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New insights into the role of GABAergic inhibition during functional reorganization of the visual cortex post-lesion

Introduction

Injuries and diseases of the central nervous system (CNS) are listed as one of the top three causes for mortality according to the World Health Organization (WHO). The most common causes of brain injuries are traumatic or ischemic events, while tumoral masses, surgeries and infections are less frequently reported. Despite the large variability in etiology, location and severity, the common denominator of a brain lesion is the irreversible damage of a region in the brain parenchyma. An important observation is that the size of the injury can enlarge in the first few days post-lesion, and therefore recruit the brain area located close to the border to the lesion, often referred to as penumbra [10], into the irreversible damage. Severe brain injuries can be life-threatening especially if additional complications occur, such as increased intracranial pressure, infections or hemorrhages. Fortunately, in recent decades, the mortality rate has been significantly reduced thanks to the implementation of preventive programs as well as to advances in the intensive care unit [42]. Despite this substantial improvement, we still need to face the fact that a large portion of brain injury survivors suffer from permanent physical and cognitive disabilities and present a high risk to develop epilepsy.

In the attempt to ameliorate the clinical picture of patients, researchers initially placed a large amount of effort into developing neuroprotective tools which should limit the size of the irreversibly damaged brain tissue. Unfortunately, these interventions have proven to be largely ineffective or showed a moderate efficacy only when applied in a very narrow temporal window after the initial insult [12]. A recently proposed, alterative therapeutic approach is to boost endogenous repair mechanisms [11]. This emerging strategy is based on reports describing that a consistent number of brain injury patients experienced a spontaneous, at least partial, recovery from the neurological deficits [29, 37, 46]. The brain seems therefore to be endowed with self-healing mechanisms.

Since neuronal regeneration is absent in most parts of the central nervous system, the main substrate for recovery is most likely to be found in the surviving brain structures spared by the lesion. In support of this hypothesis, several studies conducted in experimental animal models of cortical lesions revealed that the neuronal circuits adjacent to the damage are able to gradually replace the function of the dead tissue [7, 18]. Unfortunately, the functional and structural reorganization processes taking place following brain damage are not always beneficial for recovery. In fact, it has been shown that the surviving brain structures are also highly excitable [6, 38] and have an increased propensity to develop epileptic seizures [31, 34, 43]. The great clinical impact of this phenomena led many research groups to explore the cellular mechanisms underlying these lesion-induced functional alterations.

Brain lesions: from the clinic to animal models

Clinically, a brain lesion is a complex, multifactorial disease. The irreversible cellular damage is often followed by a series of pathophysiological events including functional disturbances in the connected brain areas, ischemia, changes in the concentration of neurotransmitters and ions in the extracellular space, inflammatory–immune reactions, astrogliosis, blood–brain barrier destruction, edema and metabolic dysfunctions [3]. Although the severity of these processes is largely variable and strongly depends on the lesion etiology, all of these factors are likely to have an impact on the activity of the surviving brain tissue and ultimately on the functional recovery. Ideally, functional changes in brain activity and their cellular correlates should be evaluated in patients suffering from brain injuries. Nonetheless, human studies are largely limited to noninvasive techniques, such as fMRI, which suffer from poor spatial and temporal resolution, or repetitive transcranial magnetic stimulation (rTMS) which provides a rather uncontrolled stimulation of a large population of neurons in the cortex.

Consequently, a deeper understanding of the cellular pathophysiology of brain injuries requires the establishment of experimental animal models. One can grossly distinguish between models trying to replicate a stroke and those trying to mimic the pathological processes typical of a clinical brain trauma. In recent years our laboratory has established a rather unique lesion model which uses the thermal energy of an infrared laser to produce localized cortical damage (**Fig. 1**). The method was initially established in the Ulf T. Eysel laboratory at the Ruhr-University Bochum [8] and was further optimized later in our lab. Whereas this method shares some similarities with

