Biochimica et Biophysica Acta 1853 (2015) 1933–1939

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

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

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ARTICLE INFO

Article history:
Received 17 September 2014
Received in revised form 17 November 2014
Accepted 19 November 2014
Available online 25 November 2014

Keywords:
Calcium channel
Cav2.1
Potassium channel
Kv1
Synaptic transmission
Axon

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.

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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

☆ This article is part of a Special Issue entitled: 13th European Symposium on Calcium.
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http://dx.doi.org/10.1016/j.bbamcr.2014.11.024
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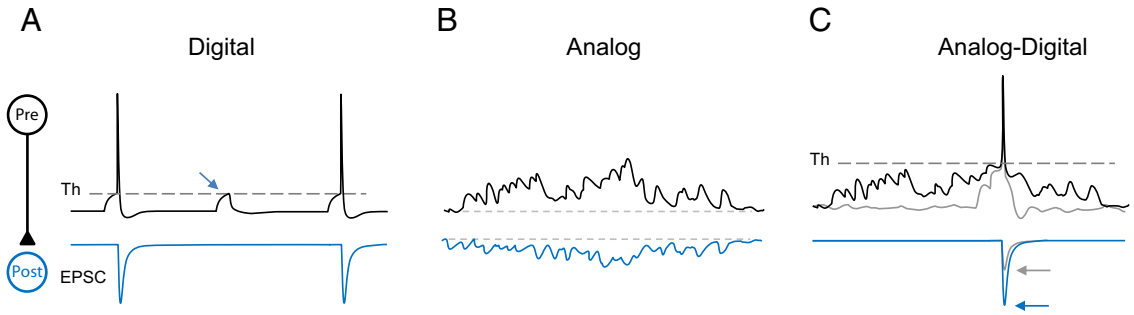

Fig. 1. Digital, analog and hybrid (analog-digital) modes of synaptic transmission. A. Digital mode of synaptic transmission in the central nervous system. Left, scheme of two synaptically connected neurons. Transmission is stereotyped and occurs in an all-or-none fashion (i.e. only if a presynaptic 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).

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

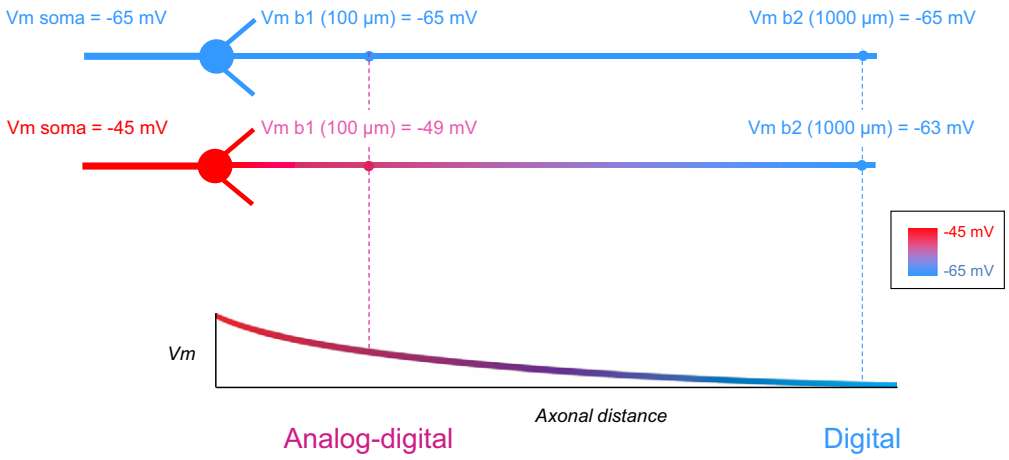

Fig. 2. Voltage decay along axons. Top, voltage distribution when the neuron is at rest (−65 mV). The voltage is constant in the soma, in the proximal presynaptic bouton (b1, 100 µm from the soma) and in the distal bouton (b2, 1000 µm from the soma). When the cell body is depolarized, (−45 mV) voltage drops along the axon because of cable properties. Bottom, voltage (Vm) decay along the axon. Note that AD transmission is restricted to proximal presynaptic bouton (b1), whereas pure digital transmission occurs at distal bouton (b2).

branch points. Each branch point acts as a local conductance increase, thus reducing the value of space constant in the axon [34]. The role of active membrane currents is not entirely clear. In principle, active conductance such as persistent sodium (Na^+) current could enhance the axon space constant by carrying subthreshold depolarization initiated in the soma over longer axonal distances. However, the large space constant of EPreSPs in hippocampal granule cell axons does not result from the activation of Na^+ channels because it is unaffected by tetrodotoxin [1]. Therefore, the large space constant observed at hippocampal granule cells or L5 pyramidal neurons may result from specific electrical properties (i.e. high membrane resistance and/or low axial resistance). The recent development of nano-scale patch-clamp recording techniques will probably allow identification of membrane properties at thin axons [30].

