SUPPLEMENTAL MATERIAL

EXPANDED MATERIALS AND METHODS

Pressure Myography

Mouse olfactory cerebral arteries (a first branch of the anterior cerebral artery) were carefully dissected, cannulated onto micropipettes, stretched to their *in vivo* lengths, pressurized to 45 mmHg and warmed to 37°C. The arteries were imaged with a CCD camera at 40x magnification during myography measurements, with luminal diameter measured using a Crescent Electronics (Windsor, Canada) video edge detector and logged using Photon Technology International FeliX32 analysis software (Horiba Canada Inc.; London, Canada). All functional experiments were conducted in 3-morpholinopropanesulfonic acid (MOPS) buffered saline, with no perfusion ([mmol/L]: NaCl 147.0, KCl 4.7, $CaCl_2$ 1.5, $MgSO_4$ 1.2, NaH_2PO_4 1.2, pyruvate 2.0, EDTA 0.02, MOPS 3.0 and glucose 5.0; all salts from *BioShop Canada Inc.*, Burlington Canada, cat# SOD002, POC308, CCL444, MAG521, SPM400, PYR302, EDT002, MOP005 and GLU501). Vasomotor responses to 10 μmol/L phenylephrine (*Millipore Sigma*; Oakville, Canada; cat# 6126) provided an assessment of vessel viability at the beginning of each experiment: arteries failing to show ≥30% constriction were excluded.

Myogenic responses were elicited by step-wise 20 mmHg increases in transmural pressure from 20 mmHg to 80mmHg. At each pressure step, vessel diameter (dia_{active}) was measured once a steady state was achieved. Following completion of all dia_{active} measurements, the MOPS buffer was replaced with a Ca^{2+}-free version and maximal passive diameter (dia_{max}) was recorded at each pressure step. Myogenic tone was calculated as the percent constriction in relation to the maximal diameter at each respective transmural pressure: tone (% of dia_{max}) = $[(dia_{max}-dia_{active})/dia_{max}]x100$, where dia_{active} is the vessel diameter in MOPS containing Ca^{2+} and dia_{max} is the diameter in Ca^{2+}-free MOPS. Analyses of vasomotor responses to phenylephrine used the same calculation, only in this case, dia_{active} represents the vessel diameter at steady state following application of phenylephrine.

Western Blotting

We utilized a standard western blot procedure for CFTR. Buffer components were purchased from *BioShop Canada Inc.* (cat# in parentheses), including Tris (TRS001), NaCl (SOD002), KCl (POC308), EDTA (EDT002), Triton-X-100 (TRX506), sodium dodecyl sulfate (SDS; SDS003), glycerol (GLY004), β-mercaptoethanol (MER002), dithiothreitol (DTT001), Na_2HPO_4 (SPD579), K_2HPO_4 (PPD303), Tween 20 (TWN510), non-fat skim milk (SKI400) and protease inhibitors (PIC004). Cerebral artery lysates were prepared by grinding artery samples in lysis buffer containing 50 mM Tris (pH 7.3), 150 mM NaCl, 2 mM EDTA, 0.1% Triton-X-100, 0.1% SDS and protease inhibitors. Following lysis, the samples were centrifuged (10 minutes at 13,500 g; at 4°C) to remove insoluble material. Immediately prior to polyacrylamide electrophoresis, additional SDS (to 2% final concentration), glycerol (to 2% final concentration), β-mercaptoethanol (to 2% final concentration) and dithiothreitol (2 mM final concentration) were added. Proteins were separated electrophoretically on 7% acrylamide gels and transferred onto polyvinylidene difluoride membranes.

The membranes were blocked for 45 minutes in 5% non-fat skim milk in phosphate-buffered saline containing 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 1.76 mM K_2HPO_4 and 1% Tween 20 (PBST; pH 7.4) and subsequently incubated overnight at 4°C with primary antibody. For primary antibody treatment, the 100-280 kDa weight range of the blot was incubated with rabbit polyclonal anti-CFTR antibody (1:1,000 in 5% milk/PBST; *Alomone Laboratories*, Jerusalem, Israel; cat# ACL-006), while the remaining range (35-100 kDa) was incubated with mouse monoclonal anti-α-tubulin antibody (1:5,000 in 5% milk/PBST; clone DM1A; *New England Biolabs Canada*; Whitby, Canada; cat# 3873). After washing, the primary antibodies were conjugated with peroxidase-labelled secondary antibody (1:2,000 in 5% milk/PBST) for 2 hours at room temperature:

the CFTR blot received peroxidase-labelled goat anti-rabbit IgG antibody (*New England Biolabs*; cat# 7074) and the tubulin blot received peroxidase-labelled horse anti-mouse IgG antibody (*New England Biolabs*; cat# 7076). The blots were then washed, exposed to chemiluminescence reagent and digitally imaged. High sensitivity chemiluminescence reagent was used for the CFTR blot (*GE Amersham*, Mississauga, Canada; cat# RPN2235) and standard chemiluminescence reagent for the tubulin blot (*GE Amersham*; cat# RPN2106). Digital images were collected with a *Bio-Rad Laboratories* (Mississauga, Canada) ChemiDoc system and analyzed with *Bio-Rad Laboratories* Image Lab software.

RNA Isolation and Reverse Transcription

Cerebral artery RNA was isolated with *Norgen Biotek* (Thorold, Canada) "Total RNA Purification Micro" spin columns (cat #35300), using the proteinase K digestion and DNA removal procedures, as directed by the manufacturer's instructions. The RNA was converted to cDNA using a "Superscript III" reverse transcription kit (*ThermoFisher Scientific*; Mississauga, Canada; cat# 18080044), according to the manufacturer's directions. Residual RNA was removed by incubating the resulting cDNA with RNAse H (0.125 U/µl; *New England Biolabs*).

Quantitative PCR

Quantitative PCR was performed using a *Bio-Rad Laboratories* CFX384 Real Time PCR Detection System. Each PCR reaction contained Power SYBR® Green PCR master mix (*ThermoFisher Scientific*) and rigorously validated primer sets (400 nmol/L in each reaction; **Supplemental Table I**). Gene targets and negative controls (water) were assessed in triplicate.

The PCR amplification consisted of 10 minutes denaturation at 95°C, followed by 40 cycles of amplification (15 s at 95°C + 60 s at 60°C). Following amplification, the amplicons were melted: the resulting dissociation curve confirmed the production of single product. Transcript expression levels in mouse tissues were calculated from the ΔCt values relative to the standard housekeeping gene glucose-6-phosphate dehydrogenase (G6PD). To confirm that G6PD was reliable for normalization, transcript expression levels were also calculated from the ΔCt values relative to hydroxymethylbilane synthase (HMBS) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Brain Fixation and Slide Preparation

At 2 days post-SAH induction, animals were anesthetized with isoflurane; their brains were perfused with phosphate buffered saline (PBS; *Millipore Sigma* cat# 8537) and then perfusion fixed with 10% buffered formalin solution (*Millipore Sigma* cat# HT501128), both via the ascending aorta. Brains were immediately dissected and post-fixed in 10% formalin for 48 hours at 4°C. The brains were then cut into coronal sections 2 mm posterior to the bregma, embedded in paraffin and sectioned in 5µm thick coronal slices and mounted onto slides. The slides were subsequently deparaffinized with xylene and rehydrated and graded levels of in ethanol distilled water.

Immunohistochemistry

Prior to blocking, slides were treated with citrate-based Antigen Unmasking Solution at 96°C for 30 minutes (*Vector Laboratories*; Burlingame, USA; cat# H-3300-250). The slides were subsequently permeabilized with 0.3% Triton X-100 in PBS for 1 hour at room temperature and then blocked with 10% goat serum (*Millipore Sigma* cat# G9023) in PBS containing 1% bovine serum albumin (BSA; *BioShop Canada Inc.* cat# ALB001) for 30 minutes at room temperature.

Cleaved Caspase-3 / NeuN: A subset of slides were double-stained for the apoptosis marker ***cleaved caspase-3*** and the neuronal marker ***NeuN***. Slides were incubated with rabbit monoclonal anti-active cleaved caspase-3 overnight at 4°C (clone C92-605; 1:200 dilution in 1% BSA in PBS; *BD Biosciences Canada*; Mississauga Canada; cat# 559565) and subsequently conjugated with

Alexa Fluor 488-labeled goat anti-rabbit IgG for 1 hour at room temperature (1:500 dilution in 1% BSA in PBS; *ThermoFisher Scientific*; cat# A11008). The slides were then incubated with mouse monoclonal anti-NeuN antibody for 1 hour at room temperature (Clone A60; 1:200 dilution in 1% BSA in PBS; *Millipore Sigma* cat# MAB377) and subsequently conjugated with Alexa Fluor 568-labeled goat anti-mouse IgG for 1 hour at room temperature (1:500 dilution in 1% BSA in PBS; *ThermoFisher Scientific*; cat# A11004). Cell nuclei were then stained with DAPI (2µg/ml in PBS) for 15 minutes. After washing, the specimens were mounted with CC Mount (*Millipore Sigma*; cat# C9368).

Iba-1: A subset of slides were stained for the microglial-specific marker ***ionized calcium binding adaptor molecule 1 (Iba1)***. Slides were incubated with rabbit anti-Iba-1 overnight at 4ºC (1:750 dilution in 1% BSA in PBS; *FujiFilm Wako Chemicals USA Corp*; Richmond, USA; cat# 019-19741) and subsequently conjugated with Alexa Fluor 488-labeled goat anti-rabbit IgG for 1 hour at room temperature (1:500 dilution in 1% BSA in PBS; *ThermoFisher Scientific*; cat# A11008). Cell nuclei were then stained with DAPI (2µg/ml in PBS) for 15 minutes. After washing, the specimens were mounted with CC Mount.

Fluoro-Jade staining

Brain slices were serially incubated with 1% NaOH / 80% ethanol (5 minutes), 70% ethanol (2 minutes), distilled water (2 minutes) and 0.06% potassium permanganate (10 minutes). After washing with deionized water, brain slices were stained with 0.0004% Fluoro-Jade C (*Millipore Sigma ;* cat# AG325) in 0.1% acetic acid (15 minutes). The samples were then washed with deionized water, dried and mounted.

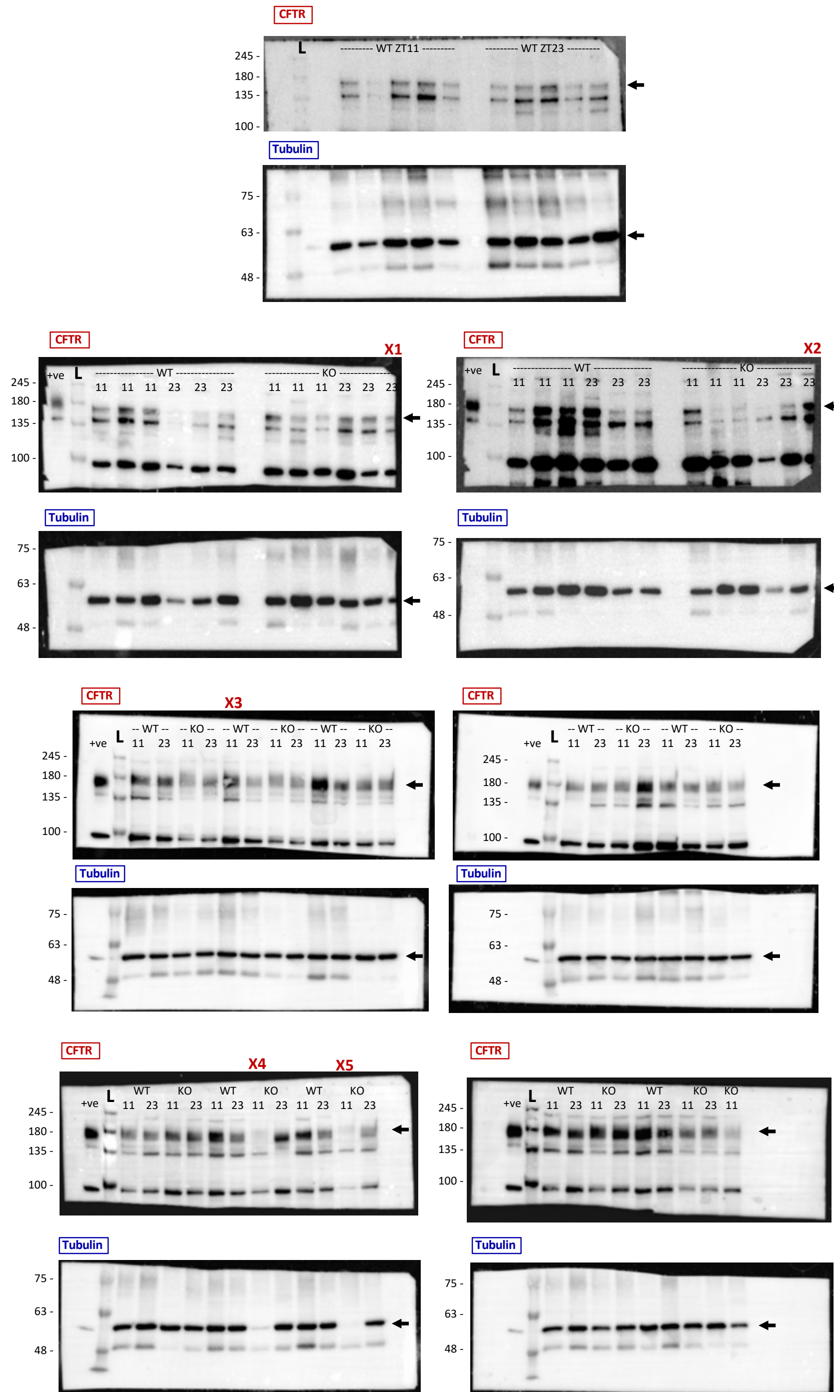
Digital Imaging and assessments

Digital immunofluorescence images at 20x or 40x magnification were acquired using a FV3000 laser confocal microscope under constant settings (Olympus Life Science, Richmond Hill, Canada).

