SI Material and Methods

Atrial trabeculae. Inotropic, lusitropic and arrhythmic effects. Experimental design.

After excision, right atrial appendages were immediately placed into oxygenated, modified Tyrode 's solution and transported to the laboratory in less than 10 min. Up to eight trabeculae were dissected from one appendage at room temperature in modified Tyrode's solution containing (mM): NaCl 126.7, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.05, NaH_2PO_4 0.42, EDTA 0.04, ascorbic acid 0.2 and glucose 5.0. The solution was maintained at pH 7.4 by bubbling with a mixture of 5% CO_2 and 95% O_2. Atrial trabeculae were mounted in pairs, attached to SWEMA 4-45 strain gauge transducers in an apparatus containing above solution at 37°C and stretched as described (1). Trabeculae were incubated with 5 μM phenoxybenzamine for 90 min to irreversibly block α-adrenoceptors as well as neuronal and extraneuronal uptake of catecholamines (1). The effects of NE, mediated through β_1-adrenoceptors, were investigated in the presence of 50 nM ICI118551 to block β_2-adrenoceptors (2). The effects of EPI, mediated through β_2-adrenoceptors, were investigated in the presence of 300 nM CGP20712A to block β_1-adrenoceptors (2). The effects of 5-HT (3) and forskolin were investigated in the presence of (-)-propranolol (200 nM) to prevent possible effects of endogenously released NE. Contractile force was recorded and time to half relaxation ($t_{0.5}$) was obtained from fast speed tracings (400 data points/sec) using Chart Pro for Windows version 5.51 analysis programme (ADI Instruments, Castle Hill, Australia). A single cumulative concentration-effect curve for the agonist and forskolin was determined. Any additional contraction besides the 1 Hz rhythm was considered arrhythmic.

Isolation of myocytes and whole-cell recording of $I_{Ca,L}$.

The tissue was cut into small pieces, myocytes were isolated as described previously (4) and kept in storage solution (composition in mM: KCl 20, KH_2PO_4 10, glucose 10, K-glutamate 70, β-hydroxybutyrate 10, taurine 10, EGTA 10, albumin 1, pH 7.4) at room temperature. Only striated, rod-shaped myocytes were used. The myocytes were investigated in a small perfusion chamber placed on the stage of an inverse microscope. A system for rapid solution changes allowed application of drugs in the close vicinity of the cells (Cell Micro Controls, Virginia Beach, VA; ALA Scientific Instruments, Long Island, NY, USA).

$I_{Ca,L}$ was measured at 37°C with standard voltage-clamp technique (Axopatch 200, Axon Instruments, Foster City, CA, USA), ISO2 software was used for data acquisition and analysis (MFK, Niedernhausen, Germany) as described (4). Heat-polished pipettes were pulled from borosilicate filamented glass (Hilgenberg, Malsfeld, Germany). Tip resistances were 3-5 MΩ, seal resistances were 3-6 GΩ. Cell capacitance (C_M) was calculated from steady-state current during depolarising ramp pulses (1 Vs^{-1}) from -40 mV to -35 mV. Five minutes after establishing the whole-cell configuration $I_{Ca,L}$ was measured during a test pulse from a holding potential of –80 mV at +10 mV. The experiments were performed with the following Na^+-free superfusion solution (in mM): tetraethylammonium chloride 120, CsCl 10, HEPES 10, $CaCl_2$ 2, $MgCl_2$ 1 and glucose 20, pH 7.4 (adjusted with CsOH). The pipette solution (pH 7.2) included (in mM): cesium methanesulfonate 90, CsCl 20, HEPES 10, Mg-ATP 4, Tris-GTP 0.4, EGTA 10 and $CaCl_2$ 3, with calculated free Ca^{2+} concentration of ~60 nM (computer program EQCAL, Biosoft, Cambridge, UK), pH=7.2 (adjusted with CsOH). Current amplitude was determined as the difference between peak inward current and current at the end of the depolarising step.

To compare the dependence of agonist-evoked $I_{Ca\text{-}L}$ responses on PKA in the sarcolemma Ca^{2+} channel domain, myocytes from patients with SR and AF were patched with a pipette solution containing the competitive cAMP analogue Rp-8-Br-cAMPS but unlike cAMP, does not cause the conformational PKA change leading to the release of its catalytic unit and is not hydrolysed by phosphodiesterases (5). After 5 minutes of equilibrium $I_{Ca,L}$ responses to 100 µM agonist or 10 µM forskolin were measured. Concentration-response-curves for the effect of Rp-8-Br-cAMPS were then determined and the concentration inhibiting 50% of the $I_{Ca,L}$ response to agonist and forskolin assessed. The IC_{50}s provide an indirect estimate for the quantity of cAMP and activity of PKA at the Ca^{2+} channel realm.

Measurement of L-type calcium current-triggered calcium transients

$[Ca^{2+}]_i$ transients (CaTs) were recorded at 37°C under voltage-clamp control in whole ruptured cell, using a holding potential of -80 mV and a 100-ms ramp-pulse to -40 mV followed by a 100-ms test pulse to +10 mV at 0.5 Hz as published previously (6). Briefly, $[Ca^{2+}]_i$ was quantified with two forms of Fluo-3, Ca^{2+} indicator: cell permeable and cell impermeant form of Fluo-3 (penta-ammonium salt, 100 µM). For seal formation myocytes were superfused with a bath solution containing (mM): $CaCl_2$ 2, glucose 10, HEPES 10, KCl 4, $MgCl_2$ 1, NaCl 140, probenecid 2; pH=7.4. Borosilicate glass microelectrodes had tip resistances of 2-5 MΩ when filled with pipette solution (mM: EGTA 0.02, Fluo-3 0.1 [cell impearment, Invitrogen], GTP-Tris 0.1, HEPES 10, K-aspartate 92, KCl 48, Mg-ATP 1, Na_2-ATP 4; pH=7.2). CaTs were recorded in the bath solution with addition of 4-AP (5 mM) and $BaCl_2$ (0.1 mM). pClamp Software (V10.2, Molecular Devices, Sunnyvale, CA) was used for data acquisition and analysis.

Western blots

To provide biochemical evidence for PKA- and CaMKII-mediated phosphorylation of proteins involved in agonist-evoked inotropism, lusitropism and arrhythmias, we searched for an experimental condition that allowed us to obtain vigorous increases of phosphoproteins. Our hypothesis was that atrial samples, immediately frozen at the surgical theater, might be under the influence of marked increases of endogenously released catecholamines, due to surgical stress. The released catecholamines could conceivably activate PKA and CaMKII, thereby altering responses to exogenous catecholamines. This hypothesis is also consistent with a report of increased sympathetic innervation in persistent human AF (7). We therefore compared the phosphorylation of PLB at Ser-16 and Thr-17 in trabeculae immediately frozen at surgery with trabeculae from the same atrium set up to contract a 1 Hz in an organ bath for 1 h, to allow dissipation of endogenous catecholamines and their effects.

Trabeculae from atria of patients with SR or AF were exposed 5 min to 10 µM each of NE (in the presence of ICI118551 50 nM to block β_2AR), EPI (in the presence of CGP20712A 300 nM to block β_1AR), 5-HT and forskolin (in the presence of (-)-propranolol 200 nM) and frozen in liquid nitrogen for Western analysis. Inotropic and lusitropic responses were recorded. Trabeculae from the same atrium, exposed to the corresponding β-blockers but not to the agonists or forskolin, were frozen at the same time.

