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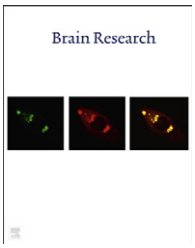

Review

Two independent forms of activity-dependent potentiation regulate electrical transmission at mixed synapses on the Mauthner cell

*Roger Cachope, Alberto E. Pereda**

Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY 10461, USA

ARTICLE INFO

Article history:
Accepted 9 May 2012
Available online 4 July 2012

Keywords:
Gap junction
Connexin 36
Endocannabinoid
Long-term potentiation
NMDA
Dopamine
PKA
CaMKII
Auditory

ABSTRACT

Mixed (electrical and chemical) synaptic contacts on the Mauthner cells, known as Club endings, constitute a valuable model for the study of vertebrate electrical transmission. While electrical synapses are still perceived by many as passive intercellular channels that lack modifiability, a wealth of experimental evidence shows that gap junctions at Club endings are subject to dynamic regulatory control by two independent activity-dependent mechanisms that lead to potentiation of electrical transmission. One of those mechanisms relies on activation of NMDA receptors and postsynaptic CaMKII. A second mechanism relies on mGluR activation and endocannabinoid production and is indirectly mediated via the release of dopamine from nearby varicosities, which in turn leads to potentiation of the synaptic response via a PKA-mediated postsynaptic mechanism. We review here these two forms of potentiation and their signaling mechanisms, which include the activation of two kinases with well-established roles as regulators of synaptic strength, as well as the functional implications of these two forms of potentiation.

Special Issue entitled Electrical Synapses.

Contents

*Correspondence to: Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, USA. Fax: +1 718 430 8821.
E-mail address: alberto.pereda@einstein.yu.edu (A.E. Pereda).

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http://dx.doi.org/10.1016/j.brainres.2012.05.059

1. Introduction

In contrast with mammalian electrical synapses that generally have limited experimental access, the wide distribution and sometimes particular sub-cellular localization of some electrical synapses in some species have provided with advantageous experimental models in which basic properties of electrical transmission can be more easily studied (Bennett, 1977). This is the case of a special class of auditory afferents terminating on the lateral dendrite of the teleost Mauthner cells known as Large Myelinated Club Endings (Bartelmez, 1915; Bartelmez and Hoerr, 1933; Bodian, 1937; Robertson, 1963; Furshpan, 1964). These endings are identifiable "mixed" (electrical and chemical) synaptic terminals that offer the unique opportunity to correlate physiological properties with biochemical composition and specific ultrastructural features of individual synapses (Pereda et al., 2004). A wealth of evidence shows that electrical transmission at these afferents is very dynamic and is mediated by teleost homologs of connexin36 (Cx36) (O'Brien et al., 1996, 1998), the main neuronal connexin (Condorelli et al., 1998), which is responsible for electrical coupling at neocortical inhibitory interneurons and inferior olivary cells, among many cell types (Connors and Long, 2004). The widespread distribution of these neuron-specific connexins and of some of the proposed regulatory mechanisms raises the possibility that the observed properties could also pertain to most electrical synapses.

This article does neither attempt to be a comprehensive review of the plasticity of electrical synapses in general nor a detailed description of the physiology and anatomy of the Club endings. We concentrate here on an essential aspect of the physiology of these terminals: the activity-dependent potentiation of electrical (and chemical) transmission observed at these mixed synapses and the proposed underlying mechanisms.

2. The Club endings

The Club endings are single terminations of saccular afferents (~85 in number) (Bodian, 1937) on the distal portion of the lateral dendrite of the Mauthner cells (Fig. 1A). The Mauthner cells are a pair of unusually large reticulospinal neurons involved in tail-flip escape responses in fish, which are triggered by diverse sensory stimuli, particularly auditory (Eaton et al., 2001). These uncommonly large cells are anatomically and physiologically identifiable and constitute a valuable preparation for the study of the cellular correlates of behavior (Eaton et al., 2001; Korn and Faber, 2005; Faber and Pereda, 2011; Pereda and Faber, 2011). Auditory afferents that terminate as Club endings on the Mauthner cell provide essential auditory information to this decision-making neuron for the initiation of an escape response (Korn and Faber, 2005; Curti and Pereda, 2009; Faber and Pereda, 2011; Pereda and Faber, 2011).

A wealth of anatomical and electrophysiological data shows that Club endings support both chemical and electrical modalities of transmission (Lin and Faber, 1988a; for review see Pereda et al., 2004). In fact, these contacts provided one of the first demonstrations of gap junction plaques (Robertson, 1963) and electrical transmission (Furshpan, 1964) in the vertebrate central nervous system. Detailed electron microscopic studies, including freeze-fracture techniques (Tuttle et al., 1986), have shown that while the specializations corresponding to chemical transmission predominate in the periphery, gap junction plaques are located on most of the surface area of the terminal. The plaques range in number from 63 to 243 gap junctions, and the total area they occupy is about 20% of the synaptic area (Tuttle et al., 1986). These gap junctions are formed by Cx35 (Pereda et al., 2003a), the fish ortholog of the widely expressed Cx36. Recent data indicates that a second homolog of Cx36, Cx34.7, is also present at these terminals (Rash et al., 2010). From the electrophysiological point of view, a presynaptic impulse generates a "mixed" excitatory response. That is, stimulation of the posterior branch of the VIII nerve, where these fibers run, evokes an electrical potential followed by a chemically mediated excitatory postsynaptic potential (Fig. 1B). Due to the fast time constant of the Mauthner cell (~400 μs) both components can be easily distinguished (Fukami et al., 1965).

While electrical transmission is supported by the existence of an unusually large number of gap junction plaques, chemical transmission is mediated by the release of glutamate from ~15 release sites (Lin and Faber, 1988b). The pharmacological characteristics and voltage dependence of the synaptic currents are consistent with glutamate being the

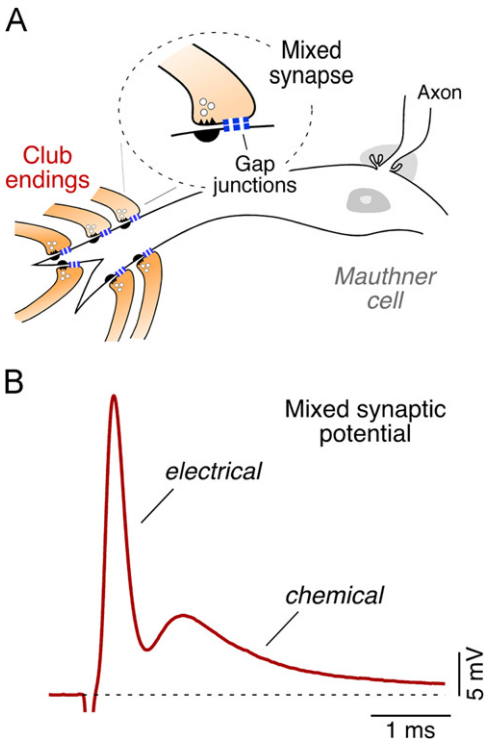

Fig. 1 – Club endings exhibit mixed synaptic transmission. (A) VIII nerve afferents (Club endings) terminate as single mixed synaptic contacts (mixed synapse) on the lateral dendrite of the Mauthner cell (B) VIII nerve stimulation evokes a mixed electrical and chemical synaptic response (trace represents the average of 20 individual responses).