Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: January 31, 2023

Citation: Smith D. J. M., 2023. Cryptochrome: An ancient blue light photoreceptor impacts modern mammalian physiology, Medical Research Archives, [online] 11(1). https://doi.org/10.18103/mra.v11i1.3523

DOI: https://doi.org/10.18103/mra.v11i1.3523

ISSN: 2375-1924

RESEARCH ARTICLE

Cryptochrome: An ancient blue light photoreceptor impacts modern mammalian physiology

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Abstract

Cryptochromes, evolutionally conserved and retained in mammals as transcriptional regulators having a repressive role in the transcription-translation feedback loop, the molecular mechanism behind the control of the endogenous mammalian circadian clock. This clock mechanism regulates the oscillation of a huge number of clock-controlled output genes. This in turn is responsible for modification of the physiological response of most organs and tissues, to coordinate with diurnal and seasonal changes in light and nutrient availability. Cryptochromes have also been found to participate in additional signalling cascades, outside of the circadian system, forming supplementary feedback loops that initiate cross-talk between systems influencing metabolism, inflammation and DNA damage response to maintain cellular homeostasis. This physiological organisation system has developed from Palaeolithic man but is still relevant in our modern world.

Introduction

A photoactive pigment is an organic molecule that absorbs in the near ultraviolet-visible light range and on the absorption of a photon initiates a chemical reaction. A photoreceptor is an apoprotein containing a photoactive pigment, the chromophore.

Rhodopsin, the photoreceptor for vision, was discovered in 1877 and because of the rich history of opsin research, the notion that all photo-sensory responses, mediated by the eye, are initiated by opsins became widely accepted. The discovery that in addition to the Vitamin A based opsins, the eye contains a second Vitamin B_2 based pigment, cryptochrome, was unexpected and initially rejected[1]. Research on circadian rhythms revealed, however, that there are two pathways of photo-sensory input. Visual information is processed in the cerebral cortex to construct a three-dimensional representation of the world, whereas photic information for the circadian system is processed in the hypothalamic, suprachiasmatic nucleus (SCN), to provide the 4^{th} external dimension, time, the assessment of which is an essential requirement for awareness of the impacting milieu and provide an adaptive physiological response.

Opsins are transmembrane proteins attached to a chromophore, the photo-receptors for vision in mammals, which incorporate retinal as the chromophore[2].

Light for vision is absorbed by rods and cones in the outer retina, near the pigment epithelium utilising rhodopsin, whereas light for the circadian clock is absorbed by intrinsically photosensitive ganglion cells, utilising a different opsin, melanopsin[3]. Signal transduction for both is through the optic nerve. However, the axons for vision continue to the cortex, whereas the circadian axons exit at the chiasma and go up to the suprachiasmatic nuclei in the anterior hypothalamus.

Cryptochromes (CRYs), blue light photoreceptor proteins present in both plants and animals, have structural homology with and are derived from photolyases, belonging to the flavoprotein family, that exist in all kingdoms of life. They have two domains, a photolyase homology region and an extended C terminal, divergent in length and sequence identity[4]. Photolyases are still retained as bacterial enzymes, activated by light and involved in repair of UV-induced DNA damage. Eukaryotes utilise flavin adenine dinucleotide (FAD) and methyl-tetrahydrofolate (MTHF) as chromophores, having lost DNA repair function, now delegated to nucleotide and base excision repair (NER and BER), mechanisms that allow for repair of a wider range of DNA damage lesions[5,6,7], but retaining the DNA binding property of photolyases[8,9]. Mammalian cryptochromes no longer participate in photoreception but have been co-opted as transcriptional repressors through their ability to bind to DNA allowing them to interact directly with the transcriptional activator dimer CLOCK/BMAL1 on DNA. Cryptochromes also work outside the core clock transcription-translation loop to regulate transcription throughout the genome. They participate in additional

signalling cascades forming feedback loops that initiates cross-talk between systems influencing metabolism, inflammation and DNA damage response to maintain cellular homeostasis.

Vertebrate CRYs are vestigial flavoproteins and are not photoactive

All CRYs are classified as flavoproteins. Animal CRYs best described role is as a circadian clock component. This circadian function is variable, either light-dependent or light-independent.

Type I animal CRYs are blue-light photoreceptors responsible for entrainment of light in invertebrates eg. Drosophila.

