Science Advances
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Supplementary Materials for

Deconstruction of an African folk medicine uncovers a novel molecular strategy for therapeutic potassium channel activation

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Published 14 November 2018, *Sci. Adv.* **4**, eaav0824 (2018)
DOI: 10.1126/sciadv.aav0824

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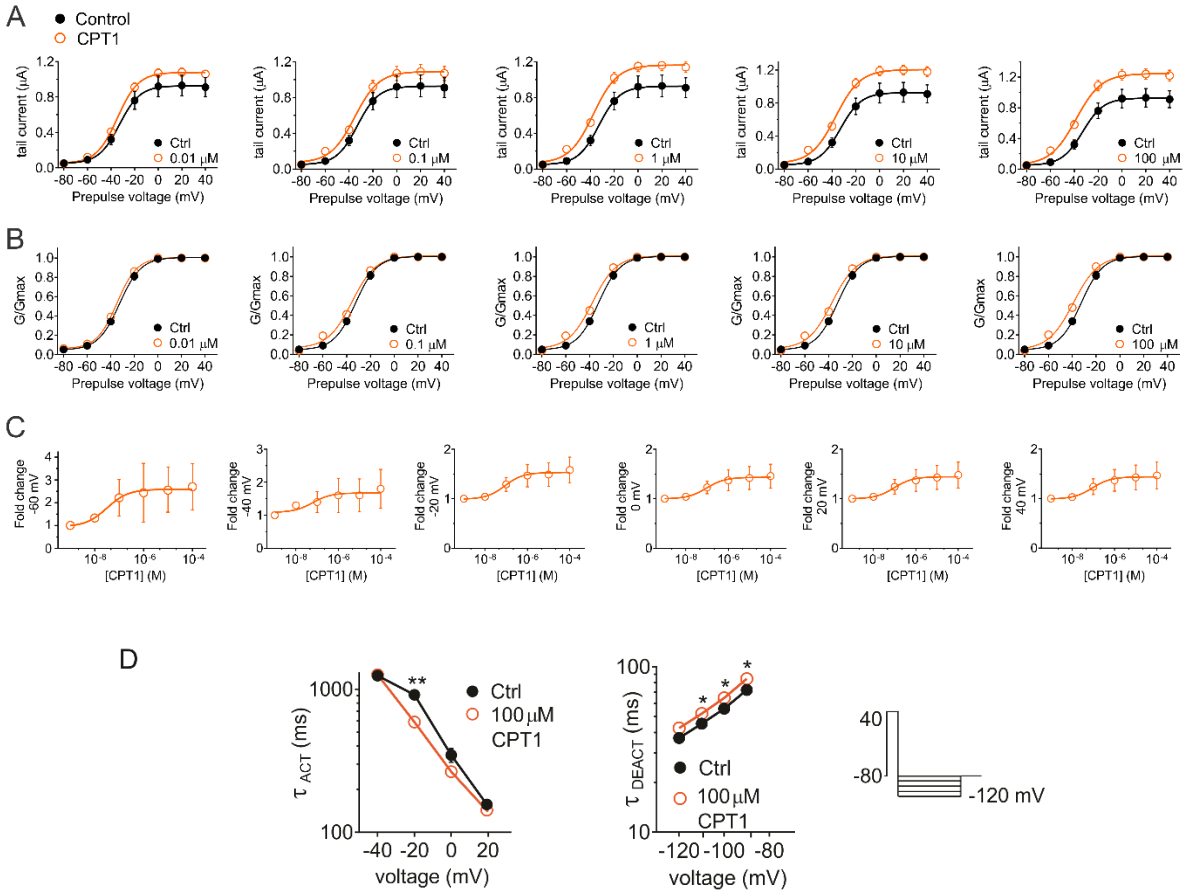

Fig. S1. Effects of CPT1 on KCNQ1 channels. (**A**)Mean tail current versus prepulse voltage relationship for KCNQ1 channels in the absence (black) and presence (orange) of CPT1, *n* = 4-6. (**B**)Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 4-6. (**C**)Dose response of KCNQ1 channels between -40 and +40 mV, *n* = 4-6. Error bars indicate SEM. (**D**)Mean activation (*left*) and deactivation (*right*) rates versus voltage for KCNQ1 before (Ctrl) and after wash-in of CPT1 (100 μM) (*n* = 6-7; *P < 0.05; **P < 0.01). Activation rate was quantified using voltage protocol as in Fig. 1D. Deactivation rate was quantified using voltage protocol shown on right.

