Focus Issue on Neuroscience: Molecular Components of Circadian Rhythms and Oscillations

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In conjunction with this week's Neuroscience special issue of *Science* called Sleep, Dreams, and Memory (http://www.sciencemag.org/cgi/content/summary/294/5544/1047), the STKE presents a focus issue on Neuroscience. Organisms have circadian clocks, which cycle approximately every 24 hours and coordinate their behavior in response to environmental cues. A light-sensitive master clock is located in the suprachiasmatic nucleus of the brain, whereas clocks in the periphery of the body are thought to be set, in a light-independent manner, by signals emanating from the suprachiasmatic nucleus. Pando and Sassone-Corsi (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/107/re16) review how the central and peripheral clocks might communicate and provide feedback to one another and the factors that are important for fine-tuning the oscillations of these clocks. The identity of a bona fide mammalian photoreceptor protein has remained elusive. The authors suggest that several molecules might function, singly or in concert, to perceive light cues in mammals. Circadian rhythm and the molecular mechanisms that control it have been studied in other organisms. Related material in the STKE archive includes the Review by Woodgett (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/100/re12) in which the role of glycogen synthase kinase-3 (GSK-3) in controlling circadian periodicity of the fruit fly is described as one of the biological functions of GSK-3.

Melatonin is thought responsible for the entrainment of the suprachiasmatic nucleus, through a process requiring the activation of specific melatonin receptors. In their Perspective, Masana and Dubocovich (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/107/pe39) focus on the functions of the melatonin receptors MT_1 and MT_2, which belong to the family of G protein-coupled receptors (GPCRs). The existence of a third receptor, MT_3, is less certain. MT_1 receptor activation inhibits the phosphorylation (and activation) of the adenosine 3′,5′-monophosphate (cAMP) responsive element binding protein (CREB) transcription factor, whose activity is required for resetting of the master clock. On the other hand, the activation of MT_2 receptors leads to phase advances in the central clock in mice and to regulated dopamine release from the retina. Melatonin receptors are believed to signal through the G_i and G_q members of the G protein family. Connections Maps by Iyengar and colleagues show the canonical view of the signaling pathways initiated by G_q (http://stke.sciencemag.org/cgi/cm/CMP_6680) and G_i (http://stke.sciencemag.org/cgi/cm/CMP_7430).

In addition to articles focused on sleep and circadian rhythms, *Science* (http://www.sciencemag.org/content/vol294/issue5544/#review) and *STKE* have several pieces that relate to the molecular nature of neurological disease and regulation of the synapse.

Several Perspectives in the STKE archive encompass how insights into normal neuronal function and neurological disease have been gleaned from understanding synaptic activity at a detailed molecular level. Therapeutic strategies based on neuronal signaling pathways are evaluated both by Roth (http://stke.sciencemag.org/cgi/content/abstract/OC_sigtrans;2000/45/pe1), in a critique of the book "Cerebral Signal Transduction: From First to Fourth Messengers" and by Gough (http://stke. sciencemag.org/cgi/content/full/OC_sigtrans;2001/76/pe1), in a synopsis of an STKE-sponsored symposium on drug targets. These Perspectives highlight how putative treatments for depression, drug addiction, and bipolar disorder are based on our current understanding neuronal communication. A Perspective from Kriegstein and Owens (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/95/pe1) also discusses how the inhibitory neurotransmitter GABA may actually have excitatory action in the developing brain, further expanding our understanding of excitability disorders, such as epilepsy. The details and controversy regarding the phosphorylation and activation of the transcription factor CREB in neurons is pondered by Impey and Goodman (http://stke.sciencemag.org/cgi/content/full/ OC_sigtrans;2001/82/pe1), as CREB-dependent gene expression is thought to be regulated by synaptic activity. Finally, a Review by Galli and Haucke (http://stke.sciencemag.org/ cgi/content/full/OC_sigtrans;2001/88/re1) underscores how synaptic vesicle dynamics now includes both a slow and fast life cycle at work at the nerve terminal. Animations that accompany the Galli and Haucke Review demonstrate the various synaptic vesicle cycling models.

For those interested in dissecting signaling pathways through GPCRs, like the melatonin receptors, or in manipulating neurons to express target proteins, two Protocols in the STKE archive describe detailed methods for achieving these goals. McAllister (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2000/51/pl1) provides detailed methods for the preparation of brain slice cultures, isolated neuronal and astrocyte primary cell cultures, bioloistic transformation of these preparations, and immunostaining techniques to analyze protein expression. Chang et al. (http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2000/47/pl1) describe how to synthesize and apply membrane permeable peptides to selectively disrupt GPCR signaling through a specific G protein or receptor.

We encourage you to explore the coordinated focus on Neuroscience at STKE and in *Science*.

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Featured in this Focus Issue on Neuroscience

- **Perspective** by M. I. Masana, M. L. Dubocovich, Melatonin receptor signaling: Finding the path in the dark. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/107/pe39.
- **Review** by M. P. Pando, P. Sassone-Corsi, Signaling to the mammalian circadian clocks: In pursuit of the primary mammalian circadian photoreceptor. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/107/re16.

Related Resources at STKE

- **Review** by J. R. Woodgett, Judging a protein by more than its name: GSK-3. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/100/re12.
- **Review** by T. Galli, V. Haucke, Cycling of synaptic vesicles: How far? How fast! *Science's STKE* http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/88/re1.
- **Book Review** by B. L. Roth, Neuronal signal transduction pathways: Wasteland or the promised land? *Science's STKE* (2000), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2000/45/pe1.
- **Meeting Report** by N. R. Gough, Signal transduction pathways as targets for therapeutics. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/76/pe1.
- **Perspective** by A. R. Kriegstein, D. F. Owens, GABA may act as a self-limiting trophic factor at developing synapses. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/95/pe1.
- **Perspective** by S. Impey, R. H. Goodman, CREB signaling-timing is everything. *Science's STKE* (2001), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2001/82/pe1.
- **Protocol** by K. McAllister, Biolistic transfection of neurons. *Science's STKE* (2000), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2000/51/pl1.
- **Protocol** by M. S. S. Chang, J. P. Tam, E. Sanders-Bush, Dissecting intracellular signaling pathways with membrane-permeable peptides. *Science's STKE* (2000), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2000/47/pl1.
- **ST on the Web** — In Protein Databases (http://stke.sciencemag.org/cgi/ul/sigtransUl;CAT_4), see the GPCRDB: Information System for G Protein-Coupled Receptors (http://www.gpcr.org/) and the PDSP Drug Database (http://pdsp.cwru.edu/pdsp.asp).
- **ST on the Web** — In Model Organisms (http://stke.sciencemag.org/cgi/ul/sigtransUl;CAT_6), see Mouse Genome Informatics (http://www.informatics.jax.org/) and The Mouse Atlas and Gene Expression Database (http://genex.hgu.mrc.ac.uk/).
- **Connections Map** by R. Iyengar, P. Ram, Canonical $G\alpha_q$ pathway. *Science's STKE* (as seen November 2001), http://stke.sciencemag.org/cgi/cm/CMP_6680.
- **Connections Map** by R. Iyengar, D. Aaronson, Canonical $G\alpha_i$ pathway. *Science's STKE* (as seen November 2001), http://stke.sciencemag.org/cgi/cm/CMP_7430.

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