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Late expression of FosB transcription factor in 4-aminopyridine-induced seizures in the rat cerebral cortex

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Summary

In this study, the immunolocalization of FosB transcription factor was investigated in acute and chronic experimental models of seizures induced by 4-aminopyridine. Wistar rats were injected intraperitoneally daily with 5 mg/kg 4-aminopyridine for 1, 4, 8 and 12 days and sacrificed 24 h after the last injection. Corresponding control groups received the solvent of 4-aminopyridine. Immunohistochemistry revealed an increase in FosB immunolabelling in the frontal cortex in 4-aminopyridine-treated animals compared to controls, both in acute and chronic time course groups. The dentate gyrus displayed elevated FosB immunopositivity only after repeatedly applied convulsant (4-aminopyridine), i.e. following 4, 8 and 12 days of treatment, but no significant immunolocalization was observed in the hippocampus proper. The neuronal localization of FosB after 12 days of 4-aminopyridine-induced convulsions was analysed by means of FosB-parvalbumin double immunolabelling. The increased number of double-labelled cells was significant in the frontal cortex, hilum of the dentate fascia and region CA1 of the hippocampus. We conclude that the studied neocortical and allocortical areas showed a different pattern of FosB immunolocalization, which suggests a relative deficiency of transcriptional regulation in the Ammon's horn and may be responsible for distinct response to seizure-induced cellular insult.
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Introduction

Acute and chronic application of a great variety of stimuli to the brain have been shown to lead to differential responses reflecting short-term and

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long-term neural plasticity. Thus, the cellular consequences of repeated seizure activity characteristic of epilepsy differ from that of a single, acute seizure episode. This fact is demonstrable by the expression of transcription factors (TFs), proteins that control gene expression in response to receptor activation.

Fos-family TFs exert their effects via heterodimeric complexes that constitute the AP-1 complex and activate or repress the transcription of many neurobiologically important target genes (Herdegen and Leah, 1998). While c-fos and full-length FosB are induced rapidly and transiently in specific brain areas after different types of stimuli, the truncated form of FosB gene, named ΔFosB, codes for a highly stable protein with a half-life of approximately 1 week and functions as a type of 'molecular switch' that gradually converts acute responses into relatively stable adaptations that underlie long-term neural and behavioural plasticity to repeated stimuli (Nestler et al., 1999).

Long-lasting induction of specific Fos-family antigens has been shown to accompany several forms of neural and behavioural plasticity related to drug addiction (Hope et al., 1994; Nye and Nestler, 1996; Moratalla et al., 1996), stress responses (Perotti et al., 2003), the clinical actions of psychotherapeutic drugs (Hiroi and Graybiel, 1996), electroconvulsive antidepressant treatment (Hope et al., 1994), certain lesions (Doucet et al., 1996; Mandelzys, 1997) and epileptogenesis (Morris et al., 2000; Madsen et al., 2006). The investigation of seizures induced by systemically applied kainate using reverse transcriptase–polymerase chain reaction technique proved that ΔFosB expression lasted for only 6 h and the persistently expressed 35-kDa Fos-related protein revealed by Western blot analysis was thus considered different from ΔFosB (Bing et al., 1997). However, recent studies demonstrated that unlike the protein, the half-life of ΔFosB mRNA is only slightly longer than that of full-length FosB (Alibhai et al., 2007). These data indicate the possibility that the persistent expression of Fos-related antigens detected after different stimuli is due to the accumulation of the spliced variant of the FosB gene named ΔFosB. Moreover, *in vitro* studies confirmed that ΔFosB DNA encodes the expression of all of the multiple chronic Fos-related antigens (Chen et al., 1997).

The epileptogenic effects of the potassium channel blocker 4-aminopyridine (4-AP) has been extensively studied in acute experiments. c-fos expression, that can be regarded as a tool to study neuronal activation and seizure spread (Morgan and Curran, 1991), has a characteristic pattern and is maximal at 1–3 h following systemic 4-AP administration in the hippocampus and neocortex Mihály et al. (2001, 2005). However, repeatedly elicited 4-AP seizures are expected to cause qualitatively different cellular modifications as compared to a single seizure episode.

The present study aimed to investigate the late distribution of FosB proteins after daily induced seizures by intraperitoneal application of 4-AP. We also investigated the neurochemical characterization of a part of the FosB-positive neuronal population, by means of double immunolabelling for FosB and parvalbumin (PV).