For cleaved caspase-3 and Fluoro-Jade, 20x magnification image overlays were constructed with freely-available ImageJ 1.44p software (National Institutes of Health, USA): positively-stained neuronal cells were counted in the cortical region of the full coronal brain slice.

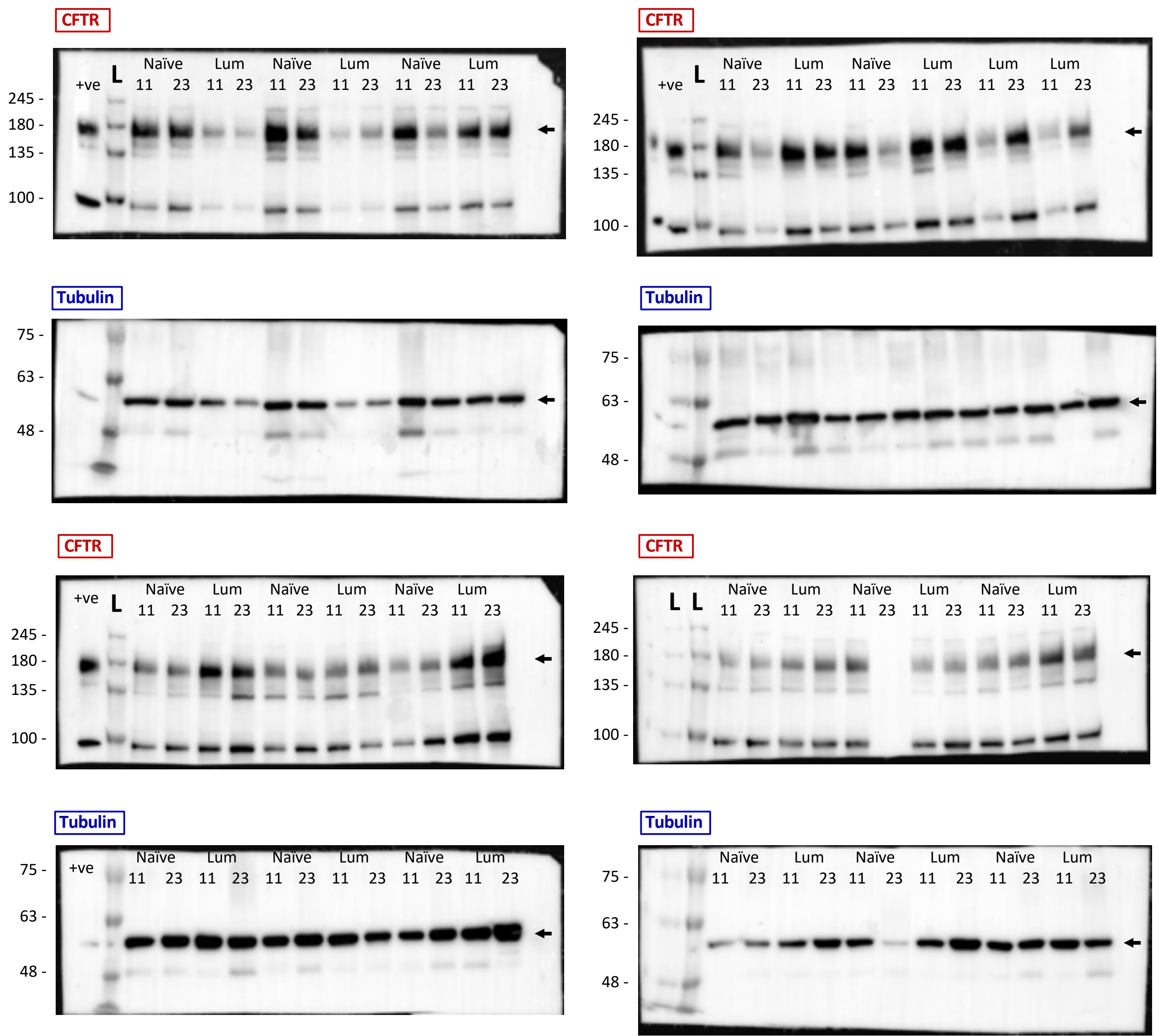
For Iba-1-stained microglial cells, 4 cortical images (20x magnification; 2 temporal and 2 parietal) and 2 hippocampal images were analyzed. The images were converted into a 16-bit binary image and a constant threshold was applied. Iba-1 staining was quantified as an "area fraction" (i.e., the percentage area of positive of Iba-1 staining relative to the field of view).

For microglial soma size measurements, images at 40x magnification were utilized. The images were converted into an 8-bit binary image to delineate a clear border between the microglia and the background fluorescence. All microglia within the field of view were counted and assigned a random number. A random number generator was used to select 8 microglia per field for soma quantification. The area of the soma was determined manually under blinded conditions using ImageJ software.



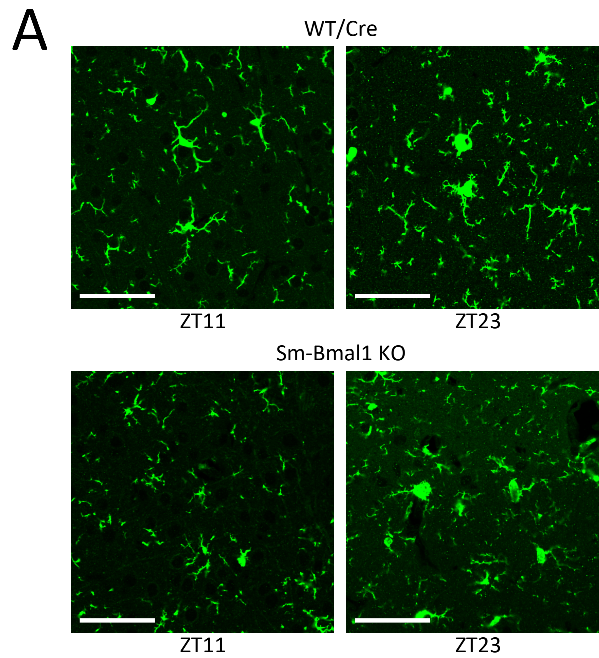
Supplemental Figure I: Uncropped western blot images for CFTR / tubulin expression in cerebral arteries from Bmal1 knockout mice and wild-type controls.

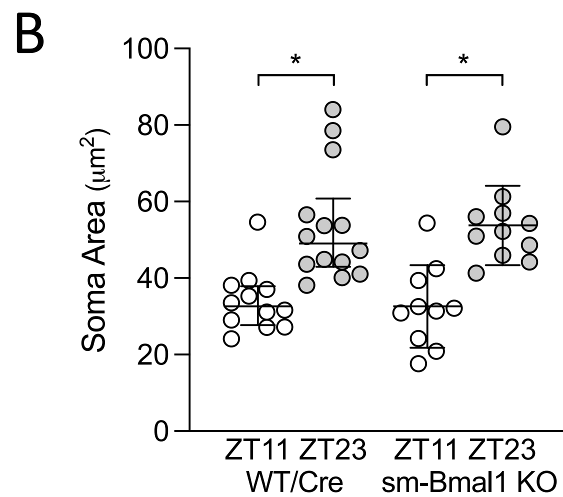
Shown are the uncropped, annotated western blots probing for cystic fibrosis transmembrane conductance regulator (CFTR) and tubulin expression in cerebral artery lysates prepared from tamoxifen-treated, Cre-expressing wild-type control mice (WT) and smooth muscle cell-specific Bmal1 knockout mice (KO) at Zeitgeber Time 11 (11) and Zeitgeber Time 23 (23). The ladder is designated as “L” and the positive control is designated as “+ve”. There were 5 exclusions made for technical reasons: X1/X2 were inadvertently cut by the edge of the membrane, X3 has a transfer defect and X4/X5 have low tubulin expression that made accurate quantification impossible. Data are summarized in Figure 5B.



Supplemental Figure II: Uncropped western blot images for CFTR / tubulin expression in cerebral arteries from lumacaftor-treated mice.

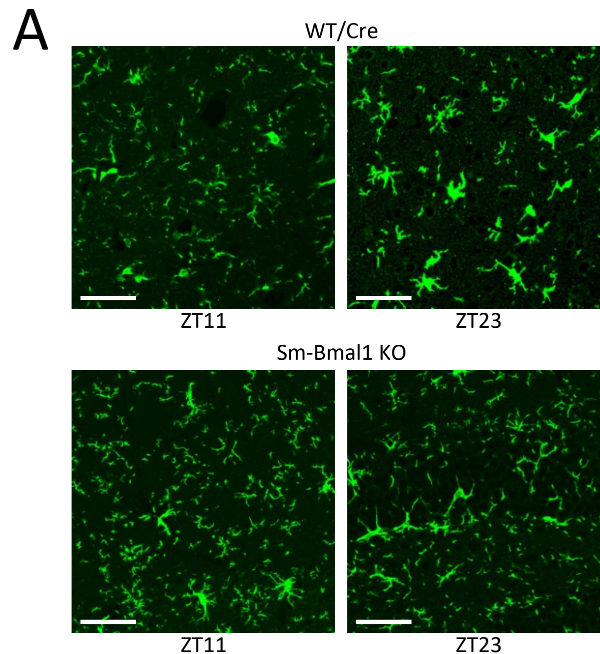
Shown are the uncropped, annotated western blots probing for cystic fibrosis transmembrane conductance regulator (CFTR) and tubulin expression in cerebral artery lysates prepared from lumacaftor-treated (3mg/kg/day i.p. for 2 days; Lum) and vehicle-treated naïve mice at Zeitgeber Time 11 (11) and Zeitgeber Time 23 (23). The ladder is designated as “L” and the positive control is designated as “+ve”. Data are summarized in Figure 5E.

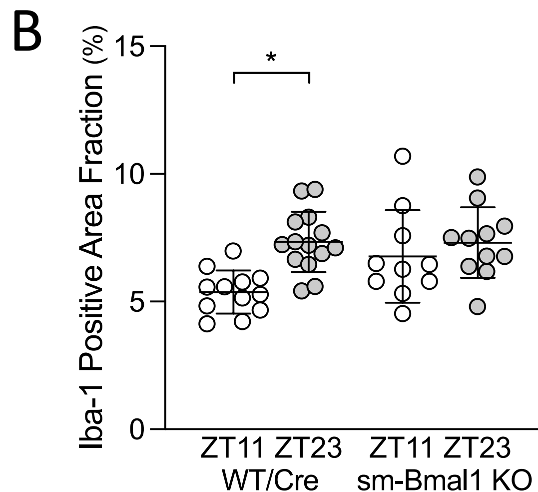




Supplemental Figure III: Cortical microglial morphology following subarachnoid hemorrhage.

