## NEWS AND VIEWS

patients are identified later in life, the damage caused by NMDA receptor hypofunction may already have been done. Restoring NMDA receptor signaling may not be sufficient to reverse the pathophysiology and reduce the symptoms of the disease.

The glutamate hypothesis of schizophrenia has survived this test. We now know with a fair degree of confidence that an interneuronspecific decrease in NMDA receptor signaling can induce changes in the GABA system similar to those seen in schizophrenia. We further suspect that this reduced signaling is particularly influential during a particular developmental window. Whether or not this reduction in NMDA receptor signaling actually

happens in individuals with schizophrenia, the model can be used to answer a host of important questions. Will restoring NMDA receptor function during adulthood reverse these changes, or is the system already locked in to its fate? Are the changes in pathophysiology and behavior causally related? Is NR1 deletion in any specific cortical region particularly important in the syndrome? And, perhaps most importantly for patients, can therapies, new or extant, reverse the behavioral consequences of NR1 hypofunction? Each of these questions can be addressed as the NR1 deletion model is studied in greater depth, as long as each study is designed with an appropriate hypothesis in mind.

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## Ion pumps get more glamorous

## David L Glanzman

A new study shows that the Na<sup>+</sup>/K<sup>+</sup> ATPase can function as an integrator of spike activity and interacts with a K<sup>+</sup> conductance to provide a cellular short-term memory of locomotion in the Drosophila larval motor circuit.

I suspect I am not the only behavioral neuroscientist who finds the subject of ion pumps to be sleep inducing. Naturally, the importance of ion pumps to basic neuronal function is appreciated. By constantly pushing Na<sup>+</sup> ions out of and K<sup>+</sup> ions into neurons, Na<sup>+</sup>/K<sup>+</sup> pumps generate the difference in charge across the neuronal cell membrane that is the basis of the resting membrane potential. Nevertheless, I have long regarded the subject of ion pumps in much the same way I regarded botany as an undergraduate student: I recognized its importance, but was content to leave the study of this subject to others, as its scientific attractiveness to me was scant. But now a new study by Pulver and Griffith<sup>1</sup> suggests that a lowly ion pump can have a more glamorous mechanistic role than I had imagined. The authors show that a  $Na^+/K^+$  pump in motor neurons of fruit fly larvae can subserve motor memory, albeit over a short span of time.

Drosophila larvae advance through waves of contractions of their body wall musculature

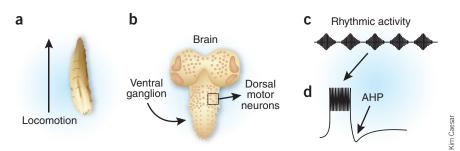


Figure 1 Neural activity related to locomotion in Drosophila larvae. (a) Movement of the larva is produced by peristaltic waves of contraction of the body wall musculature. The rhythmic contractions of the body segments are coordinated by a central pattern generator. (b) The CNS of the Drosophila larva. The motor neurons that drive locomotion are located in the dorsal region of the ventral ganglion. (c) Rhythmic pattern of firing of the motor neurons during locomotion, as recorded extracellularly from the ventral nerve. The pattern of motor neuron firing is generated by the central pattern generator. (d) A single burst of action potentials in a dorsal motor neuron during locomotion, as recorded with a whole-cell patch electrode. An AHP (arrow) follows the burst. The AHP lasts for several seconds and is produced by the Na<sup>+</sup>/K<sup>+</sup> ion pump. The amplitude of the AHP encodes the number of action potentials in a motor neuron burst, independent of the pattern of firing. In addition, the AHP interacts with an A-type K<sup>+</sup> current to provide a cellular memory of previous activity in the motor neurons by modulating the onset of the first action potential in a burst.

that are segmentally coordinated by a central pattern generator (Fig. 1a). The central pattern generator causes motor neurons in the ventral ganglion of larvae to fire in highfrequency, rhythmic bursts (Fig. 1b,c); this rhythmic firing then drives the peristaltic contractions of the body wall that produce larval locomotion<sup>2</sup>. Each action potential burst in the motor neurons is followed by an afterhyperpolarization (AHP; Fig. 1d),

a negative membrane potential (~20 mV below the resting potential) that typically lasts for  $15-20 \text{ s}^1$ .

Pulver and Griffith<sup>1</sup> first sought to identify the intrinsic membrane currents that underlie the AHP. Electrophysiologically recording from a pair of motor neurons, the authors found that the AHP was abolished by blocking sodium channels in the neurons with the neurotoxin tetrodotoxin. In contrast, potassium currents

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did not appear to be involved in the AHP, as indicated by the lack of a change in the input resistance of the cell membrane of the motor neurons during the AHP. The authors also found that the amplitude of the AHP did not change when the membrane potential of the motor neurons was held at different negative potentials approaching the reversal potential for potassium (-107 mV in these neurons). Taken together, these results strongly suggest that the AHP is mediated by a Na<sup>+</sup>/K<sup>+</sup> pump (the Na<sup>+</sup>/K<sup>+</sup> ATPase). This idea is supported by the finding that the AHP was blocked by ouabain, a classic inhibitor of Na<sup>+</sup>/K<sup>+</sup> ATPase. The authors used the cell type-specific GAL4-UAS system<sup>3</sup> to express a dominant-negative form of the Na<sup>+</sup>/K<sup>+</sup> ATPase subunit in the motor neurons, which mimicked the effects of ouabain in that the AHPs were substantially reduced. This reduction in the amplitude of the AHPs substantially decreased the speed of crawling in the genetically altered larvae.

