Second International Calcium Channel Conference - Placencia, Belize
March 28 – April 2, 2010

Novel T-type blockers identified in $Ca_V3.2$ state-dependent fluorescent assay effectively suppress seizures

Elizabeth Tringham[1], Kristy Kuplast[2], Janette Mezeyova[1], Emma Braine[3], Stuart Cain[4], Manjula Weerapura[1], Cyrus Eduljee[1], Xinpo Jiang[1], Paula Smith[1], Jerrie-Lynn Morrison[1], Kim Powell[3], Nigel Jones[3], David Parker[1], Hassan Pajouhesh[1], Terence J O'Brien[3] and Terrance Snutch[4]

[1]*Neuromed Pharmaceuticals Limited, 301-2389 Health Sciences Mall, Vancouver, BC, Canada*
[2]*Epizyme Incorporated, 840 Memorial Drive, Cambridge, Massachusetts, USA*
[3]*Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, 4th Floor, Clinical Sciences Building, Royal Melbourne Hospital, Royal Parade, Parkville, Victoria, 3050 Australia*
[4]*Michael Smith Laboratories, 219-2185 East Mall, University of British Columbia, Vancouver, BC, Canada*

Epilepsy is a complex disorder of spontaneous recurrent seizures where voltage-gated ion channels are favored as drug targets as they are essential for the initiation and propagation of neuronal firing and are likely to be involved in seizure generation and maintenance. In particular, T-type calcium (Ca^{2+}) channels have been implicated in the pathophysiology of absence epilepsy and other seizure types as well as the mechanism of action of anti-absence drugs. Current treatments for absence epilepsy, such as exthosuximide and valproate, are believed to act via GABA receptors, sodium channels and Ca^{2+} channels, however, the contribution of Ca^{2+} channels to the method of action of the existing absence treatments is still somewhat unclear. To assess the role of T-type channels in different seizure types, novel, selective T-type Ca^{2+} channel antagonists, NP169941 and NP169944 were identified in a state-dependent fluorometric imaging plate reader assay and their effects confirmed on exogenously expressed $Ca_V3.2$ and native T-type calcium channels. Further, we demonstrate that these compounds have a potent effect in-vivo by suppressing absence seizures in the Genetic Absence Epilepsy Rats from Strasbourg and correlated this with effects on neuronal burst firing in-vitro. These novel blockers significantly slowed the cycle frequency of the SWDs in GAERS, in contrast to the effect of ethosuximide and valproate, indicating a differential action on the thalamocortical to current absence treatments. NP169944 also suppressed seizures in 100 % of animals tested in the 6 Hz and MES mouse models with an ED_{50} of 102 mg/kg and 59 mg/kg respectively.