Materials and methods

Animals and their treatment

Generalized seizures were induced daily by the intraperitoneal injection of 5 mg/kg 4-AP dissolved in physiological saline (0.67 mg/ml) to adult Wistar rats weighing 180–220 g. The experiments were conducted in accordance with prevailing laws and ethical considerations, and with the written permission of the University Ethical Committee on Animal Experiments.

A total of 24 rats were used for the experiments. Daily 4-AP treatment was applied to four groups of three rats for 1, 4, 8 and 12 days, respectively. The corresponding control groups received daily injections of saline. The animals were observed for 120 min following the injection and their motor seizures were evaluated according to the Racine scale (Racine, 1972). Five stages were distinguished based on the severity: stage 1 – mouth and facial movements; stage 2 – head nodding; stage 3 – forelimb clonus; stage 4 – rearing; stage 5 – full motor seizure (rearing and falling with loss of postural control).

The animals were sacrificed 24 h after the last injection. Rats were briefly anesthetized with diethylether and perfused transcardially with 200 ml of 0.1 M PBS, pH 7.4, followed by 300 ml of 4% phosphate-buffered paraformaldehyde, pH 7.4. The brains were rapidly removed, postfixed in 4% paraformaldehyde for 24 h and then cryoprotected with 30% sucrose in 0.1 M phosphate buffer overnight at room temperature. Frozen coronal plane sections were cut using a cryostat (Reichert-Jung Cryocut 1800) at a thickness of 24 μm. Every third section was processed for immunohistochemistry.

Immunohistochemistry

Sections were incubated in 0.2% Triton X-100/PBS for 20 min, followed by washing in three changes of PBS. Then 20% normal pig serum (NPS; Sigma) was applied for 1 h to block nonspecific labelling.

Sections from rats injected for 1, 4 and 8 days were used for immunohistochemical analysis of FosB protein, while sections from the 12-days-treated rats were used for simple FosB and double FosB+parvalbumin immunolabelling. Since antibodies selective for ΔFosB are not available, we used a rabbit polyclonal antiserum raised against an internal region of FosB (sc-48; Santa Cruz Biotechnology), that has been shown to recognize both FosB and ΔFosB (Perotti et al., 2005). The antibody was used diluted 1:4000 in 0.05 M PBS containing 10% NPS. The sections were incubated in the primary antibody overnight at room temperature. The biotinylated secondary antibody (goat anti-rabbit IgG; Vector Laboratories, CA) was diluted 1:40 in PBS, and sections were incubated for 1 h. After additional washing, sections were transferred to streptavidin-peroxidase (1:1000; Jackson ImmunoResearch), and incubated for 1 h. Then the sections were washed and processed using 0.05% 3,3-diaminobenzidine tetrahydrochloride (DAB; Sigma) containing 0.3% nickel sulphate and 0.01% hydrogen peroxide. After 20 min of incubation, the chromogen yielded a black reaction product.

Double immunolabelling was performed using primary antibody cocktails: mouse anti-PV (Sigma), diluted 1:100,000 and rabbit anti-FosB (Santa Cruz Biotechnology), diluted 1:500. The sections were incubated in the primary antibody cocktail overnight at room temperature, then transferred to the secondary antibody cocktail: biotinylated anti-mouse IgG (Sigma), diluted 1:600, and unlabelled goat anti-rabbit IgG (Vector Laboratories) diluted 1:40. The sections were incubated for 1 h in the secondary antibody cocktail and then transferred to streptavidin-peroxidase (1:1000; Jackson ImmunoResearch). The streptavidin-peroxidase was developed by using 0.05% DAB (Sigma) with 0.01% hydrogen peroxidase. Following a wash in TBS, the sections were transferred to peroxidase-anti-peroxidase (PAP; Jackson ImmunoResearch), diluted 1:1000, and incubated for 1 h. The PAP was developed using 0.05% DAB (Sigma) with 0.3% nickel sulphate and 0.01% hydrogen peroxide, as described previously. No counterstain was applied. The sections were dehydrated with an ascending series of ethanol (40%, 70% and 100%), cleared in xylene and mounted with Entellan (Fluka).