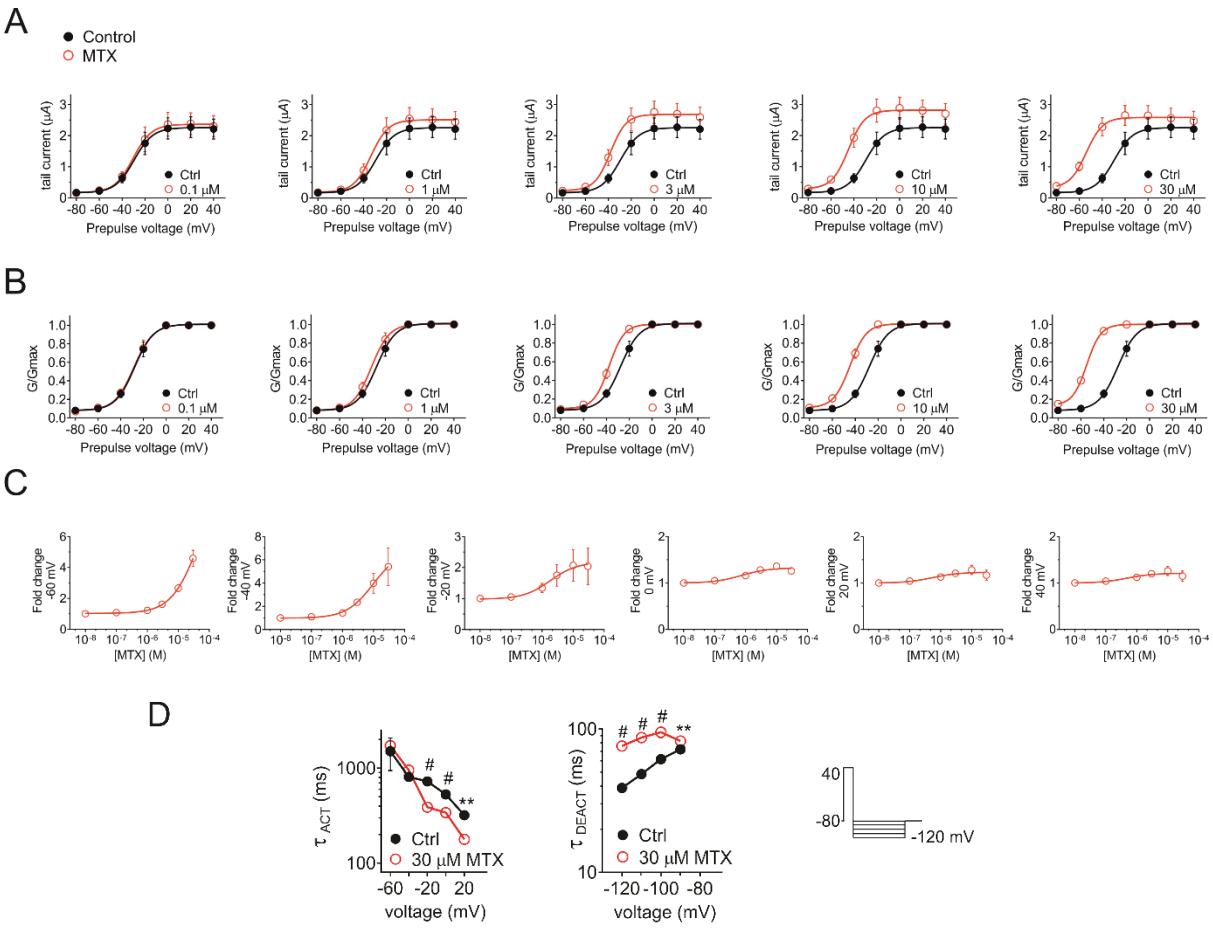

Fig. S2. Effects of MTX on KCNQ1 channels. (**A**)Mean tail current versus prepulse voltage relationship for KCNQ1 channels in the absence (black) and presence (red) of MTX, *n* = 7. (**B**)Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 7. (**C**)Dose response of KCNQ1 channels between -40 and +40 mV, *n* = 7. Error bars indicate SEM. (**D**)Mean activation (*left*) and deactivation (*right*) rates versus voltage for KCNQ1 before (Ctrl) and after wash-in of MTX (30 μM) (*n* = 7; *P < 0.05; **P < 0.01; # P<0.0001). Activation rate was quantified using voltage protocol as in Fig. 1D. Deactivation rate was quantified using voltage protocol shown on right.