Type II animal CRYs are light independent circadian regulators, where they act as transcriptional repressors. There are two gene homologues, *Cry1* and *2,* producing two proteins, CRY1 and 2 with distinct biochemical functions. CRY 1 generates cell autonomous circadian rhythms in fibroblasts and tissues outside the SCN, while CRY2 cannot[10,11]. They lack structural features necessary to bind flavin-cofactors securely and so are not photoactive. This makes it unlikely that they can participate in photo-magnetoreception. Present in vertebrates and invertebrates. Mammalian type II CRYs also couple the circadian clock to metabolism, in part, through interaction with glucocorticoid receptors.

The molecular basis for the difference in biological function between type I and II animal CRYs is their differential binding to flavin. Drosophila CRY (DCRY) binds the blue-light chromophore and redox co-factor, FAD in its fully oxidised form, much like photolyase. FAD is bound to DCRY in a U shape with the adenine in close proximity to the alloxazine. Type II CRY has proved difficult to express and isolate with bound FAD and it is hypothesised that this differential binding ability influences interaction with the different partners and genetic networks that separate clock function in vertebrates and invertebrates[12].

Nuclear receptors

Type II animal CRYs, CRY1/2, also broadly interact with nuclear receptors (NRs) and modify their transcriptional activity[13]. Nuclear receptors are ligand sensing transcription factors with both DNA and ligand binding sites. Ligands are usually lipophilic substances such as hormones, steroids and vitamins[14]. Binding to the ligand induces conformational changes that can up or down-regulate gene expression, and thus, regulate physiology by adapting transcription. Regulation of transcription by NRs depends on interaction with corepressors and coactivators. Steroid hormone receptors are enriched in the cytoplasm, in the absence of a ligand, but translocate to the nucleus upon agonist ligand binding to then also bind with DNA. Recruitment of a coactivator allows transcription. Non-steroid-binding NRs are bound to DNA and corepressors in the absence of a ligand. Binding of an agonist ligand displaces the corepressor in favour of a coactivator, allowing transcriptional initiation. CRYs bind, independently of other clock factors, to many genomic sites enriched for NR recognition motifs, acting as co-repressors

for many NRs. In this way the circadian clock exercises some control over NR-mediated regulation of transcription. NRs are functionally and mechanistically implicated as key components of both universal and adaptive circadian clock mechanisms and thus regulating the clock itself. This bidirectional interaction impacts diverse aspects of mammalian physiology and metabolism[15].

