

Chair's introduction

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This meeting comes at an exciting time. Neuroscientists are beginning to realize that we have overlooked half the brain! This is the part of the brain composed of non-neuronal cells: myelinating glia, astrocytes and microglia. For far too long neuroscientists had an artificially narrow conceptual view of the nervous system. I love the following quote from Robert Pirsig's book *Zen and the Art of Motorcycle Maintenance*: "The truth comes knocking on the door. And you say "Go away. I'm looking for the truth". And so it goes away.' There is something missing in our textbook image of nerve endings on post-synaptic neurons. The black spaces between these structures are full of cells—astrocytes—but they are completely missing from most figures. We can use Ca^{2+} -sensitive dyes to see what these astrocytes are doing, and when we do, we find that these non-neuronal cells are communicating. We see now that there are two separate flows of information in the brain: a neuronal component of information processing propagated electrically and a glial component propagated through intercellular Ca^{2+} waves. And the two systems of cellular communication interact. The neurons communicate with glia, and glia can in turn communicate back to neurons and regulate the flow of information through the brain. How and why are these non-neuronal cells doing this (Fig. 1)?

We know something about how they do this. Stan Kater and colleagues looked at cultured astrocytes using a Ca^{2+} -sensitive dye and performed a clever experiment to determine if the intercellular communication between astrocytes required cell–cell contact, or whether astrocytes communicate by releasing signalling molecules (Hassinger et al 1996). They scratched the cells away to create a cell-free zone in a monolayer of astrocytes in culture to determine whether this communication is mediated only by a flow of ions through gap junctions between cells. This cell-free zone acted like a fire-break in a forest. Then they initiated a Ca^{2+} wave in the astrocytes to see whether the signal propagated across the cell free zone: it did. The results showed clearly that astrocytes are communicating by sending signals through the media, in a similar way to neurons communicating at synapses. One of the key signalling molecules, quickly identified, was ATP.

Early investigators in the field of neuron–glia interactions were not used to thinking about ATP as an intercellular messenger. But people quickly began to

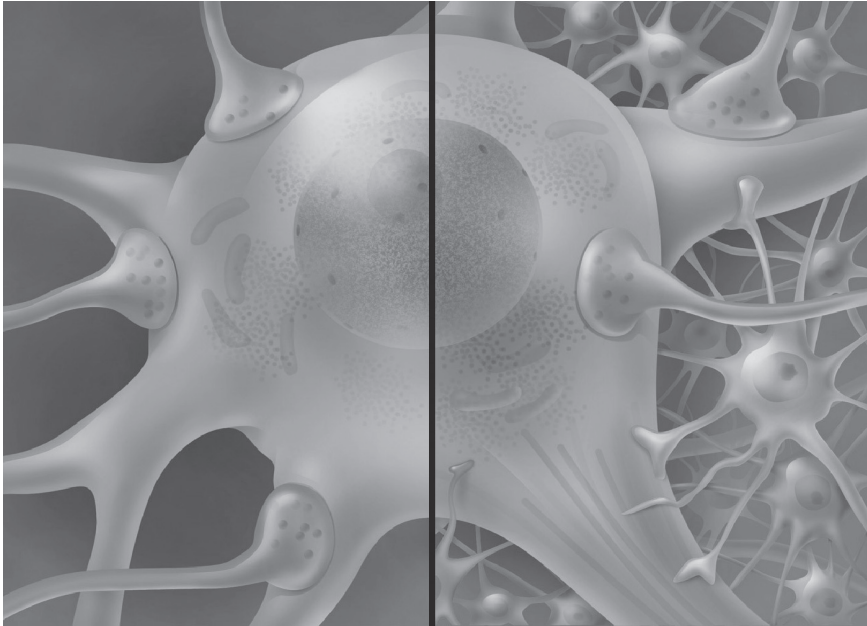


FIG. 1. The textbook view of the nervous system (left) typically excludes glia (right), which communicate among themselves using intercellular calcium waves and regulate synaptic transmission. Purinergic signalling is a major mechanism of intercellular communication between glia, and between neurons and glia.

address questions such as how ATP could be released from an astrocyte (Eduardo Lazarowski will cover this in the book), and which receptors on astrocytes can be activated by ATP (Geoff Burnstock and Maria Abbracchio will address this subject). Once these receptors are activated, it is important to determine how they signal intracellularly (Joe Neary and Beth Stevens will address this in their papers). Glial biologists immediately wanted to know how they could begin studying this system of purinergic communication (Ken Jacobson will discuss the pharmacology that allows us to activate and inactivate certain purinergic receptors). Then the field began to appreciate that as ATP breaks down to adenosine it activates different types of purinergic receptors, and that there is an extracellular set of enzymes that regulate this degradation and synthesis (Herb Zimmerman will talk about this important aspect of purinergic signalling).

