



**Supplemental Figure 1.** Microscopic kinetics for the antagonist SR-95531. A) The  $K_D$ ,  $k_{off}$ , and  $k_{on}$  for SR-95531 was determined for each receptor type by examining the current response to 30 mM GABA following a pre-incubation in a series of concentrations of SR-95531 (1  $\mu$ M shown above). B) Deconvolution of GABA-evoked currents after SR-95531 pre-equilibration from control currents (no pre-equilibration) reveals the time course of SR-95531 unbinding. Deconvolved traces were fit to the equation  $A(t) = [P_\infty - (P_\infty - P_0)\exp(t/\tau_u)]^N$ , where  $A(t)$  is the fraction of available receptors (antagonist not bound at any site),  $P_0$  and  $P_\infty$  are the probabilities that a single binding site is available initially at  $t=0$  and at steady state as  $t \rightarrow \infty$ ,  $\tau_u$  is the time constant of antagonist unbinding from each site ( $k_{off-SR} = 1/\tau_u$ ), and  $N$  is the number of binding sites (Jones et al., 2001). C) Dose response curves for the equilibrium antagonist occupancy in the absence of GABA  $A(t=0)$  were fit to the normalized hill equation  $I/I_{max} = 1 - 1/[(K_{D-SR}/[SR-95531])^N + 1]$ .