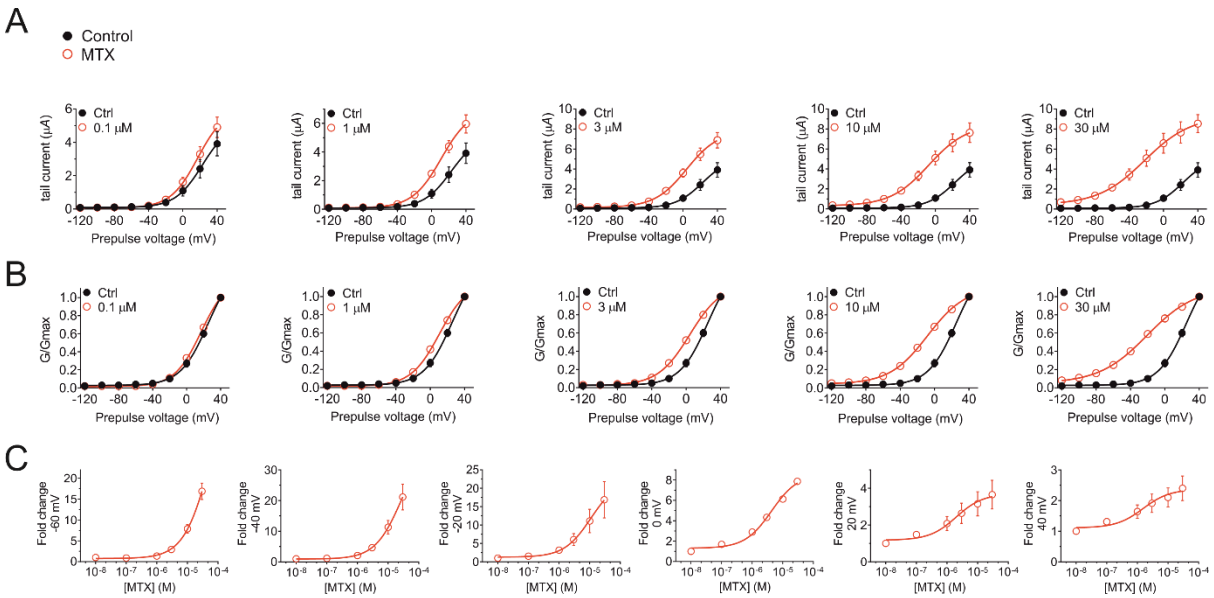

Fig. S3. Effects of MTX on KCNQ1/KCNE1 channels. (**A)**Mean tail current versus prepulse voltage relationship for KCNQ1/KCNE1 channels in the absence (black) and presence (red) of MTX, *n* = 5. (**B)**Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 5. (**C)**Dose response of KCNQ1/KCNE1 channels between -40 and +40 mV, *n* = 5. Error bars indicate SEM.

