A powerful new Alzheimer's disease model

Karl Herrup, Professor of Neurobiology
Ryad Benosman, Professor of Ophthalmology

Motivation

- The last new drug for Alzheimer's was approved in 2003
- Dozens of clinical trials for new compounds have failed
- We badly need new disease models
  - To understand the biology
  - To link Alzheimer's to the aging process
  - To identify the targets for therapeutic intervention

Project Description

- The project combines the bioengineering expertise of the Benosman lab with the cell biological resources of the Herrup lab
  - Cortical neurons will be grown on multielectrode arrays to establish neuronal networks in a dish
  - A lenti virus will drive the expression of the Amyloid Precursor Protein (APP)
  - The response of the network to the changes in the axon initial segment will be monitored

Context

- The genetics of Alzheimer's identifies APP as a disease gene.
- The field has assumed that the genetics meant that the beta-amyloid fragment of APP was driving Alzheimer's disease
- We will test the alternative hypothesis that APP by way of its effect on the axon initial segment is the true driver of the disease

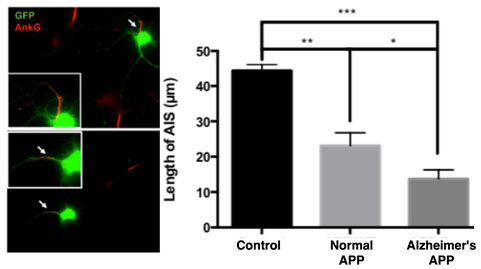

Figure. Elevated APP protein shortens the initial segment

The figure above shows the preliminary data supporting the shorten of the axon initial segment after APP expression. The change would be predicted to make the neuron harder to fire and thus reduce network activity.

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We propose to use the network properties of cultured neurons to identify the forces driving the Alzheimer's disease process

Project Deliverables

- Establish conditions for culturing neurons on the microelectrode array.
- Define the ground state behavior of the neural networks
- Determine the effects of wild type and mutant APP expression on the network
- The preliminary data will be a springboard of preliminary data for competitive grant applications to NIH and NSF
  - The network properties will serve as an advanced drug screening platform
  - The network changes we observe will be validated in living animals
  - The predicted changes in the axon initial segment will be charted in human brain

Potential Impact

- Our disease models of Alzheimer's disease have proven to be nearly worthless in interpretive and predictive value
- Proving the validity of our new model of APP function will offer a fresh and useful area to target new drugs and therapies.

References and/or Acknowledgements

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