or nutritional state can lead to changes in seasonality are less clear in other taxa (e.g. birds: Caro and Visser, 2009; Valle et al., 2020). Ultimately, studies that permit fine discrimination between direct responses to temperature cues versus temperature-induced metabolic effects are rare and for that reason this difference will not be a central focus of the review. In the sections that follow, we will highlight recent advances in our understanding of central and peripheral temperature perception. When temperature and temperature-mediated metabolic cues are integrated by the central nervous system they could have systemic effects on timing by affecting seasonal retrograde TH signaling pathways in the PT and/or hypothalamus, or act on specific downstream processes, for example the HPG/BPG axis. As we will see below, this is another area where we often lack sufficient data to distinguish between these two regulatory possibilities.

3.1. Peripheral temperature perception

Work in laboratory rodents has established that environmental temperature is perceived cutaneously by neurons expressing ion channels from the transient receptor potential (TRP) family. Nilius and Owsianik (2011) identify 7 total different TRP families based on protein homology [TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin) and TRPN (NOMPC-like)] and different channels within this family respond to temperatures within specific ranges. For example, TRPM-8 is important for sensing low temperatures (<27 °C) (Bautista et al., 2007; Matos-Cruz et al., 2017) while TRPV-1 is thought to detect noxious high temperatures (>42 °C) (Davis et al., 2000; Laursen et al., 2016). TRPV-3 (Moqrich et al., 2005) and TRPV-4 (Lee et al., 2005) become activated at temperatures of 32–39 °C and 25–34 °C respectively, although TRPV-3 may also enhance responses to noxious high temperatures (Moqrich et al., 2005).

There are important taxonomic differences in peripheral temperature perception at both broad and narrow taxonomic scales (reviewed

in: Gracheva and Bagriantsev, 2015). While heat receptors (TRPV-1 and TRPA-1) have been identified in fish, frogs, snakes, birds, and mammals, surveys of fish genomes to date have failed to identify the gene encoding for TRPM-8 (Gracheva and Bagriantsev, 2015), so it is unclear what the primary mechanisms for cold temperature perception is within this group. However, behavioral data offer strong support that fish have the capacity to respond to low temperatures (e.g. Sakakura and Tsukamoto, 1997). Across groups, the relative importance of each TRP channel differs: for example, the importance of TRPA-1 for peripheral temperature perception is debated in mammals (e.g. Chen et al., 2013; Moparathi et al., 2016) but it works in concert with TRPV-1 to detect noxious high temperatures in lizards, snakes, and birds (Saito et al., 2012). Thresholds for TRP activation also differ across taxa. TRPV-1 appears to be involved in the perception of extremely high temperatures across taxa, but the threshold for activation of TRPV-1 appears to vary widely across lineages (Gracheva and Bagriantsev, 2015; Laursen et al., 2016; Saito et al., 2012). Similarly, activation temperatures of TRPM-8 also differs among taxa (Matos-Cruz et al., 2017; Myers et al., 2009). Likewise, the TRPV-3 channel is activated by moderate heat in humans and rodents ($\sim 37^\circ\text{C}$; Peier et al., 2002; Xu et al., 2002), but acts as a cold receptor in amphibians ($\sim 16^\circ\text{C}$; Saito et al., 2011). Critically, even within groups, modifications to the structure of TRPV-1 could be a mechanism by which lineage-specific sensitivity to high temperatures has evolved. Indeed, preliminary evidence in *Xenopus* species suggests that differences in activation of these channels parallels phylogenetic differences in thermal niches (Saito et al., 2019, 2016). Finally, while the importance of TRP channels for temperature sensing is clear, the recent discovery of a cold-sensing glutamate receptor (GluK2) found in mammals and fish (Gong et al., 2019) suggests that our current understanding of the mechanisms involved in temperature sensing in vertebrates is incomplete.

3.2. Core body temperature perception

Cutaneous TRP channels are not the only mechanism by which temperature can be perceived. Temperature is also perceived in the body core, for example in the brain (typically the pre-optic area or POA), spinal cord, and abdomen (Morrison and Nakamura, 2011). Although it is proposed that core temperature perception serves to enhance responses initiated by cutaneous receptors in particularly extreme thermal environments (Morrison and Nakamura, 2011), we briefly review a few works that have attempted to connect core temperature perception and seasonal transitions.