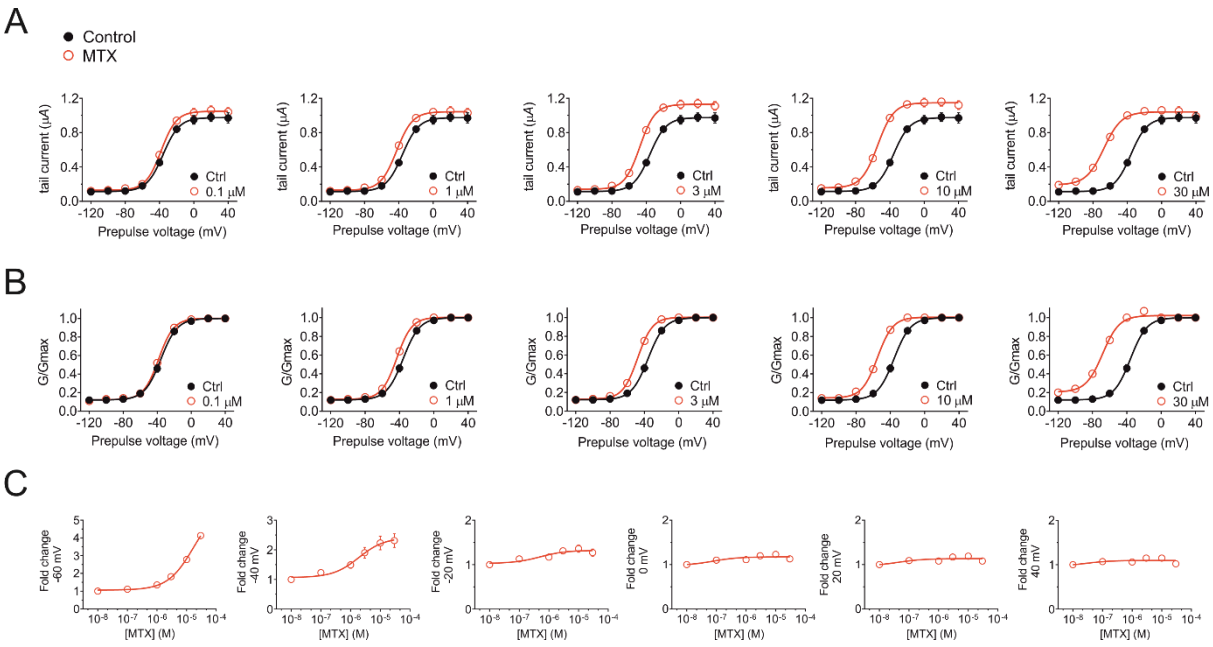

Fig. S4. Effects of MTX on KCNQ1/SMIT1 channels. (**A)**Mean tail current versus prepulse voltage relationship for KCNQ1/SMIT1 channels in the absence (black) and presence (red) of MTX, *n* = 5. (**B)**Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 5. (**C)**Dose response of KCNQ1/SMIT1 channels between -40 and +40 mV, *n* = 5. Error bars indicate SEM.

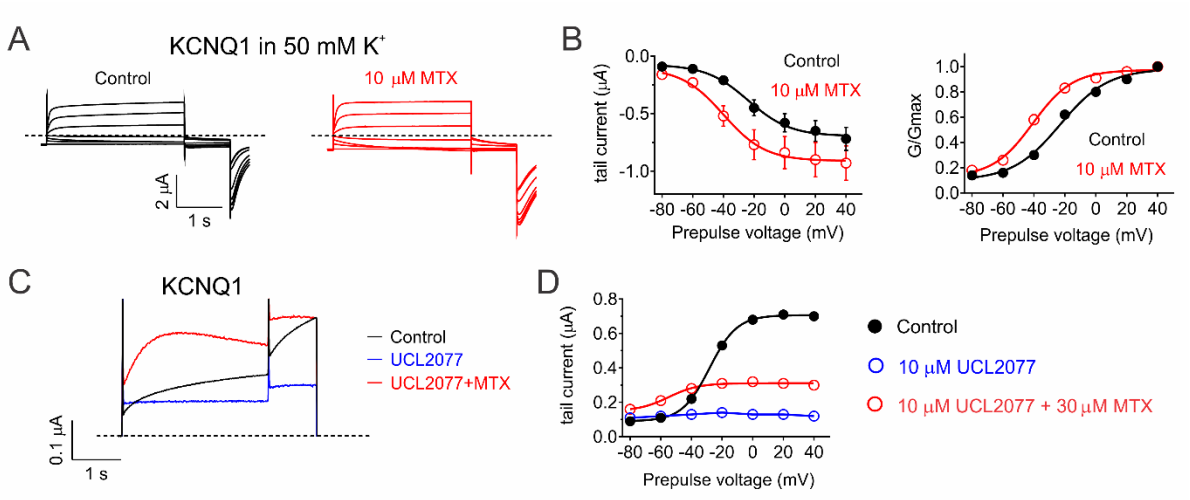

Fig. S5. Interaction of MTX with permeant ions and UCL2077.