Western blot analysis was performed as described (6). Total protein was extracted from frozen trabeculae by homogenization using 3% SDS. After SDS-polyacrylamide gel electrophoresis and transfer to nitrocellulose, incubation with the antibodies was performed. If possible commercially available antibodies were used. Antibodies for total phospholamban (PLB), as well as Ser-16 and Thr-17 phosphorylated PLB (1:5000) were from Badrilla (Leeds, UK); for SERCA2 (1:2000) from Santa Cruz (Dallas, DTX, USA); for total troponin I (Tn-I) (1:30000) from Millipore (LOT-Number 24031450, Billerica, USA); for Ser-23/24

phosphorylated Tn-I (1:1000) from Cell Signaling (Danvers, MA; USA); calsequestrin (CSQ) (1:2500) from Thermo Scientific (Rockford, IL, USA). Antibodies against total and Ser-282 phosphorylated myosin-binding protein C (Prot-C) (1:1000) were custom generated by Lucie Carrier (Department of Experimental Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Germany). Antibodies against total ryanodin2 receptor (RyR2) (1:1000), phosphorylated RyR2-Ser-2808 (1:1000) and RyR2-Ser-2814 (1:3000) were custom generated by Xander Wehrens (Baylor College of Medicine, Houston, Texas, USA). The peroxidase-conjugated secondary antibodies donkey anti-goat were from Santa Cruz (Dallas, Texas USA). Goat anti-mouse and goat anti-rabbit, both from Sigma-Aldrich (St.Loius, MO, USA) and were used to visualize and quantify protein levels.

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6. Voigt N et al. (2012) Enhanced sarcoplasmic reticulum Ca^{2+} leak and increased Na^{+}-Ca^{2+} exchanger function underlie delayed afterdepolarisations in patients with chronic atrial fibrillation. *Circulation* 125:2059-2070.

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Legends to SI Appendix; Figures

SI Appendix; Figure 1. Effect of 5-HT on $I_{Ca,L}$ and CaT parameters

A, B. Original plots of single experiments demonstrate the effects of 5-HT (100 μM dotted line) in a cardiomyocyte from patients with SR (**A**) and AF (**B**). Left ordinate shows CaT amplitude (nM), right ordinate – $I_{Ca,L}$ (pA/pF). Squares – CaT amplitude; circles – $I_{Ca,L}$. Insets show original traces to 5-HT for $I_{Ca,L}$ and CaT. N.b. that the CaT is biphasic in patients with SR but not with AF. **C.** Mean±SEM values of $I_{Ca,L}$ before (-) and after (+) 5-HT application. **D.** Mean±SEM values of CaT amplitude before (-) and after (+) 5-HT application. **E.** Mean±SEM values of diastolic $[Ca^{2+}]_i$ before (-) and after (+) 5-HT application. **F.** Mean±SEM values of systolic $[Ca^{2+}]_i$ before (-) and after (+) 5-HT application. * P<0.05, ** P<0.01, *** P<0.001 vs. mean basal values calculated with paired t-tests. Numbers at columns indicate myocytes/patients.

SI Appendix; Figure 2. Effect of forskolin (FSK) on $I_{Ca,L}$ and CaT parameters

A, B. Original plots of single experiments demonstrate effect of FSK (10 μM dotted line) in a myocyte from patients with SR (**A**) and AF (**B**). Left ordinate shows CaT amplitude (nM), right ordinate – $I_{Ca,L}$ (pA/pF). Squares – CaT amplitude; circles – $I_{Ca,L}$. Insets show original traces to FSK for $I_{Ca,L}$ and CaT. N.b. that the CaT is biphasic in myocytes from patients with

SR but not from patients with AF. **C.** Mean±SEM values of $I_{Ca,L}$ before (-) and after (+) FSK application. **D.** Mean±SEM values of CaT amplitude before (-) and after (+) FSK application. **E.** Mean±SEM values of diastolic $[Ca^{2+}]_i$ before (-) and after (+) FSK application. **F.** Mean±SEM values of systolic $[Ca^{2+}]_i$ before (-) and after (+) 5-HT application. ** P<0.01, *** P<0.001 vs. mean basal values calculated with paired t-tests. Numbers at columns indicate myocytes/patients.

SI Appendix; Figure 3. 5-HT and forkolin (FSK) cause biphasic CaTs in patients with SR but not with AF.

A - D. Mean values of normalized CaT traces (dark lines) and SEM (light lines) before and after the administration of 5-HT (100 μM) or FSK (10 μM) in myocytes from patients with SR (**A**, **B** blue lines) and AF (**C, D** red lines). Mean values of CaT decay ($K(s^{-1})$) before (-) and after the administration of (+) 5-HT (**E**) or FSK (**F**). Mean±SEM values of time to maximum CaT peak before (-) and after (+) the administration of (+) 5-HT (**G**) or FSK (**H**). ** P<0.01, *** P<0.001 vs. mean basal values. ## P<0.01 vs. mean basal values from patients with SR, calculated with paired t-tests. Numbers at columns indicate myocytes/patients.

Figure S4. Isoproterenol (ISO) increases $I_{Ca,L}$, CaTs, elicits SDCRs and produces biphasic CaTs in cardiomyocytes from patients with SR.

A. Mean values of normalized CaT traces (dark lines) and SEM (light lines) before and after the administration of ISO (1 μM) (blue lines). **B**. Mean±SEM values of $I_{Ca,L}$ and CaT amplitude before (-) and after (+) Iso application. **C.** Examples of original CaT traces before and after ISO exposure in a cardiomyocyte from a patient with SR. Inserts show enlarged part of the traces. Arrows indicate spontaneous Ca^{2+} release. ** P<0.01, *** P<0.001 vs. mean basal values. Numbers at columns indicate myocytes/patients

SI Appendix; Figure 5. Protein levels of PLB, SERCA2, Prot-C, Tn-I and RyR2 are not different between patients with SR or AF.

Left: mean±SEM values from densitometric analyses expressed in arbitrary units (a.u.). n indicates trabeculae/patients. Right: representative immunoblots from pairs of trabeculae obtained from patients with SR and AF. CSQ = calsequestrin.

SI Appendix; Figure 6. Basal phosphorylation levels of PLB-Ser-16, Prot-C-282, Tn-I-Ser-23/24, RyR2-Ser-2808, PLB-Thr-17 and RyR2-Ser-2814 are not changed in AF.

Mean±SEM values from densitometric analyses expressed in arbitrary units (a.u.). n indicates number of patients. Please note that data are pooled with controls from Figure S7.

SI Appendix; Figure 7. Phosphorylation of PLB, RyR2, Prot-C and Tn-I by PKA, are similarly enhanced by NE, EPI and 5-HT in SR and AF, while CaMKII-catalysed phosphorylation of PLB and RyR2 tend to be reduced in AF.

PKA-catalysed phosphorylation by NE (β_1), EPI (β_2) and serotonin ($5\text{-}HT_4$) of PLB-Ser-16, Prot-C-Ser-282, Tn-I-Ser-23/24, RyR-Ser-2808 are unchanged (Figure S7A), while CaMKII-catalysed phosphorylation tend to be reduced in patients with AF (open columns) compared to patients with SR (black columns) patients (PLB-Thr-17 and RyR-Ser-2814) (Figure 7B). Mean±SEM values from densitometric analyses expressed in arbitrary units (a.u.). Data were obtained from pairs of trabeculae exposed to the agonists and their respective untreated controls. *P<0.05, **P<0.01, *** P<0.001, comparisons between agonists and basals. n indicates number of pairs from one patient. Representative immunoblots on top of each bar graph.

