Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Altered responsiveness to photic stimuli contribute to circadian disruption in cystic fibrosis

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ARTICLE INFO

Keywords:
Cystic fibrosis
Circadian rhythms
Suprachiasmatic nucleus

ABSTRACT

Background: People with cystic fibrosis (pwCF) and animal models show evidence of disrupted circadian rhythms (CR). CRs are controlled by light sensitive neurons of the suprachiasmatic nucleus (SCN). Characterizing how the CF SCN responds to light will inform mechanisms behind CR disruption and help to inform CR based treatments to mitigate CF symptoms exacerbated by circadian disruption.

Methods: Mice were entrained and subsequently exposed to a 30 min light pulse one hour after usual lights out. The magnitude of the resulting phase delay in subsequent activity onset and molecular correlates of photic input at the SCN were then compared between CF and WT mice.

Results: Light induced phase delays of activity onset in CF mice were reduced compared to WT controls. Reduced behavioral responses were also associated with altered molecular responses in the SCN, including attenuated cFOS levels in CF vs WT SCN. Data show that phosphorylation of ribosomal protein 6 (pS6) is reduced in CF, while targets down stream of 4E-BP1 such as vasoactive intestinal polypeptide levels (VIP) appear the same between genotypes.

Conclusions: Behavioral and molecular responses to a light pulse differ between CF and WT mice. Together these data suggest that similar photic input from the retina is being received by the SCN of CF and WT mice, but the mounted intracellular response to that photic input differs in CF. Investigation into these differences will be integral to understanding circadian disruption in CF and informing future intervention for CF symptoms known to be exacerbated by circadian disruption.

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. CFTR is expressed in many tissue types, where its lack of function is associated with tissue specific maladies; therefore, CF is considered a multisystem disorder [2]. Historically CF was identified as a disease affecting the pancreas. Infants died as a consequence of pancreatic insufficiency, which was managed by pancreatic enzyme replacement therapy [3]. With that advance, life expectancy increased, and respiratory manifestations of CF became the leading cause of mortality for people with cystic fibrosis (pwCF) [4] Now with the advent of highly effective modulator therapies (HEMT), manifestations of the lung are being well managed for those pwCF who carry mutations eligible for HEMT, again increasing life expectancy. Identifying and managing the manifestations of dysfunctional CFTR in other tissue types, especially those known to be impacted by aging such as the central nervous system (CNS), has now become necessary.

It is becoming clear that manifestations of CFTR loss impact the functioning of the CNS. PwCF have levels of anxiety and depression that exceed that expected for the general population [5,6]. Sleep disturbance and circadian dysregulation are also exhibited independent of respiratory exacerbations [7], suggesting circadian disruption is a centrally mediated complication. A complication of impaired sleep and negative mood is increased risk of neurodegenerative disease. Recent work shows that CF mouse models show age related tauopathy and decreased neuronal responsiveness in brain regions critical for learning and memory such as the hippocampus, suggesting that pwCF may be at risk of cognitive decline as they age [8].

A common factor linking all these centrally mediated phenotypes is

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https://doi.org/10.1016/j.jcf.2026.03.020
Received 3 September 2025; Received in revised form 12 January 2026; Accepted 25 March 2026

light sensitivity. Circadian disruption and poor sleep quality are directly impacted by light exposure [9]. Depression is also linked to altered light sensitivity and bidirectionally related with circadian and sleep disruption [10,11]. Anxiety, depression, circadian disruption and poor sleep quality can be exacerbated by altered light sensitivity and are all risk factors for cognitive decline associated with aging.

Light as a synchronizing stimulus of circadian rhythms has been an area of research for decades [12]. The neuroanatomical path through which light travels from the retina to the master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and the biochemical effect that light has on the transcription translation feedback loop (TTFL) of core circadian clock genes (*bmal-1, clock, per* and *cry* genes) to align behavior and physiology to the solar day has been well characterized [13]. Briefly, photic information about light is conveyed from intrinsically photosensitive retinal ganglion cells (ipRGCs) of the retina via a monosynaptic pathway to the SCN via release of two neurotransmitters, glutamate and pituitary adenylate cyclase activating peptide (PACAP) [14].

