

Supplementary Figure 1. Persistent decrease of potentiated transmission by CaMKII inhibitor is not due to LTP decay during application. In two pathway control experiments (●, –; N = 4), LTP induced in one pathway (100 Hz, 1 s) was stable during ACSF solution changes at similar times as in test experiments with Ant-CaMKIINtide application (○, 3 μ M, superimposed).

Supplementary Figure 2. Antennapedia (Ant) does not affect synaptic transmission or cell membrane potential. Summary of whole-cell voltage-clamp experiments conducted in CA1 neurons during bath application of Ant (5 μ M, 20 min; N = 5). **A.** Stable synaptic currents (EPSC) recorded during Ant application. *Inset*, average of 10 EPSC sample traces. Calibration: 10 ms, 200 pA. **B.** Stable whole-cell holding current (-65 mV, holding potential) during the experiments shown in A.

Supplementary Figure 3. Effect of CaMKII inhibitor is not activity-dependent. **A.** Decrement in basal transmission due to inhibitor is compared in two pathways; in one synaptic stimulation was continuous throughout the 30 minute drug application; in the other pathway stimulation was turned off immediately after application of inhibitor; the effect of inhibitor was then tested after a 20 minute stimulation-free period (n = 9). The dashed line represents the ratio if the magnitude of the fEPSP during continuous stimulation equals the magnitude after an interruption of test stimuli. **B.** Multi-unit recording (tungsten electrode) of spike rate (top) shows no increase in spike rate during application of inhibitor that greatly reduced fEPSP (bottom). Similar results were obtained in 4 other experiments. Thus, although CaMKII can affect various voltage-dependent conductances (Lu et al., 1994; Robinson et al., 2004; Varga et al., 2004), the result changes do not strongly affect spontaneous activity.

Supplementary Figure 4. Effect of CaMKII inhibitor is observed when NMDARs are blocked. A representative experiment [showing the effect on basal transmission of Ant-CaMKIINtide when applied in the presence of APV, demonstrating](#) that the effect of CaMKII inhibition does not require NMDA receptors. Similar results were observed in 8 experiments.

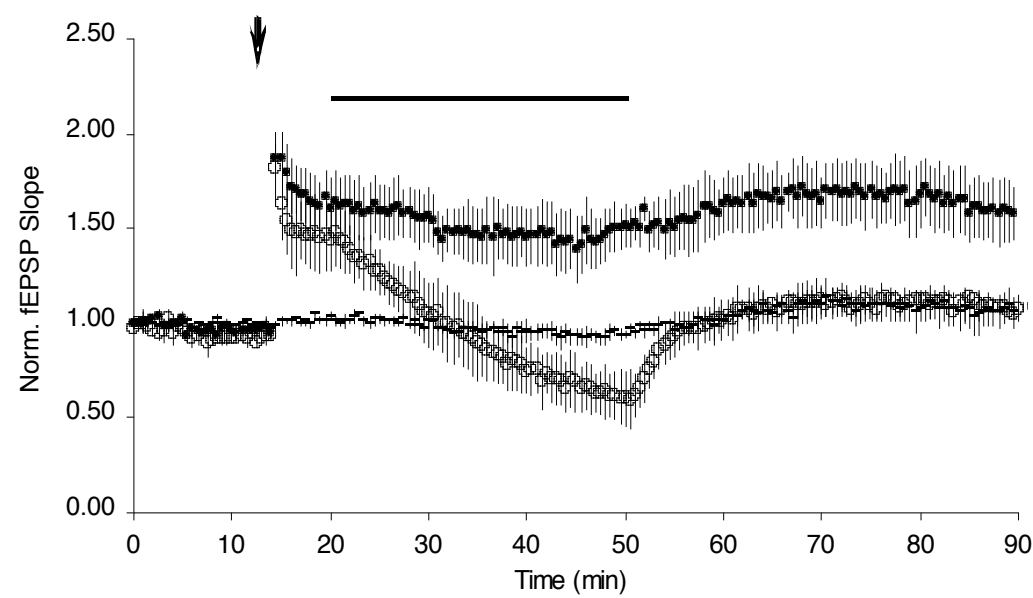
Supplementary Figure 5. The non-recovering (persistent) component of transmission is observed in both the LTP and naïve pathways. Non-recovering component of the effect on basal transmission is compared to that on the potentiated pathway to show that the percent recovery after

washout of Ant-CaMKIINtide is comparable in both pathways. (dashed line represents the ratio if the magnitude of the non-recovering component of fEPSP in both pathways are equal).

