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Commentary

Synaptic transporters are deceived if they think themselves free

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This inscription would surely please the followers of Spinoza and his inescapably deterministic universe. But, in fact, some aspects of synaptic function are proving more deterministic than stochastic. For example, the fluid mosaic of perisynaptic membranes is all but fluid. Apparently, neurotransmitter action does not benefit from the freedom of all molecular constituents involved, but from selectively bonding most of them. Only neurotransmitter and other small molecules, ions and water are relatively unhindered to flow, and that is within pathways demarcated by membranes full of distractions. This may ensure that neurotransmitter-related currents are dense enough to maximize the information contents of synaptic events.

Glutamate is the major neurotransmitter in the brain and can also act as a potent excitotoxin, reasons why neurobiologists and neurologists strive to find ways to understand and modulate synaptic excitatory action. Both the concentration and permanence of glutamate in the brain's extracellular space are tightly controlled by a family of glutamate transporters. The two most important of these transporters, GLAST (also known as EAAT1) and GLT-1 (also known at EAAT2), are principally expressed by astrocytes [1].

The regulation and manipulation of glutamate transporter activity has been a topic of intense research interest over the past two decades, as it has been speculated that glutamate transporter function or dysfunction is implicated in the development or devastation characteristic of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis. Even the clearance of glutamate from the synapse by the astrocyte depends, at least in several key brain structures, upon astrocytic glutamate transporters, which are fundamental to lessen the glutamate biosynthetic needs of the neuron by virtue of facilitating glutamate recycling without resorting to the tricarboxylic acid cycle or to presynaptic reuptake each time that more glutamate is needed [3,5,7].

The work by Ritter et al. in this issue of *Neuroscience Letters* uncovers a robust interaction between the glutamate transporter GLAST and the scaffold protein NHERF-2 in astrocytes. This interaction increases the stability and activity of GLAST. Of note, NHERF-1, a molecular analog of NHERF-2, has also been reported to function as a binding partner of GLAST [4]. These observations raise the intriguing possibility that GLAST activity may be differentially regulated in select populations of astrocytes depending on whether astrocytes express NHERF-1, NHERF-2 (or both, or neither). Furthermore, GLAST is selectively localized to the almost ubiquitous perisynaptic processes that astrocytes wrap around synapses. Such topological organization may strategically position GLAST to perform the critical function of fine-tuning glutamatergic signaling [6]. Undoubtedly, future efforts will be directed to understand whether GLAST localization to these perisynaptic astrocytic processes is controlled by its interactions with the NHERF proteins. Also of note, the GLAST interaction with NHERF proteins represents a novel potential target for drugs aimed at modulating GLAST function. Indeed, small inhibitors have already been developed with the purpose of binding to the NHERF PDZ domains, thus blocking NHERF interactions with other molecular partners [2].

Synapses are tripartite structures [8]. Whereas much is known about the regulation of transporters, receptors and ion channels by scaffold proteins in neurons, very little is known about such signaling complexes in astrocytes. Given the critical role that astrocytic glutamate transporters play in governing synaptic transmission in the brain, however, it would be surprising if these transporters were not subject to specialized regulation in astrocytes at least as complex and physiologically important as that observed in neurons. The paper by Ritter et al. in this volume takes an important step toward elucidating the mechanisms by which astrocytes control their glutamate transport activity.

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