Modified intrinsic excitability in transgenic mouse models of progressive beta-amyloidopathy

https://www.neurodegenerationresearch.eu/survey/modified-intrinsic-excitability-in-transgenic-mouse-models-of-progressive-beta-amyloidopathy/

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Country

United Kingdom

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Modified intrinsic excitability in transgenic mouse models of progressive beta-amyloidopathy

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Research Abstract

Alzheimer’s disease (AD) is the major cause of dementia in the elderly. Our laboratory is interested in characterising neurophysiological deficits that arise in AD and understanding their causal mechanisms. To do this we apply a variety of electrophysiological methods to study of pre-clinical animal models of AD-related pathology. Much of our work employs transgenic mice which over-produce Abeta peptides, molecules that are widely believed to play a crucial role in the pathophysiology of AD. In recent years, work with such mice, by ourselves and others has

begun to reveal significant disturbances to synchronous network activity in the cortex and hippocampus, brain structures with crucial roles in cognitive function. In vivo EEG recordings reveal network hyperexcitability in these areas, which in some laboratories resembles epileptic activity. It is proposed that these disturbed patterns of network activity are likely to contribute to cognitive dysfunction in AD. As well as performing our own in vivo recordings, we have been investigating cellular level neurophysiological factors that could be the cause of these disturbed patterns of neuronal activity. Our work has focussed on modifications to intrinsic neuronal excitability, an aspect of neurophysiology well known to contribute to network hyperfunction in epilepsy. Using patch clamp recording from CA1 pyramidal cells in hippocampal slices, we have identified robust changes to intrinsic neuronal excitability and action potential waveforms in 2 different Abeta overproducing mouse lines. We also used nucleated macropatch recordings to identify a ~50% loss of voltage-gated sodium currents from the cell bodies of these neurones; potassium currents were, in contrast, entirely unaltered. All of these changes were absent in young animals, and their presence seems to parallel Abeta burden since they arise earlier in the more aggressive PSAPP double transgenic line. This application requests funding to follow up these findings in much greater detail. Our goals include: 1) Generating a more detailed understanding of the timecourse with which both altered excitability and sodium current depression arise. 2) Determining if similar changes to those observed in pyramidal cells occur in GABAergic interneurones. 3) Establishing if the changes to either excitability and/or Na+ channels can be reversed by pharmacological interventions that reduce CNS amyloid load. 4) Using dynamic clamp to establish if altered sodium current levels are solely responsible for the altered intrinsic excitability. 5) Examining if related changes to excitability and ion channels levels are seen in the axonal or dendritic compartments.

Further information available at:

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