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Review Article

Circadian redox rhythms in the regulation of neuronal excitability

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ABSTRACT

Oxidation-reduction reactions are essential to life as the core mechanisms of energy transfer. A large body of evidence in recent years presents an extensive and complex network of interactions between the circadian and cellular redox systems. Recent advances show that cellular redox state undergoes a ~24-h (circadian) oscillation in most tissues and is conserved across the domains of life. In nucleated cells, the metabolic oscillation is dependent upon the circadian transcription-translation machinery and, vice versa, redox-active proteins and co-factors feed back into the molecular oscillator. In the suprachiasmatic nucleus (SCN), a hypothalamic region of the brain specialized for circadian timekeeping, redox oscillation was found to modulate neuronal membrane excitability. The SCN redox environment is relatively reduced in daytime when neuronal activity is highest and relatively oxidized in nighttime when activity is at its lowest. There is evidence that the redox environment directly modulates SCN K^+ channels, tightly coupling metabolic rhythms to neuronal activity. Application of reducing or oxidizing agents produces rapid changes in membrane excitability in a time-of-day-dependent manner. We propose that this reciprocal interaction may not be unique to the SCN. In this review, we consider the evidence for circadian redox oscillation and its interdependencies with established circadian timekeeping mechanisms. Furthermore, we will investigate the effects of redox on ion-channel gating dynamics and membrane excitability. The susceptibility of many different ion channels to modulation by changes in the redox environment suggests that circadian redox rhythms may play a role in the regulation of all excitable cells.

1. Introduction

The suprachiasmatic nucleus (SCN) of the hypothalamus is the master regulator of the circadian rhythms in mammals. It generates the daily rhythms of behavior, metabolism, and other important physiological processes. The main driver of the circadian clock is a transcription-translation feedback loop of core circadian genes. However, emerging evidence suggest that metabolic oscillators also play a crucial role in the generation of circadian rhythms. Circadian rhythms in cycles of oxidation and reduction have been reported in a broad array of mammalian tissues and cell types and are conserved across the domains of life [1]. The discovery of a near-24-h oscillation of redox state in the SCN also revealed that cellular metabolic state could modulate neuronal excitability, an integral component of SCN timekeeping, via modification of redox-sensitive K^+ channels [2]. These studies demonstrate that redox homeostasis is dynamic, displays circadian characteristics, and may play a role in the regulation of daily rhythms of electrically excitable cells.

Since the pioneering work of Hodgkin and Huxley [3], the scientific community has developed deep insights into neuronal membrane dynamics. Neuronal excitability is linked directly to ion channel activity. A change in permeability of ions across the plasma membrane can lead to significant changes in resting membrane potential. The electrical properties of neurons and other excitable cells rely on many different

Abbreviations: AA, ascorbic acid; BK, large conductance Ca^{2+}- and voltage-activated K^+ channel; ChT, chloramine-T; CK1, casein kinase 1; CNS, central nervous system; CO, carbon monoxide; CRY, cryptochrome; DHA, dehydroascorbic acid; DRG, dorsal root ganglion; DTNB, 5,5-dithio-bis-(2-nitrobenzoic acid); DTT, dithiothreitol; ER, endoplasmic reticulum; FAD, flavin adenine dinucleotide; GPx, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide; Kv, voltage-gated potassium channel; HVA, high-voltage-activated; IP_3, inositol triphosphate; LVA, low-voltage-activated; MetO, methionine sulfoxide; MsrA, methionine sulfoxide reductase; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NAMPT, nicotinamide phosphoribosyltransferase; NO, nitric oxide; NOX, NADPH oxidase; NPAS2, neuronal PAS domain protein 2; PER, period; PPP, pentose phosphate pathway; Prx, peroxiredoxin; ROR, RAR-related orphan receptor; ROS, reactive oxygen species; RyR, ryanodine receptor; SCN, suprachiasmatic nucleus; SIRT1, sirtuin 1; SIRT3, sirtuin 3; Trx, thioredoxin; VIP, vasoactive intestinal peptide; V_m, membrane potential

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types of voltage-gated, ligand-gated, and leak channels that are permeable to ions such as Na^+, K^+, Cl^-, and Ca^{2+}. Membrane potential (V_m) is determined by the differential distribution of these ions. Ion channels are regulated by a vast number of ligands, post-translational modifications, and other mechanisms. They are susceptible to modulation by phosphorylation, second messengers, gaseous signaling molecules such as carbon monoxide (CO) and nitric oxide (NO), and by the redox environment [2,4–7].

Cellular redox encompasses the dynamic regulation of reactive oxygen species (ROS), antioxidants, and redox-sensitive metabolic cofactors. ROS have been viewed historically as toxic. There are many studies regarding their detrimental effects to the body and contributions to disease and aging. However, there is also increasing evidence that ROS signaling is integral to a multitude of normal cellular processes and signaling pathways [8–10]. ROS generation and redox homeostasis are no longer only relevant as sources of oxidative stress. Mounting evidence in the past few years shows circadian rhythms in redox state are an intrinsic and dynamic feature of all cell types and may contribute to daily regulatory processes.

Intrinsic circadian oscillations of signaling molecules exist in the SCN and hippocampus, opening windows of excitability and susceptibility. Cyclic changes that gate activity have been termed "iterative metaplasticity" to describe states permissive for plasticity mechanisms that are expressed as daily cycles [11]. In nucleated cells, the molecular circadian clock is reciprocally connected to the redox system. These interactions produce daily rhythms in redox state which can then modulate neuronal activity via regulation of ion channels [2]. Thus, day/night differences in redox state may play a role in the generation of daily changes in brain states that underlie the potential to establish long-lasting changes in brain function that we know as memory. Indeed, changes in the redox state have been found to modulate cognitive decline [12,13].

In this review, we examine fundamental features of circadian rhythms, the role of the SCN as master circadian clock, and explore the reciprocal connections between circadian timekeeping and the cellular redox oscillation, including the redox modulation of neuronal excitability. Then, we consider the many reports of redox modification of ion channel activity. We propose that circadian regulation of neuronal excitability via redox-sensitive ion channels may not be unique to the SCN.

