Chapter 3

Long-Term Potentiation-Associated Gene Expression: Involvement of the Tumour Protein p53

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Abstract

Long-term potentiation of synaptic transmission (LTP) is one of the most studied manifestations of neuroplasticity and hippocampus is a classic object for the study of LTP mechanisms. The early phase of LTP depends on modifications of pre-existing synaptic proteins and the late phase of LTP needs *de novo* protein synthesis and gene expression. LTP-associated dynamics of the transcriptome and mechanisms of coupling synaptic activity with gene expression are intensively studied, but due to the vast complexity of the issue, abundance of unresolved questions remains in this field. The diversity of brain cell types is one of the main challenges. Until relatively recently, the analysis of molecular and genetic aspects of neuroplasticity has usually been confined to neuronal populations. Meanwhile, glia substantially contributes to synaptic transmission regulation. Astrocytes release various gliotransmitters, which modulate synaptic transmission and plasticity. S100B is one of those glia-derived regulatory factors. Learning in rats is accompanied by an increase in S100B expression in various brain regions including the hippocampus. The present study is focused on the neuroplasticity-associated *S100B* expression upregulation using long-term post-tetanic potentiation in rat hippocampal slices. In this chapter, we present a short review of published articles devoted to the analysis of gene expression during LTP formation including studies of the mechanism of LTP-associated *S100B* upregulation in hippocampus.

Keywords: hippocampus, CA1, long-term potentiation, gene expression, p53, *S100B*, *Bax*

1. Introduction

Long-term alterations in the strength of synaptic transmission are a key physiological mechanism of learning and memory. To explain the formation of conditioned reflexes, Donald Hebb

proposed that simultaneous or quasi-simultaneous discharge of two neuronal populations leads to the establishment of a functional connection between them [1]. The first attempts to find "Hebbian synapses" were undertaken by Jan Bureš [2, 3]. In his experimental model, sound or tactile sensory conditioned stimulus (CS), which slightly changed a frequency of neuronal discharges, was reinforced by a depolarizing current delivered through a recording microelectrode (unconditioned stimulus, US), which caused a strong neuronal discharge. In some neurons, responses to CS essentially increased after appropriate combination of CS and US. Interestingly, most significant effects were observed in the hippocampus [4], which is critical for acquisition and retrieval of some forms of memory [5, 6]. However, the persistence of plastic changes in this and other similar experimental models (tens of minutes) was relatively low in comparison with memory traces (reviewed in [7]).

The discovery of LTP in the hippocampus was a next essential step in the research of cellular and molecular mechanisms of synaptic plasticity [8]. LTP is the most studied form of plasticity associated with alterations in synaptic strength. A fairly common model of LTP is the increase in responses of postsynaptic neurons to stimulation of presynaptic fibers after high frequency stimulation (HFS)—tetanization or theta-stimulation—of the afferents. LTP is widely accepted as a neuronal mechanism of learning [9–11]. LTP that is dependent on glutamate receptors of NMDA type (NMDAR) is the most widespread in CNS and the most studied. LTP of perforant fiber-granular cell synapses in the dentate gyrus (DG) and LTP of Schaffer collateral (SC)-pyramidal cells in the area CA1 of the hippocampus are classic examples of this kind of LTP.

There are two main phases of LTP: the early phase lasting usually less than 1 hour and the late phase lasting several hours or longer (months). The early phase of LTP is based on post-translational modifications of pre-existing synaptic proteins and the late phase of LTP requires *de novo* protein synthesis and gene expression [12–14]. According to varying estimates, within 4–8 h after induction, LTP is maintained due to the translation of pre-existing mRNAs, while transcription is necessary for later stages [15–17]. However, the disturbance of CREB-dependent gene expression due to inhibition of CREB coactivator TORC1 leads to a decline in LTP maintenance, which became evident as early as 75 min after induction of LTP [18]. Such contradictions might reflect varying demand for gene expression in different experimental conditions or difficulties in accounting for the side effects of intracellular signalling network disturbance. As a rule, the later inhibitors of translation or transcription are applied after the induction of LTP, the less they influence the maintenance of the late phase of LTP [19]. Transcription and translation within a time window ≤2 h after the induction of LTP are most critical for the persistence of LTP [20].

