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TUTORIAL

New studies on hair cell regeneration in birds

Robert J. Dooling and Micheal L. Dent

Department of Psychology, University of Maryland, College Park, MD 20742 USA

Abstract: The discovery of hair cell regeneration in birds a little over a decade ago raises a number of obvious and exciting questions about basic functional and neural plasticity in the vertebrate auditory system. Because many birds must learn the complex, species-specific, acoustic signals they use for communication just as humans must learn the sounds of speech, the finding of hair cell regeneration in birds also raises other interesting questions. One of these questions concerns the relation between hearing loss and vocal production. Another question concerns the effect of full or partial hearing recovery on vocal behavior. The purpose of this paper is to review what is known about the functional (*i.e.* behavioral) consequences of hair cell loss and subsequent hair cell regeneration in birds, to point out the relevance of this work for human hearing recovery, and to suggest some directions for future research.

Keywords: Bird, Hearing, Audition, Hair cell, Vocalizations

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1. INTRODUCTION

Long before the discovery of hair cell regeneration in birds, there was intense interest in the role that hearing played in vocal learning and vocal behavior. The experimental manipulation in many of these studies was extirpation of the sensory epithelium of the inner ear, rendering the bird completely deaf. In songbirds, such deafening early in life can have a profound effect on the development of learned vocalizations [1], while deafening later in life often yields more complicated and sometimes more subtle effects. Some songbirds, such as white-crowned sparrows (*Zonotrichia leucophrys*) and chaffinches (*Fringilla coelebs*), can maintain their vocal repertoire for years if deafened in adulthood after song crystallization [2]—a finding initially thought to be related to the fact that these birds, once they learn their songs in youth, normally do not change their song-syllable repertoires as adults (closed-ended learners). By contrast, canaries (*Serinus canaria*), which add and delete song notes seasonally throughout adulthood (open-ended learners), show signs of song disruption within a week of deafening, and profound deterioration within a month [3].

Recent experiments with zebra finches (*Taeniopygia guttata*) and Bengalese finches (*Lonchura striate* var. *domesticus*) have suggested that the story may be more complicated. While both finches are closed-ended learners, zebra finches show signs of song syllable disruption only after 1–2 months of deafening followed by profound deterioration in song over a period of several months [4]. Bengalese finches, on the other hand, show marked changes in song structure even within a few days of deafening, followed by deterioration of song phonology similar to that of zebra finches over a matter of months [5].

The difference in the time course and pattern of vocal degradation between these two species may be due to differences in the flexibility of adulthood song structure [5]. Though neither species normally changes its adult syllable repertoire, zebra finches produce song syllables in a highly stereotyped order, whereas Bengalese finches demonstrate plasticity in syllable ordering or syntax. Thus, in this case, auditory feedback is necessary for song maintenance in adulthood but the dependent characteristic is the flexibility in suprasegmental features (*e.g.*, the syntax and rate of syllables).

The complexity of the effects of deafening in adulthood can also be seen in a recent study of the calls and warble song of a small Australian parrot, the budgerigar (*Melopsittacus undulatus*). These birds are interesting because they show significant vocal plasticity in learning and modifying on the basis of social experience in both their calls (contact calls) and their species-specific song (warble) throughout adulthood [6]. Deafened adult birds vocalized less frequently, became less social, and showed both suprasegmental and segmental changes in both their contact calls and their warble song [7]. Contact calls of adult-deafened birds showed abnormalities in acoustic

structure within days to weeks following cochlear extirpation with strikingly abnormal changes evident in vocalizations by 6 months. These results add to previous data showing that budgerigars deafened early in life, or reared in acoustic isolation, also fail to develop normal contact calls [8].

In summary, the evidence from a variety of vocal learning studies in birds shows that complete deafening early in life—and often later in life—has a profound effect on central nervous system processes controlling vocal production. For these reasons, birds that rely on learning to develop and maintain a complex vocal repertoire provide unique animal models to investigate the effects of hair cell regeneration.

