Timing- and Pattern-Dependent Long-Term Depression During Mouse Barrel Cortex Development

Abhishek Banerjee

A thesis submitted in partial fulfilment of
the requirements for the degree of
Doctor of Philosophy at the University of Oxford

Lady Margaret Hall
University of Oxford
Hilary Term 2010

ABSTRACT

Long term depression (LTD) plays an important role in the refinement of neocortical maps during early postnatal development. Synapse formation and refinement in the cortex during development rely on synaptic plasticity, the cellular mechanisms of which are poorly understood. The aim of this thesis was to investigate timing- and pattern-dependent LTD at excitatory synapses in the mouse barrel cortex during development.

This thesis first describes the developmental profile and N-methyl-D-aspartate (NMDA) receptor GluN2 subtype-dependence of timing-dependent plasticity at layer 4–to–layer 2/3 synapses. A developmental dissociation of timing-dependent plasticity was observed where timing-dependent LTD (t-LTD) was found during early development (postnatal day, P6-8) but disappeared after P25. In contrast, timing-dependent LTP (t-LTP) only appeared in the second postnatal week of development (P11-15) and persisted in the adult cortex. This bidirectional plasticity also showed a GluN2 subtype-dependent dissociation. Whereas t-LTP was dependent on GluN2A subunit-containing NMDA receptors, t-LTD was dependent on GluN2C/D subunit-containing NMDA receptors.

This thesis also reports a novel anti-Hebbian form of NMDA receptor-dependent plasticity, in which presynaptic layer 4 neurons drive their presynaptic long-term self-depression without the involvement of postsynaptic action potentials or calcium. This mechanism suggests that, during development, presynaptic self-depression occurs when specific spike patterns (presynaptic burst-spike) in the presynaptic neuron are unsuccessful in driving postsynaptic activity.

Finally, this thesis addresses how t-LTD induction rules differ in vertical intracolumnar layer 4–to–layer 2/3 and horizontal cross-columnar layer 2/3–to–layer 2/3 synapses in the barrel cortex. Distinct GluN2 subunit expression in vertical and horizontal synapses regulated the time-window of t-LTD induction. It is also shown that different excitatory intra- and cross-columnar synapses onto the same postsynaptic layer 2/3 neurons can have different molecular requirements for the induction of t-LTD, and that they also interact to induce heterosynaptic associative LTD. These findings may have important implications for understanding the cellular mechanisms of experience-dependent plasticity and its relevance to the computational principles of cortical circuit operation.