Pre- and postsynaptic factors controlling synaptic efficacy at central synapses

M.C. Bellingham and M.L. Kerr, School of Biomedical Sciences, University of Queensland, St. Lucia, Queensland 4072, Australia. (Introduced by D.J. Adams)

Synaptic efficacy is a measure of the strength of postsynaptic electrical signals arising from synaptic release of chemical neurotransmitters. Both pre- and postsynaptic factors can alter synaptic efficacy. Most synapses are located on dendrites, whose passive and active electrical properties can distort recorded signals arising from remote synapses. These distortions are avoided at certain central synapses, such as that between the endbulbs of Held and bushy cells in the cochlear nucleus, where the glutamate-releasing presynaptic terminals of cochlear nerve fibres direct contact the bushy cell soma. Whole cell patch clamp recordings of eEPSCs were made from bushy cells (n=113) in cochlear nucleus slices obtained from postnatal day (P) 4-21 rats anaesthetised with sodium pentobarbitone (20 mg/kg i.p.), in order to investigate pre- and postsynaptic factors contributing to developmental changes in synaptic efficacy.

Postsynaptic changes: At endbulb-bushy cell synapses, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated single fibre evoked EPSCs (eEPSCs) increase in amplitude with age while N-methyl-D-aspartate receptor (NMDAR)-mediated eEPSCs decrease in amplitude and decay time constant. The functional characteristics of AMPARs and NMDARs depend on subunit composition. NMDARs with NR2B subunits have high Ca^{2+} permeability and long decay time constant, are typically more common in neonatal brains and may play an important role in synapse development. We investigated developmental changes in subunit composition of postsynaptic receptors using subunit-specific antagonists. Ifenprodil (10μM), an NR2B subunit-selective NMDAR antagonist, reduced NMDAR eEPSC amplitude to 24±3% (mean±SEM, n=13) of control in P4-8 rats, significantly greater than NMDAR EPSC reduction in P10-17 rats (40±4% of control, n=13) suggesting that NR2B subunits are exchanged during development to probably NR2A subunits. Pentobarbitone (100 μM), which selectively inhibits AMPARs containing GluR2 subunits, reduced AMPAR EPSC amplitude in P4-6 rats to 51±2% of control (n=4), to 73±5% (n=3) at P8-11 and to 40±14% (n=3) in P12-15 rats. The intracellular polyamine spermine blocks Ca^{2+}-permeable AMPARs lacking GluR2 subunits at positive voltages. After inclusion of spermine (100μM) in the electrode solution, the mean rectification index (RI) of AMPAR EPSC I-Vs increased with age (P4-6, RI=1.2±0.5 (n=5), P7-11, RI= 4.5±0.5 (n=8), P12-15, RI= 5.6±0.8 (n=10). suggesting that AMPARs in older animals are likely to lack GluR2 subunits and be more Ca^{2+} permeable.

Presynaptic changes: Paired stimuli at 5-140 ms caused marked facilitation of 2^{nd} eEPSC amplitude at P4-7 (mean ratio±SEM at 10 ms = 1.7 ± 0.1, n=17), marked depression at >P11 (0.6±0.05, n=17), and a mixture of facilitation and depression at P8-10 (1.0±0.15, n=18). Depletion of the synaptic vesicle pool by 10 stimuli at 100 Hz caused eEPSC amplitude depression at all ages (P4-7, 0.03±0.04, n=7; P8-10, 0.02±0.03, n=6; >P11, 0.13±0.08, n = 13). Recovery from depletion was similar at short delays but slower at >P11 for longer delays. Varying external Ca^{2+} caused larger changes in eEPSC amplitude and paired pulse ratio at ages <P11, indicating that sensitivity of synaptic release to external Ca^{2+} altered with development.

Conclusions: These data suggest that presynaptic factors regulating Ca^{2+}-sensitive synaptic release and short term plasticity, and that subunit composition of postsynaptic AMPARs and NMDARs can be rapidly modified during synaptic development. It is proposed that Ca^{2+} influx through NMDA receptors may contribute to these developmental changes, so to increase synaptic efficacy with large and rapid AMPA responses at mature synapses.