2. RECOVERY OF COMPLEX SOUND PERCEPTION AND VOCAL PRODUCTION

The ultimate value of this regenerative capacity depends on whether it results in functional recovery not only of hearing, but also of vocal behavior. Behavioral recovery, as typically defined, refers only to a return of absolute auditory sensitivity to near pretrauma levels [9–11], though recent work shows recovery of auditory filter widths and modulation transfer functions following hair cell regeneration [12].

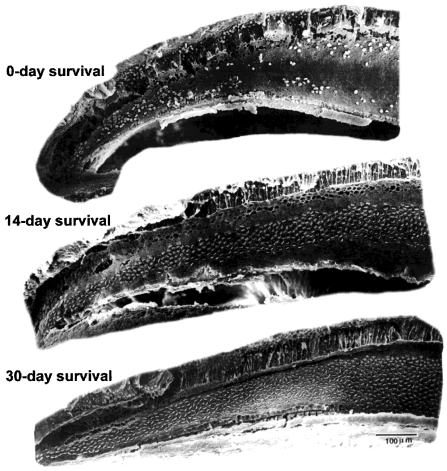

Fig. 1 The basal (high-frequency) half of the papillae of budgerigars sacrificed after 8 days of injection with kanamycin (0-day survival), 14-day survival, and 30-day survival. There is almost complete loss of hair cells after 8 days of kanamycin injections, recovery is well under way by 14 days following the termination of injections, and hair cell number is back to normal by 30 days following injections but with clear disturbance in the orientation patterns of the hair-cell stereocilia. (from Dooling *et al.*, 1997, copyright 1997 National Academy of Sciences U.S.A.)

Until recently, little was known about the recovery of more complex auditory behavior, and nothing was known about the effect of hearing loss and recovery on the production or recognition of learned vocalizations. Studies in humans show that hearing-impaired children use high-pitched vocalizations and show abnormal variations in fundamental frequency and abnormal stress patterns [13]. It is also well established that the characteristics of vocal output disintegrate following profound hearing loss in post-lingually deafened children [14] and adults [15]. Interestingly, some experiments also show that the speech of cochlear-implant patients immediately undergoes specific changes when the implant is turned off [16].

Because budgerigars learn new vocalizations throughout life, they provide excellent models for vocal and auditory recovery following hair cell regeneration. We trained budgerigars using operant conditioning with food reward to detect pure tones, discriminate among complex sounds such as contact calls, and even to produce such calls. We then examined the recovery of hearing, call discrimination, and the recovery of precision in vocal production following ototoxic drug-induced hearing loss. Hearing loss was induced by injecting budgerigars with kanamycin (200 mg/kg/day). Figure 1 shows the effect of 8 days of kanamycin administration on the inner ear of budgerigars. After 6 days of kanamycin injections, virtually all of the hair cells are missing in the basal 40% of the papilla [17]. Hair cells begin to be replaced (regenerated) in the basal 40% during the next 6–7 days, while hair cell damage (swelling, stereocilia abnormalities) begins to be seen in the distal one-half of the papilla. Within 4 weeks of the last kanamycin injection, hair-cell number is almost back to normal, and by 12 weeks hair cell number is within normal limits ($\pm$1 SD).

Before injection with kanamycin, the birds were trained and tested on a number of auditory tasks involving pure tones and discriminations among natural and synthetic contact calls. As expected following extensive hair cell loss, absolute thresholds at all frequencies were elevated considerably following treatment but recovered to within 15–20 dB of pre-injection thresholds within 8 weeks. Contact calls from different birds are usually quite different and easy to discriminate, while discriminating synthetic contact calls modeled after natural ones provides a more difficult test. The relatively easy discrimination between contact calls from different birds was unaffected 4 weeks following kanamycin treatment, while the more difficult discrimination between a natural contact call and its synthetic analogue was significantly impaired for several months, improving to pre-injection performance levels only after 5–6 months [17]. These results are shown in Fig. 2.