We have previously described evidence consistent with altered light sensitivity in CF mice. CF mouse models display activity onset that is advanced into the light phase in a 12 h LD cycle, with decreased consolidation of their activity across 24h compared to WT mice [15,16]. These data suggest that CF mice may be less sensitive to light in the early part of their active phase, as expected phase delays to algin activity onset seen in WT mice with the transition to darkness are not occurring. Further, CFTR is expressed within neurons of the SCN and multiple cell types in the eye in both people and CF mice including, the cornea, lacrimal gland, and retinal pigmented epithelium [17,18]. Reports of patients with altered dark adaptation, cataracts, and altered tear production all suggest that ocular health and function are impacted by CFTR mutations [19].

The SCN is made up of approximately 20 000 neurons bilaterally [20]. These neurons function independently as individual clock cells showing rhythmic expression of TTFL components [21]. In vivo and in slice culture these neurons remain synchronous with one another through predominantly vasoactive intestinal polypeptide (VIP) and arginine vasopressin (AVP) signaling between these neurons [22]. Importantly, photic input to this pathway has a bidirectional impact on the phase of the circadian clock. The neurons of the SCN are maximally active during the light phase and relatively quiescent during the dark phase. As a result neurons there are relatively insensitive to light during the light phase, as cells are relatively active and maximally expressing the light sensitive *per* transcripts, however during the dark phase light produces phase delays in the first half of the dark phase and phase advances in the second half of the night, as cells are relatively quiescent in the SCN at these times and light exposure increases their activity and rapidly induces transcription of the *per* genes at either the falling or rising phase of its rhythm respectively delaying or advancing the TTFL [23,24].

The goal of this study was to investigate whether the altered circadian rhythms observed in pwCF and animal models are the result of impaired light sensitivity. Here we explore mechanistically the response the of the SCN to a 30 min light pulse at circadian time (CT)13 in CF and WT mice. CF mice behaviorally exhibit a significantly smaller phase delay at this time suggesting decreased light sensitivity. Therefore previously identified molecular correlates of light exposure at the SCN were examined, including the immediate early gene cFOS and phosphorylated ribosomal protein 6 (pS6) which informs not only levels of neuronal activity but also downstream mTOR signaling [24–27].

2. Methods

2.1. Mice

Male and Female C57BL/6J mice with CFTR+/+ (WT) or G542X CFTR -/- (CF) mice[1] were provided by the CF Mouse Models Resource Center at Case Western Reserve University. Two cohorts of WT and CF mice both male and female (n=5/genotype/cohort) were used in these experiments. Each cohort was on average 28 weeks at the beginning of activity monitoring. Mice were housed in disposable cages equipped with a running disk (actimetrics, ACT-557-WLP), in a 12:12 LD cycle (~60 lux during the light phase: <1 lux during the dark phase). Running disks were monitored continuously in 30 sec epochs with the clocklab data acquisition system (Actimetrics AM-CW01). Mice were entrained to the LD cycle for a minimum of three weeks, standard rodent chow and water were provided ad libitum throughout these experiments. All protocols were approved by the Animal Care and Use Committee at Case Western Reserve University (Protocol 2017-0047).