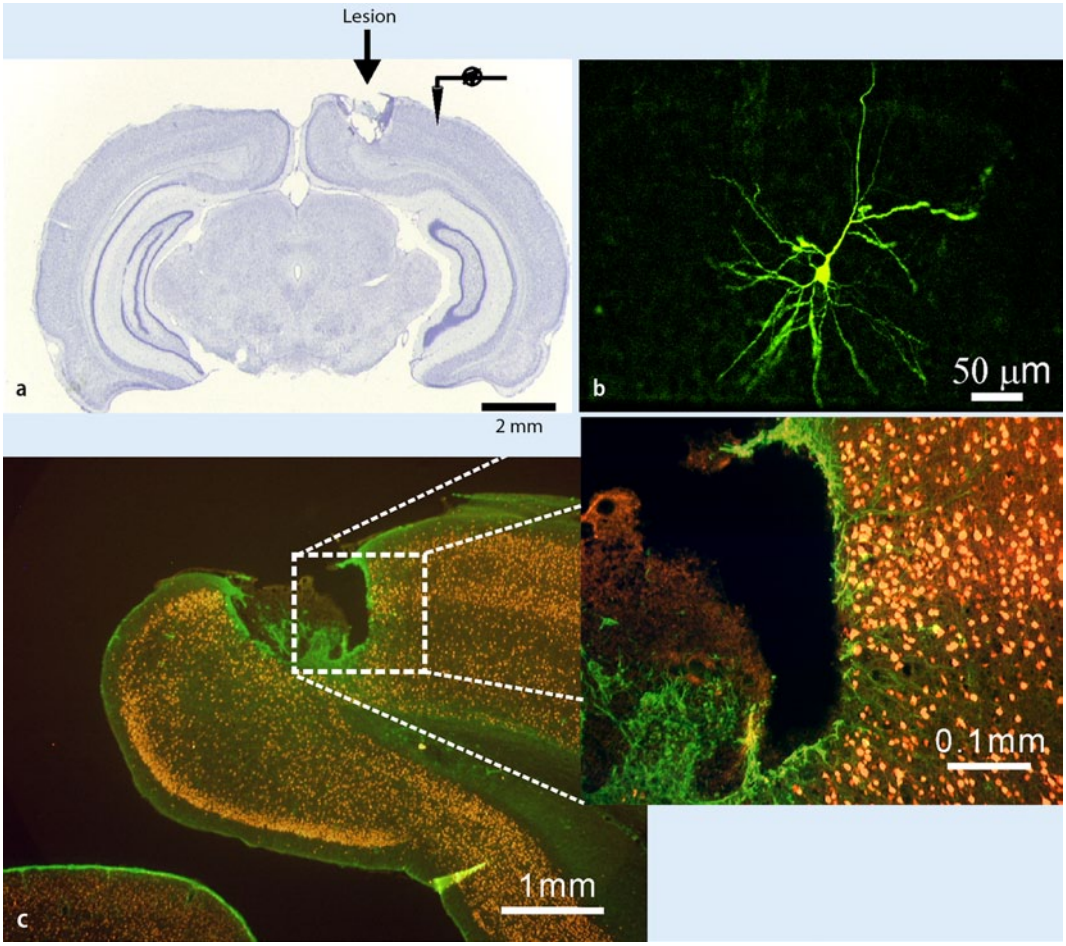

Fig. 1 ◀ Characterization of the infrared laser induced cortical lesion. **a** Nissl-stained coronal section containing the lesion in the right visual cortex, 3 days after the injury. The schematic drawing illustrates the location of patch-clamp recordings (at around 1 mm distance from the border of the lesion). **b** Confocal image of one representative lucifer yellow-labeled layer 2/3 pyramidal neuron. **c** Double immunofluorescence staining for the neuronal marker, NeuN (*red*) and the marker of reactive astrocytes, GFAP (*green*). The rectangle dashed area is magnified on the right. NeuN-stained neurons appear morphologically healthy at distances >100–200 µm from the lesion border, indicating absent or very limited secondary brain damage. The GFAP staining shows that the gliosis reaction was moderate and largely limited to close proximity to the injury. (Modified from [16, 17, 45])

a penetrating cortical trauma, the model is unique in using the energy of a laser light instead of a mechanical force to produce the injury. There are a number of advantages to employ a laser for this purpose: (1) the model offers an excellent reproducibility in terms of size and location of the injury, (2) the boundaries between damaged and healthy tissue are clearly defined, (3) edema and secondary brain damage are either very moderate or not present, and (4) the reactive astrogliosis reaction is spatially limited to the border close to the lesion (◘ **Fig. 1**). These features makes the laser lesion model optimal to study how the loss of a brain area can directly influence the physiology of the surviving brain tissue with the minimal interference from the secondary pathophysiological processes related to brain injury. The laser lesion model is therefore a complementary tool, which in combination with the diverse experimental brain injury models nowadays available, can be useful to replicate all distinct aspects of clinical brain injuries.