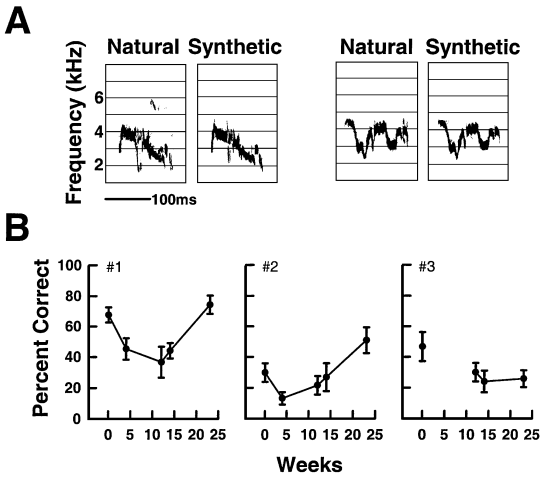

Fig. 2 (A) Sonograms of natural contact calls recorded from two different birds and their synthetic analogues. (B) Percent correct for each of three budgerigars discriminating among the five natural contact calls and their synthetic analogues before treatment with kanamycin and at various times during recovery. Discrimination performance of two birds eventually returned to pre-injection levels or better, whereas one bird still showed significant impairment even after 23 weeks of recovery. (from Dooling *et al.*, 1997, copyright 1997 National Academy of Sciences U.S.A.)

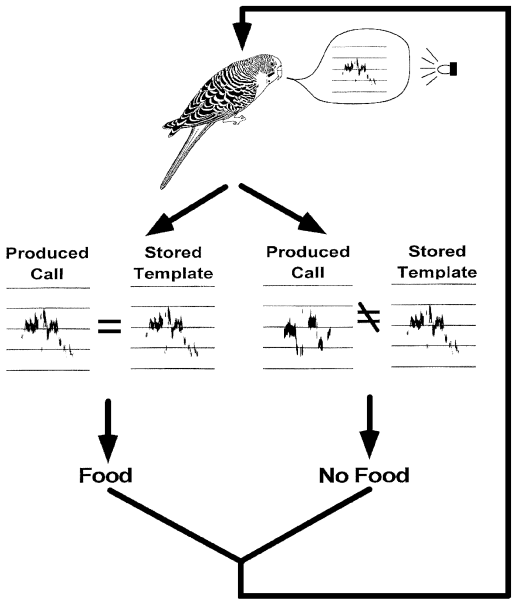

Fig. 3 A schematic of the methods used for the vocal production training procedures. Birds were trained to produce a vocalization that matched a template. If the call was correct, the bird was rewarded with food. If the bird was not correct, no food was presented.

In a second set of experiments, we utilized a vocal training procedure developed by Manabe and his colleagues [18,19] to test whether the precision in vocal production was permanently affected by the temporary hearing loss. Figure 3 shows a simple schematic of this procedure. Using operant conditioning, two male budgerigars were first trained to produce a contact call to a flashing LED. Only if the contact call matched a template stored in computer memory was the bird rewarded with food.

Each bird was then trained to produce different contact calls to two different LEDs. Birds were trained to produce one contact call when the left LED was illuminated and a different contact call when the right LED was illuminated. After the birds reached an asymptotic level of performance at the most stringent criterion, they were injected with kanamycin for 8 days. The relation between hearing loss following kanamycin injections and changes in the precision of vocal production is shown in Fig. 4.

Figure 4A shows the typical recovery function for absolute thresholds at 2.86 kHz in one budgerigar before, during, and after an 8-day course of kanamycin. Threshold elevation began on the sixth day of injections, reached its greatest elevation about 2 days after the last injection, and returned to within 23 dB of pre-injection levels at about 6 weeks after injections. Figure 4B shows the vocal template-matching performance for the two call types before, during, and after an 8-day course of kanamycin in two different birds. Vocal behavior was impaired during kanamycin injections, but recovered to previous performance levels within 10–15 days following kanamycin injections. The bird's ability to produce a vocal match to a stored contact call recovered to pre-injection levels of precision before auditory recovery, approaching asymptote at about 8 weeks. Similar effects are obtained following acoustic overexposure, indicating that the loss of vocal precision is most likely due to an auditory deficit rather than a generalized effect of kanamycin. This suggests that only a small amount of hearing (or, more accurately, hearing recovery) is necessary to guide nearly normal vocal precision in vocal production.

