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Excitatory effects of GABA in established brain networks

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Although GABA remains the predominant inhibitory neurotransmitter of the brain, there are numerous recent examples of excitatory actions of GABA. These actions can be classified in two broad categories: phasic excitatory effects, as follow single activation of GABAergic afferents, and sustained excitatory effects, as follow prolonged activation of $GABA_A$ receptors. Evidence reviewed here indicates that, contrary to common belief, these effects are not restricted to embryonic or neonatal preparations.

Introduction

Activation of $GABA_A$ receptors leads to opening of channels that are permeable to HCO_3^- and Cl^-. Under physiological conditions, the corresponding currents have a reversal potential (E_{GABA}) close to the neuronal resting potential. In recent years, it has become increasingly clear that the resulting effects on the postsynaptic cell can be either inhibitory or excitatory. In particular, it has been realized that E_{GABA} is developmentally regulated such that activation of $GABA_A$ receptors is mostly excitatory in neonatal brain preparations, but becomes inhibitory later in development [1–3]. The excitatory action of GABA early in life is presumably important for neuronal development and network formation.

Superimposed on the evolution of GABA action during development, there appear to be important differences in the effects of this neurotransmitter depending on experimental conditions and tissue specificity. Thus, it has been recognized for some time that in dorsal root ganglion neurons, Cl^- homeostasis differs from that in many brain neurons, so that in these cells $GABA_A$ receptor activation leads to depolarization [1]. In the past few years, $GABA_A$-receptor-induced excitation has also been discovered in mature brain preparations – such findings are the subject of this review. Here, 'mature' means that networks are already established and fulfill their normal function. However, it is important to note that many studies, particularly of brain slices, have actually been performed using juvenile preparations.

Phasic excitatory effects of $GABA_A$ receptor activation in mature GABAergic synapses

A recent study of cortical pyramidal cells from three-to-four-week-old rats showed that activation of dendritic GABAergic synapses leads to cell depolarization [4]. If activation of such a GABAergic afferent is combined within a certain time window (~5–10 ms) with a depolarization mimicking subthreshold glutamate-mediated excitation, action potentials are emitted (Figure 1a,i), showing that the GABAergic afferent enhances the cell excitability. Interestingly however, a similar depolarization elicited by a GABAergic afferent in the somatic domain has the opposite effect on cell excitability – that is, it inhibits firing (Figure 1a,ii). Depolarization occurs in this system simply because the resting potential (~ −85 mV) is more negative than E_{GABA} (~ −70 mV).

Thus, even relatively negative E_{GABA} values are compatible with excitatory effects of GABAergic afferents. In the cortex and amygdala, interneurons have a more depolarized E_{GABA} value than pyramidal cells [5] so that, in interneurons, strongly excitatory effects of stimulation of GABAergic afferents can be expected. The same pattern is found in the cerebellum: whereas Purkinje cells of two-to-four-week-old rats have an E_{GABA} value near −85 mV, that of interneurons (stellate and basket cells of the molecular layer) is near −58 mV [6]. Consequently, activation of presynaptic GABAergic afferents leads in some interneurons to a postsynaptic spike or to a train of spikes (Figure 1b,i). In other interneurons, however, activation of presynaptic GABAergic afferents has the opposite effect: hyperpolarization and a strong reduction of the spike frequency (Figure 1b,ii). Analysis of many such experiments reveals that both E_{GABA} and the cell resting potential have significant cell-to-cell differences, and that the nature of the synaptic response is determined by the sign of the difference between the two parameters. This system conforms to the simple view that depolarizing responses are excitatory, and hyperpolarizing responses are inhibitory (although it is important to note that this scheme is far from universal; Box 1). The interneuron network of the cerebellar molecular layer thus possesses both excitatory and inhibitory GABAergic synapses simultaneously, and is an interesting preparation for studying conditions that control the switch from excitatory to inhibitory.

