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Review

Return of function after hair cell regeneration

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ABSTRACT

The ultimate goal of hair cell regeneration is to restore functional hearing. Because birds begin perceiving and producing song early in life, they provide a propitious model for studying not only whether regeneration of lost hair cells can return auditory sensitivity but also whether this regenerated periphery can restore complex auditory perception and production. They are the only animal where hair cell regeneration occurs naturally after hair cell loss and where the ability to correctly perceive and produce complex acoustic signals is critical to procreation and survival. The purpose of this review article is to survey the most recent literature on behavioral measures of auditory functional return in adult birds after hair cell regeneration. The first portion of the review summarizes the effect of ototoxic drug induced hair cell loss and regeneration on hearing loss and recovery for pure tones. The second portion reviews studies of complex, species-specific vocalization discrimination and recognition after hair cell regeneration. Finally, we discuss the relevance of temporary hearing loss and recovery through hair cell regeneration on complex call and song production. Hearing sensitivity is restored, except for the highest frequencies, after hair cell regeneration in birds, but there are enduring changes to complex auditory perception. These changes do not appear to provide any obstacle to future auditory or vocal learning.

This article is part of a Special Issue entitled "Inner Ear Development and Regeneration".

1. Introduction

Understanding how molecular and genetic cues regulate and control hair cell regeneration is critical if we are to discover a way to regenerate hair cells in humans. Ultimately, though, the goal is to restore functional hearing. Birds offer a unique model for achieving this goal. They are the only animal model where it is possible to restore hearing through hair cell regeneration and then examine the effect of these newly created hair cells on the recovery of complex auditory perception that supports vocal learning and production. Several studies have shown that both young and adult birds experience hair cell loss in response to acoustic trauma or ototoxic insult. This loss is subsequently followed by restoration of hair cell numbers through a mitotic or conversion response and culminates in physiological and even behavioral recovery of auditory sensitivity within a matter of weeks (Corwin and Cotanche, 1988; Ryals and Rubel, 1988; Tucci and Rubel, 1990; Girod et al., 1991; Hashino et al., 1991; Lippe et al., 1991; Saunders et al., 1992,1996; Ryals et al., 1999). Recent reviews of the recovery of auditory function following hair cell regeneration in birds have focused primarily on electrophysiological measures of the auditory system (compound action potential (CAP), auditory brainstem response (ABR), etc.) or changes in hair cell responses using otoacoustic emissions (e.g. Smolders, 1999; Saunders and Salvi, 2008). While these physiological measures are highly correlated with the return of hearing, behavioral measures of hearing most directly address the actual recovery of auditory perception. Dooling et al. (2008) reviewed both physiological and behavioral studies of the return of hearing after hair cell regeneration. The current review summarizes some of these same behavioral studies (Dooling et al., 2008) with a clear focus on the relation between auditory function and vocal production as the "gold standard" for understanding the true behavioral consequences of recovery following hair cell regeneration.

The two primary methods by which hair cells have been damaged in order to induce the regenerative response in birds are acoustic overstimulation and ototoxic injury. Both of these

Abbreviations: CAP, compound action potential; ABR, auditory brainstem response; BWS, Belgian Waterslager canary; DPOAE, distortion product otoacoustic emission; BP, basilar papilla; SPL, sound pressure level; PTS, permanent threshold shift.

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conditions result in loss of hair cells; in the case of acoustic overstimulation other inner ear structures such as supporting cells, tegmentum vasculosum and neural synapses are also damaged or destroyed. Because acoustic overstimulation does not selectively damage hair cells, and because it has been difficult to damage a continuous sheath of hair cells along the epithelium without causing damage to other inner ear structures using noise exposure, studies of functional hearing return after acoustic trauma have not been particularly informative about the ability of regenerated hair cells to restore functional hearing. In fact, Saunders and Salvi in a recent review (2008) conclude that hair cell regeneration likely plays a relatively minor role in the recovery of physiological function following acoustic trauma in birds. On the other hand, studies using ototoxic injury are much more structurally specific to hair cells and can damage an extensive and continuous sheath of hair cells along the basilar papilla. Thus the current review will focus on behavioral studies of the recovery of auditory sensitivity and complex perception after ototoxic injury.

Finally, several studies have taken advantage of the avian model to study the relationship between the return of auditory function and changes in vocal learning or production. The interplay between auditory learning and vocal production has great relevance to the ultimate goal of restoration of complex communication through a regenerative therapy and so these studies will also be a focus of the review. In addition, we will explore the potential role of genetic hearing loss on the ability for regenerated hair cells to provide recovery of functional hearing by reviewing auditory sensitivity and perception in the Belgian Waterslager canary (BWS). The Belgian Waterslager canary has a genetic hearing loss but also retains the ability to regenerate hair cells. This unique model may provide insight into the potential influences or limitations that underlying genetic pathology has on the ability to restore auditory function through regeneration.