Two recent studies suggest that fish may perceive and integrate core body temperatures directly in brain regions implicated in seasonal pathways. TRPV-1 and TRPV-4 are present in photo-detecting cells in the pineal gland of rainbow trout (*Oncorhynchus mykiss*) (Nisembaum et al., 2015), leading authors to propose that the pineal could be a site for integration of daylength and temperature cues. Increased temperatures also led to increased TRPV-4 expression in the brain and pituitary of chum salmon (*Oncorhynchus keta*) (Lee et al., 2021). It is interesting to speculate that, as ectotherms, fish might utilize central temperature receptors in circuits regulating seasonality. More work is needed in this area.

While temperature perception in the body core may be more important for ectotherms than endotherms, a few studies in birds show that the expression of TRPs in the hypothalamus change in response to temperature treatments, typically in concert with changes in TRP expression in the skin. TRPV-4 expression increased in both the skin and in the hypothalamus of photo-stimulated black headed buntings (*Emberiza melanocephala*) exposed to elevated 35°C ambient temperatures (Sur et al., 2020). In contrast, red-headed buntings (*Emberiza bruniceps*) exposed to an ambient temperature of 38°C exhibited reduced TRPM-8 expression in the hypothalamus relative to controls held at 22°C , whereas TRPV-4 expression was unaltered (Trivedi et al., 2019). Additionally, expression of TRPM-8 in the skin and hypothalamus

appeared elevated under long day conditions in black-headed buntings (Sur et al., 2020). Although the observed changes in TRP expression in the hypothalamus are interesting, it is unclear if these are driven by core body temperature as hypothalamic temperatures were not measured in these studies and TRP channels are generally triggered by larger temperature fluctuations than would be expected in the core of an endothermic bird or mammal. However, it has recently been shown that CDC-like kinases are highly responsive to physiological temperature changes and can globally alter splicing and gene expression (Haltenhof et al., 2020). These CDC-like kinases have been proposed to connect 1 to 2°C circadian changes in body temperature with posttranscriptional control of gene expression (Haltenhof et al., 2020; Preußner and Heyd, 2018), but whether they play any role in seasonal physiology remains unknown.

4. Seasonal neuroendocrine remodeling in response to temperature cues

Once ambient temperatures are perceived, the pre-optic area likely plays an important role in receiving temperature information, processing it, and integrating it into downstream pathways (reviewed in: Caro et al., 2013). Yet, exactly which seasonal neuroendocrine pathways receive this information is hard to pinpoint. Similarly, it is not clear where (or how) temperature-mediated metabolic cues may interface with seasonal pathways, although there are numerous possibilities (e.g. leptin, ghrelin, hypothalamic-pituitary-adrenal axis). Studies investigating the influence of temperature on retrograde TH signaling are recent and rare (e.g. Ikegami et al., 2015; Renthlei et al., 2021; Trivedi et al., 2019; van Rosmalen et al., 2021). Far more common are studies describing temperature regulation of specific seasonal processes such as reproduction (HPG and BPG axes) (e.g. Kriegsfeld et al., 2000a; Lutterschmidt, 2012; Shahjahan et al., 2017), smoltification in fish (e.g. McCormick et al., 2000), and migration in birds (Sur et al., 2020). Due to taxonomic differences in seasonal neuroendocrine regulation, we review integration of temperature cues separately by taxonomic group.

4.1. Birds

People have been documenting the arrival timing of migratory birds for decades and numerous studies have examined the effects of climate change on timing of migration or egg laying (e.g. Charmantier and Gienapp, 2014; Crick et al., 1997; Usui et al., 2017). The role of seasonal retrograde TH signaling in timing these events has only recently been elucidated (Bentley et al., 2013; Majumdar et al., 2014; Mishra et al., 2017; Nakao et al., 2008; Sharma et al., 2018; Yamamura et al., 2006; Yasuo et al., 2005; Yoshimura et al., 2003), yet several studies have examined temperature impacts on this pathway. These studies suggest both high and low temperatures can impact retrograde TH signaling and downstream seasonal phenotypic changes. For example, Eurasian tree sparrows (*Passer montanus*) on long days (14L:10D) exposed to 30 days of high ambient temperatures (30°C) had lower expression of TSH β and DIO2 and increases in DIO3 and GnIH in the PT/hypothalamus relative to 20°C controls (Renthlei et al., 2021). The warming-induced decreases in TSH β led to increased GnIH and decreased GnRH expression (Renthlei et al., 2021). In contrast, photo-stimulated red-headed buntings held for 2.5 weeks at 38°C had increased expression of TSH β and DIO2 in hypothalamus/PT punches, but temperature had no effect on EYA3 or DIO3 expression (Trivedi et al., 2019). The observed temperature-induced increases in TSH β and DIO2 led to an increase in GnRH (and not GnIH) in red-headed buntings, facilitating gonadal growth (Trivedi et al., 2019). In Japanese quail (*Coturnix japonica*), reproductively competent birds subjected to short days at either 23°C or 9°C showed similar profiles of TSH β expression in the pars tuberalis and DIO2 and DIO3 in the third ventricle during testicular regression, even though the testes of quail at 9°C regressed faster (Ikegami et al., 2015). These studies offer evidence for an effect of temperature on seasonal

