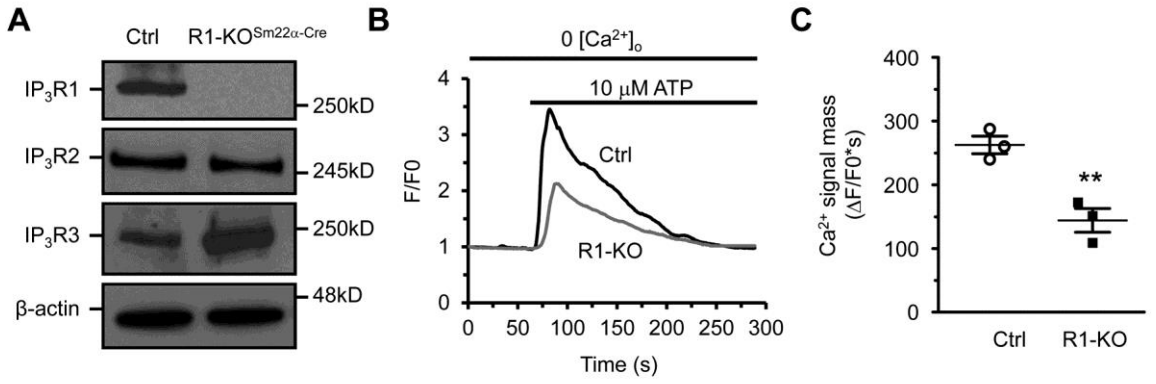
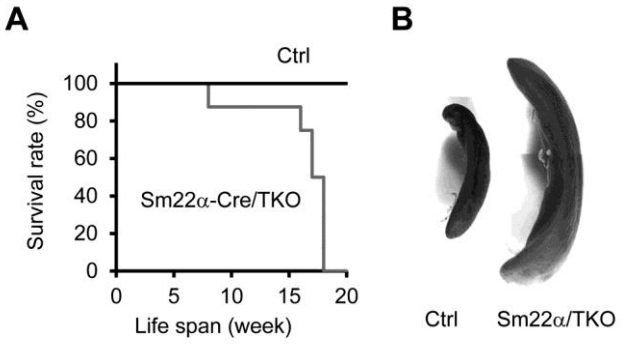
Gene name	Forward primer (5' → 3')	Reverse primer (3' → 5')
Itpr1	CTCTGTATGCGGAGGGATCTAC	GCGGAGTATCGATTCATAGGAC
Itpr2	CTTCCTCTACATTGGGGACATC	GGCAGAGTATCGATTCATAGGG
Itpr3	AGCCAAGCAGACTAAACAGGAC	GCCGCTTGTTCACAGTTAAGTA
Ryr2	GCAAGCCAGACTGCATGACC	AAATCGCAATGCCCAGCTTC
Ryr3	ATGACGATGAGCCGGATATGAAG	ACGCCCACGTACATGTGGAA
Cav1.2	CCAAGAACCAGCACCAG	CCCACAACAATCAAGGC
Stim1	GGCCAGAGTCTCAGCCATAG	TCCACATCCACATCACCATT
Stim2	TCCCTGCATGTCACTGAGTC	GGGAAGTGTCGTTCCTTTGA
Plcb1	CCAAGCGAAACCAGGACAAC	ACGCTCTGGATCAGATCTTCTGT
Adra1a	AGGCTGCTCAAGTTTTCTCG	CAGATTGGTCCTTTGGCACT
Adra1b	GGGAGAGTTGAAAGATGCCA	TTGGTACTGCTGAGGGTGTC
Adra1d	CGCTGTGGTGGGAACCGGCAG	ACAGCTGCACTCAGTAGCAGGTCA
Tbxa2r	CCTTGTTCTCACCGACTTCC	GCTGAACCATCATCTCCACC
Htr2a	CCGCTTCAACTCCAGAACCAAAGC	CTTCGAATCATCCTGTACCCGAA
Ednra	CTCCATCTGGATTCTTTTCCTT	CTTGGTAAAACTCCATGAACT
Agtr1a	GCATCATCTTTGTGGTGGG	ATCAGCACATCCAGGAATG
Agtr2	GATGGAGGGAGCTCGGAACT	TTGAACTGCAGCAACTCCAAATT
Gapdh	TGGCCTTCCGTGTTCCTAC	GAGTTGCTGTTGAAGTCGCA