SI Appendix; Figure 8. Basal phosphorylation of PLB-Ser-16 by PKA and PLB-Thr-17 by CaMKII in atrial trabeculae from patients with SR are reduced in trabeculae from patients with AF, frozen in the operation theatre. Marginal phosphorylations in trabeculae from both patients with SR and AF, frozen after contracting 1 h in an organ bath, are not different. Several atrial trabeculae were obtained from each patient. One half of the trabeculae was frozen at the operation theater (OT), the other half after contracting for 1 h in an organ bath (OB). Mean±SEM values from densitometric analyses expressed in arbitrary units (a.u.). Patient numbers shown in columns. ***P<0.001 OT vs. OB; # P<0.05, ### P<0.001 OT samples from SR patientes vs. OT samples from patients with AF. Representative western blots of OT and OB from the same patient. -8, -7, -6 are log values of norepinephrine concentrations from the same patient with SR or AF. CSQ = calsequestrin.

SI Appendix; Figure 9. Inotropic and lusitropic effects of NE, EPI, 5-HT and forskolin (FSK) do not differ between trabeculae from patients with SR or AF.

Data from atrial trabeculae, contracting for 1 h, exposed for 5 min to 10 µM of the agonists and forskolin and finally frozen for western blot assays. Open columns, basals; closed columns, effects of the agonists and forskolin. Left-hand panels, data from patients with SR; right-hand panels, data from patients with AF (red). All effects were significant (P<0.01). Data are mean±SEM values from the number of patients shown in columns.

SI Appendix, Table 1 Patient characteristics

SI Appendix; Table 1A. Patients with sinus rhythm (SR) and chronic atrial fibrillation (cAF) used for contractility and arrhythmia experiments.

Written informed consent was obtained from all patients. Patients with SR and AF were from the Gustav Carus Hospital, Dresden University of technology, ethics committee (Document EK 1140 82202).

	SR	**cAF**
n	174	120
Gender [m/f]	132 / 42	75 / 45*
Age [years]	67.1 ± 0.8	72.0 ± 0.7*
BMI [kg/m^2]	27.7 ± 0.3	28.5 ± 0.4
Hypertension, n	141	107
Diabetes mellitus, n	60	52
Hyperlipidaemia, n	104	82
CAD, n	106	32*
AVD/MVD, n	49	48
CAD + AVD/MVD, n	19	40*
LVEF [%]	52.4 ± 1.1 (173)	54.2 ± 1.4 (118)
LVEDP [mmHg]	16.9 ± 0.9 (89)	16.6 ± 0.9 (62)
LA [mm]	41.9 ± 0.5 (127)	49.2 ± 0.7* (107)
LVEDD [mm]	51.3 ± 0.6 (127)	51.5 ± 0.7 (107)
Cardiovascular medication (n)		
Digitalis	13	40*
ACE-Inhibitors	129	79
AT_1-blockers	15	17
β-blockers	130	93
Ca^{2+}-channel-blockers	20	21
Diuretics	69	79*
Nitrates, n	32	17
Lipid-lowering drugs	79	52

Abbreviations: AT, angiotensin receptor; AVD, aortic valve disease; CAD, coronary artery disease; cAF, chronic atrial fibrillation; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MVD, mitral valve disease; SR, sinus rhythm.

*P<0.05 calculated from Student's two-tailed t-test for continuous variables and from χ^2 test for categorical variables.

SI Appendix, Table 1B. Patients used for calcium currents and calcium transients

	SR	cAF
n	209	153
Gender [m/f]	155 / 54	86 / 67*
Age [years]	67.5 ± 0.6	71.8 ± 0.6*
BMI [kg/m^2]	28.1 ± 0.3	27.9 ± 0.4
Hypertension, n	186	131
Diabetes mellitus, n	76	59
Hyperlipidaemia, n	155	103
CAD, n	114	41*
AVD/MVD, n	57	75*
CAD + AVD/MVD, n	38	37
LVEF [%]	56.1 ± 1.0 (201)	53.1 ± 1.2 (145)
LVEDP [mmHg]	17.5 ± 0.9 (102)	16.7 ± 0.8 (84)
LA [mm]	41.6 ± 0.4 (158)	48.9 ± 0.8* (121)
LVEDD [mm]	50.3 ± 0.6 (158)	52.0 ± 0.7* (121)
Cardiovascular medication (n)		
Digitalis	5	54*
ACE-Inhibitors	128	91
AT_1-blockers	18	26
β-blockers	144	125
Ca^{2+}-channel-blockers	31	25
Diuretics	58	82*
Nitrates, n	38	26
Lipid-lowering drugs	100	61

Abbreviations: AT, angiotensin receptor; AVD, aortic valve disease; CAD, coronary artery disease; cAF, chronic atrial fibrillation; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MVD, mitral valve disease; SR, sinus rhythm.

*$P<0.05$ calculated from Student's two-tailed t-test t-test for continuous variables and from χ^2 test for categorical variables.

SI Appendix; Table 1C. Patients used for western blots

	SR	cAF
n	36	33
Gender [m/f]	26 / 8	22 / 11
Age [years]	70.2 ± 1.4	72.2 ± 1.4
BMI [kg/m^2]	27.4 ± 0.6	27.8 ± 0.9
Hypertension, n	32	31
Diabetes mellitus, n	12	11
Hyperlipidaemia, n	29	26
CAD, n	21	9*
AVD/MVD, n	6	15*
CAD + AVD/MVD, n	9	9
LVEF [%]	50.6 ± 2.4 (34)	52.7 ± 2.4 (27)
LVEDP [mmHg]	22.0 ± 4.7 (5)	16.5 ± 2.0 (8)
LA [mm]	40.7 ± 0.8 (34)	49.3 ± 1.1* (31)
LVEDD [mm]	49.8 ± 1.3 (33)	51.1 ± 1.4 (31)
Cardiovascular medication (n)		
Digitalis	0	11*
ACE-Inhibitors	26	23
AT_1-blockers	0	2
β-blockers	28	29
Ca^{2+}-channel-blockers	5	6
Diuretics	4	5*
Nitrates, n	7	4
Lipid-lowering drugs	21	18

Abbreviations: AT, angiotensin receptor; AVD, aortic valve disease; CAD, coronary artery disease; cAF, chronic atrial fibrillation; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MVD, mitral valve disease; SR, sinus rhythm.

*P<0.05 calculated from Student's two-tailed t-test t-test for continuous variables and from χ^2 test for categorical variables.

SI Appendix; Table 2

Comparison of basal force and the effects of agonists and forskolin (FSK) in atrial trabeculae from patients with SR or AF

Agent	NE		Epi		5-HT		FSK	
Rhythm	SR (222/127)	AF (84/51)	SR (226/130)	AF (75/47)	SR (200/110)	AF (102/56)	SR (29/21)	AF (17/14)
basal Force (mN)	6.23±0.30	1.71±0.24***	4.73±0.27^{+++}	1.34±0.32***	5.65±0.28^{+++}	1.24±0.24***	4.94±0.84^{+++}	1.76±0.67***
R_{max} (mN)	5.63±0.27	6.53±0.52	7.63±0.32	6.59±0.63	5.65±0.28	0.88±0.32***	7.20±0.78	7.08±0.32
max. Force (mN) (basal + R_{max})	11.86±0.42	8.24±0.60***	12.36±0.48	7.93±0.81***	10.46±0.43	2.12±0.35***	12.16±0.78	9.64±1.95
-logEC_{50} (M)	7.06±0.03	6.56±0.05***	7.45±0.03	6.67±0.07***	6.98±0.03	6.62±0.04***	6.32±0.10	5.50±0.14***

