This Week in The Journal

● Cellular/Molecular

BACE1 Disrupts cAMP Signaling

Yaomin Chen, Xiumei Huang, Yun-wu Zhang, Edward Rockenstein, Guojun Bu, et al.

(see pages 11390–11395)

Amyloid-β is generated by cleavage of amyloid precursor protein, first by β-secretase (BACE1), then by γ-secretase. Whereas γ-secretase mutations cause familial, early-onset Alzheimer's disease (AD), increased expression and activity of BACE1 occurs in the more common, late-onset, sporadic form. In both cases, increased production of toxic Aβ likely is the main driver of AD, but abnormal processing of other secretase targets might contribute to pathology. Furthermore, Chen et al. suggest that BACE1 can produce adverse effects independently of its secretase activity. BACE1 associates with adenylate cyclase via its transmembrane domain, and overexpression of BACE1 in rodents reduced levels of cAMP, activity of cAMP-dependent protein kinase, and activation of cAMP response element-binding protein. These effects occurred even when the secretase activity of BACE1 was disabled. In contrast, BACE1 knock-out increased cAMP levels and its downstream effects. Interestingly, both overexpression and deletion of BACE1 reduced levels of the synaptic proteins synaptophysin and PSD-95.

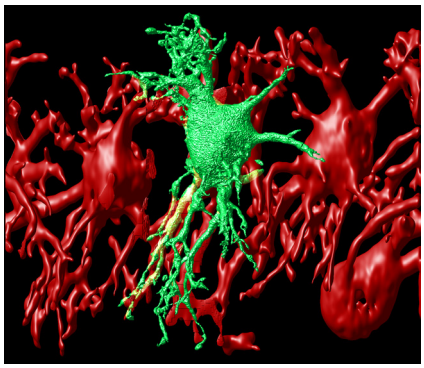
▲ Development/Plasticity/Repair

Presynaptic Silence Causes Dendrite Retraction

Yuan Wang and Edwin W Rubel

(see pages 11495–11504)

In chickens, cochlear afferents project to the ipsilateral nucleus magnocellularis (NM), which projects bilaterally to the nucleus laminaris (NL). NL neurons detect interaural time differences, which are important for sound localization. Auditory input to NL neurons is segregated: axons from the ipsilateral NM synapse on dorsally directed dendrites, while axons from the contralateral NM synapse on



Chicken NL neurons receive inputs from the ipsilateral and contralateral ear on dorsal and ventral dendrites, respectively. See the article by Wang and Rubel for details.

ventral dendrites. Dorsal and ventral dendritic trees normally are similar in size, but severing afferents from the contralateral NM causes rapid retraction of ventral dendrites, without significantly altering dorsal dendrites. In principle, dendritic retraction could be caused by the loss of synaptic input or by inhibitory molecules released from degenerating axons; work by Wang and Rubel supports the former hypothesis. Injecting tetrodotoxin into one ear—thus reducing spiking of downstream NM neurons—caused retraction of ipsilateral dorsal dendrites and contralateral ventral dendrites. Interestingly, after recovery from tetrodotoxin, both dendritic arbors regrew to control length.

■ Behavioral/Systems/Cognitive

Neonatal Undernutrition Stunts Kisspeptin Axon Growth

Emilie Caron, Philippe Ciofi, Vincent Prevot, and Sebastien G. Bouret

(see pages 11486–11494)

Gonadotropin-releasing hormone (GnRH) is essential for the onset and maintenance of reproductive function. Pulsatile release of GnRH from hypothalamic neurons in the median preoptic nucleus (MEPO) stimulates release of pituitary gonadotropins, which in turn regulate ovulation, spermatogenesis, and release of estrogen and testosterone. At puberty, GnRH neurons are activated by increased kisspeptin release from neurons of the hypothalamic arcuate (ARH) and anteroventral periventricular nuclei, which project to the MEPO. Physiological stressors, such as low energy stores, reduce kisspeptin synthesis and thus delay puberty. Caron et al. suggest that impairment of the kisspeptin system also contributes to delayed puberty induced by neonatal undernutrition. Female mice that were underfed as a result of being placed in artificially large litters had a lower density of ARH-derived kisspeptin-positive fibers in the MEPO at the time they reached puberty, compared with controls. Moreover, the reduction persisted into adulthood, even though mice received food *ad libitum* after weaning.

♦ Neurobiology of Disease

Carbonylation of Complex I Parallels Epileptogenesis

Kristen Ryan, Donald S. Backos, Philip Reigan, and Manisha Patel

(see pages 11250–11258)

Traumatic brain injury can lead, after a latent period, to progressive development of spontaneous recurrent seizures. Epileptogenesis is thought to involve loss of specific populations of GABAergic neurons together with formation of recurrent excitatory circuits via axonal sprouting. The molecular events underlying neurodegeneration and sprouting are incompletely understood. Reactive oxygen species (ROS) often accumulate after brain injury, prompting Ryan et al. to hypothesize that oxidative modification of components of the mitochondrial electron transport chain (ETC) may contribute to neurodegeneration during epileptogenesis. In a rat model, oxidative carbonylation of an arginine residue in ETC complex I increased in the hippocampus immediately after status epilepticus. Carbonylation levels remained constant during the latent period, but increased again as spontaneous seizures appeared. Computer models predicted that the modification disrupts electron transfer, and indeed, a decrease in complex I activity paralleled increases in carbonylation. This is expected to further increase ROS levels, and the resulting oxidative stress may underlie degeneration.