Impact of *OPRM1* A118G on synaptic transmission in both human and mouse neurons

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The A118G Single Nucleotide Polymorphism (SNP) in *OPRM1* gene causes the replacement of asparagine with aspartate at position 40 (N40D) of the mu opioid receptor (MOR) and is hypothesized to be associated with drug and alcohol use disorders. However, the mechanism by which this gene variant contributes to addiction disorders is largely unknown. To address this, we used isogenic human stem cell lines carrying A118G gene variants as well as a knock-in mouse model A112G, which are heterologous variants of A118G in humans, to conduct synaptic physiology analysis. We found that in N40 and D40 inhibitory-induced neuronal (iN) cells, DAMGO dose-dependently suppressed synaptic release and neuronal excitability; however, the DAMGO mediated suppression on inhibitory synaptic transmission was significantly stronger in D40 MOR human iN cells. In the A112G mouse model, we focused on the modulatory effects of DAMGO on excitatory and inhibitory inputs to ventral tegmental area (VTA) dopaminergic (DA) neurons projecting to the Nucleus Accumbens medial shell (mAcb sh). We found that DAMGO suppressed both inhibitory and excitatory input in VTA-to-mAcb sh projecting neurons and this effect was stronger in AA118 than GG118 OPRM1 mice. We postulate that the differential effects caused by the N40D SNP could be mediated by differential expression of MORs or altered downstream signaling, whereas species-specific discrepancies can come from 1) different maturation stages in iN cells vs. mature mouse neurons or 2) complexity of 2D isolated human neuronal culture vs. mouse brain slices with intact local VTA circuitry. Currently we are in the process of determining the mechanism by which the N40D SNP impacts synaptic transmission and the cause for differential regulation mediated by MOR variants in mouse vs. human, which we expect will give greater insight into the fundamentals of opioid receptor signaling.