Interplay between the endocrine and circadian systems in fishes

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Abstract

The circadian system is responsible for the temporal organisation of physiological functions which, in part, involves daily cycles of hormonal activity. In this review, we analyse the interplay between the circadian and endocrine systems in fishes. We first describe the current model of fish circadian system organisation and the basis of the molecular clockwork that enables different tissues to act as internal pacemakers. This system consists of a net of central and peripherally located oscillators and can be synchronised by the light–darkness and feeding–fasting cycles. We then focus on two central neuroendocrine transducers (melatonin and orexin) and three peripheral hormones (leptin, ghrelin and cortisol), which are involved in the synchronisation of the circadian system in mammals and/or energy status signalling. We review the role of each of these as overt rhythms (i.e. outputs of the circadian system) and, for the first time, as key internal temporal messengers that act as inputs for other endogenous oscillators. Based on acute changes in clock gene expression, we describe the currently accepted model of endogenous oscillator entrainment by the light–darkness cycle and propose a new model for non-photic (endocrine) entrainment, highlighting the importance of the bidirectional cross-talking between the endocrine and circadian systems in fishes. The flexibility of the fish circadian system combined with the absence of a master clock makes these vertebrates a very attractive model for studying communication among oscillators to drive functionally coordinated outputs.

Key Words
- circadian rhythms
- clock genes
- glucocorticoids
- ghrelin
- leptin
- melatonin
- orexin

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Introduction

The circadian system is responsible for the temporal organisation of several physiological, metabolic and behavioural activities, allowing the functioning of animals to be synchronised with predictable environmental changes (i.e. zeitgebers). The light–darkness (LD) cycle is the most important external zeitgeber for the vertebrate circadian system (Hastings *et al.* 2007, Albrecht 2012, Schibler *et al.* 2015), but food availability (Stephan 2002, Albrecht 2012, Patton & Mistlberger 2013) and temperature cycles (Buhr *et al.* 2010, Poletini *et al.* 2015, Schibler *et al.* 2015) are also important. These environmental factors are considered the 'inputs' of the circadian system, whereas the rhythms that are generated are called the 'outputs' or 'overt rhythms'. The circadian system is composed of a third element, the core clock, which is synchronised by the inputs and drives the outputs (Hastings *et al.* 2007, Albrecht 2012).

Daily locomotor activity and hormonal rhythms are two of the most studied outputs of the circadian system

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in vertebrates. The dependence of melatonin, pituitary hormone and glucocorticoid rhythms on the LD cycle has been studied for decades in mammals (Pevet & Challet 2011, Kalsbeek *et al.* 2012, Lin *et al.* 2015) and fishes (Falcón *et al.* 2007, 2010). However, it is known that many other hormones and neuropeptides (orexin, ghrelin, leptin and insulin) also exhibit daily oscillations (Patton & Mistlberger 2013, Tinoco *et al.* 2014, Challet 2015, Sánchez-Bretaño *et al.* 2015*a*, Schibler *et al.* 2015). Circadian clocks were once thought to be located only in the central nervous system. However, increasing evidence suggests that the circadian system is formed by a network of central and peripheral oscillators (including endocrine organs; Fig. 1) that are coordinated to drive the overt rhythms (Albrecht 2012, Schibler *et al.* 2015). In this more complex model of circadian organisation, hormones can not only directly control the circadian outputs but also participate in the synchronisation of other timekeepers, as shown in Fig. 1. This concept has been well-developed in mammals (Albrecht 2012, Patton & Mistlberger 2013, Challet 2015, Schibler *et al.* 2015), but remains practically unexplored in fishes.

In this review, we analyse the interplay between the circadian and endocrine systems in fishes. We first describe the current model of fish circadian system organisation. We then focus on two central messengers (melatonin and orexin) and three hormones (ghrelin, leptin and cortisol) due to their importance in synchronising the circadian system in mammals and/or their recognised roles as nutritional status signals (Pevet & Challet 2011, Albrecht 2012, Patton & Mistlberger 2013, Challet 2015, Schibler *et al.* 2015). We consider these hormones as outputs, reviewing what is known to date about the origin of their rhythmicity and also as putative inputs, whereby they act as temporal endogenous messengers that may entrain endogenous clocks.

We do not discuss other important endocrine rhythms in fishes, such as the reproductive hormones, because they have been reviewed previously (Bromage *et al.* 1990, Falcón *et al.* 2010, Migaud *et al.* 2010,

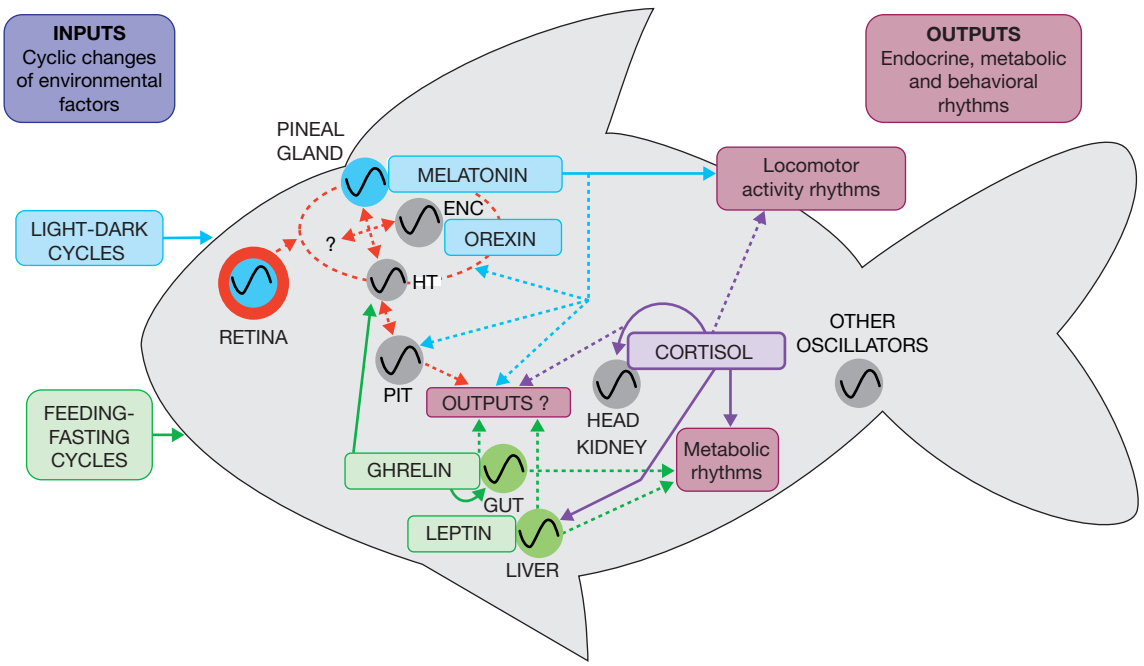

Figure 1
The fish circadian system: a net of circadian oscillators. The fish circadian system is composed of a net of oscillators that are widely distributed throughout the entire organism. These oscillators are entrained by external inputs, such as the light–darkness and feeding–fasting cycles and should be linked to generate outputs (such as locomotor activity and metabolic rhythms) in a coordinated manner. The retina, pineal gland and probably some deep brain photoreceptors are directly targeted by light, which then entrains the endogenous clocks in such structures (shown in blue). Other organs that contain circadian clocks, such as the gut and liver, are probably targeted by any feeding- or metabolic-related signals, which mainly synchronise these oscillators to the energetic status of the animal (shown in green). The head kidney is probably entrained by both external signals (shown in purple). These endocrine organs (pineal gland, pituitary gland, gut, liver and head kidney) release hormones (melatonin, pituitary hormones, ghrelin, leptin and cortisol) in a time-dependent pattern, which may provide a temporal message to specific-hormone receptors. This diagram only shows the most studied endocrine organs that are functionally related to the circadian system; however, other oscillators also probably exist. The continuous lines indicate the connections that are currently known to exist in fishes, whereas the dashed lines illustrate hypothetical connections that have not yet been reported. ENC, other encephalic nuclei; HT, hypothalamus; PIT, pituitary gland. For more information, see the text.