In the next sections, we will summarize data on changes in neuronal activity and synaptic transmission in the vicinity of cortical lesions, a few days after lesion induction, and we will try to explain how these functional changes may compromise or promote recovery.

Cortical lesion-induced changes in neuronal excitability

Focal cortical injuries have been found to induce abnormal excitability in the surviving cortical circuits. This increased neuronal activity has mainly been observed in the first few days following the insult and seems to be independent on the etiology or severity of the lesion [6, 38]. In the attempt to disclose the cellular mechanisms underlying this altered excitability, several in vitro electrophysiological works disclosed robust alterations in synaptic transmission. Some studies reported an enhanced excitatory transmission either due to an increase in presynaptic glutamate release [21, 22] or to increased activity of NMDA receptors [26, 30, 45]. Although changes in glutamatergic transmission may have a robust impact on hyperexcitability, changes in inhibitory synaptic transmission are even more profound and more frequently reported. For this reason we decided, in the last few years, to focus our research on the investigation of changes in inhibitory transmission following brain injuries. The ultimate goal would be to understand how such complex alterations may influence neuronal network excitability and function.

Functional changes in GABAergic inhibition following cortical injuries

Cortical inhibitory interneurons are well known for their capability to modulate neuronal excitability through the release of GABA, the main inhibitory neurotrans-

mitter in the mammalian cerebral cortex. Nonetheless, a growing body of evidence suggests that the function of this extremely heterogeneous population of cortical inhibitory cells goes far beyond a simple control of neuronal excitability. Cortical interneurons are involved in numerous other specific physiological processes, ranging from the control of neural plasticity [36] to the modulation of high cognitive functions [41]. Therefore, the alterations in inhibitory transmission following cortical lesions are likely to affect not only the excitability but also the plasticity and the functional properties of the surviving neuronal circuits.

These reasons led numerous research groups to investigate the cellular correlates of such lesion-induced disturbances in GABAergic transmission. Importantly, some synaptic changes were consistently observed independent of the lesion model that was employed. At the presynaptic site the spontaneous release of GABA was found to be reduced [16, 21], while postsynaptically, many studies reported a reduction in the expression of specific subunits of $GABA_A$ receptors [35, 38, 39]. At first, these results led to the conclusion that focal lesions in the neocortex cause a suppression of inhibition in the surviving brain areas. However, accumulating lines of evidence suggest that this view is far too simplistic. New findings, many of which are presented in the following sections, suggest that cortical injuries affect inhibition in a complex manner leaving open the question of whether the overall inhibitory strength may be reduced.

Phasic versus tonic inhibition following cortical injuries

GABAergic-mediated inhibition can be subdivided into phasic and tonic components. Recent electrophysiological data revealed that, on the one hand, the phasic component of GABAergic synaptic signaling is, to some extent, impaired following focal cortical lesions, whereas, on the other hand, the tonic component is rather enhanced ([4, 16], **Fig. 2**). Phasic synaptic transmission refers to the action potential-dependent and temporally precise release of neurotransmitter from presynaptic terminals followed by activation of postsynaptic receptors. The impaired phasic inhibition after cortical lesions refers mainly to the frequently reported reduction in GABA release. However, tonic inhibition depends on to the constitutive activation of extrasynaptic $GABA_A$ receptors. These receptors have a high affinity to GABA and can, therefore, be activated by low concentrations of neurotransmitter normally present in the extracellular space after escaping the synaptic cleft (ambient GABA)

Interestingly, we found that this form of tonic inhibition was enhanced in the cortical tissue surrounding the infrared laser light induced lesion in rat visual cortex [16]. The same finding was also reported following photothrombotic injury in the mouse sensorymotor cortex [4], suggesting that this phenomenon may generally take place as a consequence of an extensive neuronal damage and is likely to play an important role in setting the neuronal excitability level following lesions. Furthermore, Clarkson et al. [4] revealed that the lesion-mediated enhancement in tonic inhibition was primarily due to impairment in the reuptake function of the astrocytic GABA transporter, GAT-3/4. This dysfunction led to an increase in ambient GABA and consequently higher activation of peri-extrasynaptic $GABA_A$ receptors (**Fig. 3**).

