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RESPONSE PATTERNS TO SOUND ASSOCIATED WITH LABELED GLOBULAR/BUSHY CELLS IN CAT

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Abstract—The mammalian cochlear nucleus (CN) consists of a diverse set of neurons both physiologically and morphologically that are involved in processing different aspects of the sound signal. One class of CN neurons that is located near the entrance of the auditory nerve (AN) to the CN has an oval soma with an eccentric nucleus and a short-bushy dendritic tree and is called a globular/bushy cell (GBC). They contact the principal cells of the medial nucleus of the trapezoid body (MNTB) with the very large calyx of Held that is one of the most secure synapses in the brain. Because MNTB cells provide an inhibitory input to the lateral superior olive (LSO), a structure purported to play a role in lateralizing high frequency sounds, GBC physiology is of great interest. Results were obtained with intracellular recording and subsequent labeling with neurobiotin of 32 GBCs along with a number of cells characterized extracellularly as likely GBCs in the cochlear nucleus (CN) of cat. Their poststimulus discharge response pattern to repeated tones varies from a primarylike pattern, i.e. similar to the AN, to a primarylike pattern with a 0.5–2 ms notch after the initial spike, to an onset pattern with a low-sustained rate. They can represent low frequency tones and amplitude modulated signals exceptionally well with a temporal code. Published by Elsevier Ltd on behalf of IBRO.

Key words: cochlear nucleus, intracellular, neurobiotin, primarylike-with-notch, globular/bushy cells.

The mammalian cochlear nucleus (CN) contains a set of physiologically and morphologically diverse neurons that are involved in processing different aspects of the sound signal. It provides the substrate for selectively enhancing information that upstream auditory centers require to perform their functions, whether they are involved with sound localization, sound identification, or signaling "escape now or forever be silent." The number of proposed cell types in the CN ranges from 9 (Osen, 1969) to 22 (Brawer et al., 1974) to 55 (Lorente de Nó, 1981) with the difference largely resulting from the difference in Nissl versus Golgi staining techniques, and presumably because observers can be considered either "lumpers" or "splitters" when classifying morphologies. A large range of physiological cell types has also been proposed based on the post-stimulus time histogram (PSTH) formed in response to relatively short tones (25–50 ms) at the characteristic frequency (CF) of the neuron. For example, Pfeiffer (1966) identified onset, primary-like and chopper responses in the ventral CN. Subsequently, PSTH response patterns have been greatly elaborated (Bourk, 1970; Blackburn and Sachs, 1989), and the relation of these PSTH patterns to the underlying morphology has been a subject of study. The introduction of intracellular labeling of physiologically characterized cells provided a firm basis for correlating physiological and morphological cell types (e.g. Rhode et al., 1983; Rouiller and Ryugo, 1984). Intracellular studies in brain-slices resulted in the biophysical characterization of several types of ion channels for many CN cell types, which also aided in the search for physiological–morphological correlations (e.g. Oertel, 1983; Manis and Marx, 1991; Rothman and Manis, 2003a,b; Cao et al., 2007; Oertel et al., 2008).

There are several PSTH-defined cell categories that display a marked onset response characterized by a high ratio of initial to steady-state discharge rate. These include 1) the onset-ideal (OnI, Godfrey et al., 1975) PSTH response type that originates from octopus cells in the postero-ventral cochlear nucleus (PVCN) as were morphologically characterized by Osen (1969); 2) onset-choppers (OnC) identified as large multipolar cells in the PVCN by Smith and Rhode (1989); and 3) primarylike-with-notch (PLn) units, onset with an L-shaped post-stimulus time histogram (OnL) units, and primarylike (PL) units. PLn, OnL and PL units arise from globular/bushy cells (GBCs), which exhibit a characteristic eccentric nucleus and are mostly located in the nerve root area (NRA) of the CN which Osen (1969, 1970) named the central region of the ventral CN. The OnL pattern in cat has been described as having only an onset spike at low intensities that transitions to the OnL pattern at higher intensities (Godfrey et al., 1975). In the guinea-pig anteroventral cochlear nucleus (AVCN), OnL patterns have also been associated with stellate cells (Winter and Palmer, 1995; Arnott et al., 2004).

An intriguing feature of these onset-PSTH types is that each cell type displaying such responses either appears to be inhibitory or to excite an inhibitory postsynaptic neuron (see review: Cant and Benson, 2003). OnC's are hypothesized to provide glycinergic wideband-inhibitory inputs to the dorsal cochlear nucleus (DCN) and PVCN, and project to the contralateral CN (Smith et al., 2005, 1989; Arnott et al., 2004). OnI (octopus cells) units project to the contralat-

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Abbreviations: AM, amplitude modulated; ANF, auditory nerve fiber; AVCN, anteroventral cochlear nucleus; AW, analysis window; CF, characteristic frequency; CN, cochlear nucleus; EPSP, excitatory postsynaptic potential; GBC, globular/bushy cell; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; NRA, nerve root area; OnC, onset-chopper; OnI, onset-ideal; OnL, onset with an L-shaped post-stimulus time histogram; PL, primarylike; PLn, primarylike-with-notch; PSTH, post-stimulus time histogram; PVCN, posteroventral cochlear nucleus; SPL, sound pressure level; SR, spontaneous rate; TMTF, temporal modulation transfer function; VNLL, ventral nucleus of the lateral lemniscus; VS, vector strength.