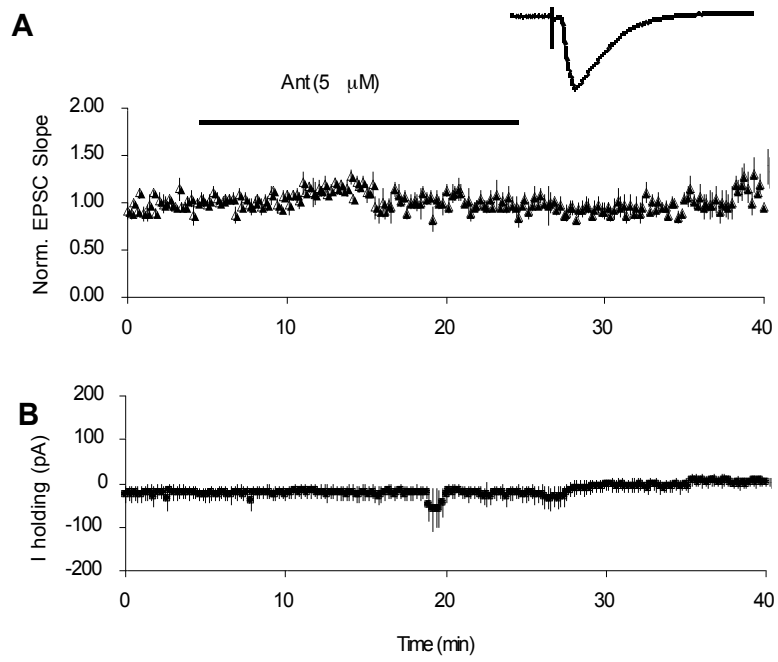
Supplementary Figure 6. The non-recovering component is unlikely to be due to continued presence of inhibitor. After a 10 min baseline, Ant-CaMKIINtide was locally applied through the recording electrode for 20 min (20 μ M inside the pipette). This resulted in a decrement in the fEPSP. After inhibitor application was stopped, there was partial recovery, but a large non-recovering component was evident ($0.48\% \pm 0.10\%$, $n = 4$). Because trapped intracellular inhibitor could diffuse away from the site of local application, it is unlikely that the non-recovering component is due continued presence of intracellular inhibitor.

Supplementary Fig. 7. Representative test and control experiment to test the reversal of saturated LTP by CaMKII inhibitor. **A.** LTP was saturated in one pathway (4 tetani; 100 Hz/1 s, spaced 2 min apart), a single additional tetanus was applied 10 min later to check saturation. After the single tetanus applied at $t = 25$ min to check saturation, no additional potentiation was observed ($-0.5 \pm 1.5\%$, inhibitor; $-3.4 \pm 1.6\%$, no inhibitor). Approximately 100 mins later, a second series of 4 tetani failed to induce further potentiation. 15 minutes later, LTP was induced in the naïve pathway with the same pattern of high frequency stimulation. Note that at 115 min, stimulation strength was decreased. This was necessary to make the fEPSP the same size as after inhibitor application (see part B). Only if this equality holds (see part C) can the magnitude of LTP induced be directly compared after inhibitor application or without inhibitor application. **B.** The same experimental procedure as in A, but the slice was treated for 30 min with Ant-CaMKIINtide (5 μ M) during the 100 min period. Potentiation was observed in the formerly saturated pathway. Insets show average response at 120min. (just before the tetani) and at 25min. after tetani. Calibration: 0.2mV; 4msec. **C.** The strength of stimulation on both pathways of the control experiments was reduced to mimic the non-recovering component in the inhibitor application experiments. The adjusted control fEPSP slope at the time of LTP induction (~ 2 hr) in A and B was similar for experiments with and without inhibitor (tetanized, 0.44 ± 0.11 (inhibitor) vs 0.41 ± 0.10 (control), $p > 0.5$; naïve, 0.25 ± 0.08 vs 0.33 ± 0.10 , $p > 0.05$).

