

P013 Probing the NR2B subunit in the rodent and human CNS with novel defined pharmacological and immunological tools
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The NMDAR2B subunit is the focus of increasing interest as a therapeutic target in a wide range of CNS pathologies. Due to significant pharmaceutical endeavour, an impressive collection of chemical series has been developed, which targets the NR2B subunit. The apparent superior preclinical and clinical data for the second and third generation NR2B compounds is likely to reflect subtype selectivity, a unique mode of action and cellular location of the NR2B receptors in the CNS. In immunohistochemical studies probing rodent and *human* hippocampus and cortex, the pattern of NMDAR NR2B subunit-like immunoreactivity paralleled almost exactly that determined for the NR1 subunit in both brain structures. Interestingly, it also showed considerable overlap with that found for NR2A. We have provided evidence for two distinct classes of NR2B-directed NMDA receptor antagonists, one which binds with high affinity irrespective whether another NR2 subunit type is present (Ro-25,6981), and a second class which is affected significantly by the presence of another NR2 subunit type within the receptor complex, exemplified by CP-101,606. These will *define*, for the first time, the contribution of distinct NR2B-containing NMDA receptor subtypes in mammalian brain physiology, and human CNS pathologies.