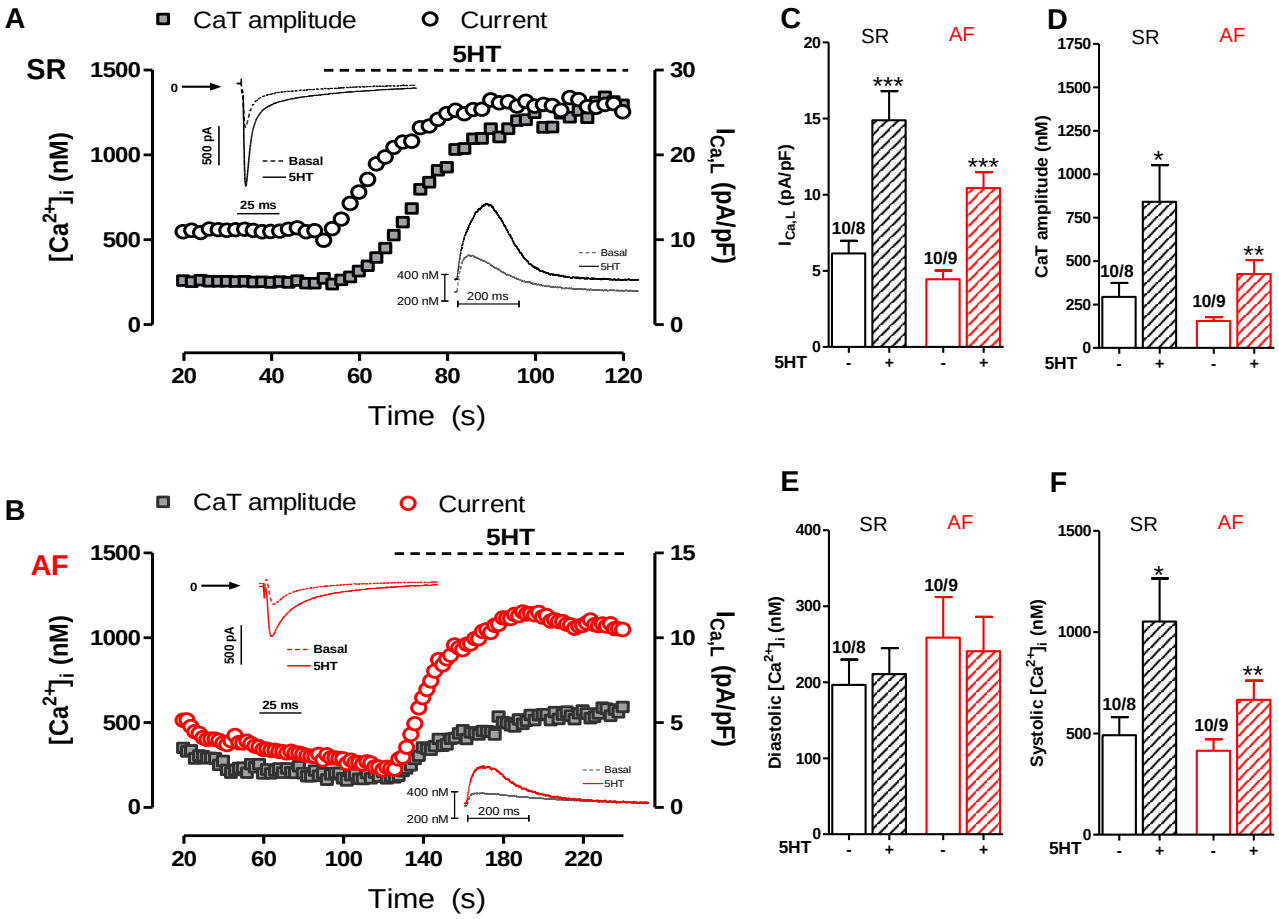
Legends: *** P<0.001 vs. respective SR group; +++P<0.001 vs. basal values of NE SR group
[a] Trabeculae/patients
R_{max} Maximum response

SI Appendix; Table 3

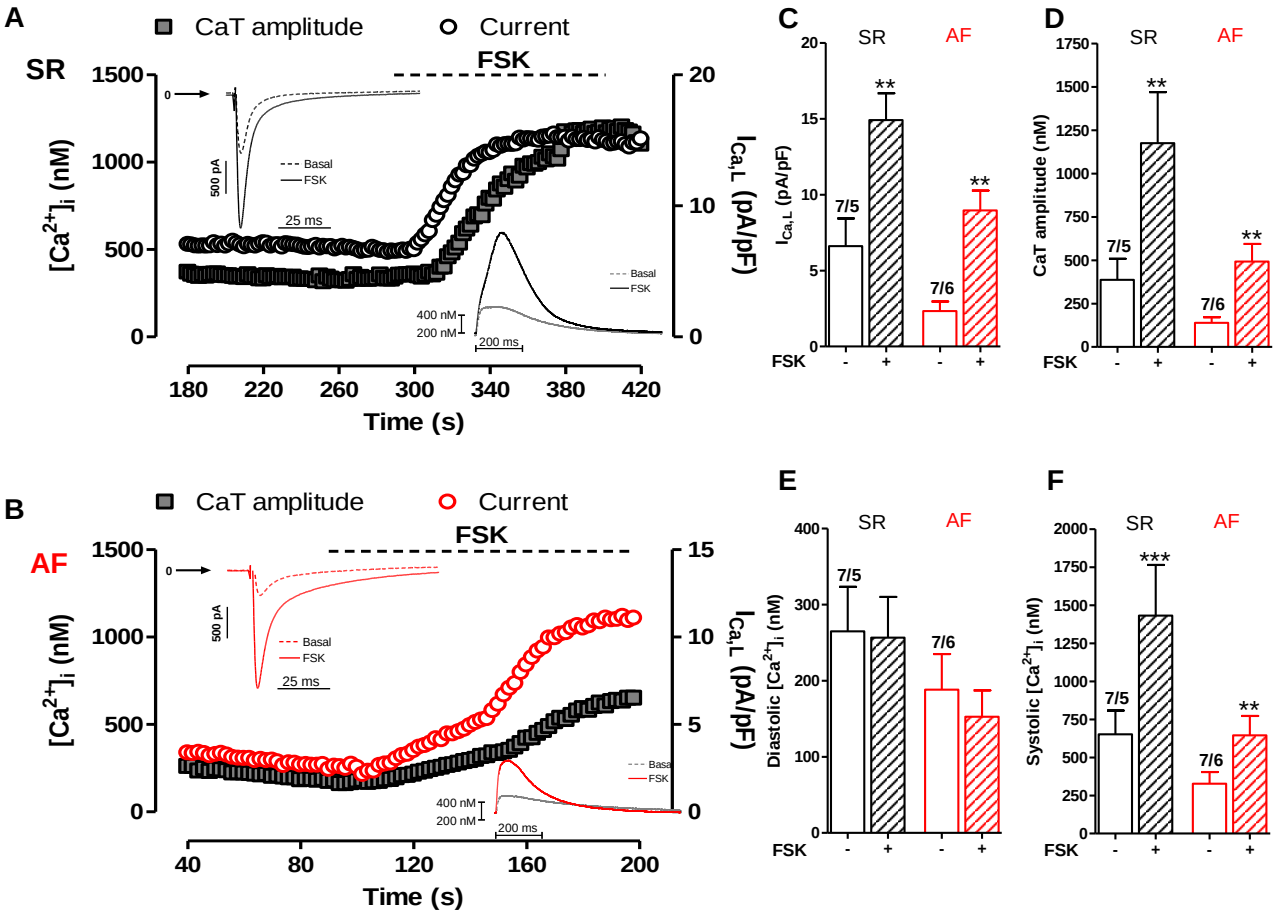
Comparison of $I_{Ca,L}$ and the effects of agonists and forskolin (FSK) in myocytes from patients with SR or AF