2. Changes in auditory sensitivity

In order for hair cells to be functional they must form and express the appropriate ionic channels and currents. Levic et al. (2007) showed that individual regenerated hair cells harvested after ototoxic injury in adult chickens recapitulated the ionic currents shown in developing hair cells. Other less direct measures of regenerated hair cell viability, such as the cochlear microphonic and distortion product otoacoustic emissions, have also shown some return of function following regeneration (see Saunders and Salvi, 2008 for review). The cochlear microphonic shows substantial but incomplete recovery 11–14 weeks after ototoxic injury and hair cell regeneration (Chen et al., 2001; Sun et al., 2002), confirming recovery of transduction currents in regenerated hair cells. Distortion product otoacoustic emission (DPOAE) thresholds, input–output responses and amplitudes show partial to full recovery with the most consistent lingering decline at the highest frequencies (Chen et al., 2001; Norton and Rubel, 1990; Durham et al., 2000). Because avian hair cells apparently lack the somatic motility of mammalian outer hair cells (He et al., 2003), it has been suggested that these measures of cochlear non-linearity are a function of stereocilia bundle resonance (Koppl, 2011). Hair cell bundle irregularities have been reported in regenerated hair cells (Duckert and Rubel, 1993) and Saunders and Salvi (2008) suggest that these continuing abnormalities may be responsible for the lack of full DPOAE recovery, especially at the highest frequencies. ABR and CAP measures of auditory function suggest that threshold sensitivity returns to normal levels within 30–70 days after cessation of ototoxic drug administration for all but the highest frequencies (see for Smolders, 1999; Saunders and Salvi, 2008 for review). Thus physiological evidence predicts that behavioral threshold sensitivity should return to normal levels for all but the highest frequencies after ototoxic injury.

We know that hair cells are restored in birds through supporting cell mitotic division and differentiation as well as a through direct conversion or transdifferentiation (Shang et al., 2010). Electrophysiological studies have yet to work out a way to differentiate the functional contribution of hair cells restored through either of these mechanisms separately. However, ABR thresholds showed recovery of sensitivity in some but not all birds in a recent study where cell division was blocked in vivo (Lin et al., 2008). Further, mammalian hair cell restoration initiated through transdifferentiation resulted in some recovery of auditory brainstem evoked potential sensitivity (Izumikawa et al., 2005).

While physiological measurements might be able to help tease out the contribution of particular anatomical elements to changes in sensitivity, behavioral responses reveal the perceptual consequences of those changes. Fig. 1 shows behavioral audiograms measured after ototoxic drug administration in budgerigars (A), European starlings (B) and canaries (C). The findings are similar in all three species; hearing loss is greatest at the highest frequencies initially after antibiotic injection and recovery is most complete for the lowest frequencies. Recovery appears to plateau by 8 weeks post-injection. This functional loss and recovery follows a frequency pattern predicted by the hair cell loss which initially occurs at the base (highest frequencies on the place frequency map) and proceeds to more apical (lower frequency) regions of the basilar papilla (BP). Interestingly, hair cell numbers recover to within 1 standard deviation of normal within 2–3 months after antibiotic injections but behavioral thresholds continue to show

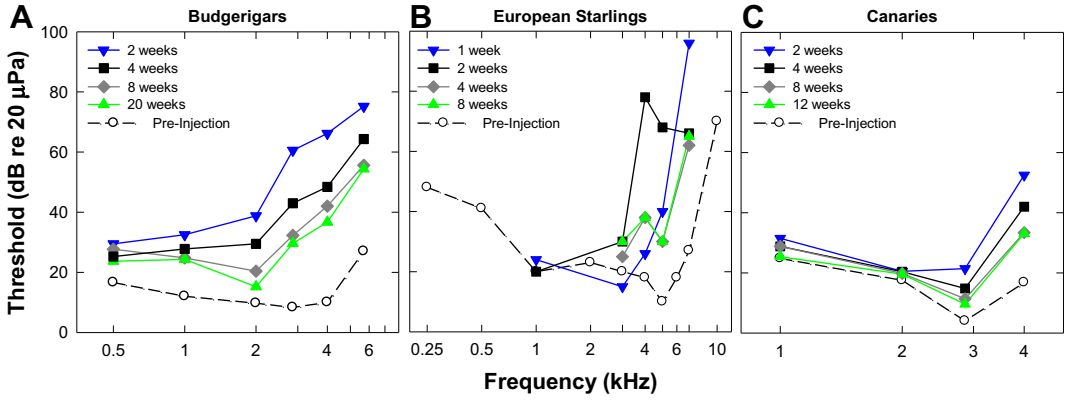

Fig. 1. Behavioral pure tone threshold data are shown for A) budgerigars (Dooling et al., 2006), B) European Starlings (Marean et al., 1993), and C) canaries (unpublished data).