2.2. Immunohistochemistry

On the day of tissue collection lights did not come on at ZT0, mice in the light pulse condition were subject to a 30 min light pulse (~60 lux) from CT13-13.5 and returned to darkness for 60 min to allow for

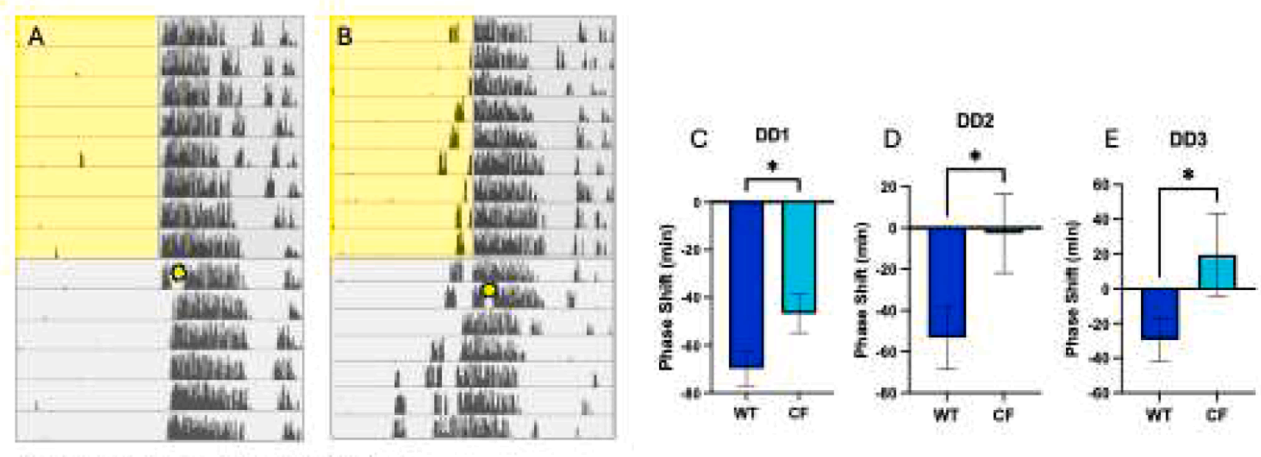

Fig. 1. Light Induced Phase Shift of Locomotor Activity at ZT 13.
Representative actograms from WT (A) and CF (B) mice. Periodogram analysis showed no difference in period under LD in CF and WT mice, however CF mice displayed a significant reduction in amplitude in the locomotor rhythm (data not shown), CF mice showed a significant decrease in the magnitude of the light induced phase shift of DD1, t=2.096 (19), p=0.05 and DD2 t=2.092 (19), p=0.03post light pulse (C) and (D). On day 3 in DD CF mice were advanced relative to WT controls (E), reflecting the significant in endogenous tau under DD detected by chi-square periodogram (data not shown).

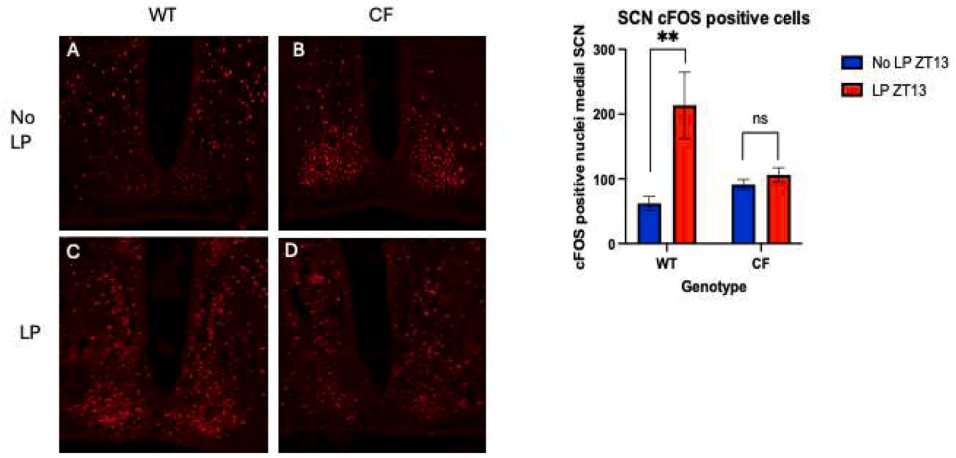

Fig. 2. Light Induced cFOS expression in the SCN to a 30 min light pulse at ZT13 in WT and CF mice.
Representative micrographs of cFOS in the SCN of WT (A and C) and CF (B and D) mice. Light reliably induces cFOS induction in the SCN at ZT 13 in WT mice above no light pulse controls (A,C) t=2.974 (5), p=0.016. When comparing the CF mice (B and D) however there was no significant difference between light pulse and no light pulse controls. Further cFOS expression basally appears elevated although this comprison did not reach signifiance t=2.131 (11), p=0.056.

