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Previews

Noradrenaline Enhances Signal-to-Noise Ratio of Inhibitory Inputs in the Dorsal Cochlear Nucleus

Shaul Hestrin[1,*]
[1]Department of Comparative Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
*Correspondence: shaul.hestrin@stanford.edu
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What are the mechanisms that enhance the response to behaviorally relevant external stimuli? In this issue of *Neuron*, Kuo and Trussell show that in the dorsal cochlear nucleus, noradrenaline functions to simultaneously reduce spontaneous inhibitory inputs while increasing evoked inhibition.

Neurons are bombarded by ongoing excitatory and inhibitory inputs. What are the mechanisms that allow a neuron to detect the arrival of an input carrying an important message requiring an immediate specific response? In this issue of *Neuron*, Kuo and Trussel (2011) reveal a robust mechanism that begins to answer this question by exploring the effects of noradrenaline (NA) on inhibitory inputs at fusiform cells, the principal cells of the mouse dorsal cochlear nucleus (DCN). Inhibitory inputs in DCN fusiform cells occur as spontaneous IPSCs (sIPSCs) or as feedforward inhibition generated by parallel fiber excitation of cartwheel cells (eIPSCs). Surprisingly, NA dramatically reduced sIPSCs while increasing eIPSCs. Cartwheel cells are the source of both the spontaneous and the evoked IPSCs in fusiform principal cells. Thus, Kuo and Trussell systematically investigated the synaptic mechanisms between cartwheel cells and DCN principal cells to explain the opposing effects of NA.

First, they examined the possibility that NA enhances parallel fiber input at cartwheel cells. However, they demonstrated that NA does not affect excitatory postsynaptic (EPSC) inputs in cartwheel cells. Next, they examined whether cartwheel connection with fusiform cells is modulated by NA. Paired recordings between presynaptic cartwheel cell and postsynaptic fusiform cells indicated that this synapse is also insensitive to NA. They further showed that changes in the membrane potential of cartwheel cells do not affect sIPSCs in fusiform cells. Thus, NA does not appear to act via its conventional presynaptic mechanisms (Berridge and Waterhouse, 2003; Waterhouse and Woodward, 1980).

Next, they considered the possible impact of NA on spontaneous spiking of cartwheel cells. They first showed that cartwheel to fusiform cells exhibit activity-dependent synaptic depression. Further using paired recordings, they showed that the recovery from synaptic depression is slow (time constants of 5–6 s). Given that cartwheel cells exhibit spiking at about 8–13 Hz (Davis and Young, 1997; Golding and Oertel, 1997), their synapses are not allowed to recover and exhibit ongoing depression. Thus, spontaneous spiking in cartwheel cells has two consequences. First, this activity generates sIPSCs in their postsynaptic cells, i.e., fusiform cells, and second, this ongoing spiking activity generates persistent synaptic depression. Using cell-attached recording, Kuo and Trussell showed that the spontaneous spiking of cartwheel cells is silenced by application of NA. Thus, by blocking ongoing spiking, NA reduced sIPSCs and at the same time increased feedforward IPSCs by allowing recovery from the persistent synaptic depression. Furthermore, the authors demonstrate that both NA silencing of sIPSCs and enhancement of feedforward inhibition is mediated solely by α2-adrenergic receptors. Although the downstream effectors of NA receptor activation in cartwheel cells were not addressed, modulation of GIRK channels could be a likely candidate (Williams et al., 1985).

Short-term plasticity is conventionally thought of as an activity-dependent process regulating synaptic strength (Zucker and Regehr, 2002). In a typical experiment, the impact of increasing levels of activity on synaptic strength is investigated. Given that in vivo and sometimes in vitro neurons exhibit ongoing activity, reducing neuronal firing will affect synaptic strength as well. Under these conditions, when synaptic connections exhibit activity-dependent synaptic depression, reducing spiking will appear as facilitation (or pseudo facilitation) caused by recovery from synaptic depression. Similar phenomena have been previously investigated in other systems (e.g., Abbott et al., 1997; Galarreta and Hestrin, 2000).

