Designing Inhibition

Sedation and Anesthesia Mediated by Distinct GABA<sub>A</sub> Receptor Isoforms


The discovery of general anesthetics >150 years ago made surgery feasible, but their mechanism of action is still poorly understood. Although once thought to act by altering membrane fluidity, recent studies implicate membrane receptors and channels as the site of action of anesthetics. The general anesthetic etomidate selectively potentiates β2- and β3-subunit-containing GABA<sub>A</sub> receptors. Now Reynolds et al. report that the two receptor subtypes differentially affect sedation and anesthesia. A single asparagine residue, N265, in the second transmembrane domain controls etomidate sensitivity. Thus the authors made a mouse with a β2 N265S mutation. The mutant mice had normal expression and properties of GABA<sub>A</sub> receptors, but β2-containing receptors were now etomidate-insensitive. Interestingly the mutant mice remained sensitive to the anesthetic properties of the drug, suggesting that β3-containing receptors are sufficient to produce anesthesia. In contrast, the sedative properties of a subanesthetic dose were present only in wild-type mice, suggesting that β2-containing receptors mediate the sedative effects. These results provide additional support to the idea that the actions of general anesthetics are anything but general, but rather act on specific proteins with actions determined by the expression pattern of those proteins. Such studies should give drug designers the strength to carry on.

Making “Demented” Neurons

Analysis of Neurons Created from Wild-Type and Alzheimer’s Mutation Knock-In Embryonic Stem Cells by a Highly Efficient Differentiation Protocol

Yoichiro Abe, Keisuke Kouyama, Taisuke Tomita, Yusuke Tomita, Norimitsu Ban, Mikiro Nawa, Masaaki Matsuoka, Takako Niikura, Sadakazu Aiso, Yoshiko Kita, Takeshi Iwatsubo, and Ikuo Nishimoto

One hurdle in the advancement of research into the mechanisms of Alzheimer’s disease (AD) and other neurodegenerative diseases is the absence of an available source of “demented” neurons for cellular and molecular diseases. Abe et al. provide one approach to this problem. They used a two-step genetic engineering protocol to generate cultured neurons with an AD genotype. First they introduced an amyloid precursor protein (APP) mutation that causes familial AD (V642I) into embryonic stem (ES) cells using knock-in technology. They then used an in vitro protocol to differentiate a high percentage of ES cells into postmitotic neurons. The neurons expressed typical neuronal markers and showed increased production of APP. The V642I cells also showed increased secretion of the APP cleavage product Aβ42, the neurotoxic fragment that is a component of senile plaques in AD. The V642I cells did not show increased apoptotic death during the 3 weeks in culture and did not express hyperphosphorylated tau. These “AD” neurons and this strategy may be useful for studies of APP processing as well as other neurodegenerative diseases.

Efficacy of Retinal Spikes in Driving Cortical Responses

Prakash Kara and R. Clay Reid

Retinal ganglion cells (RGCs) connect to simple cells of layer 4 of the primary visual cortex via relay neurons in the lateral geniculate nucleus. Kara and Reid took on the seemingly heroic task of determining the effect of a single RGC on the activity of simple cortical cells. Studies by Lee et al. in the 1970s had indicated that it was possible to detect such disynaptic connections. In the current work, the authors made simultaneous recordings from 284 cell pairs. The 12% of pairs that were functionally connected showed shared spatial and temporal features, receptive fields, and sign (i.e., ON or OFF). The second of a pair of retinal spikes also increased the efficacy of driving a cortical cell (“paired-spike enhancement”). It appears that even a single retinal cell can drive a simple cortical cell, consistent with highly precise and efficacious synaptic transfer in these visual pathways.