retrograde TH signaling, although they also pinpoint important species and life history stage differences in the temperatures that elicit effects. This is consistent with earlier work demonstrating that the impacts of temperature on reproductive physiology is dependent on sex and lineage (Maney et al., 1999; Silverin et al., 2008; Wingfield et al., 2003, 1997, 1996).

It is also possible that temperature information could be integrated downstream of the hypothalamus in birds, although this has not been well explored. Temperature manipulation studies in Great tits (*Parus major*) have shown that the hypothalamus, liver, and ovary all show changes in gene expression in response to temperature manipulations, although strong statements about causal relations between (or independence of) expression changes across tissues are difficult (Laine et al., 2019). At the very least, the potential for regulation of reproductive timing at the level of the gonad has been shown in food and other stressor manipulation studies conducted in zebra finches (*Taeniopygia guttata*) (Ernst et al., 2016; Lynn et al., 2015), although we are unaware of additional temperature focused research in avian taxa at this time.

4.2. Mammals

Although there has been limited research investigating the impact of temperature on the neuroendocrine regulation of the timing of seasonal transitions in mammals, several studies on voles reveal the retrograde TH signaling pathway and reproductive axis are temperature sensitive. One recent study in juvenile common voles (*Microtus arvalis*) found no effect of ambient temperature (10 °C versus 21 °C) on PT *TSHβ*, but expression of *DIO2* along the third ventricle was reduced in animals held at 10 °C (van Rosmalen et al., 2021). This suggests the melatonin-sensitive PT may be relatively insensitive to ambient temperature conditions. Interestingly, a follow-up study revealed that, relative to common voles, temperature had a larger effect on TSH receptor (TSHr) and *DIO2* in tundra voles (*Microtus oeconomus*) exposed to spring photoperiods, yet while the mass of reproductive organs of common voles was highly sensitive to temperature, the mass of the reproductive organs of tundra voles was not (van Rosmalen, 2021). Thus, the expression of key components of the TH signaling pathway sometimes does not appear to correspond with downstream effects on the reproductive axis. This parallels findings in one study in arctic ground squirrels (*Urocitellus parryi*) that used a pronounced warming of ambient temperature (30 °C versus 2 °C controls) midwinter to prevent hibernation and found no effect of temperature treatment on PT *TSHβ* expression or gonadal growth, but did find increased *DIO2* expression along the third ventricle (Chmura et al., 2022).

A few additional studies demonstrate effects of temperature on reproductive signaling along the HPG axis. Prairie voles (*Microtus ochrogaster*) held on short days and low temperatures (8 °C) were more likely to undergo gonadal regression than animals on short days and mild ambient temperatures (20 °C). These 8 °C voles also had lower *GnRH* positive cell counts in the POA than 20 °C voles (Kriegsfeld et al., 2000a) and showed suppression of *proGnRH* suggesting a decrease in *GnRH* synthesis (Kriegsfeld et al., 2000b). In small mammals that become reproductively competent early in their first year of life, there is also potential for temperature to affect growth and reproductive development. Juvenile Brandt's voles (*Lasiopodomys brandtii*) exposed to cold ambient temperatures (4 °C) had lower *KISS-1* expression on day 26 post-birth compared to animals in warm (23 °C) temperature conditions (Zhang et al., 2015); however, the authors propose that this may have been mediated by plasma leptin as an indicator of energetic status, rather than a direct effect of temperature on central signaling systems, as cold exposed animals had mobilized their adipose stores to meet higher thermogenic demands (Zhang et al., 2015). However, van Rosmalen (2021) found that the critical post-weaning photoperiod needed to activate *TSHβ* expression in the PT of tundra voles was temperature dependent, although this had no significant effect on testes mass or plasma testosterone concentrations. Altogether, these studies reveal that

