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FINAL REPORT

Project / Program Title		Electrophysiological, Molecular Biological and Computational Investigation of Sodium Channel Modulation by Antiepileptic Drugs
Name		Dr Christopher French
Award Received		2015 Thyne Reid Foundation Career Development Fellowship
Report Date		31 July 2018
Chief Investigator / Supervisor		Dr Christopher French
Administering Institution		The Royal Melbourne Hospital
Funding Period	Start Date:	1 January 2015
	Finish Date:	31 December 2015

PROJECT SUMMARY

Antiepileptic drugs, while effective in may cases, still fail to suppress seizures in about a third of patients. There is a great need to understand the precise mechanism by which existing medications exert their effect before better ones can be produced. This study has cast new light on how common drugs like phenytoin affect their main brain targets. Additionally, a method to assess what drug combinations are more likely to be effective using a “brain in a petri dish approach” has been developed that could potentially greatly enhance how physicians choose existing drugs to treat seizures.

PROJECT AIMS / OBJECTIVES

Several aims were proposed

1) Phenytoin does nor affect the process of “fast inactivation” in sodium channels – this was demonstrated experimentally and reported in Zheng et al 2016; it affects a new form of inactivation termed “intermediate” discovered in these experiments (see French et al, 2015) and slow inactivation

2) The binding site for phenytoin is most likely different from the current consensus site, and is likely to be in the extracellular voltage sensor region – see Zheng et al 2016, Boiteux et al 2014, Boiteux et al 2016,

3) An additional aim was later developed, to see if relative efficacy of drug combinations for epilepsy could be assessed in vitro – this proved to be the case – see Taing et al, 2017

SIGNIFICANCE AND OUTCOMES

We have shown i) that sodium channel modulators such as phenytoin a) have novel effects on slow inactivation in sodium channels, as opposed to the previous hypothesis that these drugs affected “fast” inactivation. Ii) We have also shown that the binding site for these drugs is likely to be extracellular, rather than intracellular, which has considerable implications for drug design. Iii) we have shown that it may be possible to evaluate drug combination efficacy in vitro, which could potentially be used to guide clinical drug prescription and improve seizure control in epileptic patients.

PUBLICATIONS / PRESENTATIONS

Publications

- Boiteux, C., Vorobyov, I., French, R. J., French, C., & Yarov-yarovoy, V. (2014). Local anesthetic and antiepileptic drug access and binding to a bacterial voltage-gated sodium channel. Proceedings of the National Academy of Sciences, 111(36), 13057–13062. http://doi.org/10.1073/pnas.1408710111 (published after RACP grant proposal submitted)
- Taing, K. D., O’Brien, T. J., Williams, D. A., & French, C. R. (2017). Anti-Epileptic Drug Combination Efficacy in an In Vitro Seizure Model – Phenytoin and Valproate, Lamotrigine and Valproate. Plos One, 12(1),
- French, C. R., Zeng, Z., Williams, D. A., Hill-Yardin, E. L., & O’Brien, T. J. (2015). Properties of an Intermediate-duration Inactivation Process of the Voltage-gated Sodium Conductance in Rat Hippocampal CA1 Neurons. Journal of Neurophysiology, (November 2015)
- Zeng, Z., Hill-Yardin, E. L., Williams, D. A., O’Brien, T. J., Serelis, A., & French, C. R. (2016). The Effect of Phenytoin on Sodium Conductances in Rat Hippocampal CA1 Pyramidal Neurons. Journal of Neurophysiology,
- Celine Boiteux, Chris French, Toby W. Allen (2016) Modulation of a Bacterial Voltage-Gated Sodium Channel by the Anti-Epileptic Drug Lacosamide Biophysics Journal Volume 110, SPECIAL ISSUE 3, 111a, February 16, 2016
- Submitted Wong et al “A functional in vitro model of brain tumour growth in organotypic slice cultures” J Neurosci Methods

Abstracts/Posters

- Kim DT, French CR Anti-epileptic Drug Combination Interactions in an In Vitro Seizure Model’ Australian Epilepsy Society 2015, Scientific Award;
- French CR A Simplified Model of Direct Interaction with Sodium Channel Voltage Sensors Explains Apparent State Dependency of Phenytoin and May Suggest Novel Binding Sites Australian Epilepsy Society 2015
- Taing, KD et al Sodium Valproate Enhances Inhibition in an In Vitro Seizure Model Australian Epilepsy Society 2016
- French CR, Chong H, An In-Vitro Brain Tumour Preparation for Modelling Tumour-induced Epilepsy Australian Epilepsy Society 2016
- French CR Computer Modelling of Seizure Suppression by Phenytoin on Epileptic Networks Using a Novel Model Incorporating a Direct Voltage-sensor Interaction Epilepsy Australian Epilepsy Society 2016

- French CR Nav Inhibition by Phenytoin Explained by Voltage Sensor Interaction; Gordon Conference “Mechanisms of Epilepsy & Neuronal Synchronization “ 2016
- French CR “How do Drugs Cause Seizures as Side Effects?” oral presentation, RMH research Week 2016
- French CR “An In Vitro Brain Tumour Model for Tumour-associated Epilepsy” Acquired Epileptogenesis' Symposium KMB Feb 6 2017
- French CR “An In Vitro Brain Tumour Model for Tumour-associated Epilepsy” “Epilepsy Melbourne” Symposium, 2017
- French CR “Some Basic research Approaches to Clinical Epilepsy Questions” RMH research Week oral presentation, 2017
- French CR “Modulation of the Voltage Gated Sodium Channel by Antiepileptic Drugs-Review of the Binding Site and Mechanisms of Action” University of Pittsburgh, Department of Computational and Systems Biology, July 2018