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Nakane *et al.* 2013, Nishiwaki-Ohkawa & Yoshimura 2016) and because the role of gonadal hormones as internal inputs in fishes has been less explored than other hormones to date (Nakane *et al.* 2013, Martins *et al.* 2015, Takeuchi *et al.* 2015).

Organisation of the fish circadian system

The fish circadian system consists of a variety of oscillators that are located in numerous (if not all) tissues (Fig. 1). The molecular functioning of this set of oscillators is similar in peripheral and central clocks and is based on translational–transcriptional feedback loops of a set of genes called clock genes, whose mRNA levels and proteins oscillate on a c. 24-h basis (reviewed in Reppert & Weaver 2002, Hastings *et al.* 2007, Albrecht 2012, Schibler *et al.* 2015). The functioning of the fish molecular clock has been deeply studied in zebrafish (*Danio rerio*; reviewed in Cahill 2002, Vatine *et al.* 2011, Idda *et al.* 2012 and schematised in the core of Fig. 2). The main loop is formed by the positive elements brain and muscle ARNT-like 1 (Bmal1) and circadian locomotor output cycles kaput (Clock), which form a heterodimer

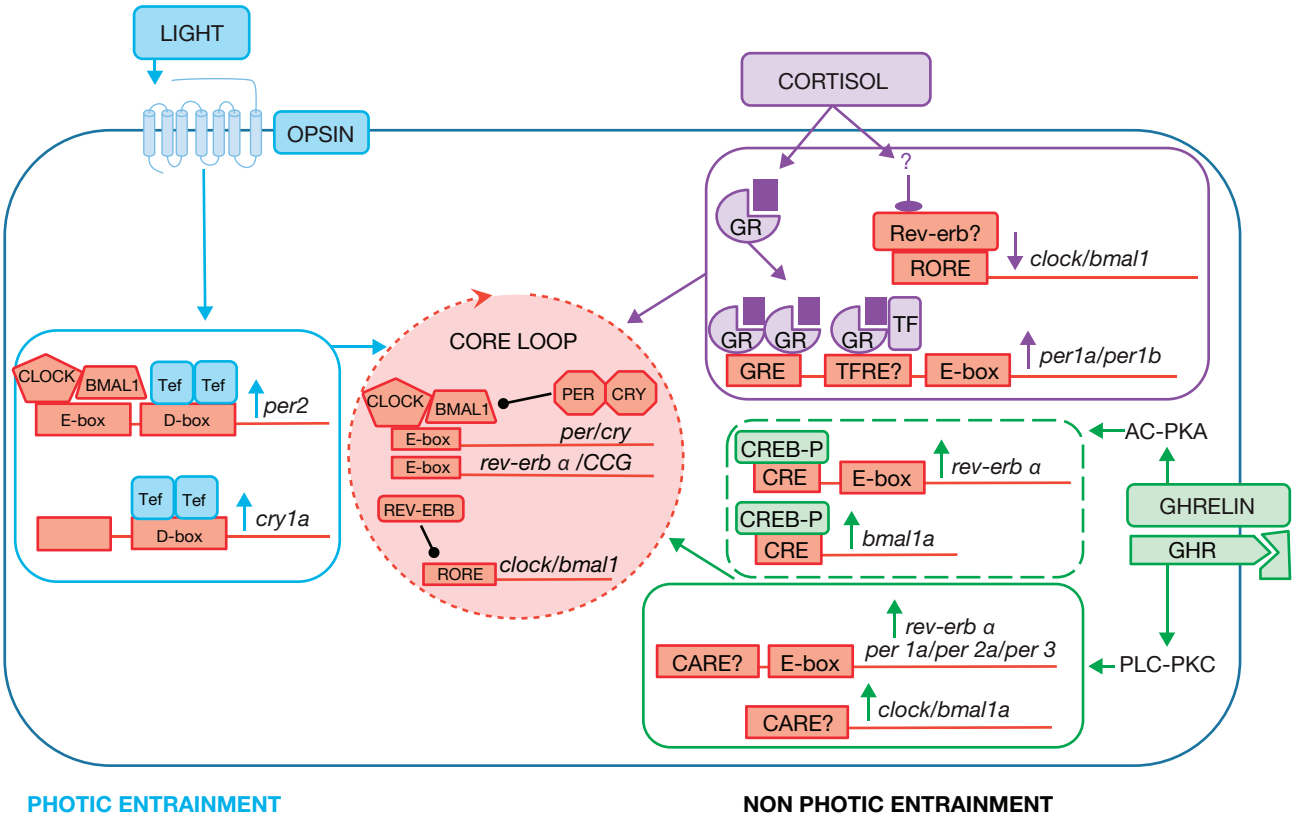

Figure 2
Hypothetical model of entrainment of circadian oscillators by light and hormonal inputs in fishes: putative mechanisms for the synchronisation of endogenous clocks. The molecular core of the endogenous oscillators is thought to be synchronised by exogenous (light) or endogenous (hormones) temporal messengers through the induction or repression of specific clock genes (for more information, see the text). Events that occur in the cytoplasm and nuclei (gene transcription) have not been separated to simplify the figure. In each box, only putative response elements that are involved in each response (light, cortisol or ghrelin) are shown. The molecular core of the clock, i.e. the feedback loops that sustain the 24-h clock gene oscillations, is represented as the central circle in red, with some of the main elements inside. This molecular mechanism can be entrained by the light–darkness cycle via the light-evoked induction of *cry1* and *per2*, which involves functional E- and D-boxes and the Tef transcription factor in zebrafish (Tamai *et al.* 2007, Vatine *et al.* 2009, 2011). We also propose alternative mechanisms whereby hormones such as cortisol and ghrelin can entrain the molecular clocks. Cortisol induces *per1a* and *per1b*, while repressing *bmal1a* and *clock* in the goldfish liver, with this repression possibly being mediated by the Rev-erb transcription factor (Sánchez-Bretaño 2016). Ghrelin induces a variety of clock genes in the goldfish liver (Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations), which is mainly mediated by the PLC-PKC pathway and, to a lesser extent, the AC-PKA pathway (Sánchez-Bretaño 2016). AC-PKA, adenylyl cyclase-protein kinase A; CARE, calcium response element; CCG, clock-controlled genes; CRE, CREB response element; CREB-P, CREB phosphorylated; GHR, ghrelin receptor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; PLC-PKC, phospholipase C-protein kinase C; RORE, RAR-related orphan receptor response element; Tef, thyrotroph embryonic factor; TF, transcription factor; TFRE, transcription factor response element.

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that acts as a transcription activator. This then binds to the E-box regulatory site in the promoter of the negative elements *period* (*per*) and *cryptochrome* (*cry*) to increase their expression. The dimer Per-Cry in turn inhibits the dimer Clock-Bmal (Reppert & Weaver 2002, Hastings *et al.* 2007, Vatine *et al.* 2011, Albrecht 2012). The Clock-Bmal heterodimer also induces the expression of genes known as clock-controlled genes, which are considered the outputs of the clock, by binding to the E-boxes in their promoters (Hastings *et al.* 2007, Vatine *et al.* 2011, Albrecht 2012). The main loop is stabilised by an auxiliary loop that includes the retinoic acid-related orphan receptor (Ror) and Rev-erb transcription factors, which act through a Ror response element (RORE) site to regulate *bmal1* transcription (Guillaumond *et al.* 2005, Albrecht 2012, Schibler *et al.* 2015). The functioning of this molecular mechanism is comparable in mammals and teleosts, with the involvement of homologous genes, although several copies of these genes have been reported in fishes (Vatine *et al.* 2011, Sánchez-Bretaño *et al.* 2015*b*).