Agent	NE		Epi		5-HT		FSK	
Rhythm	SR (160/97)	AF (79/33)	SR (226/130)	AF (75/47)	SR (196/96)	AF (113/50)	SR (84/52)	AF (50/43)
basal $I_{Ca,L}$ (pA/pF)	9.09±0.48	4.12±0.46***	7.54±0.46^{+++}	3.95±0.49***	6.88±0.28^{+++}	3.35±0.21***	7.70±0.48^{+++}	3.23±0.58***
R_{max} (pA/pF)	11.41	8.73	14.43	10.6	12.35	8.00	12.47	8.31
max. $I_{Ca,L}$ (pA/pF) (basal + R_{max})	21.5±0.77	12.85±0.62***	21.97±0.45	14.01±0.72***	19.23±0.49	11.35±0.38***	20.17±1.12	11.54±0.75***
-logEC_{50} (M)	5.79±0.15	6.12±0.22	6.03±0.11	5.83±0.22	6.33±0.12	6.13±0.15	6.35±0.12	6.42±0.74

Legends: *** P<0.001 vs. respective SR group; +++P<0.001 vs. basal values of NE SR group
[a] Trabeculae/patients
R_{max} Maximum response



SI Appendix; Figure 1



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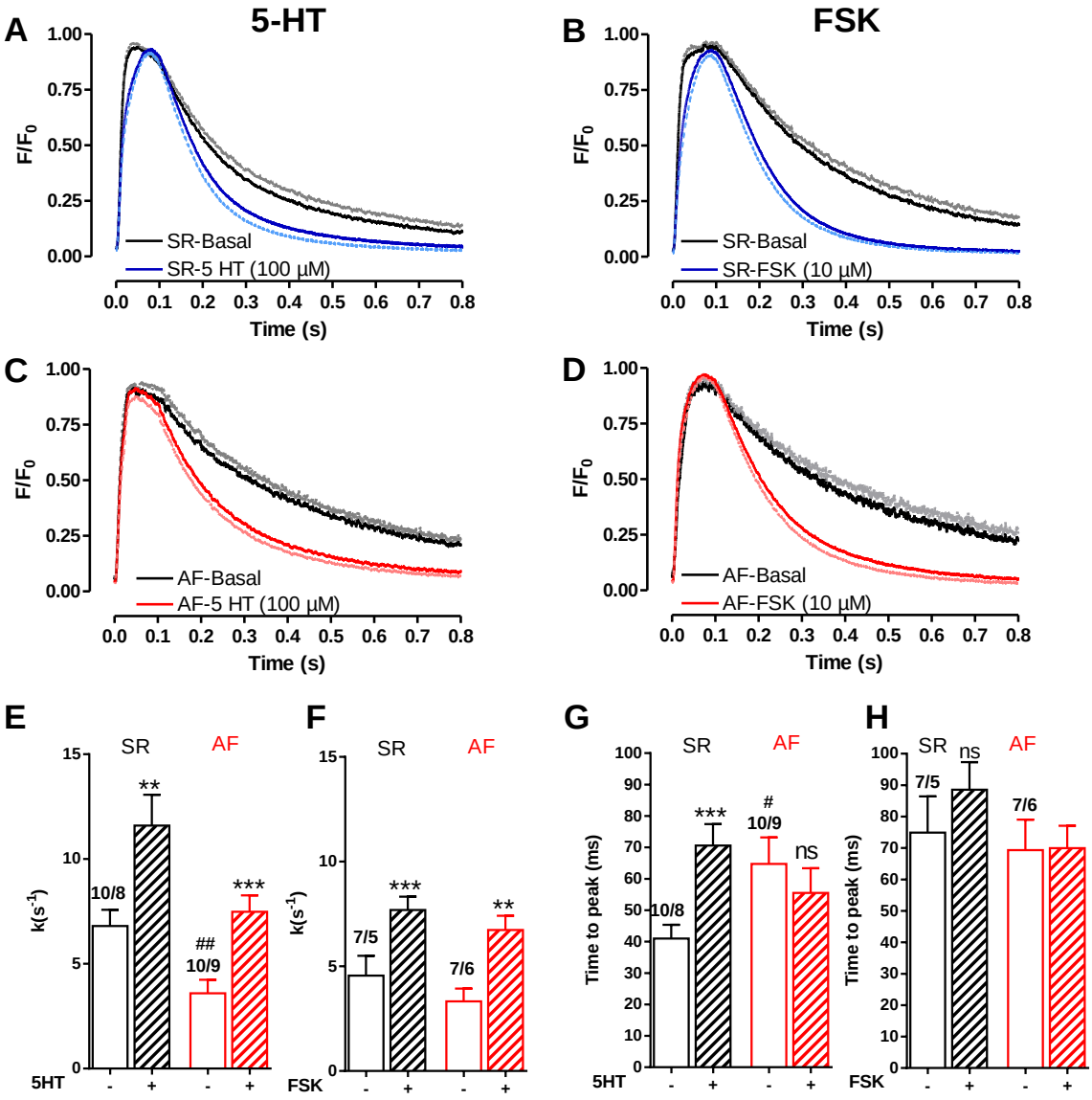

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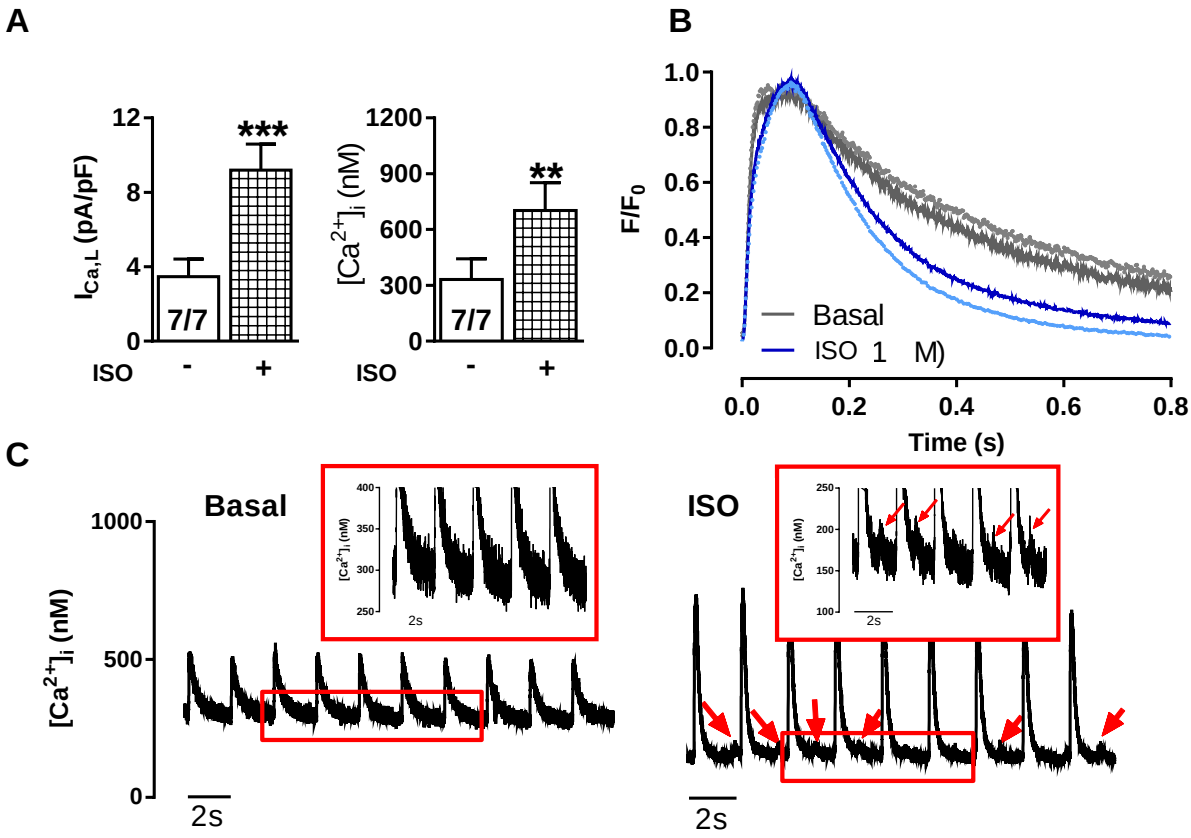