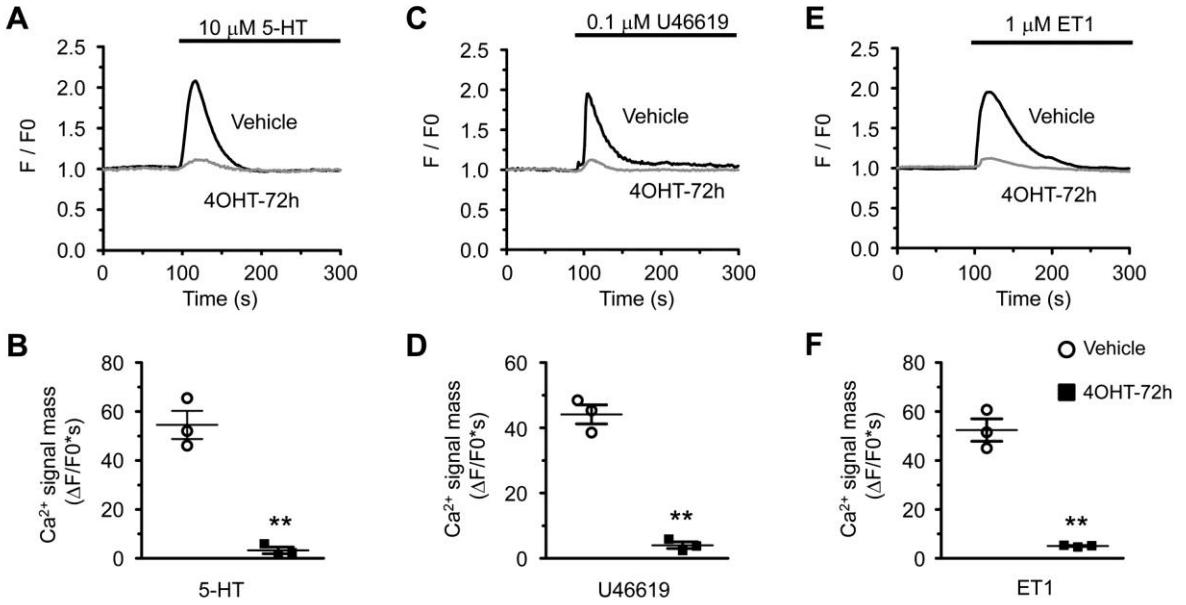
Supplementary table 1: Primers utilized for qRT-PCR analyses.



