**Development of a GPR52 agonist as a novel therapeutic for schizophrenia**

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**Introduction.** GPR52 is an orphan G protein-coupled receptor which is highly expressed in the striatum and has been proposed as a novel target for schizophrenia. Its localisation on striatopallidal neurons, where it is thought to functionally oppose D2 signalling, highlights the potential of a GPR52 agonist to treat the positive symptoms of schizophrenia. GPR52 is also co-localised with dopamine D1 receptors on cortical pyramidal neurons, where agonism of the receptor could improve cognition by indirectly potentiating D1 signaling in the prefrontal cortex. NXE0041178 is a selective GPR52 agonist with excellent preclinical pharmacokinetic properties (Poulter et al, 2025).

**Aims**. We explored whether NXE0041178 could modulate corticostriatal signaling in ex vivo rat brain slices and demonstrate pharmacodynamic effects in preclinical models which would support its progression as a potential treatment for schizophrenia.

**Methods**. Whole-cell patch-clamp recordings from striatal spiny projection neurons and extracellular field-potential recordings were made in the presence of 10 μM NXE0041178 using coronal corticostriatal slices from male Sprague-Dawley rats. Reversal learning was tested following NXE0041178 administration (1-30 mg/kg, PO) in female Lister Hooded rats previously treated with PCP (2 mg/kg, IP) twice daily for 7 days. Hyperlocomotor responses to d-amphetamine (0.5 mg/kg, SC) and caffeine (15 mg/kg, SC) were explored in male Sprague-Dawley rats following 60 minutes pre-treatment with NXE0041178 at doses ranging from 1 to 30 mg/kg, PO.

**Results.** Corticostriatal synaptic transmission was significantly reduced in the presence of NXE0041178 when assessed with both intracellular patch clamp recording and extracellular field recording. NXE0041178 reversed the subchronic PCP-induced reversal learning deficit and psychostimulant-induced hyperlocomotion in rats across a range of doses.

**Discussion.** NXE0041178 was found to modulate corticostriatal signaling, improve cognitive performance in the subchronic PCP rat model and block psychostimulant-induced hyperlocomotion in rodents, thereby supporting GPR52 agonism as a novel approach to treat multiple symptom domains in schizophrenia.

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