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GLIA: LISTENING AND TALKING TO THE SYNAPSE

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Preface

Glial cells are emerging from the background to become more prominent in our thinking about integration in the nervous system. Given that glial cells associated with synapses integrate neuronal inputs and can release transmitters that modulate synaptic activity, it is time to rethink our understanding of the wiring diagram of the nervous system. It is no longer appropriate to consider solely neuron–neuron connections; we also need to develop a view of the intricate web of active connections among glial cells, and between glia and neurons. Without such a view, it might be impossible to decode the language of the brain.

Summary

● Glial cells have been largely regarded as merely the supportive elements in the nervous system. However, recent evidence indicates that the glia have an active role in modulating synaptic transmission. In fact, communication between neurons and glia is bidirectional, as neuronal activity can elicit changes in glial calcium levels.
● Different molecules released by neurons can affect intracellular Ca^{2+} levels in glial cells. Glutamate has received a lot of attention in this regard, and it has been shown to modulate glial Ca^{2+} levels both in culture and *in situ*.
● The increases in Ca^{2+} levels experienced by individual glial cells can propagate across large distances in the form of Ca^{2+} waves. The mechanism of propagation seems to involve both intracellular and extracellular signals (inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) and ATP, respectively). It is likely that $Ins(1,4,5)P_3$ diffusion through gap junctions is important for short-range wave propagation, whereas ATP might be more relevant for propagation across larger distances.
● ATP is not the only transmitter released by astrocytes. This cell type can also release glutamate in a calcium-dependent manner that probably involves exocytosis. D-serine is another molecule released by astrocytes, although its release mechanism is not known. Similarly, the pathway responsible for ATP release remains to be discovered but is unlikely to involve vesicle fusion.
● Transmitters released by astrocytes can modulate synaptic transmission, giving rise to the concept of 'tripartite synapses'. Evidence regarding this modulation has been obtained both in culture and *in situ*, and it seems to affect basal synaptic transmission, as well as plastic phenomena. Moreover, glial cells can also modulate neuronal activity through a direct pathway that involves gap junctions between neurons and glia.

● The reciprocal communication between neurons and glia adds degrees of freedom to brain function. For example, increases in astrocytic calcium elicited by the activity of a given synapse could affect the function of synapses at distant locations through the spread of the calcium signal within the same astrocyte. Is this phenomenon ever observed *in situ* ? What are the functional consequences of this lateral, much slower, signalling pathway? Future experiments will aim to address these questions.

back to top