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Altered sensory processing in response to novel DREADD-induced inactivation of GABA in pedunculopontine tegmental nucleus

Background: Sensory processing deficits are associated with certain psychiatric illnesses, such as schizophrenia and autism spectrum disorder (ASD). Sensory filtering and sensorimotor gating are evolutionarily conserved preattentive responses that filter and block redundant sensory stimuli that would otherwise overwhelm our brains. To date, underlying mechanisms of these deficits are undefined. Prepulse inhibition (PPI) of the acoustic startle response (ASR) is a behavioural measure of sensorimotor gating and reflects neural filtering of unnecessary stimuli. PPI occurs when an acoustic stimulus of relatively weak intensity diminishes the ASR of a subsequent acoustic pulse of higher intensity.

Lesions of the midbrain pedunculopontine tegmental nucleus (PPT) disrupt PPI. The PPT is comprised of a heterogeneous collection of neurons, namely, cholinergic, glutamatergic, and GABAergic neurons. We predict GABAergic neurons of the PPT play a fundamental role in PPI of the ASR, which have been overlooked in prior studies.

Methods: In the current study, we delivered a novel GABA-targeting DREADD (designer receptors exclusively activated by designer drugs) virus into the PPT of rats, and subsequently quantified PPI of the ASR in response to chemogenetic inactivation of PPT GABAergic neurons.

Discussion: We predict that this novel recombinant adeno-associated virus (rAAV) will inhibit PPT GABA and will disrupt PPI of the ASR. Our study will denote the effectiveness of this novel DREADD approach, provide a deeper mechanistic understanding of sensory processing deficits, and shall clarify the role of PPT GABAergic neurons in PPI of the ASR.

Interdisciplinary Reflection: Understanding mechanisms of disrupted animal behaviour, and combining that with human psychiatric research will aid in drug development to cure devastating neuropsychological diseases.