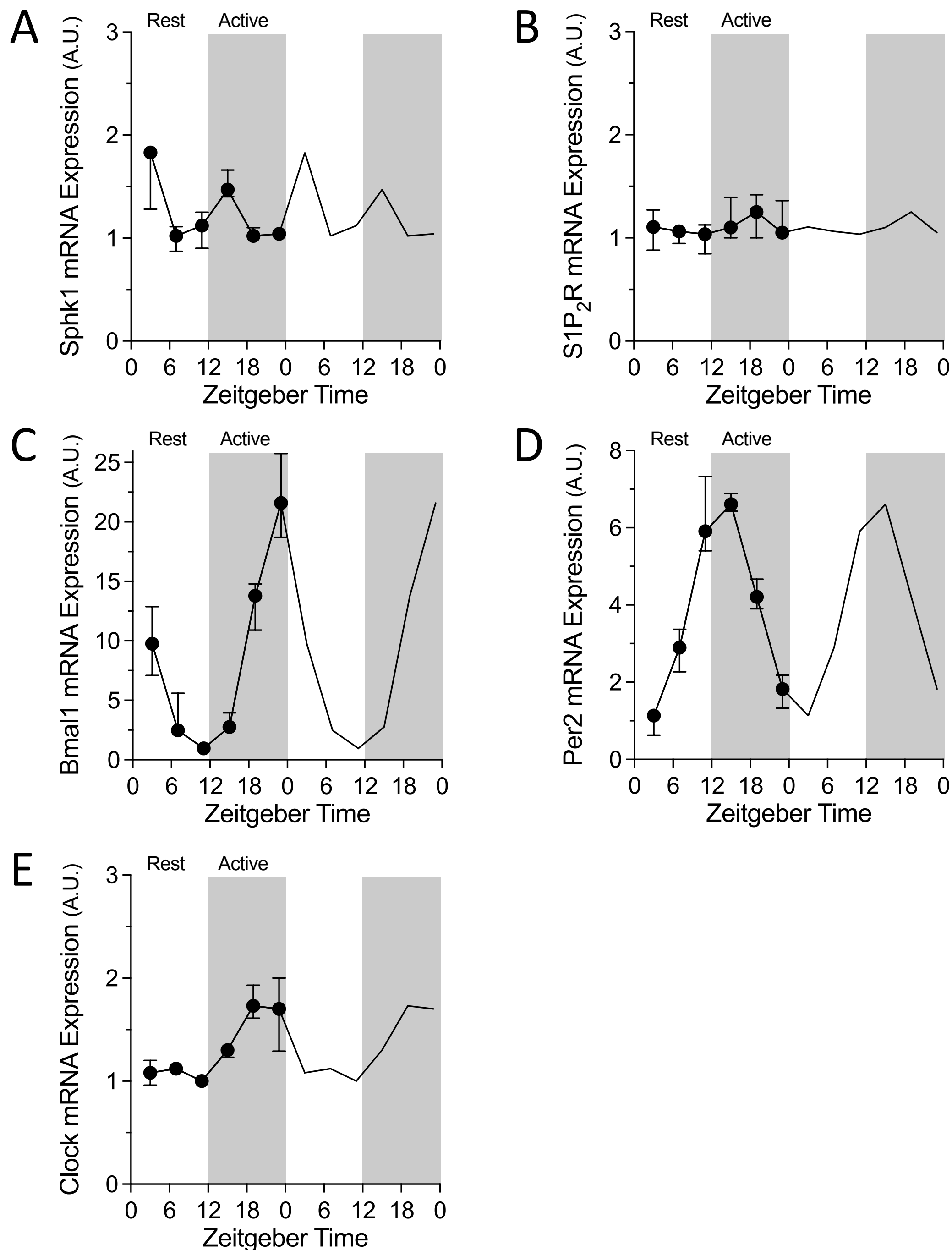
(A) Representative high-magnification images of cortical cells stained with the microglia marker *ionized calcium-binding adaptor protein-1* (Iba-1). Brain tissue was isolated at 2 days post-subarachnoid hemorrhage (SAH) from Cre-expressing wild-type controls (WT/Cre; n=12-14) and smooth muscle cell-specific Bmal1 knockout mice (sm-Bmal1 KO; n=10-11). In both WT/Cre and sm-Bmal1 KO samples, microglial cells displayed a more activated morphology at ZT23, characterized by larger/elongated soma size, thicker processes and low ramification complexity. Bar = 40 μm. **(B)** In both WT/Cre and sm-Bmal1 KO mice, microglial soma area is larger when SAH is induced at ZT23, relative to ZT11. WT/Cre data are presented as medians ± interquartile range. * denotes $P<0.05$ for ZT11 versus ZT23.





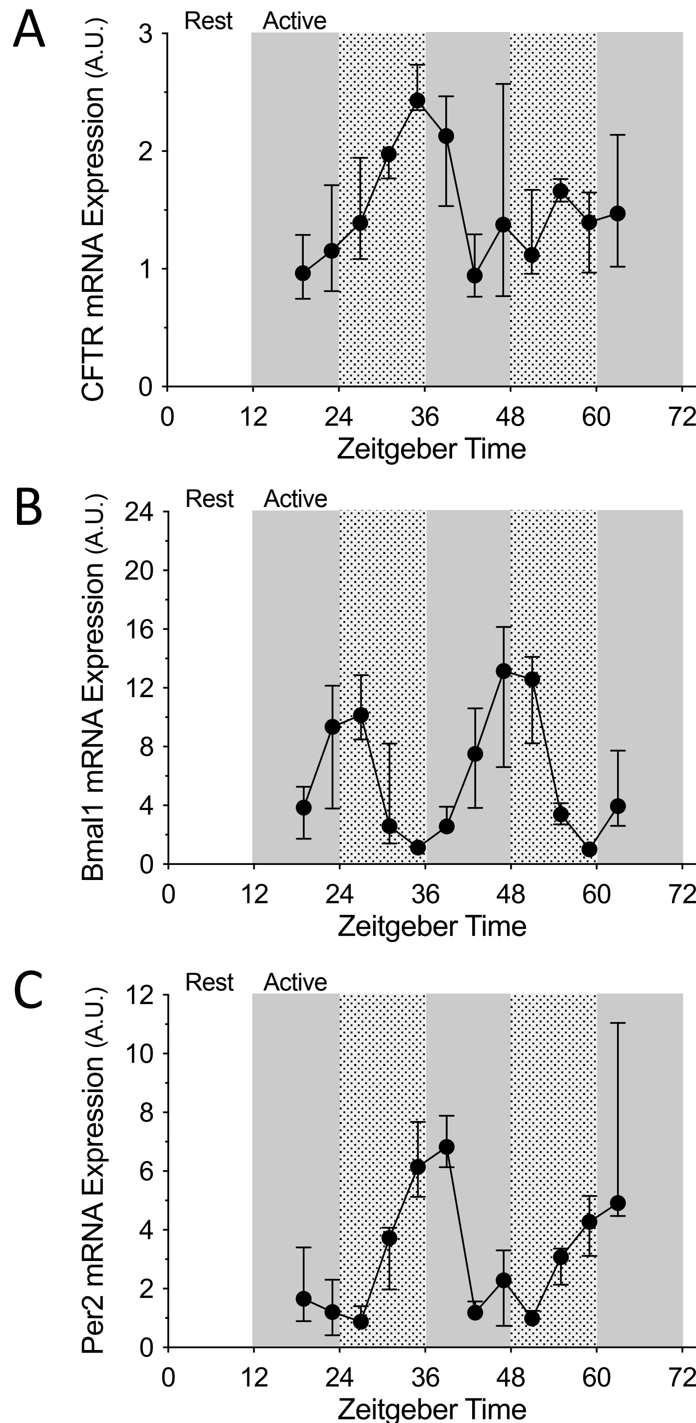
Supplemental Figure IV: Hippocampal microglial cell activation in subarachnoid hemorrhage.

(A) Representative images of *ionized calcium binding adaptor molecule 1 (Iba-1)* staining in the hippocampal regions of coronal brain slices isolated at 2 days post-subarachnoid hemorrhage (SAH) from Cre-expressing wild-type controls (WT/Cre; n=13-14) and smooth muscle cell-specific Bmal1 knockout mice (sm-Bmal1 KO; n=10-11). SAH was induced at either Zeitgeber time 11 (ZT11) or Zeitgeber time 23 (ZT23). Bar = 60 µm. **(B)** Quantification of Iba-1 staining, presented as the *positive area fraction* (i.e., the percent area of the image positively stained for Iba-1). In wild-type controls, hippocampal microglial cell activation is higher when SAH is induced at ZT23, relative to ZT11; this differential is lost in sm-Bmal1 KO mice. * denotes $P<0.05$ for ZT11 versus ZT23.



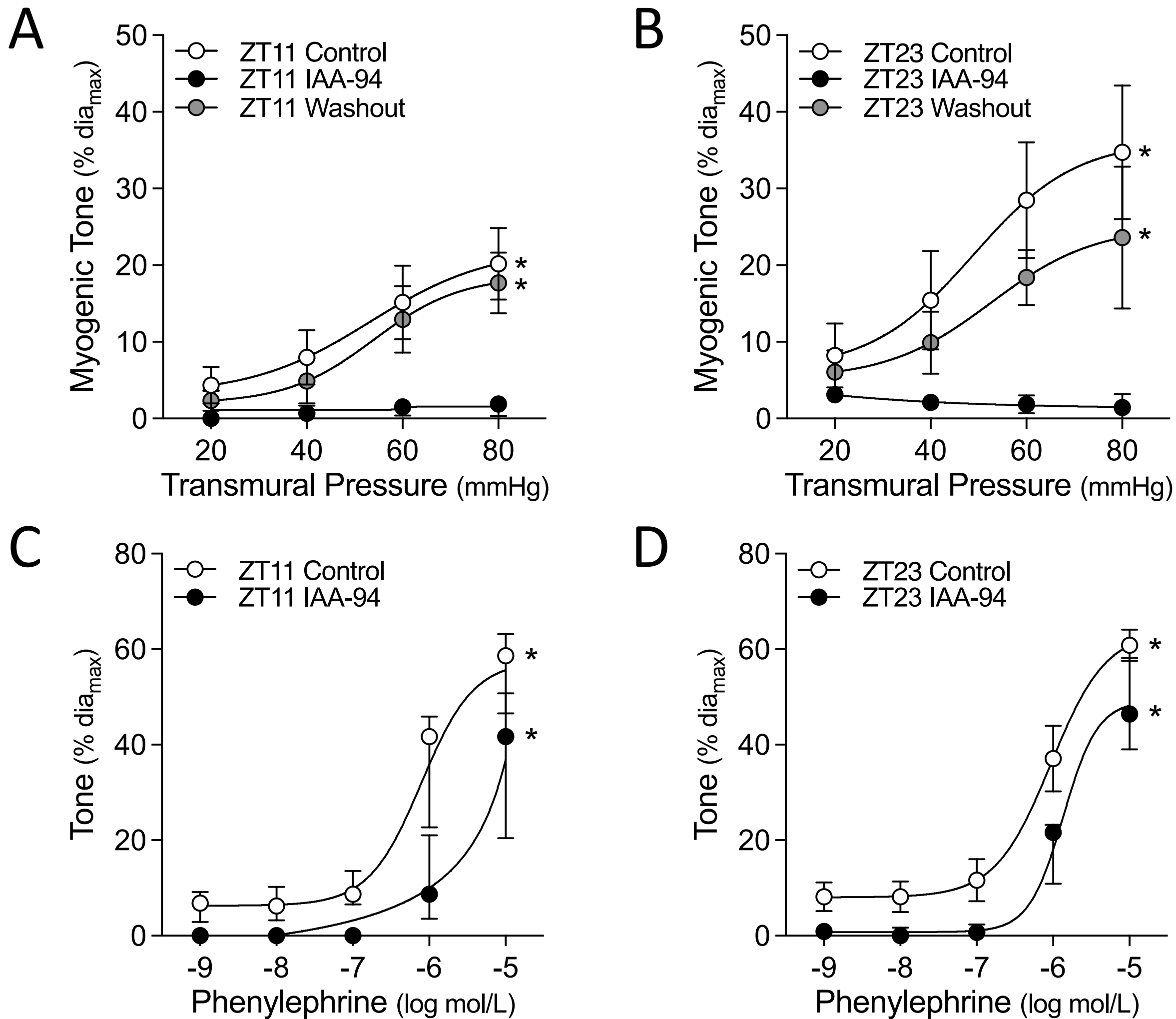
Supplemental Figure V: mRNA expression in Zeitgeber time.

Cerebral artery **(A)** sphingosine kinase 1 (Sphk1), **(B)** sphingosine-1-phosphate receptor 2 ($S1P_2R$), **(C)** brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1), **(D)** period circadian regulator 2 (Per2) and **(E)** circadian locomotor output cycles kaput (Clock) mRNA expression is plotted over Zeitgeber time. All data are presented as medians ± interquartile range; the connecting lines are "double-plotted" to better illustrate the rhythms or lack thereof. White shading indicates "lights on", dark shading indicates "lights off". Sphk1 and $S1P_2R$ do not possess a circadian expression rhythm (P=N.S. by JTK cycle, n=2-4, see Supplemental Table VII). Bmal1, Per2 and Clock, all integral components of the core molecular clock, possess a statistically significant circadian expression rhythm ($P<0.05$ by JTK cycle, n=3; see Supplemental Table VII).



Supplemental Figure VI: Circadian mRNA expression under constant dark conditions.

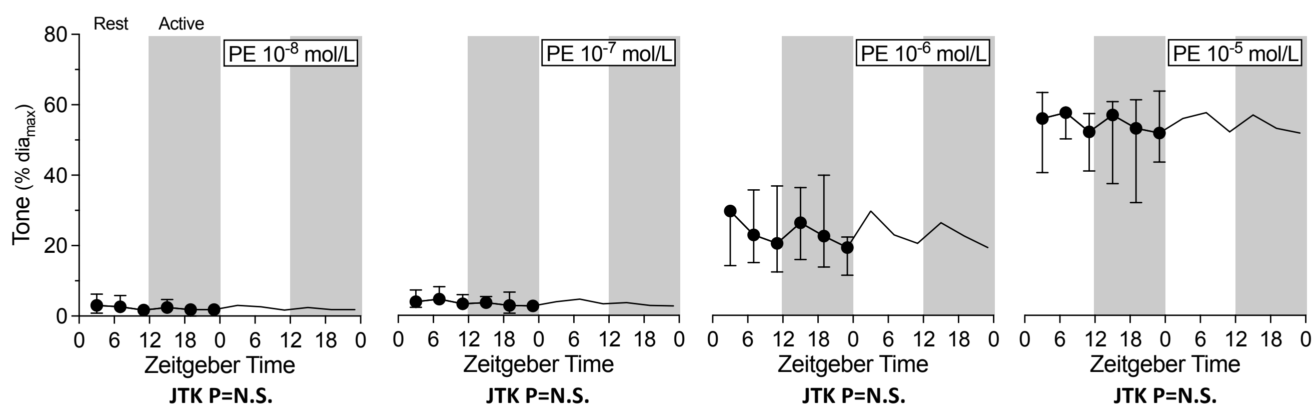
Cerebral artery **(A)** cystic fibrosis transmembrane conductance regulator (CFTR), **(B)** brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1) and **(C)** period circadian regulator 2 (Per2) mRNA expression is plotted over Zeitgeber time. All data are presented as medians ± interquartile range; white shading indicates "lights on", dark shading indicates "lights off" and speckled shading indicates darkness when the lights would normally be on. All three transcripts possess a statistically significant circadian expression rhythm that persists under constant dark conditions ($P<0.05$ by JTK cycle, $n=4$, see Supplemental Table VI1).