Having identified the mechanism of the AHPs and shown that AHPs are involved in larval locomotion, Pulver and Griffith<sup>1</sup> then asked whether the AHPs can serve as spike integrators in the motor neurons. To test this, they compared the AHPs after prolonged injections of steady-state current in the motor neurons with the AHPs after brief bouts of on-off current designed to produce bursts of firing in the motor neurons that mimicked their rhythmic firing during locomotion. The authors found that the AHP amplitude was proportional to the number of action potentials evoked in the motor neurons, regardless of whether the neurons fired constantly or in bursts. Thus, the AHP functions as a pattern-independent 'counter' of action potentials in the motor neurons during locomotion, keeping track of the numbers of spikes the neuron had just fired by proportionally adjusting the amplitude of the AHP to the total number of spikes in a burst, independent of pattern of activity.

Finally, in what was perhaps the study's most surprising finding, Pulver and Griffith<sup>1</sup> found that the AHP could have a mnemonic role during rhythmic activity in the ventral nerve cord of larvae. The authors injected a rhythmic current into the motor neurons that was designed to mimic the synaptic input that

the neurons would receive as a larva crawled. The amplitude of the AHP increased with multiple bursts; furthermore, this increase in AHP amplitude produced a substantial delay in the occurrence of the first spike in the burst as the burst cycle number increased. Previous work has shown that delays to the first spike in bursting larval motor neurons are the results of the activation of an A-type potassium current encoded by the Drosophila shal gene<sup>4</sup> (A-type potassium currents are transiently activated when a neuron is hyperpolarized). Thus, activity-induced AHPs in the motor neurons interact with the shal current during locomotion. Moreover, this interaction persists for several seconds after rhythmic activity has ceased. Following a train of 20 bouts of rhythmic activity in the motor neurons, the delay in the appearance of the first spike in a subsequent burst remained substantially longer than that in the first burst of firing for up to 5 s. Therefore, the delay to the first spike in a burst encodes the time since prior locomotory activity in the larva.

These results indicate that ion pumps can, unexpectedly, subserve information-processing roles in neurons. The AHP mediated by the Na<sup>+</sup>/K<sup>+</sup> ATPase can be used to count the number of spikes that a larval motor neuron has fired during a locomotor cycle. Previous computational models for how neurons might keep track of their own activity have focused on sensors of intracellular calcium<sup>5</sup>. As the authors point out, however, intracellular calcium levels are not always well correlated with firing in neurons and, moreover, calciumsensing mechanisms are unlikely to operate over a time scale of more than 1 s, as a result of the rapidity with which intracellular calcium levels decay after neuronal firing<sup>6</sup>. In contrast, sodium concentration is more directly linked to activity, as action potentials involve the opening of voltage-gated sodium channels. Furthermore, Pulver and Griffith's<sup>1</sup> results, as well as those of others<sup>7</sup>, indicate that activity can modify intracellular concentrations of sodium over time scales of several seconds.

Perhaps the most intriguing computational role for the Na<sup>+</sup>/K<sup>+</sup> ATPase-dependent AHP revealed in Pulver and Griffith's study<sup>1</sup> is its ability to store a short-term memory of recent activity in the motor neurons. Notably, the duration of this memory is intermediate between calcium signaling and events such as gene transcription, which are much slower, with a time scale of minutes and hours. As Pulver and Griffith<sup>1</sup> point out, the time scale over which the pump-mediated memory operates is relevant to a variety of rhythmic behaviors, including respiration, locomotion, feeding and swimming, all of which involve oscillations in the range of 0.5-2 Hz<sup>8-11</sup>. However, the precise role of the AHP-generated memory in the locomotive behavior of Drosophila larvae is unclear.

Despite the lack of a conclusive behavioral role for the memory encoded by the AHP, Pulver and Griffith's study<sup>1</sup> represents a valuable contribution to our understanding of the various ways by which neural circuits can record the history of their activity. Changes in synaptic strength<sup>12</sup>, modulation of ionic membrane currents<sup>13</sup> and, now, activity of ion pumps<sup>1</sup> can all contribute to memory. Delineating the mnemonic roles of these various mechanisms, as well as their temporal properties and potential interactions, represents a daunting challenge for a comprehensive cellular account of learning and memory. But progress is undeniably being made on this important biological problem. And thanks to Pulver and Griffith, at least one neuroscientist will never again find ion pumps to be quite so drab.

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