$GABA_B$ receptors and intrinsic excitability

Most electrophysiological studies on inhibitory transmission focus on fast synaptic signaling mediated by ionotropic $GABA_A$Rs. Nonetheless, the neurotransmitter GABA can also activate metabotropic $GABA_B$Rs. $GABA_B$Rs are G protein-coupled receptors capable of modulating neuronal excitability in a complex manner. $GABA_B$ receptors expressed at presynaptic terminals are known to suppress GABA release mainly by reducing the influx of Ca^{2+} through voltage-gated calcium channels. The activation of these receptors seems to offer negative feedback essential to maintain GABAergic transmission within physiological levels [24]. An interesting hypothesis that remains to be tested is whether an increased ambient GABA which is likely to occur following brain injuries may also be able to negatively modulate phasic GABA release by acting on presynaptic $GABA_B$ receptors (**Fig. 3**). Postsynaptic $GABA_B$Rs, on the other hand, can reduce neuronal excitability mainly by increasing the membrane K^+ conductance [24]. Data from our laboratory revealed that a change in the activity, or in the expression, of postsynaptic $GABA_B$Rs may be responsible for an increase in the input resistance of layer 2/3 pyramidal neurons in the cortical tissue surrounding our laser-induced lesion [17]. This potential alteration in $GABA_B$Rs activity may contribute, together with the increase in tonic $GABA_A$R-mediated inhibition, to set the level of neuronal excitability following injuries.

Abstract

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Abstract
Cortical injuries are a leading cause of death and disability worldwide. The first weeks post-lesion are usually crucial to predict the final outcome of patients. While most of them experience a spontaneous, at least partial, restoration of function, in some the clinical picture is complicated due to the development of epileptic seizures. A substantial number of studies suggest that these phenomena may be triggered by complex functional alterations in intracortical inhibition, often observed in perilesional cortical areas. Pathophysiological changes in GABAergic transmission are indeed likely to alter plasticity, excitability, and function of cortical circuits. The development of more efficient therapeutic strategies may, therefore, require a deep understanding into lesion-induced changes in inhibition at both the cellular and neuronal network levels. In this review, we gather together information from recent studies which have focused on dissecting alterations at inhibitory synapses as well as in the function of different subclasses of interneurons following cortical lesions.