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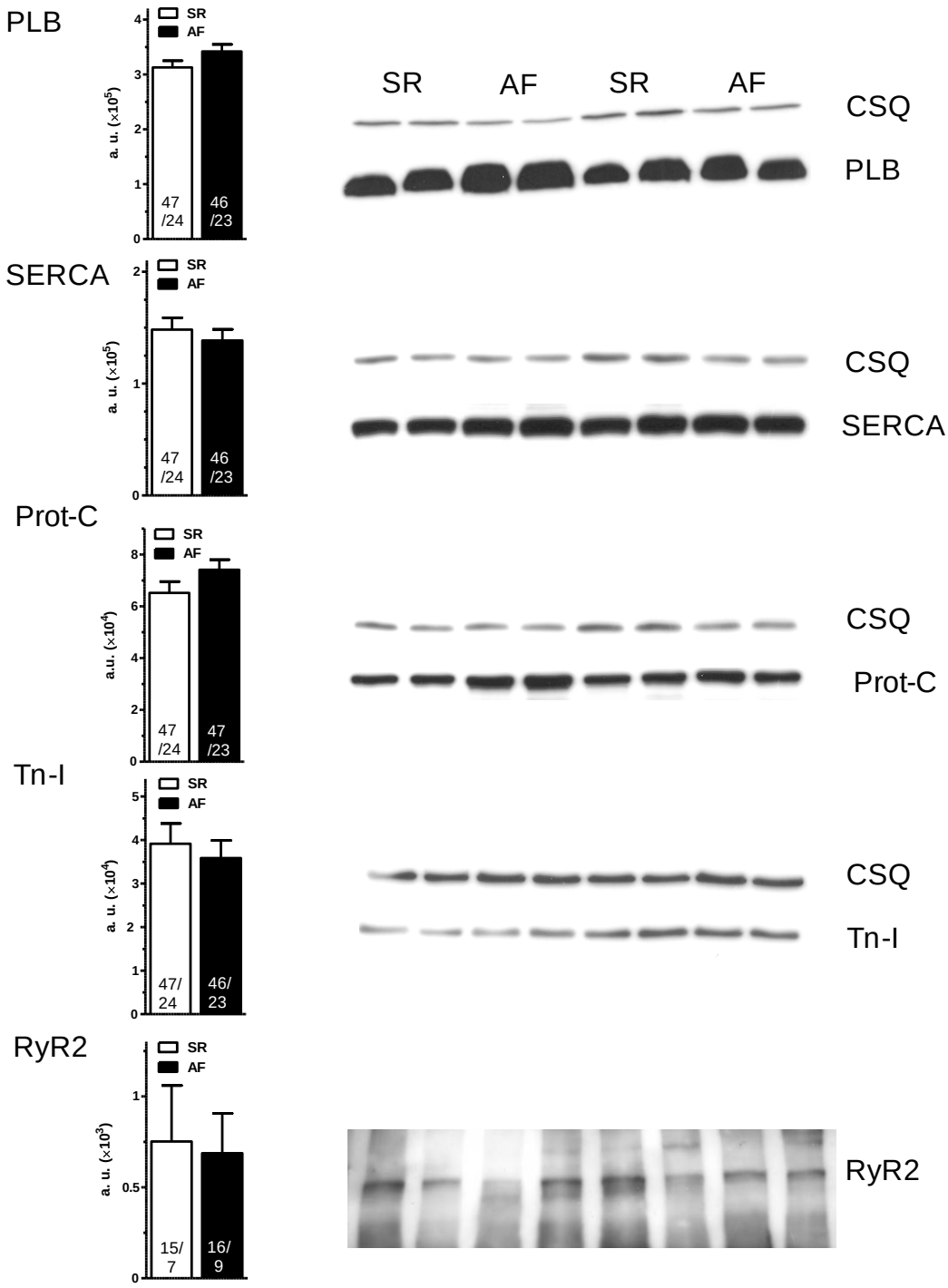