In chick nucleus magnocellularis cells, which are located in the cochlear nucleus and receive GABAergic projections from the superior olivary nucleus, E_{GABA} is maintained at a very depolarized level (−25 mV) up to ten days after hatching, well after hearing is established [7]. In this preparation, even though GABA-mediated

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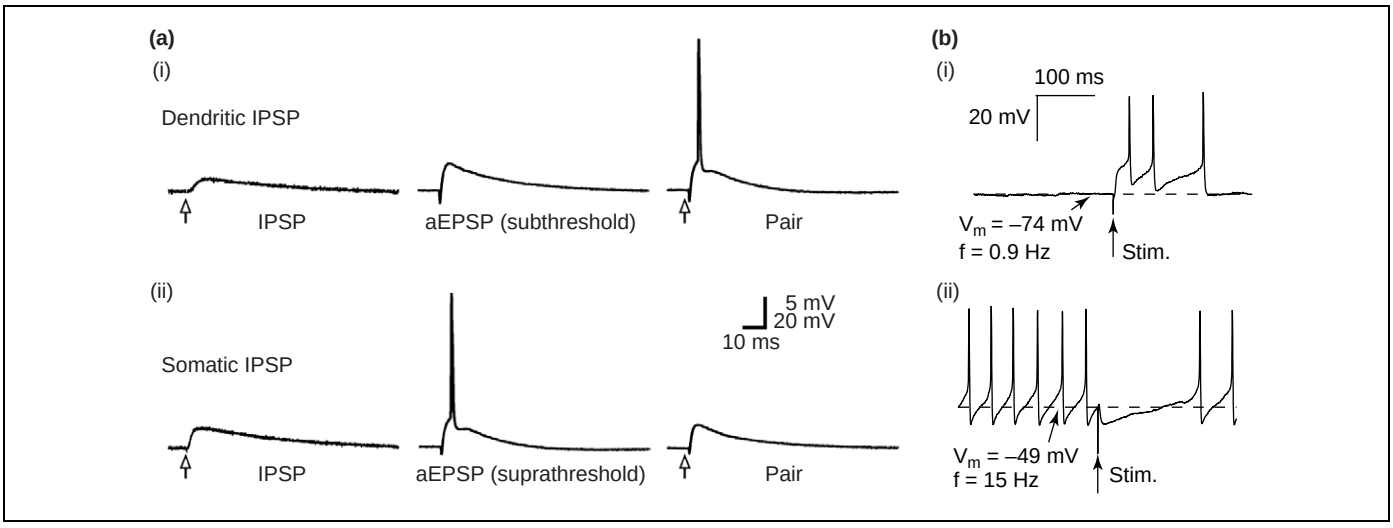

Figure 1. Excitatory versus inhibitory GABAergic synapses in mature brain preparations. **(a)** Cortical slice. (i) Whereas separate activation of dendritic synapses by an inhibitory postsynaptic potential (IPSP) and somatic current injection (aEPSP) both lead to subthreshold depolarization, combination of the two produces an action potential. (ii) By contrast, activation of somatic synapses by an IPSP converts a depolarizing somatic current injection from suprathreshold to subthreshold. Reproduced, with permission, from Ref. [4]. **(b)** Cerebellar slice. (i) Stimulation (stim.) of GABAergic synapses leads to a burst of action potentials. (ii) In another cell, a similar stimulation inhibits firing. The cell in (i) had a low resting potential ($V_m = -74$ mV) and resting firing frequency (f = 0.9 Hz), whereas that in (ii) had a higher resting potential ($V_m = -49$ mV) and resting firing frequency (f = 15 Hz). (a) and (b) respectively represent recordings from pyramidal cells and basket cells; they were obtained with gramicidin perforated-patch recording, to preserve intracellular anion homeostasis. Reproduced, with permission, from Ref. [6] © (2003) the Society for Neuroscience.

synaptic potentials are depolarizing, they are not suprathreshold for single stimuli. When a train is given, just one spike is generated near the beginning of the train (usually in response to the second stimulation). In this sense, the GABAergic input can be considered excitatory. However, GABA-mediated trains inhibit spikes induced by simultaneous glutamate inputs, and from this point of view they are inhibitory [7].

