In combination with work in rocky intertidal (*12*), grassland (*13*, *14*), and other habitats (*15*), this new work suggests that local recruitment limitation may be a universal feature of sessile species. The issue, now, is which of at least three alternative recruitment-limitation hypotheses actually explains the high-local diversity of such habitats. Is diversity maintained by a trade-off between recruitment ability versus competitive ability (*8*)? Or, does recruitment limitation allow local coexistence of species that already are capable of regional coexistence (*9*)? Or, does recruitment limitation so slow the rate of competitive displacement that high-local diversity can be maintained, without any such trade-offs, by a regional equilibrium between extinction and the evolution of new species (*16*)? Or, is there a diversity of explanations for diversity?

The growing consensus on the importance of recruitment limitation puts us a significant step closer to understanding the mystery of Earth's high diversity. This mystery was of only academic interest 40 years ago, but the preservation of Earth's diversity is an increasingly important societal goal. Habitat destruction and fragmentation, invasions by exotic species, and nutrient pollution all cause loss of local diversity and species extinctions. Our ability to preserve maximal diversity in the face of this increasingly great human domination of the world's ecosystems, however, requires a much more complete understanding of diversity. The causes and conservation of Earth's diversity remain one of the greatest challenges facing ecology and society.

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17. I thank N. Haddad for his comments.

PERSPECTIVES: NEUROSCIENCE

Energy on Demand

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How does the coordinated activity of neurons translate into a sensation or a thought? Experimental methods to address this central question of neuroscience range from characterization of the molecular and cellular basis of neuronal activity to noninvasive studies of the living animal. Recent techniques that can image the functioning brain offer a promising bridge between the cells and molecules of neuroscience and the complexities of the mind.

Through positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), it is now possible to see "the brain at work," to visualize which brain areas are activated (and in certain cases inhibited) by specific tasks. The spatial and temporal resolution of PET and fMRI provide an intermediate step in linking neuronal activity to behavior: The signals detected reflect the activity of neuronal ensembles in ~1 mm^3 with acquisition times as short as seconds. Until recently, however, it has not been clear exactly what neuronal activity is measured in PET and fMRI experiments.

The basic principle of brain imaging was formulated by Sherrington more than a century ago, when he suggested that neuronal activity and energy metabolism are tightly coupled. Indeed, PET and fMRI do not detect brain activity directly but rather measure signals that reflect brain energy consumption. How then is neuronal activity related to these measures of energy consumption? Energy is delivered to the brain by the oxidation of glucose from the blood. PET monitors changes in blood flow, glucose usage, or oxygen consumption, while fMRI signals reflect the degree of blood oxygenation and flow.

Thus, the metabolic signals detected by functional brain imaging techniques bring us part way to understanding how neuronal processes such as action potentials and neurotransmitter release lead to a given brain activity and its resulting behavioral state. To make further progress, it has been essential to identify and quantitate the specific cellular and molecular mechanisms of neuronal activity that are coupled to energy metabolism.

New data obtained in vitro and in vivo have identified the neurotransmitter glutamate and astrocytes, a specific type of glial cells, as pivotal elements in the stoichiometric coupling of energy-requiring neuronal activities and energy metabolism. These results have related functional imaging signals and brain energy metabolism to specific neurotransmitters and thereby suggest novel solutions to a wide range of questions about brain activity.

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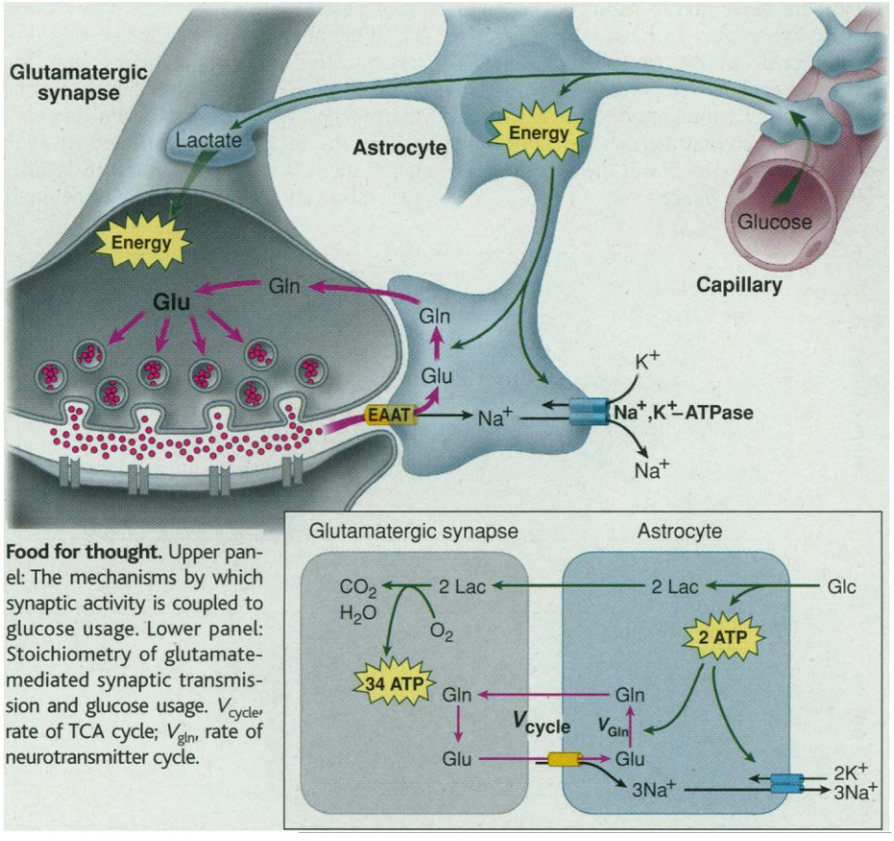
Glutamate, by far the dominant excitatory neurotransmitter of the brain, is released by ~90% of the neurons during excitation, after which it diffuses across the synaptic cleft and is recognized by receptors on the postsynaptic neuron (see the figure). Glutamate released from neurons must rapidly be removed from the synapses to set the stage for the next transmission. This is primarily accomplished by a highly efficient uptake system in the astrocytes that surround every glutamatergic synapse (see the figure). Glutamate is taken up by astrocytes via specific transporters that use the electrochemical gradient of Na^+ as a driving force, resulting in a tight coupling between glutamate and Na^+ uptake (*1*) (see the figure). The astrocyte is then confronted with a dual task: disposing of glutamate and reestablishing the Na^+ gradient. The gradient is maintained by activation of the Na^+- and K^+-dependent adenosine triphosphatase (Na^+,K^+-ATPase), and glutamate is converted into glutamine, a reaction catalyzed by glutamine synthetase. Glutamine is subsequently released by astrocytes and taken up by neuronal terminals, where it is enzymatically reconverted to glutamate to replenish the neurotransmitter pool of glutamate (see the figure). Both glutamine synthesis and the Na^+,K^+-ATPase require adenosine triphosphate (ATP). There is no mechanism for ATP exchange between astrocytes and neurons, so each cell must supply its own energy.

