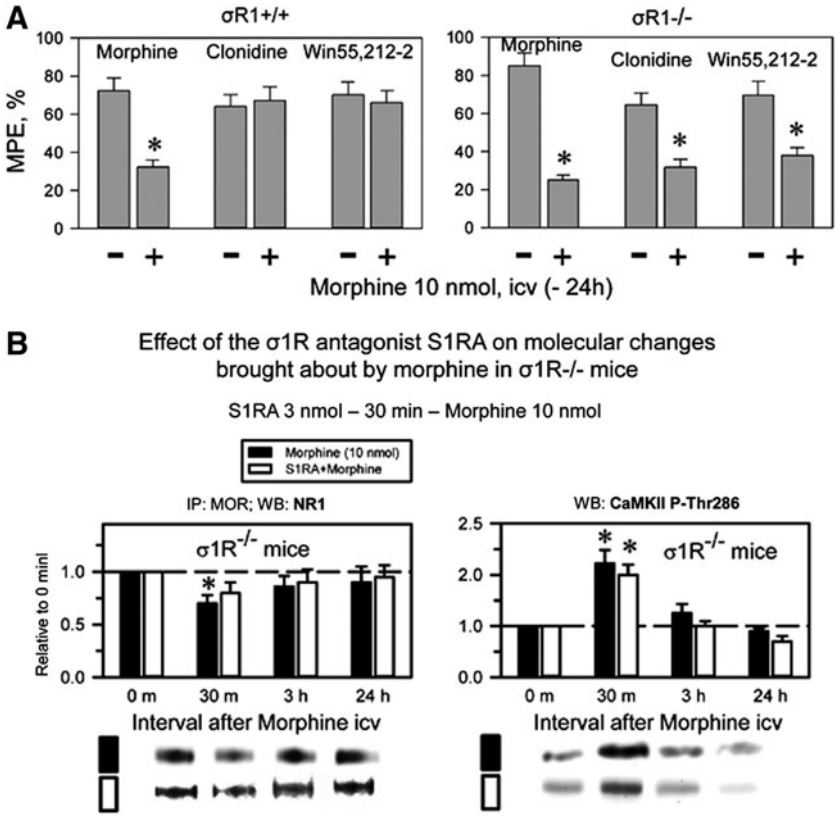

SUPPLEMENTARY FIG. S6. The absence of σ1Rs disconnects NMDAR negative influence from MOR signaling. **(A)** Morphine produces heterologous tolerance in $\sigma 1R^{-/-}$ mice. Groups of four mice each were injected icv with 10 nmol morphine and the analgesic effect of morphine, 150 nmol clonidine, and 20 nmol WIN55,212-2 was assessed 24 h later (30 min after morphine and the agonist of α2-adrenoceptors clonidine, 10 min after the cannabinoid). *Significantly different from the respective control group that received the priming dose of morphine, ANOVA, Student–Newman–Keuls test, $p < 0.05$. **(B)** Morphine promotes little activation of the NMDAR-CaMKII pathway in $\sigma 1R^{-/-}$ mice: effect of S1RA. Mice were icv-injected with 10 nmol morphine, and the *ex vivo* assays were performed at the postopioid time intervals indicated. The administration of S1RA to $\sigma 1R^{-/-}$ mice did not alter these molecular effects of morphine.