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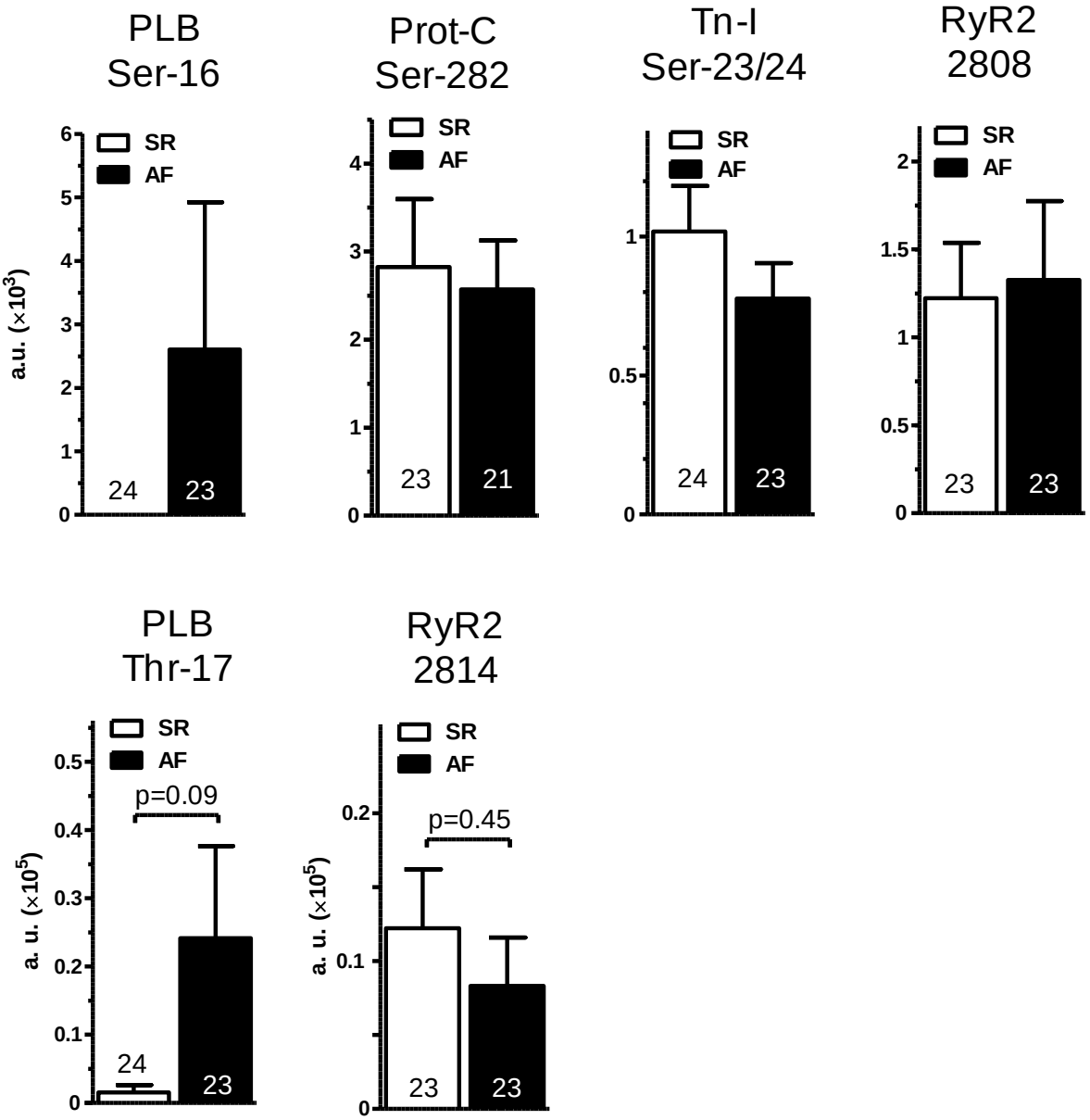
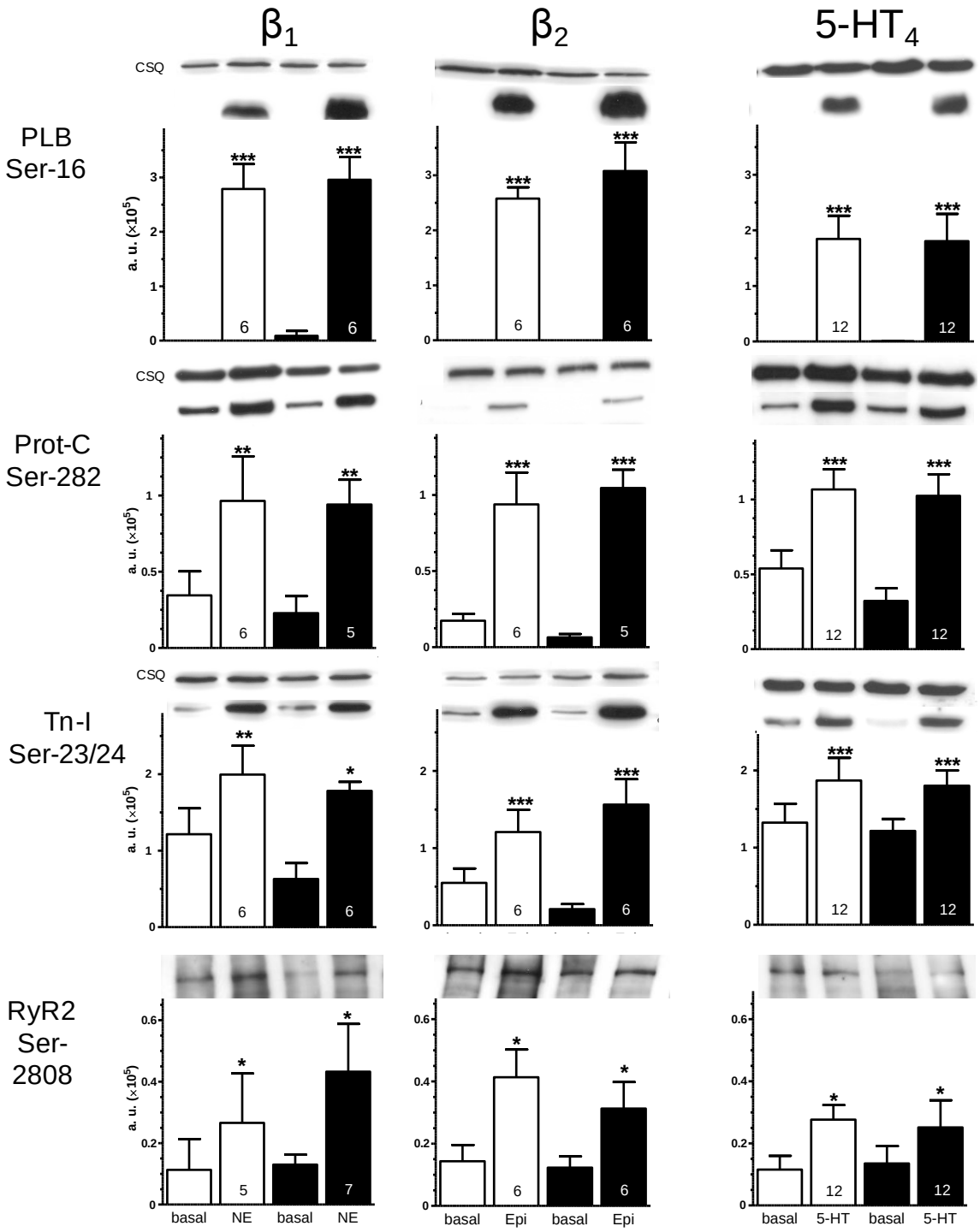
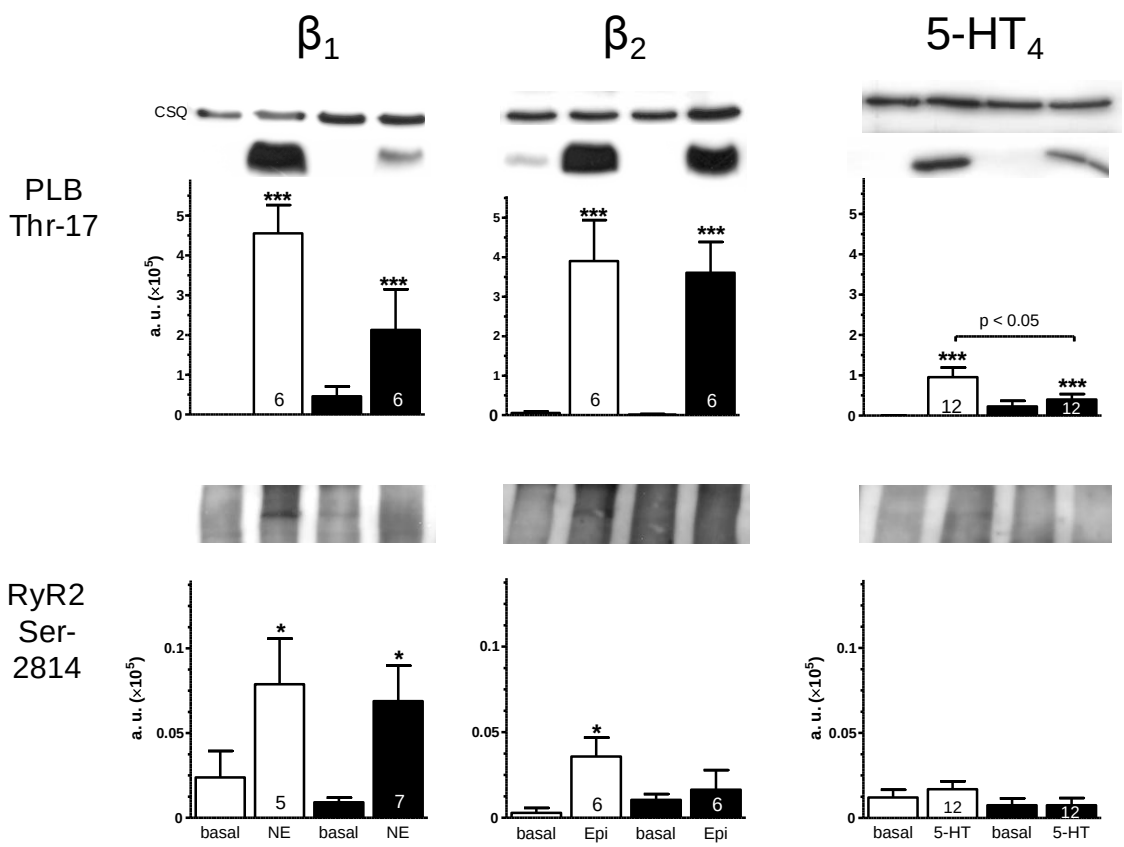