Evaluation of immunolabelling and statistical analysis

The quantitative analysis was performed on five histological sections per animal. Areas of interest were selected on the basis of the same stereotaxic coordinates (Paxinos and Watson, 1998): from regions CA1, CA2, CA3 of the Ammon's horn, the granule cell layer of the dentate fascia, the hilum of the dentate fascia, and from the frontal cortex. In the neocortex, the areas of interest included all neocortical layers (I–VI) from the pia mater to the subcortical white matter. The hilum of the dentate fascia was outlined manually, according to Amaral (1978), and used as areas of interest. The immunoreactive cells were counted using a Nikon Eclipse 600 microscope equipped with a Spot RT Slider digital camera (1600 × 1200 dpi in 8 bits), and the Image Pro Plus 4 morphometry software (Media Cybernetics, Silver Spring, MD). Following background subtraction, the threshold was adjusted so that all positively labelled cells could be recognized. Cell counts were then normalized to 1 mm^2. The statistical analysis was performed with the SPSS 9.0 computer program. Differences between control and 4-AP treated groups were analysed by a paired *t*-test. P values of <0.05 were considered statistically significant.

Results

4-AP-precipitated seizure behaviour

Following the injection of the convulsive dose of 4-AP, the animals displayed behavioural seizures which lasted for 60–80 min. The characteristic symptoms occured within approximately 10 min of injection and developed gradually, as described previously (Mihály et al., 1990). Initially, animals exhibited increased exploratory activity which was followed by tremors of the vibrissal muscles, shivering, forelimb clonus with increasing frequency moving to the development of generalized tonic-clonic seizure with loss of postural control. After a postictal period of 10–20 min, some of the animals displayed generalized seizure again.

The analysis of the daily elicited seizure symptoms according to the Racine scale proved that the convulsion pattern changed slightly towards the end of the experiment: decreases of the seizure intensity were observed, i.e. after 4-AP administration the animals developed a single full motor seizure (stage 5) instead of two seizures, or displayed less severe, stage 4, symptoms.

Immunohistochemical results

The FosB immunohistochemistry revealed a very weak labelling in the Ammon's horn of both the control and 4-AP treated rats in every time-course group. A very small number of weakly labelled cell nuclei were found in this hippocampal region and it was therefore not evaluated by statistical analysis.

The dentate gyrus was characterized by more striking FosB immunolabelling (Figure 1). There was a significant increase in FosB-immunopositivity in the 4-AP treated animals compared with controls after 4, 8 and 12 days of treatment. Increase in immunopositivity after a single 4-AP treatment did not reach statisitical significance in comparison to the corresponding control level (Figure 2a).

Neocortical FosB-immunoreactivity increased significantly after 4-AP elicited convulsions at every time point compared to controls (Figure 2b).

In the brain sections from animals treated for 12 days from both 4-AP injected and control animals, parvalbumin-positive neurons were distributed in every layer of the frontal cortex. In the hippocampus, parvalbumin-positive neurons were present mainly in the pyramidal layer of the Ammon's horn and in the hilar region, while the granule cell layer comprised scattered parvalbumin-immunopositive cells. No significant changes were revealed in the overall number of parvalbumin-immunopositive cells in any of the investigated brain regions after 4-AP treatment. There was, however, a significant increase in double-labelled neurons after 4-AP treatment in comparison to control levels in the neocortex, hilum of the dentate gyrus and region CA1 (Figure 3).

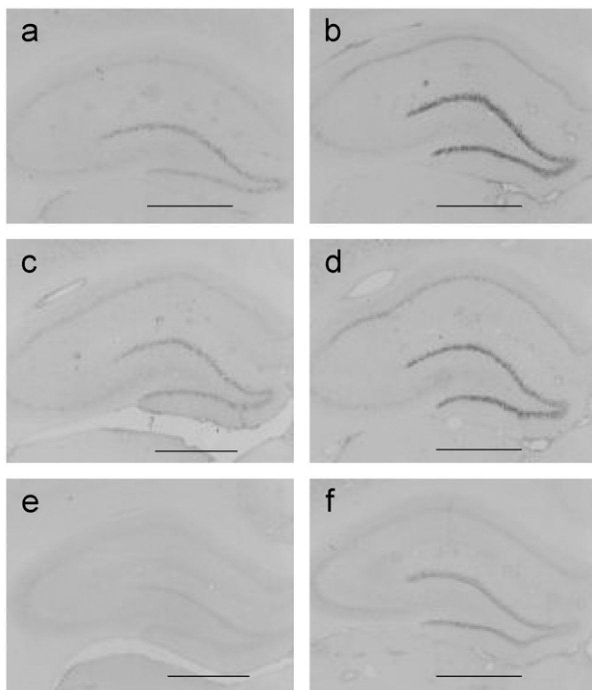

Figure 1. Low magnification photomicrographs illustrating the distribution of FosB immunoreactive cell nuclei in the hippocampus of 4-AP treated (b, d, f) and control (a, c, e) rats after 4 days (a, b), 8 days (c, d) and 12 days (e, f) of treatment. Scale bar: 1 mm.