2. LTP and neural activity-regulated genes

Identification of genes regulated by neuronal activity (ARGs) and clarification of the mechanisms of this regulation is an intensively developing research area. The families of transcription factors (TFs) thus far found to be critically involved in synaptic plasticity and memory formation include CREB, C/EBP, AP-1, Egr, and Rel/NFκB [21, 22]. Important advances in this

field have been achieved by using microarrays and high-throughput sequencing. Hundreds of ARGs have been identified with complex expression dynamics after various kinds of stimulation: seizures, chemical stimulations, behavioural tasks, and HFS [20, 22–24]. Among transcriptomic studies of LTP in the hippocampus, works with induction of LTP in DG *in vivo* prevail. Exceptions include HFS-induced LTP in DG mini-slices [25] and chemically induced LTP in CA3/CA1 mini-slices [20] in mice.

Remarkably, the ARG lists from different authors showed little overlap [22]. One of the multiple reasons of this is a highly dynamic temporal regulation of the neuronal activity-regulated gene expression. For example, the level of *Fos* mRNA increased 30 min after tetanization, then returned to the initial level after 60 min, and again increased 120 min after LTP induction in the CA1 field of rat hippocampal slices [26]. Only 8 genes were overlapping from 226 and 190 genes differentially expressed 20 min and 5 h, correspondingly, after LTP induction in DG *in vivo* [24, 27]. Rapid dynamics of transcriptional profiles was demonstrated also in the hippocampus after learning [28] and in mice hippocampal mini-slices after induction of LTP [20, 25]. Therefore, the duration of LTP-inducing stimulation is of special significance for reproducibility of gene expression data, particularly when early stages of the transcriptional response are examined. Meanwhile, the duration of LTP-inducing stimulation in different works varies from 1.5 min [25] to 45 min [23]. Moreover, analysed time points are quite diverse in different experiments.

Temperature is also a factor influencing gene expression dynamics in brain slices. For example, differential expression of *Egr1* was not detected in the CA1 region of hippocampal slices after induction of LTP at room temperature [29], while at a temperature of ≥30°C, LTP induction led to the increase in the level of *Egr1* mRNA in the area CA1 [20, 26, 30, 31].

In addition, the comparison of datasets generated in different studies is complicated by the limited access to original data. Only partial lists of ARGs, which passed arbitrarily designed significance filters, were often presented by authors. Nevertheless, differential expression of some genes is reproduced quite frequently. This is particularly true for early genes, association of which with LTP was already demonstrated in earlier works on this issue, such as *Fos, Jun, Egr1, Arc, Homer1,* and *Bdnf* [32, 33], which are well known.

One of the most serious problems is a great diversity of the brain cell types, which is reflected in the diversity of their transcriptomes [34, 35]. For example, granular cells of the DG and pyramidal cells of the CA1-CA4 regions of the hippocampus differ in their transcriptomes [36], which can exhibit distinct dynamics after LTP induction [29]. Dorsal and ventral subregions of the rodent area CA1 also differ in their transcriptomes [37]. LTP induction alters gene expression not only in neurons but also in glial cells [20, 38, 39]. The role of glia in a structural, metabolic, and trophic support of neurons is well known. Undoubtedly, neuron life support is crucial for all brain functions including learning. For example, learning in rats is associated with an increase in extracellular lactate concentration in the brain, and disruption of lactate export out of astrocytes or import into neurons disturbs long-term memory and LTP in hippocampus [40]. In addition, glial cells directly participate in synaptic transmission [41, 42]. Astrocytes respond to neurotransmitters by an increase in intracellular calcium concentration followed by secretion of gliotransmitters modulating synaptic transmission and plasticity.

Therefore, adequate research of LTP-associated gene expression must include an analysis of the cellular localization of observed phenomena, which is quite laborious. The task is somewhat easier, when ARGs are cell-specific.

One of such relatively cell-specific genes is *S100B*. In the adult brain, S100B protein is synthesized mainly in astrocytes. It is constitutively secreted and its secretion can be regulated by a number of factors [43] including neuronal activity [44]. In physiological (nanomolar) concentrations, it possesses neurotrophic activities [43] and modulates neuronal activity [44] and synaptic plasticity [45]. *S100B*-knockout mice have enhanced LTP in the area CA1 of the hippocampus, enhanced spatial memory in the Morris water maze test, and enhanced fear memory in the contextual fear conditioning [45].