transcription and translation of protein products. At CT14.5 mice were euthanized with CO_2 and perfused with 30ml of 0.1M phosphate buffered saline (PBS, pH~7.4) followed by 30 ml of 4% paraformaldehyde in PBS (PFA, pH~7.4). Brains were removed and postfixed in PFA at 4°C overnight. Brains were then cryoprotected in a 30% sucrose solution in PBS at 4C. Brains were then sectioned (30μm) coronally and stored in PB antifreeze solution at -20°C.

To visualize cFOS, pS6 and VIP sections were treated separately at room temperature with rocking as follows. Sections were rinsed (6 × 5min in PBS) and incubated for 30 min in 0.3% H_2O_2 in PBS. Rinsed (3 × 5 min in PBSX, PBS with 0.15% triton-100) and then blocked in 10% normal donkey serum (Jackson Immunoresearch, Cat# 017-000-121) in PBSX for 2hrs. Followed with primary antibody (cFOS 1:500, synaptic systems cat #226008: pS6 1:250, cell signalling cat# D68F8, VIP 1:4000, immunostar cat# 20077-2345001) for 24h. Tissues were rinsed, then incubated in secondary antibodies (alexafluor plus 680 donkey anti rabbit (1:500), alexafluor plus 594 donkey anti rabbit (1:250), or alexafluor plus 488 donkey anti rabbit (1:250)) for 2h. Tissues were rinsed, mounted and cover slipped with vectasheild mounting media with DAPI (Vector, cat# H-1500-10).

Slides were then imaged on a Zeiss axiocam slide scanner at 20X. Images generated by the slide scanner were then analyzed in FIJI. For the analysis of cFOS, the cell counter plug in was used within an region of interest (ROI) of the SCN modeled from the Allen brain atlas reference atlas, anchored to the optic chiasm and third ventricle. For the pS6 and VIP analysis mean fluorescence intensity was measured with the ROI of the SCN and compared.

2.3. Data analysis

Behavior data were analyzed using clock lab analysis software V6.0 to determine activity onsets. Activity onsets were then averaged on the 7 days in LD prior to the light pulse, and compared to activity onset the three days after the light pulse. These phase shifts were then statistically compared using Deltagraph Prism software, using an unpaired t-test.

Histological results from FIJI were also statistically compared using Deltagraph Prism software, again using unpaired t-tests.

3. Results

3.1. Attenuated light induced phase delay in CF mice

To assess the sensitivity of the circadian system to light in CF mice, both WT and CF mice were entrained to a standard 12:12 LD cycle for a minimum of 3 weeks. Upon stable entrainment (Fig. 1a,b) all mice were released into constant darkness. Mice were subsequently exposed to a 30-minute light pulse at CT13, an hour after the lights would have turned off. Then left in constant darkness for 5-7 days to assess for light induced changes in the phase of activity onset. Baseline activity in LD was assessed using Chi-square periodograms, there was no significant difference in period between genotypes under these conditions, however the amplitude of the behavioral rhythm was significantly weaker in the CF mice. In response to the CT 13 light pulse CF mice showed an attenuated light induced phase delay compared to WT controls on day 1 of constant darkness (DD) (Fig. 1C), t=2.096(19), p=0.05. Where the average phase delay was 69.8 minutes in WT compared to 46.8 min in the CF mice. This difference between genotypes was maintained on DD2, (Fig. 1D). On DD3 CF mice were advanced relative to WT controls, reflecting their shortened tau in comparison to WTs.