Activity-driven changes in the sign of GABAergic synapses

The aforementioned examples illustrate the fact that apparently modest differences in E_{GABA} can have dramatic functional consequences. This raises the question of whether neuronal activity can significantly alter this parameter.

In mature hippocampal pyramidal cells, the effects of single stimulations of GABAergic inputs are inhibitory. However, if a high-frequency train is delivered, GABAergic synapses become depolarizing (after ~1 s) and enhance firing. This is accompanied by accumulation of Cl^- in neurons, and increased concentration of K^+ in interstitial fluid [8]. New evidence using intracellular Cl^- recording (as measured using the fluorescent probe 6-methoxy-*N*-ethylquinolium iodide, MEQ) confirms that the intracellular Cl^- concentration ($[Cl^-]_i$) rises in CA1 pyramidal cells during such trains, and suggests a close link between Cl^- accumulation and enhanced excitability [9]. In the CA3 region, the activity-driven E_{GABA} shift is much faster and larger in interneurons than in pyramidal cells [10]. The contrast between the two neuron types might be due to differences in surface-to-volume ratio, in intracellular carbonic anhydrase activity or in plasma membrane Cl^- transporters. In any case, it is interesting that in the hippocampus, high-frequency stimulation induces different E_{GABA} changes in interneurons and principal cells; these are reminiscent of the different E_{GABA} values observed under resting conditions in the corresponding neuronal classes of the cortex and cerebellum.

Although the $[Cl^-]_i$ increase measured by Isomura *et al.* [9] was transient, another study indicates that,

Box 1. Defining an excitatory GABA action

There is sometimes confusion concerning the meaning of the words 'excitatory GABA action'. Although a high $[Cl^-]_i$ value makes it easier to observe such an action, it has been pointed out many times that a depolarizing effect of GABA should not be taken as synonym for an excitatory effect. Thus, in the spinal cord GABA depolarizes primary afferent nerve terminals, yet inhibits transmission [1]. Likewise, in peptidergic terminals, GABA-induced depolarization leads to Na^+ channel inactivation and reduces presynaptic GABA release [30]; Figure 1b illustrates another example of an inhibitory depolarizing response. In a frequently found pattern, a depolarizing GABA-mediated potential leads to a sequence of inhibition and excitation. Inhibition lasts for the duration of the GABA-mediated conductance, and is due to the fact that this conductance tends to clamp the cell potential near the equilibrium potential for Cl^-, which is typically below the spike firing threshold ('shunting inhibition'; e.g. see Ref. [31]).

It is also important to distinguish between the effects of brief GABA application, as occurs during single synaptic transmission, and the effects of longer application of $GABA_A$ receptor agonists. This review first focuses on single synaptic effects. They are considered excitatory if a single activation of a GABA afferent facilitates (Figure 1a,i) or elicits (Figure 1b,ii) spiking of the postsynaptic cell. Effects of longer $GABA_A$ receptor stimulation, as occurs during application of exogenous agonists, are considered later in this review. Even though sustained $GABA_A$ receptor activation often stops action potential firing, owing to shunting inhibition, it can lead to elevation of $[Ca^{2+}]_i$ (Figure 3). This elevation might serve as a positive signal for many cellular processes, but it might also trigger phenomena that can hardly be considered excitatory, including inhibition of spike firing following activation of Ca^{2+}-dependent K^+ channels. Thus, postsynaptic elevation of $[Ca^{2+}]_i$ cannot be taken as a proof for excitatory GABA action.

