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Review

Modulation of spike-evoked synaptic transmission: The role of presynaptic calcium and potassium channels☆

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ABSTRACT

Action potentials are usually considered as the smallest unit of neuronal information conveyed by presynaptic neurons to their postsynaptic target. Thus, neuronal signaling in brain circuits is all-or-none or digital. However, recent studies indicate that subthreshold analog variation in presynaptic membrane potential modulates spike-evoked transmission. The informational content of each presynaptic action potential is therefore greater than initially expected. This property constitutes a form of fast activity-dependent modulation of functional coupling. Therefore, it could have important consequences on information processing in neural networks in parallel with more classical forms of presynaptic short-term facilitation based on repetitive stimulation, modulation of presynaptic calcium or modifications of the release machinery. We discuss here how analog voltage shift in the presynaptic neuron may regulate spike-evoked release of neurotransmitter through the modulation of voltage-gated calcium and potassium channels in the axon and presynaptic terminal. This article is part of a Special Issue entitled: 13th European Symposium on Calcium.

1. Introduction

Synaptic transmission is a dynamic process. At the presynaptic side, neurotransmitter release can be enhanced during repetitive stimulation as the result of elevation of residual calcium, the presence of high-affinity calcium-binding sites with slow kinetics, fast calcium buffering, or modulation of the release machinery [32,45,49]. All these modulations suppose that the somatic electrical state does not influence neurotransmitter release at the presynaptic terminal. We review here recent data indicating that the electrical state of the soma alters presynaptic ion channels controlling spike-waveform or basal calcium concentration and subsequently modulate neurotransmitter release.

1.1. Digital information in synaptic circuits

Neuronal information is usually conveyed in synaptic circuits by action potentials. The proximal region of the axon (the axon initial segment, AIS) contains a high density of sodium channels, therefore constituting a hot spot for generating action potentials that are actively propagated along the axon [25]. Neuronal information is therefore transmitted to the postsynaptic neuron as discrete amounts of neurotransmitter released by the presynaptic neuron in an all-or-none mode. This mode of neuronal signaling is thus digital: the neuron either fires or it does not and neurotransmitter release follows this binary mode (Fig. 1A). Digital synapses are able to signal activity far from the site of spike initiation without voltage dissipation because active currents regenerate action potentials along the axon [10,17]. Another major advantage of digital signaling is its relatively low energy cost. The kinetics of voltage-gated currents underlying the action potential are tuned to minimize energy consumption [2,36]. However, it has also several limitations. Because of its discrete nature, the coding of information by a single digital synapse is generally poor.

1.2. Analog synaptic transmission

Neuronal information is not only transmitted in a digital mode. Subthreshold activity that originates in the dendrites and the soma can be conveyed along the axon to the presynaptic element where it determines the flow of neuronal information, via analog coding. Examples of pure analog transmission of neuronal information can be found in the inner ear or in the retina where photoreceptors, bipolar and horizontal cells signal photo-stimulation by producing graded potentials without action potentials [46]. These cells generally release transmitter continuously (tonic release) and their high rate of spontaneous release is directly modulated by membrane potential fluctuations (Fig. 1B). Similar examples of graded transmission in the absence of spiking activity have also been described in invertebrate neurons [27]. Synapses translating analog presynaptic membrane potential fluctuation into graded tonic release of transmitter display a significantly higher rate of information transfer than synapses using presynaptic spike train coding. The dynamic range at tonic-releasing analog synapses is indeed

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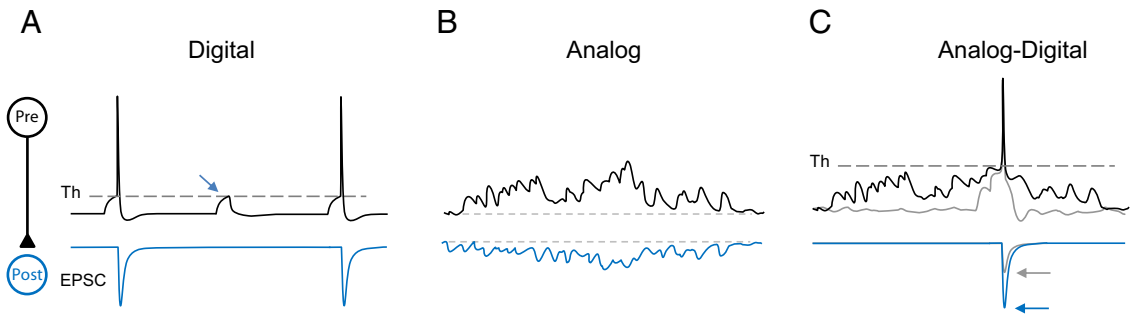

