Session 396 - NMDA Receptors II

396.11 / E6 - Characterisation of two NMDA NR2B subunit (grin2b) antagonists across tests of impulsivity and attention

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Abstract
NMDA NR2B subtype selective antagonists are currently in clinical development for a variety of indications, including major depression. We previously reported the selective NR2B NMDA antagonists Ro 63-1908 (Ro) and traxoprodil, increased premature responding in a rat 5-choice serial reaction time task (5-CSRTT) suggesting an effect on impulsive action (Higgins et al (2005) Psychopharmacology 179: 85-98). The present studies extend these investigations to a Go-NoGo and delay discounting task, and the 5-CSRTT under test conditions of both regular (5s) and short (2-5s) multiple ITI. Dizocilpine was included for comparison. Male Long-Evans rats were used in all experiments. Both Ro 63-1908 (0.1-1mg/kg SC) and traxoprodil (0.3-3mg/kg SC) increased premature and perseverative responses in both 5-CSRT tasks and improved attention when tested under a short ITI test condition (e.g. premature: vehicle: 11.8$\pm$2.6 responses, Ro 1 mg/kg: 68.3$\pm$17.6 responses; P<0.01). Ro 63-1908 but not traxoprodil increased motor impulsivity (false alarms) in a Go-NoGo task (vehicle: 8.1$\pm$1.5 responses, Ro 1 mg/kg: 14.3$\pm$2.5 responses; P=0.02). Dizocilpine (0.01-0.06mg/kg SC) affected both measures of motor impulsivity and marginally improved attention. In an ascending delay discounting test of impulsive choice, both dizocilpine and Ro 63-1908 decreased impulsive choice (i.e. increased choice for the larger, delayed reward), while traxoprodil showed a similar trend (e.g. AUC measure: vehicle: 1006$\pm$167 units, Ro 1 mg/kg: 1358$\pm$199 units; P<0.01). Motor stimulant effects were evident following Ro 63-1908 (0.3-3 mg/kg SC), but not traxoprodil (1-10 mg/kg SC) treatment - although no signs of motor stereotypy characteristic of dizocilpine dose (>0.1 mg/kg) were noted. The findings of both NR2B NMDA antagonists affecting measures of impulsive action and compulsive behavior may underpin emerging evidence to suggest glutamate signaling through the NMDA NR2B receptor plays an important role in behavioural flexibility (e.g. Holmes et al (2013) Nature Neurosci. 16: 1101-1110.). The profiles between Ro 63-1908 and traxoprodil were not identical, perhaps suggesting differences between members of this drug class on behaviour.