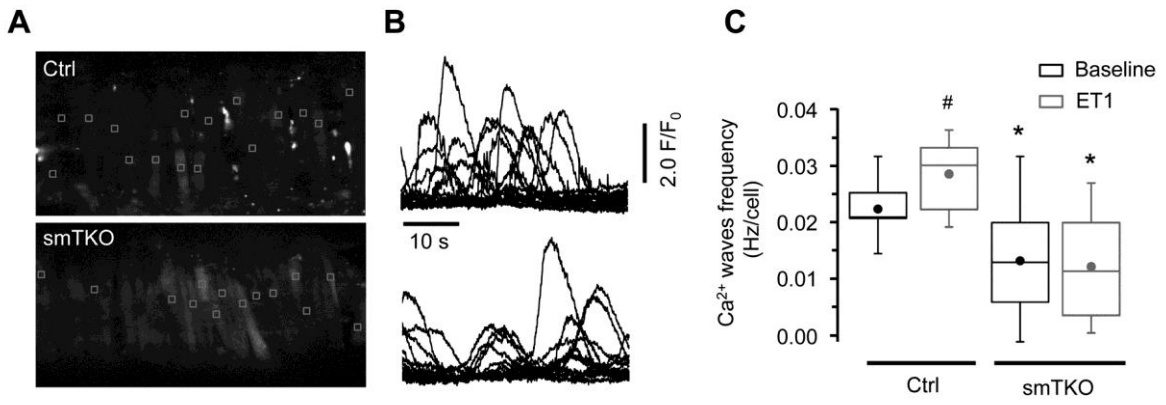
Supplementary Figure 1. **Deletion of IP_3R1 in VSMCs was not sufficient to abolish intracellular Ca^{2+} release induced by ATP.** (**A**) Expression of IP_3Rs in aortas isolated from control (Ctrl) and $IP_3R1^{f/f}$/Sm22α-Cre^{+} mice. IP_3R3 was increased when IP_3R1 was deleted in aortas. (**B**) Representative curves of Ca^{2+} release induced by 10 μM ATP in cultured control (black) and IP_3R1-KO (grey) VSMCs. The cells were incubated in Ca^{2+}-free solution for 1-2 min to avoid Ca^{2+} entry via membrane ionotropic purinergic receptors prior to the administration of ATP. (**C**) Averaged Ca^{2+} signal mass calculated from the time course of Ca^{2+} release induced by ATP in VSMCs. n=3 independent experiments per group. Significance was determined by 2-tailed, unpaired Student's *t* test. Data represent mean ± SEM (error bars). **P < 0.01 versus control.



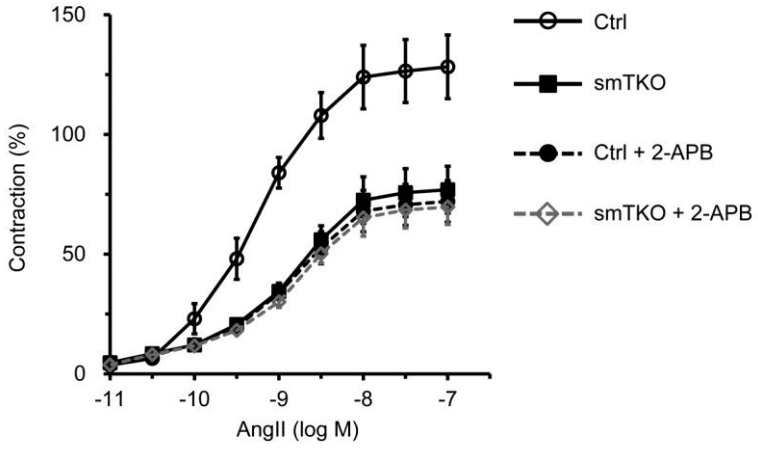
Supplementary Figure 2. **Deletion of all three IP_3R subtypes by Sm22α-Cre resulted in premature lethality after birth.** (**A**) Kaplan-Meier survival curves of control (Ctrl) and $IP_3R1^{f/f}IP_3R2^{f/f}IP_3R3^{f/f}$/Sm22α-$Cre^{+}$ (Sm22α-Cre/TKO) mice. n=8 mice per group. (**B**) Spleens isolated from control and Sm22α-Cre/TKO mice showing that the spleen from Sm22α-Cre/TKO mice was enlarged.



Supplementary Figure 3. Ca^{2+} responses induced by vasoconstrictors that don't activate ionotropic receptor in control and IP_3R-deleted VSMCs. Cells were incubated with 5 μM fluo-4-AM at 37℃ for 30 min, and imaged in regular physiological saline solution containing 1.8mM [Ca^{2+}]. (**A, C, E**) Representative curves of Ca^{2+} release induced by 10 μM 5-HT (**A**), 0.1 μM U46619 (**C**), and 1 μM ET1 (**E**) in cultured VSMCs treated with vehicle (black) or 4OHT (grey) for 72 hours. (**B, D, F**) Averaged Ca^{2+} signal mass was calculated from the time course of Ca^{2+} release stimulated by 5-HT (**B**), U46619 (**D**), and ET1 (**F**), respectively. n=3 independent experiments per group. Significance was determined by 2-tailed, unpaired Student's *t* test. Data represent mean ± SEM (error bars). **P < 0.01 versus control.