However, *S100B*-knockout animals are more prone to seizures during kindling, than wild-type controls [46], which can be, in part, a consequence of enhanced LTP, since there are parallels between kindling and LTP [47]. Disturbed calcium homeostasis in glial cells of mutant mice [48] is also a possible reason of their susceptibility to seizures, since calcium waves in astrocytes play an important role in epileptogenesis [49]. Thus, normal S100B expression is necessary for proper functioning of neuroglial networks. However, at high (micromolar) doses, S100B is toxic [43]. S100B is used as a marker of brain damage, since it can cross the blood-brain barrier and several brain pathologies are associated with elevated levels of S100B in the serum [50]. The *S100B* allele with increased gene expression is a putative risk variant for bipolar disorder [51]. Therefore, chronically increased *S100B* expression, in combination with additional adverse factors, can be harmful. In this context, the fact that learning in rats can increase S100B level in the hippocampus and other brain regions [52, 53] is of special interest.

To study the mechanisms of the neuroplasticity-associated *S100B* expression upregulation, we have modelled this phenomenon using long-term post-tetanic potentiation in rat hippocampal slices [39, 54–60].

3. LTP-associated expression of *S100B* and other p53 target genes in rat hippocampal slices

The increase in *S100B* mRNA level was detected in area CA1 of slices prepared from rat dorsal hippocampus as soon as 10 min after tetanization of Schaffer collaterals, and the maximal increase in *S100B* mRNA level occurred 20–30 min after tetanization [39, 59]. Low frequency stimulation, which does not induce LTP, does not alter *S100B* expression [54]. The level of S100B protein increased significantly 20 min after tetanization [59] and remained elevated up to 240 min after tetanization.

Transcription factor p53, well known as a key regulator of apoptosis, proved to be one of the TFs determining *S100B* mRNA dynamics after LTP induction. We analysed a 2 kb promoter region proximal to the first of the two alternative transcription starts of the rat *S100B* gene and identified putative p53-responsive elements (pREs) partially matching the canonical p53 binding sequence RRRCWWGYYY$(n)_{0\text{-}13}$RRRCWWGYYY [61, 62]. One example is presented in **Figure 1**. This is the only pRE we recovered, which apparently resembles one of the pREs

identified in a similar promoter region of the human gene *S100B* [63]. The mouse *S100B* promoter also contains a pRE, which is similar to the rat pRE (**Figure 1**). It is tempting to speculate that this conserved site is particularly important for *S100B* regulation in rodents and humans. We used chromatin immunoprecipitation to study p53 binding to three loci in *S100B* promoter with pREs within them (**Figure 1**). The p53 binding to all these sites in *S100B* promoter strongly correlated with *S100B* mRNA dynamics in a time window 10–40 min after SC tetanization [60]. Interestingly, the p53 binding to the conserved site was most expressed.

The increase in p53 DNA-bound fraction was not associated with the increase in total p53 protein, which suggests p53 activation was due to post-translational modifications. The total p53 protein level even decreased in the area CA1 20 min after LTP induction, while *p53* mRNA level did not change [60]. Therefore, the p53 protein degradation accelerated or/and *p53* mRNA translation slowed in the early phase of LTP.

To confirm that LTP-associated p53 binding to *S100B* promoter is functional, we carried out experiments [57, 58] with the inhibitor of p53-dependent transcription, pifithrin-β and p53 activators, nutlin-3 and EX-527, which are inhibitors of p53 negative regulators ubiquitin ligase Mdm2 and deacetylase Sirt1, correspondingly. The two p53 activators increased the basal level of *S100B* mRNA. However, LTP induction in their presence led to further significant increase in *S100B* mRNA level. Moreover, p53 inhibitor pifithrin-β incompletely suppressed tetanization-induced *S100B* upregulation [57]. This suggests that some additional factors contributed to *S100B* transactivation in our experiments, besides p53.