The notion of axonal space constant is crucial for analog-digital signaling because it describes how voltage spreads along the axon and modulates the biophysical properties of ion channels located in presynaptic terminals. This modulation depends on the gating characteristics of the current. For instance, a modest subthreshold depolarization will be more effective on voltage-gated currents with low activation/inactivation thresholds (i.e. near the resting membrane potential) than on those with high activation/inactivation thresholds (i.e. far from the resting membrane potential). Consequently, analog-digital facilitation will spread over long distances if the underlying mechanism involves low threshold conductance, such as the D-type current, a conductance implicated in ADF in neocortical neurons [24].

As many CNS neurons establish local recurrent connections, analog-digital enhancement is therefore likely to play a major role in a potentially large number of cortical, hippocampal and cerebellar excitatory and inhibitory circuits [12,24,42,48]. An important consequence of the size of the axon space constant is that pure digital and hybrid signaling may coexist within the same axon. In cortical pyramidal cell axons, local connections established by presynaptic boutons located in the proximal bouquet of axon collaterals are likely to function in a hybrid analog-digital way, whereas long projecting axon collaterals may essentially work under the digital mode. For example, at excitatory connections between layer 5 pyramidal neurons, the larger analog-digital facilitation (ADF) is observed at local connections [24]. In addition, a similar spatial dichotomy has recently been reported in CA3 pyramidal neurons where analog-digital facilitation is observed at proximal synapses established with other CA3 neurons but not at synapses with distal CA1 neurons [34]. In this way, analog-digital signaling increases the computational repertoire of neuronal communication.

3. Mechanisms of analog-digital facilitation

Two mechanisms have been reported to account for the analog-digital enhancement of transmission in central synapses.

3.1. ADF resulting from inactivation of presynaptic Kv1 channels

First, depolarization of the somatic region of the presynaptic neuron may enhance synaptic transmission as the consequence of voltage-inactivation of a specific type of K^+ channel (Fig. 3).

- Kv1 channels in the axon and presynaptic terminals

Axons contain a high density of voltage-gated K^+ channels (Kv) of the Kv1 family. Kv1 channels (KCNA, Shaker) belong to the family of potassium channels with 6 trans-membrane segments. The pore-forming channel is composed of hetero-tetramers of Kv1 α subunits that generally contain Kv1.1, Kv1.2 or Kv1.4 subunits [13,33,38]. The biophysical properties of the current are strongly influenced by both the subunit composition of the tetramers and the presence of ancillary subunits. A recent study using electron microscopy coupled to freeze-fracture replica immunolabeling technique indicates that Kv1.1 channels are located on the axon initial segment (AIS) and the presynaptic terminals in the CA1 region [23]. These channels are blocked by 4-aminopyridine or by dendrotoxin, a toxin from the venom of the mamba snake (dendroaspis). They generate a D-type current which is strongly inactivated by small depolarizations from resting membrane potential [44], suggesting that its contribution to ADF will be important even in distal regions of the axon, where analog subthreshold depolarization is minimal. In neocortical and hippocampal pyramidal neurons, for example, the Kv1 channels generate a fast-activating but slowly-inactivating D-type current (I_D) that reduces spike duration [8,24,41,43]. Pharmacological blocking of I_D with 4-aminopyridine or dendrotoxin broadens the spike in the axon and at presynaptic terminals measured electrophysiologically or with voltage-imaging techniques in cortical pyramidal cells [8,20,24].

- Properties of Kv1-dependent ADF

The properties of ADF are mainly imposed by the biophysics of the Kv1-mediated D-type current. For example, the kinetics of the analog-digital enhancement are slow and fit well with the inactivation kinetics of I_D ([4,24,42]). In fact, no ADF is observed with brief analog depolarization (~100–200 ms) and ADF appears only after several seconds of presynaptic depolarization.

