**Assessment of novel ago-PAMs of the cannabinoid CB1 receptor in mouse models of intractable epilepsy**

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**Background and aims:**Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare childhood intractable epilepsies, characterized by treatment-resistant seizures and associated developmental deficits. Registration of cannabidiol (CBD) for these syndromes motivates research interests on targeting cannabinoid system for anti-seizure drug development. Orthosteric agonistic targeting cannabinoid receptors displays anticonvulsant effects. In addition, engaging allosteric site of cannabinoid 1 receptors (CB1) offers pharmacological advantages to avoid intoxicating effects induced by orthosteric binding. A novel class of allosteric agonists with positive allosteric modulators (ago-PAMs) can magnify the actions of the endogenous ligands via increasing their binding affinity or efficacy. We aimed to evaluate the anti-seizure profiles of two CB1 receptor ago-PAMs, GAT591 and GAT1102.

**Methods:** Antiseizure activity was assessed against hyperthermia-induced seizures in a *Scn1a+/-*mouse model of Dravet syndrome. We then elaborated on the most promising compounds in the maximal electroshock (MES) test in mice and the *Gabrb3+/D120N*mouse model of Lennox-Gastaut syndrome.

**Results:** GAT591 and GAT1102 exhibited anti-seizure effects against hyperthermia-induced generalised tonic-clonic seizure (GTCS) in *Scn1a+/-*mice, with GAT1102 displaying greater potency than GAT591 at a lower effective dose. Additionally, GAT1102 was also effective in protecting mice against MES-induced GTCS, whereas GAT591 did not show similar effects. Despite its robust anti-seizure activities against GTCS, GAT1102 increased the number of atypical absence seizures in the *Gabrb3+/D120N* mice.

**Conclusion:** Collectively, these results show that GAT591 and GAT1102 have treatment potential for febrile seizures in Dravet syndrome but not in the Lennox-Gastaut syndrome model.