2. Circadian rhythms

The 24-h cycle of day and night generated by the Earth's rotation has accompanied and driven the evolution of most organisms. As a result, myriad life forms, from some prokaryotes to all eukaryotes, have developed intrinsic daily rhythms in cellular processes, behavior, and metabolism. The self-sustained circadian oscillation provides an evolutionary advantage as it allows organisms to coordinate their internal states and anticipate changes in the timing and duration between night and day so that cellular, physiological, and behavioral events occur at appropriate times. Misalignment of the internal clock with the external environment can disrupt these functions and lead to disease [14–17].

3. The mammalian suprachiasmatic nucleus as master clock

The mammalian circadian system is organized hierarchically into a master oscillator and secondary oscillators in the brain and body. The suprachiasmatic nucleus (SCN) of the hypothalamus is the master circadian clock in mammals that synchronizes peripheral clocks in other brain regions and organ systems [18–20]. The SCN is a pair of small nuclei on either side of the third ventricle, directly above the optic chiasm in the anterior hypothalamus (Fig. 1) [21]. Each nucleus is composed of approximately 10,000 tightly compacted cells whose collective activity is considered to be the central “pacemaker” of circadian rhythm [22]. Destruction of the SCN results in the loss of daily rhythms in sleep-wake cycle, body temperature, locomotor activity, drinking, and endocrine release [23,24].

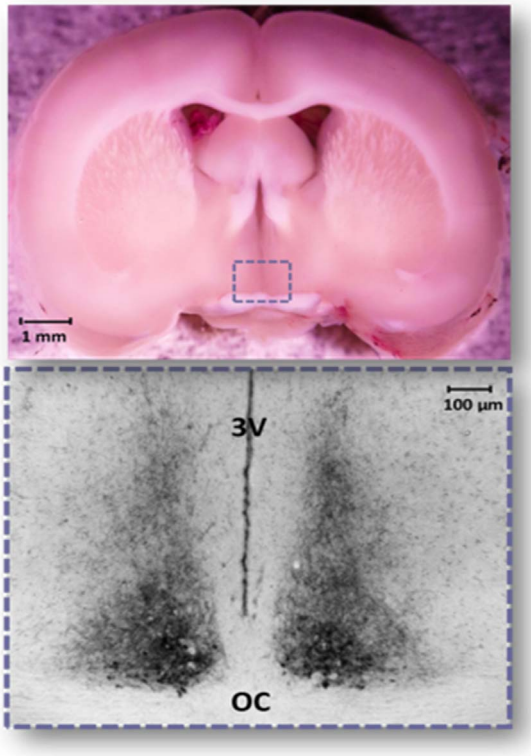

Fig. 1. The mammalian circadian clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. *Upper:* In this fresh coronal section of the brain of a rat, the SCN lies near the base (within the dashed box). *Lower:* Vasoactive intestinal peptide (VIP) immunoreactive staining shows the pair of small hypothalamic nuclei is positioned medially, on either side of the third ventricle (3 V), and directly superior to the heavily myelinated optic chiasm (OC).

3.1. Oscillation of clock genes and proteins in the SCN

Circadian rhythms are generated by a transcription-translation feedback loop of clock genes and proteins that form an oscillatory molecular clock [25]. This core molecular clock consists of a heterodimeric complex of protein products of the genes *CLOCK* and *BMAL1,* which positively regulate the expression of *Period* (*Per1, 2, and 3*) and *Cryptochrome* (*Cry1 and 2*) genes. The accumulated protein products form their own heterodimeric transcriptional repressor complex of PER and CRY that represses the activity of CLOCK and BMAL1. The transcriptional-translational loop of these core clock genes repeats with a period of approximately 24 h and is the basis for the mammalian molecular clock.

An additional interlocking feedback loop involves the BMAL1/CLOCK-mediated transcription of nuclear receptor genes, *Rev-Erbα/β* and *RAR-related orphan receptor alpha (Rorα*). To complete the circadian loop, REV-ERB and ROR proteins then compete for binding sites within the promoters of *Bmal1* and *CLOCK,* where REV-ERB inhibits transcription and ROR initiates transcription. Additionally, casein kinase 1 (CK1)-mediated phosphorylation contributes to timekeeping through the destabilization of PER proteins [26]. Post-translational modifiers like protein kinases and small molecule messengers such as cAMP and Ca^{2+} play important roles to determine and modify the intrinsic circadian rhythm [27–32]. Together, these modifiers work to synchronize firing rate, gene expression, and secretion across the SCN.

3.2. Oscillation of neuronal activity in the SCN

Circadian rhythms in SCN electrical activity were first revealed via *in vivo* recordings by Inouye and Kawamura in 1979 [33]. The activity of the SCN neuronal population oscillates: it is nearly electrically silent at night but exhibits significantly higher frequency during the day, peaking at midday [2,34,35]. This rhythm exists endogenously and will persist for days in an SCN brain slice without input from other brain regions or the external environment [34,36,37]. Interestingly, this high level of spontaneous action potentials occurs during the day regardless of whether the species is nocturnal or diurnal [38]. The SCN is able to generate these neuronal activity rhythms *in vivo,* in slice, and in dispersed cell culture [36,39,40].

Circadian oscillation in neuronal electrical activity is generated at the level of individual neurons. The spontaneous firing of SCN neurons emerges from modulation of a combination of intrinsic currents. These currents can be divided into those that provide excitatory drive and depolarization during the day, those that maintain a regular pattern of action potentials, and those that produce the hyperpolarization that renders SCN neurons silent at night [38]. Underlying activity rhythms are day/night changes in resting membrane potential. Studies have shown the resting membrane potential of neurons in the SCN is most depolarized during midday and most hyperpolarized in the early night [2]. The daytime depolarization of SCN neurons is accompanied by a decrease in overall K^+ conductance while a larger K^+ conductance at night results in hyperpolarization [41,42]. The differences in membrane potential and ionic conductances during the day and night persist even in the absence of synaptic activity and are likely clock-driven [43].

Whereas neuronal activity in the SCN could be interpreted as an output of the molecular clock that mediates communication with other brain regions, research from the past 20 years has established that neuronal activity is an important component of rhythmic gene expression. A decade ago, a landmark study showed that electrically silencing *Drosophila melanogaster* pacemaker neurons stops the free-running rhythms of core molecular clock components PERIOD and TIMELESS, as well as behavioral activity rhythms [44]. Furthermore, a recent study showed that optogenetic activation and suppression of SCN neuronal firing in mice can reset the phase and alter the period of the molecular clock, respectively [45]. These conceptual advances establish that the molecular rhythm and neuronal activity rhythm are, in fact, linked as core clock mechanisms.