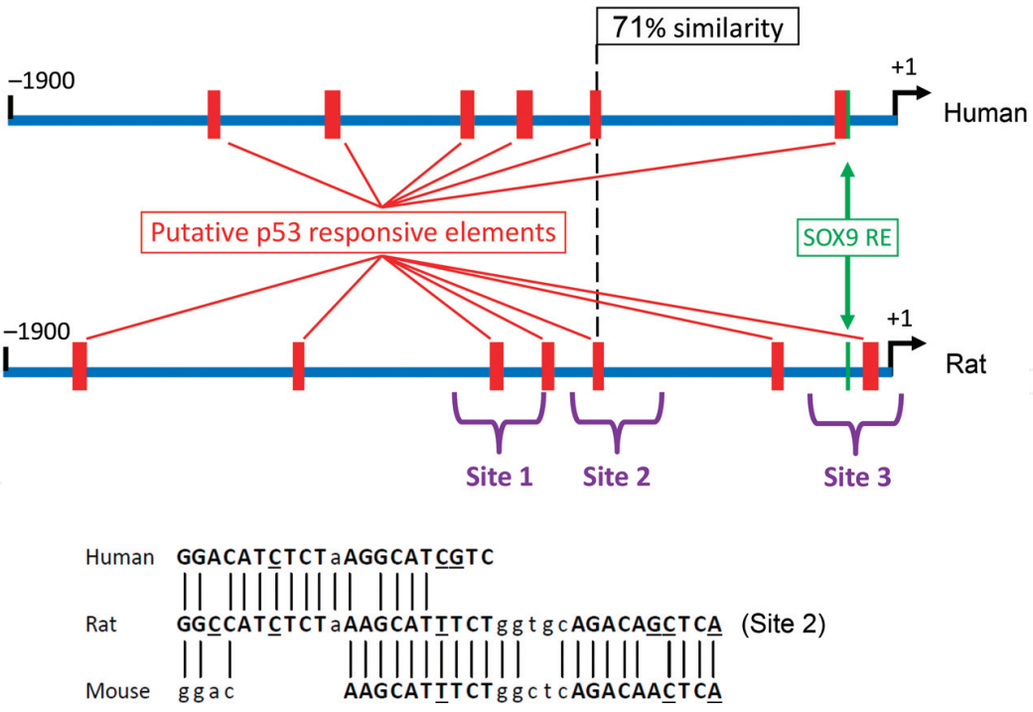

Figure 1. Putative p53 responsive elements in the promoters of rat, human, and mouse genes *S100B*. Top—Schematic representation of human and rat *S100B* promoters, which are aligned relative to conserved SOX9 responsive elements. "+1"— Transcription starts. Boxes indicate positions of pREs. Sites 1/3 were tested for p53 binding. Bottom—Sequences of pRE in the rat *S100B* site 2 and homologous pREs of human and mouse *S100B* promoters. Capitalized letters denote sequences partially matching to the consensus RRRCWWGYYY. Mismatches are underlined. Vertical lines indicate nucleotides conserved among rat and human or rat and mouse genes *S100B*.

Thus, LTP in the area CA1 of the hippocampus is associated with transient p53 activation, which is one of the reasons of increased S100B synthesis. The decrease in p53 protein level after SC tetanization indicates that p53 negative regulators are activated soon after LTP induction. As mentioned above, p53 negative regulators include ubiquitin ligase Mdm2 and deacetylase Sirt1. Mdm2 negatively modulates p53 transcription activity, protein stability, and mRNA translation [64, 65]. Ubiquitination of lysine residues of p53 promotes its export from the nuclei followed by its degradation in proteasomes [66]. Thus, acetylation of lysine residues is an important element of p53 activation promoting its stabilization and import into the nucleus, while deacetylation decreases this activity and facilitates ubiquitination of lysine residues. Deacetylases controlling p53 acetylation status include NAD-dependent deacetylases, Sirt1 and Sirt2 [67, 68], and nonselective inhibitor of sirtuins tenovin-1 inhibits Mdm2-dependent degradation of p53 [69].

For evaluation of the contribution of Mdm2 and Sirt1 in tetanization-induced p53 protein downregulation, we studied the effects of Mdm2 inhibitor nutlin-3 and Sirt1 selective inhibitor EX-527 on the level of p53 protein after LTP induction. Inhibition of Mdm2 or Sirt1 fully prevented tetanization-induced decrease in p53 protein level [56, 57]. Therefore, Sirt1/Mdm2 tandem plays a key role in the p53 protein level decrease after LTP induction in the area CA1 of the hippocampus.

