This Week in The Journal

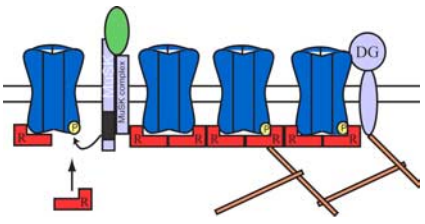
● Cellular/Molecular

Agrin-Dependent Clustering of Acetylcholine Receptors

Lucia S. Borges, Sergey Yechikhov, Young I. Lee, John B. Rudell, Matthew B. Friese, Steven J. Burden, and Michael J. Ferns

(see pages 11468–11476)

Rapid, effective neural transmission depends on clustering of neurotransmitter receptors at postsynaptic sites, which is mediated by interactions between receptors and scaffolding proteins. Clustering of acetylcholine receptors (AChRs) at the neuromuscular junction has been widely studied, and many of the molecules required for clustering have been identified. Still, many questions remain. AChR clustering requires agrin, which is secreted by nerve terminals and activates muscle-specific kinase (MuSK). MuSK phosphorylates AChR subunits, promoting clustering, but how phosphorylation regulates receptor interactions with scaffolding proteins is not known. Using chimeric proteins constructed with various intracellular domains of AChR subunits, Borges et al. found that the only essential domain was the one phosphorylated by MuSK. Agrin-dependent phosphorylation of this domain enabled it to interact with the scaffolding protein rapsyn, thus increasing the number of rapsyn molecules bound to AChR. This could improve clustering by packing receptors more tightly or by anchoring receptors more firmly to the cytoskeleton.



Model of molecular interactions at the neuromuscular junction. Agrin (green)-dependent phosphorylation (yellow) of AChR (blue) increases the number of rapsyn molecules (red) bound to the receptor and stabilizes the receptor cluster. See the article by Borges et al. for details.

▲ Development/Plasticity/Repair

Glial Chain Migration

Benoît Aigouy, Léa Lepelletier, and Angela Giangrande

(see pages 11635–11641)

During development, cells often migrate in large groups or chains. Usually a few cells at the front of a chain explore the environment and determine the migratory path, with the remaining cells following by an unknown mechanism. Aigouy et al. examined glial chain migration along nerves *in vivo* in developing *Drosophila* wings. Ablation of four cells at the front of the migrating chain severely disrupted migration, leading to gaps in the chain and/or cessation of migration. Such defects were not seen when follower glia were ablated, suggesting that only a few pioneer glia were required to guide migration. Unlike typical migrating cells, the pioneer glia did not detach their trailing edges from the substrate as they moved forward. Instead the trailing edge remained attached, producing a cytoplasmic extension that could be 60 μm long. Follower glia contacted these trailing extensions as they migrated, suggesting the extensions guide the followers.

■ Behavioral/Systems/Cognitive

Probability Distortions in the Brain

Philippe N. Tobler, George I. Christopoulos, John P. O'Doherty, Raymond J. Dolan, and Wolfram Schultz

(see pages 11703–11711)

People often make decisions that do not accurately reflect the probability of reward. For example, people may choose an option that is rarely rewarded more often than warranted by its average payoff. Tobler et al. have examined where this "probability distortion" occurs in the brain. They showed subjects stimuli that had no subjective value, and paired each stimulus with a reward on some percentage of trials. After many trials, subjects were asked to rate the value of the stimuli. Many subjects overrated stimuli that had relatively low probability of reward and underrated stimuli that had high probability of reward. This value distortion was reflected in activity in the dorsolateral prefrontal cortex. In contrast, some subjects underrated stimuli with low reward probability and overrated stimuli with high reward probability, and this distortion was reflected by activity in the ventral frontal cortex. The former distortion decreased with experience, while the latter distortion increased.

♦ Neurobiology of Disease

Dual Role of Microglia in Alzheimer's Disease

Sebastian Jimenez, David Baglietto-Vargas, Cristina Caballero, Ines Moreno-Gonzalez, Manuel Torres, Raquel Sanchez-Varo, Diego Ruano, Marisa Vizuete, Antonia Gutierrez, and Javier Vitorica

(see pages 11650–11661)

Alzheimer's disease (AD) is characterized by neurofibrillary tangles, amyloid plaques, and activated microglia, but it is not clear whether these features cause the neurodegeneration associated with the disease, or if instead they represent the brain's attempt to protect itself from toxic agents. This week Jimenez et al. report that microglia can be either neuroprotective or neurodegenerative in a mouse model of AD, depending on their activation state. When amyloid plaques first appeared, activated microglia were exclusively localized around the plaques. These microglia did not express potentially cytotoxic molecules. Instead, the microglia phagocytosed plaques, suggesting they help to clear amyloid deposits. In older animals, concomitant with a 15-fold increase in soluble amyloid-β and the onset of pyramidal cell death, activated microglia were more widespread. Those that surrounded plaques retained the neuroprotective phenotype, but elsewhere microglia expressed pro-inflammatory and potentially toxic molecules. *In vitro* studies showed that oligomeric soluble amyloid induced the pro-inflammatory microglial phenotype.