In summary, findings from several species show that noise-induced or drug-induced damage to hair cells in the basilar papilla of birds can result in both temporary and permanent threshold shifts [20–23]. While there can be rather large species differences, hair cell regeneration appears to result in almost complete recovery of absolute thresholds, measures of auditory filter width, frequency difference limens, intensity difference limens, and even the production of vocalizations [10, 17, 23, 24]. Otherwise said, these results show that a "new" auditory periphery gained through hair cell regeneration results in sufficient functional recovery that a bird can again perceive,

learn, and produce complex acoustic communication signals. The ability to track the time course of such recovery in a vertebrate auditory system may have particular significance for the effective use of auditory prosthetic devices, such as cochlear implants, for the severely hearing impaired [25].

3. THE SPECIAL CASE OF BELGIAN WATERSLAGER CANARIES

Canaries have been a favorite species of aviculturists for some time, and were bred for their plumage and distinctive songs [26]. One strain, the Belgian Waterslager canary, has become particularly noted for its loud, clear song. Over the years, canaries of this strain have been the focus of scientific studies on the behavior and neurobiology of vocal learning [27] as well as neurogenesis in the vertebrate central nervous system [28].

A number of years ago, Okanoya and his colleagues were the first to discover that Belgian Waterslager canaries have thresholds at frequencies above 2 kHz that are 20–40 dB higher than the thresholds of other strains of canaries, as well as other birds [29]. Figure 5 shows the average audiograms of Belgian Waterslager canaries and canaries of various mixed strains.

These findings, in the face of the capability for hair cell regeneration, were surprising. Additional experiments by Okanoya examined the hearing of cross-bred canaries, and results suggested that this auditory deficit is inherited. Auditory thresholds from canaries obtained by cross-breeding a Waterslager and a mixed breed canary vary from the completely normal pattern of threshold sensitivity found in normal canaries to the elevated pattern of threshold sensitivity found in Belgian Waterslagers, with some offspring showing an intermediate pattern [30].

In a series of studies examining the behavior of hearing psychophysically, physiologically (cochlear microphonic and VIIIth nerve cochlear action potential), and histologically through scanning electron microscopy (SEM), a serious and chronic pathology in the inner ear of Belgian Waterslager canaries was discovered [31]. Figure 6 shows SEM sections of the basilar papillae from normal and Belgian Waterslager canaries. Normal canaries have on average about 3,000 hair cells in their inner ear while Belgian Waterslagers have, on average, about 2,100 hair cells. In addition, Belgian Waterslager canaries show a hair-cell mosaic and stereovillar bundles that are obviously disturbed. Bundle shapes vary from almost normal, elongated bundles, to almost round bundles, to irregular bundle shapes and even to occasional bundles that had separated into several sub-bundles on the hair cell surface. Some bundles consisted of very few stereovilli, while some hair cells had isolated stereovilli of rather large dimensions located on their surface. Also, in normal canaries, the orientation of the bundle on the hair cell surface was very orderly, but in Belgian Waterslager canaries this orientation was rather distorted. For most Belgian Waterslager canaries, the width of the papilla was also quite severely affected. In the most severely affected birds, an additional type of 'abnormal' hair cell was also prominent. These hair cells had a small surface area that was covered to a varying degree by microvilli, with the stereovillar bundle being often quite small. In addition, there were occasional microvilli-rich patches that had absolutely no stereovillar bundle recognizable under the SEM.