Daily rhythms in clock genes (an essential property of endogenous clocks) have now been reported in a variety of tissues across several fish species, including the retina, pineal gland, brain, pituitary gland, liver, gut, gonads and head kidney (Park *et al.* 2007, Davie *et al.* 2009, Velarde *et al.* 2009, Huang *et al.* 2010, López-Olmeda *et al.* 2010, Cavallari *et al.* 2011, Patiño *et al.* 2011, Azpeleta *et al.* 2012, Martín-Robles *et al.* 2012, Nisembaum *et al.* 2012, Vera *et al.* 2013, Sánchez-Bretaño *et al.* 2015*b*,*c*, Costa *et al.* 2016; Fig. 1). In these tissues, the transcripts of the positive elements of the core clock (*bmal1* and *clock1*) peak during the photophase, whereas the transcripts of the negative elements (*per* and *cry*) increase at the end of the scotophase, as seen in the zebrafish model (Cahill 2002, Vatine *et al.* 2011). One exception to this pattern is the *per2* gene, which is directly induced by light in zebrafish (Vatine *et al.* 2009) and likely other teleosts (Velarde *et al.* 2009, Patiño *et al.* 2011, Nisembaum *et al.* 2012).

Cell-autonomous and self-sustaining clock gene rhythms have also been described in several cell lines cultured *in vitro* in zebrafish (Tamai *et al.* 2005) and cavefish (*Phreatichthys andruzzii*; Cavallari *et al.* 2011), but the existence of such widespread oscillations *in vivo* remains unknown. Recently, high day–night variations in *per1b* mRNA levels were observed in some diencephalic nuclei of goldfish (*Carassius auratus*), but no changes were observed in the telencephalon (Sánchez-Bretaño *et al.* 2015*c*). Similarly, some brain structures of zebrafish lack some of the core clock genes, even if such areas are photosensitive (Moore & Whitmore 2014). This suggests that not all brain regions are endogenous oscillators *in vivo*, highlighting the unresolved organisation of the circadian system in fishes.

It is evident that the organisation of the circadian system in fishes is less hierarchical than that in mammals, where the suprachiasmatic nuclei (SCNs) function as the master clock that entrains other central and peripheral oscillators (Albrecht 2012, Schibler *et al.* 2015). Such a master clock has not yet been clearly identified in fishes although the pineal gland plays a key role in its circadian system (Cahill 2002, Noche *et al.* 2011, Idda *et al.* 2012, Moore & Whitmore 2014, Sánchez-Bretaño *et al.* 2015*c*). Furthermore, the peripheral and central oscillators in fishes appear to be in phase or even more advanced in the peripheral tissues (Cermakian *et al.* 2000, Sánchez-Bretaño *et al.* 2015*c*), suggesting that these pacemakers may be independently synchronised. In some fish species, the locomotor activity patterns are also flexible and dependent on food availability (goldfish; Aranda *et al.* 2001, Feliciano *et al.* 2011) or metamorphosis (Senegalese sole, *Solea senegalensis*; Blanco-Vives *et al.* 2012). These characteristics of the fish circadian system make the investigation of endocrine signalling in the interplay among endogenous oscillators particularly interesting.

A model of the fish circadian system in which the oscillators are synchronised to different inputs is presented in Fig. 1. The LD cycles would entrain the light entrainable oscillators (LEOs) and the feeding–fasting cycles would entrain the food entrainable oscillators (FEOs). This classification is presented in a functional way, without involving anatomical structures, as the same tissue could be acting as a clock that is entrained by the LD cycles, the feeding–fasting cycles and perhaps other zeitgebers. The dependence of clock gene expression rhythms in the central and peripheral tissues on LD cycles has been demonstrated in a number of teleost species, including zebrafish (López-Olmeda *et al.* 2010), Atlantic salmon (*Salmo salar*; Huang *et al.* 2010), rainbow trout (*Oncorhynchus mykiss*; Patiño *et al.* 2011), goldfish (Nisembaum *et al.* 2012, Sánchez-Bretaño *et al.* 2015*b*), sea bream (*Sparus aurata*; Vera *et al.* 2013) or Nile tilapia (*Oreochromis niloticus*; Costa *et al.* 2016).

LD synchronisation is mediated by acute light-induced effects on clock gene expression in both mammals (Hastings *et al.* 2007) and fishes (Cahill 2002, Vatine *et al.* 2011). Light resets the clock, inducing *per2* and *cry1a* expression in photosensitive structures via the D-box and E-box elements (Fig. 2; for more information

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see Tamai *et al.* 2007, Vatine *et al.* 2009, 2011, Idda *et al.* 2012). *In vitro* studies in zebrafish showed that all cells lines are light responsive, including those derived from peripheral tissues such as the heart or liver (Tamai *et al.* 2005). Furthermore, *per2* and *cry1a* are induced by light in multiple brain regions both *in vivo* and *in vitro* (Moore & Whitmore 2014), and rhythmic bioluminescence in *per3-luciferase* transgenic animals is re-entrained to new LD cycles in explants of encephalic regions (Moore & Whitmore 2014). However, in the same study, the authors demonstrated that not all brain nuclei are photosensitive, raising the possibility that even in zebrafish, the different oscillators are not as independently entrained by light as initially thought (Moore & Whitmore 2014). A widespread photosensitive ability may not be a rule in other teleosts as, to date, the existence of photoreceptors has been demonstrated in the pineal gland, retina and deep brain photoreceptors (Menaker *et al.* 1997, Davies *et al.* 2015, Hang *et al.* 2016; blue in Fig. 1), but not in peripheral tissues, although their existence cannot be ruled out (Davies *et al.* 2015). Indeed, goldfish *per2* is not light induced in the liver *in vitro* (E Isorna, AL Alonso-Gómez & MJ Delgado, personal observations), suggesting that the liver of this teleost is not light sensitive, matching previous findings for the gut (Nisembaum *et al.* 2012). Thus, some unknown neural or endocrine messengers that connect photosensitive oscillators to other clocks are likely to exist in fishes. This hypothetical functional organization would enable the entrainment of these clocks to the LD cycle, as occurs in mammals (Hastings *et al.* 2007, Albrecht 2012, Schibler *et al.* 2015).

The fish circadian system is also very sensitive to feeding–fasting cycles (Fig. 1). The most robust evidence that rhythms in food availability synchronise the circadian system is the food anticipatory activity (FAA), i.e. the increase of locomotor activity in anticipation of feeding time (Stephan 2002). FAA has been demonstrated in numerous species of fishes, including goldfish (Aranda *et al.* 2001, Feliciano *et al.* 2011), zebrafish (López-Olmeda *et al.* 2010) or sea bream (Vera *et al.* 2013). Furthermore, it also occurs in the cavefish, which is a blind fish that somehow maintains a molecular clockwork over a c. 47-h period despite lacking entrainment by LD cycles (Cavallari *et al.* 2011). Thus, the functional organisation of the circadian system is highly adaptive, even when it is synchronised by less canonical zeitgebers such as feeding inputs.