4. Extra-SCN clocks

Rhythms of core clock genes are found in cells and tissues throughout the body and in regions of the brain outside of the SCN. These molecular rhythms persist when cells or tissues are maintained in culture in the absence of the SCN. Because non-SCN cells also contain these endogenous molecular oscillators, the molecular circadian clock is now recognized as a fundamental component of all cells [46,47]. However, the SCN alone behaves as the master clock. A key difference between the SCN and peripheral oscillators with respect to emergent behavior is in their network properties. SCN explants are capable of sustaining synchrony via synaptic and neuropeptidergic coupling mechanisms. While isolated cells and cells within cultured peripheral tissue can oscillate independently of one another [48], they are coupled within tissues in the body [47].

In complex organisms, the circadian system is comprised of multiple oscillators. Peripheral oscillators are not directly entrained by light, so they rely on the SCN for synchronization within tissues and to the external environment. Circadian oscillations have been identified within various structures of the central nervous system. Robust rhythms in core clock gene expression and electrical activity have been observed in extra-SCN hypothalamic nuclei, the olfactory bulb, amygdala, cerebellum, cerebral cortex, and hippocampus [49–51]. These areas differ in phase, ability to sustain rhythmicity, and their relationship to the SCN. The SCN entrains other oscillators partly through efferent projections, but primarily through release of diffusible factors such as peptides and hormones [52,53]. Circadian oscillations in the liver and hippocampus can be entrained by external cues other than light. Restricted feeding is a salient signal for entraining the circadian clocks of these peripheral oscillators, whereas the SCN is relatively unaffected [54].

5. Circadian rhythms and metabolism

A large body of evidence has demonstrated circadian rhythmicity in metabolism. Plasma concentrations of glucose and insulin show a day/night pattern in mammals and the SCN is required for this rhythmicity [55]. In addition, glucose utilization in the SCN is rhythmic, with the highest level of uptake in the subjective day when SCN neuronal activity peaks [56]. Furthermore, circadian rhythms and metabolism are inextricably linked. Food acts as a powerful *zeitgeber* (time-giver, German) and the circadian clock contributes to metabolic homeostasis by shifting physiological processes to support changes in activity [57]. Animal models that lack a functional circadian clock show not only a lack of rhythmicity, but also abnormal metabolic phenotypes [58].

Transcriptomic studies reveal that nearly half of the mouse genome oscillates with a near-24-h rhythm in an organ-specific manner [59]. Strikingly, many of the genes that show circadian oscillation are involved in metabolic functions [60,61]. Metabolomic screens of mice and humans have found that large amounts of metabolites are rhythmic even when conducted in constant environmental conditions. Furthermore, nuclear hormone receptors that participate in fatty acid and glucose metabolism as well as metabolic hormones, like glucagon and insulin, display circadian oscillation [62,63]. Recently, work from Feeney et al. demonstrated that in eukaryotes, the level of intracellular Mg^{2+} displays circadian rhythmicity and can feed back to regulate clock periodicity [64]. What makes this finding exciting is that Mg^{2+} is a necessary cofactor for ATP to be biologically active, thus giving circadian significance to global cellular energetics and vice versa. These combined data strongly suggest that metabolism is influenced by circadian rhythm and there is increasing evidence that these metabolic fluctuations can feed back to regulate elements of the clock.

6. Cellular redox signaling

Energy metabolism is linked to redox homeostasis. On a cellular level, metabolic state is represented by the redox state. Redox is the potential to donate or receive electrons for biochemical processes and redox state can be defined by the balance of oxidizing and reducing potential. This can be evaluated biochemically by the ratio of small molecule cellular redox pairs, such as glutathione disulfide (GSSG)/glutathione (GSH), nicotinamide adenine dinucleotide (NAD^+/NADH), nicotinamide adenine dinucleotide phosphate ($NADP^+$/NADPH) or dehydroascorbic acid (DHA)/ascorbic acid (AA) (Fig. 2). These redox molecule pairs are sensitive to electron flow and to fluctuations in the reducing/oxidizing potential of the cellular environment.

Cells possess multiple regulators of redox state. GSH is the most abundant free thiol in cells and is primarily responsible for maintaining a physiological intracellular redox environment. Reduced GSH is oxidized to GSSG, and the GSH/GSSG ratio is frequently used to assess overall redox state [65]. The thioredoxin (Trx) system is another ubiquitous thiol-reducing complex. Like GSH, thioredoxins serve as electron donors to reversibly reduce intracellular protein disulfides and maintain redox homeostasis [66]. Peroxiredoxins (Prxs) are a family of peroxidases that scavenge and reduce hydrogen peroxide (H_2O_2) as regulators of the cellular redox environment. Mammals express six different Prx isoforms (Prx1–Prx6) with distinct subcellular distributions in different brain regions and cell types. Upon encountering H_2O_2, Prxs go through several levels of oxidation. The reduced thiol (-SH) reacts to form a sulphenic acid (-SOH), then sulphinic acid ($-SO_2H$), and

