configurations (Zorumski et al., 1989; Lester and Jahr, 1992; Lester et al., 1993; Krupp et al., 2002). To overcome this potential obstacle, we constructed dose–response plots using the predicted and measured peak current values, which appear to be less affected by intracellular factors. With this analysis, the predicted EC_{50} values were: 0.2, 3.6, and 0.3 µM for Models 1, 2, and 3, respectively (Fig. 4 C). The measured glycine EC_{50} = 3.9 µM was closest to the value predicted by Model 2. Therefore, these results also lend support to Model 2.

Glycine dependence of macroscopic current desensitization

Next, we simulated macroscopic currents after long (5-s) applications of glutamate (1 mM) in the continuous presence of high (100 µM) or low (0.5 µM) glycine concentrations and examined the extent (I_{ss}/I_{pk}) and time course of macroscopic desensitization (Fig. 5 A). Models 1 and 3 predicted currents with similar shapes regardless of glycine concentration: I_{ss}/I_{pk}, 0.8 versus 0.78 and 0.79 versus 0.73 for Models 1 and 3, respectively (Fig. 5 B). However, Model 2, which also predicted a modest desensitization level in high glycine (I_{ss}/I_{pk}, 0.8), produced current traces that desensitized more (I_{ss}/I_{pk} = 0.17) and faster in low glycine. As illustrated in Fig. 5 A, and noted above, experimentally recorded whole-cell currents elicited by glutamate in high glycine desensitize deeper (smaller I_{ss}/I_{pk} ratio) than any of our single-channel–derived models predict. However, when comparing the effects of glycine on the current desensitization level, only Model 2 predicted the dramatic change observed experimentally. Remarkably, this result

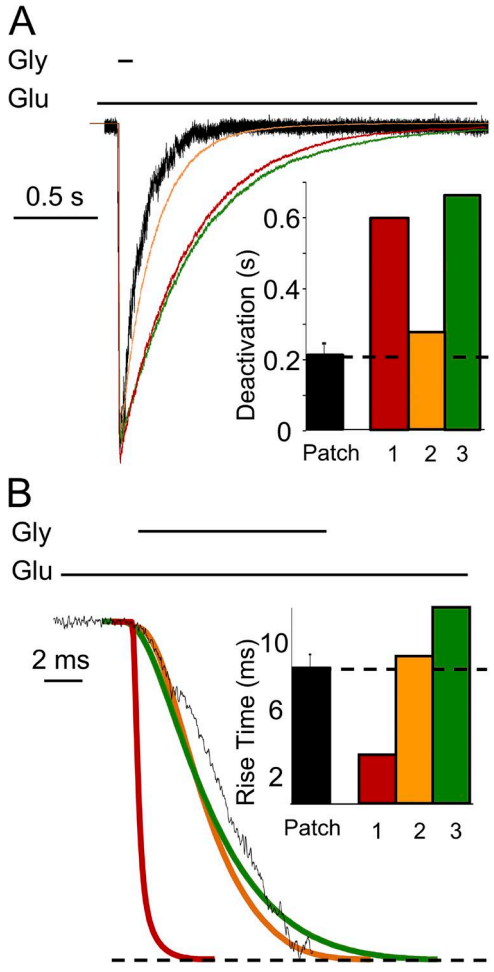

Figure 3. Macroscopic response to brief glycine exposure. Currents were recorded from multichannel outside-out patches exposed to 0.1 mM glycine (10 ms) and with 1 mM glutamate present (black; error bars are ± SEM), or were simulated in similar conditions with Models 1 (red), 2 (orange), and 3 (green) illustrated in Fig. 1. (A) Deactivation and (B) rise times were quantified for experimental and simulated traces.

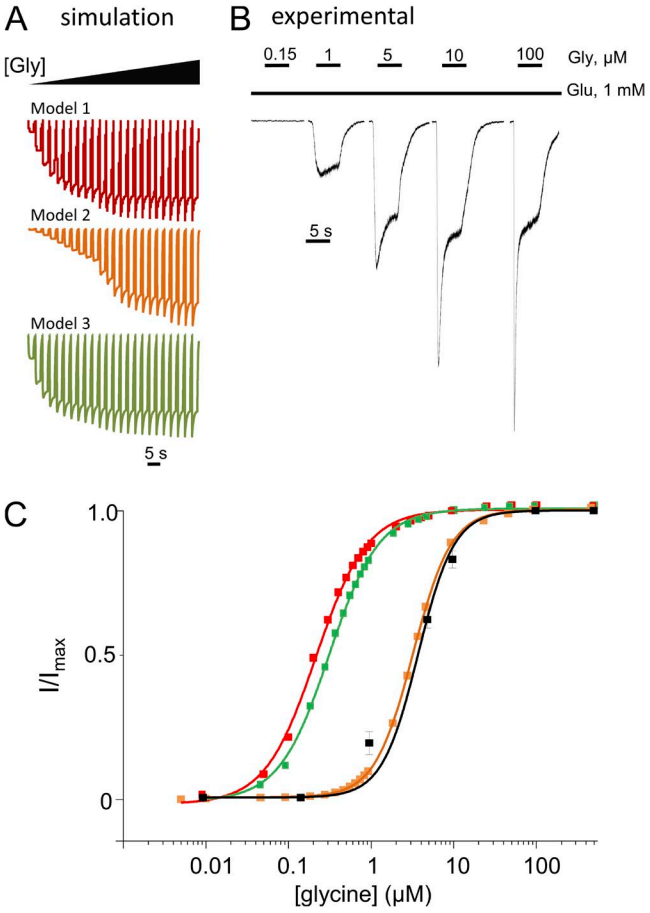

Figure 4. NMDA receptor glycine dose–response. (A) Simulated traces (100 channels, 10 pA/each) with Models 1, 2, and 3 (from Fig. 1), and 5-s pulses of glycine of increasing concentrations (5 nM–500 µM). (B) Recorded whole-cell currents in response to 5-s pulses of glycine (as indicated) and 1 mM Glu. (C) Dose–response curves were calculated by fitting the Hill equation to peak current amplitudes measured experimentally (black) or obtained from simulations (color). EC_{50} = 3.9 µM, for the experimental traces (error bars are ± SEM) and 0.2, 3.6, and 0.3 µM, for Models 1 (red), 2 (orange), and 3 (green), respectively.