All error bars indicate SEM. (**A**). Averaged KCNQ1 traces with 50 mM bath K^+ in the absence (Control) or presence of 10 μM MTX (*n* = 7). Dashed line indicates zero current level in this and all following current traces. (**B**). Mean effects of 10 μM MTX in 50 mM bath K^+ on KCNQ1 raw tail currents at -30 mV after prepulses as indicated (*left*) and G/Gmax (*right*) (from traces as in A; *n* = 7). (**C**). Averaged KCNQ1 traces, in the absence (Control) or presence of UCL2077 (10 μM) alone or with 30 μM MTX (*n* = 6-11). Cells were held at -80 mV, pulsed to -40 mV for 3 s, followed by a -30 mV tail pulse (1 s). (**D**). Mean KCNQ1 raw tail currents at -30 mV after prepulses as indicated, in the absence (Control) or presence of UCL2077 (10 μM) alone or with 30 μM MTX (from traces as in **C**; *n* = 6-11).

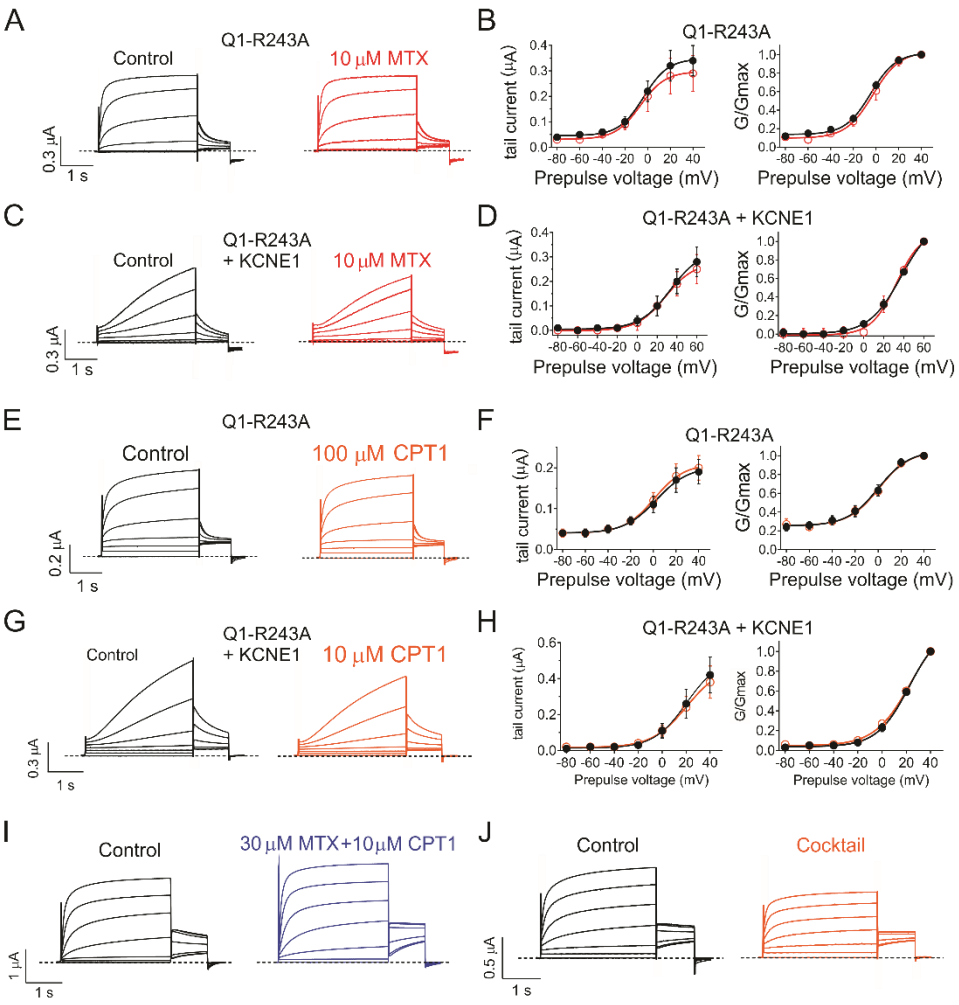

Fig. S6. MTX and CPT1 bind to R243 on the KCNQ1 S4-S5 linker. All error bars indicate SEM. (**A**). Averaged KCNQ1-R243A traces in the absence (Control) or presence of 10 µM MTX (*n* = 8). Dashed line indicates zero current level in this and all following current traces. (**B**). Mean effects of 10 µM MTX on KCNQ1-R243A raw tail currents at -30 mV after prepulses as indicated (*left*) and G/G_{max} (*right*). (**C**). Averaged KCNQ1-R243A/KCNE1 traces in the absence (Control) or presence of 10 µM MTX (*n* = 5). (**D**). Mean effects of 10 µM MTX (from traces as in **C**; *n* = 5) on KCNQ1-R243A/KCNE1 raw tail currents at -30 mV after prepulses as indicated (*left*) and G/G_{max} (*right*). (**E**). Averaged KCNQ1-R243A traces in the absence (Control) or presence of 100 µM CPT1 (*n* = 10). (**F**). Mean effects of 100 µM CPT1 (as in E; *n* = 10) on KCNQ1-R243A raw tail currents at -30 mV after prepulses as indicated (*left*) and G/G_{max} (*right*). (**G**). Averaged KCNQ1-R243A/KCNE1 traces in the absence (Control) or presence of 100 µM CPT1 (*n* = 5). (**H**). Mean effects of 100 µM CPT1 (as in **G**; *n* = 5) on KCNQ1-R243A/KCNE1 raw tail currents (*left*) and G/G_{max} (*right*) at -30 mV after prepulses as indicated. (**I**). Averaged KCNQ1 traces in the absence (Control) or presence of 30 µM MTX + 10 µM CPT1 (*n* = 5). (**J**). Averaged KCNQ1 traces in the absence (Control) or presence of *M. oppositifolius* leaf extract cocktail (*n* = 6).

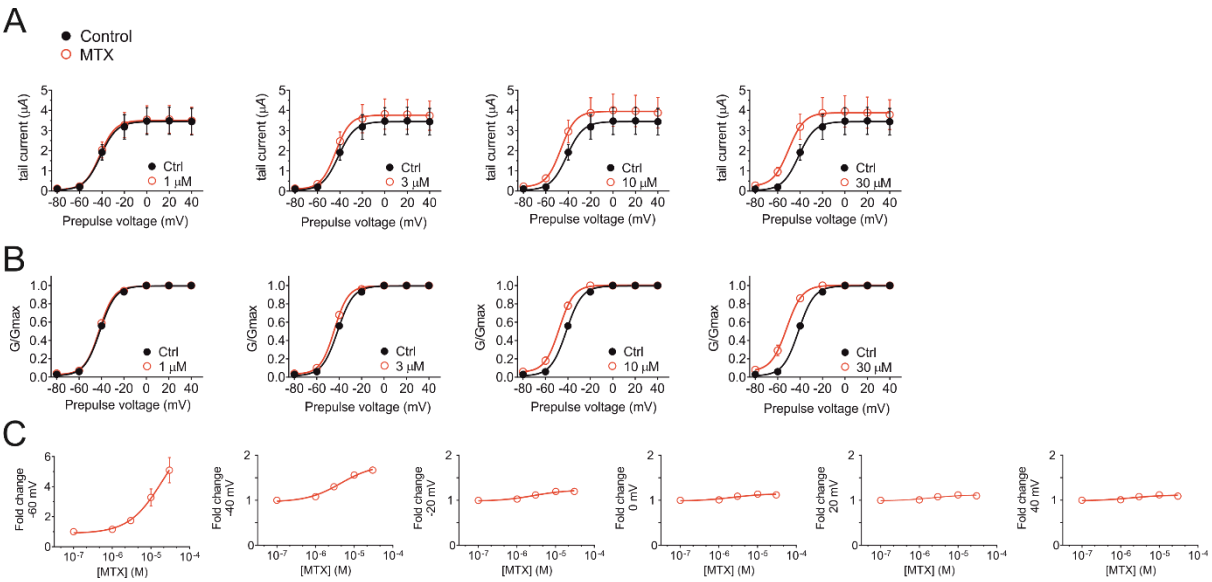

Fig. S7. Effects of MTX on KCNQ2/KCNQ3 channels. (**A**) Mean tail current versus prepulse voltage relationship for KCNQ2/KCNQ3 channels in the absence (black) and presence (red) of MTX, *n* = 5. (**B**) Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 5. (**C**) Dose response of KCNQ2/KCNQ3 channels between -40 and +40 mV, *n* = 5. Error bars indicate SEM.