Supplementary Figure-1 Lisman, JE

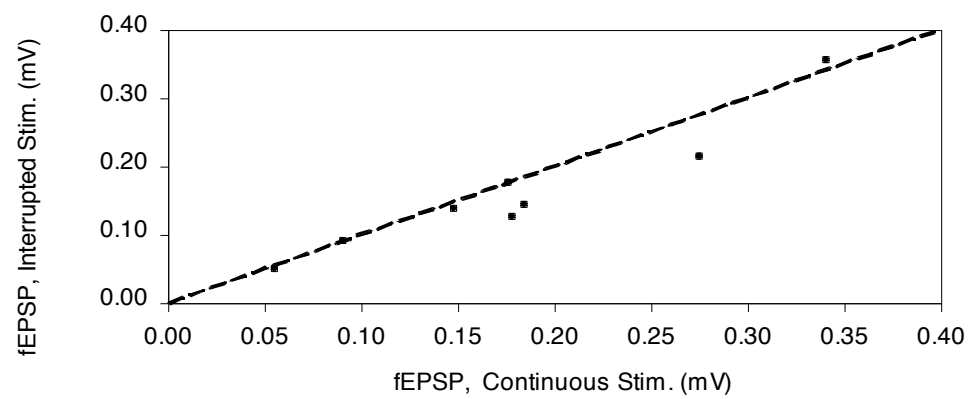


Supplementary Figure-2 Lisman, JE

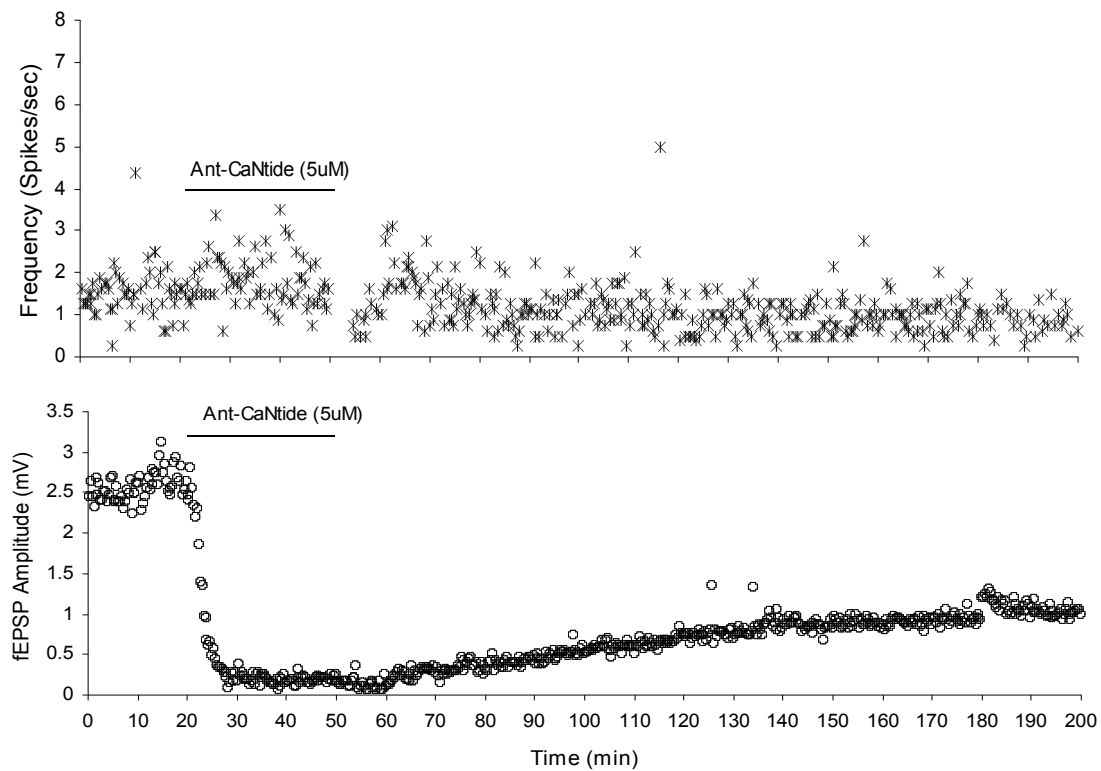


Supplementary Figure-3 Lisman, JE

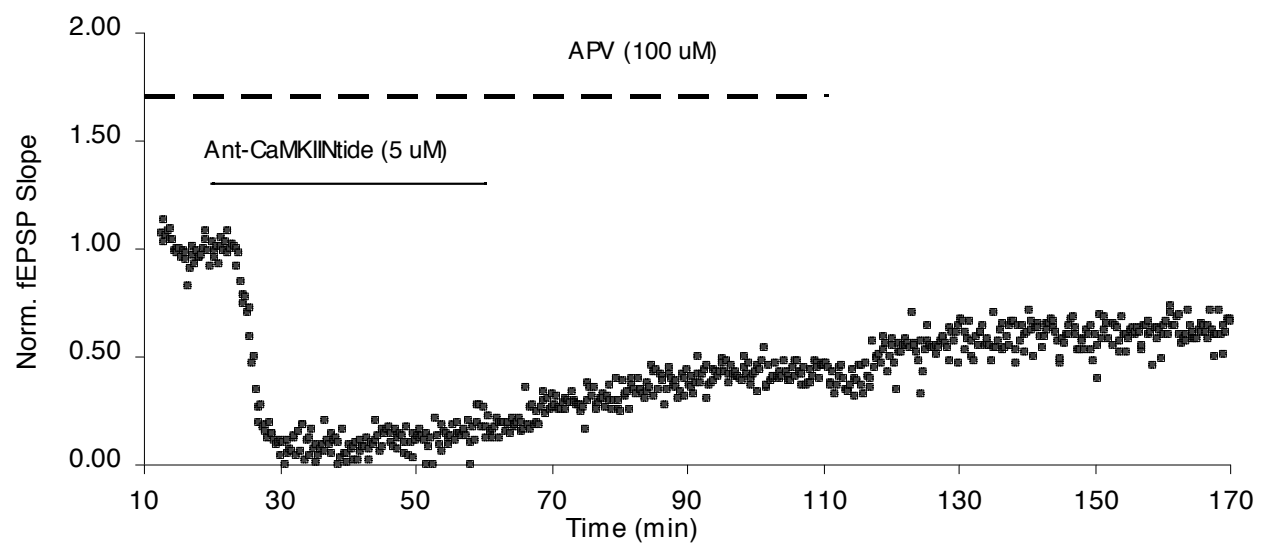