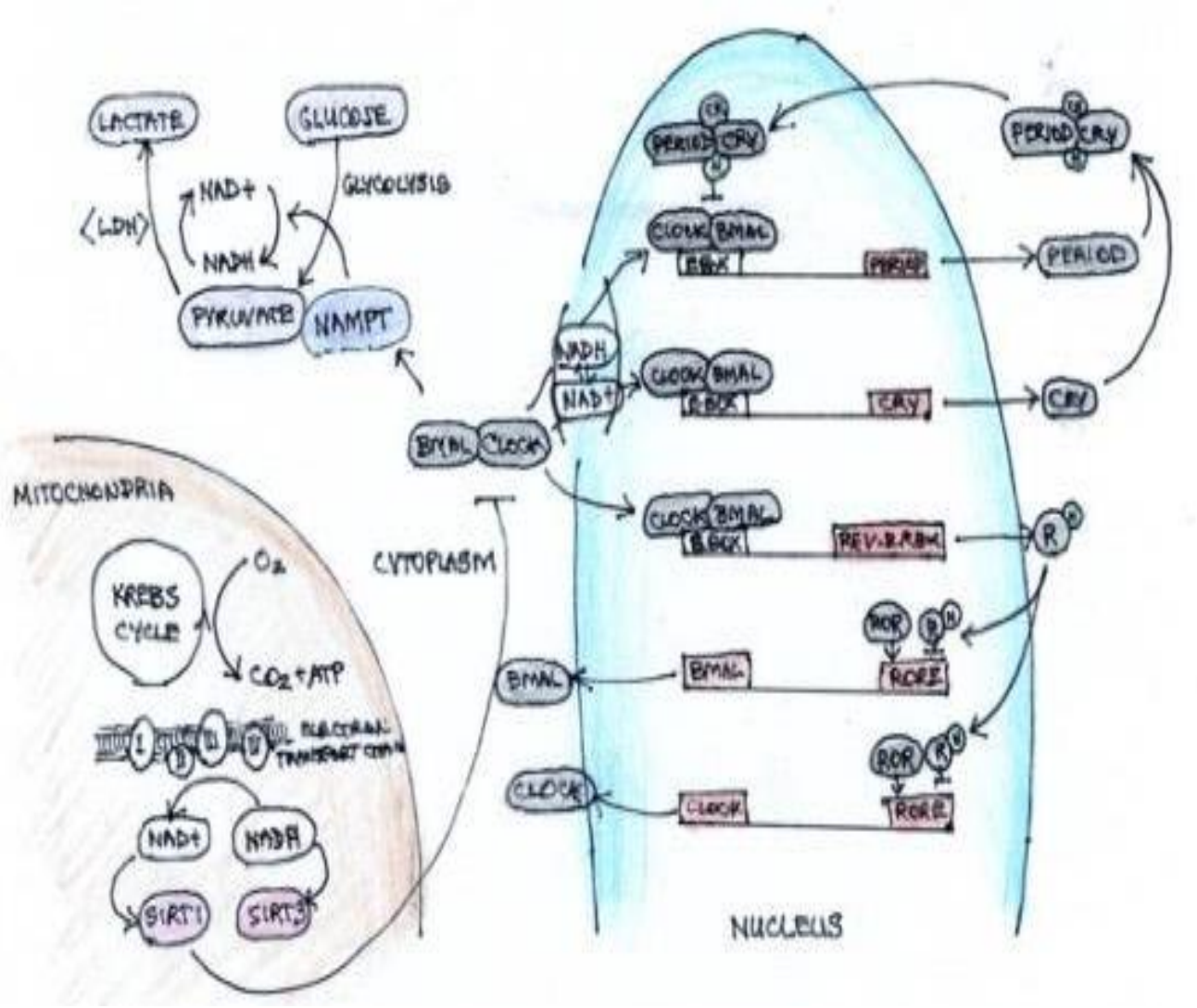

Figure 1. Cross talk between circadian and metabolic clocks.

Clock genes and proteins interact to create the transcription-translation feedback loop (TTFL) oscillator. Heterodimers of positive transcription factors CLOCK/BMAL1 (or CLOCK/NPAS2 in some brain regions) bind to E box motifs in the promoters of *period, cryptochrome* (*Cry*) and *Rev-Erbα,* activating transcription. The protein products can undergo various post-translational modifications in the cytoplasm. PERIOD and CRY heterodimerise, translocate to the nucleus and repress the transcriptional activity

by CLOCK/BMAL1. An additional feedback loop involves REV-ERBα (R, nuclear heme receptor, a negative regulator) and ROR (a positive regulator), which compete for binding to and regulation of ROREs within the *bmal1* promoter. It can also bind to ROREs in the *period* and *Cry* promoters regulating transcription. Elements within molecular loops are sensitive to redox state which can modulate both binding and transcriptional activity. DNA binding affinity of BMAL and CLOCK are controlled by the NAD+/NADH ratio. NAMPT acts as the rate limiting enzyme in mammalian NAD+ biosynthesis and its expression is regulated by core clock elements. NAD+ and heme (H) denote redox-sensitive nodes on clock proteins. NAD+, nicotinamide adenine dinucleotide; NMAPT, nicotinamide phosphoribosyl-transferase; NPAS2, neuronal PAS domain protein 2; ROR, retinoic acid-related orphan receptor: RORE, retinoic acid-related orphan receptor response element; SIRT1, sirtuin1.

Glucocorticoid receptor

Glucocorticoids are produced in the adrenal cortex and are known for their hormonal regulation of a wide spectrum of physiological processes, including metabolism, cardiovascular, and immunological function. Circulating levels show circadian rhythmicity with peak levels during the onset of activity, indicating a clock regulated process. They bind to, and activate glucocorticoid receptors (GR), a significant nuclear receptor but also a critical component mediating circadian clock entrainment in peripheral tissues. A lack of expression of GR in the SCN and elevated levels of glucocorticoids in the morning, indicates that it is acting as a resetting cue for the peripheral clock and non-SCN nuclei, including pituitary, hypothalamus and hippocampus[16]. The identification of GR elements in several clock genes, including *Per 1* and *2*, further suggests that GR is a critical regulator for clock gene expression at a molecular level[17]. Light is traditionally considered the most influential zeitgeber, or entrainment cue, the universal resetting mechanism, via the central pacemaker in the SCN. This regulates endogenous corticosteroid levels through the action of the sympathetic nervous system on the adrenal gland, independent of glucocorticoid action on the hypothalamus-pituitary-adrenal axis[18]. This highlights the intricate layering of organisation for transduction of photic signals employed by mammalian physiology that, at least in part, utilise hormones such as glucocorticoids to transduce photic signals to peripheral tissues, which are not intrinsically photo-responsive. Although, this fact is not totally resolved in the case of melanocytes which have photosensitive proteins and transduction machinery. Can the skin directly sense light?[19,20.]