Keywords
Epilepsy · Stroke · Brain ischemia · Cortical lesions · Pathophysiology

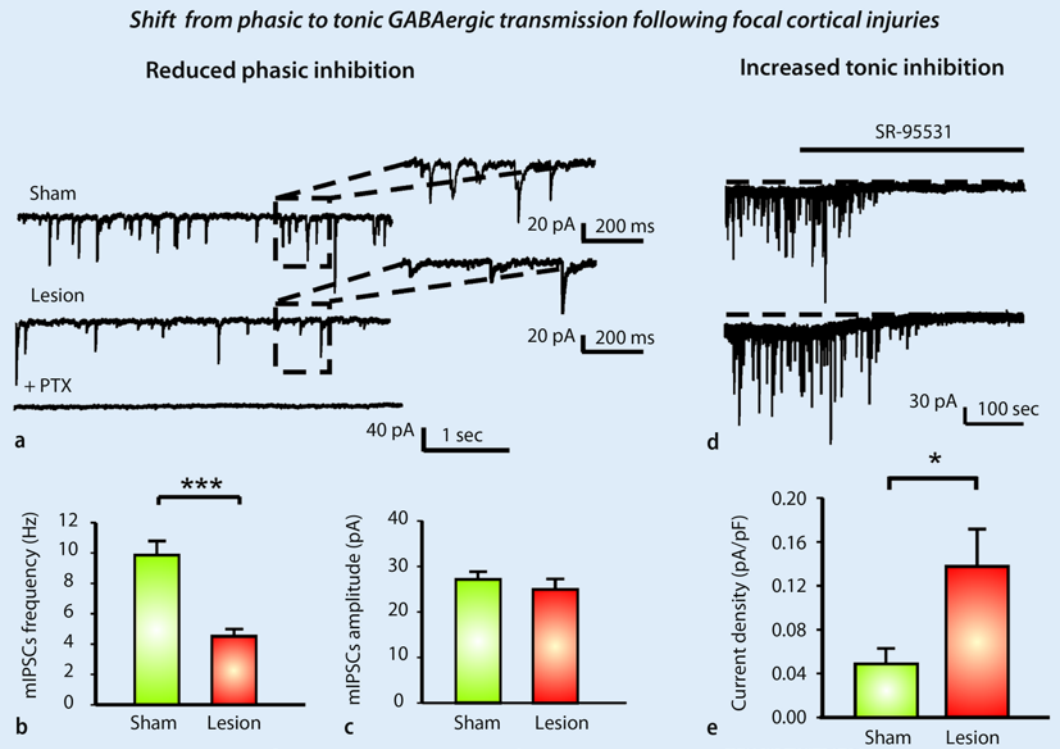

Fig. 2 ▲ Lesion-induced parallel suppression of phasic and enhancement of tonic inhibition. **a** Representative traces of miniature IPSCs recorded in voltage clamp at −80 mV in presence of glutamate receptors blockers. A magnification of the rectangle areas is shown on the right side for clarity. Bath application of 50 µM picrotoxin (PTX) abolished all events demonstrating that they were due to the activation of $GABA_A$Rs. **b**, **c** Diagram showing the mean mIPSCs frequency and amplitude, respectively. **d** Representative traces of spontaneous IPSCs recorded at −80 mV in the presence of glutamate-receptor blockers. Tonic inhibition can be quantified by measuring the amplitude of the outward current (positive shift in holding current) produced by bath application of 100 µM SR-95531, a specific blocker of $GABA_A$ receptors. The inhibitory tonic current density was obtained dividing the amplitude of tonic inhibition by the capacitance in each neuron. **e** Summary diagram showing a significant increase in the mean inhibitory current density post-lesion. (Modified from [16])

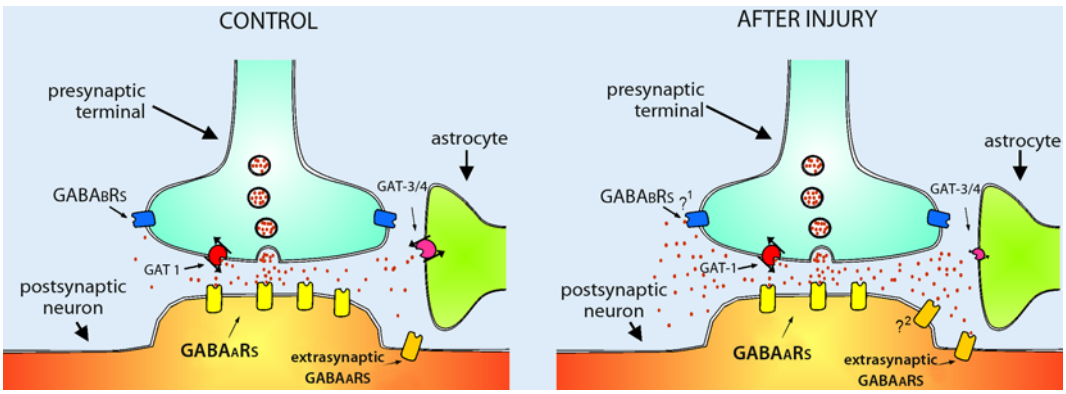

Fig. 3 ▲ Cellular mechanisms underlying the excessive tonic inhibition post-lesion. The schematic drawings exemplify a GABAergic synapse in a control animal (*left*) and after injury (*right*). After focal brain injuries an impaired reuptake function of the GABA transporter, GAT-3/4 is believed to be responsible for an elevated ambient GABA. The higher extracellular GABA concentration will consequently lead to an enhanced tonic inhibition through an increased activation of extrasynaptic $GABA_A$Rs. The higher ambient GABA may also increase the activation of presynaptic $GABA_B$Rs ($?^1$) leading to a parallel suppression of phasic GABA release. Additionally, changes in the subunit composition, in the expression or localization of $GABA_A$Rs ($?^2$) may also contribute to the excessive tonic inhibition postlesion