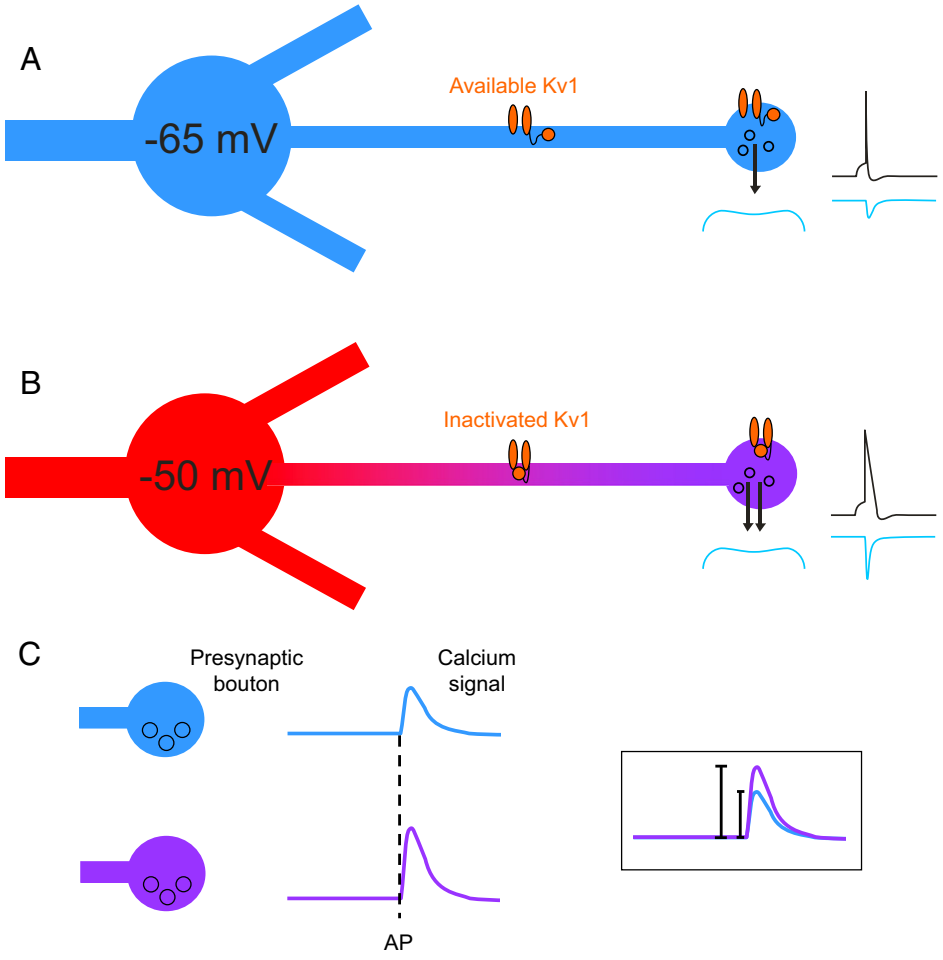

Fig. 3. Kv1-dependent analog-digital facilitation. A. With digital-only signaling the neuronal membrane voltage (Vm) is held at −65 mV, Kv1 channels remain available, resulting in a rapid termination of the spike response. B. Analog subthreshold depolarization (−50 mV at the soma) propagates from the somatic compartment and along the axon to the terminal, resulting in inactivation of Kv1 channels. This produces a broadening of the action potential and results in enhanced spike-evoked Ca^{2+} entry and incremented neurotransmitter release. C. Calcium signals produced by the spike in the digital-only signaling (blue) or in the analog-digital signaling (purple). Note the increased amplitude of the spike-evoked calcium transient (inset).

• Spike broadening enhances presynaptic calcium

The broadening of the presynaptic spike resulting from voltage inactivation of Kv1 channels increases the presynaptic Ca^{2+} current. This has been shown using two distinct methodological approaches. First, the presynaptic calcium current evoked by presynaptic depolarization having the characteristics of narrow or broad action potentials can be measured using patch-clamp recordings from large presynaptic terminals such as the mossy-fiber terminal in the hippocampus [5] or the calyx of Held [7]. In small *en passant* boutons, spike-evoked Ca^{2+} transients can be measured using calcium imaging. In fact, voltage inactivation of Kv1 channels causes a significant enhancement of the Ca^{2+} transient in the presynaptic terminal that is evoked by the propagating spike in the presynaptic terminal [4,47]. The modulation of this Ca^{2+} transient is critical since Ca^{2+} chelation with EGTA in the presynaptic neuron abolishes ADF in L5 pyramidal neurons [42] and CA3 hippocampal cells (Bialowas et al., 2014).