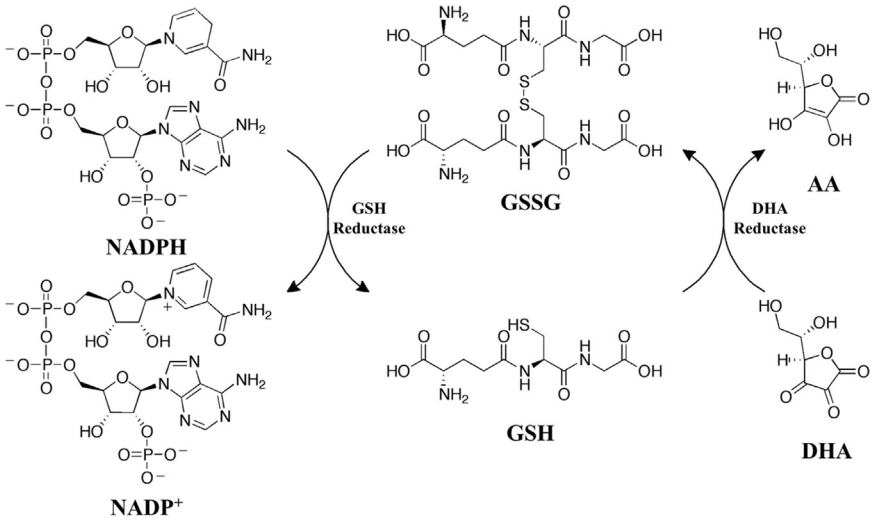

Fig. 2. Cellular redox state is determined by several redox cofactor pairs. Redox state can be evaluated by the balance of small molecule redox cofactor pairs that are sensitive to the oxidizing/reducing potentials of the cell. These reversible reactions are regenerated enzymatically. Depicted are glutathione disulfide (GSSG)/glutathione (GSH), nicotinamide adenine dinucleotide (NAD^+/NADH), nicotinamide adenine dinucleotide phosphate ($NADP^+$/NADPH), and dehydroascorbic acid (DHA)/ascorbic acid (AA).

a fully oxidized sulphonic acid (-SO_3H) [67].

Relative to its size, the brain consumes a disproportionately large amount of O_2 and is highly sensitive to oxidative stress and damage. Reactive oxygen species (ROS), such as H_2O_2, superoxide anion (O_2^-), and hydroxyl radical ($HO^•$), are frequently implicated in oxidative damage and pathogenesis of disease. O_2^- is generated primarily as a by-product of mitochondrial oxidative phosphorylation and also by NADPH oxidase (NOX) enzyme complexes [68]. Only moderately reactive, O_2^- is rapidly converted to H_2O_2 by superoxide dismutases. H_2O_2 is more inert and capable of diffusing through cellular membranes [69]. In low levels, H_2O_2 can act as a local signaling molecule and, in high levels, can have cytotoxic effects [70]. H_2O_2 is catalytically broken down to H_2O by scavenging enzymes such as catalase (Prxs), or glutathione peroxidases (GPx), which keep ROS levels contained. More reactive than either O_2^- or H_2O_2 is $HO^•$, which can be generated from H_2O_2 in the presence of metal ions via the Fenton reaction. A careful overall balance in production and neutralization of oxidants is maintained using a variety of mechanisms. When ROS levels rise significantly and overwhelm the antioxidant defense system, oxidative stress can occur and cause damage to cellular structures [71]. However, small changes in ROS are integral to many biochemical processes. Accumulating evidence suggests that ROS also play important roles in intracellular signal transduction and many physiological processes [72–74].

Protein amino acid residues are major targets of cellular oxidants. Many of the effects of signaling via ROS are through the reversible modification of exposed cysteine and methionine residues of redox-sensitive proteins. Cysteines and methionines have reactive sulfur-containing side chains that make them more susceptible to redox modifications than other amino acids. The thiol (–SH) functional groups of cysteine residues make them especially susceptible to oxidation. Upon exposure to H_2O_2, the redox-sensitive thiol can be reversibly oxidized to reactive sulphenic acid (-SOH) or further oxidized to sulphinic acid (-SO_2H) and irreversibly to sulphonic acid (-SO_3H) [75]. Non-enzymatic and reversible disulfide bond formation with a nearby cysteine is the most common product of -SOH cysteine oxidation [76].

The redox state of sulfur-containing amino acids is tightly regulated by GSH. GSH is a major source of cellular cysteine. Its linkage to redox-sensitive cysteine residues within proteins is termed S-glutathionylation. This transient incorporation of GSH into cellular protein via reactive thiols is a metabolically driven form of post-translational modification [77]. Redox-sensitive methionine residues do not form disulfide bonds and, instead, are oxidized to methionine sulfoxide (MetO) by a variety of different ROS [78]. The reduction of oxidized methionine is catalyzed by the enzyme methionine sulfoxide reductase (MsrA) [79]. The redox modification of these sulfur-containing amino acids can result in functional changes to protein structure and/or activity.

7. Redox-molecular clockwork interactions

There is compelling evidence that redox state may play a regulatory role in the circadian clockwork. Reduced forms of the redox cofactors NAD(H) and NADP(H) have been shown to enhance DNA-binding activity of the core clock proteins BMAL1 and CLOCK, while their oxidized forms inhibit it. Even minute changes in cellular redox state can affect binding activity of these circadian transcriptional activators [80]. The BMAL1/CLOCK heterodimer regulates the expression of nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme in the NAD^+ salvage pathway [81,82]. This relationship is the driving force for rhythmic levels of NAD^+, which in turn activate NAD^+-dependent histone deacetylases, sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) [82,83]. SIRT1, an important element of metabolic control, displays circadian oscillatory activity, and alters PER2 stabilization and CLOCK function [84–86]. SIRT1 is localized in the mitochondrial matrix where it mediates the deacetylation of metabolic enzymes (Fig. 3).

Heme, a protein cofactor that acts as a sensor of cellular redox state, is another component in the metabolism-circadian relationship. Heme reversibly binds to the circadian nuclear receptors REV-ERBα and REV-ERBβ in a redox state-dependent manner and modulates their activity, providing a link between energy sensing and an arm of the molecular clock [87–89]. Heme also binds to neuronal PAS domain protein 2 (NPAS2), a CLOCK paralog that binds to BMAL, and modulates its DNA-binding activity [90]. Another link between metabolism and circadian systems comes from the clock's sensitivity to the AMP/ATP ratio through AMP-activated protein kinase (AMPK)-mediated phosphorylation of CRY and casein kinase I (CK1) [91]. Phosphorylation of CRY results in its degradation, and phosphorylation of CKIε increases its activity and accelerates the degradation of PER2. Most recently, Hirano et al. showed that in mammalian cells, CRY proteins are stabilized by the redox cofactor flavin adenine dinucleotide (FAD) [92].