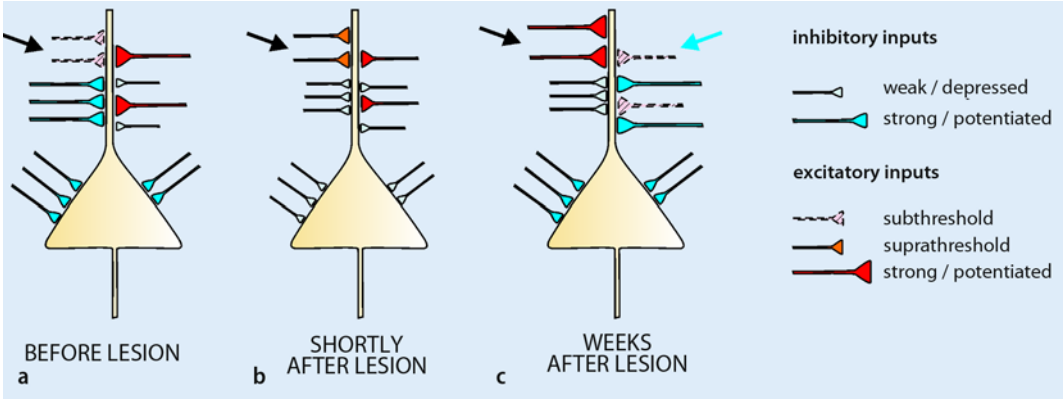

Fig. 4 ▲ Schematic illustration representing a model pyramidal neuron in the cortex surrounding the lesion with its excitatory and inhibitory inputs before, shortly after and a few weeks after the lesion occurrence. This model shows the potential cellular mechanisms responsible for the functional rewiring of neuronal networks following cortical injuries. **a** Before the occurrence of a cortical lesion some excitatory inputs are subthreshold (*arrow*) being masked by strong inhibitory inputs, **b** early after the cortical lesion occurrence (first week post-lesion) subthreshold connections can be converted into functional (*suprathreshold*) ones (*arrow*) by the lesion-induced weakening of inhibitory inputs, **c** some weeks after the lesion, experience-dependent plastic processes will likely lead to the reinforcement of some of the new functional inputs, which turn out to be behaviorally relevant after the lesion (*black arrow*) and to the suppression of excitatory inputs which became irrelevant (*blue arrow*). For clarity many cellular and subcellular elements have been omitted, this draw represents therefore an oversimplification of a real scenario. (From [15])

Net suppression of inhibition after cortical injury?

The above mentioned lesion-induced changes in inhibition describe complex alterations in GABAergic signaling. However, it is still unclear whether the opposite changes, for instance in tonic and phasic inhibition, can cancel each other out in a way that the overall inhibitory strength remains unaltered. Our hypothesis is that the answer to this question is not a simple yes or no. We rather believe that the net change in inhibition may depend on the brain state and on the activation level of certain interneuronal populations.

Level of inhibition may depend on the brain state

Most of the studies focusing on synaptic transmission following injuries have been performed in acute cortical slices. In this in vitro preparation, synaptic activity is low and single neurons rarely generate spontaneous action potentials. On the contrary, in vivo, neurons and in particular GABAergic interneurons can fire at relatively high frequency. To examine changes in inhibition in a context more closely related to the in vivo scenario, we challenged GABAergic synapses with a high frequency, repetitive extracellular stimulation. Surprisingly, the inhibitory current experience by the postsynaptic cells during the entire high frequency stimulation was significantly higher in the tissue surrounding the cortical injury. The main reason for this increase was a prolongation in the decay time of inhibitory postsynaptic currents (IPSCs) post-lesion [16]. The lesion-induced prolonged kinetics caused single IPSCs to largely outlast the interstimulus interval duration. As a consequence single IPSCs summated upon successive stimuli producing a larger inhibitory charge. This finding led to the conclusion that the overall inhibitory strength following brain injuries may depend on the level of activity in neuronal circuits. Following brain lesions, a suppression of GABA release may be found during periods of low activity. Nonetheless, during periods of sustained activity (where presynaptic inhibitory interneurons may fire trains of action potentials at high frequency) the inhibitory postsynaptic currents may actually be increased.