Astrocytic end-feet, enriched in glucose transporters, cover virtually all capillary walls in the brain (see the figure). Thus, the morphology and cytological relationship of astrocytes with the vasculature and the neu-

ropil provide these cells with the necessary functional connections to sense synaptic activity and to couple it with glucose uptake. Experiments in pure cultures of astrocytes have provided the necessary molecular resolution to analyze this coupling (*2, 3*). Activation by glutamate of its transporter stimulates glucose uptake into astrocytes; glucose is processed glycolytically, resulting in the release of lactate as an energy substrate for neurons. One glucose consumed by glycolysis to lactate produces two ATP molecules. One ATP is used by the Na^+,K^+-ATPase for the extrusion of three Na^+ ions; the other ATP is used for the synthesis of glutamine from glutamate. Lactate so produced may be either oxidized in the astrocyte or released for oxidation in the neuron (*4, 5*). This cascade of molecular events provides a direct mechanism for coupling glutamate-mediated synaptic transmission with glucose usage, one of the signals detected by PET imaging (*2*).



Food for thought. Upper panel: The mechanisms by which synaptic activity is coupled to glucose usage. Lower panel: Stoichiometry of glutamate-mediated synaptic transmission and glucose usage. V_{cycle}, rate of TCA cycle; V_{gln}, rate of neurotransmitter cycle.

Nuclear magnetic resonance (NMR) experiments with ^{13}C have provided evidence of this molecular and cellular coupling in the intact cortex and have established the stoichiometry of glucose consumption and glutamate/glutamine cycling. The flux from glutamate to astrocytic glutamine (V_{cycle}) was measured in rat and human cortex by measuring the flow of carbon derived from [1-^{13}C]glucose into the brain glutamate and glutamine pools. This flux, with very small corrections, directly measures the glutamate/glutamine (glu/gln) cycle, hence, reflecting the degree of activity at glutamatergic synapses (*6*). In the same experiments, the rate of the tricarboxylic acid (TCA) cycle (V_{TCA}) was determined from the incorporation of labeled [1-^{13}C]glucose into cerebral glutamate. One-half of V_{TCA} is a measure of the cortical glucose oxidation rates (*7*). The energy demands of glutamatergic neurons are shown by the NMR measurement to account for 80 to 90% of total cortical glucose usage (*6*).

As a means of measuring the relationship between glucose consumption and glutamate neurotransmitter cycling, the rates of V_{cycle} and glucose oxidation ($^1/_2V_{TCA}$) were measured in vivo in anesthetized rats under a range of brain activities from deep isoelectric (meaning no electroencephalographic activity) to awake. The results fit well to a linear equation:

$$^1/_2V_{TCA} = 1.04V_{cycle} + 0.10$$

in units of micromoles per gram per minute. The intercept (when $V_{cycle} = 0$) reflects the small fraction (≈15%) of glucose oxidation not coupled to the glu/gln neurotransmitter cycle. The experimental results of one glucose consumed for each glutamate cycled in vivo agrees with expectations from the proposed model of astrocytic clearance of glutamate, indicating that glutamate neurotransmitter cycling is the major mechanism for driving cortical glucose usage (*6*). Preliminary results on human cortex yield similar stoichiometries (*7*).

The large flux through the glu/gln cycle supports a model in which much of the glucose metabolism measured in functional imaging studies is coupled to glutamate-driven astrocytic glucose uptake, as described in the figure. If, as seems likely, this model holds during neuronal activation, then the major fraction of the changes in glucose usage measured by functional imaging in these studies will be directly related to excitatory glutamate neurotransmitter release. Other neurotransmitter systems can also be incorporated into this model. The primary inhibitory neurotransmitter γ-aminobutyric acid (GABA) flows in a similar neurotransmitter cycle between neurons and astrocytes. Because GABA is now routinely measured by in vivo NMR (*8*), the relationship between GABA release and glucose oxidation is also quantifiable.

Quantitation of neurotransmitter cycling through brain imaging can be applied to studies of cognition and behavior. At present, functional imaging identifies the location of changes in brain activity but provides no insight into the total neuronal activity involved in a process. As a consequence, the study designs and interpretations are based on psychological studies and have rarely incorporated the biological information implicit in the image (*9*). The results summarized here promise a functional imaging that links psychological understanding of behavior and cognition with neurobiology so as to understand functional regulation at the synaptic level.

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