It is interesting to contrast the results reported here with previous study of NA impact on inhibitory synapses among cerebellar stellate cells (Kondo and Marty, 1998). In the cerebellum, NA increased the rate of spontaneous IPSCs while reducing evoked IPSCs (Kondo and Marty, 1998). These effects are most likely the result of NA increasing the firing rate of stellate cells without affecting synaptic release per se (Kondo and Marty, 1998). Thus, the mechanisms underlying NA effect on DCN cartwheel cells and on cerebellar stellate cells are strikingly similar in principal, although they produce opposite outcomes.

The results presented here raise two important issues. First, it is likely that high activity of locus coeruleus (LC) neurons during vigilant states will result in increased concentration of NA. However, as pointed out by Kuo and Trussell, the spatial and temporal concentration of NA in relation to activity of locus coeruleus is not known. Kuo and Trussell have shown that NA reduces spontaneous cartwheel spiking, but other cellular components may also be targeted by NA. Further, whether LC axons release NA diffusely over all elements in the DCN or alternatively can modulate select targets is an open question. Second, and more important, how the impact of NA on cartwheel

cells affects information processing in the DCN remains to be elucidated. The authors present a feasible model whereby NA modulation of cartwheel cells may function to filter auditory information during states of attention and wakefulness. Further analysis of the physiological action of NA can be advanced by controlling activity of LC axons and studying the impact of endogenously released NA. It was shown recently that optogenetic approaches can be used to selectively activate LC axons (Carter et al., 2010). The findings by Kuo and Trussell present the opportunity to experimentally address the functional significance of NA modulation by applying these optogenetic tools to investigate how NA release from LC axons impacts the strength of cartwheel cell synapses in vitro and auditory information processing in the DCN in vivo. It is thus safe to predict that in the near future the elegant analysis of NA action accomplished by Kuo and Trussell in vitro will be integrated together with in vivo studies of NA action in intact animals.

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How Glutamate Receptor Subunits Mix and Match: Details Uncovered

Kasper B. Hansen[1,*] and Stephen F. Traynelis[1]
[1]Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kbhanse@emory.edu
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Until now, the atomic details explaining why certain subunits prefer to coassemble has been lacking in our understanding of glutamate receptor biogenesis. In this issue, Kumar et al. describe the structural basis by which preferential subunit assembly occurs for homomeric and heteromeric kainate-type glutamate receptors.

The requirement for assembly of multiple subunits to form a functional oligomeric complex is a shared property among ligand-gated ion channels. Several different gene products for channel subunits exist within virtually all ion channel families. This subunit multiplicity in theory allows the cell to tailor specific populations of receptors to match the needed physiological roles, a process that is typically considered dynamic. Receptors comprised of different subunit combinations often have strikingly different subcellular localization or trafficking properties and may activate and desensitize differently in response to agonist binding. The potential for cells to fine tune receptor properties through altering subunit combination is a prominent feature of the ionotropic glutamate receptors, which are the primary mediators of excitatory synaptic transmission (Traynelis et al., 2010). Following cloning of the 18 different glutamate receptor subunits almost two decades ago, it soon became apparent that certain combinations of subunits preferred to coassemble to form functional receptors in heterologous expression systems, and groups of subunits that coassembled nicely matched known receptor subfamilies (AMPA-, kainate-, and NMDA-type). This led to the obvious hypothesis that mechanisms must exist to tightly control the specificity and stoichiometry of subunit assembly. The idea that subunit assembly is tightly regulated became more intriguing when it was discovered that some neurons express several different glutamate receptor subunits capable of forming multiple homomeric and heteromeric receptor subtypes, yet only distinct subunit combinations seemed to be functionally expressed (e.g., see Lu et al., 2009). These observations hinted that assembly is not a simple stochastic process and that not all subunits are free to mix and match even within subfamilies of glutamate receptors.

Recent work on a variety of fronts has cast a spotlight on the roles of the extracellular amino-terminal domains (ATDs) of the glutamate receptor subunits (Hansen et al., 2010). These regions form a semiautonomous domain of ~400 amino