The A, B, C and D of NMDA receptor modulation

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N-Methyl-D-aspartate (NMDA) receptors are a member of the ionotropic glutamate receptor family of ligand-gated ion channels that mediate the majority of excitatory neurotransmission in the mammalian CNS. They are expressed primarily in the CNS but also in peripheral locations such as pancreatic islet cells, sensory nerve terminals in skin and cardiac ganglia. Seven subunits of the NMDA receptor have been identi_ed, NR1, NR2A-D and NR3AB2, they assemble as a tetramer consisting of two NR1 subunits and either two NR2 subunits or a combination of NR2 and NR3 subunits. Activation of NMDA receptors requires the simultaneous binding of glutamate and glycine. Calcium entry through NMDA receptors plays an important role in development and synaptic plasticity and is proposed to underlie higher processes such as learning and memory. It is also proposed to play a role in a number of neurological diseases such as epilepsy and Alzheimer's. Indeed, memantine is an NMDA antagonist which has been approved for the treatment of moderate to severe Alzheimer's. NMDA antagonists may also be targets for the treatment of neuropathic pain, major depression and Parkinson's disease.

We present data of NMDA receptor combinations NR1 with either NR2A, 2B, 2C or 2D expressed in HEK cells recorded on a high throughput automated patch clamp system. NMDA-mediated responses were elicited using glutamate and glycine. Mean current amplitudes varied from -127 ± 9 pA for NR1/NR2C (n = 188), -288 ± 21pA for NR1/NR2D (n = 191), -1.72 ± 0.19 nA for NR1/NR2A (n = 360) and -2.99 ± 0.33 nA for NR1/NR2B (n = 372) receptor combinations. The currents mediated by NR1/NR2A were potentiated by pregnenolone sulfate with an EC of approximately 40 µM (n = 284). NR1/NR2B-mediated currents were potentiated by spermine with an EC of 134 µM (n = 290) and blocked by ketamine with an IC of 2.26 ± 0.38 µM (n = 321). The currents mediated by NR1/NR2C and NR1/NR2D were potentiated by CIQ with an EC of 4.3 µM (n = 169) and 5.5 µM (n = 149), respectively. Interestingly, we could detect di□erences in potency of compounds such as ifenprodil on NR1/NR2A versus NR1/NR2B containing receptors. In addition to NMDA expressed in cell lines, we have also investigated the presence of NMDA receptors in stem cellderived neurons. Glutamate (in combination with glycine) was used to elicit NMDA-mediated responses using automated patch clamp and MEA. In this way, we could record whole cell patch clamp data and compare this with extracellular field potential recordings in intact neuronal networks of stem cellderived neurons.