

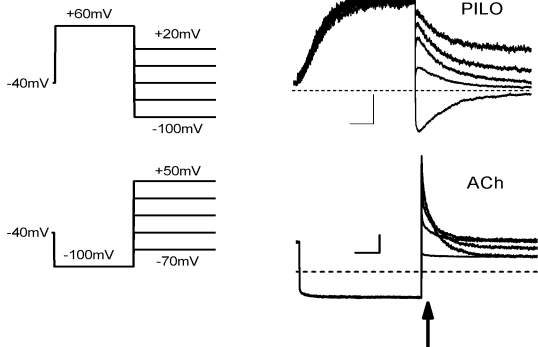
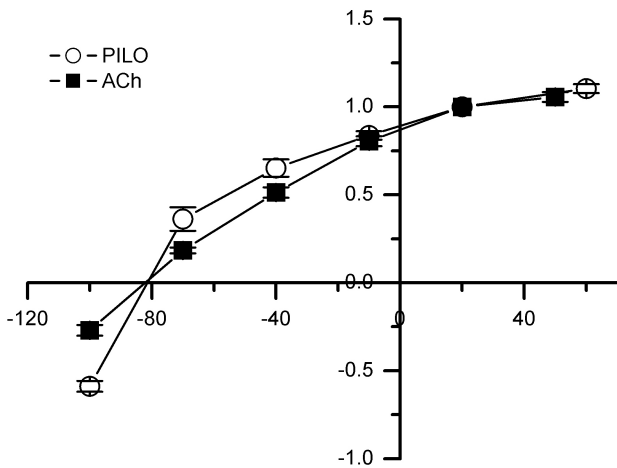
**Suppl. Fig. 1. “Fully-activated” current-voltage relationships for PILO- and ACh-activated current.** *A*, Currents elicited by 3  $\mu$ M PILO (top) and 100 nM ACh (bottom) using the protocols shown at the left. Scale bars correspond to 0.5 s and 200 pA. *B*, Fully-activated I-V curves measured as a relationship between the instantaneous current (arrow) and the membrane voltage of the test pulse, normalized to the current obtained at +20 mV ( $n = 5-12$ ).

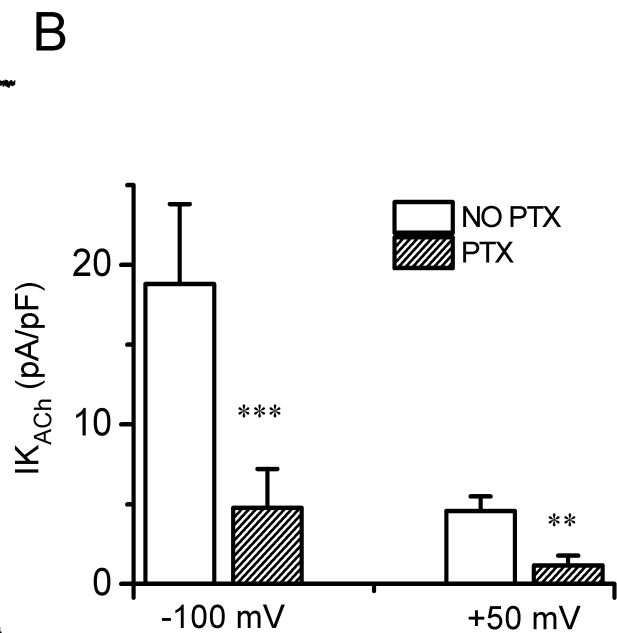
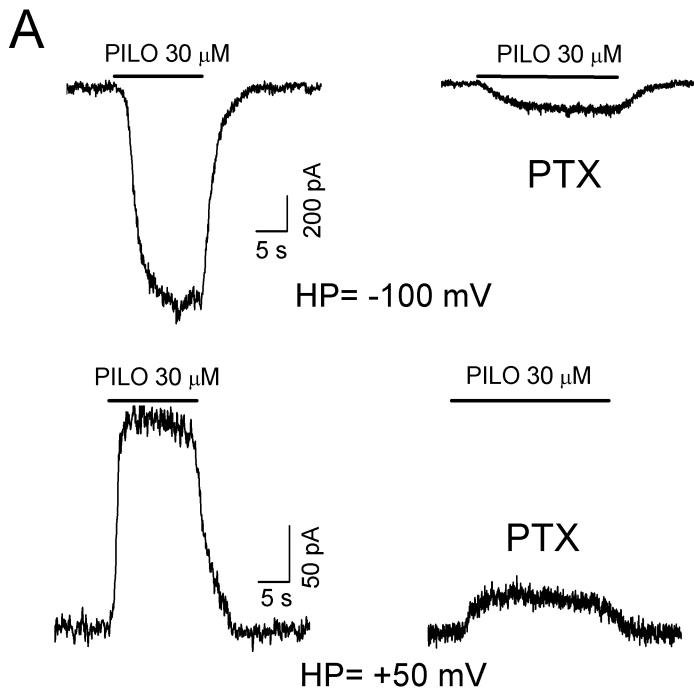
**Suppl. Fig. 2. PTX markedly reduces  $I_{K_{ACh}}$  activation by PILO.** *A*, Representative current traces showing the effect of brief application of 30  $\mu$ M PILO at HP -100 mV in a control atrial myocyte (left) and a myocyte pre-incubated with PTX (right). *B*, currents elicited as in *A*, but HP +50 mV. *C*, Summary of current magnitude elicited by PILO application under control conditions and in cells pre-incubated with PTX (5  $\mu$ g/ml). Data represent mean  $\pm$  SEM at HP -100 and +50 mV.  $N = 5$  cells in control and PTX treatment groups.

