Research Briefings

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Neuronal circuits and computation

A SINGLE NEURON IN THE BRAIN CAN RECEIVE SIGNALS SIMULTANEOUSLY FROM TENS OF THOUSANDS OF UPSTREAM NEURONS. TO INVESTIGATE THE COMPUTATIONS NEURONS CARRY OUT AS THEY RESPOND TO THESE SIGNALS, WE USE CELL-TYPE SPECIFIC MANIPULATIONS OF GENE EXPRESSION, ELECTROPHYSIOLOGY, BEHAVIOURAL EXPERIMENTS AND COMPUTATIONAL MODELING. BY UNDERSTANDING NEURONAL COMPUTATIONS WE HOPE TO DEVELOP NEW APPROACHES TO TREATMENT OF NEUROPSYCHIATRIC DISORDERS.

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The billions of neurons found in the brain can be divided into many different types, each specialized to perform a particular function. To understand the healthy brain and to develop new approaches to treatment of neuropsychiatric disorders, it is important that we understand how each neuronal cell type responds to signals it receives from upstream neurons.

Cell-type specific computation

We focus on ion channels that control the way a neuron responds to signals from upstream neurons (Figure 1). We are particularly interested in an ion channel called HCN1, which is found in brain areas important for memory. We previously found that the HCN1 ion channel has distinct roles in experimental models of motor and conscious memory (Nolan et al., 2003, 2004). We also found distinct computational roles for these channels in the different neuronal circuits responsible for each type of memory. These studies demonstrate that the functions of molecules that control responses to synaptic input depend upon the cell-type specific context in which they are expressed.

Very recent evidence suggests that deficits in HCN1 signaling could be important in epilepsy and schizophrenia. However, it is not known if HCN1 channels play causal or compensatory roles in either disorder, or how distinct functions of HCN1 channels in different cell-types will affect symptoms or treatment of either disorder. We are now investigating cell type specific roles of HCN1. Our long-term goal is to establish general principles whereby ion channels expressed by particular neuronal cell types contribute to normal cognitive function and to nervous system disorders.

Tuning neuronal computation

We recently found that within a population of neurons of the same type, responses to synaptic inputs are tuned to the information that each neuron encodes during behaviour (Garden et al., 2008). It's well known that there are distinct morphological and biophysical classes of neuron, which also have distinct molecular

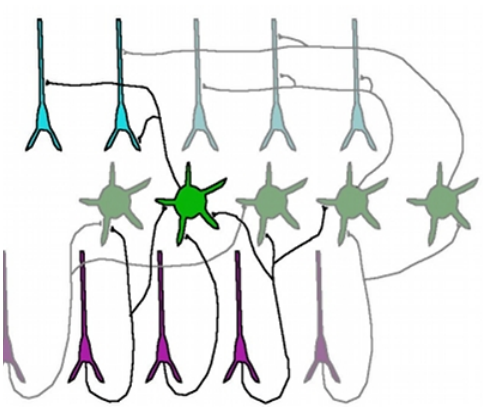

Fig 1.Neuronal computation. In this cartoon, the highlighted green neuron receives signals from three neurons (purple) and sends an output to two neurons (blue). The computational rules used by the green neuron determine its influence on the blue neurons. For example, the green neuron may produce an output when any of the purple neurons are active. Alternatively, the green neuron might only produce an output when all three purple neurons are active at the same time.

profiles. Our new data suggest that superimposed on the mechanisms that define distinct types of neuron, are additional mechanisms that tune the properties of neurons according to their specific functional role.

These results raise questions about how such tuning arises, what the consequences are for behavior and whether deficits in tuning provide plausible explanations for puzzling neural circuit disorders, such as schizophrenia and autism. We are now carrying out experiments to begin to address these questions

Molecular tools

The ability to manipulate specific molecules in well defined populations of neurons will be important to understand neuronal function and to develop treatments for nervous system disorders. To address this goal we are developing viral vectors to knock-down or over-express ion channels expressed in specific populations of neurons (Figure 2). We are then able to make electrophysiological recordings from single neurons in which these specific manipulations are used to modify computations the neuron can carry out.

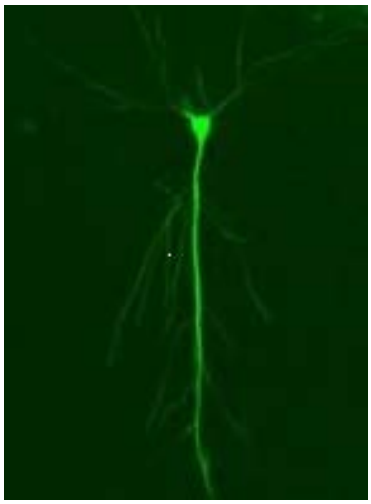

Fig 2. Introducing new genes into neurons using viruses. This neuron has been infected with a virus that expresses a yellow fluorescent protein that is used to identify the neuron. We are using similar methods to express novel transgenes in neurons and to knockdown native genes

Computational tools

To develop a rigorous understanding of experimental results and to drive future studies, we routinely combine experimental studies with theoretical models. However, most current models account only for the average activity of the greater than one million ion channels found in a single neuron, while accurate simulation may require that activity of each individual channel is accounted for. To address this we recently developed new computational tools that enable the activity of all of the individual ion channels within a single neuron to be simulated in realistic models that fully account for neuronal morphology (Figure 3). Further details are available from the project website (www.psics.org).

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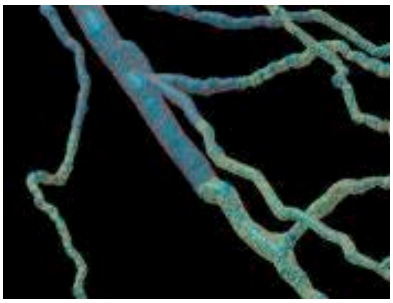

Fig 3. A model neuron. The close up image of a simulated neuronal dendrite shows the location of individual ion channels. Software that we have developed enables activity of all of the ion channels distributed across a neuron's processes to be simulated.

Selected References

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