To reveal mechanisms of *S100B* expression regulation in more detail, we studied the influence of inhibitors of several intracellular regulatory network elements on tetanization-induced *S100B* expression [55, 57, 58]. **Figure 2** illustrates our current hypothesis concerning mechanisms of LTP-associated *S100B* upregulation. The obtained results indicate that NMDAR and

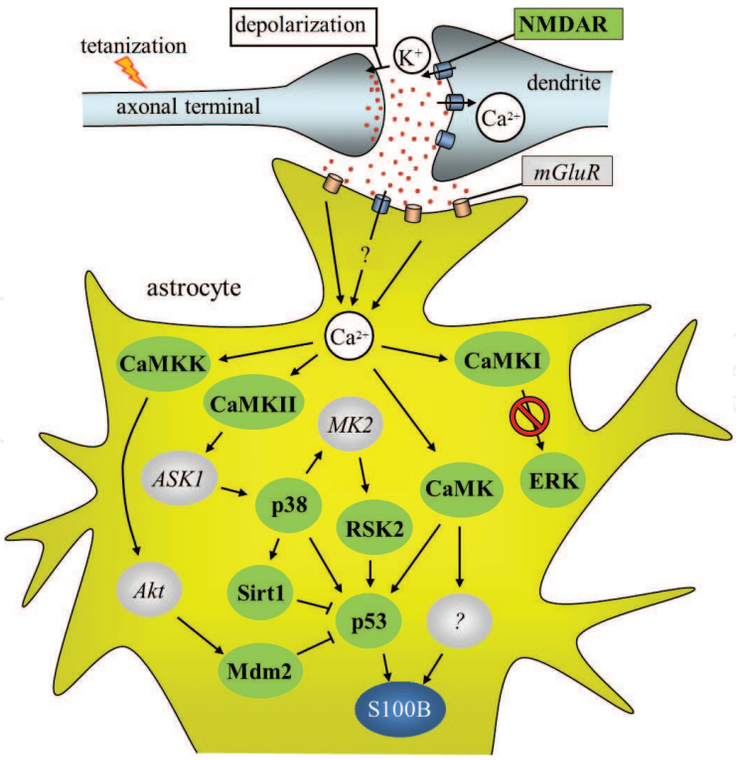

Figure 2. Putative mechanism of *S100B* regulation during LTP. Dots in synaptic cleft— glutamate. mGluR—metabotropic glutamate receptors; Akt, ASK1—protein kinases; and CaMKK—CaMK kinase. Involvement of the factors shown in bold was tested in experiments with appropriate inhibitors; hypothetical intermediates are shown in italics.

Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) are essentially involved in neuronal activity-regulated *S100B* expression. However, contributions of separate CaMKs were not determined, since pan-CaMK inhibitor was used.

It is an open question, furthermore, where NMDARs participating in *S100B* regulation are located. The presence of functional NMDARs in adult rodent astrocytes has not been evidenced reliably. However, neuronal NMDAR activation could lead to an increase in extracellular potassium concentration (due to potassium efflux through postsynaptic NMDARs) followed by presynaptic terminal depolarization and enhanced glutamate release [70], which can increase intracellular calcium levels through activation of metabotropic glutamate receptors and induction of gene expression in astrocytes.

Mitogen-activated protein kinase (MAPK) p38 and 90 kDa ribosomal S6 kinases (RSKs) are also involved in *S100B* expression induction, while participation of MAPK/ERK and protein kinases C is unlikely [58]. MAPK/ERK plays an important role in LTP-associated gene regulation, and RSKs are believed to mediate its long-term effects [19, 71]. Nevertheless, the fact that inhibition of ERK cascade did not suppress tetanization-induced *S100B* transactivation [58] is not surprising. It seems that neurons and astrocytes differ in their mechanisms of Ca^{2+}-dependent MAPK/ERK activation, since glutamate application did not activate MAPK/ERK in cultured astrocytes, in contrast to neurons [72].

Then, how are RSKs activated during LTP in astrocytes in this case? There are alternative ways of RSK regulation. For example, in dendritic cells, RSKs can be activated through MAPK p38–MK2 [73]. Protein kinase MK2 is also expressed in microglia, neurons, and astrocytes [74]. Therefore, theoretically, Ca^{2+}-dependent *S100B* transactivation through the CaMK–ASK1–p38–MK2–RSK2–p53 pathway is possible (**Figure 2**).