temperature-dependent modulation of the photoperiodic response is common in voles although at present it is unclear whether temperature effects predominantly occur through changes in PT *TSHβ* expression, or by altering the expression of downstream targets such as *DIO2*, *KISS*, or *RFRP-3*. *RFRP-3* may be a particularly interesting target to investigate because one study suggests it is regulated by temperature, independent of nutritional status in laboratory mice (Jaroslawska et al., 2015). Notably effects vary across vole species. Understanding the factors that drive intra and inter-specific temperature sensitivity requires further research, though latitude is likely to play a pivotal role (van Rosmalen, 2021). Finally, a combination of in vivo and in vitro studies suggest the potential for further regulation of reproduction at the level of the gonads (e.g. Anjum et al., 2014; Singh et al., 2011), however to date we are unaware of studies investigating the responsiveness of gonadal "neuropeptides" to temperature in mammals.

4.3. Fish

Although many fish studies have examined temperature effects on life history transitions, few have determined whether these temperature effects occur through sensitivity of the central seasonal TH signaling pathway. This is unsurprising given that researchers are just beginning to understand central time-keeping pathways in fish and, as ectotherms, ambient temperature effects may manifest through concomitant changes in body temperature. Across the literature on temperature and seasonality, teleosts are especially well-represented with work at all levels of the BPG axis (reviewed below). In less studied taxa, like elasmobranchs, there are some works in the field and lab flagging temperature effects on circulating hormones (e.g. Elisio et al., 2019; Mull et al., 2008), but little work has occurred at higher levels of regulation. Thus, most of the research below comes from teleost lineages.

Despite the absence of studies examining effects of ambient temperature on central TH signaling, there are works examining temperature effects on melatonin even though it seems like melatonin plays a modifying role, rather than a driving role, in regulating seasonal transitions (reviewed in: Migaud et al., 2010). TRP channels (*TRPV-1*, *TRPV-4*) are present in the pineal of fish and in-vitro cell culture studies conducted in tissue from rainbow trout suggest that changes in TRP activation can influence circadian cycles of melatonin (Nisembaum et al., 2015). Other studies in both teleosts and lamprey show that changes in temperature may affect the amplitude of circadian cycles of melatonin production in the pineal (Max and Menaker, 1992) and plasma melatonin (Max and Menaker, 1992; Nisembaum et al., 2020; Porter et al., 2001; Samejima et al., 2000).

A large body of literature focused on the timing of spawning investigates the effects of temperature on the BPG axis (reviewed in: Miranda et al., 2013). The hypophyseal form of *GnRH* in fishes is lineage-dependent (Di Yorio et al., 2019) and most temperature studies focus on *GnRH-1/GnRH-3* and gonadotrophins. A few studies investigate the effects of temperature on *KISS* and *GnIH*, although whether elevated *KISS* is essential for reproduction (Tang et al., 2015) and whether *GnIH* has a positive or negative effect on reproductive maturation in fishes may be lineage-specific (Di Yorio et al., 2019) and is a matter of ongoing investigation. In contrast to most avian and mammalian studies, it is more common for fish studies to have at least three temperature treatments that are "low", "medium", and "high" relative to some aspect of the species' ecology. Collectively, research suggests that the BPG axis is activated at mid-range temperatures and suppressed at both temperature extremes, although it is important to note that the factors determining experimental temperature selection likely differed widely across studies which can make cross-study comparisons difficult. Low and high temperature extremes suppress expression of *KISS-2* as well as *KISS-2* receptor expression during the spawning season in the grass puffer (*Takifugu niphobles*) (Shahjahan et al., 2017). Similarly, both low (15 °C) and high (35 °C) temperature extremes decrease *KISS-2* mRNA in multiple brain regions of male zebrafish (*Danio rerio*). In the zebrafish,

GnRH-3 neurons have receptors for *KISS-2* (Ogawa et al., 2020), and accordingly temperature extremes (15 °C and 35 °C versus 27 °C) also decrease *GnRH-3* (Shahjahan et al., 2013). Mid-range temperatures (27 °C) enhance expression of brain *GnRH-3* relative to lower temperature controls (23 °C) in tropical male and female blue gourami (*Trichogaster trichopterus*: David and Degani, 2011; Levy et al., 2011). Female red-seabream (*Pagrus Chrysophrys major*) in elevated water temperatures of 24 °C (compared to 17 °C controls) have lower levels of brain *GnRH-1* (Okuzawa and Gen, 2013). *GnRH-1* decreases at low and high temperature treatments in the grass puffer, but has no significant effect on *GnRH-2* or *GnRH-3* (Shahjahan et al., 2017). Few studies investigate *GnIH*, however Rahman et al. (2019) show that both low and high temperature treatments decrease expression of *GnIH* and *GnIH-R* in male grass puffers.