Fig. 1. Digital, analog and hybrid (analog-digital) modes of synaptic transmission. A. Digital mode of synaptic transmission in the central nervous system. Left, scheme of two synaptically connected neurons. Transmission is stereotyped and occurs in an all-or-none fashion (i.e. only if a presynaptic action potential is elicited). Note that subthreshold depolarization (arrowheaded) produces neither a presynaptic spike nor a postsynaptic response. Th, spike threshold. B. Analog transmission is a graded mode of transmission of presynaptic voltage fluctuations. The two horizontal dashed lines indicate the baselines. The blue trace represents post-synaptic activity. C. Hybrid analog-digital (AD) transmission. Both subthreshold fluctuations and spiking activity are transmitted. Note that when the presynaptic spike is produced after a prolonged period of depolarization (upper black trace) the spike-evoked synaptic response (blue trace) is enhanced compared with when there is no prolonged depolarization (upper and lower gray traces). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

very large and a single analog synapse is virtually able to continuously encode infinite information levels. For instance, graded synapses in the fly retina transmit more than 1500 bits of information per second, i.e. one or two orders of magnitude larger than spiking neurons [6,15]. However, this comes at the price of high energy consumption. For example, photoreceptors in the retina continuously release their neurotransmitter at high rate (20–80 vesicles per active zone per second), indicating that each active zone may release as many as a few million vesicles per day [21]. Another drawback of analog signaling is that it is constrained by biophysical laws such as voltage dissipation along neuronal processes over long distances. Therefore, pure analog signaling in neurons is better suited for local rather than distal transmission of information.

1.3. Analog-digital signaling: analog signaling at spiking synapses

There is now evidence that analog signaling exists at spiking synapses where neurotransmitter release is not tonic but evoked by action potentials. Hybrid analog-digital enhancement of synaptic transmission at spiking synapses initially described in invertebrates [29,37,39,40] has been more recently reported in many mammalian synapses of the CNS including cortical [24,42,48], cerebellar [9,12], and hippocampal excitatory synapses ([1,18,34]; Bialowas et al., 2014). In these examples, synaptic transmission evoked by single APs is enhanced as the result of analog-mediated depolarization (10–30 mV) of the presynaptic element for a few tens to hundreds of milliseconds (Fig. 1C). Combining analog and digital signaling at central synapses should in principle offer two main advantages: low energy-cost and dynamic transfer of neuronal information.

Analog-digital facilitation (ADF) is expressed in a highly heterogeneous range of synapses in terms of morphology (*en passant* boutons and giant terminals), neurotransmitter (GABA or glutamate) and brain regions (neocortex, hippocampus & cerebellum). ADF involves three major steps: i) the depolarization of the presynaptic element causing ii) modulation of voltage-gated ion channels along the axon and subsequently iii) the enhancement of neurotransmitter release. In cerebellar synapses established between GABAergic interneurons of the molecular layer, subthreshold depolarization facilitates spike-evoked release of GABA [12]. In hippocampal dentate granule cell axons (mossy fibers), the combination of analog depolarization spreading from the soma in the form of an excitatory presynaptic potential (EPreSP) and digital signaling in the form of an AP, enhances glutamatergic transmission at the mossy fiber-CA3 cell synapse [1]. For local connections such as these that occur over relatively short distances between L5 pyramidal neurons in the neocortex, hippocampal CA3 pyramidal neurons or GABAergic interneurons in the cerebellum, the analog-mediated component of the facilitation of synaptic transmission is on average 1–2% per mV of somatic depolarization ([12,24,42]; Bialowas et al., 2014).

ADF is mediated by an elevation in glutamate [3,24] or GABA [9,12] release as indicated by the reduced paired-pulse ratio (PPR), i.e. the ratio of synaptic responses for a pair of presynaptic stimuli. Intriguingly, however, in the case of the hippocampal mossy fiber-CA3 cell synapse, short-term facilitation tested with repeated presynaptic stimuli is unchanged [1], suggesting that, as discussed later, glutamate release is not changed in a conventional way.

If general principles emerge in ADF mechanisms, important differences also exist among synapses. For instance, the temporal requirement for ADF is highly heterogeneous. In L5 pyramidal neurons, ADF is observed after several seconds of presynaptic depolarization [24,42] whereas a few tens of milliseconds of analog subthreshold depolarization is sufficient to induce ADF at mossy fiber-CA3 cell synapses [1] or at cerebellar GABAergic synapses [9]. At CA3–CA3 connections, the temporal requirement of ADF is not clear [34].

2. A prerequisite for analog-digital signaling: voltage propagation in axons

Whether analog voltage changes produced in the somatodendritic regions are capable of spreading along the axon over long enough distances to reach synapses constitutes a prerequisite for analog-digital facilitation (Fig. 2). The process of voltage propagation is based on the electrical properties of the axon membrane. First theorized by W. Rall, it was shown that voltage response decays exponentially along passive cables [31]. The voltage drop along the axon can be characterized by the space constant, i.e. the axonal distance for which voltage drops to 37% of its initial value. Space constant depends on both geometrical and electrical factors of the axon: i) the axon membrane resistance determined by the relative contribution of conducting (pore-forming proteins) and non-conducting (lipids) molecules and ii) axial resistance controlled by the intra-axonal medium and the axon diameter. Thus, a large space constant is generally obtained for low intra-axonal resistance or high axonal membrane resistance.

In hippocampal dentate granule cells, excitatory post-synaptic potentials (EPSPs) generated in the dendrite travel all along the axon, and can be measured with a patch-pipette in mossy fiber terminals (i.e. EPreSP) [1]. The axonal space constant for this transient depolarizing event (~50–100 ms) has been estimated as ~450 μm in hippocampal granule cells [1]. In neocortical pyramidal neurons, the axonal space constant of steady-state voltage modulation in the soma yields values of 420–550 μm [24,42]. The space constant varies as a function of the frequency, failing rapidly at high frequency (see supplementary information in [42]). The axon space constant also depends on the presence of