The first evidence of a molecular clock-independent circadian oscillation came in the form of redox rhythms [93]. Both sulphinic and sulphonic forms of peroxiredoxin are considered “hyper-oxidized.” A circadian oscillation of hyper-oxidized Prx proteins has been observed in red blood cells. The presence of this rhythm in cells that lack a nucleus established that circadian metabolic cycles can exist independently of the core molecular clock based on transcription-translation. However, in embryonic fibroblastic cells from *mCry1/2 -/-* mice, hyper-oxidized Prx rhythms are altered [93]. Therefore, in nucleated

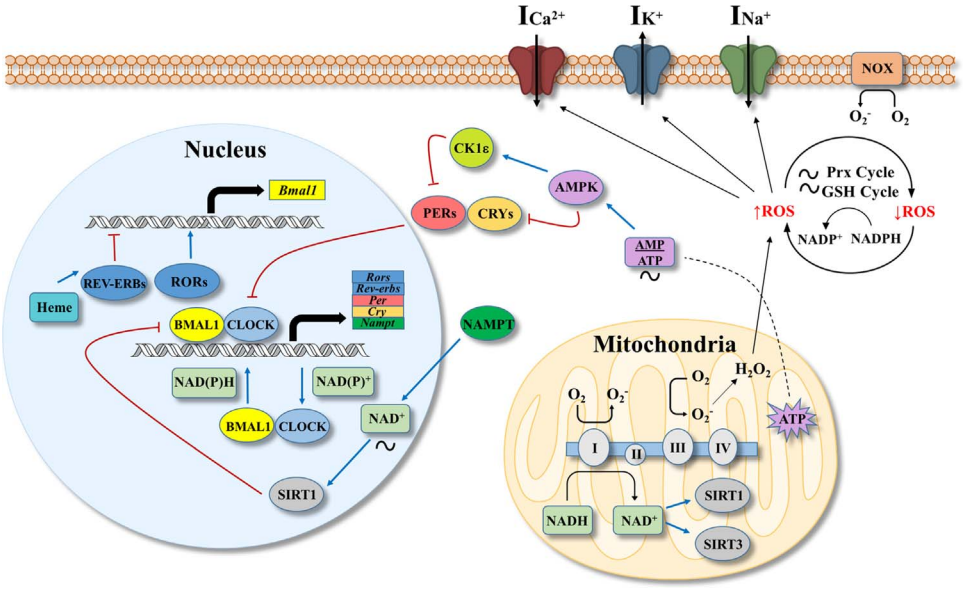

Fig. 3. Interactions between cellular metabolism, the circadian molecular clock, and ion channels. The core molecular clock consists of positive elements, such as circadian locomotor output kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1), that positively regulate the expression of PERs and CRYs, which comprise negative elements, repressing the activity of CLOCK and BMAL1 [26]. An additional feedback loop involves the BMAL1/CLOCK-mediated transcription of REV-ERB and RAR-related orphan receptor (ROR) proteins that inhibit and initiate *Bmal1* transcription, respectively. Casein kinase 1 (CK1) enzymes contribute to timekeeping through phosphorylation and destabilization of PER. Reduced forms of NAD(H) and NADP(H) enhance DNA-binding activity of BMAL1 and CLOCK, while oxidized NAD^+ and $NADP^+$ inhibit their DNA binding [80]. Nicotinamide phosphoribosyltransferase (NAMPT) is a rate-limiting enzyme in the NAD^+ biosynthetic pathway and is the driving force for rhythmic levels of cellular NAD^+ which, in turn, activate NAD^+-dependent histone deacetylases, sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) [82,83]. SIRT1 has been found to exhibit circadian oscillatory activity and alter clock gene expression. SIRT3 is located in the mitochondria where it mediates metabolic processes. Heme is a known sensor of cellular redox state that binds to nuclear receptors REV-ERBα and REV-ERBβ and modulates their activity [87,88]. AMP-activated protein kinase (AMPK) is an important sensor of cellular energy state activated by a high AMP/ATP ratio. AMPK mediates phosphorylation of CRY and CK1 [91]. Phosphorylation of CRY marks it for degradation and phosphorylation of CK1 increases its activity and accelerates degradation of PER2. The balance between ROS levels and antioxidant defense systems, such as peroxiredoxins (Prx) and glutathione (GSH), contribute to the overall redox state. Ca^{2+}, K^+, and Na^+ ion channels have been shown to be sensitive to redox modifications.

cells, there is interplay between a non-translational redox-based oscillator and the clock gene-dependent oscillator. This redox cycle of Prxs is conserved broadly across domains of life, from prokaryotes to the rodent SCN [1]. These findings raise the possibility that rhythms in metabolism may be an ancient timekeeping oscillator [94].

Recent studies have identified the pentose phosphate pathway (PPP) as a regulator of circadian redox rhythms. Glucose utilization through the PPP is essential for replenishing the cytoplasmic NADPH content as well as for the generation of nucleotide and amino acid precursors. NADPH availability is required for the regeneration of cellular antioxidants, such as GSH, and prevention of oxidative stress. By pharmacological and genetic inhibition of the PPP, Rey and colleagues demonstrated that NADPH availability is able to alter both the phase and period of the molecular clock in human osteosarcoma cells [95]. A similar study found that PPP inhibition affects only clock gene expression amplitude and phase with no changes in periodicity [96]. These inconsistencies may be explained by the differences in inhibitors and cell types employed. Taken together, these data suggest that metabolic and redox mechanisms can modulate the core circadian clock.

This is by no means an exhaustive list of known circadian-metabolism interactions. However, these findings provide strong support for metabolic regulation of the core molecular clock and vice versa. In mammalian systems, redox rhythms work in concert with molecular circadian timekeeping and have both input and output roles.

8. Circadian redox rhythms and SCN neuronal excitability

Corresponding circadian oscillations of redox state and neuronal excitability were observed in the SCN of rats and mice [2]. Through measurement of FAD/NAD(P)H, glutathiolation, and DHA/AA ratios, Wang et al. reported that the SCN redox environment is at its most reduced in the mid-subjective day and most oxidized in the early subjective night. Strikingly, midday corresponds to the peak in spontaneous action potentials and most depolarized state of membrane potential (V_m), assessed by patch clamp recording of SCN neurons. Early night corresponds to the lowest levels of spontaneous action potentials and V_m of SCN neurons is most hyperpolarized. The circadian redox rhythm is not present in arrhythmic *Bmal1-/-* mice, suggesting that it is dependent upon a functional circadian molecular clock [2].