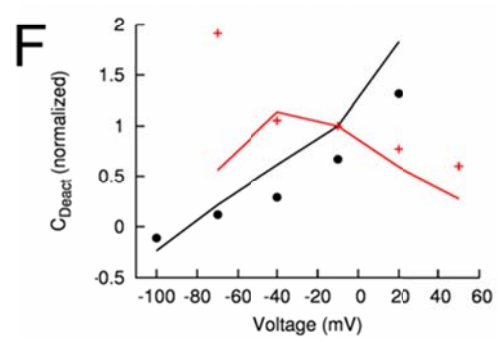
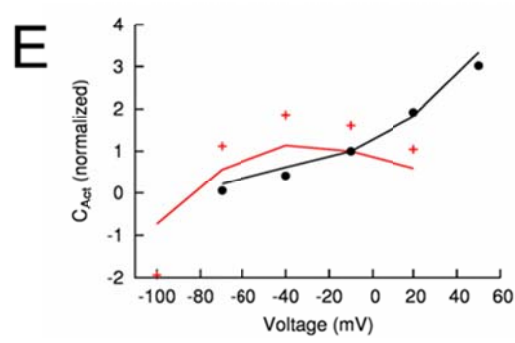
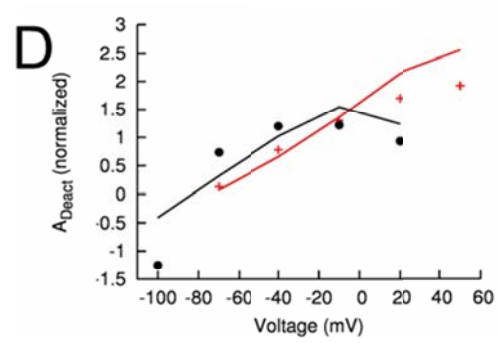
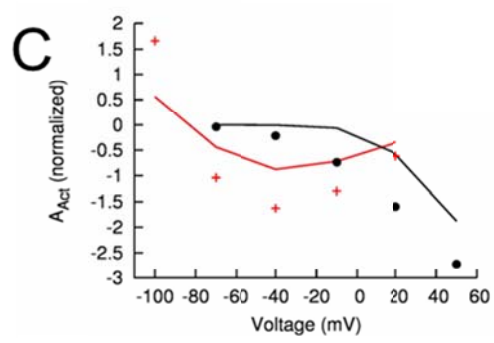
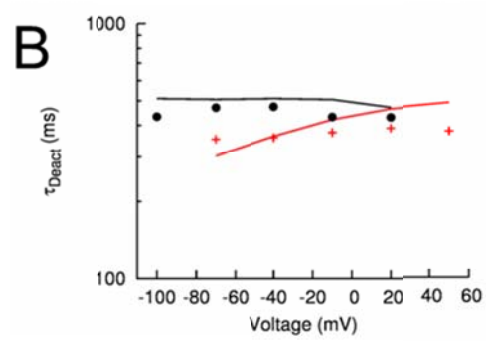
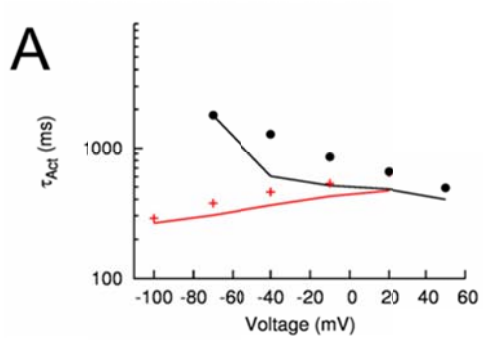
**Suppl. Fig. 3. Comparison of the kinetic features of modeled and measured  $I_{K_{ACh}}$ .** Features result from a mono-exponential fit of the measured and modeled data for activation and deactivation kinetics using the voltage protocol in Figure 5. Features result from a mono-exponential fit ( $I(t)=C+A e^{-t/\tau}$ ) of the measured and modeled data for activation (A,C,E) and deactivation (B,D,F). Measured ACh and PILO data are shown with red plus symbols and black dots, respectively. Modeled ACh and PILO data are shown with red and black lines, respectively.