Not only does the canonical clock systemically regulate circadian corticosteroid levels but CRY protein directly binds to the GR. *Cry1/Cry2* double knock out mice have grossly elevated glucose levels that indicates dysregulation of GR activity. Another canonical clock component, CLOCK, has been shown to acetylate GR and influence the association of GR with DNA[21]. Thus, both the circadian glucocorticoid production and the

cognate receptor function appear to be intimately related to both CRY and CLOCK.

Clock involvement in gluconeogenesis

During fasting, mammals maintain normal glucose homeostasis by stimulation of hepatic gluconeogenesis[22]. An increase in circulating glucagon and epinephrine, two hormones that activate hepatic gluconeogenesis, triggering cyclic adenosine monophosphate (cAMP) mediated phosphorylation of cAMP response element-binding protein (Creb) and de-phosphorylation of the Creb-regulated transcriptional co-cactivator-2, two key transcriptional regulators of this process[23]. Hepatic gluconeogenesis is also regulated by the circadian clock which coordinates glucose metabolism with changes in the external environment. Zhang et al show Creb activation during fasting is mediated by Cry1/2, which are rhythmically expressed in the liver. Expression of Cry1 is elevated during night to day transition, Zeitgeber time (ZT) 22-1, decreasing fasting gluconeogenesis gene expression by blocking glucagon-mediated increase in intracellular cAMP concentration and in protein kinase A (PKA)-mediated phosphorylation of Creb. Cry proteins modify G protein coupled receptor activity directly though interaction with the G protein, $G_{s\alpha}$ [24].

Nuclear receptor subfamily members REV-ERB alpha and beta.

It was, however, the orphan nuclear receptor, REV-ERBα that was found to be the first mechanistic link for direct NR regulation of the clock. REV-ERBα and β are heme-dependent transcriptional repressors[25]. Retinoid orphan receptors (RORs) promote transcriptional activation. They both recognise the same DNA binding sites, ROR response elements (ROREs), and are thought to establish a dynamic opposing regulatory circuit[26]. Orphan NRs are key regulators of core clock function and many NRs are rhythmically expressed. Clock proteins, including CRY, and indirect effects like the rhythmic abundance of ligands and rhythmic transcription of co-activators or co-repressors convey time of day information to regulate NRs and ultimately physiology.

Both REV-ERBs bind to the *Bmal1* promoter and to the regulatory regions of other clock control genes, including *Cry*. Analysis of BMAL1, REV-ERBα and β binding sites revealed that nearly all clock and clock related genes were occupied by these three transcriptional regulators[27].

ROR expression correlates with histone acetylation and chromatin accessibility enabling activation of clock gene expression, whereas REV-ERBs block ROR and negatively regulate expression though deacetylation.

E-boxes and nuclear receptor response elements (NREs) are in close proximity with the binding sites of core clock regulators such as Cry. Clock mutations and orphan NR deletions result in metabolic alterations, *in vivo*[27]. The interrelationship between these elements emphasises a critical role in energy homeostasis.