Imposed changes in redox state cause immediate changes in excitability [32]. Thus, unlike the transcription-translational relationship of changes in the molecular clock to SCN physiology, redox modulates neuronal excitability by tight coupling. A parallel relationship between redox state and membrane potential of SCN neurons suggests metabolic state has a modulatory role in membrane excitability. Patch-clamp electrophysiology showed that redox state regulates SCN neuronal excitability via post-translational modulation of K^+ channels. The relatively reduced daytime environment decreases hyperpolarizing K^+ currents, which results in membrane depolarization and increased neuronal activity. Conversely, the oxidized nighttime environment potentiates K^+ currents, resulting in membrane hyperpolarization and reduced neuronal activity. Application of pharmacological blockers suggests that both leak and A-type K^+ channels in SCN neurons are sensitive to redox environment and mediate changes in membrane excitability (Fig. 4) [2]. These findings established a new connection between redox state and neuronal excitability in the SCN: metabolic state can be a modulator, rather than only the result, of neuronal activity.

Extending beyond the central nervous system (CNS), endogenous redox oscillations can have modulatory effects on other excitable cells in the body. For instance, there is considerable research on how the heart responds to ROS. The redox environment can affect cardiac excitability via modulation of Ca^{2+}, Na^+, and K^+ ion channels [97]. Furthermore, a growing number of studies are focused on the relationship between redox and pain pathways, specifically, the effects of redox modulation of ion channels and excitability in peripheral sensory neurons [98–100].

9. Redox modulation of K^+ channel activity

Ion channels permeable to K^+ are components of the plasma membrane of most mammalian cells. K^+ channels play central roles in the regulation of neuronal excitability via the resting membrane potential, the repolarization phase of action potentials, and firing frequency [7]. Alterations in their activity can lead to changes in many aspects of neuronal activity. Four major classes of K^+ channels can be identified when grouped by common characteristics and function: voltage-gated, Ca^{2+}-activated, inward-rectifying, and leak K^+

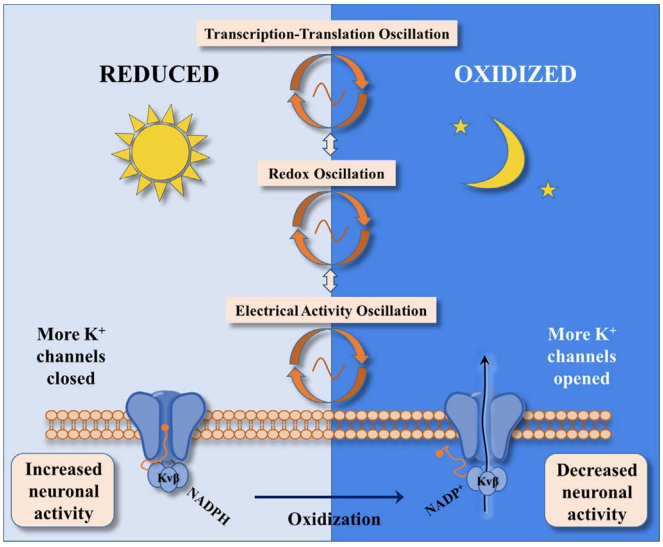

Fig. 4. Day-night oscillation of the redox environment modulates SCN neuronal excitability. In the relatively reduced daytime environment, more K^+ channels close and the neuronal membrane becomes more depolarized, bringing the membrane potential closer to threshold for action potentials. In the relatively oxidized nighttime environment, more K^+ channels open and the neuronal membrane becomes hyperpolarized [2]. Some voltage-gated K^+ channels have been shown to have oxidoreductase Kvβ subunits that bind the redox cofactor NADPH, which determines gating dynamics [101]. This confers sensitivity to the local redox environment.

channels. In this section, we will discuss the redox sensitivity of voltage-gated, Ca^{2+}-activated, and inward-rectifying K^+ channels, which have been more thoroughly studied.

9.1. Voltage-gated K^+ channels

Voltage-gated potassium (Kv) channels form a large and evolutionarily conserved family of ion channels that play essential roles in the generation and propagation of electrical impulses in excitable cells. Each Kv channel contains four α−subunits that form the pore structure and may also contain auxiliary β−subunits that modify channel activity [102]. Kv channels can be physiologically divided based on inactivation properties into fast-inactivation A-type K^+ channels and delayed-rectifier K^+ channels. Rapid inactivation occurs via the "ball and chain" mechanism where the N-terminus of an α− or β−subunit blocks the pore and inhibits ion flow [103]. This is also sometimes referred to as "N-type inactivation."

Several rapidly inactivating (A-type) Kv channels have been found to be sensitive to the redox environment. Ruppersberg et al. showed that A-type K^+ channels cloned from mammalian brain can be modulated by intracellular GSH. In an oxidized state, reversible formation of a disulfide bond forms in the inactivating gate, preventing it from closing/inactivation. Application of reduced GSH rapidly restored fast-inactivation of the channel [104]. This modulation of inactivation properties may lead to changes in hyperpolarization or depolarization of the membrane. Similar redox modulation of β−subunit cysteine residues can determine inactivation states [103,105]. Additionally, subsequent studies have shown that the oxidation of methionine in Kv channels rapidly reverses the inactivated state of the channel [106].

Several types of delayed-rectifier K^+ channels are expressed in the CNS with distinct channels localized to specific areas [107]. In freshly dissociated CA1 neurons from the rodent hippocampus, application of H_2O_2 inhibits delayed rectifier K^+ currents. The effect is completely abolished by the addition of membrane-permeable thiol-reducing agents, indicating the involvement of sulfhydryl groups [108]. Furthermore, oxidation by H_2O_2 increases M-type K^+ current in superior cervical ganglion (SCG) neurons and, consequently, decreases neuronal resting membrane potential [109]. These effects result in reduced neuronal excitability and are reversed by the reducing action of dithiothreitol (DTT). The mammalian Shaker family channels (Kv1) can undergo inactivation from their associated β subunits (Kvβ). Studies have shown that the Kvβ subunits are oxidoreductase enzymes that bind and utilize NADPH, coupling channel activity with cellular redox [105]. Oxidation of Kvβ-bound NADPH limits N-type inactivation by obstructing the N-terminus from blocking the channel, leading to a potentiated K^+ current (Fig. 4) [101].

