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Previews

TrkB Works at Postsynaptic Sites

The classical view of neurotrophins as target-derived survival factors in the developing nervous system has changed dramatically in the last few years, perhaps due to the application of improved perturbation techniques and more detailed analyses of cellular phenomena. Brain-derived neurotrophic factor (BDNF) and its corresponding TrkB receptor have been found to be involved in many aspects of neural plasticity, ranging from regulation of synaptic strength to structural plasticity of neural circuits. For example, BDNF, acting through TrkB receptors, can rapidly modulate synaptic transmission (Berninger and Poo, 1996; Black, 1999) and is also involved in modifying axonal as well as dendritic morphology (Cohen-Corey and Fraser, 1995; McAllister et al., 1999). Either chelating the endogenous TrkB ligands BDNF or NT-4/5 or infusing excess TrkB ligands prevents the formation of ocular dominance columns in mammalian primary visual cortex, a classical model of activity-dependent synaptic plasticity (Cabelli et al., 1995, 1997). Thus, the TrkB-mediated signaling pathway plays diverse roles in synaptic patterning in the developing nervous system. Little is known, however, about the roles of neurotrophins and the Trk receptors in the maintenance of neuronal connections, despite the fact that they are expressed in many parts of the nervous system throughout life.

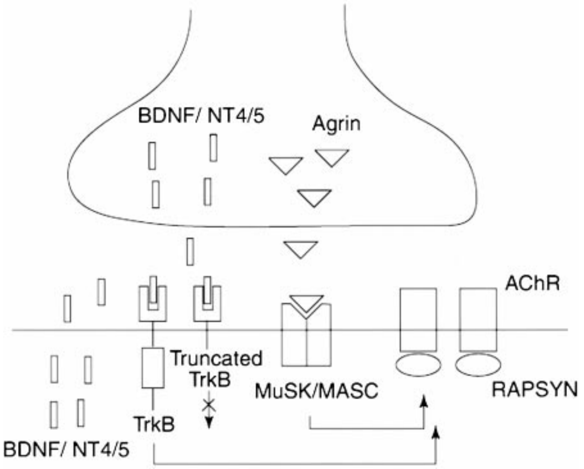
Gonzalez and colleagues (1999 [this issue of *Neuron*]) provide several lines of evidence suggesting that TrkB signaling plays an important role in maintaining postsynaptic ACh receptors (AChRs) at neuromuscular junctions in vivo. Because mutant mice lacking TrkB die at birth, the disruption of the normal TrkB signaling in muscle fibers was achieved in a dominant-negative fashion by using an adenovirus vector to overexpress inactive truncated TrkB (trkB.t1). Two to four weeks after overexpressing the truncated TrkB in either neonatal or adult muscle in vivo, the authors observed many small punctate AChR clusters that often contained low receptor density. This is in contrast to the contiguous AChR branches normally found at the neuromuscular junction. Interestingly, this disruption of the normal AChR pattern did not require the presence of nerve terminals and Schwann cells: overexpressing truncated TrkB in cultured myotubes also caused disassembly of preexisting AChR clusters. This suggests that the TrkB signaling in the muscle fiber could operate in an autocrine fashion, since BDNF and NT-4/5 are expressed in muscle.

As truncated TrkB normally exists in muscle fibers and its function is not entirely clear, one concern about this overexpression paradigm is the generation of nonspecific effects. It is conceivable that the concentration of overexpressed truncated TrkB is well outside the physiological range, so that the observed effect may be nonspecific to the disruption of TrkB-mediated signaling. This concern, however, is alleviated by two experimental observations. First, the disruption of receptor clusters was specific for truncated TrkB because overexpression of homologous truncated TrkA had no effect on the pattern of receptor clusters. Furthermore, in mutant *trkB*$^{+/-}$ mice in which the level of TrkB expression is reduced, small punctate AChR regions are also observed. The morphological similarity of receptor clusters in *trkB*$^{+/-}$ and truncated TrkB–overexpressing muscle fibers is consistent with the view that TrkB-mediated signaling is involved in the AChR clustering.