Supplemental Figure VII: Chloride channel blockade abolishes cerebral artery myogenic tone.

In *Panels A and B*, myogenic vasoconstriction was assessed in olfactory cerebral arteries under control conditions, following chloride channel inhibitor treatment (100 µmol/L indanyloxyacetic acid 94 [IAA-94] for 30 minutes *in vitro*) and following washout (30 minutes in buffer). IAA-94 reversibly abolishes myogenic vasoconstriction at both **(A)** ZT11 (n=5 paired comparisons) and **(B)** ZT23 (n=5 paired comparisons). Specifically, elevating pressure increases myogenic tone in the control and washout conditions, but not in the IAA-94-treated condition. In *Panels C and D*, phenylephrine-stimulated vasoconstriction was assessed in olfactory cerebral arteries under control conditions and following IAA-94 treatment (100 µmol/L for 30 minutes *in vitro*). Unlike myogenic tone, IAA-94 treatment does not abolish phenylephrine-stimulated vasoconstriction at either **(C)** ZT11 (n=5 paired comparisons) and **(D)** ZT23 (n=5 paired comparisons). * denotes $P<0.05$ for an effect of pressure / phenylephrine by either a repeated measures ANOVA or Freidman's test.

In *Panels A and B*, the control and wash curves are analyzed with a repeated measures ANOVA. In *Panel A*, the IAA-94 curve is presented as medians ± interquartile range and analyzed with a Freidman's test; in *Panel B*, the IAA-94 curve is analyzed with a repeated measures ANOVA. In Panel C, all data are presented as medians ± interquartile range and analyzed with a Freidman's test. In Panel D, the control curve is analyzed with a repeated measures ANOVA; the IAA-94 curve is presented as medians ± interquartile range and analyzed with a Freidman's test.



Supplemental Figure VIII: Cerebral artery phenylephrine responses in lumacaftor-treated mice.

Phenylephrine-stimulated vasoconstriction in olfactory cerebral arteries isolated from lumacaftor-treated wild-type mice plotted over Zeitgeber time (n=5-6). All data are presented as medians ± interquartile range; the connecting lines are "double-plotted" to better illustrate lack of rhythmicity (P=N.S. for a circadian rhythm by JTK cycle, see Supplemental Table VII). White shading indicates "lights on", dark shading indicates "lights off".

Supplemental Table I: Quantitative PCR primer information.

Gene	Primer Sequences (5' to 3')	Size (bp)	Efficiency	Accession no.
Bmal1	GCCACCAACCCATACACAGA TCTTCCCTCGGTCACATCCT	124	1.09	NM_007489.4
Per2	CACACTGCTGCCCTGAGTTC ATCTGAGGACCAGCAGCACA	120	0.98	NM_011066.3
Clock	TGCAGGTACCTTGCTCTGGA GGTTTAACGCCAGCCTCAAG	108	1.00	NM_007715.6
CFTR	CTGGACCACACCAATTTTGAGG GCGTGGATAAGCTGGGGAT	162	1.05	NM_021050.2
Sphk1	TGGGGCTATGACTTGGAAAG CCAGGGAAGGTCCCTAAGAG	125	0.97	NM_011451.3
$S1P_2R$	ATGGGCGGCTTATACTCAGAG GCGCAGCACAAGATGATGAT	137	1.02	NM_010333.4
GAPDH	AGGTCGGTGTGAACGGATTTG TGTAGACCATGTAGTTGAGGTCA	123	0.94	NM_008084.2
G6PD	CACAGTGGACGACATCCGAAA AGCTACATAGGAATTACGGGCAA	103	1.02	NM_008062
HMBS	CCCGTAACATTCCAAGAGGA CCTGTGCCCTACAGACCAGT	147	1.08	NM_013551.2

Abbreviations: Bmal1 = brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1, Per2 = period circadian regulator 2, Clock = circadian locomotor output cycles kaput, CFTR = cystic fibrosis transmembrane conductance regulator, Sphk1 = sphingosine kinase 1, $S1P_2R$ = sphingosine-1-phosphate receptor 2, GAPDH = glyceraldehyde 3-phosphate dehydrogenase, G6PD = glucose-6-phosphate dehydrogenase, HMBS = hydroxymethylbilane synthase. The column heading “size” refers to the amplicon product size in base pairs (bp).

Supplemental Table II: Cohort information.

Genotype	Sex	Intervention	Zeitgeber Time	Experimental Endpoints	Weight (g)	n	SAH Mortality
Wild-Type	M	--	ZT3/ZT7/ZT11/ZT15/ZT19/ZT23	Myography	20-25	29	--
Wild-Type	M	Lumacaftor (in vivo)	ZT3/ZT7/ZT11/ZT15/ZT19/ZT23	Myography	23-26	18	--
Wild-Type	M	CFTR(inh)-172 (in vitro)	ZT11/ZT23	Myography	20-25	9	--
Wild-Type	M	IAA-94 (in vitro)	ZT11/ZT23	Myography	20-25	7	--
Wild-Type	M	--	ZT3/ZT7/ZT11/ZT15/ZT19/ZT23	mRNA / qPCR	20-25	24	--
Wild-Type	M	--	Constant Dark (12 time points)	mRNA / qPCR	20-25	48	--
Wild-Type	M	Lumacaftor/Vehicle (in vivo)	ZT11/ZT23	Western Blot	21-26	45	--
Wild-Type	M	SAH Surgery / Lumacaftor (in vivo)	ZT11	Histology, Modified Garcia Scores	21-26	14	0
Wild-Type	M	SAH Surgery / Lumacaftor (in vivo)	ZT23	Histology, Modified Garcia Scores	21-26	12	0
Wild-Type	M	--	ZT11/ZT23	Blood Donor for SAH	21-26	26	--
WT/Cre	M	SAH Surgery	ZT11	Histology, Modified Garcia Scores	25-30	14	1
WT/Cre	M	SAH Surgery	ZT23	Histology, Modified Garcia Scores	25-30	14	0
WT/Cre	M	--	ZT11/ZT23	Blood Donor for SAH	25-30	28	--
WT/Cre	M	--	ZT11/ZT23	Myography	20-25	9	--
WT/Cre	M	--	ZT11/ZT23	Western Blots	20-25	41	--
sm-Bmal1 KO	M	SAH Surgery	ZT11	Histology, Modified Garcia Scores	25-30	11	1
sm-Bmal1 KO	M	SAH Surgery	ZT23	Histology, Modified Garcia Scores	25-30	11	0
sm-Bmal1 KO	M	--	ZT11/ZT23	Blood Donor for SAH	25-30	22	--
sm-Bmal1 KO	M	--	ZT3/ZT7/ZT11/ZT15/ZT19/ZT23	Myography	20-25	21	--
sm-Bmal1 KO	M	--	ZT11/ZT23	Western Blots	20-25	26	--
					Experimetnal Mice:	353	
					Blood Donor Mice:	76	
					Total Mice:	429	

Column *"n"* refers to the number of mice utilized for the experimental series and column *"SAH Mortality"* refers to the number of mice that died as a result of the SAH surgical procedure. This study used male mice only.

Abbreviations: M = male; SAH = subarachnoid hemorrhage; sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT/Cre = tamoxifen treated, Cre-expressing wild-type control; ZT = Zeitgeber time.

Supplemental Table III: Experimental timeline information.

Year	Experimental Endpoints	Data Set	Sets	Concurant	Figures
1	Myography	WT Circadian Rhythm Assessment	--	No	1A,B
1	mRNA / qPCR	RNA Circadian Rhythm Assessment	--	No	5A, Sup 3
1	mRNA / qPCR	Constant Dark Rhythm Assessment	--	No	Sup 2
2	Myography	CFTR(inh)-172	--	No	5 C,D
2	Western blot	CFTR expression (WT/Cre only)	1 (n=5)	No	5B
3	Myography	sm-Bmal1 KO Rhythm Assessment	--	No	1C,D
3	Myography	WT/Cre ZT11/ZT23	--	Yes	2B
3	SAH Garcia and Histology	WT/Cre and sm-Bmal1 KO	--	Yes	2-4, Sup 1
3	Western blot	CFTR expression (WT/Cre and sm-Bmal1 KO)	3 (n=4-5)	No	5C
3	Western blot	CFTR expression (WT + Lum)	2 (n=5-7)	Yes	5E
3	Myography	WT + Lum Circadian Rhythm Assessment	--	Yes	5F, Sup 5
3	SAH Garcia and Histology	WT + Lum	--	Yes	6
3	Myography	IAA-94	--	No	Sup 4

Western blot data was collected in multiple, independent experiments that were merged. The column *"Sets"* refers to the number of independent experiments, with group sizes listed in parentheses.

Abbreviations: SAH = subarachnoid hemorrhage; sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT/Cre = tamoxifen treated, Cre-expressing wild-type control; WT + Lum = wild type mice treated with 3mg/kg/day lumacaftor for 2 days prior to experimental assessment; ZT = Zeitgeber time.

Supplemental Table IV: Article Figure Data and Normality/Variance Statistics – Circadian Rhythm Assessments.