under certain circumstances, the concentration change can be made virtually permanent (on the timescale of a standard electrophysiological recording, ~30 min). In hippocampal cultures and slices, it was recently shown that combining stimulation of GABAergic afferents with postsynaptic spiking results in a long-term change in $[Cl^-]_i$, provided that the two stimuli are applied repetitively within a time window of ~20 ms [11] (Figure 2). Pharmacological evidence indicates that the long-term E_{GABA} increase requires a postsynaptic increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) following activation of L-type Ca^{2+} channels. The change in E_{GABA} amounts to ~4 mV following a 30-s-long train of paired stimulations at 5 Hz; this would be sufficient to switch the sign of a synapse from inhibitory to excitatory. Woodin *et al*. suggest that altered activity of Cl^- transporters, possibly the K^+–Cl^- cotransporter KCC2, is responsible for the effect. Consistent with this possibility, sustained interictal-like activity in hippocampal CA1 cells downregulates KCC2 mRNA and protein expression [12]. Thus, the notion emerges that neuronal activity can change E_{GABA} in two ways. First, changes in $[Cl^-]_i$ result from sustained or repetitive activation of $GABA_A$ receptors; these changes are transient and relax with a time constant of ~1 min [13]. Second, in certain circumstances (probably involving an increase in $[Ca^{2+}]_i$ in addition to that of $[Cl^-]_i$), the properties of the Cl^- transporters are modified, so that the set-point of the system is altered, resulting in long-term changes in E_{GABA}.

The activity-dependent rise of $[Cl^-]_i$ in the hippocampus is thought to be due to the mixed permeability of $GABA_A$-receptor-gated channels for Cl^- and HCO_3^-. Each presynaptic spike induces small entry of Cl^- and exit of HCO_3^-; if internal HCO_3^- concentration is renewed from diffusing CO_2 by intracellular carbonic anhydrase, the system continues to increase $[Cl^-]_i$ [14]. Consistent with this view, the enhanced cell firing induced by high-frequency stimulation was blocked by inhibiting intracellular carbonic anhydrase [15]. This effect appears late in development [later than postnatal day (P)15 in rat] and is due to the expression of a specific subtype of carbonic anhydrase, called CAVII, in pyramidal cells [15]. Thus, expression of this carbonic anhydrase provides a means to obtain excitatory $GABA_A$-receptor-triggered actions that differ mechanistically from those obtained early in life by direct membrane depolarization [16].

Modifications in $[Cl^-]_i$ during the day–night cycle

Because GABAergic synapses of mature brain circuits operate so close to their switch point, they can be used to reverse the operation of a circuit. A few years ago, Wagner *et al.* [17] showed that in the suprachiasmatic nucleus, which largely drives the day–night cycle in mammals, GABAergic inputs are excitatory during the day and inhibitory during the night. They proposed that the sign-change occurred because of a shift of E_{GABA}. More recently, it was shown that muscimol applications increase $[Ca^{2+}]_i$ in a larger proportion of suprachiasmatic nucleus cells during the day than at night [18].

Increased $[Cl^-]_i$ in pathological conditions

As already discussed here, repetitive extracellular stimulation of the hippocampus at a high rate increases $[Cl^-]_i$ and consequently renders GABAergic synapses excitatory.