3.2. Altered neuronal activity in response to light within the SCN of CF mice, as measured by cFOS expression

Neurons in the SCN display an established rhythm in cFOS expression across the day, with levels being maximal during the light phase. Many labs have shown that light exposure in the early dark phase is associated with a large induction of cFOS expression relative to no light pulse controls [24]. Here we show that as expected WT mice show this significant induction of cFOS in the SCN to a light pulse at CT 13 (Fig. 2, A,C, and E) t=2.974(5)p=0.016. However, CF mice fail to show a significant increase in cFOS (Fig. 2 B, D and E). This lack of response may be partially due to relatively high levels of cFOS activity basally in the CF mice at CT13 suggesting that neural activity is not as suppressed in the dark phase compared to WT controls (Fig. 2A and B).

3.3. Altered molecular signaling along the mTORC1 pathway within the SCN of CF mice, as measured by pS6

It has been reported that the SCN shows circadian activation of the mammalian target of rapamycin (mTOR) cascade, which is induced by light exposure only during the dark phase. This light induced induction of the mTOR pathway at night appears to be ERK dependent as pharmacological inhibition of ERK blocks this light induced response [25, 26]. We examined whether this light induced induction of the mTOR pathway was altered in CF mice based on the observed behavioral and cFOS differences discussed above. As expected, WT mice showed more

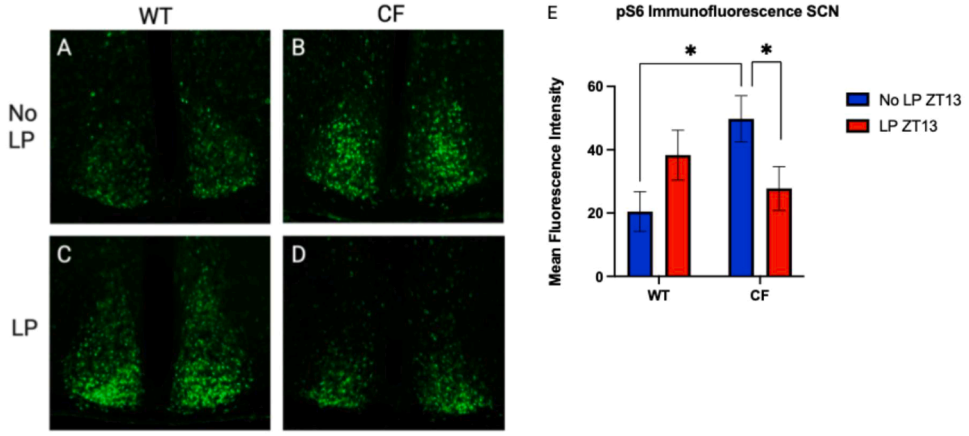

Fig. 3. Light Induced phosphorylation of ribosomal protein 6 (pS6) in the SCN of WT and CF mice.
Representative micrographs of pSˆ in the SCN of WT (A and C) and CF (B and D). A light pulse at ZT13 did not significantly elevate pS6 in the WT SCN, t=1.702 (7), p=0.06 (A and C). pS6 was significantly elevated in CF mice vs WT at ZT13 basally (A and B) t=2.954 (7), p=0.02. Interestingly a light pulse at this time was associated with decreased pS6 levels in teh SCN of CF mice (B and D), t=2.189 (7), p=0.03.