9.2. Ca^{2+}-activated K^+ channels

The large conductance Ca^{2+}- and voltage-activated K^+ (BK) channels contribute to a variety of functions, including the regulation of membrane excitability and intracellular Ca^{2+} concentration. BK channels are activated during action potentials by membrane depolarization and Ca^{2+}entry through voltage-sensitive Ca^{2+} channels. Fast BK activation leads to hyperpolarization and closure of Ca^{2+} channels [110]. Under physiological conditions, intracellular Mg^{2+} also is capable of enhancing BK channel activity with low affinity independent of the high affinity Ca^{2+} binding site [111–113]. BK channels are essential for circadian pacemaker neuronal firing in the SCN with peak activity that suppresses spontaneous firing at night [114]. Daily expression of SCN BK channels shows circadian rhythmicity in the absence of light and is dependent on the intrinsic molecular clock [115–117]. Although BK channel expression is decreased during the day and BK activity is sensitive to the intracellular Ca^{2+} concentration, N-type inactivation of BK channels also contributes to the decrease in daytime K^+ current that modulates SCN firing rhythms [114].

Similar to voltage-gated K^+ channels, BK channels contain a tetrameric pore formed of α subunits that may be associated with auxiliary β subunits that confer various functional properties to the channel [118]. BK channels have been shown to be directly modulated by redox state with somewhat inconsistent results. Direct application of reducing and oxidizing agents modulates activity of human Ca^{2+}-activated K^+ (BK) channels expressed in Xenopus oocytes and human embryonic kidney cells. The thiol-reducing agent DTT enhances and stabilizes channel activity while the oxidizing agent H_2O_2 decreases the channel open probability [119].

In dissociated adult rat hippocampal pyramidal neurons, application of GSSG, oxidized glutathione, increases channel open probability and thus activity, while application of GSH, reduced glutathione, reverses the effects [120]. Another study using cultured neonatal rat hippocampal neurons reported the opposite results: GSSG decreases channel activity and GSH activates the channels [121]. These conflicting results may be explained by the heterogeneity of ion channels due to the variety of accessory subunits. BK channels have four known β subunits and each modulates channel function in different ways [122]. Additionally, BK channels have both cysteine and methionine residues that are redox sensitive; oxidation of the different amino acids appears to have opposite effects on channel activity [123–125].

9.3. Inward rectifying K^+ channels

Unlike most K^+ channels, inwardly rectifying K^+ (K_{ir}) channels are characterized by greater inward flow rather than outward flow. They are an important class of K^+ channels that contribute to regulation of membrane potential and activity in excitable cells. Structurally, K_{ir} channels are tetramers with subunits of two transmembrane domains and cytoplasmic N- and C-terminal domains linked by a conserved pore region [126–128]. Under physiological conditions, these channels display greater conductance when membrane potential is more negative than the reversal potential of K^+ and permit less flow when membrane potential is more positive [129–131]. Inward flow of ions through K_{ir} channels is due to interactions with intracellular Mg^{2+} and polyamines, which physically block the cytoplasmic region preventing ion efflux [132–134].

High-resolution kinetic analyses demonstrate that K_{ir} channels are susceptible to redox regulation. Ruppersberg and Fakler first observed that presence of the reducing agent DTT in the buffer solution altered the kinetics of K_{ir}2.1channels expressed in Xenopus oocytes [135]. Furthermore, application of DTT reversibly increased channel activity of G protein-coupled inwardly rectifying K^+ (GIRK) channels K_{ir}3.1/3.4 [136]. This modulatory activity depends upon a specific cysteine residue in the *N*-terminus because mutation of this cytoplasmic residue abolishes redox-mediated effects. Beyond redox modifications, the dependence of K_{ir} and BK channel activity on cytoplasmic Mg^{2+} availability raises the interesting question of whether circadian oscillation in intracellular Mg^{2+}concentration can also exert rhythmic modulatory effects on ion-channel kinetics. Thus, there are multiple potential avenues for circadian metabolic regulation of neuronal excitability.

10. Redox modulation of Ca^{2+}channel activity

Calcium has the unique role of contributing to the membrane electrical potential as well as acting as a second messenger in the cytoplasm. Intracellular Ca^{2+} is an important regulator of neurotransmitter release, ion channel activation, gene regulation, and action potential generation [137]. Elevated cytosolic Ca^{2+} in neurons comes from the endoplasmic reticulum (ER) or the extracellular space.

10.1. Voltage-gated Ca^{2+} channels

Ca^{2+} influx from the extracellular space is achieved primarily through several voltage-gated Ca^{2+} channels and Ca^{2+}-permeable cation channels. Voltage-dependent Ca^{2+} channels can be classified based on their sensitivity to activation into high-voltage-activated (HVA) and low-voltage-activated (LVA) channels. LVA channels are also known as "transient" T-type channels. HVA channels are further subdivided into L-, N-, P, Q-, and R-type channels. Both L-type and T-type Ca^{2+} currents contribute to the excitatory drive of SCN neurons in the morning, and the L-type current amplitude shows a diurnal rhythm [38].

T-type Ca^{2+} channels have been widely implicated in redox sensitivity of nociceptive neurons [138]. A study using dissociated primary sensory dorsal root ganglion (DRG) neurons demonstrated that T-type currents are significantly enhanced in the presence of a sulfhydryl-reducing agent and inhibited in the presence of a sulfhydryl-oxidizing agent, suggesting that T-type Ca^{2+} channels are redox sensitive [139]. Interestingly, the same study by Todorovic et al. showed that while redox reagents affected the T current in DRG cells, none had an effect on the HVA current, event at high concentrations. Furthermore, the presence of reducing agents enhances neuronal excitability of peripheral nociceptors through T-type channel modulation [98,99]. Studies show that the Ca_v3.2 isoform of T-type Ca^{2+} channels is the target of redox modulation [139–141]. Consistent with these results, Ca_v3.2 T-type currents in the thalamus are enhanced by thiol-reducing agents L-cysteine and DTT, while the oxidizing agent 5,5-dithio-bis-(2-nitrobenzoic acid) (DTNB) inhibits the currents [142].

Many studies have demonstrated that L-type Ca^{2+} currents are affected by reducing and oxidizing agents. However, most of these were conducted in non-CNS cells. Thiol-specific oxidizing and reducing agents have been shown to modulate L-type Ca^{2+} channels in cultured cardiomyocytes and smooth muscle cells. Oxidizing agents increased the basal L-type current and reducing agents decreased the current in some cells whereas oxidizing agents inhibited the current in other cells [131,143,144]. There is evidence that changes to current activity in the presence of H_2O_2 and thiol-oxidizing agents is due to *S*-glutathionylation of the L-type Ca^{2+} channel [145,146]. These conflicting effects of oxidation may reflect differences in subunit composition, cell type, and membrane voltage.