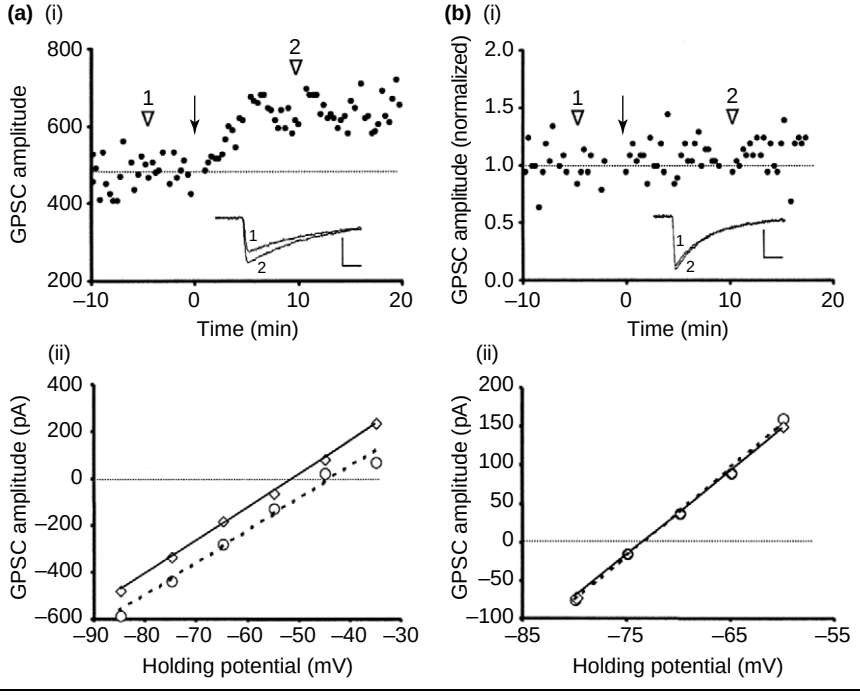

Figure 2. Long-term change in $[Cl^-]_i$ following concerted presynaptic and postsynaptic stimulation – paired recordings from hippocampal neurons in culture. **(a)** Pairing presynaptic and postsynaptic stimulations (5 Hz for 30 s; stimulation at time 0 indicated by the black arrow) leads to long-lasting enhancement of GABA-mediated postsynaptic current (GPSC) amplitudes (i). The peak amplitude of GPSCs reverses at a less-negative potential after the pairing protocol (circles and dotted line) than before (diamonds and continuous line), indicating a rise in $[Cl^-]_i$ (ii). **(b)** If a time interval as short as 75 ms is inserted between presynaptic and postsynaptic stimulations, no effect is seen. Inserts in (a,i) and (b,i) represent averaged traces before (1) and after (2) stimulations. Scale bars, 100 pA and 20 ms. Reproduced, with permission, from Ref. [11].

Likewise, in some cells recorded from hippocampal slices taken from patients suffering from epilepsy, $[Cl^-]_i$ is abnormally elevated, and GABAergic synapses are excitatory [19]. This raises the possibility that elevated $[Cl^-]_i$ could be not only the consequence but also the cause of bursts of brain activity [20].

Another pathological situation in which high $[Cl^-]_i$ has been documented is ischemia. $[Cl^-]_i$ increase is observed after a few minutes of subjecting brain slices to ischemic conditions, and GABAergic synapses are thought to then become excitatory. This probably has important consequences for subsequent brain damage, because drugs interfering with GABA transmission can significantly reduce this damage [21].

Finally, it was recently shown that after prolonged constriction of the sciatic nerve (a model of chronic pain), $[Cl^-]_i$ is elevated in superficial dorsal horn cells, and that applications of exogenous GABA increase $[Ca^{2+}]_i$ [22]. Interestingly, expression of KCC2 appears inhibited in dorsal horn neurons of the injured side compared with those on the control side, indicating that repetitive painful stimuli trans-synaptically increase $[Cl^-]_i$ through an action on KCC2.

Progenitor neuronal cells

Following the realization that some progenitor cells divide and differentiate into neurons in the adult brain, much effort has been recently devoted to the characterization of these progenitor cells, in particular in the subventricular zone. Although these cells are found in adults, they resemble neonatal neurons as far as Cl^- homeostasis is concerned. Indeed, neuronal progenitor cells recorded in brain slices from adult mice, like those recorded in cultures from neonatal rats [23], express $GABA_A$ receptors and display depolarizing responses to GABA application [24]. Because these cells contain GABA, an autocrine GABA signaling mechanism was suggested [24,25]. Furthermore, it was shown that, in the adult mouse, application of GABA or bicuculline respectively reduces or enhances the speed of migration of neuronal progenitor cells [26]. It was suggested that astrocytes modify the migration speed by controlling the GABA concentration surrounding the neuronal progenitor cells, and that this control involves an alteration of $[Ca^{2+}]_i$ in the migrating cells [26].

