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## Presentation Abstract

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Title: Differential expression of presynaptic NMDA receptors in layer-5 neurons of the mouse visual cortex

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Abstract: NMDA receptors are ideally suited as detectors of coincident pre and postsynaptic activity in Hebbian plasticity, since they require both glutamate and depolarization to open and trigger the calcium transients that elicit plasticity. This classical view on NMDA receptor functionality necessitates a postsynaptic location, yet NMDA receptors have been found presynaptically at several synapse types. Using acute slices, we investigate the expression and functional role of presynaptic NMDA receptors (preNMDARs) in several neuronal types in layer 5 (L5) of mouse visual cortex.

As an indication of preNMDAR expression, we looked for a reduction of mEPSCs frequency after NMDAR blockade. Consistent with prior studies in rat, D/L-APV (200  $\mu$ M) reversibly suppressed mEPSC frequency ( $76 \pm 5\%$ ;  $p < 0.01$ ,  $n=10$ ) in mouse L5 pyramidal cells (PYs), but did not affect amplitude ( $p=0.3$ ) or rise time ( $p=0.7$ ). In agreement, APV application reversibly depressed AMPA EPSPs evoked at 30 Hz at monosynaptic connections between pairs of L5 PYs ( $61\% \pm 4\%$  of baseline,  $n=12$ ) compared to controls ( $95\% \pm 9\%$ ,  $n=11$ ;  $p < 0.01$ ). CV analysis was consistent with a presynaptic effect of APV ( $p < 0.01$ ).

We then investigated the effect of APV on mEPSC frequency in L5 interneurons (INs) positive for parvalbumin (PV; JAX transgenic strain #007677) and found it to be heterogeneous and seemingly bimodal. Indeed, using hierarchical clustering, PV+ INs were readily segmented into two distinct types. As in PYs, APV caused a significant reversible depression of mEPSC frequency in Type-1 PV+ INs ( $70 \pm 5\%$ ,  $p < 0.05$ ,  $n=4$ ), but there was no effect in Type 2 ( $96 \pm 2\%$ ,  $p=0.14$ ,  $n=7$ ). Input resistance ( $302 \pm 36 \text{ M}\Omega$ ,  $142 \pm 14 \text{ M}\Omega$ ,  $p < 0.01$ ) and spike height ( $58 \pm 4 \text{ mV}$ ,  $40 \pm 4 \text{ mV}$ ,  $p < 0.05$ ) of Type-1 and 2 PV+ INs were also significantly different. In keeping with the mEPSC experiments, two monosynaptic excitatory inputs onto Type-1 INs showed a reversible APV-

induced suppression (19%,  $p < 0.001$ ; 46%,  $p < 0.05$ ) that was not apparent in unitary inputs onto Type-2 cells ( $78 \pm 4\%$ ,  $n=10$ ;  $81 \pm 10\%$  in controls,  $n=6$ ;  $p=0.8$ ).

These results suggest that expression of functional preNMDARs in neocortical L5 is differential and cell specific. Given their impact on neurotransmission, preNMDARs may specifically regulate information flow and activity in local microcircuits.

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