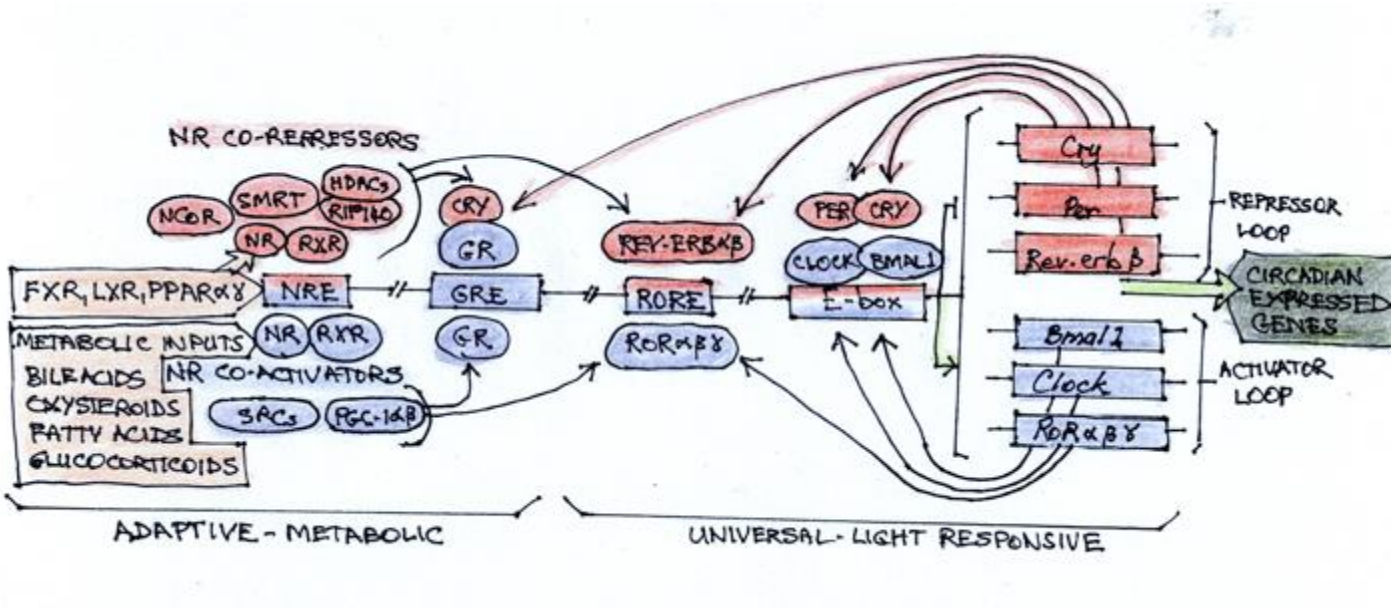

Figure 2. Regulation of the mammalian circadian clock by nuclear receptors, co-repressors and co-activators.

NRs bind to NREs found in all core clock genes and help orchestrate positive and negative gene expression. Many NRs share occupancy at NREs, suggesting multiple orders of redundancy, compensation and/or co-regulation at these circadian control points in the genome. FXR, Farnesoid X (Bile acid) receptor; HDAC, histone deacetylase; LXR, Liver X receptor; NCoR, nuclear receptor co-repressor; PGC-1, PPARγ co-activator; PPAR, Peroxisome proliferator activator receptor; RIP 140, receptor inactivating protein 140; RXR, Regnane X receptor; SMRT, Silencing mediator of retinoic acid & thyroid hormone receptor; SRC, steroid receptor co-activator.

Other nuclear receptors

The number of NRs expressed in a circadian fashion is extensive[28] with more than half displaying tissue-specific cycling, particularly metabolic, such as liver, skeletal muscle, and white and brown adipose tissue. Comparatively, only 5-10% of transcripts oscillate at a transcription-wide level[29], NRs having been selected to coordinate cyclic clock patterns with metabolism. Extensive overlap of multiple NR binding sites, in vivo[30] suggesting that the coordinated action of multiple NRs may be required for normal circadian transcriptional regulation. Nuclear cofactors function as docking points for epigenetic regulators, such as histone deacetylases (HDACs) and acetyltransferases (HATs) that modulate chromatin structure to repress or activate transcription. A post-transcriptional modifier common to circadian clock components and NRs is FBXL3, an ubiquitin F3 ligase, that interacts with both CRY1 and ERV-ERBα[31], suggesting that NRs are important components of the circadian clock system and need to be coordinated within it.

CRY1 interacts with oncogenic transcription factors

Shafi et al found CRY1 to be a pro-tumorigenic factor in prostate cancer, induced by androgens, associated with oncogenic transcription factors and resulting in poor outcomes[32]. CRY1 cistrome mapping showed CRY1 bound to regulatory regions encoding core circadian clock machinery, as expected, but binding to these genes represented only a small fraction (2.5%) of CRY1 binding events, indicating that CRY1 holds functions distinct from the other circadian clock repressors[33]. Investigation of CRY1 functions outside of circadian regulation, revealing enrichment for growth factor signalling, DNA repair and metabolic processes. As well as components of the Fox A1/androgen receptor (AR) complex that may go on to promote AR signalling and cellular proliferation[34], they identified several oncogenic transcription factors such as c-Myc and Hlf-1α. Their analysis revealed that CRY1 governs transcriptional programs of cancer relevance, including DNA replication, cell cycle regulation and multiple DNA repair processes. They then went on to show that a reduction in surviving cells after ionising radiation in CRY1 depleted cells and maintained cell growth after DNA damage in CRY1 activated cells. These findings demonstrated CRY1 modulation of cell cycle checkpoint control and cell proliferation in response to double strand breaks (DSB), implicating CRY1 in promoting cancer cell survival[32].