$[Ca^{2+}]_i$ rise

A widely used criterion in studying excitatory GABA action is an increase in postsynaptic $[Ca^{2+}]_i$. This effect has not so far been described following a single synaptic stimulus, and all studies seeking to increase postsynaptic $[Ca^{2+}]_i$ resort to prolonged activation of $GABA_A$ receptors. In neonatal preparations, such applications are assumed to increase $[Ca^{2+}]_i$ because GABA agonists depolarize the cells above the activation threshold of voltage-dependent Ca^{2+} channels; there is no reason to doubt this interpretation. However, several results indicate that, in more mature preparations, more complicated pathways operate. Therefore, care should be taken not to assume that postsynaptic $[Ca^{2+}]_i$ elevation always reflects postsynaptic excitation (Box 1).

Early reports of GABA-induced increases in $[Ca^{2+}]_i$ were obtained using cultures of neurons (up to several weeks old) from cerebellum or hippocampus [27,28]. In the first example, the Ca^{2+} responses outlasted GABA applications by minutes, long after the expected offset of $GABA_A$ receptor activation [27]. By contrast, responses to glutamate receptor agonists returned quickly upon washout of the agonist. In the second study, the increase in $[Ca^{2+}]_i$ elicited by a comparatively short (duration of $\sim$1 s) agonist application recovered much more slowly than the GABA-induced current after prolonged GABA application, indicating that recovery from desensitization utilizes distinct mechanisms for the two responses [28]. Based on these observations, Segal suggested that the coupling between $GABA_A$ receptor activation and Ca^{2+} response involves slow kinetics, and is more complex than depolarization-driven activation of Ca^{2+} channels.

The exact nature of this link has long remained elusive. Very recently however, the issue has been re-addressed in interneurons of the cerebellar molecular layer, which display a robust Ca^{2+} response to muscimol applications at up to P20 [29] (Figure 3a). In these cells, E_{GABA} is on average equal to the resting potential, so that a simple depolarization-driven Ca^{2+} entry would not have an effect. The Ca^{2+} response to muscimol was found to have two phases: an early peak that is accompanied by mild cell depolarization, and a sustained phase during which the cell repolarizes to near the resting level. The early phase appears to be linked to a gradual $[Cl^-]_i$ increase, driven by the mixed permeability of GABA-activated channels for Cl^- and HCO_3^- [14]. The associated increase in $[Ca^{2+}]_i$ rise is proposed to occur as part of a regulatory volume decrease triggered by the increased osmotic tension accompanying the $[Cl^-]_i$ rise (Figure 3b). The second phase of the Ca^{2+} response includes participation from ryanodine-sensitive Ca^{2+} stores and L-type Ca^{2+} channels.

Conclusion and perspectives

It is an unfortunate, but inescapable, outcome of the recent work summarized here that the clean separation between positive glutamate and negative GABA has to be abandoned. For this reason, the traditional inhibitory postsynaptic potential (IPSP) and inhibitory postsynaptic current (IPSC) denominations are starting to be replaced by GABA-mediated postsynaptic potential (GPSP) and GABA-mediated postsynaptic current (GPSC) in some publications [6,11]. Thus, it is not enough to determine the pharmacology of a synaptic connection to establish its physiological role, and much painstaking work lies ahead to find out exactly what effect each individual GABAergic synapse has on the postsynaptic cell. The same applies presumably to glycinergic synapses, which have not been discussed here because of lack of space. The work needed appears formidable, because it involves in each case several tests in different stimulation conditions, and the use of various techniques, including gramicidin perforated-patch and cell-attached recordings, which are particularly demanding and prone to experimental artefacts.