Increases or decreases in GnRH are accompanied by corresponding changes in pituitary *GnRH-R*, *LHβ* and *FSHβ* (David and Degani, 2011; Levy et al., 2011; Okuzawa and Gen, 2013). Several additional studies that focus only on the pituitary also show that higher than normal temperatures decrease gonadotrophins (Soria et al., 2008), though effects are photoperiod dependent (stickleback: Hellqvist et al., 2004; salmon: Taranger et al., 2015). There is some evidence that mid-range temperatures also lead to the highest expression of pituitary prolactin (male blue gourami: David and Degani, 2011) and growth hormone (female blue gourami: Levy et al., 2011; male grass puffers: Rahman et al., 2019). Combined, the consistent suppressive effects of high temperature have led researchers to propose that this mechanism may be particularly important for reproductive termination. These studies provide convincing evidence that temperature affects seasonal neuroendocrine regulation of reproduction at least at the level of GnRH and potentially at higher levels via KISS and GnIH. At present it is unclear whether temperature acts directly on the BPG axis, via TH signaling upstream, indirectly via metabolic signaling, or some combination of the three.

While there is strong evidence for temperature regulation at the level of the brain in fish, there is also evidence that temperature has direct effects at the level of the gonad or other locations within the periphery. Interestingly, *LHβ* and *FSHβ* are also expressed in the pejerrey (*Odonesthes bonariensis*) gonad and their expression is reduced at elevated temperatures (Elisio et al., 2012) as is expression of *LHβ* receptor. A study in salmon also suggests that photoperiod and temperature may interact in complex ways to influence the expression of *LHβ* and *FSHβ* receptors in the gonad (Taranger et al., 2015). Another recent review highlights that TH signaling in the periphery may be particularly important in fish thermal signaling (Little et al., 2020). This is an important reminder that, especially in ectotherms, peripheral regulation may also play an important role in seasonal phenotypic transitions.

4.4. Reptiles and amphibians

Although numerous studies report the phenology of reptiles and amphibians is being altered by climate change (e.g. Edge et al., 2017; Ljungström et al., 2015; Prodon et al., 2017) the regulation of seasonality is much less understood in these taxa. Recently there are some studies that offer avenues for understanding how temperature cues may be integrated into seasonal pathways upstream. In several reptiles and amphibians, the amplitude of daily melatonin rhythms in the pineal, parietal eye, or in circulating plasma may be amplified by high temperatures or nearly abolished by low temperatures (reviewed in: Mayer et al., 1997) and work in the green anole (*Anolis carolinensis*) suggests that temperature can entrain circadian cycles of melatonin under constant photoperiods (Firth et al., 1999). The depressive effects of low temperature treatment on the amplitude of melatonin rhythms may persist for 2 weeks or more after animals are returned to higher temperatures (Lutterschmidt and Mason, 2009). At least one study proposes that low body temperatures may entrain endogenous circannual rhythms in red sided garter snakes (*Thamnophis sirtalis parietalis*),

although the mechanisms through which this might occur have not been identified (Lutterschmidt et al., 2006).

The red sided garter snake is a common study system for reptilian studies of seasonality and two very recent studies offer some insight into seasonal thyroid hormone signaling pathways and the GnRH system. One study suggests that 6 weeks of low (4 °C) temperature dormancy decreases levels of TSH in the infundibulum of the pituitary, however 6 weeks of exposure to 12 °C had no effect on TSH levels (Winters et al., 2022). This study also finds no change in DIO3 or GnRH staining in either the 4 °C or 12 °C group after 6 weeks of treatment, relative to the pre-treatment group (Winters et al., 2022). However, another study finds that 8 weeks of exposure to low (4 °C) temperatures increases GnRH staining compared to pre-treatment baseline (Lutterschmidt et al., 2022). This study, however, found no significant effect of 6 weeks of exposure to hibernation temperatures (10 °C vs 4 °C) on GnRH staining (Lutterschmidt et al., 2022). Many studies in this species have focused on the effects of temperature on courtship behavior specifically, likely because the red garter snake exhibits a temporally dissociated reproductive system in which maximal androgen levels are not coincident with mating and courtship behavior. Cold exposure (4 °C) followed by warmer (28 °C) temperatures is important for activating courtship (Krohmer and Crews, 1989) and warm winter hibernacula temperatures delay onset of courtship (Lutterschmidt and Mason, 2009). Courtship is abolished with both lesion to the anterior-hypothalamus POA (Krohmer and Crews, 1987) and pinealectomy (Mendonça et al., 1996; Nelson et al., 1987) and can be altered by treatments that augment or block melatonin action (Lutterschmidt and Mason, 2009; Mendonça et al., 1996). The hypothalamic-pituitary-adrenal (HPA) axis has also been proposed as a potential mediator by which temperature could affect life history timing, although data are equivocal in red garter snakes (reviewed in: Lutterschmidt, 2012; Lutterschmidt et al., 2022) and other taxa (Brischoux et al., 2016; Holden et al., 2021). This species is a strong candidate for further work on the mechanisms by which temperature is integrated into seasonality.