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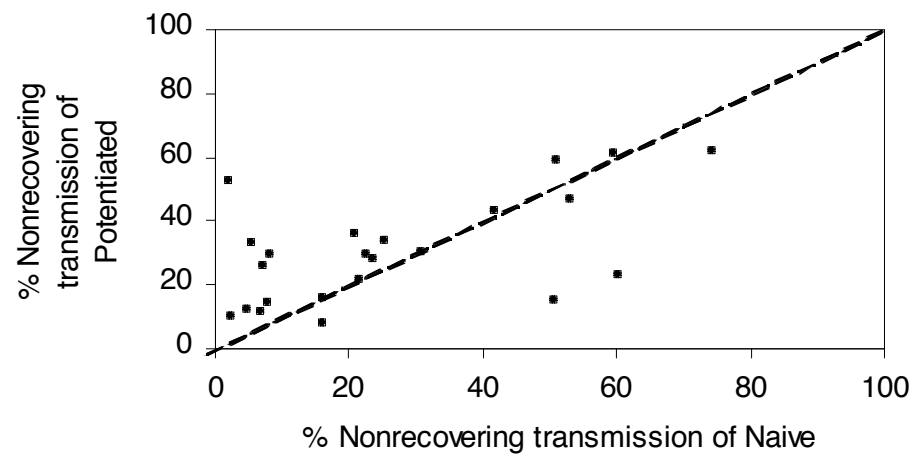
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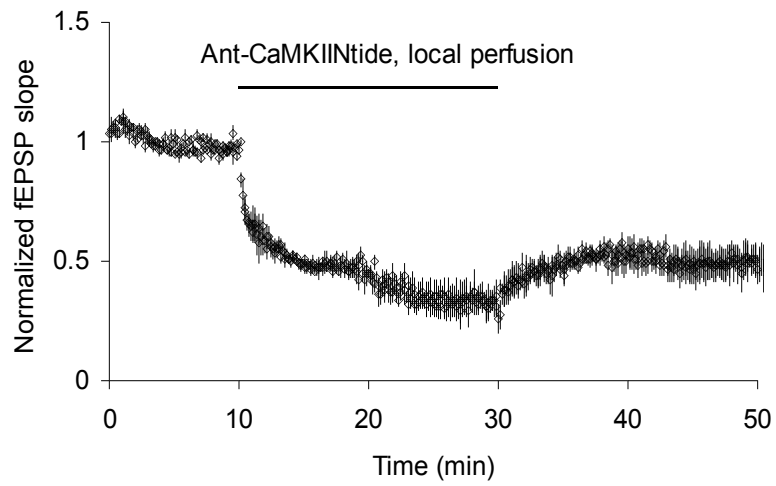
Supplementary Figure-4 Lisman, JE