Figure	Genotype	Parameter	Level	ZT3	n	N	ZT7	n	N	ZT11	n	N	ZT15	n	N	ZT19	n	N	ZT23	n	N	Normality and Variance Statistics
1A	Wild-Type	Myogenic	20 mmHg	12.3±8.2	6	4	3.5±7.4	6	5	7.4±5.6	6	4	8.3±4.7	6	4	9.3±6.4	8	6	16.0±6.0	6	6	$W_{ZT3}(6)$ = 0.96, p = 0.82; $W_{ZT7}(6)$ = 0.92, p = 0.48; $W_{ZT11}(6)$ = 0.99, p = 0.98; $W_{ZT15}(6)$ = 0.93, p = 0.61; $W_{ZT19}(8)$ = 0.78, **p = 0.02**; $W_{ZT23}(6)$ = 0.90, p = 0.41; Brown-Forsythe F(5,32) = 0.35, p = 0.881
1A	Wild-Type	Myogenic	40 mmHg	21.9±9.2	6	4	13.9±5.5	6	5	14.0±10.7	6	4	16.7±10.7	6	4	17.1±8.7	8	6	27.1±8.3	6	6	$W_{ZT3}(6)$ = 0.82, p = 0.10; $W_{ZT7}(6)$ = 0.79, **p = 0.04**; $W_{ZT11}(6)$ = 0.94, p = 0.70; $W_{ZT15}(6)$ = 0.92, p = 0.53; $W_{ZT19}(8)$ = 0.91, p = 0.36; $W_{ZT23}(6)$ = 0.96, p = 0.36; Brown-Forsythe F(5,32) = 0.51, p = 0.766
1A	Wild-Type	Myogenic	60 mmHg	30.0±11.6	6	4	21.5±7.8	6	5	18.9±6.3	6	4	23.9±6.5	6	4	24.7±6.6	8	6	34.3±7.7	6	6	$W_{ZT3}(6)$ = 0.87, p = 0.22; $W_{ZT7}(6)$ = 0.92, p = 0.50; $W_{ZT11}(6)$ = 0.80, p = 0.05; $W_{ZT15}(6)$ = 0.93, p = 0.56; $W_{ZT19}(8)$ = 0.98, p = 0.95; $W_{ZT23}(6)$ = 0.87, p = 0.23; Brown-Forsythe F(5,32) = 0.39, p = 0.853
1A	Wild-Type	Myogenic	80 mmHg	34.8±10.8	6	4	25.8±5.4	6	5	27.1±4.5	6	4	28.8±5.8	6	4	30.3±7.2	8	6	34.7±9.0	6	6	$W_{ZT3}(6)$ = 0.92, p = 0.51; $W_{ZT7}(6)$ = 0.85, p = 0.16; $W_{ZT11}(6)$ = 0.93, p = 0.60; $W_{ZT15}(6)$ = 0.96, p = 0.84; $W_{ZT19}(8)$ = 0.93, p = 0.49; $W_{ZT23}(6)$ = 0.94, p = 0.65; Brown-Forsythe F(5,32) = 0.79, p = 0.568
1B	Wild-Type	Phenylephrine	10 nmol/L	9.3±13.6	6	4	2.7±4.7	5	4	6.4±7.5	6	4	3.0±13.8	6	4	5.2±6.8	8	6	19.2±7.9	6	6	$W_{ZT3}(6)$ = 0.88, p = 0.27; $W_{ZT7}(5)$ = 0.98, p = 0.92; $W_{ZT11}(6)$ = 0.86, p = 0.20; $W_{ZT15}(6)$ = 0.83, p = 0.11; $W_{ZT19}(8)$ = 0.90, p = 0.29; $W_{ZT23}(6)$ = 0.80, p = 0.06; Brown-Forsythe F(5,31) = 1.39, p = 0.257
1B	Wild-Type	Phenylephrine	100 nmol/L	14.8±22.3	6	4	7.0±11.1	5	4	10.2±4.1	6	4	7.2±18.4	6	4	11.5±9.2	8	6	27.8±11.5	6	6	$W_{ZT3}(6)$ = 0.93, p = 0.59; $W_{ZT7}(5)$ = 0.89, p = 0.38; $W_{ZT11}(6)$ = 0.73, **p = 0.01**; $W_{ZT15}(6)$ = 0.81, p = 0.08; $W_{ZT19}(8)$ = 0.92, p = 0.44; $W_{ZT23}(6)$ = 0.91, p = 0.45; Brown-Forsythe F(5,31) = 1.60, p = 0.190
1B	Wild-Type	Phenylephrine	1 µmol/L	40.8±31.1	6	4	30.5±27.6	5	4	35.2±6.0	6	4	30.1±25.2	6	4	37.8±33.3	8	6	50.1±15.7	6	6	$W_{ZT3}(6)$ = 0.94, p = 0.69; $W_{ZT7}(5)$ = 0.91, p = 0.45; $W_{ZT11}(6)$ = 0.94, p = 0.67; $W_{ZT15}(6)$ = 0.86, p = 0.18; $W_{ZT19}(8)$ = 0.92, p = 0.47; $W_{ZT23}(6)$ = 0.96, p = 0.81; Brown-Forsythe F(5,31) = 2.30, p = 0.069
1B	Wild-Type	Phenylephrine	10 µmol/L	58.2±13.7	6	4	60.9±10.4	5	4	53.2±9.3	6	4	55.3±17.1	6	4	58.0±7.4	8	6	62.2±10.4	6	6	$W_{ZT3}(6)$ = 0.86, p = 0.19; $W_{ZT7}(5)$ = 0.95, p = 0.76; $W_{ZT11}(6)$ = 0.96, p = 0.85; $W_{ZT15}(6)$ = 0.85, p = 0.17; $W_{ZT19}(8)$ = 0.98, p = 0.94; $W_{ZT23}(6)$ = 0.92, p = 0.53; Brown-Forsythe F(5,31) = 0.65, p = 0.652
1C / 3B	sm-Bmal1 KO	Myogenic	20 mmHg	2.6±6.2	6	3	1.7±3.9	5	3	4.5±3.6	6	3	2.4±4.0	11	6	4.2±6.3	5	3	2.6±2.2	6	3	$W_{ZT3}(6)$ = 0.88, p = 0.28; $W_{ZT7}(5)$ = 0.95, p = 0.73; $W_{ZT11}(6)$ = 0.82, p = 0.08; $W_{ZT15}(11)$ = 0.86, p = 0.06; $W_{ZT19}(5)$ = 0.88, p = 0.32; $W_{ZT23}(6)$ = 0.95, p = 0.71; Brown-Forsythe F(5,33) = 0.95, p = 0.464
1C / 3B	sm-Bmal1 KO	Myogenic	40 mmHg	5.3±7.2	6	3	4.8±3.6	5	3	11.4±6.7	6	3	3.8±6.1	11	6	4.5±7.8	5	3	5.2±3.7	6	3	$W_{ZT3}(6)$ = 0.69, **p < 0.01**; $W_{ZT7}(5)$ = 1.00, p = 0.99; $W_{ZT11}(6)$ = 0.93, p = 0.60; $W_{ZT15}(11)$ = 0.81, **p = 0.01**; $W_{ZT19}(5)$ = 0.81, p = 0.11; $W_{ZT23}(6)$ = 0.94, p = 0.66; Brown-Forsythe F(5,33) = 0.41, p = 0.841
1C / 3B	sm-Bmal1 KO	Myogenic	60 mmHg	9.5±10.0	6	3	6.1±4.9	5	3	16.4±11.9	6	3	9.6±14.1	11	6	5.0±9.7	5	3	9.4±4.3	6	3	$W_{ZT3}(6)$ = 0.71, **p < 0.01**; $W_{ZT7}(5)$ = 0.74, **p = 0.02**; $W_{ZT11}(6)$ = 0.82, p = 0.09; $W_{ZT15}(11)$ = 0.85, **p = 0.04**; $W_{ZT19}(5)$ = 0.69, **p = 0.01**; $W_{ZT23}(6)$ = 0.85, p = 0.17; Brown-Forsythe F(5,33) = 0.85, p = 0.526
1C / 3B	sm-Bmal1 KO	Myogenic	80 mmHg	16.0±14.7	6	3	9.9±7.4	5	3	20.7±12.7	6	3	12.4±15.8	11	6	6.1±9.9	5	3	12.8±4.5	6	3	$W_{ZT3}(6)$ = 0.86, p = 0.18; $W_{ZT7}(5)$ = 0.85, p = 0.20; $W_{ZT11}(6)$ = 0.85, p = 0.16; $W_{ZT15}(11)$ = 0.87, p = 0.09; $W_{ZT19}(5)$ = 0.69, **p = 0.01**; $W_{ZT23}(6)$ = 0.81, p = 0.07; Brown-Forsythe F(5,33) = 1.74, p = 0.152
1D	sm-Bmal1 KO	Phenylephrine	10 nmol/L	4.6±7.7	6	3	2.1±2.7	5	3	11.5±10.6	6	3	2.5±6.2	11	6	5.9±7.2	5	3	2.9±5.5	6	3	$W_{ZT3}(6)$ = 0.88, p = 0.27; $W_{ZT7}(5)$ = 0.99, p = 0.99; $W_{ZT11}(6)$ = 0.94, p = 0.63; $W_{ZT15}(11)$ = 0.64, **p < 0.01**; $W_{ZT19}(5)$ = 0.98, p = 0.93; $W_{ZT23}(6)$ = 0.88, p = 0.27; Brown-Forsythe F(5,33) = 0.62, p = 0.686
1D	sm-Bmal1 KO	Phenylephrine	100 nmol/L	6.6±10.0	6	3	3.5±4.6	5	3	14.0±11.6	6	3	5.4±8.1	11	6	5.9±8.0	5	3	5.0±5.3	6	3	$W_{ZT3}(6)$ = 0.89, p = 0.33; $W_{ZT7}(5)$ = 0.96, p = 0.79; $W_{ZT11}(6)$ = 0.89, p = 0.32; $W_{ZT15}(11)$ = 0.70, **p < 0.01**; $W_{ZT19}(5)$ = 0.90, p = 0.41; $W_{ZT23}(6)$ = 0.93, p = 0.63; Brown-Forsythe F(5,33) = 0.70, p = 0.628
1D	sm-Bmal1 KO	Phenylephrine	1 µmol/L	30.3±9.8	6	3	19.0±15.6	5	3	45.4±13.2	6	3	29.1±30.7	11	6	21.5±18.5	5	3	21.8±6.6	6	3	$W_{ZT3}(6)$ = 0.95, p = 0.75; $W_{ZT7}(5)$ = 0.95, p = 0.75; $W_{ZT11}(6)$ = 0.92, p = 0.50; $W_{ZT15}(11)$ = 0.92, p = 0.36; $W_{ZT19}(5)$ = 0.91, p = 0.46; $W_{ZT23}(6)$ = 0.88, p = 0.31; Brown-Forsythe F(5,33) = 2.03, p = 0.101