• Relationship between presynaptic calcium and exocytosis

Calcium ions are required for exocytosis. However the relationship between the presynaptic Ca^{2+} charge (i.e. the total amount of Ca^{2+} ions) and the exocytosis is not linear. At many CNS synapses, the postsynaptic current (*PSC*) can be described by a power law ($PSC = ax^m$, where x is the presynaptic Ca^{2+} concentration, a is a constant and m the power coefficient). The power coefficient is an indicator of the cooperativity of Ca^{2+} binding to presynaptic Ca^{2+} sensor proteins of the vesicle release machinery and varies considerably from synapse to synapse. For instance, this coefficient is 1.6 at the output synapses of hippocampal basket cells, indicating a relatively low cooperativity [11]. But it may reach 5 at the synapse formed by the calyx of Held [19]. In this latter case, very small variations in presynaptic calcium concentration resulting from small subthreshold analog modulation of the spike waveform may lead to an extremely large increase in neurotransmitter release. Thus, analog-digital modulation of synaptic transmission might be extremely heterogeneous among synapses.

3.2. ADF produced by elevation of basal calcium concentration

Propagated depolarization can also facilitate synaptic transmission by the opening of voltage-gated Ca^{2+} channels which results in an elevation in basal Ca^{2+} concentration in presynaptic terminals (Fig. 4). At rest (i.e. −65 mV), intraterminal Ca^{2+} concentration is ~100 nM and can increase up to 1 μM upon subthreshold depolarization (~−50 mV; [3]). This increase can easily be measured in thin cerebellar axons