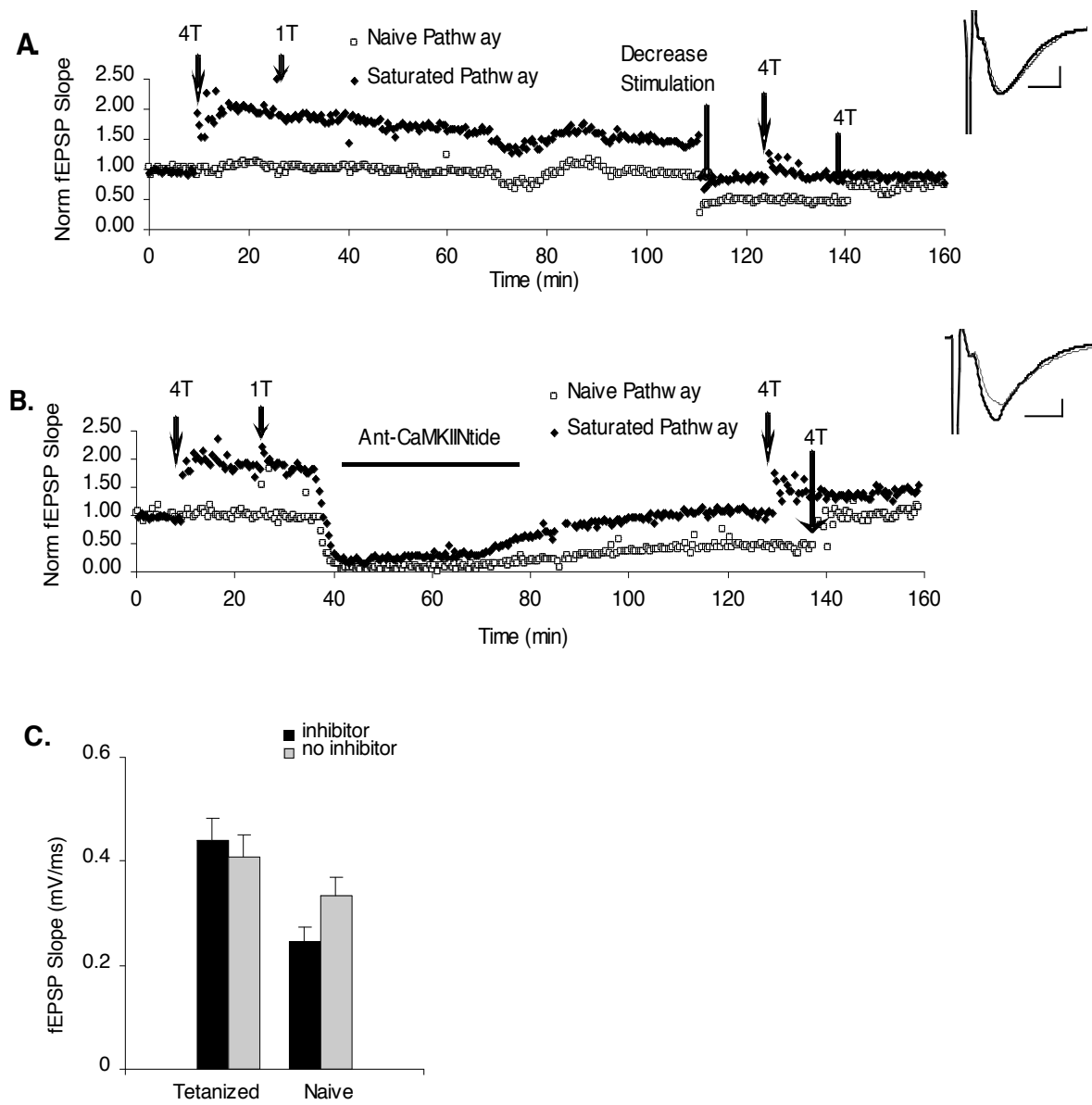
Supplementary Figure-5 Lisman, JE



Supplementary Figure-6 Lisman, JE



Supplementary Figure-7 Lisman, JE



References in Supplementary Material:

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- Robinson NC, Huang P, Kaetzel MA, Lamb FS, Nelson DJ (2004) Identification of an N-terminal amino acid of the CLC-3 chloride channel critical in phosphorylation-dependent activation of a CaMKII-activated chloride current. *J Physiol* 556:353-368.
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