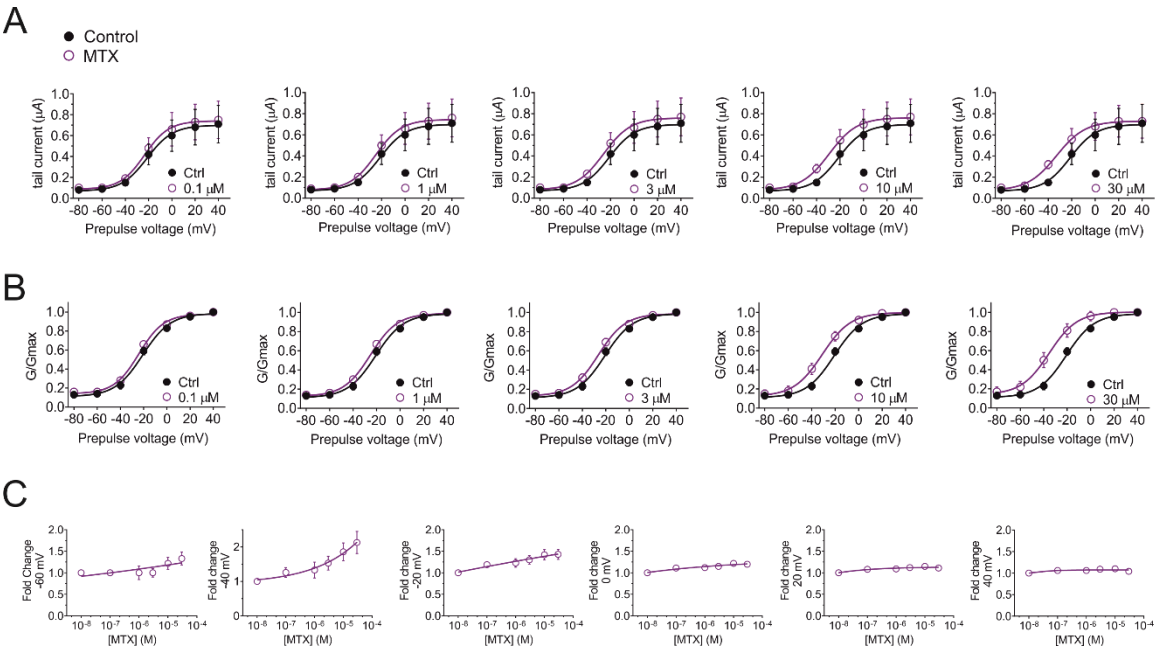

Fig. S8. Effects of MTX on KCNQ2-R213A/KCNQ3 channels. (**A**)Mean tail current versus prepulse voltage relationship for KCNQ2-R213A/KCNQ3 channels in the absence (black) and presence (red) of MTX, *n* = 6. (**B**)Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 6. (**C**)Dose response of KCNQ2-R213A/KCNQ3 channels between -40 and +40 mV, *n* = 6. Error bars indicate SEM.