10.2. Intracellular Ca^{2+} channels

Intracellular Ca^{2+} stores are released from the endoplasmic reticulum (ER) by the inositol triphosphate (IP_3) receptor in IP_3-mediated release and Ca^{2+}-induced Ca^{2+} release via the ryanodine receptor (RyR) on the ER. Ample evidence demonstrates that the activity of RyR is sensitive to the cellular redox environment. RyRs are Ca^{2+} channels embedded in the membrane of the endoplasmic reticulum and are responsible for release of Ca^{2+} from intracellular stores. RyR are susceptible to many posttranslational modifications, with redox modification being one of them. The sulfhydryl groups of RyR cysteine residues are subject to reversible S-nitrosylation and S-glutathionylation, which can affect channel structure and activity. Additionally, oxidizing agents increase RyR opening probability while reducing agents have the opposite effect [147–149]. The RyR is most active under oxidizing conditions, making redox state a potential regulator of intracellular Ca^{2+} signaling. It is noteworthy that the activity of the RyR in the SCN undergoes tight circadian regulation. RyR are sensitive to activation in early night, when the oxidation state of the SCN is maximal [2150].

11. Redox modulation of Na^+ channel activity

Voltage-dependent sodium channels underlie the generation of action potentials in many excitable cell types. The fast-inactivating Na^+ current initiates action potentials, however, the Na^+ current also has a voltage-dependent non-inactivating component in some cells [151]. This persistent Na^+ current is a key component of the excitatory drive for SCN neurons to be spontaneously active [38]. Like K^+ and Ca^{2+} channels, Na^+ channels are susceptible to redox modulation. Wang and colleagues observed that application of Chloramine-T (ChT), an oxidant that targets both cysteine and methionine residues, inhibits channel inactivation in toad myelinated nerve fibers and squid giant axons [152,153]. Further investigation revealed that it is the oxidation of methionine residues by ChT that attenuates fast inactivation of some Na_v isoforms [154]. These studies show oxidation of several methionine residues suppresses inactivation; however, the cysteine residues of Na^+ channels are also targets of redox modulation. In cultured neuroblastoma cells, thiol oxidizers significantly inhibited Na^+ currents, which could be fully reversed by thiol-reducing agents DTT and intracellular GSH [155].

12. Circadian redox modification of membrane excitability in Drosophila melanogaster

The *Drosophila melanogaster* circadian system provides perhaps the most direct example for the interconnections between redox status, neuronal excitability, and the core components of the circadian clock. Approximately 150 neurons have been identified as the circadian clock circuit in the *Drosophila* CNS. These neurons are organized into clusters that include the large and small lateral ventral neurons (lLNvs and sLNvs), which play important roles in timekeeping [156]. Electrical properties of these pacemaker neurons show diurnal variation with higher resting membrane potential and greater frequency of spontaneous firing during the subjective day than the subjective night [157]. Similar to the SCN, this oscillation in excitability helps maintain circadian rhythmicity and also is subject to circadian regulation [44,158,159].

In this system, Cryptochrome (CRY) is photosensitive and functions as a blue light photoreceptor that regulates circadian entrainment [160,161]. CRY is expressed in clock neurons and interacts with the core circadian machinery by binding to Timeless (TIM) upon light activation to initiate its degradation. Light-activated CRY is also known to regulate the firing rate of lLNv arousal neurons through modification of K^+ channel conductance [162]. In fact, CRY is coupled to neuronal electrical activity by redox modulation of ion channels. Upon light

activation, the CRY chromophore flavin adenine dinucleotide (FAD) is reduced. This change in redox state is coupled to redox-sensitive β subunits of the voltage gated K^+ channels, leading to rapid membrane depolarization [163].

13. Conclusion

The balance between generation of ROS and availability of antioxidant defense systems in the cell is reflected in the redox state. There is increasing evidence that small changes in ROS can regulate diverse cellular processes and pathways. Many proteins, including ion channels, can be modified by oxidizing or reducing reactions. The discovery of endogenous and conserved circadian redox oscillations brings time-of-day significance to all cellular processes that are susceptible to redox regulation. Wang and colleagues demonstrated that circadian redox environment of the SCN can modulate K^+ ion channel activity and thus neuronal excitability [2]. This is the first and, to our knowledge, only example of the modulation of neuronal excitability by redox state in a circadian-dependent manner in mammals.

The SCN is unique among brain regions in that synchronized neuronal firing is independent of synaptic input, depending instead upon modulation of multiple intrinsic currents for daytime excitatory drive and nightly silencing. It is not difficult to appreciate how circadian redox regulation of key ion channels can rhythmically modulate SCN neuronal activity. However, it is challenging to infer the relationship between redox state and neuronal activity in other brain regions where studies have focused primarily on high-resolution relationships between redox and ion channel kinetics; insight on cellular changes in membrane potential and excitability due to redox modulation of specific ion channels in these regions is lacking. We predict that this relationship may vary across brain regions on a case-by-case basis depending on neuronal and circuit properties. This important area remains to be explored.

Numerous reports have demonstrated redox regulation of ion channels that contribute to cellular excitability. Thus, it is likely that circadian rhythms in redox state extend beyond the SCN to diverse brain regions where they may contribute to regulation of neuronal excitability. Furthermore, the circadian timing system is present in all tissues and cellular redox state has emerged as a contributor to tissue-specific rhythmicity. The redox oscillation has the potential to orchestrate the activation state of ion channels that underlie daily oscillations of electrical activity in all excitable cells throughout the body, enabling a nuanced fluctuation of excitable states. Redox-driven modulation of ion channels may be a fundamental form of regulation of physiological processes. The likelihood of this scenario raises the urgency of understanding the cellular and molecular groundwork and timing mechanisms that generate the metabolic redox oscillator and their relationship to the transcription-translation oscillator. Establishing these interconnections will shed light on the general role of cellular redox state in circadian timekeeping and in physiological regulation broadly.

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Author disclosure statement

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