CRY1 mediates DNA repair networks

The identification of an association between AR, DNA repair and CRY1 prompted investigation of CRY1 mediated repair networks by Shafi's group. They found that numerous networks were sensitive to CRY1 depletion, including UV response, Mismatch repair (MMR), NER and homologous recombination (HR). The only DNA repair process previously linked to the circadian clock was NER[35]. They found that CRY1 regulates double strand break (DSB) repair in a cascading, temporal fashion inducing sensors and mediators of HR, followed by HR effectors. In response to DNA damage, CRY1 is initially stabilised and then directly binds to key HR factors in a systematic manner to enhance DSB repair[32]. Figure 3.

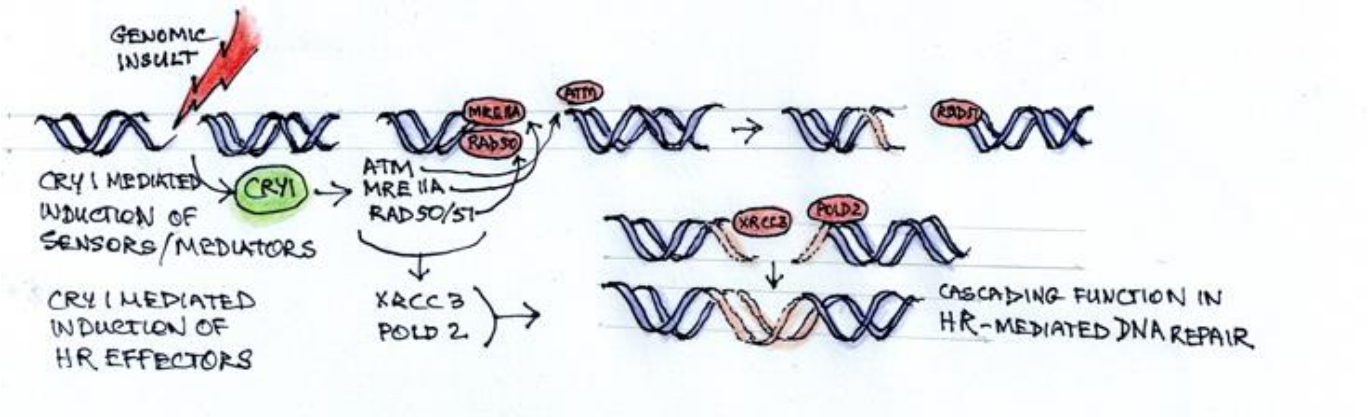

Figure 3. CRY1 regulates DNA DSB repair.

In response to DNA damage, CRY1 is stabilised and directly binds to key HR factors in a cascading, temporal, systematic manner to enhance DNA repair, inducing firstly, HR sensors and mediators, followed by effectors.

Transduction of the geomagnetic field in humans

Magnetoreception, is a sense that allows an organism to detect the earth's magnetic field to perceive direction, altitude or location. Animal with this sense include arthropods, molluscs and vertebrates. The sense is mainly used for orientation and navigation but it may help some animals to form regional maps. This sensory modality is established in a range of vertebrates but its presence in humans has so far yielded only inconclusive experimental results. Although many migrating and homing animal are sensitive to Earth's magnetic field, most humans are not consciously aware of geomagnetic stimuli. Either we have lost the ancestral system through evolution or it lacks a conscious component with detectable neural activity and no perceptual awareness.

Wang et al report strong, specific human brain response to rotations of Earth-strength magnetic fields. Geomagnetic stimulation resulted in a drop of amplitude in α EEG oscillations (8-13Hz). Called α event-related desynchronization (α-ERD). This response has previously been associated with sensory and cognitive processing of external stimuli, including visual, auditory, and somato-sensory cues. α-ERD response to the geomagnetic field was triggered by horizontal rotations when the static magnetic field was directed downwards (experiments conducted in the northern hemisphere), but not upwards, implying a local population effect rather than generic physical effect. The neural response was sensitive to static components of the magnetic field and polarity. They suggested that this eliminated free-radical 'quantum compass' mechanisms like the cryptochrome hypothesis, which can only detect axial alignment and not polarity. Figure 4. They felt that the most plausible mechanism was Ferromagnetism, i.e. the presence of a ferromagnetic transduction element, such as biologically precipitated crystals of magnetite (Fe_3O_4)[36].