5. Temperature in the context of other environmental cues

While this review focused on the influence of temperature in modulating neuroendocrine seasonal pathways typically activated by photoperiodic changes, it is important to recognize that a variety of other supplementary cues are used to modulate seasonal life-history transitions, including reproductive timing (reviewed in: Ball and Ketterson, 2008; Chmura et al., 2020; Davies and Deviche, 2014; Migaud et al., 2010; Tolla and Stevenson, 2020). For example, the availability of food, water, and conspecifics provides a myriad of olfactory, auditory, visual, and tactile cues that affect seasonal timing (e.g. Cheng, 1992; Hau et al., 2000; Hegstrom and Breedlove, 1999; Nelson et al., 1983; Stevenson et al., 2008; Voigt et al., 2007; Wingfield et al., 2012). However, the degree to which these cues affect TH signaling versus downstream targets along the reproductive axis remains unclear. Studies in birds suggest that social cues may be mediated by hypothalamic *DIO2* and *DIO3* (Perfito et al., 2015 but see Ernst and Bentley, 2016) and a study in fish suggests that nutritional cues may influence levels of *EYA3* (Doyle et al., 2021). Food restriction has also been shown to alter *KISS* expression in the arcuate nucleus of Siberian hamsters (*Phodopus sungorus*; Paul et al., 2009) whereas in house finches (*Haemorrhous mexicanus*), which like all birds lack a functional *KISS* system, food restriction appeared to inhibit GnRH secretion (Valle et al., 2015). While the perception and transduction of each cue type will exhibit important differences, collectively this research provides evidence that seasonal TH signaling may be modified by cues other than photoperiod and temperature. Importantly, the influence of temperature on seasonal timing may be dependent upon physiological state and/or the presence of other permissive cues. For example, work in the ground squirrel system suggests that animals may be sensitive to temperature cues at specific times of the year (Chmura et al., 2022; Barnes and York, 1990).

Similarly work in birds (Wingfield et al., 1997) and fish (Levy et al., 2011) suggests that social stimuli may be necessary for temperature to have an effect on reproductive activation in some taxa. This context dependence may be critical for understanding cases when temperature manipulations yield surprising results and is strong evidence that temperature is integrated into complex seasonal programs.

6. Summary thoughts

This body of work clearly illustrates that the effects of temperature are non-linear and lineage dependent. While this is not a new idea, far too often temperature is described as a unidirectional cue with consistent and predictable results depending upon whether treatments represent a temperature increase or decrease. This review shows that many temperature effects follow an inverted-u shaped relationship or an even more complex pattern depending upon photoperiodic or developmental history. While this points to the importance of experiments using multiple temperature treatments, this will not be possible in all cases. As a next best practice, we propose that authors clearly describe the selection of temperature treatments used in experiments within the context of the natural history of the organism they are studying. Understanding where temperatures fall within typical temperatures of the species' native habitat and how the selected temperatures may or may not affect an organism's metabolic rate is critical context for interpreting results. This will also facilitate more robust cross-taxonomic syntheses of results.

The past decade has witnessed a growth in our understanding of how temperature cues are integrated into neuroendocrine pathways regulating seasonality. Recent advances in our understanding of TRP channel activation offers one possible avenue by which mechanisms could generate cross-taxonomic differences in temperature sensitivity. While there is robust evidence that temperature cues affect brain/hypothalamic regulation of reproduction, it is not clear whether this occurs directly at the level of KISS/GnIH/GnRH or through higher regulation by seasonal TH signaling. It is also too early to exclude the possibility of regulation at the level of the pituitary and gonad (Bentley et al., 2017; Tsutsui and Ubuka, 2018), in addition to or in isolation from higher levels of coordination. This will continue to be a productive area of work as we seek to improve our understanding of seasonal neuroendocrine plasticity.

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