This Week in The Journal

● Cellular/Molecular

Ketogenic Diet Increases ATP Release and Activates A_1 Receptors

Masahito Kawamura Jr, David N. Ruskin, and Susan A. Masino

(see pages 3886–3895)

High-fat, low-carbohydrate (ketogenic) diets can reduce seizure frequency in some forms of epilepsy. Ketogenic diets stimulate biogenesis of mitochondria, reduce blood glucose levels, and increase cellular ATP, but the molecular mechanisms by which they prevent seizures are not clear. Kawamura et al. have developed an *in vitro* model of the ketogenic state by decreasing the concentration of extracellular glucose and increasing intracellular ATP in rat hippocampal slices. Under these conditions, CA3 pyramidal neurons exhibited an outward current, hyperpolarization, and decreased PSC frequency. These effects required functional gap junctions and adenosine A_1 receptors, and the outward current required ATP-sensitive potassium channels. These results suggest that when extracellular glucose is low and intracellular ATP is high, ATP is released from pyramidal neurons via gap junction hemichannels and is dephosphorylated extracellularly to adenosine. Adenosine then activates adenosine A_1 receptors and ATP-sensitive potassium channels, thus lowering neuronal excitability, which is expected to reduce seizure frequency.

▲ Development/Plasticity/Repair

Alcohol and Methamphetamine Similarly Affect Brain Morphology

Elizabeth R. Sowell, Alex D. Leow, Susan Y. Bookheimer, Lynne M. Smith, Mary J. O'Connor, *et al.*

(see pages 3876–3885)

Prenatal exposure to certain drugs causes permanent changes to the brain. But because many people who abuse one drug also abuse others, determining which drug caused observed changes is usually difficult. For example, although most women who use methamphetamine during pregnancy also use alcohol and tobacco, previous studies compared children exposed prenatally to methamphetamine to children exposed to no drugs, making it impossible to determine which drug caused changes in brain morphology. Attempting to resolve this question, Sowell et al. compared brains of children exposed prenatally to methamphetamine and alcohol to those of children exposed to alcohol alone. Similar changes were found in both groups, but some were more severe in those exposed to methamphetamine. Unfortunately, the authors were unable to determine whether subjects' mothers had used other drugs besides methamphetamine or whether the mothers consumed the same amount of alcohol, so the extent to which the measured changes were caused by methamphetamine exposure remains uncertain.

■ Behavioral/Systems/Cognitive

Bumblebee Photoreceptor Classes Have Different Response Speeds

Peter Skorupski and Lars Chittka

(see pages 3896–3903)

The precision with which the nervous system can encode sensory information is limited by metabolic costs. For example, to accurately encode rapidly fluctuating signals, the membrane time constant must be reduced by increasing conductance, which necessitates increased activity of sodium–potassium pumps (which consume the bulk of neurons' energy) to maintain the proper resting membrane potential. Therefore, evolutionary pressures to balance the cost and benefits of precision generally drive sensory systems to be only as precise as they need to be. For example, photoreceptors in fast-moving animals respond more quickly to changes in illumination than those in slower moving animals. Skorupski and Chittka show that variations in processing speed also occur across different photoreceptor classes of a single species. In bumblebees, green-sensitive photoreceptors, which are responsible for motion processing, had faster response speeds than blue-sensitive or UV-sensitive photoreceptors, which are primarily used for color discrimination at slower flight speeds.

In bumblebees, green photoreceptors have faster response speeds than other photoreceptor classes. See the article by Skorupski and Chittka for details.

♦ Neurobiology of Disease

Metabotropic Glutamate Receptors Regulate APP Processing

Soong Ho Kim, Paul E. Fraser, David Westaway, Peter H. St. George-Hyslop, Michelle E. Ehrlich, *et al.*

(see pages 3870–3875)

Amyloid precursor protein (APP) is cleaved by either α-secretase or β-secretase to produce a C-terminal fragment of 83 or 99 amino acids (C83 or C99), respectively. β-Amyloid (Aβ), the peptide that accumulates in Alzheimer's disease (AD), is generated by cleavage of C99 by γ-secretase; whether the most toxic species, Aβ_{42}, is produced depends on where γ-secretase cleaves C99. Previous studies showed that processing of APP is regulated by synaptic activity, and Kim et al. report that activating different types of metabotropic glutamate receptors (mGluRs) results in accumulation of different APP cleavage products. In cortical synaptoneurosomes—isolated presynaptic compartments attached to postsynaptic compartments—from mice expressing an AD-associated form of APP, activation of group I mGluRs produced sustained increases in C83, C99, and Aβ_{40}, but not Aβ_{42}. Activation of Group II mGluRs caused only transient increases in C99 and Aβ_{40}, but sustained increases in C83 and Aβ_{42}. These results suggest mGluRs differentially regulate cleavage by γ-secretase.