At the Novartis Foundation meeting on P2 purinoceptors 10 years ago, many of the people in this room were grappling with the nature of P2 receptors, how the various types were distinct from each other, how they signalled and which drugs should be used to selectively activate or inactivate these receptors. The tools

weren't really ready to launch into functional studies at that time, but now we are able to begin doing this and explore the functional consequences of ATP signaling between neurons and glia.

ATP is key in regulating glial interactions with neurons and glial regulation of synaptic transmission. ATP is released with neurotransmitter and it acts upon purinergic receptors in perisynaptic glia. The glial cells in turn release any number of neuromodulatory substances to regulate postsynaptic or presynaptic function. The astrocytes can then communicate among themselves by sending ATP signals through astrocytic networks to perhaps affect another synapse to modulate neurotransmission at a distant site. We have at this meeting Richard Robitaille who will be talking about his work on perisynaptic glia at the neuromuscular junction, and then we will move to the retina where Eric Newman will talk about purinergic receptors regulating neuronal firing patterns in the retina. We will then move into the brain with Phil Haydon's work on adenosine and ATP regulating synaptic function by interactions with perisynaptic astrocytes in the hippocampus.

There is more to nervous system function than just the millisecond to millisecond interactions at synapses. In my lab, we are interested in how the brain develops and modifies its structure and function through experience and learning. These are slow processes, and neuron–glia interactions may be particularly well suited to participate in slower nervous system phenomena.

In the field of nervous system development, ATP and purinergic receptors have not really entered into our thinking, but I think this is something that will soon change. Let me give an example of a developmental process that is regulated by impulse activity, and may involve neuron–glia interactions. Jeff Lichtman has data showing that early in development all muscle fibres are innervated by multiple axons, but shortly after birth all but one are eliminated, leaving one muscle fibre innervated by only one axon. Jeff's lab is able to visualize, in living animals over several days, the withdrawal of these synapses by using fluorescently labelled neurons. In some of the images they have noticed ghost-like fingers pulling these withdrawing axons away. Working with a colleague, Wes Thompson, they did the opposite experiment, engineering a mouse with fluorescent glia (Schwann cells), so now the axons appear as ghosts. As the axon withdraws, it follows the path dictated by the glial cell (W. Thompson, personal communication and T. Mischak and J.W. Lichtman, personal communication). It is now becoming clear that we will never understand synapse formation and remodelling if we fail to consider the interactions between neurons and glia. Understanding this process of activity-dependent regulation of nervous system development comes down to a question of cell–cell communication: what are the molecules that mediate these kinds of communication. The kinds of molecules people in the development field traditionally think of are growth factors, peptides and cell adhesion molecules. Moses Chao will expand this view by presenting his work that combines purinergic receptors and

neurotrophins, showing that there are interactions between purinergic receptors and the sorts of molecules that neurobiologists are more accustomed to thinking about in nervous system development.

ATP is important in communication among all kinds of glia in the brain as well as with neurons, including interactions with the vasculature, microglia, axons and synapses. We'll have a talk on neuro-immune interactions (by Francesco Di Virgilio) and I'll talk a bit about interactions between myelinating glia and axons (as will Beth Stevens). We'll also have a presentation on the role of glia in pain involving purinergic signalling (by Kazuhide Inoue).

Our goal at this meeting is to consider neuron-glia interactions and the involvement of purinergic signalling. We now realize that so many aspects of brain function involve interactions between neurons and glia that it is no longer possible to ignore the involvement of glia. Many of these processes involve purinergic receptors. We want to fuse two fields, bringing together neurobiologists and glial biologists. Stéphane Oliet doesn't work on purinergics, as far as I know, but he does beautiful work on neuron-glia interactions in remodelling of synapses in the CNS. We have the top glial biologists here: Martin Raff, Rhona Mirsky, Kris Jessen and Boris Zalc. Then we have people who work on purines in neurons, glia and other cells: Mike Schwarzschild, Mike Salter, Peter Illes and Stanko Stojilkovic. Our goal is to work to find a synthesis of these two fields (purinergic signalling and neuron-glia interactions) and explore the common ground between them. We want to produce a book that will be a tool for the field, which glial biologists can use to learn about purinergic receptors and those of us working in purinergic receptors can use to learn about glia.

References

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