In vitro characterisation of novel GPR55 agonists with nanomolar human and rat potency and differential desensitisation profile

R Hewer, L Christie, M Roberts, T Cheung, K Doyle, L Dickson, X Xu, K Page, N Brice, L Dawson, M Carlton, R Bürli
Cerevance Ltd, Cambridge UK

Using Cerevance's NETSseq discovery platform, we performed an in-depth cell type-specific transcriptomic analysis from multiple human brain regions and identified GPR55 as a receptor specifically expressed in striatal medium spiny neurons (MSN) and downregulated in tissue from donors with Parkinson's disease (PD) when compared to non-neurodegenerative disease control donors. We hypothesised that GPR55 signalling would reduce PD-induced MSN excitability and potentially improve Parkinsonian-related imbalances in striatal neurocircuitry. Due to the absence of GPR55-selective activators with both human and rodent activity, we performed a HTS campaign to identify novel GPR55 activators. We generated a robust screening cascade, enabling hit confirmation and further optimization. In addition, we characterised the downstream signalling pathways resulting from GPR55 activation. The desensitisation potential of compounds was examined using beta-arrestin recruitment assays and correlated with functional receptor desensitisation observed in calcium flux assays. Potent (nM) lead molecules were evaluated using patch-clamp electrophysiology in rodent MSNs; as hypothesised GPR55 activation decreased the frequency of MSN firing. We have identified the first highly potent human and rat GPR55 activators that can be used to further understand the role of GPR55 in the brain and disease.