How does TrkB regulate AChR clustering at the postsynaptic site? It is known that nerve-derived agrin is both necessary and sufficient to induce receptor clustering. The agrin signaling pathway has not yet been fully elucidated. Current wisdom is that agrin clusters and activates a transmembrane protein tyrosine kinase, MuSK, which is responsible for phosphorylation of other synaptic components including AChRs, possibly through a different kinase (Sanes and Lichtman, 1999). Thus, in mammalian muscle, agrin-induced AChR clustering requires multiple steps involving phosphorylation of several synaptic components. In addition, tyrosine phosphatases are also involved in regulating the formation of receptor clusters and the stability of preexisting receptor clusters (Dai and Peng, 1998). The activated TrkB receptors could directly influence AChR clustering by phosphorylating any of these components. Alternatively, TrkB could indirectly alter the stability of preexisting AChR clusters through effects on the AChR anchoring proteins or components of the cytoskeleton (see figure). Interestingly, recent studies have shown that TrkB-mediated signaling inhibits agrin-induced AChR clustering on cultured myotubes (Well et al., 1999), suggesting that TrkB may play a different role in initial AChR clustering from its role in maintaining preexisting clusters.

The unique advantage of studying receptor clustering at neuromuscular junctions is that the high density of AChRs at the postsynaptic sites makes it possible to detect subtle morphological changes. It would be interesting to know whether TrkB affects primarily ACh receptor clustering or other properties of muscle fibers such as sodium channel clustering. Knowing more details concerning the time course of the disassembly of AChR clusters after overexpressing truncated TrkB, perhaps by following the same junction over time, may provide insight into whether TrkB regulates clustering of new AChRs and/or maintains the preexisting receptors. For example, if the disruption of receptor patterning observed by Gonzalez et al. (1999) occurs well before the normal half-life of the receptors (about 10 days), we could infer that TrkB is essential for the maintenance of preexisting receptors. It would also be interesting to overexpress full-length TrkB in *trkB*$^{+/-}$ mutant mice to see if TrkB is sufficient to maintain the normal pattern of receptor clusters.

Recent studies indicate that synaptic activity rapidly regulates the stability of receptors at the neuromuscular junction in vivo (Akaaboune et al., 1999). The work by Gonzalez and colleagues (1999) raises the possibility



TrkB Signaling Regulates AChR Clustering at the Neuromuscular Junction

that TrkB may be involved. It is worth noting that neuronal activity can markedly increase BDNF expression in hippocampal neurons. Furthermore, BDNF rapidly and substantially increases responsiveness of NMDA receptors, probably by enhancing tyrosine phosphorylation of the NMDA receptor subunits NR1 and NR2B in the postsynaptic density (Black, 1999). Thus, in addition to its traditional role in cell survival, TrkB may play an important role in activity-dependent regulation of both the responsiveness and stability of postsynaptic receptors. Such activity-dependent regulation of postsynaptic receptor properties may underlie the mechanisms for the induction of long-term potentiation, a correlate of learning and memory (Malenka and Nicoll, 1999).

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Whisking Away Space in the Brain

Information about the world around us continuously bombards the brain. The salient features of this stream of input are reflected in the mosaic of maps that tile the neocortex. These maps are highly dynamic and can be sculpted by the very experiences they represent. Thus, a lost limb's cortical space is reallocated to other body regions, an open eye comes to dominate the visual response after a period of monocular occlusion, or a routinely encountered tone is overrepresented in auditory cortex (Buonomano and Merzenich, 1998). What these and myriad other examples collected over the past 40 years all have in common is that inputs with a competitive advantage will enlarge their territory within the limited confines of sensory neocortex. A report by Polley et al. (1999 [this issue of *Neuron*]) now challenges the view that bigger is better.

Polley and colleagues found that removing all but a single whisker on one side of a rat's face can induce either a lasting expansion or a *contraction* of its functional representation in the barrel cortex. The key variable appears to be how that whisker is used during the time the map is being reshaped. If the animals are simply returned to their "boring" home cage, an expansion occurs as expected. However, given brief opportunities to actively explore a "novel" environment, the single whisker representation contracts. Both expansion and contraction reverse upon regrowth of the deprived whiskers. These intriguing observations suggest a mechanism drawn from three emerging themes of cortical function.

The first is that the central concept of the receptive field is undergoing a profound change. In the traditional view, feedforward connections from the periphery—such as one whisker's input into a single cortical barrel—drive their primary targets to fire action potentials and thereby define the receptive field of those cells. Recent evidence reveals that the influence of any given input to cortex extends well beyond its primary zone of termination (Gilbert, 1998). In the visual system, for example, line segments outside the receptive field can influence the orientation tuning of a cell to a line segment within the receptive field. The substrate for these contextual influences lies in the rich plexus of lateral intracortical connections. The findings of Polley et al. (1999) hinge on the method of optical imaging of intrinsic signal responses, which is exquisitely sensitive to these subthreshold interactions. Under their conditions, it is quite evident that the flow of activity upon striking a single whisker radiates across several barrels.

Second, the possibility that a spared whisker representation may then *contract* naturally draws attention to suppressive or inhibitory processes. Sensory deprivation can regulate short-term depression at individual