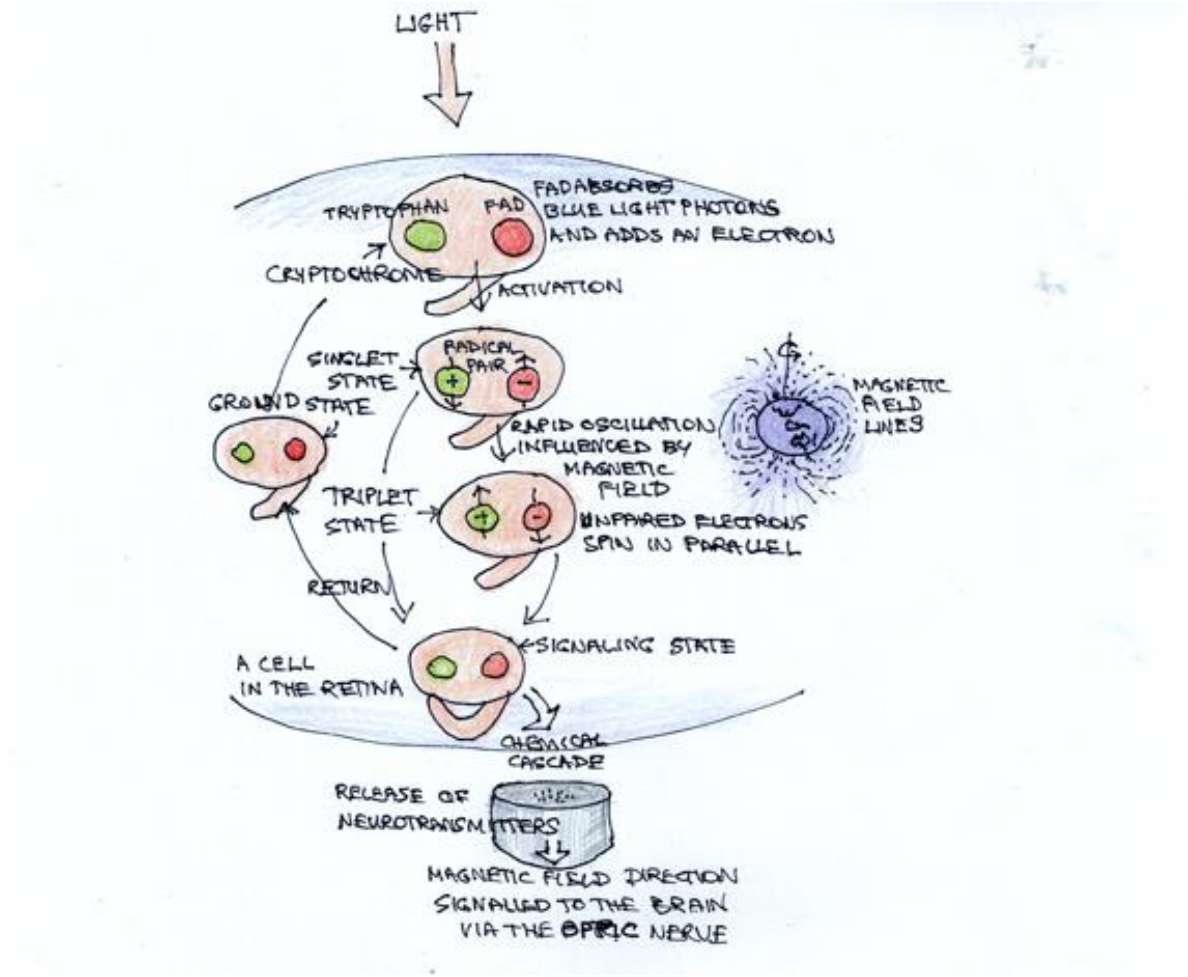

Figure 4. Cryptochrome theory

Cry forms a pair of radicals with correlated spins when exposed to blue light. Magnetoreception is hypothesised to function through the surrounding magnetic field on the correlation (parallel or antiparallel) of these radicals, which affects the life-time of the activated form of Cry. Activation of Cry may affect the light sensitivity of retinal neurons, with the result that the animal can sense the magnetic field.