Another important message of this review is that GABAergic synapses operate close to the critical point

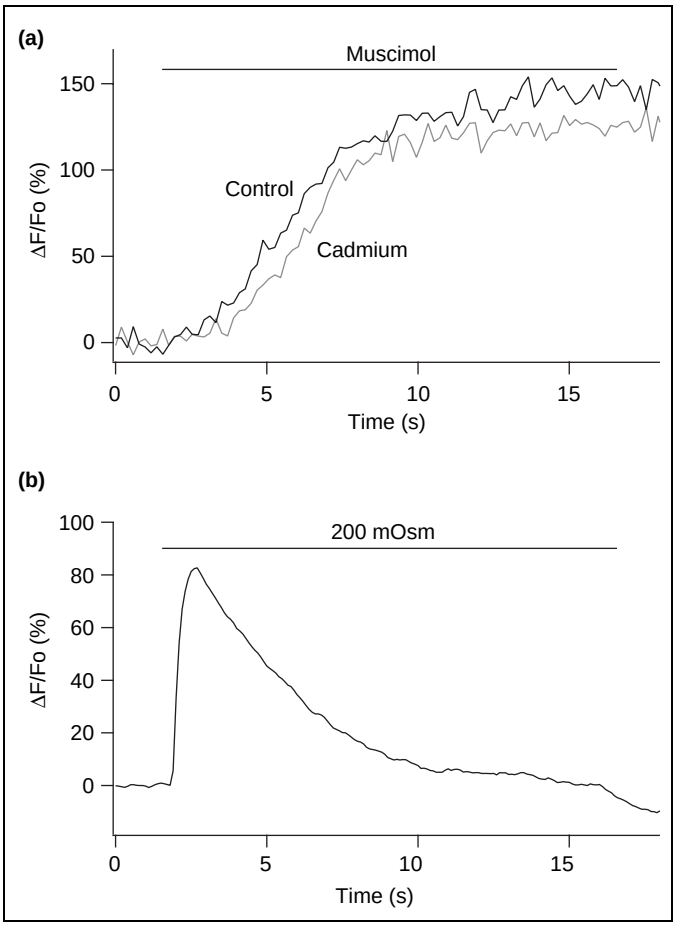

Figure 3. Muscimol-induced and hypo-osmotically-induced increases in $[Ca^{2+}]_i$ in cerebellar basket cells. **(a)** Application of the $GABA_A$-receptor-specific agonist muscimol leads to a $[Ca^{2+}]_i$ rise (measured as the relative increase in fluorescence, or ΔF/Fo ratio, reported by the Ca^{2+}-sensitive dye OG-1) in cerebellar basket cells. This is not significantly inhibited by the Ca^{2+}-channel blocker cadmium, indicating that onset of the $[Ca^{2+}]_i$ rise is not due to activation of voltage-dependent Ca^{2+} channels. **(b)** In another cell, application of a hypo-osmotic solution leads to a $[Ca^{2+}]_i$ rise. This indicates that osmotic stress induces Ca^{2+} responses. During prolonged muscimol application, such stress could be produced by intracellular accumulation of Cl^-. The $[Ca^{2+}]_i$ rise in (b) is transient; likewise, that in (a) displayed a transient peak followed by a much lower plateau (not shown). The difference in timescale between the osmotically-driven signal and that induced by muscimol can be explained by the fact that in the latter case, muscimol must induce an increase in $[Cl^-]_i$ before the resulting osmotic stress can elevate $[Ca^{2+}]_i$. Reproduced, with permission, from Ref. [27].

where the sign of the effects switches over. In fact, a given synapse can display inhibitory effects with one protocol and excitatory effects with another. Interestingly, relatively minor $[Cl^-]_i$ alterations in the postsynaptic cell can operate the sign switch; such alterations might be brought about either by physiologically relevant parameters (e.g. status of the day–night cycle) or by pathological conditions. Thus, GABAergic synapses appear much more versatile than previously thought. An important challenge for future research will be to understand better the cellular mechanisms and functional roles of these fascinating sign changes.

Finally, an unexpected outcome of recent research in this area has been the finding that GABA-induced $[Ca^{2+}]_i$ rises are not necessarily a consequence of depolarization-triggered action potential firing. The cellular mechanism that is suggested in cerebellar interneurons – osmotically-driven $[Ca^{2+}]_i$ elevation [29] – needs to be better understood and further tested in several preparations. It will be particularly important to explore the intracellular pathways involved in this response, and also the functional consequences of the resulting $[Ca^{2+}]_i$ increase.

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