OIST OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY

Seminar by:

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DATE: Tuesday, February 17, 2015
TIME: 13:00-14:00
VENUE: Seminar Room B503, Level B, Lab 1

TITLE:

Dopamine neurons, synapses and susceptibility in Parkinson's disease

ABSTRACT:

Genes, protein aggregates, environmental toxins and other factors associated with Parkinson's disease (PD) are widely distributed in the nervous system and affect many classes of neurons. Theories that explain the loss of dopamine neurons in Parkinson's disease (PD) must account for the fact that a consistent feature of PD is the exceptional and selective vulnerability of dopamine neurons of the substantia nigra pars compacta (SNc). It is this sub-population of dopamine neurons, among all the different sub-types of dopamine neurons, and indeed all other neurons in the brain, that are the most sensitive to dying in PD. Furthermore, it is this population of dopamine neurons that shows greatest sensitivity to toxins, even general mitochondrial poisons like rotenone and greatest sensitivity in genetic forms of PD. What is it about these neurons that makes them so susceptible in PD? Although there are molecular differences between susceptible and non-susceptible dopamine neurons, there is very little difference in the electrical activity and afferent synapses of different populations of dopamine neurons in the SNc that could account for differential susceptibility (Brown et al 2009; Henny et al 2012). However, the axon and synaptic output of SNc dopamine neurons are remarkably different to other populations of dopamine neurons and to all other neurons in the brain. Individual dopamine neurons give rise to hundreds of thousands of synapses in their target region in the striatum where their connections are not targeted but provide a massive and dense network (Moss & Bolam 2008, 2010). This is an order of magnitude greater than other types of dopamine neurons and several orders of magnitude greater than other neuron types in the brain. Single-cell filling by Matsuda and colleagues (2009) are consistent with this proposal. They have shown than the total axon of an individual SNc dopamine neuron in the rat can be up to 78 cm in total length (mean length 46.6 cm). We propose that this massive axonal arbour, which is probably an order of magnitude even greater in humans (about 1 million synapses), will put a high energetic demand on the neurons for normal cell biological functions and, more importantly, the generation and propagation of action potentials and the subsequent recovery of the membrane potential. Any stressor, e.g. oxidative stress, genetic mutations, mitochondrial poisons or dopamine neurotoxins, will have a preferential effect on these neurons because they are energetically 'on-the-edge' and the perturbations leading energy demand out-stripping supply, die-back and eventual cell death (Bolam & Pissadaki 2012).

In order to address this hypothesis we have used a computational approach. We generated a biology-based computational model of the axons of individual dopamine neurons and examined the energetic impact imposed on SNc dopamine neurons by their extensive, unmyelinated axonal arbour. We attempted to calculate the energy cost of action potential propagation throughout the large axonal arbours (Pissadaki & Bolam, 2013). The main finding is that the energy demand associated with action potential conduction is related in a supra-linear manner to the axonal size and complexity. We concluded that there is an exponentially higher energy demand of large axons (equivalent to rat SNc neurons) compared to smaller axons (equivalent to rat ventral tegmental area dopamine neurons). Thus those neurons that show a greater vulnerability have a disproportionately greater energy cost for action potential propagation. This higher energy demand of their massive and complex axonal arbours, together with unique molecular features, may underlie their selective vulnerability in Parkinson's disease.

REFERENCE:

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