1D	sm-Bmal1 KO	Phenylephrine	10 µmol/L	57.4±8.6	6	3	58.3±11.9	5	3	63.9±5.7	6	3	58.6±15.7	11	6	46.7±27.9	5	3	54.9±5.5	6	3	$W_{ZT3}(6)$ = 0.91, p = 0.46; $W_{ZT7}(5)$ = 0.96, p = 0.84; $W_{ZT11}(6)$ = 0.87, p = 0.21; $W_{ZT15}(11)$ = 0.90, p = 0.21; $W_{ZT19}(5)$ = 0.90, p = 0.42; $W_{ZT23}(6)$ = 0.96, p = 0.83; Brown-Forsythe F(5,33) = 3.32, **p = 0.016**
5A	Wild-Type	CFTR mRNA	--	1.1±0.4	4	4	1.2±0.5	4	4	1.8±0.4	4	4	1.5±0.1	4	4	1.0±0.3	4	4	1.0±0.6	4	4	$W_{ZT3}(4)$ = 0.89, p = 0.37; $W_{ZT7}(4)$ = 0.95, p = 0.69; $W_{ZT11}(4)$ = 0.98, p = 0.88; $W_{ZT15}(4)$ = 0.94, p = 0.67; $W_{ZT19}(4)$ = 0.89, p = 0.38; $W_{ZT23}(4)$ = 0.98, p = 0.92; Brown-Forsythe F(5,18) = 0.98, p = 0.459
6B	WT + Lum	Myogenic	20 mmHg	3.0±5.7	6	3	1.7±4.0	5	3	1.6±2.9	5	3	2.6±1.4	6	3	3.7±4.5	6	3	0.9±1.1	5	3	$W_{ZT3}(6)$ = 0.86, p = 0.20; $W_{ZT7}(5)$ = 0.84, p = 0.16; $W_{ZT11}(5)$ = 0.89, p = 0.36; $W_{ZT15}(6)$ = 0.78, **p = 0.04**; $W_{ZT19}(6)$ = 0.91, p = 0.47; $W_{ZT23}(5)$ = 0.78, p = 0.05; Brown-Forsythe F(5,27) = 2.22, p = 0.082
6B	WT + Lum	Myogenic	40 mmHg	5.3±5.3	6	3	4.5±7.2	5	3	3.3±4.1	5	3	3.4±4.3	6	3	4.5±4.5	6	3	0.9±6.3	5	3	$W_{ZT3}(6)$ = 0.99, p = 0.99; $W_{ZT7}(5)$ = 0.68, **p = 0.01**; $W_{ZT11}(5)$ = 0.92, p = 0.51; $W_{ZT15}(6)$ = 0.80, p = 0.06; $W_{ZT19}(6)$ = 0.94, p = 0.65; $W_{ZT23}(5)$ = 0.83, p = 0.13; Brown-Forsythe F(5,27) = 0.14, p = 0.981
5C / 6B	WT + Lum	Myogenic	60 mmHg	6.9±6.1	6	3	7.5±11.7	5	3	6.0±7.1	5	3	6.7±8.1	6	3	6.9±9.3	6	3	5.3±7.9	5	3	$W_{ZT3}(6)$ = 0.84, p = 0.13; $W_{ZT7}(5)$ = 0.86, p = 0.23; $W_{ZT11}(5)$ = 0.86, p = 0.23; $W_{ZT15}(6)$ = 0.89, p = 0.34; $W_{ZT19}(6)$ = 0.87, p = 0.24; $W_{ZT23}(5)$ = 0.85, p = 0.18; Brown-Forsythe F(5,27) = 0.94, p = 0.941
6B	WT + Lum	Myogenic	80 mmHg	10.1±7.5	6	3	15.2±15.8	5	3	9.9±10.5	5	3	7.1±12.3	6	3	14.1±16.1	6	3	9.8±6.0	5	3	$W_{ZT3}(6)$ = 0.86, p = 0.19; $W_{ZT7}(5)$ = 0.94, p = 0.63; $W_{ZT11}(5)$ = 0.81, p = 0.10; $W_{ZT15}(6)$ = 0.84, p = 0.12; $W_{ZT19}(6)$ = 0.93, p = 0.60; $W_{ZT23}(5)$ = 0.89, p = 0.34; Brown-Forsythe F(5,27) = 0.92, p = 0.484
Sup V-A	Wild-Type	Sphk1 mRNA	--	1.8±0.6	3	3	1.0±0.2	3	3	1.1±0.4	3	3	1.5±0.3	3	3	1.0±0.1	3	3	1.0±0.1	2	2	$W_{ZT3}(3)$ = 0.80, p = 0.12; $W_{ZT7}(3)$ = 0.98, p = 0.73; $W_{ZT11}(3)$ = 0.98, p = 0.72; $W_{ZT15}(3)$ = 0.93, p = 0.50; $W_{ZT19}(3)$ = ND; $W_{ZT23}(2)$ = ND; Brown-Forsythe F(5,11) = 0.46, p = 0.799
Sup V-B	Wild-Type	$S1P_2R$ mRNA	--	1.1±0.4	4	4	1.1±0.2	4	4	1.0±0.3	4	4	1.1±0.4	4	4	1.3±0.4	4	4	1.1±0.4	3	3	$W_{ZT3}(4)$ = 0.98, p = 0.93; $W_{ZT7}(4)$ = 0.89, p = 0.39; $W_{ZT11}(4)$ = 0.93, p = 0.61; $W_{ZT15}(4)$ = 0.86, p = 0.27; $W_{ZT19}(4)$ = 0.96, p = 0.76; $W_{ZT23}(3)$ = 0.83, p = 0.20; Brown-Forsythe F(5,17) = 0.52, p = 0.757
Sup V-C	Wild-Type	Bmal1 mRNA	--	9.8±5.8	3	3	2.5±3.5	3	3	1.0±0.5	3	3	2.8±1.5	3	3	13.8±3.9	3	3	21.6±7.0	3	3	$W_{ZT3}(3)$ = 1.00, p = 0.91; $W_{ZT7}(3)$ = 0.83, p = 0.18; $W_{ZT11}(3)$ = 0.95, p = 0.58; $W_{ZT15}(3)$ = 0.87, p = 0.31; $W_{ZT19}(3)$ = 0.93, p = 0.47; $W_{ZT23}(3)$ = 0.99, p = 0.80; Brown-Forsythe F(5,12) = 0.97, p = 0.475
Sup V-D	Wild-Type	Per2 mRNA	--	1.1±0.6	3	3	2.9±1.1	3	3	5.9±1.9	3	3	6.6±0.5	3	3	4.2±0.8	3	3	1.8±0.9	3	3	$W_{ZT3}(3)$ = 0.86, p = 0.27; $W_{ZT7}(3)$ = 0.99, p = 0.84; $W_{ZT11}(3)$ = 0.93, p = 0.49; $W_{ZT15}(3)$ = 0.98, p = 0.76; $W_{ZT19}(3)$ = 0.99, p = 0.79; $W_{ZT23}(3)$ = 0.99, p = 0.83; Brown-Forsythe F(5,12) = 0.66, p = 0.659
Sup V-E	Wild-Type	Clock mRNA	--	1.1±0.2	3	3	1.1±0.0	3	3	1.0±0.1	3	3	1.3±0.1	3	3	1.7±0.3	3	3	1.7±0.7	3	3	$W_{ZT3}(3)$ = 1.00, p > 0.99; $W_{ZT7}(3)$ = ND; $W_{ZT11}(3)$ = 1.00, p = 0.88; $W_{ZT15}(3)$ = 0.95, p = 0.57; $W_{ZT19}(3)$ = 0.98, p = 0.73; $W_{ZT23}(3)$ = 0.99, p = 0.83; Brown-Forsythe F(5,12) = 2.08, p = 0.139
Sup VIII	WT + Lum	Phenylephrine	10 nmol/L	3.0±5.4	6	3	2.6±4.0	5	3	1.7±1.6	5	3	2.4±2.9	6	3	1.8±3.2	6	3	1.8±1.0	5	3	$W_{ZT3}(6)$ = 0.91, p = 0.42; $W_{ZT7}(5)$ = 0.86, p = 0.24; $W_{ZT11}(5)$ = 0.78, p = 0.05; $W_{ZT15}(6)$ = 0.77, **p = 0.03**; $W_{ZT19}(6)$ = 0.91, p = 0.43; $W_{ZT23}(5)$ = 0.76, **p = 0.04**; Brown-Forsythe F(5,27) = 1.03, p = 0.420
Sup VIII	WT + Lum	Phenylephrine	100 nmol/L	3.9±5.0	6	3	4.6±5.1	5	3	3.3±3.3	5	3	3.7±2.8	6	3	2.9±6.1	6	3	2.7±1.6	5	3	$W_{ZT3}(6)$ = 0.97, p = 0.87; $W_{ZT7}(5)$ = 0.91, p = 0.46; $W_{ZT11}(5)$ = 0.88, p = 0.32; $W_{ZT15}(6)$ = 0.74, **p = 0.02**; $W_{ZT19}(6)$ = 0.88, p = 0.26; $W_{ZT23}(5)$ = 0.91, p = 0.46; Brown-Forsythe F(5,27) = 0.76, p = 0.589
Sup VIII	WT + Lum	Phenylephrine	1 µmol/L	29.7±16.8	6	3	22.9±20.7	5	3	20.5±24.5	5	3	26.4±20.45	6	3	22.6±26.1	6	3	19.3±10.9	5	3	$W_{ZT3}(6)$ = 0.72, **p = 0.01**; $W_{ZT7}(5)$ = 0.92, p = 0.55; $W_{ZT11}(5)$ = 0.84, p = 0.17; $W_{ZT15}(6)$ = 0.97, p = 0.87; $W_{ZT19}(6)$ = 0.92, p = 0.54; $W_{ZT23}(5)$ = 0.92, p = 0.55; Brown-Forsythe F(5,27) = 0.83, p = 0.539
Sup VIII	WT + Lum	Phenylephrine	10 µmol/L	56.1±22.9	6	3	57.7±8.5	5	3	52.2±16.3	5	3	57.1±23.4	6	3	53.2±29.3	6	3	51.9±20.2	5	3	$W_{ZT3}(6)$ = 0.96, p = 0.82; $W_{ZT7}(5)$ = 0.88, p = 0.30; $W_{ZT11}(5)$ = 0.87, p = 0.26; $W_{ZT15}(6)$ = 0.79, p = 0.05; $W_{ZT19}(6)$ = 0.86, p = 0.19; $W_{ZT23}(5)$ = 0.99, p = 0.98; Brown-Forsythe F(5,27) = 0.63, p = 0.680