A daily feeding schedule (under constant light) synchronises clock gene rhythms in the optic tectum, hypothalamus, liver and gut in goldfish, at both scheduled meal times, 10:00 and 22:00 (Feliciano *et al.* 2011, Nisembaum *et al.* 2012). However, when the LD cycle is present, the rhythms exhibit greater amplitudes, suggesting that both environmental signals work together in sustaining the molecular clockwork, at least in the liver (Nisembaum *et al.* 2012, Sánchez-Bretaño *et al.* 2015*b*). When both zeitgebers (LD and feeding–fasting cycles) are present, the brain oscillators appear to be driven by the LD cycle, whereas the clock gene oscillations in the liver are more dependent on feeding schedule (zebrafish: López-Olmeda *et al.* 2010; sea bream: Vera *et al.* 2013). In goldfish, a unique meal may shift the clock gene rhythms in the liver (Feliciano *et al.* 2011), which matches the findings in mammals, where a high dependence of clock liver entrainment on feeding cues has been reported (Stokkan *et al.* 2001, Kornmann *et al.* 2007, Patton & Mistlberger 2013). Exactly how feeding–fasting cycles entrain endogenous clocks remains unknown, but it is expected that hormones, metabolites or other energy sensor molecules that cycle with feeding status induce acute changes in clock gene expression that shift the clocks (Figs 1 and 2).

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a major player in controlling biological rhythms in vertebrates. It works as a neuroendocrine signal, transducing environmental information into the circadian system. Plasma melatonin levels show a characteristic nocturnal peak in all studied species, which is an exceptional feature compared with other rhythmic hormones, whose daily profiles are more variable through the 24-h cycle depending on different factors, such as the active/rest phase and the feeding time, among others. Melatonin nocturnal rhythmic profiles are classified into three types: a discrete peak in the late dark phase, a discrete peak in the mid-dark phase and an expanded peak throughout the dark phase (reviewed in Falcón *et al.* 2010). It is currently unclear whether these different profiles have functional implications.

Initially, this indole was described as a unique pineal gland metabolite. However, it has now been demonstrated that many other tissues also synthesise melatonin, such as the gastrointestinal tract (Vakkuri *et al.* 1985, Bubenik & Pang 1997). Four enzymes are involved in its biosynthetic pathway, with arylalkylamine N-acetyltransferase (AANAT) representing the rate-limiting step (Klein *et al.* 2002). In *Actinopterygii*, at least two Aanats exist: Aanat1 (mainly in extrapineal tissues) and Aanat2 (the main

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enzyme in the pineal gland; Cazaméa-Catalan *et al.* 2014), which have distinctive enzymatic properties. This peculiarity in the fish melatonin biosynthetic pathway may indicate the differential regulation of the synthesis of this indole depending on the isoform that is expressed in each tissue.

The pineal gland acts as a sensitive photometer that transduces the LD cycle into a hormonal signal, melatonin. In some species, this activity may also be indirectly modulated by other photosensory structures, such as retinal and/or deep brain photoreceptors (Migaud *et al.* 2006, 2007, Choi *et al.* 2016). The pineal gland of teleosts (except salmonids) contains all the necessary elements to be considered a real circadian clock, with the complete core machinery (Cahill 2002, McStay *et al.* 2014). Melatonin secretion may be considered the main output of the pineal clock, which is considered a LEO. Its circadian rhythmicity is maintained under both an LD cycle and constant darkness conditions *in vivo* and *in vitro* (Bolliet *et al.* 1996, Martinez-Chavez *et al.* 2008). Salmonids are the exception to this, as rhythmic melatonin synthesis does not occur in the absence of an LD cycle (Bolliet *et al.* 1996, McStay *et al.* 2014). A molecular connection between the pineal clockwork and melatonin synthesis has been demonstrated through the existence of an E-box in the *aanat2* promoter that binds the Clock-Bmal dimer (Appelbaum *et al.* 2006, Falcón *et al.* 2009, 2010). The retina shares many chronobiological characteristics with the pineal gland and can be considered a melatonin-synthesising molecular clock in some, but not all, fish species. In the cyprinids zebrafish and goldfish, retinal melatonin rhythms are light sensitive and parallel those of the pineal gland (Cahill 1996, Iigo *et al.* 1997*a*). However, in rainbow trout (Besseau *et al.* 2006) and European sea bass (*Dicentrarchus labrax*; Iigo *et al.* 1997*b*), retinal melatonin production peaks during the daytime. Pineal melatonin has free access to the blood, which explains the close correlation between pineal synthesis and plasma melatonin levels and the huge reduction in plasma melatonin that is experienced after pinealectomy (Kezuka *et al.* 1992, Bayarri *et al.* 2003), which has very little effect on gut melatonin (Muñoz-Pérez *et al.* 2016).

Gastrointestinal melatonin has a different cellular origin (enteroendocrine cells; Fernández-Durán *et al.* 2007, Muñoz-Pérez *et al.* 2016), but exhibits the same daily rhythmicity in its synthesis as observed for pineal melatonin. However, these daily patterns are particular to each species. For example, in goldfish, gut melatonin synthesis shows a clear circadian rhythm that is in phase with that of the pineal gland (Choi *et al.* 2016), whereas in Indian carp (*Catla catla*) it is in antiphase with the pineal and circulating levels (Mukherjee *et al.* 2014). In fishes, gut melatonin is not synchronised by photic information (e.g. goldfish: Choi *et al.* 2016), but rather by feeding time, with the acrophase occurring 2–6 h after feeding, and the gut melatonin rhythm being maintained after 8 days of starvation in Indian carp (Mukherjee & Maitra 2015). Similarly, gut melatonin in goldfish also exhibits this dependence on scheduled feeding (Vera *et al.* 2007). The close correlation between the acrophases of biosynthetic enzymes (*aanat2* and *hiomt2*; Velarde *et al.* 2010) and clock genes (*per1a*, *per2a* and *cry3*; Nisembaum *et al.* 2012) in the goldfish hindgut supports the idea that gut melatonin rhythmicity is coupled to a gut molecular clock that may work independently of the pineal clock.

Melatonin acts by binding to melatonin receptors belonging to the G-protein-coupled receptor superfamily (Reppert *et al.* 1996). These receptors are widely distributed in the fish central nervous system and peripheral tissues (Park *et al.* 2006, Ikegami *et al.* 2008, Sauzet *et al.* 2008), allowing the melatonin circadian message to be broadcast throughout the organism (Fig. 1). In fish, pineal melatonin is acting on some diencephalic areas of the hypothalamus–pituitary neuroendocrine axis (Ekström & Vanecek 1992), particularly the rostral preoptic area, lateral tuberal nucleus, ventromedial thalamic nucleus and the anterior periventricular nucleus, the putative homologous to the mammalian SCN (reviewed in Falcón *et al.* 2010). Retinal melatonin mainly has a local role, where it governs some of the daily rhythms, such as retinomotor movements (Zaunreiter *et al.* 1998) or the modulation of neurotransmitter release (Ribelayga *et al.* 2004). Melatonin also entrains daily locomotor activity rhythms in mammals (Cassone *et al.* 1993), but this function has not been clearly demonstrated in fishes. A clear effect on locomotor activity pattern has only been found in some teleosts (goldfish and tench, *Tinca tinca*: López-Olmeda *et al.* 2006; European sea bass: Herrero *et al.* 2007). Moreover, melatonin influences sleep in zebrafish (Elbaz *et al.* 2013, Gandhi *et al.* 2015).