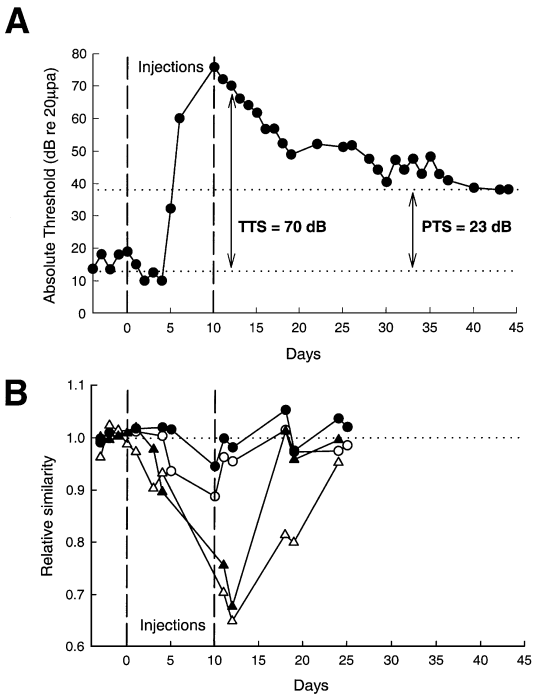

Fig. 4 (A) Absolute behavioral thresholds for one budgerigar before, during, and after injection of 200 mg/kg kanamycin. (B) Relative similarity of two contact calls (white and black symbols) produced by two birds (circles and triangles) to their respective templates before, during and after injections with the ototoxic drug kanamycin. Each bird's call similarities during and after injections are plotted relative to its average pre-injection similarity score, which was normalized to 1. Kanamycin causes a decrease in the precision of vocal production in both birds but this precision recovers within 5–15 days following the cessation of injections and well before the return of auditory function as defined by absolute thresholds, difference limens, call discrimination, and call recognition.

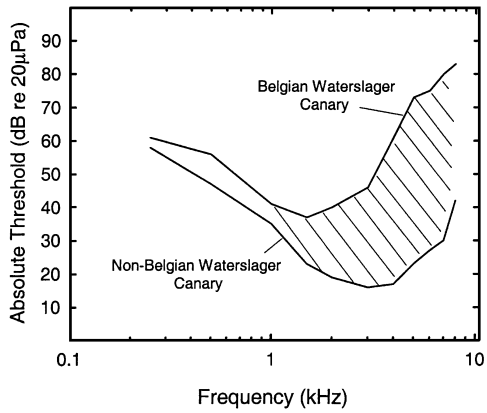

Fig. 5 Audiograms for Belgian Waterslager canaries (BWS) and non-BWS canaries. BWS canaries have over 40 dB of hearing loss at the highest frequencies relative to non-BWS canaries. (Redrawn from [37])

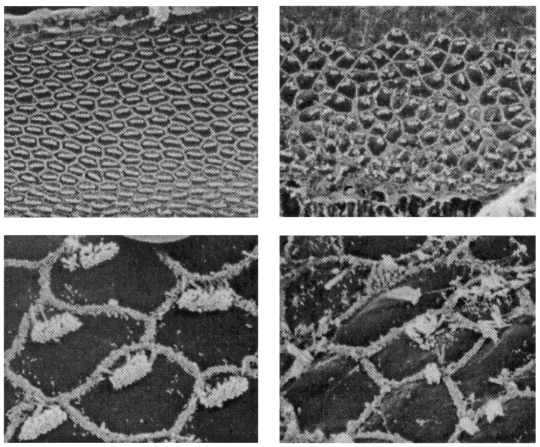

Fig. 6 Scanning electron microscopy photographs of the basilar papillae of non-BWS canaries (left photos) and BWS canaries (right photos) under lower magnification (top photos) and higher magnification (bottom photos). (Redrawn from [37])

Using markers for cellular proliferative activity bromodeoxyuridine (BrdU) and radioactive thymidine, an average of six supporting cell divisions per day were found to occur continuously in the basilar papilla of Belgian Waterslager canaries [32]. This rate of supporting cell proliferation corresponds well with estimates of the rate of hair cell differentiation derived from counts of immature-appearing hair cells, obtained by using scanning electron microscopy of the Belgian Waterslager basilar papilla. Moreover, when these birds were exposed to an intense 1 kHz pure tone, the rate of proliferation increased dramatically [33].