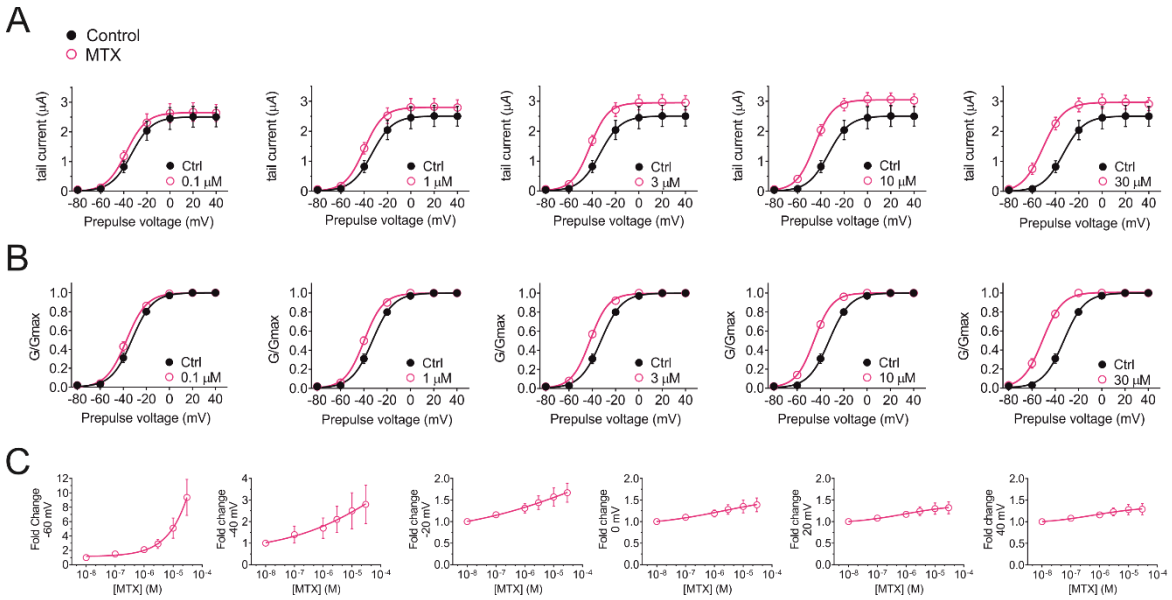

Fig. S9. Effects of MTX on KCNQ2/KCNQ3-R242A channels. (**A**)Mean tail current versus prepulse voltage relationship for KCNQ2/KCNQ3-R242A channels in the absence (black) and presence (red) of MTX, *n* = 6. (**B**)Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 6. (**C**)Dose response of KCNQ2/KCNQ3-R242A channels between -40 and +40 mV, *n* = 6. Error bars indicate SEM.

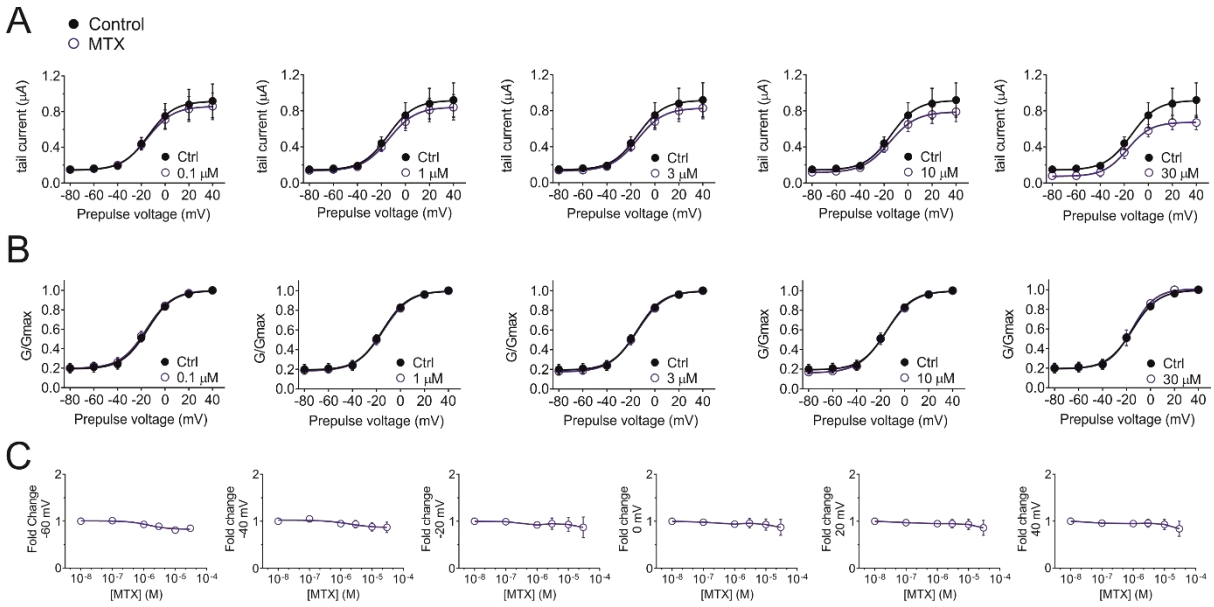

Fig. S10. Effects of MTX on KCNQ2-R213A/KCNQ3-R242A channels. (**A**)Mean tail current versus prepulse voltage relationship for KCNQ2-R213A/KCNQ3-R242A channels in the absence (black) and presence (red) of MTX, *n* = 5. (**B**)Normalized tail current versus prepulse voltage relationships as in panel A, *n* = 5. (**C**)Dose response of KCNQ2-R213A/KCNQ3-R242A channels between -40 and +40 mV, *n* = 5. Error bars indicate SEM.