Further, we questioned to what extent the short-term p53 activation in the early stage of LTP contributes to transcriptome dynamics. To estimate this contribution, we have studied the expression of several tens of genes that are directly or indirectly regulated by p53 30 min after induction of LTP [60]. The p53 activator nutlin-3 was used for the preliminary assessment of a putative participation of p53 in LTP-associated regulation of these genes. If p53 contribution to tetanization-induced expression of a gene is significant, nutlin-3 would be expected to occlude the effect of tetanization.

Based on this approach, we conclude that expression of several established p53 target genes is altered after LTP induction in a p53-independent way. They include *Apaf1, Bbc3, Bid, Cdkn1a, Dnmt1, Egfr, Egr1, Mdm2, Mlh1, Pcna*, and *Tp73*. However, some genes might be regulated by p53: *Bax, Bcl2, Btg2, Ccnb1, Check2, Dapk1, Gadd45a, Prkca*, and *Pten*. Sometimes, p53 contribution is shadowed by other factors, which act in the same (*Btg2*) or in the opposite (*Ccnb1, Check2, Dapk1*, and *Prkca*) direction as p53. It remains to be determined, whether p53 interacts with other factors within the same cells, or LTP-associated regulation of *Btg2*, *Ccnb1*, *Check2*, *Dapk1*, and *Prkca* in the hippocampus is cell-specific.

Some of these results are consistent with the data obtained previously by other researchers. For example, a neuronal activity-dependent decrease in the level of mRNA of the proapoptotic protein Bbc3 was observed in neuronal cultures [75, 76] and in mini-slices of areas CA3/CA1 of the hippocampus [20]. Moreover, Léveillé et al. [76] also concluded that this decrease did not

depend on p53. Similarly, an increase in *Btg2* mRNA level was often reproduced in LTP models [20, 25, 27, 77] and observed in neuronal cultures [75]. Since *Btg2* is a target gene of the TF CREB, which plays a key role in neuroplasticity, the neuronal activity-driven increase in *Btg2* expression is usually *a priori* associated with the CREB activity. However, our results demonstrate a complex regulation of *Btg2* after LTP induction, and perhaps p53 takes part in it.

It should be noted, however, that our suggestion that p53 participates in LTP-associated regulation of *Bax*, *Btg2*, and some other genes mentioned above is preliminary and needs more direct evidence such as provided by chromatin immunoprecipitation.

4. Conclusion

De novo transcription plays an important role in long-term neuroplasticity underlying memory formation. Synaptic rearrangement is associated with substantial shifts in the brain transcriptome, analysis of which is necessary for the clarification of neuroplasticity mechanisms. The functional outcome of transcription in memory stabilization and storage was thoroughly discussed recently [21]. Here, we propose a hypothesis about a possible function of the p53-dependent transcription in LTP-associated processes.

Although p53 is known mostly as a key factor of apoptosis, its function is really much broader [78, 79] and sometimes prosurvival [80]. Intracellular regulatory cascades associated with LTP formation overlap with pathways regulating p53 activity, which indicates that, theoretically, p53 can be activated after LTP induction [58]. For example, active (phosphorylated) CREB directly interacts with p53, thus increasing its transcriptional activity [81].

During LTP formation in the area CA1 of the hippocampus, the increase in p53 transcriptional activity leads to *S100B* upregulation [59]. Taking into consideration that S100B suppresses LTP [45], we suggest that the increase in *S100B* expression is a part of the mechanism of synaptic scaling, a goal of which is to keep synaptic connection strengths within an optimal range necessary for proper functioning of a neuronal network. Heterodendritic metaplasticity [82] can be one of the manifestations of this mechanism. In the area CA1 of the hippocampus, priming stimulation delivered to inputs to the basal dendrites of pyramidal cells generates metaplastic inhibition of LTP and facilitates long-term depression (LTD) at inputs to the apical dendrites, hundreds of microns away and on the other side of the soma. Interestingly, astrocytes are involved in this form of metaplasticity. Thus, we proposed that an increase in S100B level associated with LTP [39] or learning [52, 53] prevents excessive enhancement of excitatory synaptic connections and reduces a risk of seizures.

