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Review

The auditory corticocollicular system: Molecular and circuit-level considerations

Kevin A. Stebbings [a], Alexandria M.H. Lesicko [a], Daniel A. Llano [a, b, c, *]

[a] Neuroscience Program, UIUC, USA
[b] Department of Molecular and Integrative Physiology, UIUC, USA
[c] Beckman Institute, Urbana, IL, USA

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ABSTRACT

We live in a world imbued with a rich mixture of complex sounds. Successful acoustic communication requires the ability to extract meaning from those sounds, even when degraded. One strategy used by the auditory system is to harness high-level contextual cues to modulate the perception of incoming sounds. An ideal substrate for this process is the massive set of top-down projections emanating from virtually every level of the auditory system. In this review, we provide a molecular and circuit-level description of one of the largest of these pathways: the auditory corticocollicular pathway. While its functional role remains to be fully elucidated, activation of this projection system can rapidly and profoundly change the tuning of neurons in the inferior colliculus. Several specific issues are reviewed. First, we describe the complex heterogeneous anatomical organization of the corticocollicular pathway, with particular emphasis on the topography of the pathway. We also review the laminar origin of the corticocollicular projection and discuss known physiological and morphological differences between subsets of corticocollicular cells. Finally, we discuss recent findings about the molecular micro-organization of the inferior colliculus and how it interfaces with corticocollicular termination patterns. Given the assortment of molecular tools now available to the investigator, it is hoped that his review will help guide future research on the role of this pathway in normal hearing.

1. Introduction

Sounds rarely exist in isolation. The temporal features used to extract meaning from sounds evolve over multiple and overlapping time scales. For example, in speech, phonemic cues evolve over milliseconds, syntactic cues over hundreds of milliseconds, and semantic cues over seconds. It is currently not known how are these temporally-discordant streams are integrated. A potential substrate for such processing is the hierarchically-organized, massive set of descending projections found in the auditory system. A specific subset of these projections, the corticocollicular (CC) system, has received substantial attention given its large size and complexity. In addition, a large number of studies have demonstrated that stimulation of the auditory cortex (AC) significantly alters inferior colliculus (IC) response properties across multiple species, including bats (Zhang et al., 1997; Yan and Suga, 1998), mice (Yan and Ehret, 2001, 2002; Yan et al., 2005), ferrets (Bajo et al., 2010), rats (Sun et al., 2007; Anderson and Malmierca, 2013), cats (Mitani et al., 1983) and guinea pig (Nakamoto et al., 2008, Nakamoto et al., 2010). Despite the wealth of data obtained from these physiological studies, our understanding of the neural circuits underlying these changes remains poor. In other descending pathways, such as the corticothalamic pathway, detailed analyses of heterogeneities in synaptic morphology and physiology have led to insights about the functional roles of this pathway (Reichova and Sherman, 2004; Groh et al., 2008; Ojima and Murakami, 2011). Similarly, it is likely that molecular and circuit level analyses of the CC pathway will uncover the mechanisms by which the AC influences the IC.

Abbreviations: A1, Primary auditory cortex; AAF, Anterior auditory field; AC, Auditory cortex; AChE, Acetylcholinesterase; APV, (2*R*)-amino-5-phosphonovaleric acid, (2*R*)-amino-5-phosphonopentanoate; CC, Corticocollicular; CCx, Caudal cortex; CF, Characteristic frequency; CN, Central nucleus; CNIC, Central nucleus of the inferior colliculus; D, Dorsal; DC, Dorsal cortex of the inferior colliculus; EC, External cortex; ECIC, External cortex of the inferior colliculus; GABA, Gamma-amino butyric acid; GAD, Glutamic acid decarboxylase; IC, Inferior colliculus; I_h, Hyperpolarization-activated cation current; LC, Lateral cortex of IC; NADPH-d, Nicotinamide adenine dinucleotide phosphate-diaphorase; PTN, Paracentral tectal nuclei; SOC, Superior olivary complex; Te1, Temporal area 1; VGLUT1, Vesicular Glutamate transporter 1; VGLUT2, Vesicular Glutamate transporter 2

* Corresponding author. 2355 Beckman Institute, 405 N. Mathews, Urbana, IL 61801, USA. Tel.: +1 217 244 0740; fax: +1 217 333 1133.
E-mail address: d-llano@illinois.edu (D.A. Llano).

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This review addresses unanswered questions emerging from physiological studies involving recordings in the IC after cortical stimulation or silencing. For example, one of the dominant theories of CC function (the "egocentric selection" theory) suggests that the AC can shift the peaks of tuning functions of IC neurons towards the peak of the tuning functions from the cortical source (Suga, 2012). In the frequency domain, this theory implies that IC neurons receive excitatory AC input across more than one frequency channel, such that conditioned frequencies away from an IC neuron's characteristic frequency can influence its tuning function. The difference in characteristic frequency between the AC stimulation site and the IC neuron being modulated is quite variable, and can be as much as 10 kHz in the mouse, which corresponds to at least 0.5–1.0 octaves (Yan and Ehret, 2002). This difference in characteristic frequencies suggests that individual IC neurons may receive input across a broad range of frequencies, pointing to a substantial degree of convergence in this pathway. In addition, shifts in a frequency tuning curve that involve decreases in responses to sound at the characteristic frequency imply that the CC pathway must involve frequency-specific inhibition of responses to ascending acoustically-driven input. Finally, the overwhelming majority of physiological studies have been done in the central nucleus of the IC (CNIC), while most of the CC pathway has terminations in the non-primary regions of the IC, suggesting a potential role for local-circuit interactions in the expression of corticofugal modulations of IC tuning functions. Other theories besides egocentric selection have been postulated about the role of feedback in sensory systems, such as an involvement in attention (Baluch and Itti, 2011) or predictive coding (Bastos et al., 2012). The latter, which may be manifested as stimulus-specific adaptation, has been examined in the CC pathway of rats, and has been shown to be highly heterogeneous. That is, silencing of the AC led to no change (approximately 50% of IC neurons), or to an increase or a decrease in the degree of stimulus-specific adaptation in IC neurons (Anderson and Malmierca, 2013), suggesting that the impact of the AC on acoustic responses IC is non-uniform and may depend on which specific subcircuits within the CC system are stimulated or suppressed.