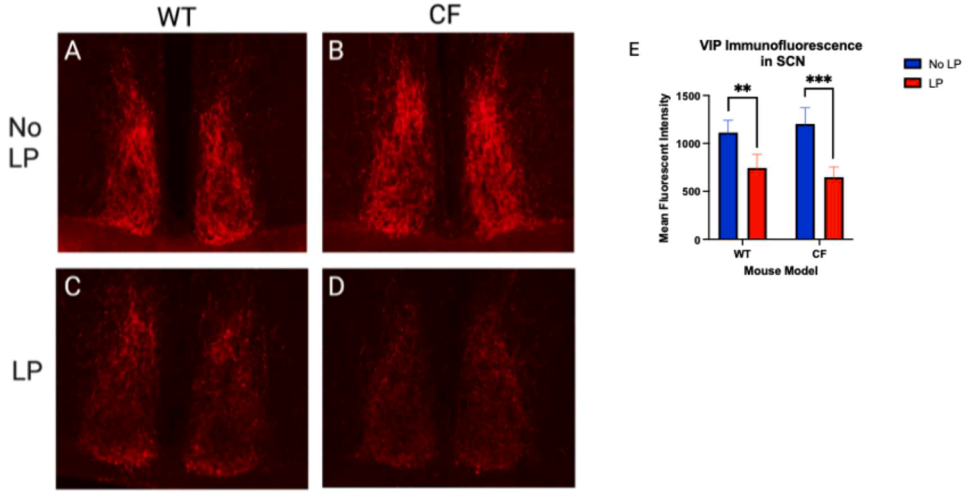

Fig. 4. VIP levels in the SCN with and without a LP in WT and CF mice at ZT 13. Representative micrographs of VIP staining in the SCN of WT (A and C) and CF (B and D) mice. There was no difference in the amount of VIP contained in teh SCN of CF and WT mice at ZT13. In both WT and CF mice a light pulse resulted in a significant decrease in VIP levels.

positive pS6 labeled cells in the SCN in the LP vs NoLP condition (Fig. 3 A, C) although this wasn't significant t=1.702(7)p=0.06. Interestingly, and not dissimilar from the cFOS results, pS6 was shown to be basally elevated in the SCN of the CF mice compared to WT controls at CT13 (Fig. 3 A, B, E) t=2.954(7)p=0.02. Suggesting that inducible transcription via mTOR activation is higher in CF mice at this time compared to their WT counterparts. Further, CF mice showed the reverse response to a light pulse at CT13, with a significant reduction in pS6 levels compared to non-light pulsed controls (Fig B, D,E) t=2.189(7)p=0.03.

3.4. Examination of VIP levels within the SCN of CF mice as a measure of neuronal synchrony across the neurons of the circadian clock

It is conceivable that the altered behavioral and molecular responses within the SCN of CF mice could be due to a lack of synchronicity of individual neurons within the SCN. For example, if populations of cells are out of phase with each other, their response to light will as a result differ in both magnitude and direction, therefore preventing a coordinated and robust response to an incoming photic signal. The phase of SCN neurons is synchronized by multiple factors, one of the best characterized being VIP. While not testing the phase of SCN neurons directly, we decided to assess whether there were differences in the amount VIP in SCN neurons at CT13, as if differences were detected, it would suggest neuronal synchronization within the SCN could be a mechanism to follow up on. Robust staining for VIP was observed in both WT and CF SCN at CT 13 in the no light pulse condition with no evidence of differences between the two genotypes (Fig. 4 A,B,E). As expected, light resulted in a decrease of VIP content with in the SCN of the WT mice (Fig. 4 C, E) as it has been reported that light exposure at this time is associated with VIP release to SCN efferents [22,28,29]. It was not expected that light would induce a significant decrease in VIP in the SCN of the CF animals (Fig. 4 D, E) as other light induced markers discussed above have been attenuated.

4. Discussion

This study was designed to investigate the mechanisms underlying the circadian disruption previously reported in CF mice and pwCF [16,30,31] It is widely reported that light at ZT13 elicits a replicable phase delay of activity onset associated with a shift in the TTFL, and an increase in neuronal activity in WT mice. Here we show that the phase delay observed to a 30 min LP at CT13 is significantly attenuated in CF