Melatonin is one of the few hormones that is involved in the regulation of circannual rhythms in animals. In mammals, it has been well established that the *pars tuberalis* is important in regulating seasonal reproduction and that melatonin plays a role in modifying clock gene expression in this tissue (Hanon *et al.* 2008, Yasuo *et al.* 2009). However, fish do not possess such an anatomically distinct *pars tuberalis* in the pituitary gland, and the involvement of melatonin in the fish reproductive cycle

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is only supported by a few studies. However, effects of melatonin have been described at the hypothalamic (Popek *et al.* 2005, Alvarado *et al.* 2015), pituitary (Khan & Thomas 1996, Sébert *et al.* 2008) and gonadal (Chattoraj *et al.* 2005) levels.

The candidate function of melatonin as an input to the central circadian oscillator is supported by the observed coexpression of melatonin receptors with *clock* and *per1b* genes in some encephalic areas in rainbow trout (Mazurais *et al.* 2000) and goldfish (Sánchez-Bretaño *et al.* 2015*c*).

In summary, pineal melatonin is the best known direct hormonal output of an endogenous clock that is entrained by LD cycles. This melatonin acts as a temporal messenger throughout the organism. It is likely that gut melatonin is also linked to putative peripheral clocks, which appear to be synchronised by different cues, such as feeding schedule.

Orexin

Orexins (orexin-A and orexin-B), which are also known as hypocretins, are neuropeptides that are derived from a single precursor polypeptide, pre–pro-orexin (Wong *et al.* 2011). The architecture of the orexin system (gene sequence, cell bodies, fibres and receptors) in the brain of fishes exhibits a general pattern that is common to all studied groups of vertebrates (Wong *et al.* 2011, López *et al.* 2014, Volkoff 2015*a*). The orexin system regulates neural activities that are responsible for coordinating daily functions across a range of taxa from fish to mammals, such as feeding behaviour, energy balance, locomotor activity and the sleep–wake cycle (reviewed in Matsuda *et al.* 2012, Gao & Hermes 2015).

Studies in fish have indicated that there are interactions between orexin signalling and the circadian system, as previously reported in mammals (Gao & Hermes 2015). Orexin fibres project to the pineal gland, the SCN (or its homologous in fish) and brain regions that are related to the regulation of sleep and arousal, such as the aminergic nuclei, raphe, locus coeruleus and histaminergic neurons (Wong *et al.* 2011, Volkoff 2012, López *et al.* 2014). Sleep-related experiments in zebrafish have shown that orexin-overexpressing larvae are hyperaroused and have dramatically reduced abilities to initiate and maintain rest at night (Prober *et al.* 2006); and orexin receptor-knockout zebrafish exhibit short and fragmented sleep patterns (Yokogawa *et al.* 2007, Panula 2010). Experiments using this fish mutant have also indicated that orexin can modulate pineal melatonin production and sleep consolidation (Appelbaum *et al.* 2009). Furthermore, the number of synapses in orexin axons projecting into the pineal gland follows a daily rhythm in zebrafish larvae, which appears to be primarily driven by the circadian clock (Appelbaum *et al.* 2010). Consistent with these wake-promoting effects of orexin, increased activity of hypothalamic orexin neurons in zebrafish are associated with periods of increased locomotor activity (Naumann *et al.* 2010); and hypothalamic orexin expression in orange-spotted grouper (*Epinephelus coioides*; Yan *et al.* 2011), goldfish (Hoskins & Volkoff 2012*a*) and Atlantic cod (*Gadus morhua*; Hoskins & Volkoff 2012*b*) exhibits daily fluctuations, with the highest values occurring during the active phase.

Short-term periprandial changes in the expression of orexin have been observed in fishes. For example, orexin expression in the brain increases 1 h before the scheduled mealtime in Mexican blind cavefish (*Astyanax fasciatus mexicanus*; Wall & Volkoff 2013); and hypothalamic pre–pro-orexin expression peaks around mealtime and decreases after feeding in Atlantic cod (Xu & Volkoff 2007) and orange-spotted grouper (Yan *et al.* 2011). These data suggest that orexin may serve as a short-term hunger signal and may be linked to FAA. Supporting this, orexin treatment was found to re-establish daily locomotor activity rhythms in goldfish that had been maintained in the absence of zeitgebers (constant light and fasted conditions) suggesting the involvement of this peptide in the generation of FAA (Nisembaum *et al.* 2014*a*).

These daily variations in orexin expression may be related to the daily rhythms of clock genes; indeed, daily variations in the hypothalamic expression of orexin in goldfish have been related to clock genes oscillations (Hoskins & Volkoff 2012*a*), and cross-talking between orexin signalling and the molecular clockwork has also been recently reported in this species (Nisembaum *et al.* 2014*a*). The finding that *per* genes in the hypothalamus and foregut are upregulated 3 h after an intracerebroventricular orexin injection indicates that this peptide may act as an input to these oscillators and regulate their daily functioning in goldfish (Nisembaum *et al.* 2014*a*). Moreover, *in situ* hybridisation studies in this teleost have revealed that some of the brain regions that exhibit day/night differences in *per1b* expression (Sánchez-Bretaño *et al.* 2015*c*) also possess orexin receptors (Facciolo *et al.* 2012). In this sense, recent data in mammals have suggested that the REV-ERBs may be involved in the repression of orexinergic gene expression (Feillet *et al.* 2015, Amador *et al.* 2016). However, to date,

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it is unknown in fish if orexinergic genes may also be a clock target (Rev-erb target).

Together, these findings indicate that orexin not only is under the control of the molecular clock but also plays an important role in meal anticipation, acting as an input of the circadian system in fishes.

Leptin

Leptin is an anorexigenic peptide that regulates energy homeostasis in mammals and several fish species (reviewed in Gorissen & Flik 2014, Londraville *et al.* 2014). Several different leptin isoforms have been found in fishes, the main one of which is leptin-a (Londraville *et al.* 2014). Leptin is predominantly expressed in the fish liver, which is an important energy-storing tissue, rather than in adipose tissue as in mammals (Gorissen & Flik 2014, Londraville *et al.* 2014). Given its general role as an anorexigenic hormone, leptin expression is expected to increase after feeding and decrease after fasting, as reported in mammals, where plasma levels of this adipokine oscillate in a diurnal fashion, with increased values after food ingestion (Challet 2015, Kumar *et al.* 2015). In fishes, leptin expression also exhibits an acute and transient postprandial increase in the liver, with hepatic leptin-a expression generally increasing 6 h and 9 h after feeding in teleosts such as common carp (*Cyprinus carpio*; Huising *et al.* 2006), goldfish (Tinoco *et al.* 2012), Atlantic salmon (Moen & Finn 2013), orange-spotted grouper (Zhang *et al.* 2013) and Mandarin fish (*Siniperca chuatsi*; Yuan *et al.* 2016).

Daily variations in the mRNA expression of leptin and the subsequent expected changes in hormone circulating levels in the blood will also be linked to the daily locomotor activity rhythm, as this is a well-known output of the circadian system. To our knowledge, the daily profile of leptin expression in fishes has only been studied in Atlantic salmon (Moen & Finn 2013), goldfish (Tinoco *et al.* 2014) and zebrafish (Paredes *et al.* 2015) to date, in which the highest levels of hepatic expression occur at the end of the day. Thus, these species would be expected to experience an increase in blood leptin during the night, as this coincides with low nocturnal activity in goldfish and zebrafish. In mammals, the daily peak in circulating leptin also occurs during the fasting/sleeping period, with levels then declining before waking (reviewed in Patton & Mistlberger 2013, Challet 2015, Kumar *et al.* 2015). All findings to date indicate that leptin facilitates a decreased appetite state during the inactive phase in animals, inhibiting the appearance of FAA.

