Spontaneous generation in early sensory development

Focus on: "Spontaneous Discharge Patterns in Cochlear Spiral Ganglion Cells Prior to the Onset of Hearing in Cats"

Sensory systems are our gateways to the outside world. How are these complex systems - sensory organ and the associated brain pathways - set up during development? Molecular cues are of course essential in establishing many basic cellular characteristics and the connections between all elements of a sensory pathway (Friauf and Lohmann 1999; McLaughlin and O'Leary 2005). However, as soon as the peripheral receptors start functioning, the incoming sensory experience commonly serves to guide the final maturation of central neural properties and circuits during a critical period (Berardi et al. 2000; Fox and Wong 2005; Grubb and Thompson 2004). Interestingly, activity-dependent plasticity may even begin before there is any sensory input. In the best-studied case, the visual system of mammals, spatially-patterned spontaneous electrical activity is generated within the retinas for a transient period before the onset of photoreceptor function (Wong 1999). This activity is believed to instruct the correct formation of central circuits through Hebbian-type activity-dependent, synaptic competition (Demas et al. 2006; Sengpiel and Kind 2002). In a challenging series of experiments published in this issue of Journal of Neurophysiology, Jones et al. (2007) show that temporally patterned spontaneous activity is also present in the auditory nerve of pre-hearing kittens in vivo. The authors were able to exclude internal body noises as artefactual stimuli and provide the strongest evidence yet that the pattern of spontaneous activity is intrinsically generated. Thus, like the retina, the cochlea appears to spontaneously generate patterned activity during a restricted pre-hearing period, which in this case also may provide the brain with an instructive signal for the refinement of central circuits.
A multitude of evidence across sensory modalities has firmly established activity-dependent plasticity as an important principle in the development of sensory systems. During a critical and limited time period, abnormal sensory experience is able to drastically and permanently alter the neural circuits laid down earlier in development. Examples include the classic monocular deprivation experiments by Hubel and Wiesel (1977), resulting in major changes to ocular dominance columns in visual cortex, the re-calibration of auditory space representations by abnormal auditory or visual experience (King et al. 2000; Knudsen 1999), changes in somatosensory cortex representations after selective whisker deprivations (Fox 1992) and the failure to eliminate inappropriate connections in the olfactory bulb upon unilateral naris closure (Zou et al. 2004). These modifications can be assumed to be adaptive under natural conditions. The young sensory system uses information from its actual environment to refine and tailor to individual conditions the topographic connections and representations along sensory pathways, beyond what is possible and could be anticipated by genetic determination alone. The mechanisms underlying these modifications, where known, are consistent with the Hebbian-type processes of synaptic long-term potentiation and depression (Berardi et al. 2003; Foeller and Feldman 2004; Fox and Wong 2005; Knudsen 1999).

Intriguingly, some activity-dependent modifications begin even before the peripheral receptors are functional or before stimuli can reach them, so, clearly, sensory experience cannot be involved. In the mammalian visual system, neural activity is necessary for the segregation of alternate layers of eye-specific projections from the retinae to the thalamus and this segregation is completed before the onset of photoreceptor function (Sengpiel and Kind 2002). The same is true for the refinement of the retinotopic projection to the midbrain (McLaughlin and O'Leary 2005; Wong 1999). Similarly, in the auditory system, several examples of activity-dependent
refinements are now known which are completed before the onset of hearing. These include sharpening of tonotopic projections between the cochlea and the brainstem (Leake et al. 2006), segregation of ear-specific input layers in the auditory midbrain (Gabriele et al. 2000) and formation of a tonotopic gradient in cell membrane physiology in an auditory brainstem nucleus (Leao et al. 2006).

Where does this essential pre-sensory activity originate? In principle, spontaneous neural discharge, as commonly present at all levels of sensory systems, could serve as a permissive signal for further development to proceed. However, in the visual system, the signal appears to be instructive, i.e. the relative levels of inputs and their spatiotemporal correlation are important. Spontaneous waves of electrical activity are generated in each retina, which results in a rhythmic bursting pattern that is highly correlated between afferents from neighbouring retinal regions, but uncorrelated between afferents from the two eyes (Wong 1999). This kind of input in theory enables the segregation of eye-specific inputs or refinements of retinotopic representations based on Hebbian-type mechanisms, and most manipulations of the spontaneous retinal activity disrupt normal development accordingly (Demas et al. 2006; Feller 2002; Sengpiel and Kind 2002; Wong 1999).

The new work by Jones et al. (2007) strongly supports the notion that similar principles apply to the auditory system and thus perhaps generally to sensory systems. They recorded the spontaneous spiking activity of cochlear ganglion cells which are directly connected to the sensory hair cells, during the pre-hearing developmental phase of the cat. The majority of cells showed a discharge pattern of irregular bursting, quite unlike the mature pattern of stochastic spontaneous discharge. Importantly, Jones et al. (2007) went to great lengths to ascertain that this bursting pattern was intrinsically generated and not the product of mechanical
stimulation associated with heart beat or respiration. This is a valid concern because the deafness to external sounds at the ages used is partly due to a closed ear canal and an immature middle ear blocking the normal sound transmission pathway (Walsh et al. 1986), while hair-cell transduction is most likely already functional, albeit immature (Goodyear et al. 2006; Lindeman et al. 1971). In a previous study, recording single units from the cochlear ganglion of embryonic chickens as young as incubation day 13 (of 21), Jones et al. (2001) found both regular and irregular spontaneous bursting. In addition, these immature patterns were gradually replaced by adult-like spontaneous rates and patterns of discharge as development progressed and disappeared within a short time after the onset of hearing (Jones and Jones 2000; Jones et al. 2001). This development closely paralleled similar observations of spontaneous bursting activity in second- and third-order auditory brainstem nuclei and confirmed earlier suggestions that the source of the activity is indeed the cochlea (Lippe 1994). Together, the cat and chicken data provide compelling evidence for temporally patterned spontaneous activity being generated in the cochlea during a restricted pre-hearing developmental period.

Lots of exciting questions remain to be answered. Where exactly is the origin of this early spontaneous cochlear activity? How is the bursting pattern generated? Is it synchronised between neighbouring hair cells and afferent neurones? A promising candidate for the origin of activity are the hair cells themselves. Around the appropriate developmental stages, auditory hair cells of chickens and mice (in the latter, specifically the inner hair cells) express an immature complement of ion channels which enables them to produce $\text{Ca}^{2+}$ spikes (Goodyear et al. 2006). Hair-cell spiking was observed spontaneously \textit{in vitro}, but whether this also occurs \textit{in vivo} remains to be explored. At the same developmental stages, efferent neurones of the brainstem form transient synapses with inner hair cells but these are retracted again
around the onset of hearing (Pujol et al. 1998). Given the rather extensive branching patterns of individual efferent axons (Simmons et al. 1990), this transient efferent innervation may provide a substrate for synchronising the activity of localised hair-cell groups in the cochlea. Immature hair cells are responsive to the efferent transmitter at this stage (Kros 2007), suggesting the synapses are functional. It has been suggested that the efferents may rhythmically drive or modulate hair-cell activity (Kros 2007; Walsh and McGee 1997). This idea has received some indirect support (Walsh and McGee 1997) and clearly deserves further attention.

Keep your ears peeled for more exciting developments.