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eral ventral nucleus of the lateral lemniscus (VNLL) where they terminate in a calyx ending on cells that are glycinergic (e.g. Adams and Wenthold, 1987; Saint Marie et al., 1997) and project to the ipsilateral inferior colliculus (IC). PLn/OnL cells have a major projection to the contralateral medial nucleus of the trapezoid body (MNTB) where they synapse on glycinergic inhibitory principal cells that project to the LSO (Bledsoe et al., 1990; Spirou et al., 1990). This connection plays a prominent role in creating an interaural level difference (ILD) coding observed in the response of LSO neurons that are used predominantly to localize high frequency sounds. MNTB neurons also project to the VNLL, where they terminate in calyceal-like endings (Adams and Wenthold, 1987). VNLL is part of a monaural ascending system purported to play a role in temporal processing of signals (Covey and Casseday, 1991).

These onset unit types typically display relatively short first-spike latencies with nearly a 100% rate-of-occurrence of the initial spike in response to short CF tones sufficiently above threshold. Each onset unit type has voltage-sensitive conductances (Trussell, 1997) and superb temporal response properties, i.e. precise firing to a particular phase of a sinusoidal stimulus, termed phase locking. This phase locking can exceed that of auditory nerve fibers (ANFs) at frequencies less than 1 kHz (Joris et al., 1994a; Joris and Smith, 2008). A consequence of such fast voltage-sensitive conductances is that converging inputs must occur within a relatively small temporal window in order to fire the postsynaptic element, when individual excitatory postsynaptic potentials (EPSPs) are not capable of discharging the postsynaptic element (McGinley and Oertel, 2006). In other words, these onset neurons behave as coincidence detectors. In engineering terms, they differentiate the signal, thereby emphasizing changes in the signal rather than coding the steady-portion (Ferragamo and Oertel, 2002). Another characteristic of units having an onset PSTH is that they generally have a large number of inputs, possibly ranging as high as 100 (Golding et al., 1995; Spirou et al., 2005).

OnI and OnC's units in the PVCN have large dendritic trees that intersect with a substantial portion of the tonotopic afferent field of ANFs having a range of CFs. This results in broader filters, i.e. lower Q_{10}'s (Q_{10}=CF/bandwidth at 10 dB above threshold), than other cell types in the CN. In contrast, PLn units may obtain their entire primary afferent input in the form of "modified end bulbs of Held" from ANFs with nearly similar CFs, and their frequency selectivity (Q_{10}) is the same as found for ANFs (Rhode and Smith, 1986a). Modified end bulbs are a smaller variant of the large one or two end bulbs that contact large spherical/bushy cells in the AVCN (Rouiller et al., 1986; Liberman, 1991). In the latter instance, they are assumed to provide secure transmission of the afferent activity to the postsynaptic element. Modified end bulbs converge on GBCs with several to more than 60 endings (Liberman, 1993; Spirou et al., 1990, 2005).

A possible outcome of a high degree of ANF convergence is that the GBC-PSTH response pattern could vary from cell to cell. Early attempts at structure/function correlation using intracellular injection of HRP (Rhode et al., 1983; Rouiller and Ryugo, 1984) indicated that PL, OnL and PLn response patterns can arise from GBCs based on a relatively small number of observations in the NRA. One likely reason for this range of GBC-PSTH properties is that there are three "distinct" populations of auditory afferents, i.e. ANFs with different spontaneous and driven spike activities (Liberman, 1978). Modeling studies demonstrated that in order to capture the range of PSTH responses seen, there is a requirement for numerous sub- and supra- threshold inputs, along with inhibitory inputs and a range of afferent spontaneous activities (Rothman et al., 1993).

Because each morphological category has a set of physiological response distributions that often overlap with those of another morphological category, it is difficult to definitively classify a unit based on the physiology when response patterns are not linked to an anatomically identified neuron. In the CN, several neuron types have onset PSTH patterns, a high degree of synchronization to low frequency tones, a range of spontaneous activity and similar maximum discharge rates. This study was undertaken to further clarify the correlation of structure and physiology of one of these cell types, the GBCs. Thirty-two full or partially labeled GBCs with 15 PLn, 12 PL and five OnL PSTH response patterns were physiologically characterized and anatomically reconstructed after being labeled with neurobiotin.

EXPERIMENTAL PROCEDURES

Young adult cats of either sex (n=129, the minimum number to obtain sufficient data on several neuron categories) were anesthetized with pentobarbital using a dose rate of 75 mg/kg. Additional doses (50 mg/kg) were administered to maintain the animal in a deeply areflexive and pain free state in accordance with National Institutes of Health guidelines. The animal was placed on a respirator and expired CO_2 was maintained at 4%. All procedures were approved by the Animal Care and Use Committee of the University of Wisconsin (Madison, WI, USA).

An opening in the skull was made over the posterior fossa. The cerebellum was partially aspirated and the remainder was lifted and pushed anteriorly with small pieces of cotton to expose the CN. Two scales were positioned alongside the CN and were used to record X and Y coordinates of electrode placements. A 2% agar solution covered the CN to reduce pulsations. A plastic chamber was cemented over the opening in the skull and then filled with warm mineral oil. A glass cover was positioned on the chamber with high vacuum grease to create a hydraulically sealed chamber and reduce brain pulsation.

Intracellular labeling of physiologically characterized neurons was attempted using micropipettes filled with 1 M KCl and a 2% neurobiotin solution. At the end of a recording session, the animal was killed with pentobarbital, perfused with 1 l of 1% paraformaldehyde and 1 l of 2% glutaraldehyde. The brain was removed, and a cross-section of the brainstem containing the CN was cut and placed in 2% glutaraldehyde overnight. The following day the material was transferred to a sucrose solution to prepare it for frozen sectioning at 60 μm.

Zero to eight neurons were labeled in any one experiment with an average of one per experiment. Penetrations were typically separated by 1 mm to facilitate physiology-to-neuron correspondence. In total, over 140 cells of various morphologies were reconstructed in varying degrees of completeness, and 32 were

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