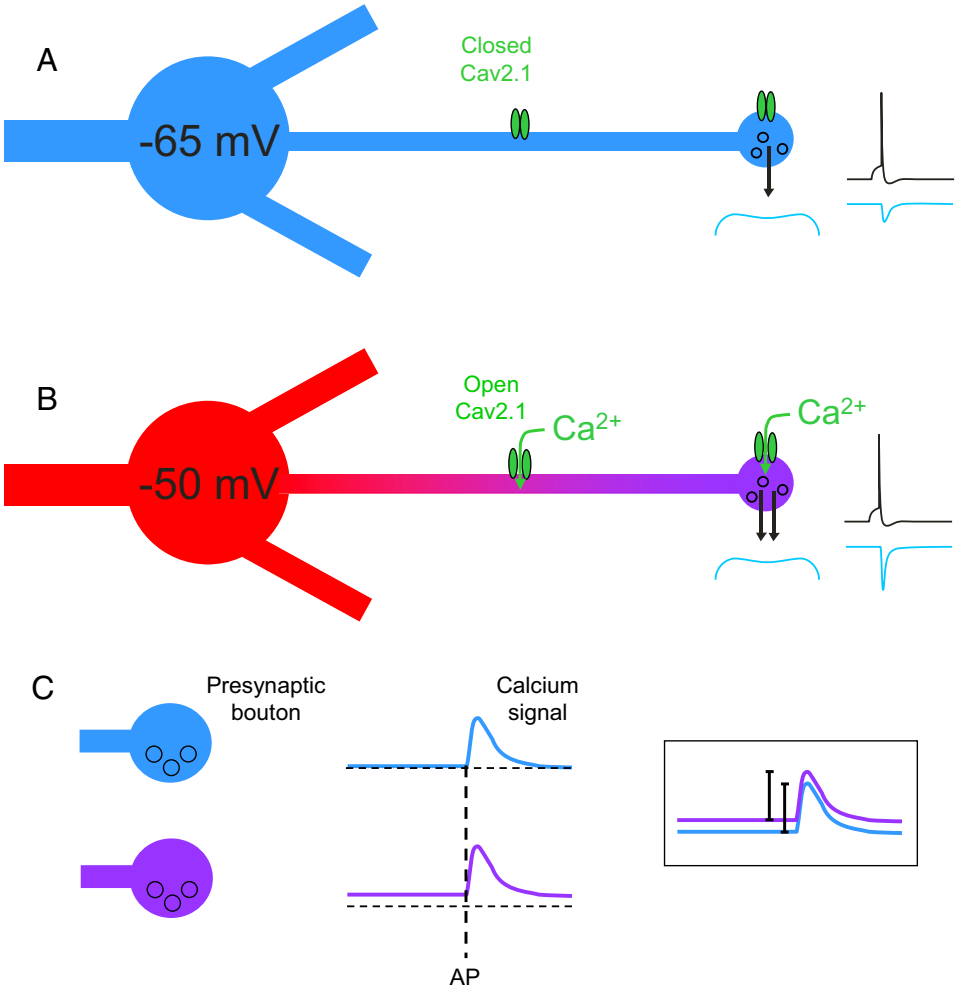

Fig. 4. Cav2.1-dependent analog-digital facilitation. A. At resting membrane potential (Vm = −65 mV), Cav2.1 (P/Q type) calcium channels are closed and can be opened only during the propagating action potential. During analog-digital signaling, partial depolarization (Vm = −50 mV) spreading from the soma to the axon opens voltage-gated calcium channels, increases calcium influx, elevates basal calcium concentration in the presynaptic bouton and enhances neurotransmitter release (indicated by two black arrows). Note that the spike shape is not affected in this case. C. Calcium signals in the presynaptic bouton in control condition (blue) and after subthreshold depolarization (purple). Note the increase in the basal calcium concentration, without change in the spike-evoked calcium transient (inset).

using fluorescent Ca^{2+}-probes [9,12]. Alternatively Ca^{2+} currents can be directly monitored with patch-clamp recording from large terminals like the calyx of Held [3]. There is a clear consensus among studies in a variety of brain areas that the voltage-gated Ca^{2+} channels responsible for this facilitation located in the axon terminal [3,9,12], or in the axon itself [47] is P/Q type Ca^{2+} channels (Cav2.1). N-type Ca^{2+} channels (Cav2.2) located in the axon terminal and the axon initial segment also participate in the increase in baseline Ca^{2+} signal upon depolarization ([47]; Bialowas et al., 2014). P/Q- and N-type channels are activated by high levels of depolarization. Thus, because of voltage attenuation along the axon, their contribution to ADF might be limited to very proximal inputs (Bialowas et al., 2014). The hippocampal mossy-fiber terminal, however, appears to be an exception, as subthreshold depolarization induces a calcium influx that is not only mediated by the classical P/Q (Cav2.1) and N (Cav2.2) type Ca^{2+} channels, but also by R-type (Cav2.3) Ca^{2+} channels [26].

The elevation in basal Ca^{2+} concentration triggered by subthreshold depolarization could have two major consequences. First, it might directly promote neurotransmitter release. In axons of cerebellar interneurons, for example, subthreshold depolarization is sufficient to increase spontaneous, spike-independent release of GABA [12]. A second possible action of elevation in basal Ca^{2+} concentration is an acceleration of the recruitment of vesicles to the active zone [28]. The principal consequence of this Ca^{2+}-induced priming of vesicles would be an increase in synchronous release when the presynaptic spike invades the axon terminal. These two effects would result in an increase in neurotransmitter release and enhanced synaptic strength.

4. Conclusion

In summary, synaptic transmission is highly modulated by changes in analog voltage resulting from synaptic activity generated in the dendrites of CNS neurons. This form of activity-dependent regulation of synaptic strength is computationally appealing because many cortical neurons establish local connections through proximal synaptic inputs. Two main mechanisms have been identified in the recent years: a spike-width-dependent facilitation in layer 5 and CA3 pyramidal cells that depends on D-type potassium channels and a basal Ca^{2+}-dependent enhancement of synaptic transmission in cerebellar interneurons. Because Kv1 channels are highly sensitive to inactivation, Kv1-dependent ADF is expected to spread over relatively long axonal distance (Fig. 5). In contrast, Cav2.1 (P/Q-type) is activated by high voltage and Cav2.1-dependent ADF is expected to affect only the very proximal part of the axon (Fig. 5).