Discussion

The cryptochrome story is all about adaptability. A molecule that arose as a blue-light receptor in early aquatic organisms is still represented in human physiological control but it has taken on a role in our new terrestrial environment. Homologous to photolyase, which evolved to deal with the threat of UV radiation in a hostile environment where solar radiation is the ultimate source of energy. This situation applies to most living organisms on the planet. Plant, animal and fungus. Living organisms have developed complex systems of defence and repair that allow for the hazards of the environment but with an added layer of complexity to also adapt to environment change over time. Not just

diurnal, as in mammals, but also extended over an evolutionary time scale.

Type I animal CRYs retain the blue-light photoreceptor function, responsible for entrainment in invertebrates. Strong binding to FAD also allows participation in photo-magnetoreception used for navigation.

In vertebrates, with evolution, photoreception is now the domain of opsins in the eye, a complex of sensors with direct access to the brain. The blue-light photoreception is no longer required but rather than elimination of a useful molecule its DNA binding capacity is utilised in a different capacity.

Type II animal CRYs of vertebrates only weakly bind FAD, and so are unlikely to be capable of photo-magnetoreception, now having a light-independent role as circadian regulators. There is a basic repetitive pattern of day and night that is accounted for with endogenous circadian systems that produce an oscillation of genetic expression over an approximate 24-hour cycle. The organism can draw on an extensive palate of molecules, proteins and genes that operate these systems of defence and repair, even utilising toxic by-products of metabolism such a reactive oxygen species, as a signalling molecule. It now becomes involved with a complex of co-repressors and activators that, not only influence transcription by E-boxes attached to elements of the circadian system but nuclear receptors and response elements. Their role within the circadian system has been extensively studied but what I consider particularly interesting is their activity outside of the circadian system. They regulate transcription throughout the genome, and participate in signalling cascades that influence metabolism through their relationship to nuclear receptors and DNA damage response despite DNA repair function being delegated to Nucleotide and base excision repair processes. Cryptochrome interacts with nuclear receptors, ligand sensing transcription factors. The ligands sensed are hormones, steroids and vitamins, so the interconnection of various systems becomes apparent and the link to circadian systems through transcriptional modification and post-transcriptional chromatin remodelling the mechanism of interaction.

The ultimate outcome is aimed at maintaining the stability of cellular homeostasis and protection of the genome. Unfortunately, this cross-talk and interconnectivity between diverse systems that allows for adaptation can be co-opted by oncogenes to enhance carcinogenic activity and resistance to therapeutics. Investigation by Shafi's group found CRY1 to be a pro-tumorigenic factor in prostate cancer, induced by androgens, interacting with oncogenic transcription factors and resulting in poor outcomes.

Conclusion

Through evolution we, as humans, have developed a complex of protective and repair systems to maintain cellular homeostasis, in common with other representatives of living organisms in nature. We think that our modern life-styles have insulated us from our ancestral past but aspects of earlier developmental levels continue to show that they can still be relevant. Cryptochrome is one such component.

An endogenous time-keeping system links us to the exogenous circadian system of the earth rotating on its axis, creating periods of light and darkness with varying exposure to solar radiation and movement of the earth around the sun, creating seasonal changes. The human must predict, respond and adapt to these cyclic changes with differences in physiological and behavioural response. There are a range of protective responses that have evolved to guard the genome, allow us to obtain nutrients and protect us from environmental toxins and dangers. The genetic imperative is still linked to a Palaeolithic, hunter, gatherer life-style, even though we consider ourselves more sophisticated. This link to the past is nowhere more clearly seen that the influence of the clock in gluconeogenesis indicating a necessity for a period of fasting to maintain normal metabolic control. If we are to gain maximum benefit from these protective systems we need to arise at dawn to entrain the circadian system and immediately become active outdoors with exposure to longer, red wavelengths of solar radiation that are not as dangerous with early exposure and condition the skin for exposure later in the day. This is the ideal time for recreational activities in the sun. Some sun exposure during the day is necessary to provide biosynthesis of Vitamin D from UVB exposure. Nocturnal darkness with minimal artificial light at night avoids interfering with production of melatonin, both Vitamin D and Melatonin having anti-proliferative effects.

We continue to defy this pattern with artificial light sources diurnally and artificial light at night. High energy and calorific foods are available continuously often with food and alcohol consumed well into the night, interfering with a required period of fasting. All nutrients can now be provided with minimal physical exertion further interfering with metabolic control.

We have moved ourselves away from natural protective systems through our modern life-style. Is it any wonder that these patterns of behaviour, including shift work increases obesity, diabetes and metabolic syndrome as well as increasing carcinogenesis.

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Conflict of interest statement:
None

Acknowledgements:
None

Funding
None.

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