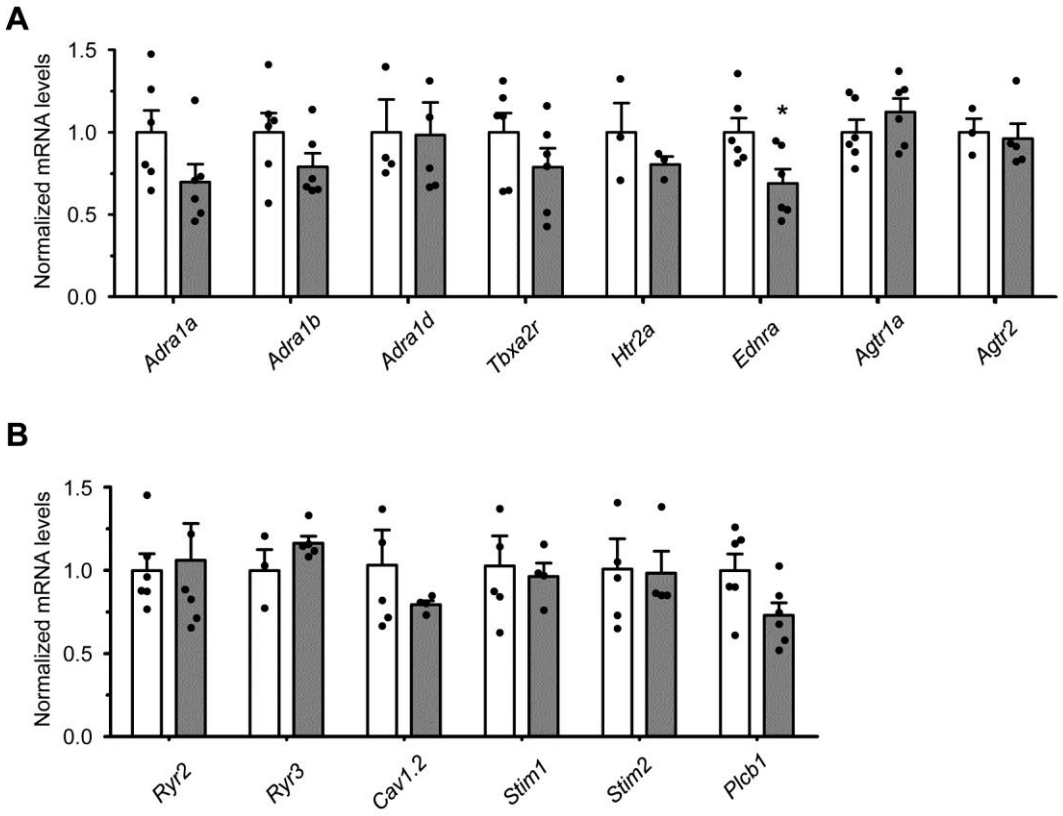


Supplementary Figure 4. Deletion of IP_3Rs affects spontaneous Ca^{2+} waves in intact VSMCs. (**A**) Ca^{2+} signals recorded in control (Ctrl) and smTKO smooth muscle cells of intact posterior cerebral artery at baseline. The boxes (12 × 12 pixels) indicate locations of changes in fluorescence ratio (F/F0) measured over 40 s in arterial smooth muscle cells. (**B**) Changes in F/F0 for respective boxes over 40 s in control (top) and smTKO (bottom) cerebral artery smooth muscle cells. (**C**) Statistical data illustrating decreased frequency of baseline and Endothelin-1 (ET1, 20 nM)-induced Ca^{2+} waves in smTKO smooth muscle cells of cerebral artery segments. n=13, 6, 28, and 16 artery segments from left to right columns, respectively. **P* < 0.05 versus control. #*P* < 0.05 versus baseline. Significance was determined by 2-way ANOVA analysis with Bonferroni post-hoc test. Data represent mean ± SEM (error bars).