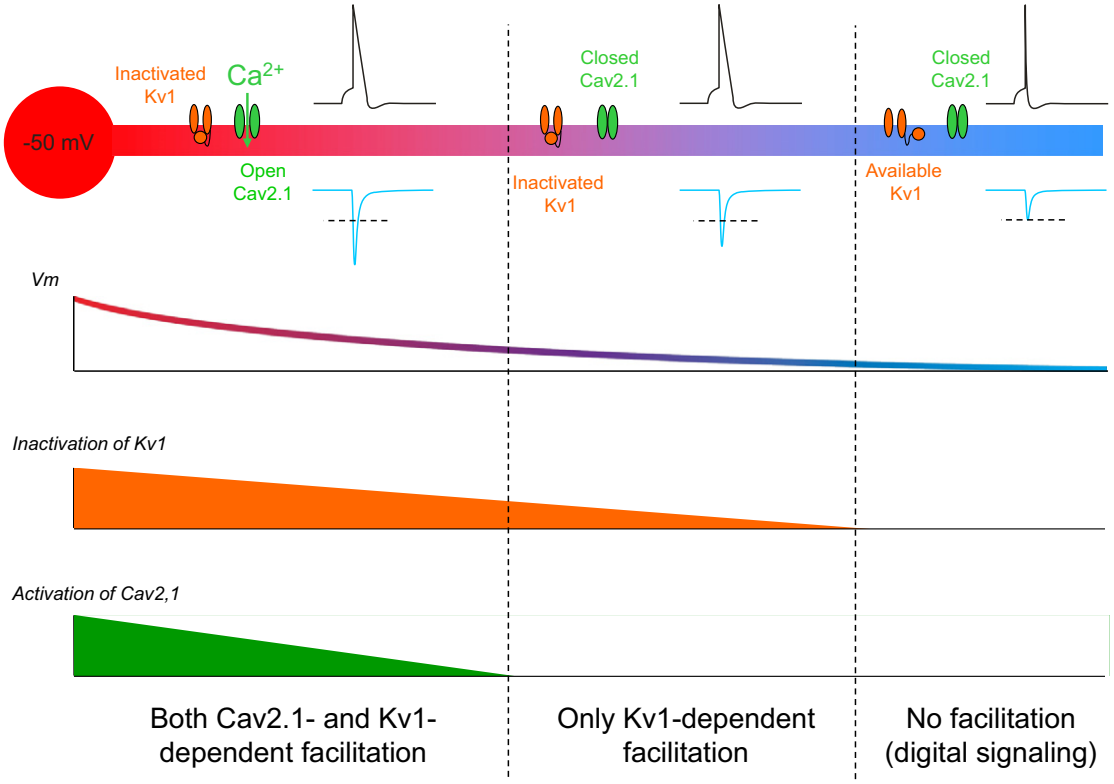

Fig. 5. Spatial extend of Kv1- and Ca2.1-dependent AD facilitation. In the proximal part of the axon, the depolarization is sufficient for inactivating Kv1 channels and activating Cav2.1 channels, resulting in a maximal AD facilitation (Kv1- and Cav2.1-dependent ADF). In the medial part of the axon, the depolarization is sufficient to inactivate Kv1 channels but cannot activate Cav2.1. In this region, only Kv1-dependent facilitation is observed. In the distal part of the axon, the depolarization originating in the soma is too small to inactivate Kv1 channels and no facilitation occurs.

Analog-digital enhancement of transmission at mossy-fiber synapses may also involve other processes because the spike width is not altered in the presynaptic terminal and facilitation is only partially reduced by calcium chelators [1,35]. Alternative mechanisms to the classical Ca^{2+}-induced modulation of exocytosis have been suggested such as Ca^{2+}-independent, but voltage-dependent exocytosis (see review in [16]). Beyond ion channels activated by depolarization, it will be important to determine the precise role of other presynaptic receptors and presynaptic proteins that may read analog voltage-shift in the presynaptic element.

The discovery of ADF incites reexamining how neuronal information is transferred in the brain. Classically, neural codes and computation are based on pure temporal patterns of spikes. However, information could be also carried by spike waveform [14,22]. So far this action-potential waveform code has been evaluated in the soma but it could well apply to Kv1-dependent modulation of spike waveform and of subsequent release in the axon.

The pre-requisite for ADF is the propagation of analog voltage along the axon. Many cortical cells have presynaptic terminals that are electronically close to the cell body, making ADF physiologically probable. There is also solid evidence for induction of ADF by physiological modulation of membrane potential. In the neocortex, somatic depolarization mimicking cortical UP states is transmitted far in the axon, indicating that ADF may occur in vivo [42]. Similarly, theta oscillations are able to induce Kv1-dependent ADF in CA3 circuits [4]. Additional experiments will be necessary to determine how other slow types of membrane depolarization resulting from release of neuromodulators, sensory stimulation or epileptic seizures also induces ADF.

Acknowledgments

Supported by Institut national de la santé et de la recherche médicale, Centre National de la Recherche Scientifique, Agence Nationale de la Recherche (ANR 11 BSV4 016 01), Fondation pour la Recherche Médicale, Ecole Normale Supérieure (doctoral grant to MZ) and French Ministry of Research.

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