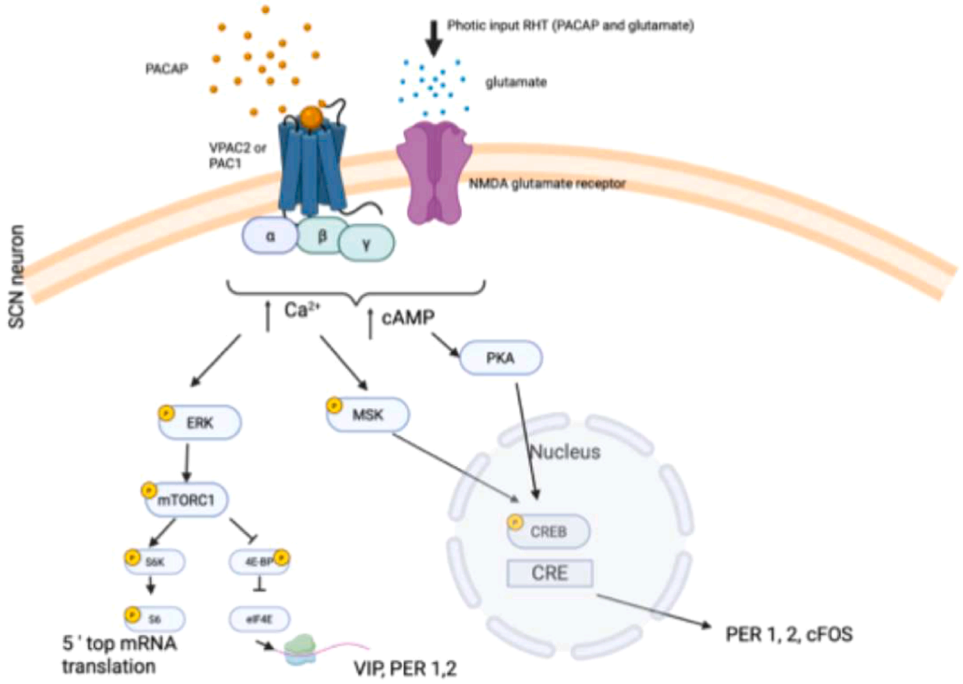

Fig. 5. Truncated overview or light induced intracellular signaling in the SCN. Photic input results in release of PACAP and glutamate that bind to respective SCN receptors, increasing intracellular calcium and cAMP. Subsequent phosphorylation of ERK/MAPK, activates mTORC1. This either activated S6K and subsequently S6 initiating 5` top mRNA translation, or inhibits 4E-BP1 that dissociates from eIF4E increasing translation of VIP, PER etc. Increased calcium and cAMP can also activate MSK or PKA ultimately phosphorylating CREB and inducing translation of CRE dependent genes like PER1, 2 and cFOS.

mice. Further this response is associated with decreased neuronal activity in the LP condition as measured by cFOS and pS6 in the CF relative to WT controls.

Our data show a significant change in photic SCN response between WT and CF mice, that is consistent with observed changes in light induced behavioral shifts between these two genotypes. It is unclear at which step of the light signaling cascade CFTR is integral to this response. Light stimuli at the retina are transduced and sent to the SCN via the retinohypothalamic tract (RHT) triggering release of two neurotransmitters, PACAP and glutamate, that bind to their respective receptors resulting in an increase in intracellular Ca2+ and cAMP levels. These responses trigger multiple intracellular pathways in a cell specific and time of day dependent fashion. Pathways shown to be altered by light in the SCN include, mTOR [32],MAPK [33], PKA [34], PKG [35] and CaMK [36]. CFTR is expressed on SCN neurons and to date no studies have been conducted to determine how the absence of CFTR impacts the response of SCN neurons to light along these pathways at any time point.

The attenuated phase delay observed in the CF mice was reflected in significantly decreased cFOS immunoreactivity relative to WT controls. cFOS levels have been shown to be elevated by light via activation of multiple pathways including activation of PKA via increased cAMP ultimately culminating in the induction of CRE driven genes like cFOS and per1 [33,37]. Activation of CFTR is dependent on cAMP activation of PKA and subsequent phosphorylation of CFTR [38]. Currently it is unknown if cAMP levels in response to light are altered within the SCN of CF mice, however downstream targets such as cFOS are differentially expressed. Investigation into cAMP activation by light upstream of cFOS could inform the observed differences in CF vs WT mice.

