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Review

The calyx of Held in the auditory system: Structure, function, and development

Maryna Baydyuk [a, *], Jianhua Xu [b, c], Ling-Gang Wu [a]

[a] National Institute of Neurological Disorders and Stroke, 35 Convent Dr., Bldg 35, Bethesda, MD 20892, USA
[b] Department of Neuroscience and Regenerative Medicine, Medical College of Georgia, Augusta University, Augusta, GA 30912, USA
[c] Department of Neurology, Medical College of Georgia, Augusta University, Augusta, GA 30912, USA

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ABSTRACT

The calyx of Held synapse plays an important role in the auditory system, relaying information about sound localization via fast and precise synaptic transmission, which is achieved by its specialized structure and giant size. During development, the calyx of Held undergoes anatomical, morphological, and physiological changes necessary for performing its functions. The large dimensions of the calyx of Held nerve terminal are well suited for direct electrophysiological recording of many presynaptic events that are difficult, if not impossible to record at small conventional synapses. This unique accessibility has been used to investigate presynaptic ion channels, transmitter release, and short-term plasticity, providing invaluable information about basic presynaptic mechanisms of transmission at a central synapse. Here, we review anatomical and physiological specializations of the calyx of Held, summarize recent studies that provide new mechanisms important for calyx development and reliable synaptic transmission, and examine fundamental presynaptic mechanisms learned from studies using calyx as a model nerve terminal.

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* Corresponding author. Present address: Department of Biology, Georgetown University, 3700 O Street, NW, Washington, DC 20057, USA.
E-mail address: mb339@georgetown.edu (M. Baydyuk).

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1. Introduction

Sound localization, a sensory processing vital for most animals, requires precise and specialized neuronal circuitry. Among several synapses with unique properties to accommodate this processing, the calyx of Held synapse receives special attention because of its morphological and electrophysiological characteristics that facilitate precise transmission of signal information. This synapse is composed of a single large nerve terminal, which originates from the globular bushy cells in the ventral cochlear nucleus (VCN), and the cell body of the principal neuron in the medial nucleus of the trapezoid body (MNTB) (Borst and Soria van Hoeve, 2012; Borst and Rusu, 2012; Schneggenburger and Forsythe, 2006). Prior to hearing onset, which occurs around postnatal day (P) 11–12 in rats and mice (Blatchley et al., 1987; Geal-Dor et al., 1993; Kamiya et al., 2001), the calyx of Held undergoes rapid morphological and functional transformation (Hoffpauir et al., 2006; Iwasaki and Takahashi, 2001; Taschenberger and Von Gersdorff, 2000; Taschenberger et al., 2002) that ensures fast and dependable relay of sound localization information. Interestingly, most of these developmental steps occur before the onset of hearing in mice, supporting the view that sensory activity does not play a major role in the formation of the calyx synapse, and its maturation is rather guided by intrinsic signaling mechanisms (Erazo-Fischer et al., 2007; Hoffpauir et al., 2006; Rodriguez-Contreras et al., 2008; Youssoufian et al., 2008). However, in other rodent species, sensory activity might play a bigger role in calyx development, suggesting species-specific differences in the role of genetic and activity-dependent components (Felmy and Schneggenburger, 2004; Ford et al., 2009).

The calyx of Held is characterized by its giant size, covering a large area of the soma of the postsynaptic principal neuron in the MNTB of an adult rat or mouse (Schneggenburger and Forsythe, 2006). The axosomatic nature of this synapse is thought to account for high speed and efficiency of synaptic transmission, setting it apart from small conventional synapses (Borst and Soria van Hoeve, 2012). The calyx nerve terminal harbors several hundred active zones, which are the sites of synaptic contact where transmitter release occurs (Sätzler et al., 2002; Taschenberger et al., 2002). A single action potential (AP) fired by the globular bushy cell in the VCN can release a large number of synaptic vesicles containing glutamate, resulting in rapid and effective activation of the postsynaptic neuron in the MNTB (Borst and Sakmann, 1996). Release strength and plasticity are efficiently controlled by the amount of calcium (Ca^{2+}) influx via the voltage-gated Ca^{2+} channels (VGCCs) and dependent on the Ca^{2+} channel number, composition, and arrangement within the active zone (Hoffpauir et al., 2006; Iwasaki and Takahashi, 1998; Meinrenken et al., 2002; Nakamura et al., 2015; Sheng et al., 2012; Wu et al., 1998, 1999). These specialized structural and functional properties of the calyx of Held nerve terminal discussed here and postsynaptic MNTB neuron discussed in greater details in other reviews (Borst and Soria van Hoeve, 2012; Kopp-Scheinpflug et al., 2011) guarantee high fidelity transmission of acoustic signal information for further processing by the auditory circuits (Trussell, 1999).