Discussion

General evaluation of FosB immunodetection

In the present study, we analysed the effects of daily intraperitoneal 4-AP injections on the immunodistribution of FosB proteins in the hippocampus and frontal cortex and observed seizure behaviour. A FosB antiserum that recognizes both FosB and isoforms of ΔFosB proteins was employed. It has been shown that full-length FosB is transiently induced after stimulation and returns to basal levels within 8–12 h, while two forms of ΔFosB have been identified as having longer half-lives: the 35 kDa protein with an estimated half-life of 28 h, and the 37 kDa protein with an estimated half-life of 208 h (Chen et al., 1997). In order to detect the immunodistribution of the highly stable FosB gene products we sacrificed the experimental animals 24 h after the last injection. Thus, most of the FosB-like immunoreactivity would be due to long lasting forms of FosB proteins.

Repeated intraperitoneal injections of 4-AP are thought to cause stress-related changes in the brain which must be distinguished from the consequences of the seizure episodes. It has been demonstrated that after repeated stressful experiences, ΔFosB expression increases in some distinct brain areas according to the type of the stressor (Perotti et al., 2003; Conversi et al., 2006). This is why we compared the results of 4-AP treated and its corresponding control group (which also received daily intraperitoneal injections) separately for each time-course experiment.

The pattern of immunolocalization reflected differential adaptation of the investigated brain regions in the four time-course groups. Following a single injection of 4-AP, only the frontal cortex displayed significant increase of FosB-like immunoreactivity. Recently, it has been suggested that ΔFosB mRNA is formed by alternative splicing of the full-length FosB mRNA and this splicing of FosB pre-mRNA is regulated by the quantity of unspliced transcript available to the splicing machinery (Alibhai et al., 2007). Thus, a first stimulus may