One point that is still being debated is whether such a daily rhythm in leptin expression could be driven by endogenous oscillators. Under constant light conditions, leptin-a expression was rhythmic in goldfish that were fed at 10:00, but was not rhythmic in those that were fed at 22:00 or randomly, suggesting that feeding time alone cannot induce daily leptin rhythms in this species (Tinoco *et al.* 2014). These hepatic leptin-a rhythms also did not shift according to the feeding time in zebrafish under an LD cycle, indicating that light is probably the dominant synchroniser (Paredes *et al.* 2015). In addition, these daily leptin rhythms may also be regulated by rhythmic endogenous factors (hormones and food-derived metabolites), as described in mammals (Challet 2015, Kumar *et al.* 2015). In particular, the leptin rhythm in the goldfish liver is related to plasma glucose levels (Tinoco *et al.* 2014), with a postprandial glucose peak preceding the leptin peak, supporting the notion that leptin is induced by glucose in the hepatocytes of grass carp (*Ctenopharyngodon idella*; Lu *et al.* 2015).

A bidirectional link between the circadian system and leptin signalling has previously been described in mammals (Kettner *et al.* 2015). In adipose tissue, the rhythmic binding of the BMAL1/CLOCK heterodimer to the *leptin* promoter potentiates C/EBPα-mediated *leptin* transcription during the early sleeping phase in mice (*Mus musculus*). However, there is currently no direct evidence that the peripheral clock regulates leptin transcription in fishes, although *bmal1a* and *clock1a* transcripts are rhythmic in the goldfish liver, exhibiting acrophases during the light phase (Sánchez-Bretaño 2016) that precede the peak in leptin expression (Tinoco *et al.* 2014). In mice, such regulation by the adipose clockwork is sufficient to drive diurnal oscillations of serum leptin, and the SCN pacemaker rhythmically potentiates the leptin-responsive neurons (Kettner *et al.* 2015). Therefore, this may explain the time-dependent effects of leptin on food intake in goldfish (Vivas *et al.* 2011). On the other hand, other studies on rodents have suggested that leptin can modulate circadian clocks, with *in vitro* experiments revealing that leptin leads to phase shifts in the SCN clock in rats (*Rattus* spp.; Prosser & Bergeron 2003, Inyushkin *et al.* 2009). *In vivo* experiments show that leptin injection potentiates behavioural light-resetting in mice, which is accompanied by a higher induction of the clock genes *Per1* and *Per2* in the SCN (Mendoza *et al.* 2011). Moreover, it has been shown that genetically obese

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mice (*ob/ob*, leptin deficiency; *db/db*, lacking the leptin receptor) exhibit disturbances in their peripheral clocks (Ando *et al.* 2011, Grosbellet *et al.* 2016). However, the modulation of circadian clocks by leptin in fishes remains unexplored.

Therefore, it seems that environmental (light and feeding) and endogenous (hormonal and metabolic) signals are involved in the daily leptin rhythms in fishes, and the leptin postprandial peak may provide post-feeding cues to the central and/or peripheral clocks.

Ghrelin

Ghrelin is a peptide that acts as a pleiotropic hormone in vertebrates. It has been implicated in the stimulation of growth hormone release from the pituitary, feeding and metabolism regulation and reproduction, among other functions, in both mammals (Al Massadi *et al.* 2015, Müller *et al.* 2015) and fishes (Kang *et al.* 2011, Shahjahan *et al.* 2014). As in other vertebrates, ghrelin in fishes is mainly synthesised in the intestinal tract, as well as in the brain (Kaiya *et al.* 2011, Eom *et al.* 2013, Zhou *et al.* 2014, Ji *et al.* 2015, Volkoff 2015*a*,*b*).

Over the last few years, several pieces of evidence have indicated a putative crosstalk between ghrelin and the circadian system in mammals. Plasma ghrelin levels display a daily rhythm that is related to the feeding cycle in many species (Cummings *et al.* 2001, Bodosi *et al.* 2004, Miura *et al.* 2004, Sanchez *et al.* 2004, Laermans *et al.* 2015), exhibiting a preprandial rise before each meal followed by a postprandial decrease in both diurnal and nocturnal mammals (Al Massadi *et al.* 2015, Jha *et al.* 2015, Müller *et al.* 2015). *In vitro* experiments in mice have demonstrated that ghrelin appears to work as an output of a FEO that is located in the oxyntic cells of the stomach (LeSauter *et al.* 2009, Laermans *et al.* 2015). Furthermore, FAA is significantly reduced in rodents that lack ghrelin receptors (LeSauter *et al.* 2009), and systemic administration of ghrelin activates a subset of specific neurons in the medial hypothalamus during FAA (Van der Plasse *et al.* 2013). Ghrelin also induces phase advances in the electrical activity of neurons in mouse SCN explants and promotes a phase advance in the rhythm of *per2* expression, suggesting that it affects the SCN clockwork (Yannielli *et al.* 2007).

In goldfish, the ghrelin transcript exhibits a daily rhythm, with a nocturnal acrophase in the hypothalamus, pituitary gland and gastrointestinal tract (Sánchez-Bretaño *et al.* 2015*a*), and plasma levels of acyl-ghrelin show periprandial variation (Blanco *et al.* 2016). Transient preprandial and postprandial changes in ghrelin mRNA levels have also been described in the brain of tilapia and zebrafish and in the telencephalon, intestinal bulb and hypothalamus of goldfish (Uniappan *et al.* 2004, Amole & Unniappan 2009, Peddu *et al.* 2009, Blanco *et al.* 2016). These findings suggest that ghrelin could be a feeding- or metabolic-related signal that synchronises FEOs and FAA in fishes (Fig. 1). This hypothesis is also supported by the fact that ghrelin modifies the locomotor activity (Matsuda *et al.* 2006, Yahashi *et al.* 2012), and a ghrelin antagonist prevents FAA (Nisembaum *et al.* 2014*b*) in goldfish.

The coexpression of ghrelin receptors and clock genes in both LEOs and FEOs supports the idea that ghrelin acts as an input signal of these clocks. In fishes, reverse transcription polymerase chain reaction (RT-PCR) has shown that ghrelin receptors are expressed in all brain regions (Chen *et al.* 2008, Small *et al.* 2009, Kaiya *et al.* 2010, Upton & Riley 2013, Sánchez-Bretaño *et al.* 2015*a*, Zhang *et al.* 2016). Furthermore, *in situ* hybridisation has revealed that the transcripts of two ghrelin receptors (*ghs-r1a* and *ghs-r2a*) are expressed in several brain regions, including the hypothalamus and preoptic lobes in zebrafish (Cruz *et al.* 2010). *ghs-r1a* mRNA-positive cells occur in almost every area in goldfish, including the pallial and subpallial telencephalic regions, many hypothalamic nuclei (including the preoptic region and the anterior periventricular nucleus), the pineal gland, the habenular nuclei, the *torus longitudinalis* and the metencephalic *valvula cerebelli* (Sánchez-Bretaño *et al.* 2015*a*). Interestingly, the expression of several clock genes has also been described within these areas: *per1b* in goldfish (Sánchez-Bretaño *et al.* 2015*c*); *per1b*, *per2*, *per3*, *clock*, *cry* and *bmal1* in zebrafish (Weger *et al.* 2013, Moore & Whitmore 2014) and *clock* in rainbow trout (Mazurais *et al.* 2000). Some of these brain areas, such as the anterior periventricular nucleus (putatively homologous to the mammalian SCN) and the pineal gland, are oscillators that allow the circadian rhythmicity to be entrained by the LD cycle (Idda *et al.* 2012, Moore & Whitmore 2014). These results support the putative role of ghrelin as a feeding- or metabolic-related signal that communicates to clocks that are synchronised by different cues (LD and feeding–fasting cycles).