Interestingly the response to light observed in the CF when examining pS6 levels was opposite to what was observed in the WTs, with pS6 being significantly reduced, while it trended to increase in the WT mice. Light has been shown to induce downstream targets of mTORC1, including the phosphorylation of ribosomal protein 6 in a time dependent manner via activation of ribosomal protein 6 kinase 1 (S6K1) and the phosphorylation of 4e-BP1. Phosphorylated 4e-BP1 in turn leads to dissociation from eIF43 increasing mRNA translation of proteins known to be important to circadian regulation including PER1 and VIP [26]. eIF4E is also a downstream target of the MAPK pathway that is also light sensitive [39]; therefore, light can influence mRNA translation in the SCN via at least two pathways that are both mTORC1 dependent and independent respectfully. mTOR signaling is altered in CF tissues, and this is the first reported difference in a target of mTORC1 signaling in the CF brain [40]

The attenuated and inverse responses observed in cFOS and pS6 to light in CF mice support the attenuated behavioral response observed. There are many mechanisms through which light could be impacting the SCN differently in CF mice. It could be via altered phototransduction at the retina. This mechanism is supported by the attenuated cFOS response but not by the increased phosphorylation of pS6 which suggests that the cells of the SCN are in fact responding to light. However, the downstream signaling to light varies between WT and CF mice. The ability of the SCN to respond to input in a coordinated way depends on synchronicity between the neurons that make up the SCN network. This synchronicity is maintained by multiple factors including VIP, AVP and GABA. To test if decreased synchronicity between SCN neurons may contribute to the observed altered response to light in CF mice, VIP levels were assessed. No difference was found between WT and CF mice, additionally VIP release due to light in the early dark phase was similar between WT and CF mice. While assessing the synchronicity of individual SCN neurons must be done via electrophysiology or clock gene reporter measurements, our data on the levels of VIP suggest if synchronization of SCN neurons contribute to our observed differences in light induced changes in the SCN in CF mice it is not due to differing levels of VIP in the SCN. These data support that the SCN of CF mice are receiving similar photic inputs from the retina but the intracellular response mounted to that input varies between WT ang CF mice. Several future studies are needed to fully determine how the loss of CFTR function is impacting responses to light in the SCN such as assessing the response to light at different phases of the light dark cycle, examining

different light intensities at each of these phases, characterizing the differences in clock gene expression in the SCN response to light, as well as electrophysiology to compare basal activity levels in the SCN of CF mice across the day and how this activity level is influenced by the application of glutamate and PACAP would be very informative.

In conclusion, our data demonstrate that loss of CFTR function alters SCN responsiveness to photic input, which is consistent with reported circadian disruption in both pwCF and animal models of the disease. Given the integral role that circadian rhythms contribute to maintaining human health, investigating the mechanisms underlying this circadian disruption and assessing therapeutic interventions such as bright light therapy, which has been shown to be therapeutic in the context of CF [41], and time restricted feeding may help to ameliorate the severity of CF associated phenotypes that are known to be impacted by circadian rhythms such as infection response, metabolism, sleep quality, and mental health concerns.(Fig. 5).

Author contributions

DPP, RD and TK conceptualized the project. DPP, EK, and DC contributed to data curration. DPP, EK, TK and RD conducted the formal anlysis. DPP, TK and RD all contributed to writing - original draft, reviewing and editing as well as funding acquisition for this work. All authors reviewed the manuscript.

Funding

We acknowledge the use of the CF Mouse Resource Center at Case Western Reserve University (CWRU) and the Mouse Behavior Core at CWRU. This work is supported by CFF RDP R447-CR11, R01 HL156928, CFF **HODGES19R1, CFF PARFYO24F0.**

Declaration of competing interest

The authors have declared no conflict of interest exists.

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