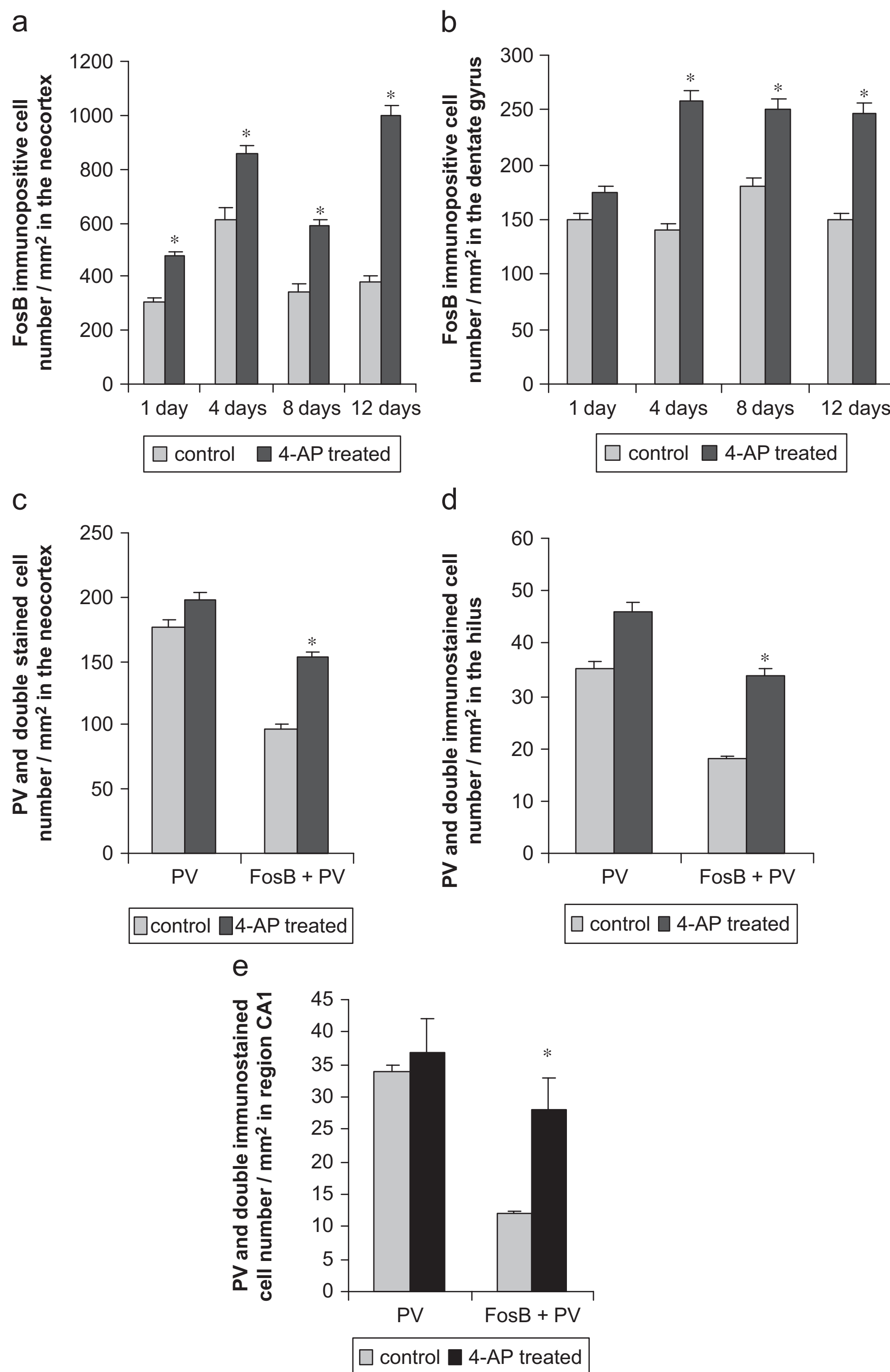

Figure 2. Results of FosB immunopositive cell counts in the dentate gyrus (a) and frontal cortex (b) of 4-AP injected and control groups after 1, 4, 8 and 12 days of treatment, and results of the counting of FosB and FosB+PV double immunopositive neurons in the frontal cortex (c), CA1 (d) and hilum of the dentate gyrus (e) in 4-AP treated and control groups after 12 days of treatment. Asterisks denote significant differences ($p<0.05$). S.E.M is indicated on the top of the column.

induce a FosB level high enough for the appearance of a significant amount of ΔFosB that could accumulate after further applied stimuli. Acute 4-AP seizure is known to result in an intense expression of c-fos that returns to control level at 8 h after the stimulus (Mihály et al., 2005).

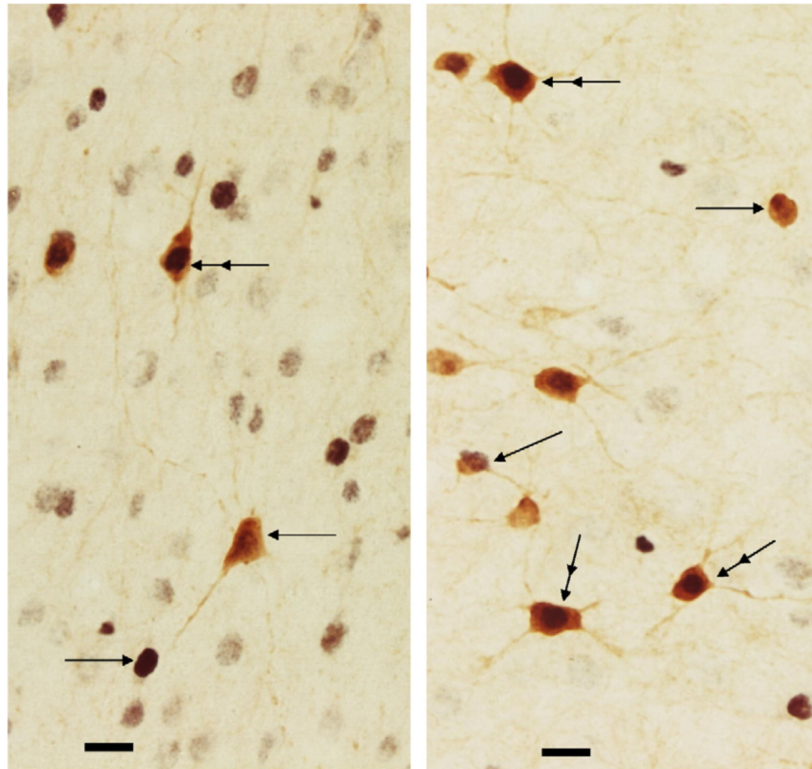

Figure 3. Appearance of the PV-FosB double immunolabelling in the neocortex. Double arrows point to the double-labelled cells, while simple arrows indicate PV-positive FosB-negative neurons and PV-negative FosB-positive cells. Scale bar: 10 μm.

