● INVITED REVIEW

Ischemic long-term-potentiation (iLTP): perspectives to set the threshold of neural plasticity toward therapy

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Abstract

The precise role of neural plasticity under pathological conditions remains not well understood. It appears to be well accepted, however, that changes in the ability of neurons to express plasticity accompany neurological diseases. Here, we discuss recent experimental evidence, which suggests that synaptic plasticity induced by a pathological stimulus, *i.e.*, ischemic long-term-potentiation (iLTP) of excitatory synapses, could play an important role for post-stroke recovery by influencing the post-lesional reorganization of surviving neuronal networks.

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Introduction

Ischemic stroke is a major cause of disability and death among neurological diseases, bearing a large impact on the therapeutic and socioeconomic burden for healthcare (Feigin et al., 2003). Its clinical course is characterized by an abrupt onset of neurological deficits followed by variable and often incomplete recovery (Miller et al., 2010). While acute disruption of blood flow causes pronounced ischemic brain injury leading to cell death in the core of the original insult, surrounding neural tissue, also called the "*penumbra*", remains less affected and to a certain degree functionally intact (Astrup et al., 1981; Calabresi et al., 2003).

During the past decades important advances have been made in better understanding the pathophysiological mechanisms underlying ischemia-induced neural cell death and the signaling pathways leading to secondary damage in the *penumbra* (Calabresi et al., 2003). However, far less attention has been dedicated to alterations in neural plasticity of surviving and only partially or indirectly affected neural networks. Since neurons (and glia) are still alive in these brain regions they are interesting targets for therapeutic intervention. Indeed, it has been indicated that plasticity in surviving networks could play an important role for post-stroke recovery, but in turn may also lead to complications such as epilepsy or memory dysfunction (*e.g.*, Crepel et al., 2003; see also Maggio and Vlachos, 2014).

In this succinct perspective article, we summarize current knowledge on ischemia-induced plasticity of excitatory synapses, *i.e.*, ischemic long-term-potentiation (iLTP). We discuss our recent finding that implicates thrombin, a factor known to play an important role in blood coagulation, in mediating iLTP and point to potential consequences for therapeutic strategies.

Ischemic long-term-potentiation (iLTP) *vs.* tetanic long-term-potentiation (tLTP)

iLTP has been first described by Crepel and colleagues (1993) and was defined as a long-lasting increase in excitatory synaptic strength triggered by acute, *i.e.*, 3 minutes of oxygen and glucose deprivation of rat hippocampal slices. It was soon recognized that this pathology-associated form of synaptic potentiation shows similarities to classic, *i.e.*, tetanic long-term-potentiation (tLIP), which is induced by local electrical stimulation in animal models (Di Filippo et al., 2008). Indeed, iLTP and tLTP share common Ca^{2+}-dependent signaling pathways: in both forms of plasticity a crucial role for N-methyl-D-aspartate receptors (NMDARs), Ca^{2+}/calmodulin-dependent protein kinase 2 (CamKII), retrograde Ca^{2+}-dependent signaling (*e.g.*, NO, endocannabinoids), intracellular Ca^{2+}-stores, protein kinase C (PKC), extracellular signal-regulated kinases (ERK) and Ca^{2+}-dependent non-lysosomal cysteine proteases (calpain) have been reported (reviewed by Di Filippo et al., 2008). In line with these findings, it has been shown that iLTP and tLTP can influence each other: if one form of LTP is induced, the ability of the neurons to express the other form is occluded (Maggio et al., 2015; Stein et al., 2015). Furthermore, recent evidence from the hippocampus discloses that the dorsal hippocampus of adult mice expresses both strong tLTP and iLTP, while the ventral hippocampus shows weaker tLTP and

iLTP (Maggio et al., 2015). Hence, similar signals seem to account for ischemic and tetanic LTP of excitatory synapses.

Nonetheless, a set of important differences between iLTP and tLTP need to be considered. (1) tLTP is a prototype of associative plasticity, which resides in the activation of distinct synapses, leading to input-specific, localized, and highly coordinated changes in intracellular Ca^{2+}-levels. Accordingly, tLTP has been linked to associative learning and memory formation. Conversely, iLTP is believed to result from a strong global Ca^{2+}-overload, which induces potentiation that is not input-specific and may therefore not necessarily serve learning and memory. (2) Although NMDARs are crucially involved in both forms of synaptic plasticity, iLTP seems to be more sensitive to NMDAR subunit composition. Specifically, expression of the NMDAR subunit NR2B has been suggested to play a central role in iLTP (Picconi et al., 2006). (3) It is important to also note that iLTP is not a general phenomenon observed in all brain regions and every cell type of the mammalian brain. In the striatum, for example, medium-sized GABAergic interneurons express iLTP, whereas cholinergic interneurons do not respond to transient oxygen and glucose deprivation with potentiation of excitatory synapses; despite the fact that both cell types can express tLTP (Calabresi et al., 2000, 2003). Apparently, similarities and differences between iLTP and tLTP and the underlying molecular mechanisms need to be further clarified. It is becoming increasingly clear, however, that Ca^{2+}-buffering capacity, NMDAR composition and intracellular Ca^{2+}-stores influence the ability of neurons to respond with excitatory potentiation upon transient ischemic attack.