Data are medians ± interquartile range. Column *"n"* refers to the number of samples or arteries assessed; column *"N"* refers to the number of mice utilized to collect the samples or vessels.

Abbreviations: sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT + Lum = wild type mice treated with 3mg/kg/day lumacaftor for 2 days prior to experimental assessment; WT/Cre = tamoxifen treated, Cre-expressing wild-type control; ZT = Zeitgeber time.

Supplemental Table V: Article Figure Data and Statistics– ZT11 / ZT23 Comparisons.

Figure	Genotype	Parameter	Level	ZT11	n	N	ZT23	n	N	Comparison Test	Statistics
2B	WT/Cre	Myogenic	20 mmHg	1.7±1.3	5	4	2.7±2.8	6	5	Repeated 2-Way ANOVA with Geisser-Greenhouse correction	Transmural Pressure (Repeated Measures): F(1.33, 13.35) = 39.40, **p < 0.001**; Zeitgeber Time (Non-Repeated
2B	WT/Cre	Myogenic	40 mmHg	3.9±1.6	5	4	8.9±4.8	6	5		Measures): F(1, 9) = 7.78, **p = 0.02**; $W_{ZT11-20}(5)$ = 0.95, p = 0.75; $W_{ZT23-20}(6)$ = 0.90, p = 0.37;
2B	WT/Cre	Myogenic	60 mmHg	9.0±1.8	5	4	17.2±7.7	6	5		$W_{ZT11-40}(5)$ = 0.97, p = 0.88; $W_{ZT23-40}(6)$ = 0.90, p = 0.38; $W_{ZT11-60}(5)$ = 0.84, p = 0.17; $W_{ZT23-60}(6)$ = 0.91, p = 0.43;
2B	WT/Cre	Myogenic	80 mmHg	13.3±1.2	5	4	24.2±8.1	6	5		$W_{ZT11-80}(5)$ = 0.82, p = 0.13; $W_{ZT23-80}(6)$ = 0.92, p = 0.48; Brown-Forsythe F(7,36) = 3.46, **p = 0.006**
2C	WT/Cre	Fluoro-Jade	--	80±45	13	13	162±69	14	14	t test	t(25) = 3.65, **p = 0.001**; F(13,12) = 2.28, p = 0.16; $W_{ZT11}(13)$ = 0.95, p = 0.66; $W_{ZT23}(14)$ = 0.97, p = 0.90
2C	WT/Cre	Caspase-3	--	160±112	13	13	303±175	14	14	t test	t(25) = 2.51, **p = 0.02**; F(13,12) = 2.43, p = 0.13; $W_{ZT11}(13)$ = 0.89, p = 0.09; $W_{ZT23}(14)$ = 0.91, p = 0.17
2D	WT/Cre	Garcia Score	--	**16.0±1.4**	**12**	**12**	**14.3±1.4**	**14**	**14**	Mann-Whitney	U(N_{ZT12} = 10, N_{ZT23} = 14) = 44, z = -2.03, **p = 0.04**
3B	sm-Bmal1 KO	Myogenic	20 mmHg	5.2±3.0	6	3	2.4±1.1	6	3	Repeated 2-Way ANOVA with Geisser-Greenhouse correction	Transmural Pressure (Repeated Measures): F(1.20, 13.24) = 78.10, **p < 0.001**; Zeitgeber Time (Non-Repeated
3B	sm-Bmal1 KO	Myogenic	40 mmHg	12.4±4.1	6	3	5.6±2.3	6	3		Measures): F(1, 10) = 10.83, **p = 0.008**; $W_{ZT11-20}(6)$ = 0.82, p = 0.08; $W_{ZT23-20}(6)$ = 0.95, p = 0.71;
3B	sm-Bmal1 KO	Myogenic	60 mmHg	18.5±5.7	6	3	9.7±3.2	6	3		$W_{ZT11-40}(6)$ = 0.93, p = 0.60; $W_{ZT23-40}(6)$ = 0.94, p = 0.66; $W_{ZT11-60}(6)$ = 0.82, p = 0.09; $W_{ZT23-60}(6)$ = 0.85, p = 0.17;
3B	sm-Bmal1 KO	Myogenic	80 mmHg	23.4±6.6	6	3	13.4±3.9	6	3		$W_{ZT11-80}(6)$ = 0.85, p = 0.16; $W_{ZT23-80}(6)$ = 0.81, p = 0.07; Brown-Forsythe F(7,40) = 1.21, p = 0.322
3C	sm-Bmal1 KO	Fluoro-Jade	--	**133±143**	**10**	**10**	**37±26**	**11**	**11**	Mann-Whitney	U(N_{ZT11} = 10, N_{ZT23} = 11) = 9, z = -3.20, **p < 0.001**; F(9,10) = 4.90, **p = 0.02**; $W_{ZT11}(10)$ = 0.93, p = 0.41; $W_{ZT23}(11)$ = 0.83, **p = 0.02**
3C	sm-Bmal1 KO	Caspase-3	--	302±173	10	10	158±77	11	11	Welch's t test	t(12.18) = 2.42, **p = 0.03**; F(9,10) = 5.05, **p = 0.02**; $W_{ZT11}(10)$ = 0.89, p = 0.17; $W_{ZT23}(11)$ = 0.95, p = 0.60
3D	sm-Bmal1 KO	Garcia Score	--	**15.5±2.3**	**10**	**10**	**16.5±2.0**	**11**	**11**	Mann-Whitney	U(N_{ZT11} = 10, N_{ZT23} = 11) = 17, z = 2.64, **p = 0.008**
4B	WT/Cre	Microglial %	--	4.8±0.8	13	13	6.1±0.6	13	13	t test	t(24) = 4.72, **p < 0.001**; F(12,12) = 1.69, p = 0.38; $W_{ZT11}(13)$ = 0.96, p = 0.77; $W_{ZT23}(13)$ = 0.95, p = 0.54
4B	sm-Bmal1 KO	Microglial %	--	5.4±1.2	10	10	6.5±1.0	11	11	t test	t(19) = 2.30, **p < 0.03**; F(9,10) = 1.40, p = 0.61; $W_{ZT11}(10)$ = 0.93, p = 0.41; $W_{ZT23}(11)$ = 0.95, p = 0.61
4D	WT/Cre	ACA Constriction	--	4.1±1.4	12	12	4.4±1.2	13	13	t test	t(23) = 0.56, p = 0.58; F(11,12) = 1.33, p = 0.62; $W_{ZT11}(12)$ = 0.91, p = 0.21; $W_{ZT23}(13)$ = 0.92, p = 0.26
5B	WT/Cre	CFTR protein	--	**1.0±0.5**	**20**	**20**	**0.6±0.4**	**21**	**21**	Kruskal-Wallis with Dunn's post-test	H(3) = 14.34, **p = 0.003**; WT11 vs. WT23 **p = 0.03**; KO11 vs. KO23 p > 0.999; WT11 vs. KO11 **p = 0.002**;
5B	sm-Bmal1 KO	CFTR protein	--	**0.6±0.3**	**14**	**14**	**0.6±0.3**	**12**	**12**		WT23 vs. KO23 p > 0.999; $W_{WTZT11}(20)$ = 0.95, p = 0.43; $W_{WTZT23}(23)$ = 0.93, p = 0.12;
5B	--	--	--								$W_{KOZT11}(14)$ = 0.88, p = 0.06; $W_{KOZT23}(12)$ = 0.81, **p = 0.01**; Brown-Forsythe F(3,63) = 0.54, p = 0.658
5E	WT+Vehicle	CFTR protein	--	1.0±0.2	11	11	0.6±0.2	10	10	ANOVA with Bonferroni corrected post-test	ANOVA F(3,41) = 4.16, **p = 0.01**; Con11 vs.Con23 **p = 0.01**; Lum11 vs. Lum23 p = 0.95;
5E	WT+Lum	CFTR protein	--	0.8±0.3	12	12	1.0±0.3	12	12		Con11 vs. Lum11 p = 0.72; Con23 vs. Lum23 **p = 0.02**; Brown-Forsythe F(3,41) = 1.34, p = 0.27
5E	--	--	--								$W_{Con11}(11)$ = 0.92, p = 0.35; $W_{Con23}(10)$ = 0.91, p = 0.28; $W_{Lum11}(12)$ = 0.94, p = 0.70;
5E	--	--	--								$W_{Lum23}(12)$ = 0.94, p = 0.45
6B	WT+Lum	Myogenic	20 mmHg	5.2±3.0	6	3	2.4±1.1	6	3	Repeated 2-Way ANOVA with Geisser-Greenhouse correction	Transmural Pressure (Repeated Measures): F(1.25, 12.20) = 20.54, **p < 0.001**; Zeitgeber Time (Non-Repeated
6B	WT+Lum	Myogenic	40 mmHg	12.4±4.1	6	3	5.6±2.3	6	3		Measures): F(1, 8) = 0.51, p = 0.494; $W_{ZT11-20}(5)$ = 0.89, p = 0.36; $W_{ZT23-20}(5)$ = 0.78, p = 0.05;
6B	WT+Lum	Myogenic	60 mmHg	18.5±5.7	6	3	9.7±3.2	6	3		$W_{ZT11-40}(5)$ = 0.92, p = 0.51; $W_{ZT23-40}(5)$ = 0.83, p = 0.13; $W_{ZT11-60}(5)$ = 0.86, p = 0.23; $W_{ZT23-60}(5)$ = 0.85, p = 0.18;
6B	WT+Lum	Myogenic	80 mmHg	23.4±6.6	6	3	13.4±3.9	6	3		$W_{ZT11-80}(5)$ = 0.81, p = 0.10; $W_{ZT23-80}(5)$ = 0.89, p = 0.34; Brown-Forsythe F(7,32) = 0.69, p = 0.682
6C	WT+Lum	Fluoro-Jade	--	234±158	14	14	136±73	12	12	Welch's t test	t(18.83) = 2.09, p = 0.05; F(13,11) = 4.75, **p = 0.01**; $W_{ZT11}(14)$ = 0.93, p = 0.33; $W_{ZT23}(12)$ = 0.90, p = 0.15
6C	WT+Lum	Caspase-3	--	197±119	14	14	143±71	12	12	t test	t(24) = 1.38, p = 0.18; F(13,11) = 2.84, p = 0.09; $WZ_{T11}(14)$ = 0.89, p = 0.09; $W_{ZT23}(12)$ = 0.93, p = 0.41
6D	WT+Lum	Garcia Score	--	**14.0±5.5**	**14**	**14**	**16.0±2.0**	**12**	**12**	Mann-Whitney	U(N_{ZT11} = 14, N_{ZT23} = 12) = 49, z = -1.77, p = 0.07
Sup III-B	WT/Cre	Soma Size	--	**32.6±10.2**	**12**	**12**	**49.1±17.8**	**14**	**14**	Mann-Whitney	U(N_{ZT11} = 12, N_{ZT23} = 14) = 12, z = -3.68, **p < 0.001**; F(13,11) = 3.39, p = 0.05; $W_{ZT11}(12)$ = 0.88, p = 0.09; $W_{ZT23}(14)$ = 0.84, **p = 0.02**
Sup III-B	sm-Bmal1 KO	Soma Size	--	32.6±10.8	10	10	53.8±10.4	11	11	t test	t(19) = 4.57, **p < 0.001**; F(9,10) = 1.08, p = 0.90; $WZ_{T11}(10)$ = 0.95, p = 0.69; $W_{ZT23}(11)$ = 0.88, p = 0.11
Sup IV-B	WT/Cre	Microglial %	--	5.4±0.8	12	12	7.3±1.2	14	14	t test	t(24) = 4.81, **p < 0.001**; F(13,11) = 1.95, p = 0.27; $WZ_{T11}(12)$ = 0.98, p = 0.97; $W_{ZT23}(14)$ = 0.96, p = 0.67
Sup IV-B	sm-Bmal1 KO	Microglial %	--	6.8±1.8	10	10	7.3±1.4	11	11	t test	t(19) = 0.78, p = 0.45; F(9,10) = 1.71, p = 0.41; $WZ_{T11}(10)$ = 0.90, p = 0.21; $W_{ZT23}(11)$ = 0.97, p = 0.92
Sup VII-A,B	Control	Myogenic	20 mmHg	4.3±2.4	5	3	8.2±4.2	5	3	(ZT11) Repeated Measures ANOVA	ZT11 ANOVA F(3,12) = 45.24, **p < 0.001**; $W_{ZT11-20}(5)$ = 0.91, p = 0.44; $W_{ZT11-40}(5)$ = 0.94, p = 0.67;
Sup VII-A,B	Control	Myogenic	40 mmHg	8.0±3.5	5	3	15.4±6.4	5	3		$W_{ZT11-60}(5)$ = 0.98, p = 0.95; $W_{ZT11-80}(5)$ = 0.81, p = 0.10; Brown-Forsythe F(3,16) = 0.34, p = 0.794
Sup VII-A,B	Control	Myogenic	60 mmHg	15.2±4.8	5	3	28.5±7.6	5	3	(ZT23) Repeated Measures ANOVA	ZT23 ANOVA F(3,12) = 52.21, **p < 0.001**; $W_{ZT23-20}(5)$ = 0.83, p = 0.14; $W_{ZT23-40}(5)$ = 0.91, p = 0.45;
Sup VII-A,B	Control	Myogenic	80 mmHg	20.2±4.7	5	3	34.7±8.7	5	3		$W_{ZT23-60}(5)$ = 0.79, p = 0.06; $W_{ZT23-80}(5)$ = 0.78, p = 0.06; Brown-Forsythe F(3,16) = 0.28, p = 0.842
Sup VII-A,B	IAA-94	Myogenic	20 mmHg	**0.0±3.6**	**5**	**3**	3.1±0.6	5	3	Friedman Test (ZT11)	ZT11 Friedman $X^2_r(3)$ = 1.14, p = 0.77; $W_{ZT11-20}(5)$ = 0.63, **p = 0.002**; $W_{ZT11-40}(5)$ = 0.87, p = 0.26;
Sup VII-A,B	IAA-94	Myogenic	40 mmHg	**0.7±1.7**	**5**	**3**	2.1±0.6	5	3		$W_{ZT11-60}(5)$ = 0.98, p = 0.93; $W_{ZT11-80}(5)$ = 0.95, p = 0.74; Brown-Forsythe F(3,16) = 0.26, p = 0.850
Sup VII-A,B	IAA-94	Myogenic	60 mmHg	**1.5±1.9**	**5**	**3**	1.8±1.2	5	3	(ZT23) Repeated Measures ANOVA	ZT23 ANOVA F(3,12) = 1.91, p = 0.17; $W_{ZT23-20}(5)$ = 0.94, p = 0.67; $W_{ZT23-40}(5)$ = 0.89, p = 0.33;
Sup VII-A,B	IAA-94	Myogenic	80 mmHg	**1.9±2.3**	**5**	**3**	1.4±1.8	5	3		$W_{ZT23-60}(5)$ = 0.95, p = 0.71; $W_{ZT23-80}(5)$ = 0.85, p = 0.20; Brown-Forsythe F(3,16) = 1.08, p = 0.386
Sup VII-A,B	IAA-94 Wash	Myogenic	20 mmHg	2.3±1.4	5	3	6.1±2.9	5	3	(ZT11) Repeated Measures ANOVA	ZT11 ANOVA F(3,12) = 69.90, **p < 0.001**; $W_{Wash20}(5)$ = 0.91, p = 0.45; $W_{Wash40}(5)$ = 0.89, p = 0.37;
Sup VII-A,B	IAA-94 Wash	Myogenic	40 mmHg	4.9±2.9	5	3	9.9±4.1	5	3		$W_{Wash60}(5)$ = 0.97, p = 0.89; $W_{Wash80}(5)$ = 0.96, p = 0.82; Brown-Forsythe F(3,16) = 0.84, p = 0.492
Sup VII-A,B	IAA-94 Wash	Myogenic	60 mmHg	12.9±4.3	5	3	18.4±3.6	5	3	(ZT23) Repeated Measures ANOVA	ZT23 ANOVA F(3,12) = 26.39, **p < 0.001**; $W_{Wash20}(5)$ = 0.91, p = 0.45; $W_{Wash40}(5)$ = 0.89, p = 0.37;
Sup VII-A,B	IAA-94 Wash	Myogenic	80 mmHg	17.8±4.0	5	3	23.6±9.3	5	3		$W_{Wash60}(5)$ = 0.97, p = 0.89; $W_{Wash80}(5)$ = 0.96, p = 0.82; Brown-Forsythe F(3,16) = 1.18, p = 0.348
Sup VII-C,D	Control	Phenylephrine	1 nmol/L	**6.8±6.3**	**5**	**3**	8.2±3.0	5	3	Friedman Test (ZT11)	ZT11 Friedman $X^2_r(4)$ = 17.48, **p = 0.002**; $W_{ZT11-9}(5)$ = 0.94, **p = 0.65**; $W_{ZT11-8}(5)$ = 0.87, p = 0.26;
Sup VII-C,D	Control	Phenylephrine	10 nmol/L	**6.2±7.0**	**5**	**3**	8.2±3.2	5	3		$W_{ZT11-7}(5)$ = 0.75, **p = 0.03**; $W_{ZT11-6}(5)$ = 0.88, p = 0.29; $W_{ZT11-5}(5)$ = 0.78, p = 0.05; Brown-Forsythe F(4,20) = 1.01, p = 0.424
Sup VII-C,D	Control	Phenylephrine	100 nmol/L	**8.7±7.0**	**5**	**3**	11.7±4.5	5	3	(ZT23) Repeated Measures ANOVA	ZT23 ANOVA F(4,16) = 203.70, **p < 0.001**; $W_{ZT23-9}(5)$ = 0.87, p = 0.27; $W_{ZT23-8}(5)$ = 0.94, p = 0.69;
Sup VII-C,D	Control	Phenylephrine	1 µmol/L	**41.7±23.2**	**5**	**3**	37.1±6.8	5	3		$W_{ZT23-7}(5)$ = 0.85, p = 0.18; $W_{ZT23-6}(5)$ = 0.93, p = 0.64; $W_{ZT23-5}(5)$ = 0.94, p = 0.63;
Sup VII-C,D	Control	Phenylephrine	10 µmol/L	**58.6±16.6**	**5**	**3**	60.8±3.3	5	3		Brown-Forsythe F(4,20) = 1.09, p = 0.390
Sup VII-C,D	IAA-94	Phenylephrine	1 nmol/L	**0.0±0.0**	**5**	**4**	**0.9±1.0**	**5**	**3**	Friedman Test (ZT11)	ZT11 Friedman $X^2_r(4)$ = 13.96, **p = 0.007**; $W_{ZT11-9}(5)$ = ND; $W_{ZT11-8}(5)$ = ND; $W_{ZT11-7}(5)$ = 0.55, **p < 0.01**;
Sup VII-C,D	IAA-94	Phenylephrine	10 nmol/L	**0.0±0.0**	**5**	**4**	**0.0±1.7**	**5**	**3**		$W_{ZT11-6}(5)$ = 0.93, p = 0.62; $W_{ZT11-5}(5)$ = 0.88, p = 0.33; Brown-Forsythe F(4,20) = 3.88, **p = 0.02**
Sup VII-C,D	IAA-94	Phenylephrine	100 nmol/L	**0.0±0.4**	**5**	**4**	**0.7±2.4**	**5**	**3**	Friedman Test (ZT23)	ZT23 Friedman $X^2_r(4)$ = 16.64, **p = 0.002**; $W_{ZT11-9}(5)$ = 0.92, p = 0.55; $W_{ZT11-8}(5)$ = 0.76, **p = 0.04**;
Sup VII-C,D	IAA-94	Phenylephrine	1 µmol/L	**8.7±17.5**	**5**	**4**	**21.6±12.3**	**5**	**3**		$W_{ZT11-7}(5)$ = 0.85, p = 0.22; $W_{ZT11-6}(5)$ = 0.69, **p = 0.007**; $W_{ZT11-5}(5)$ = 0.99, p = 0.97; Brown-Forsythe F(4,20) = 2.14, p = 0.113
Sup VII-C,D	IAA-94	Phenylephrine	10 µmol/L	**41.7±30.3**	**5**	**4**	**46.4±19.1**	**5**	**3**		