The anatomical connection between ghrelin receptors and the circadian system may also be functional. In goldfish, an acute intraperitoneal injection of ghrelin induces the expression of orexin, *per1a* and *per3* in the hypothalamus (Nisembaum *et al.* 2014*b*).

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Furthermore, the actions of ghrelin are not restricted to central oscillators, but are also exerted on peripheral oscillators. In all studied fish species to date, ghrelin receptors are expressed in the oxyntic cells and/or the mucosal and submucosal intestinal cells and in the hepatocytes (Chen *et al.* 2008, Kaiya *et al.* 2009*a*,*b*, Eom *et al.* 2014, Cai *et al.* 2015, Sánchez-Bretaño *et al.* 2015*a*; Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations), suggesting that ghrelin may also act as a local signal that entrains the stomach and/or gut oscillators. A direct effect of ghrelin on the gastrointestinal oscillator has not yet been demonstrated *in vivo* or *in vitro* in fishes. However, this has been suggested to occur in the liver of goldfish, in which an acute intraperitoneal injection of ghrelin upregulates the hepatic expression of the clock genes *per1a*, *per2a* and *per3* 1 h after injection (Nisembaum *et al.* 2014*b*). Similarly, with *in vitro* hepatic cultures, ghrelin upregulates the expression of both the positive (*bmal1a* and *clock1a*) and negative (*per1a*, *per1b*, *per2a* and *per3*) elements of the main loop of clock genes, as well as the auxiliary loop gene *rev-erb a* (Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations; Fig. 2). This ghrelin-evoked gene induction is blocked by pretreatment with inhibitors of phospholipase C (PLC), protein kinase C (PKC) and, in some genes, protein kinase A (PKA), proving that ghrelin exerts its actions via the PLC-PKC and, to a lesser extent, adenylyl cyclase (AC)–PKA intracellular signalling pathways (Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations; Fig. 2).

In summary, all of the evidence to date supports a bidirectional link between the circadian clock and ghrelin signalling in fishes, as has been found in mammals. Current data demonstrate that ghrelin rhythms in the intestine, and likely the hypothalamus and pituitary gland, could be caused by the outputs of local oscillators. Furthermore, ghrelin may also participate in the regulation of FAA by either stimulating appetite or entraining endogenous clocks through the modification of clock gene expression.

Glucocorticoids

The hypothalamus–pituitary–interrenal (HPI) axis in fishes retains the classic organisation of the main neuroendocrine systems, being activated by stressful agents that trigger the release of stress hormones, glucocorticoids and catecholamines (Wendelaar Bonga 2011). Cortisol is the main glucocorticoid that is released into the teleost bloodstream from the interrenal (adrenal) cells, which are embedded in the head kidney region and are associated with catecholaminergic cells, lymphoid cells and the posterior cardinal veins (Barandica & Tort 2008). During the onset of stress, cortisol induces several catabolic processes that provide energy to the different physiological actions that occur to restore homeostasis (Mommsen *et al.* 1999). A variety of biochemical, physiological and behavioural responses are also controlled by cortisol, such as energy metabolism, ion-osmotic regulation, immunity and growth (reviewed in Mommsen *et al.* 1999, Ellis *et al.* 2012).

Cortisol, as melatonin, is considered one of the more robust hormonal outputs of the circadian system (Fig. 1). Under unstressed conditions, glucocorticoids exhibit a robust temporal secretion in mammals, with a circadian rhythmicity that overlaps an ultradian rhythmicity (Walker *et al.* 2010, Spiga *et al.* 2014). Cortisol (or corticosterone) secretion in mammals fluctuates with the LD cycle and is clearly related to the daily behavioural pattern, with a surge being seen at the onset of the activity phase each day. The sympathetic nervous system and the SCN control such daily variations via the hypothalamus–pituitary–adrenal (HPA) axis (Haus 2007, Tonsfeldt & Chappell 2012). However, increasing evidence has revealed that multiple components of the circadian system, and particularly the adrenal clock, are involved in the regulation of glucocorticoid rhythmicity in mammals (Son *et al.* 2011, Spiga *et al.* 2014).

Such a conserved pattern of circulating glucocorticoids is not evident in fishes, where a wide variety of daily patterns of plasma cortisol have been reported depending on the species, photoperiod, season and feeding and activity patterns. In relation to the LD cycle, the acrophase of daily cortisol rhythms occurs at the early photophase in Gulf killifish (*Fundulus grandis*; Garcia & Meier 1973) and Mozambique tilapia (*Oreochromis mossambicus*; Nikaido *et al.* 2010), at the beginning of the scotophase in sea bass (Planas *et al.* 1990), tench (De Pedro *et al.* 1998) and sole (*Solea senegalensis*; López-Olmeda *et al.* 2013) and during the scotophase in brown trout (*Salmo trutta*; Pickering & Pottinger 1983) and Japanese char (*Salvelinus leucomaenis*; Yamada *et al.* 2002). Two peaks in cortisol have been described in sea bass (Cerdá-Reverter *et al.* 1998) and Atlantic salmon smolts (Ebbesson *et al.* 2008). In addition to this range of daily profiles of circulating cortisol, there is also evidence for seasonal changes in

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some salmonids (Rance *et al.* 1982, Pickering & Pottinger 1983, Thorpe *et al.* 1987), cyprinids (Kühn *et al.* 1986) and perciformes (Planas *et al.* 1990).

The feeding–fasting cycle and feeding time are powerful non-photic signals that may synchronise the daily cortisol rhythms in fishes. Indeed, periprandial cortisol changes have been observed in some teleosts, such as rainbow trout (Bry 1982, Hernández-Pérez *et al.* 2015), brown trout (Pickering & Pottinger 1983), goldfish (Spieler & Noeske 1984, Vera *et al.* 2007) and gilthead seabream (*Sparus aurata*; Montoya *et al.* 2010). However, this relationship between cortisol levels and feeding phase may be driven by the increase in locomotor activity rather than feeding time entrainment. The effect of fasting on the daily cortisol rhythm remains unclear, as starvation decreases the mean plasma cortisol level in channel catfish (*Ictalurus punctatus*; Small 2005), but increases the average cortisol levels (acting as a stressful event) without any modification to the daily cortisol rhythm in rainbow trout (Polakof *et al.* 2007, Hernández-Pérez *et al.* 2015). One interesting and almost unexplored question is whether these daily rhythmic variations in circulating cortisol in fishes are endogenous. To our knowledge, only one study has addressed this question, which indicated that the daily rhythm in plasma cortisol shows endogenous characteristics in the common dentex (*Dentex dentex*; Pavlidis *et al.* 1999).

The daily rhythms in the HPA axis have been widely reported in mammals (Kalsbeek *et al.* 2012, Spiga *et al.* 2014), whereas the existence of rhythms in the HPI axis components of fish has scarcely been investigated. A daily rhythm in circulating adrenocorticotropic hormone was demonstrated in goldfish (Singley & Chavin 1976), and more recently, a rhythmic expression of genes encoding pro-opiomelanocortin (Gilchriest *et al.* 1998, López-Olmeda *et al.* 2013), corticotropin-releasing hormone (Crh; López-Olmeda *et al.* 2013) and the Crh receptor 1 (Azpeleta *et al.* 2012) has been demonstrated. Furthermore, the similar profiles that have been observed in *crh* expression and plasma cortisol in sole suggest that the daily cortisol rhythm may be a direct consequence of hypothalamic Crh production (López-Olmeda *et al.* 2013).