Thus empirical observations of modulation in the CC pathway have generated a series of questions that require answers at the molecular and circuit-level of analysis. However, we have only now begun to understand how the circuits that underlie this pathway are organized. Given recent interest in the role of top-down modulation across cognitive and sensory systems (Boly et al., 2011; Gazzaley and Nobre, 2012; Gilbert and Li, 2013), and the expansion of optical and molecular tools now available, this review will provide investigators with an integrated view of these projections which may be useful in furthering our understanding of this system at a detailed circuit level. Given recent comprehensive reviews of the physiology of the CC pathway (Mei and Chen, 2010; Bajo and King, 2011; Suga, 2012), this review focuses on molecular and circuit-level analyses.

2. Anatomical considerations

Depending on the species, there are at least 5 distinct AC areas and at least 3 distinct IC areas (many would argue that there are more for both regions), with some of these areas showing tonotopy and others not. Therefore, two core organizational questions should be answered to better understand the function of the CC system. First, which regions of the AC project to which regions of the IC? Second, to what degree is the tonotopic organization of the AC retained in the CC pathway? These questions have been addressed across a range of species and will be summarized below.

Anatomical studies have shown that virtually all regions of the AC, including those with non-tonotopic organization and/or complex response properties, project heavily to the non-primary portions of the ipsilateral IC, primarily to the dorsal cortex (DC) and external cortex or lateral nucleus (in cat), with a minor contralateral projection (See Fig. 1 for a summary diagram across species), though this pattern may differ in primates ((Fitzpatrick and Imig, 1978), see Fig. 1F and discussed further below). For the purposes of this review, we will refer to the external cortex and lateral nucleus of the IC, which are likely homologous structures (Loftus et al., 2008), as the lateral cortex or LC, as proposed by Loftus et al. In addition, we will refer to the dorsal cortex and the pericentral nucleus of the IC (FitzPatrick, 1975) as the dorsal cortex (DC). It is important to note, however, that the three-dimensional subnuclear architecture of the IC contains considerably more complexity than this tripartite system would suggest (Morest and Oliver, 1984), and whenever possible we include descriptions of projections to additional subdivisions in this review. Evidence of a significant projection to the CNIC has been mixed, as described previously (Malmierca and Ryugo, 2011), and will be discussed below.

Corticocollicular termination patterns in the IC show high regional and sub-regional specificity. For example, in most species, injections into the primary auditory cortex (A1) or the anterior auditory field (AAF) produce two strips of labeling, generally coplanar with known isofrequency laminae of the IC; one located in the LC and the other in the DC, often encroaching into neighboring regions, such as the CNIC or the caudal cortex (CCx, see Fig. 1). There is additional heterogeneity of the CC projection to individual nuclei that has not yet been explored. For example, the projection to the LC appears to contain layer specificity (seen in Fig. 1A, B and E), and in rat and cat, appears to show distinct clustering (evident in Fig. 1B and E, inset). In addition, in the DC of the cat, the tonotopic areas of A1 and AAF project weakly to layer 1, strongly to layers 2–3 and moderately to layer 4 (Winer et al., 1998). Nonprimary parts of the AC also project prominently to the IC, and show some similarities and differences compared to the projections from A1 and AAF. The nonprimary areas tend to project to the most superficial parts of the LC and DC as well as the intercollicular zone in rat and the rostral pole and intercollicular tegmentum in cat (Andersen et al., 1980; Herbert et al., 1991; Winer et al., 1998). This projection to the superficial portions of the IC is an interesting point of divergence from cortical projections to the superior colliculus, where projections from cortical regions sitting higher in the processing hierarchy tend to project to deeper regions of the colliculus (Harting et al., 1992). In addition, as pointed out by Winer et al. (1998), another somewhat surprising finding is that the classically nontonotopically-organized areas such as the insula or temporal cortex have projections to the IC that were as highly focused as those from the primary auditory cortical regions.

The degree to which the CC system retains the tonotopic relationship present in the AC carries significant importance because of the frequency-specific effects of AC stimulation on the IC, as described above. With few exceptions (Andersen et al., 1980; Budinger et al., 2013), most anatomical tracing studies of the CC pathway studies did not involve tonotopic mapping of the AC prior to tracer injection, and therefore tonotopic relationships were inferred based on known maps and the examination of whether changes in injection site produce a systematic change in the location of the tracer in the IC, specifically in the CNIC with its known isofrequency laminae. This point of weakness in the literature will likely improve as optical mapping techniques become more commonly used in conjunction with anatomical tracing (Takemoto et al., 2014; Budinger et al., 2013; Horie et al., 2013). In an early study by Anderson et al. in the cat (1980), the investigators systematically injected tracer along the electrophysiologically-characterized tonotopic axis of the AC and found a systematic