The large synapse formed by the calyx of Held presynaptic terminal onto principal cell of the MNTB allows for direct electrophysiological analysis of presynaptic calcium currents, mechanisms of vesicle release and recycling, and for simultaneous recordings of corresponding changes in excitatory postsynaptic currents (EPSCs) (Borst et al., 1995; Chuhma and Ohmori, 1998; Forsythe, 1994; Sun and Wu, 2001; Wong et al., 2003). The unique accessibility of the calyx of Held to whole-cell recording has also been used for combined electrophysiological and calcium-imaging studies, investigating presynaptic Ca^{2+} dynamics in a single nerve terminal (Bollmann et al., 1998, 2000; Schneggenburger and Neher, 2000; Xu and Wu, 2005). Using calyx as a model, molecules important for control of vesicle exocytosis such as synaptotagmins have been determined (Kochubey and Schneggenburger, 2011; Kochubey et al., 2011; Lou et al., 2005; Sun et al., 2007). Endocytosis, a process of vesicle membrane retrieval after exocytosis, has also been studied in great detail using the calyx of Held (Renden and Von Gersdorff, 2007; Sun and Wu, 2001; Sun et al., 2002; Wu et al., 2014a; Wu et al., 2009; Yamashita et al., 2005). Here, we review morphological and physiological properties of the calyx of Held and their changes during development that make this synapse suitable for its auditory function and a useful model for studying presynaptic mechanisms of synaptic transmission and plasticity.

2. Specialized morphology and structure of the calyx of Held

2.1. Anatomy of the MNTB and its input and output projections

In the adult, the globular bushy cells of the VCN send large-diameter axons measured at 2–3 μm in diameter (Ford et al., 2015), which cross the midline of the brainstem and terminate with the calyx-type nerve terminals at the soma of principal neurons of the contralateral MNTB (Harrison and Irving, 1966; Smith et al., 1991; Spirou et al., 1990). A single MNTB principal neuron receives input from only one calyx of Held, although multiple calyceal inputs are occasionally observed (Bergsman et al., 2004; Hoffpauir et al., 2006; Kuwabara et al., 1991; Rodriguez-Contreras et al., 2006). The MNTB neurons receive additional non-calyceal excitatory and inhibitory inputs of unclear origins and functions (Hoffpauir et al., 2006; Rodriguez-Contreras et al., 2006; Smith et al., 1991). It has been shown that an inhibitory influence may originate from the ipsilateral ear and can undergo substantial modifications during the course of postnatal development (Green and Sanes, 2005). In addition, a recent study has identified the ventral nucleus of the trapezoid body as one of the major sources of glycinergic inhibitory input to the MNTB (Albrecht et al., 2014).

The MNTB principal cells provide inhibitory glycinergic projections to adjacent nuclei in the superior olivary complex, including the lateral superior olive (Kuwabara and Zook, 1991; Tollin, 2003) and the medial superior olive, which comprise circuitries important for computing interaural intensity levels and time differences, respectively, and which are the first nuclei where information from both ears converges (Banks and Smith, 1992; Brand et al., 2002; Couchman et al., 2010; Goldberg and Brown, 1968; Kuwabara and Zook, 1992). In addition, the MNTB neurons project to the superior paraolivary nuclei (Banks and Smith, 1992; Sommer et al., 1993) and to the ventral and dorsal nuclei of the lateral lemniscus (Kelly et al., 2009; Siveke et al., 2007; Smith et al., 1998; Sommer et al., 1993). In summary, the calyx of Held relays acoustic information to multiple target nuclei for further computation of sound location.

2.2. Calyx ultrastructure and its relation to transmitter release

The calyx nerve terminal possesses highly specialized ultrastructural properties as well as universal components of the basic release machinery (Borst and Soria van Hoeve, 2012). Its large size, covering ~50% of the soma of the postsynaptic neuron in the MNTB, permits to harbor 300–700 of active zones (Fig. 1A), which are morphologically similar to those observed in conventional small nerve terminals (Sätzler et al., 2002; Taschenberger et al., 2002). The active zones in the calyx have an average surface area of 0.1 μm^2 and are separated by ~0.6 μm from their nearest neighbors (Sätzler et al., 2002), similar to the dimensions estimated in hippocampal (Schikorski and Stevens, 1997) and cerebellar excitatory synapses