The recent discovery of a rhythmic expression of clock genes in the adrenal tissue of mammals strengthens the support for the existence of a functional circadian clock in this gland (Nicolaides *et al.* 2014, Spiga *et al.* 2014). However, the only report on the rhythmic expression of clock genes in fishes was in the interrenal tissue of the goldfish, where it was shown that the 24-h rhythmicity of *per1a*, *per3* and *cry3* is in antiphase to the *clock1a* rhythm, as would be expected for a functional core clock (Azpeleta *et al.* 2012). These data indicate that the interrenal tissue may act as a node within the circadian system network in fishes (Fig. 1).

Since the pioneering demonstration that the glucocorticoid hormone analogue dexamethasone can reset the circadian rhythms of clock gene expression in multiple peripheral cell types in the rat (Balsalobre *et al.* 2000), there has been increasing evidence that the circadian output of the adrenal gland plays a relevant role in synchronising the peripheral clocks in mammals (Dickmeis 2009, Kalsbeek *et al.* 2012, Schibler *et al.* 2015). So, does cortisol act as a resetting signal for the peripheral and/or central clocks in fishes? The few results currently available suggest that this is the case. Dexamethasone entrains bioluminescence rhythms in zebrafish and cavefish cell lines that have been transfected with *zfper1b-luc* (Cavallari *et al.* 2011). The molecular mechanism underlying this entrainment appears to be the glucocorticoid induction of *per1*, which has been reported to occur in the goldfish liver both *in vivo* and *in vitro* (Sánchez-Bretaño *et al.* 2016) and in cavefish cell lines (Cavallari *et al.* 2011). Similarly, in mammals, multiple glucocorticoid-response elements (GREs) are found in the *per1* gene promoter sequence (Reddy *et al.* 2007). Moreover, in goldfish, dexamethasone represses the positive elements of the liver clock (*bmal1a* and *clock1a*) in culture (Sánchez-Bretaño *et al.* 2016), supporting a putative resetting function of glucocorticoids in fishes (Fig. 2). The widespread distribution of glucocorticoid receptors in fishes (Prunet *et al.* 2006) suggests that other peripheral clocks may also be entrained by cortisol.

It has been suggested that glucocorticoids may also act as a temporal signal in the broader context of circadian functional organisation, but it is currently unknown which physiological functions are regulated by putative glucocorticoid-sensitive clocks. In this sense, cortisol has been identified as a component of a systemic signalling pathway that is required for circadian cell cycle rhythmicity in zebrafish (Dickmeis *et al.* 2007) and appears to be involved in the regulation of the melatonergic system rhythmicity in rainbow trout (Benyassi *et al.* 2001, Ceinos *et al.* 2005), catfish (*Clarias gariepinus*; Yanthan & Gupta 2007) and Mozambique tilapia (Nikaido *et al.* 2010).

Overall, these findings support the notion that cortisol acts as an input and maybe an output of the circadian system in fish. However, further investigation is required to demonstrate such an assertion and to explore the remaining unresolved questions, such as the nature

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of the inputs that synchronise the interrenal clock and cortisol rhythms.

Communication among oscillators: hormones as temporal internal messengers

Based on all the data presented here, we propose a hypothetical model of entrainment of the molecular clockwork, in which the 24-h clock gene oscillations are sustained via light and hormonal inputs (Fig. 2). The LD cycle reaches the core clock via the light-evoked induction of *cry1* and *per2* in zebrafish (via the functional E- and D-boxes and the thyrotroph embryonic factor (Tef) transcription factor; Tamai *et al.* 2007, Vatine *et al.* 2009, 2011). Based on the observed acute induced changes in gene expression, we also propose additional mechanisms whereby hormones such as cortisol and ghrelin can entrain the molecular clocks. As discussed previously, in the goldfish liver, cortisol induces *per1a* and *per1b* and represses *bmal1a* and *clock*, whereas ghrelin induces a variety of clock genes via the PLC-PKC pathway and, to a lesser extent, the AC-PKA pathway (Sánchez-Bretaño *et al.* 2016; Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations; Fig. 2).

However, the bidirectional link between the daily rhythms of clock genes in endocrine tissues and hormonal rhythms still needs to be deeply studied in fishes. In particular, it is important to know the answers to two questions: are clock gene oscillations in endocrine tissues linked to hormonal overt rhythms and are hormonal-induced changes in clock gene transcripts sufficient to induce the entrainment of the molecular core?

The answer to the first question seems clear for melatonin rhythms. Clock gene oscillations in the fish pineal gland are directly driven by LD cycles, and these oscillations, in turn, control the expression of the clock-controlled gene *aanat2*, which codes the key enzyme for melatonin synthesis (Appelbaum *et al.* 2006, Falcón *et al.* 2009). However, as stated previously, hepatic leptin expression rhythms are not always linked to clock genes daily rhythms in the liver of goldfish (Tinoco *et al.* 2014). Furthermore, although feeding time drives clock genes oscillations in the sea bream liver (Vera *et al.* 2013), it does not control the rhythms of enzymes that are involved in lipid metabolism (Paredes *et al.* 2014); and in zebrafish, lipid metabolism is linked to the LD cycle and independent of feeding time (Paredes *et al.* 2015). Thus, the physiological functions of peripheral oscillators in fishes remain unclear. The use of *in silico* analysis to search for clock-controlled genes (i.e. genes whose promoters hold putative E-box, D-box and RORE elements) would be very useful for further investigating this issue.

With regard to the second question, glucocorticoids have a clear role as internal messengers in mammals (Albrecht 2012, Kalsbeek *et al.* 2012, Schibler *et al.* 2015) and this also appears to be the case for fishes. Dexamethasone entrains bioluminescence rhythms in zebrafish and cavefish cell lines that have been transfected with *zfper1b-luc* (Cavallari *et al.* 2011), as well as clock gene rhythms in the goldfish liver *in vitro* (Sánchez-Bretaño 2016). As discussed previously, glucocorticoids probably repress the positive elements and induce the negative elements of the core clock (Sánchez-Bretaño *et al.* 2016; Fig. 2). However, whether the acute changes in clock gene expression that are induced by orexin and ghrelin *in vivo* (Nisembaum *et al.* 2014*a*,*b*) and by ghrelin *in vitro* (Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations) can reset the clock remains to be explored. Finally, considering the variety of signals that are involved in regulating clock genes, it is likely that other less-studied hormones also influence the fish clockwork. In particular, the family of *per* genes appears to be the target for different cues in fishes, including light, orexin, ghrelin and glucocorticoids (Vatine *et al.* 2009, Nisembaum *et al.* 2014*a*,*b*, Sánchez-Bretaño *et al.* 2015; Sánchez-Bretaño A, Blanco AM, Alonso-Gómez AL, Delgado MJ, Kah O & Isorna E, unpublished observations; Fig. 2) and so may be involved in shifting the molecular clock. Similarly, the light-resetting of the SCN clock and the adjustment of peripheral oscillators by glucocorticoids are also mediated by *per* genes in mammals (Albrecht 2012, Schibler *et al.* 2015).

Our hypothetical model of endogenous clock entrainment agrees with the non-hierarchical model of fish circadian organisation, in which the variety of oscillators can be entrained independently by different hormonal cues and according to the specific sensitivity of each tissue to these signals. Recently, it has been proposed that peripheral oscillators are also entrained by temperature via transient receptor potential channels, which are also involved in light synchronisation (Poletini *et al.* 2015), but the functional entrainment has not been demonstrated to date. These findings support the concept of a more flexible organisation of the circadian system in fishes than previously thought. It could be hypothesised that vertebrate ancestors would have had a variety of clocks that were widely distributed and probably independently synchronised to different

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factors (light, temperature and food), which has since evolved into a very hierarchical system in mammals and perhaps an intermediate state in fishes. As previously suggested (Idda *et al*. 2012), a versatile circadian system in fishes is expected considering the large number of teleost species and the wide variety of habitats they inhabit.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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