This Week in The Journal

● Cellular/Molecular

Measuring the Dynamics of PKA Signaling

Nicolas Gervasi, Régine Hepp, Ludovic Tricoire, Jin Zhang, Bertrand Lambolez, Danièle Paupardin-Tritsch, and Pierre Vincent

(see pages 2744–2750)

Subcellular compartmentalization of cAMP-dependent protein kinase A (PKA) determines which substrates are phosphorylated at the membrane, cytosol, and nucleus. This week, Gervasi et al. chose two reporters to examine these signaling microdomains in thalamic neurons in brain slices. To monitor PKA in the nucleus and cytosol, the authors virally expressed the AKAR2 protein, which contains a PKA substrate domain, a phosphothreonine binding domain, and two fluorophores. Fluorescence resonance energy transfer efficacy, which increases with conformational changes in AKAR2, was used to monitor PKA-dependent phosphorylation. To monitor PKA at the membrane, they used the calcium-activated potassium channels that underlie the slow afterhyperpolarization as a physiological reporter. Increases in PKA with 5-HT_7 receptor activation or direct stimulation of adenylyl cyclase with forskolin reduced the slow afterhyperpolarization potential current within 30 s. However, activation of 5-HT_7 receptors had a smaller and slower effect than forskolin on cytosolic AKAR2 and nuclear effects were slower still, reaching a maximum after 17 min.

▲ Development/Plasticity/Repair

Stress and Neurogenesis in the Rat

Rosanne M. Thomas, Gregory Hotsenpiller, and Daniel A. Peterson

(see pages 2734–2743)

We are all familiar with the immediate effects of acute psychosocial stress on our mood. Now a report from Thomas et al. this week addresses the impact of such an acute stress on new neurons in the hippocampus. To induce stress, the authors introduced a naive male intruder into an established rat colony, a maneuver that caused the dominant male resident to approach, pin down, and bite at the newcomer. The authors treated the rescued intruder with thymidine analogs at various time points relative to the stress to track changes in the birth and survival of new neurons. The episode raised corticosterone levels indicative of the stress but did not impact the number or immediate survival of proliferating cells in the dentate gyrus. However, short-term (1 week) and long-term (4 weeks) survival of newly generated neurons was reduced. No word yet on the effects on that bully, the alpha rat.

■ Behavioral/Systems/Cognitive

Single Neuronal Activity during Unstructured Arm Movements

Tyson N. Aflalo and Michael S. A. Graziano

(see pages 2760–2780)

It comes as no surprise that movements in monkeys are accompanied by single neuronal activity in the motor cortex, but it is less clear which motor parameters are most critical. For example, is it spatial, joint-based, or muscle-based? To get at this question, Aflalo and Graziano let monkeys do their own thing, thus removing the potentially confounding contribution of overly constrained movements in highly trained animals. The authors measured spontaneous arm movements in untrained monkeys using a three-dimensional tracking system and recorded from individual neurons in motor cortex. As expected from studies in restrained animals, standard tuning properties of motor cortex neurons were present. Neurons were tuned to multiple movement parameters. The total variance in neuronal activity reflected hand speed (1%), hand direction (8%), complex directional tuning (13%), final hand position (22%), and final arm posture (36%). The authors propose that these rankings reflect the importance of each parameter to arm movements.

The trail of black dots shows the front view of 514 unstructured hand movements during 10 min of testing. Each trail of dots reflects one movement sampled every 14.3 ms. The position of the monkey is outlined in gray. See the article by Aflalo and Graziano for details.

♦ Neurobiology of Disease

Methylation of PP2A and Tau/APP Phosphorylation

Estelle Sontag, Viyada Nunbhakdi-Craig, Jean-Marie Sontag, Ramon Diaz-Arrastia, Egon Ogris, Sanjana Dayal, Steven R. Lentz, Erland Arning, and Teodoro Bottiglieri

(see pages 2751–2759)

Elevated plasma levels of homocysteine are a risk factor for Alzheimer's disease. Because high homocysteine levels can inhibit methyltransferases, Sontag et al. pursued a trail of posttranslational protein modifications that might link homocysteine to tau and amyloid precursor protein (APP). Here's their rationale. The likelihood of amyloidogenic APP increases with its phosphorylation, a state reversed by protein phosphatase 2A (PP2A), which itself is affected by methylation. Previous studies have also reported downregulation of neuronal PP2A methyl transferase (PPMT) and reduced PP2A methylation in brain tissue from Alzheimer's patients. In neuroblastoma cells, the authors found that S-adenosylhomocysteine reduced PP2A methylation probably by inhibiting PPMT. In these same cells, phosphorylation of tau and APP was enhanced. In mice prone to high homocysteine levels, a high-methionine, low-folate diet also led to increased brain S-adenosylhomocysteine, downregulation of PPMT, reduced PP2A methylation, and enhanced phosphorylation of tau and APP.