Figure	Treatment	Parameter	Level	Control	n	N	Inhibitor	n	N	Comparison Test	Statistics
5C	ZT11+CFTR(inh)-172	Myogenic	20 mmHg	5.3±2.6	5	5	4.8±3.9	5	5	Repeated 2-Way ANOVA with Geisser-Greenhouse correction	Transmural Pressure (Repeated Measures): F(2.06, 8.23) = 15.26, **p < 0.001**; CFTR(inh)-172 (Repeated Measures):
5C	ZT11+CFTR(inh)-172	Myogenic	40 mmHg	7.9±3.1	5	5	5.1±3.0	5	5		F(1, 4) = 8.85, **p = 0.01**; $W_{Con-20}(5)$ = 0.97, p = 0.91; $W_{Inh-20}(5)$ = 0.87, p = 0.28; $W_{Con-40}(5)$ = 0.96, p = 0.83;
5C	ZT11+CFTR(inh)-172	Myogenic	60 mmHg	13.0±3.6	5	5	8.0±3.8	5	5		$W_{Inh-40}(5)$ = 0.89, p = 0.36; $W_{Con-60}(5)$ = 0.82, p = 0.12; $W_{Inh-60}(5)$ = 0.78, p = 0.06; $W_{Con-80}(5)$ = 0.95, p = 0.73;
5C	ZT11+CFTR(inh)-172	Myogenic	80 mmHg	16.4±3.6	5	5	11.9±3.3	5	5		$W_{Inh-80}(5)$ = 0.96, p = 0.81; Brown-Forsythe F(7,32) = 0.12, p = 0.996
5D	ZT23+CFTR(inh)-172	Myogenic	20 mmHg	5.7±1.9	5	4	8.1±1.3	5	4	Repeated 2-Way ANOVA with Geisser-Greenhouse correction	Transmural Pressure (Repeated Measures): F(1.23, 4.51) = 37.30, **p = 0.002**; CFTR(inh)-172 (Repeated Measures):
5D	ZT23+CFTR(inh)-172	Myogenic	40 mmHg	10.6±2.7	5	4	12.0±2.3	5	4		F(1, 4) = 0.17, p = 0.70; $W_{Con-20}(5)$ = 0.81, p = 0.11; $W_{Inh-20}(5)$ = 0.96, p = 0.82; $W_{Con-40}(5)$ = 0.82, p = 0.12;
5D	ZT23+CFTR(inh)-172	Myogenic	60 mmHg	17.2±3.6	5	4	17.3±4.7	5	4		$W_{Inh-40}(5)$ = 0.80, p = 0.08; $W_{Con-60}(5)$ = 0.82, p = 0.12; $W_{Inh-60}(5)$ = 0.99, p = 0.98; $W_{Con-80}(5)$ = 0.81, p = 0.10;
5D	ZT23+CFTR(inh)-172	Myogenic	80 mmHg	23.3±3.8	5	4	22.1±5.5	5	4		$W_{Inh-80}(5)$ = 0.95, p = 0.71; Brown-Forsythe F(7,32) = 0.63, p = 0.728

Non-highlighted data sets are means ± standard error of the mean; blue-highlighted data sets were subjected to non-parametric statistical analyses and are medians ± interquartile range. Column *"n"* refers to the number of samples or arteries assessed; column *"N"* refers to the number of mice utilized to collect the samples or vessels. Significant p values are highlighted in red.

Abbreviations: sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT = wild-type; WT + Lum = wild type mice treated with 3mg/kg/day lumacaftor for 2 days prior to experimental assessment; WT/Cre = tamoxifen treated, Cre-expressing wild-type control; ZT = Zeitgeber time.

Supplemental Table VI: Article Figure Data and Normality/Variance Statistics – Constant Dark Circadian Rhythm Assessments.

Zeitgeber Time	CFTR	n	Shaprio-Wilk	Bmal1	n	Shaprio-Wilk	Per2	n	Shaprio-Wilk
19	0.97±0.54	4	W(4) = 0.96, p = 0.75	3.85±3.54	4	W(4) = 0.88, p = 0.36	1.65±2.50	4	W(4) = 0.91, p = 0.47
23	1.15±0.90	4	W(4) = 0.96, p = 0.75	9.35±8.37	4	W(4) = 0.94, p = 0.68	1.21±1.89	4	W(4) = 0.98, p = 0.91
27	1.39±0.86	4	W(4) = 0.96, p = 0.75	10.14±4.37	4	W(4) = 0.96, p = 0.81	0.88±0.68	4	W(4) = 0.85, p = 0.24
31	1.98±0.26	4	W(4) = 0.96, p = 0.75	2.59±6.79	4	W(4) = 0.79, p = 0.09	3.72±2.09	4	W(4) = 0.79, p = 0.08
35	2.43±0.39	4	W(4) = 0.96, p = 0.75	1.14±0.47	4	W(4) = 0.69, **p = 0.01**	6.14±2.55	4	W(4) = 0.93, p = 0.60
39	2.13±0.93	4	W(4) = 0.96, p = 0.75	2.57±1.60	4	W(4) = 0.79, p = 0.09	6.83±1.76	4	W(4) = 0.97, p = 0.87
43	0.94±0.53	3	W(4) = 0.96, p = 0.75	7.51±6.79	3	W(4) = 0.98, p = 0.92	1.18±0.56	4	W(4) = 0.93, p = 0.58
47	1.38±1.80	3	W(4) = 0.96, p = 0.75	14.64±19.67	3	W(4) = 0.93, p = 0.57	2.28±2.58	4	W(4) = 0.91, p = 0.46
51	1.12±0.71	4	W(4) = 0.96, p = 0.75	12.59±5.89	4	W(4) = 0.86, p = 0.27	0.98±0.48	4	W(4) = 0.99, p = 0.95
55	1.66±0.19	4	W(4) = 0.96, p = 0.75	3.39±1.42	4	W(4) = 0.99, p = 0.97	3.08±1.22	4	W(4) = 0.84, p = 0.20
59	1.40±0.68	4	W(4) = 0.96, p = 0.75	1.02±0.76	4	W(4) = 1.00, p = 0.99	4.27±2.05	4	W(4) = 0.98, p = 0.91
63	1.47±0.12	4	W(4) = 0.96, p = 0.75	3.94±5.13	4	W(4) = 0.88, p = 0.32	4.91±6.57	4	W(4) = 0.69, **p = 0.01**
Brown-Forsythe			F(11,36) = 2.01, p = 0.06			F(11,36) = 1.96, p = 0.06			F(11,36) = 0.75, p = 0.6ɛ

Data are medians ± interquartile range. Column *"n"* refers to the number of samples assessed, with 1 mouse utilized per sample.

Abbreviations: sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT + Lum = wild type mice treated with 3mg/kg/day lumacaftor for 2 days prior to experimental assessment; WT/Cre = tamoxifen treated, Cre-expressing wild-type control; ZT = Zeitgeber time.

Supplemental Table VII: JTK_Cycle Analyses.

Figure	Genotype	Parameter	Level	Adjusted P	Period	Acrophase	Amplitude	n
1A	Wild-Type	Myogenic	20 mmHg	**0.008** *	24	22	3.465	6-8
1A	Wild-Type	Myogenic	40 mmHg	**0.005** *	24	22	4.936	6-8
1A	Wild-Type	Myogenic	60 mmHg	**0.002** *	24	22	4.504	6-8
1A	Wild-Type	Myogenic	80 mmHg	**0.020** *	24	22	3.670	6-8
1B	Wild-Type	Phenylephrine	1 nmol/L	1.000	24	22	2.072	5-8
1B	Wild-Type	Phenylephrine	10 nmol/L	0.717	20	2	0.049	5-8
1B	Wild-Type	Phenylephrine	100 nmol/L	0.332	28	20	0.000	5-8
1B	Wild-Type	Phenylephrine	1 µmol/L	1.000	24	0	5.296	5-8
1B	Wild-Type	Phenylephrine	10 µmol/L	0.566	20	2	1.948	5-8
1C	sm-Bmal1 KO	Myogenic	20 mmHg	1.000	24	12	0.636	5-11
1C	sm-Bmal1 KO	Myogenic	40 mmHg	1.000	20	6	1.980	5-11
1C	sm-Bmal1 KO	Myogenic	60 mmHg	0.736	20	8	1.556	5-11
1C	sm-Bmal1 KO	Myogenic	80 mmHg	1.000	20	4	3.748	5-11
1D	sm-Bmal1 KO	Phenylephrine	1 nmol/L	1.000	20	12	1.626	5-11
1D	sm-Bmal1 KO	Phenylephrine	10 nmol/L	1.000	24	12	1.768	5-11
1D	sm-Bmal1 KO	Phenylephrine	100 nmol/L	0.736	24	10	1.131	5-11
1D	sm-Bmal1 KO	Phenylephrine	1 µmol/L	0.164	24	10	5.869	5-11
1D	sm-Bmal1 KO	Phenylephrine	10 µmol/L	0.555	24	10	2.351	5-11
5A	Wild-Type	CFTR mRNA	--	**0.005** *	24	10	0.283	4
5C	WT + Lum	Myogenic	20 mmHg	1.000	24	12	0.495	5-6
5C	WT + Lum	Myogenic	40 mmHg	1.000	20	0	0.566	5-6
5C	WT + Lum	Myogenic	60 mmHg	1.000	20	0	0.530	5-6
5C	WT + Lum	Myogenic	80 mmHg	1.000	20	0	1.768	5-6
Sup V-A	Wild-Type	Sphk1 mRNA	--	1.000	20	16	0.255	2-3
Sup V-B	Wild-Type	$S1P_2R$ mRNA	--	1.000	24	18	0.092	3-4
Sup V-C	Wild-Type	Bmal1 mRNA	--	**<0.001** *	24	20	8.195	3
Sup V-D	Wild-Type	Per2 mRNA	--	**<0.001** *	24	12	2.758	3
Sup V-E	Wild-Type	Clock mRNA	--	**0.007** *	24	18	0.346	3
Sup VI-A	Wild-Type	CFTR mRNA	--	**0.005** *	28	16	0.723	4
Sup VI-B	Wild-Type	Bmal1 mRNA	--	**<0.001** *	24	6	4.671	4
Sup VI-C	Wild-Type	Per2 mRNA	--	**<0.001** *	28	18	2.298	4
Sup VIII	WT + Lum	Phenylephrine	1 nmol/L	1.000	24	10	0.354	5-6
Sup VIII	WT + Lum	Phenylephrine	10 nmol/L	1.000	24	6	0.424	5-6
Sup VIII	WT + Lum	Phenylephrine	100 nmol/L	1.000	24	6	0.778	5-6
Sup VIII	WT + Lum	Phenylephrine	1 µmol/L	1.000	24	12	1.980	5-6
Sup VIII	WT + Lum	Phenylephrine	10 µmol/L	1.000	20	2	2.652	5-6

Adjusted P is the Bonferroni-adjusted minimal P value calculated by JTK_CYCLE. *Acrophase* is the Zeitgeber time of the sinusoidal rhythm peak calculated by JTK_CYCLE. * denotes a statistically significant circadian rhythm; n refers to the number of samples at each Zeitgeber time point.

Abbreviations: sm-Bmal1 KO = smooth muscle specific Bmal1 1 knockout; WT + Lum = wild type mice treated with 3mg/kg/day lumacaftor for 2 days prior to experimental assessment.

*** Preclinical Checklist**

Preclinical Checklist: Prevention of bias is important for experimental cardiovascular research. ***This short checklist must be completed, and the answers should be clearly presented in the manuscript.*** *The checklist will be used by reviewers and editors and it will be published. See "Reporting Standard for Preclinical Studies of Stroke Therapy" and "Good Laboratory Practice: Preventing Introduction of Bias at the Bench" for more information.*

This study invovles animal models:
Yes

Experimental groups and study timeline

The experimental group(s) have been clearly defined in the article, including number of animals in each experimental arm of the study:	Yes
An account of the control group is provided, and number of animals in the control group has been reported. If no controls were used, the rationale has been stated:	Yes
An overall study timeline is provided:	Yes

Inclusion and exclusion criteria

A priori inclusion and exclusion criteria for tested animals were defined and have been reported in the article:	Yes

Randomization

Animals were randomly assigned to the experimental groups. If the work being submitted does not contain multiple experimental groups, or if random assignment was not used, adequate explanations have been provided:	Yes
Type and methods of randomization have been described:	Yes
Methods used for allocation concealment have been reported:	N/A

Blinding

Blinding procedures have been described with regard to masking of group/treatment assignment from the experimenter. The rationale for nonblinding of the experimenter has been provided, if such was not feasible:	Yes
Blinding procedures have been described with regard to masking of group assignment during outcome assessment:	Yes

Sample size and power calculations

Formal sample size and power calculations were conducted based on a priori determined outcome(s) and treatment effect, and the data have been reported. A formal size assessment was not conducted and a rationale has been provided:	Yes

Data reporting and statistical methods

Number of animals in each group: randomized, tested, lost to follow-up, or died have been reported. If the experimentation involves repeated measurements, the number of animals assessed at each time point is provided, for all experimental groups:	Yes
Baseline data on assessed outcome(s) for all experimental groups have been reported:	Yes
Details on important adverse events and death of animals during the course of experimentation have been provided, for all experimental arms:	Yes
Statistical methods used have been reported:	Yes
Numeric data on outcomes have been provided in text, or in a tabular format with the main article or as supplementary tables, in addition to the figures:	Yes

Experimental details, ethics, and funding statements

Details on experimentation including stroke model, formulation and dosage of therapeutic agent, site and route of administration, use of anesthesia and analgesia, temperature control during experimentation, and postprocedural monitoring have been described:	Yes
Different sex animals have been used. If not, the reason/justification is provided:	Yes

Statements on approval by ethics boards and ethical conduct of studies have been provided:	Yes
Statements on funding and conflicts of interests have been provided:	Yes

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