**Suppl. Fig. 4. State occupancies underlying simulated  $I_{K_{ACh}}$  using activation and deactivation voltage protocols as in Figs. 5 and 9.** State occupancies for are displayed for experimental protocols used to determine ACh-induced activating currents (top left), PILO-

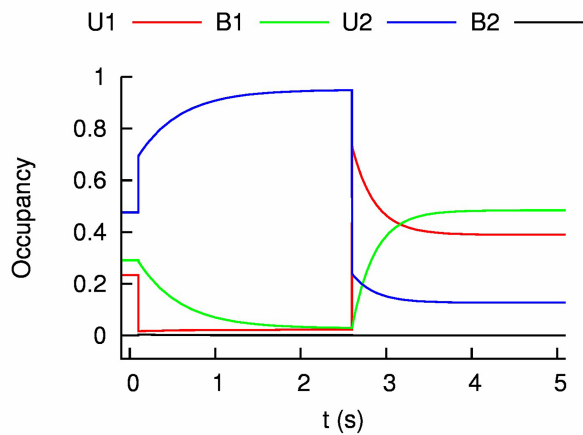
induced deactivating currents (top right), ACh-induced deactivating currents (bottom left) and PILO-induced activating currents (bottom right) as in Fig. 9.

**A****B**

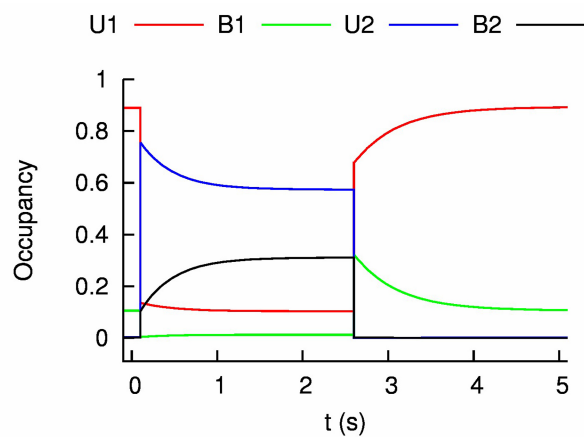




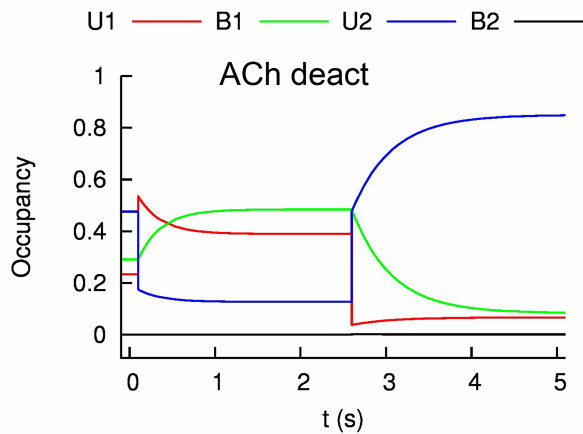
### ACh activ



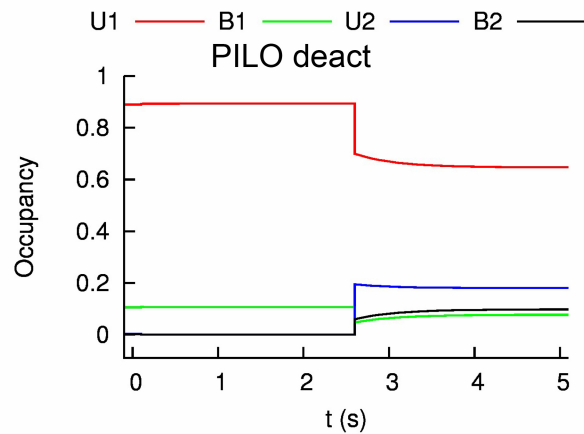
### PILO activ



### ACh deact



### PILO deact



**Suppl. Table 1: States and initial values at -100 mV for ACh and Pilo model.**

<b>States</b>	<b>Symbol</b>	<b>ACh Value</b>	<b>Pilo Value</b>
Ligand not bound, state 1	U1	0.389	0.894
Ligand bound, state 2	B1	0.483	0.106
Ligand not bound, state 1	U2	0.126	3.097e-3
Ligand bound, state 2	B2	4.342e-5	1.678e-5

**Suppl. Table 2: Parameters for models.**

<b>Parameter</b>	<b>Symbol</b>	<b>Value</b>	<b>Unit</b>