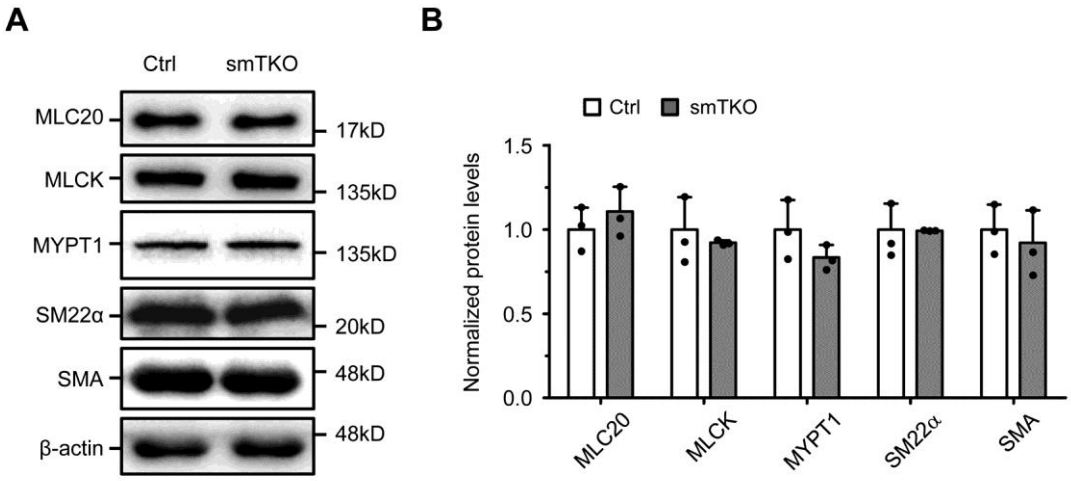


Supplementary Figure 5. The effects of 2-APB on AngII-induced contraction in control and smTKO vessels. Myographic measurements were performed on rings of first order of superior mesenteric artery. After the reference contraction was elicited by KCl, the vessels were treated with IP_3R antagonist 2-APB (50 μM) for 30 min prior to the application of AngII. Data was expressed as percentage of the peak of K^+-induced contraction. No significant difference was detected between 2-APB-pretreated control (Ctrl+2-APB) and smTKO

(smTKO+2-APB) vessels. n=6 for each group. Significance was determined by 2-way ANOVA analysis with Bonferroni post-hoc test. Data sets represent mean ± SEM (error bars).



Supplementary Figure 6. **Expression of Ca^{2+} channels and GPCRs in control and smTKO vessels.** mRNA was isolated from control (Ctrl) and smTKO aortas and gene expression was determined by RT-PCR technique. (**A**) Expression of major vasoconstrictive GPCRs including *Adra1a*, *Adra1b*, *Adra1d*, *Tbxa2r*, *Htr2a*, *Ednra*, *Agtr1a*, and *Agtr2* in control and smTKO aortas. (B) Expression of *Ryr2*, *Ryr3*, *Cav1.2*, *Stim1*, *Stim2*, and *Plcb1* were not significantly changed in smTKO vessels compared with control. n=3-6 (with vessels from 3 mice pooled as one sample) per group, Significance was determined by 2-tailed, unpaired Student's *t* test. Data represent mean ± SEM (error bars). **P* < 0.05 versus control.



Supplementary Figure 7. Expression of contractile proteins in control and smTKO vessels. The expression of myosin light chain20 (MLC20), myosin light chain kinase (MLCK), myosin-binding regulatory subunit (MYPT1), smooth muscle 22α (SM22α), and α-smooth muscle actin (SMA) were accessed by western blot (**A**), and normalized to β-actin. There is no significant difference in any of these proteins observed between control and smTKO mice (**B**). n=3 (with vessels from 2 mice pooled as one sample) per group. Significance was determined by 2-tailed, unpaired Student's *t* test. Data represent mean ± SEM (error bars).