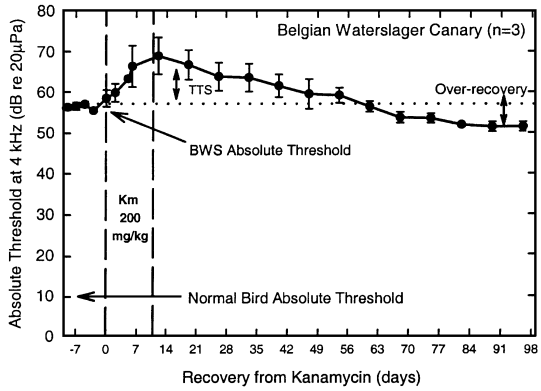

Fig. 7 Average absolute thresholds at 4 kHz for 3 BWS canaries before, during, and after a 10-day course of Kanamycin (Km) injections. The birds experience a temporary threshold shift (TTS) of over 10 dB, and eventually over-recover by about 8 dB at about 11 weeks following the injections. Error bars are SEMs. (Redrawn from [37])

Thus, it appears that it is not a lack of cochlear repair or proliferation mechanisms that underlie the chronic pathology seen in Belgian Waterslager canaries. In fact, Belgian Waterslager canaries trained for hearing tests, given injections of kanamycin, and followed through recovery showed a general pattern of loss and recovery similar to other birds (see the budgerigar results in Fig. 4). Figure 7 shows the threshold at 4 kHz before, during, and after these injections in Belgian Waterslager canaries. Following the injections, even more hearing loss than normal was induced at 4 kHz, with a time course of recovery similar to that observed in other birds, but with one intriguing exception. Hearing recovery goes beyond preinjection threshold levels by 5–10 dB. This suggests that some of the newly regenerated hair cells become and remain functional in the Belgian Waterslager canary papilla following increased proliferation due to kanamycin treatment. In other experiments, it has been shown that the number of fibers in the VIIIth nerve and the volumes and neuron numbers in the auditory brainstem nuclei are only slightly less than normal [33,34]. Thus, it is likely that the 30% fewer hair cells in the Belgian Waterslager canary papilla is the critical factor causing the elevated thresholds.

The exact nature of the Belgian Waterslager inner ear pathology remains a mystery. Because hair cell pathologies are also present in the sacculus of Belgian Waterslager canaries, Weisleder *et al*. [35] suggested that these birds are afflicted by Scheibe's like dysplasia, a cochleosaccular defect. Recent work, however, confirms that Belgian Waterslager canaries have a normal endocochlear potential [36], which shows they are affected by a neu-

roepithelial, rather than a cochleo-saccular, inner ear defect. Though birds as young as two months show the full pathology and its functional effects, it is not yet clear whether the pathology exists in newly hatched birds or develops within the first few weeks of life. Answering this question will help set the stage for pursuing the investigation of Belgian Waterslager hearing loss in the genetic domain such as unconventional myosin genes (myosin VIIA, VI, and MYO15) that are important for the appropriate formation of hair cell stereocilia bundles.

4. CONCLUSIONS

Birds have always occupied a special place in studies of acoustic communication because many species must learn the complex, species-specific acoustic signals they use for communication just as humans must learn the sounds of speech. In fact, over the last few decades, vocal learning in birds has turned out to be a premiere model for understanding the neural mechanisms involved in vertebrate vocal learning. The fact that birds can regenerate the hair cells of their inner ear may offer a new window into many of these processes. For instance, permanent, complete hearing loss causes a permanent degradation in vocal quality. Temporary hearing loss only causes a transient loss in vocal quality, which quickly recovers even before hearing is fully restored. How long can the central nervous system go without normal auditory input so that full vocal recovery is no longer possible, and what are the changes that have occurred?

The paradox of the Belgian Waterslager canary—permanent hearing loss in the face of continuous hair cell regeneration, poses similarly interesting questions. The usual question raised by hair cell loss and regeneration is what changes occur in the central nervous system in response to hair cell loss and subsequent regeneration? The Belgian Waterslager canary model poses slightly different questions. Providing we can supply these canaries with a full complement of hair cells seen in normal canaries, the question can be asked about changes occurring in the adult central auditory nervous system when it is presented with normal input from the auditory periphery for the first time. These and other questions posed by the phenomenon of hair cell regeneration in birds have enormous relevance for the design of auditory prosthetic devices in humans and the eventual amelioration of human deafness.

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