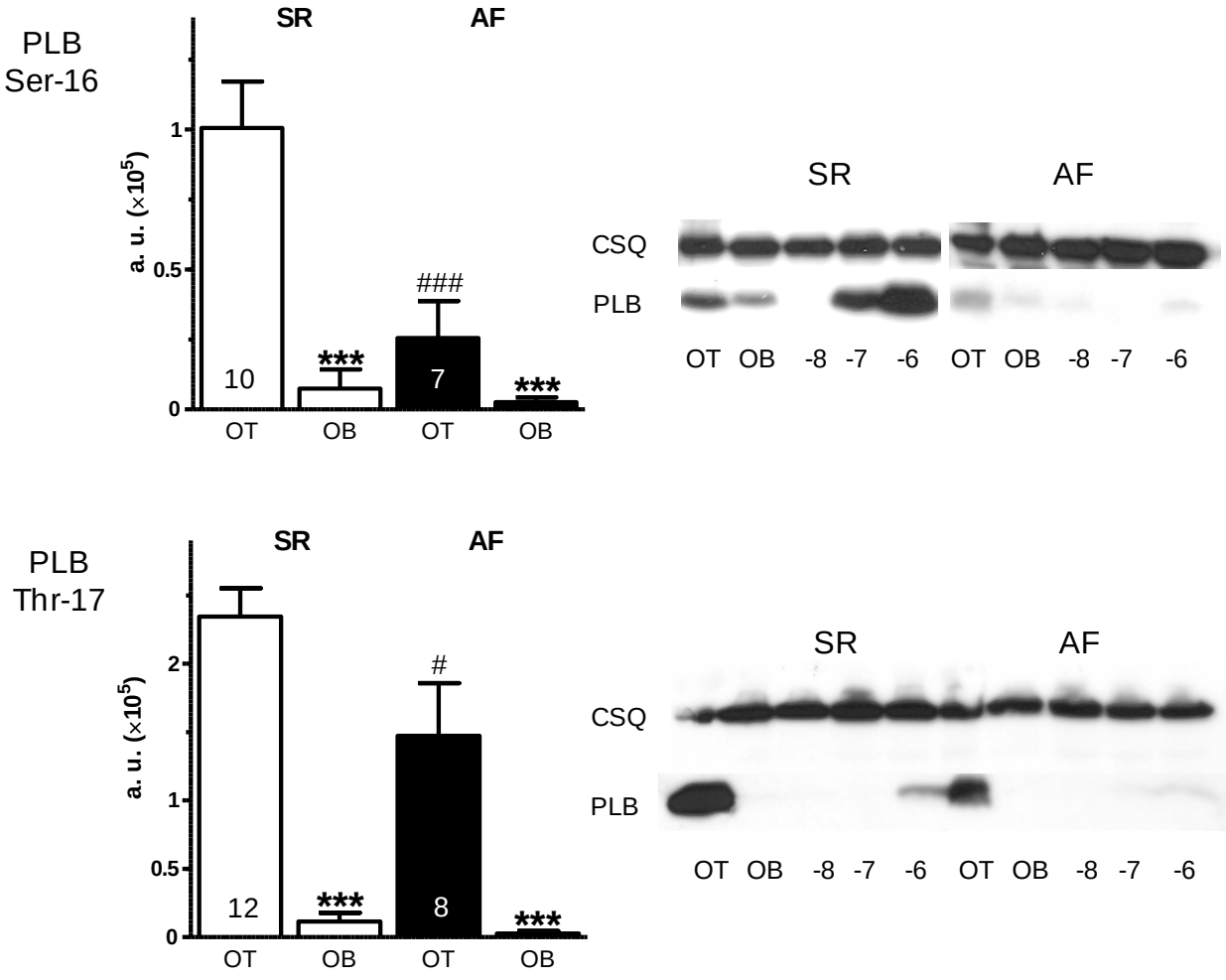
SI Appendix; Figure 6



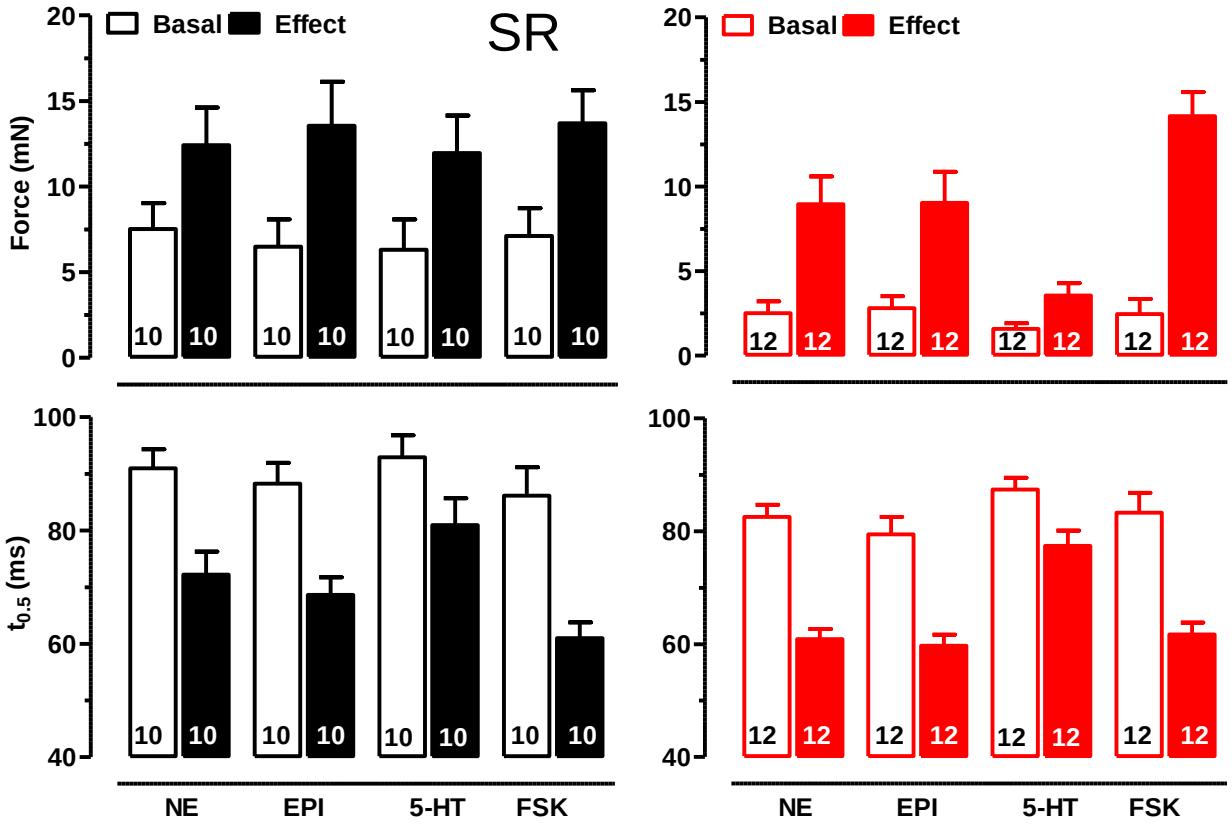
SI Appendix; Figure 7A



SI Appendix; Figure 7B



SI Appendix; Figure 8



SI Appendix; Figure 9