Lesion-induced positive shift in the reversal potential of $GABA_A$R-mediated currents

The inhibitory action of GABA is primarily controlled by the neuronal expression of the K-Cl cotransporter 2 (KCC2). This cotransporter is essential to maintain a low intracellular chloride concentration. KCC2 leads to an unequal distribution of chloride ions across neuronal membrane and, therefore, has an important role in setting the reversal potential of $GABA_A$R-mediated currents (E_{GABA})[1] close or slightly more negative than the resting membrane potential. Under these conditions the activation of $GABA_A$Rs (which are highly permeable to chloride ions) is followed by a chloride ionic flow into a neuron. The influx of these negatively charged ions leads to membrane hyperpolarization and ultimately to a negative modulation of neuronal firing. E_{GABA} is, however, not always constant but varies depending on several factors. For instance, immature neurons have a relatively high intracellular chloride concentration (mainly due to the low expression of KCC2) and, therefore, a more depolarized E_{GABA}. This is the main reason why GABA exerts a much weak-

[1] E_{GABA} is the neuronal membrane potential at which the net flow of $GABA_A$Rs permeable ions (Cl^- and to a minor extent HCO_3^- ions), across a neuronal membrane, following receptor activation, is zero. At this specific potential the concentration gradient force to drive Cl^- ions (and HCO_3^-) into a neuron, is equal and, therefore, neutralized by the electrical force that drives negatively charged ions out of a negatively polarized neuron.

er inhibitory action or it can even be excitatory at early development stages. Remarkably, an impaired chloride extrusion with a consequent depolarized E_{GABA}, has also been reported in neurons surrounding focal brain injuries [19, 27, 28, 30, 40].

The positive shift in E_{GABA} post-lesion can profoundly affect the efficacy of inhibitory transmission. These functional changes need to be carefully considered when trying to develop pharmacological agents to limit hyperexcitability. Indeed, if chloride extrusion processes are impaired, a positive modulation of $GABA_AR$s may not enhance inhibition but it may rather cause an excessive intracellular chloride accumulation which will ultimately deteriorate the inhibitory action of GABA. In the worse case, if the intracellular chloride concentration rises above a certain level and E_{GABA} becomes more depolarized than the threshold potential for spike generation, GABA may even become excitatory.

Changes in the activity of interneurons

Cortical injuries may also affect inhibitory transmission by changing the excitability of cortical interneurons. Originally, recordings from interneurons were rarely performed due to the difficulties to morphologically distinguish them from excitatory neurons in brain slices. However, in the last decade the identification of GABAergic interneurons has strongly been facilitated by the introduction of transgenic mice line expressing green fluorescent protein (GFP) in specific subtypes of GABAergic interneurons [5, 32]. Different studies are currently being performed to explore the effect of brain injuries on excitability and function of interneurons. An important question that still needs to be addressed is whether brain lesions can have different effects on distinct interneuronal subtypes. This is particularly important because each different interneuronal subclass is capable to modulate neuronal activity in a unique way by targeting distinct subcellular compartments and by acting on specific GABA receptors.

In a recent study, dual patch-clamp recordings from principal neurons and fast-spiking (Fs) GABAergic interneurons, in a traumatic cortical injury model, revealed that inhibitory transmission from this specific interneuronal subtype was impaired post-lesion [23]. Fs interneurons innervate predominately the soma and the proximal dendrites of principal cells. Impaired inhibition at this specific cellular compartment may profoundly affect action potential generation in principal neurons. This may enhance neuronal network excitability and may interfere with cortical information processing which require the temporal coordination of firing of a neuronal population. It remains to be elucidated whether inhibitory transmission from different subtypes of dendritic targeting interneurons may be similarly impaired following brain injuries.

Impact of changes in inhibition on functional recovery following brain injury

A large portion of brain injuries survivors experience improvement from the initial neurological deficits over time. This spontaneous, at least partial, restoration of function seems to be mediated by a functional remapping in the surviving brain structures. In support of this hypothesis, the peri-lesional brain areas were found to gradually start to respond to stimuli previously represented in the injured tissue [7, 18]. Looking for the cellular correlates of this phenomenon we and others found an enhanced synaptic plasticity in the cortical tissue in the vicinity of the lesion [13, 14, 25]. Fine structural changes in the turnover of dendritic spines have also been reported in a stroke lesion model [2]. The functional changes in inhibition described in the previous sections are also likely to have a significant impact on recovery. As already outlined before, the role of GABAergic transmission is not limited to the control of neuronal excitability. GABAergic inhibition has also been shown to modulate neuronal plasticity [9] and to define the response specificity of neurons [33]. In this regard, a moderate reduction in the level of inhibition has been shown to promote the induction of synaptic plasticity [1, 20] and to alter the receptive field properties of neurons [44].