Ischemic long-term-potentiation (iLTP) and post-stroke recovery

The precise role of iLTP in post-stroke recovery remains not well understood. It has been proposed that iLTP could promote neural homeostasis at an early stage of disease by readily increasing synaptic strength of all excitatory synapses of a neuron. This could be beneficial in the early phase after stroke by counteracting the stroke-induced perturbation of neuronal network activity, *i.e.*, the acute reduction in neural activity (Turrigiano, 2008). Conversely, it has been discussed that global strengthening of excitatory synapses may increase the susceptibility for hyperexcitability, seizure-like activity and excitotoxicity. Likewise, unspecific potentiation of excitatory synapses which saturates tLTP mechanisms (Stein et al., 2015) may occlude the ability of neurons to express further input-specific synaptic plasticity. Whether this mechanism is detrimental by prohibiting LTP-dependent associative learning, or protective by preventing the pathological rewiring of lesioned neuronal networks, remains unknown at present. The role of iLTP in secondary excitotoxic cell death and other functional and structural changes occurring at a later stage after stroke need to be determined as well. Thus, iLTP may assert differential, *i.e.*, beneficial and/or detrimental effects, depending on the phase of post-lesional reorganization. Considering, however, that NMDAR inhibition has been suggested to accelerate recovery after brain injury (Giaconi et al., 2012) and because iLTP is NMDAR dependent (Picconi et al., 2006), it is interesting to hypothesize that blocking iLTP may assert overall beneficial effects in post-stroke recovery.

The role of thrombin in setting the threshold of synaptic plasticity after stroke

The molecular pathways leading to iLTP have been recently further characterized (Stein et al., 2015). In this study, it could be shown that thrombin, a serine protease primarily known to regulate blood coagulation, is upregulated in acute mouse hippocampal slices following transient (3 minutes) oxygen and glucose deprivation (for recent review on thrombin see Ben Shimon, Lenz et al., 2015). Furthermore, a link between neural thrombin signaling, induction of iLTP, and the ability to express further tLTP was established: inhibition of either thrombin or its receptor, protease-activated receptor 1 (PAR1), occluded the onset of iLTP and restored the ability of neurons to express tLTP (Stein et al., 2015). These results are of considerable interest in the context of post-stroke recovery, as they suggest that thrombin could be a central regulator of ischemia-induced alterations in synaptic plasticity.

While it has been proposed that thrombin is also produced in neural tissue (Dihanich et al., 1991), the role of blood-derived thrombin needs to be considered. A common feature of several neurological diseases is an alteration and/or disruption of the "blood-brain barrier (BBB)" (Shaheen et al., 2013). Mainly formed by astrocytes and specialized endothelial cells, the BBB is involved in the regulation of the chemical environment by controlling efflux and influx of specific molecules from and into the brain. Under pathological conditions, alterations in BBB allow various blood components to enter the brain in an uncontrolled manner, which can severely affect neural function. Among them is thrombin, which has been linked to neural hyperexcitability and altered synaptic plasticity (Ben Shimon, Lenz et al., 2015). It is therefore conceivable that the breakdown of BBB and subsequent increase in brain thrombin concentration may contribute and even exacerbate iLTP effects. At this point, however, we have to concede that the contribution of blood *vs.* brain-derived thrombin in iLTP and post-stroke recovery has yet to be clarified. Regardless of these considerations, thrombin has been firmly linked to iLTP induction (Stein et al., 2015), which suggests an important role of the blood-brain interface in adjusting the ability of neurons to express plasticity after ischemic stroke.

Summary and conclusion

As recently discussed, a better understanding of the role of distinct forms of synaptic plasticity for the course of neurological diseases appears to be urgently needed (Maggio and Vlachos, 2014). Studying the role of iLTP, *i.e.*, a form of plasticity that is triggered by a pathological stimulus, and comparing it to tLTP represents an attractive strategy to gain

better understanding of the role of plasticity at the interface between health and disease. However, more work will be required to address the underlying molecular mechanisms of iLTP and its biological significance for post-stroke recovery. In this context, we consider our recent findings on the role of thrombin in iLTP of major significance. Notably, direct or indirect thrombin inhibitors are used in clinical practice for prevention of ischemic strokes in some patients (Verheugt and Granger, 2015). It will therefore be important to determine whether these drugs assert their beneficial effects not only by acting as anticoagulants, but also by interfering with thrombin/PAR1 mediated iLTP, which could set the threshold of plasticity toward improved post-stroke recovery. Considering that thrombin may enter the brain in several major neurological diseases, it is interesting to hypothesize that drugs modulating thrombin/PAR1 mediated synaptic plasticity could prove suitable for the treatment of various neurological diseases associated with alteration in BBB integrity. Although it is challenging to transfer basic research knowledge on iLTP into clinical practice, we look forward to new exciting findings on the role of thrombin/PAR1 mediated iLTP and its consequences for the post-lesional reorganization of neuronal networks. These studies may support the development of novel diagnostic and therapeutic strategies for patients with ischemic brain injury.

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