In addition, LTP-associated upregulation (perhaps, also p53-dependent) of the proapoptotic protein of Bcl2 family Bax is of special interest in the context of neuroplasticity. This protein is involved in a mechanism of NMDAR-dependent LTD in the area CA1 of the hippocampus. Bax-mediated limited activation of caspases leads to the internalization of AMPA-type glutamate receptors, thus weakening synaptic strength [83]. Therefore, as in the case with *S100B*, *Bax* upregulation after LTP induction might reflect the formation of a negative feedback, which makes excitatory glutamatergic connections prone to LTD. This hypothesis suggests that the

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Bax level increases in neurons. As shown in **Figure 3**, Bax is really expressed mainly in pyramidal cells of the area CA1 and it is rarely detectable in S100B-producing cells in acute rat hippocampal slices.

Finally, at physiological doses, S100B possesses trophic and protective properties [43]. Btg2 is also capable of rendering neurons more resistant against excitotoxicity and promoting neuronal survival under stress [75]. Thus, LTP-associated alterations in the expression of p53 target genes are capable of mediating neuroprotective and trophic effects of neuronal activity.

Indeed, the answer to the question of how nuclear activity alters brain functioning will only be achieved by using a systems biology approach, in which the focus moves from single genes to

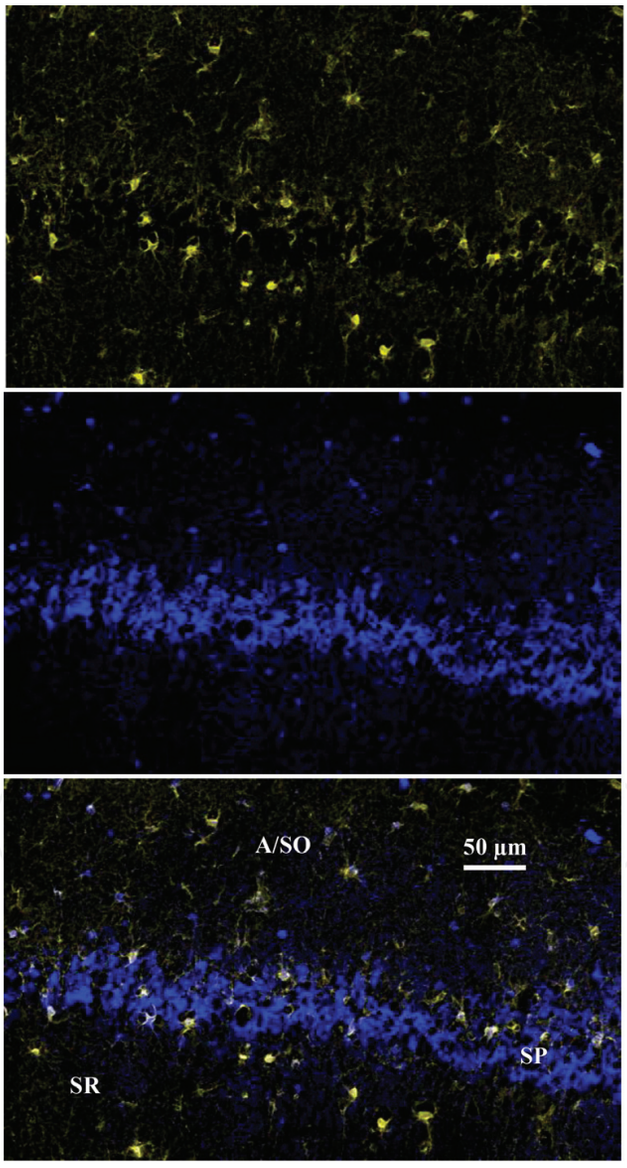

Figure 3. S100B and Bax immunoreactivity in the area CA1 of a rat hippocampal slice 30 min after tetanization of Schaffer collaterals. The same area is presented in all frames. Top—S100B-positive cells; middle—Bax immunoreactivity, bottom—the above images are merged. The section thickness is 30 μm. A/SO, alveus/stratum oriens; SP, stratum pyramidale, SR, stratum radiatum.

gene network interactions [22]. Moreover, profound molecular changes following hippocampal slice preparation suggest the need for careful interpretation of gene expression regulation results when using the acute slice as a model to study physiological responses [38, 84]. In particular, it needs to be determined whether p53 is activated in the brain after LTP induction in vivo or in behavioural tasks such as learning. Further investigation of p53 and its target gene roles in neuroplasticity should be undertaken to improve existing knowledge of the regulation of gene expression in the brain and its role in plasticity and neuropathology.

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