Based on these data, we proposed a cellular model to suggest how the reduced GABA release post-injury may be beneficial for recovery by promoting neuronal plasticity and functional remapping in the surviving brain structures [15]. The model is based on the assumption that the neocortex is characterized by a dense and exuberant connectivity. Under physiological circumstances many excitatory connections are silent or too weak to activate their postsynaptic targeted neuron. We believe that the initial depression in phasic GABA release following brain damage may cause a local and temporally defined increase in neuronal membrane excitability, which may be sufficient to convert some silent inputs into functional ones. The consequence of unmasking silent connections is an initial enlargement in the receptive field of neurons. An increase in the size of the receptive fields of neurons has indeed been experimentally observed after a focal lesion in the visual cortex [7]. Subsequently a stable remapping of neuronal circuits may occur based on experience dependent plasticity rules. Importantly, the inputs unmasked by the reduced inhibition will compete with the already functional ones and, in the new context, if some originally silent connections turn out to be behaviorally relevant they will be reinforced following Hebbian plasticity rules (**Fig. 4**). Contrary to the reduced phasic GABAergic transmission, the excessive tonic inhibition found post-lesion has been shown to be detrimental for recovery [4]. This finding suggests that pharmacological agents specifically antagonizing the tonic component of GABAergic transmission may represent a new therapeutical target to promote recovery after brain injuries. Modulating the level of tonic inhibition requires, however, extreme caution because an excessive reduction or a modulation at a wrong time point post-lesion may exacerbate hyperexcitability and increase neuronal death [4].

Conclusion

The described complex functional alterations in GABAergic transmission are likely to contribute to the pathophysiological processes following brain injuries. They cause alterations in neuronal excitability and dysfunction in neuronal network processing. Nonetheless, these chang-

es do not appear to be only detrimental for recovery. An interesting hypothesis is that they could be part of an evolutionary preserved program engaged following brain damage to guarantee in first line the survival and, secondly, the long-term recovery of an individual. In support to this hypothesis, many studies suggest that a moderate suppression in phasic GABAergic transmission may promote neuronal plasticity and functional reorganization processes. The consequent instability in neuronal network function and excitability may be the inevitable price to pay. Thus, the main challenge remains to elucidate whether it is possible to distinguish between uniquely harmful pathophysiological processes and physiological alterations able to promote plasticity and, therefore, beneficial for the long-term recovery. Only a clear distinction between positive and negative physiological changes would permit the development of therapeutic strategies aimed at minimizing the deleterious processes without preventing the beneficial effects on neural plasticity.

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T. Mittmann (born in 1964 in Cologne) is currently Professor for Neurophysiology at the University Medical Center (UMC) of the Johannes-Gutenberg-University Mainz, Germany. He studied Biology in Mainz and Marburg. In 1995 he finished his PhD thesis with Prof. Uwe Heinemann on "Lesion- and ischemia-induced functional changes in cortical neurons". From 1995–1997, he was a Feodor-Lynen Research fellow of the Alexander v. Humboldt Foundation and worked on "Persistent sodium currents in dendrites of cortical neurons" with Profs. Wayne. Crill & Bertil Hille, Dept. Physiol. & Biophysics, Univ. of Washington, Seattle, USA. From 1997-2008, he was a Research Assistant at the Inst. for Physiology, Ruhr-University Bochum with Prof. Ulf Eysel. In 2004, he completed his Habilitation in Physiology. Current research topics include (1) disclosure of new endogenous, neuroplastic and homeostatic mechanisms of functional reorganization following focal brain injuries and (2) the role of the neuronal NO-guanylylcyclase-cGMP signal cascade for glutamatergic and GABAergic neurotransmission.

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B. Imbrosci (Ph.D.) studied Medical Biotechnology at the University of Milano, Italy. She subsequently moved to Germany where she joined the International Graduate School of Neuroscience (IGSN), based at the University of Bochum. There, she conducted her PhD under the supervision of Prof.Dr. Ulf T.Eysel and Prof.Dr.Thomas Mittmann. During her doctoral research she has been investigating the effects of focal cortical injuries on neuronal plasticity. After receiving her PhD in 2010 she moved to the University of Mainz as a postdoctoral researcher where she has been continuing, together with Prof. Mittmann, to study the neurophysiological changes occurring after a brain injury with particular emphasis on inhibitory transmission.

Compliance with ethical guidelines

Conflict of interest. B. Imbrosci and T. Mittmann have made no statement.

The accompanying manuscript does not include studies on humans or animals.

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