Temperature	T	309	K
Extracellular concentration of K <sup>+</sup>	[K <sup>+</sup> ] <sub>o</sub>	5.4	mM
Intracellular concentration of K <sup>+</sup>	[K <sup>+</sup> ] <sub>i</sub>	130	mM



**Suppl. Table 3: Features for model fitting and their fit errors**  $E_i = \frac{\|f_{m,i} - f_{e,i}\|_2}{\|f_{e,i}\|_2}$ .  
 (\*) A weighting factor of 2 was applied to emphasize this feature.

<b>Feature</b>	<b>ACh model</b>	<b>Pilo model</b>
$\tau_{ACT}^*$	0.4490	0.2502
$A_{ACT}$	0.5460	0.4323
$C_{ACT}$	0.4860	0.4677
$\tau_{DEACT}^*$	0.3662	0.6258
$A_{DEACT}$	0.2620	0.4611
$C_{DEACT}$	0.5403	0.1102
$Max_{-100mV}(B1+B2)$	0.5453	0.3227
$Min_{60mV}(B1+B2)$	0.0293	0.7831

**Suppl. Table 4: Rate constant parameters for ACh and Pilo model**

Parameter	Symbol	ACh Value	Pilo Value	Unit
	$\alpha_0$	10000	10000	$s^{-1}$
	$Z_\alpha$	0.7374	1.676	
	$\beta_0$	1445	161060	$s^{-1}$
	$Z_\beta$	0.07652	0.3184	
	$\gamma$	2.442	0.06237	$s^{-1}/\mu M$
	$\delta$	1.964	1.756	$s^{-1}$
	K	0.0002756	4.577	
	[L]	0.1	3	$\mu M$