We expect that c-fos is replaced by FosB, as literature data refer to the reciprocal repression at the promoter region of these genes (Herdegen and Leah, 1998). It is therefore plausible that the pattern of c-fos induction is predicting a certain pattern of FosB expression after a single stimulus.

FosB immunolocalization in the frontal cortex and the behavioural pattern of the chronic 4-AP seizures

The FosB immunopositivity in the frontal cortex was increased after 4-AP convulsions at every time point in the experiments reported here. The qualitative changes that are denoted by long-term FosB expression should be considered in relation to the transcriptional regulation of target genes. According to the literature, glutamate receptor subunit expression has been identified as belonging to FosB-regulated gene products. The rearrangement of the distribution of *N*-methyl-D-aspartate (NMDA) receptor subunits including the upregulation of NMDAR1 with decreased NMDA-induced inward currents in pyramidal neurons and a parallel desensitization of motor seizure after repeated electroconvulsive seizures have been shown to be associated with the expression of FosB in the frontal cortex (Hiroi et al., 1998).

The intense immunolabelling of FosB in the frontal cortex may also be correlated with a gradual reduction in the severity of seizure behaviour in our chronic 4-AP experiments. In the chronically treated groups, we did observe a gradual reduction in severity of the motor seizure symptoms evaluated by the Racine scale. Such a correlation could be further clarified by future studies of changes in NMDA receptor ditribution after 4-AP seizures.

FosB immunolocalization in the hippocampus

The hippocampal immunolocalization of FosB reflects differences between the Ammon's horn and dentate gyrus after repeated 4-AP convulsions. The regions of the Ammon's horn displayed a very weak FosB-like immunoreactivity compared with the dentate gyrus. This may also be indicative of an insignificant level of the adaptive changes of NMDA receptors, similar to those observed in the frontal

cortex and a consequent vulnerability to excitotoxicity to glutamate. This is in accordance with a reported vulnerability of the hippocampal regions CA1 and CA3 to infusion of convulsive dose of 4-AP in the hippocampus where the resulting excitotoxic neuronal damage has been shown to be mediated by NMDA receptor activation (Pena and Tapia, 2000).

Moreover, it has been demonstrated that seizure preconditioning induces a much broader transcriptional response in the dentate granule cell layer than in the pyramidal cell layers and activates a series of neuroprotective genes in the dentate gyrus that are induced at a significantly lower level in the Ammon's horn (Borges et al., 2007). Many of these genes implicated in neuronal growth and regeneration are known to be regulated by ΔFosB (Miura et al., 2005). Changes in immunoreactivity in the dentate gyrus were not statistically significant following the first day of seizure. However, the chronic treatments resulted in significantly increased FosB-like immunoreactivity in this hippocampal region. Repeated seizures are known to induce neurogenesis of dentate granule cells (Scharfman et al., 2003), Therefore, it is plausible that in our experiments the strong labelling of FosB in the dentate gyrus may also be related to this phenomenon.

These issues seem to reflect a neuroprotective effect of persistent presence of FosB that is characteristic of the dentate gyrus rather than of the hippocampus proper. However, the function of the FosB protein is believed to be more complex, as it has a region-specific role in the regulation of different target genes in distinct cell populations that are still not entirely characterized by the existing literature. Furthermore, it is known that depending on the level of FosB protein or the length of time that it is expressed, it can activate or repress gene transcription (McClung et al., 2004). *In vivo* and *in vitro* studies revealed a large number of target genes for ΔFosB, some of them in association with cellular fates including apoptosis (Tahara et al., 2003) and proliferation (Miura et al., 2005). Related to injury events, ΔFosB has been demonstrated to have long-lasting elevated levels in the hippocampus after pilocarpine-induced status epilepticus (SE) followed by recurrent spontaneous seizures, suggesting that this TF may play a role in epileptogenesis (Morris et al., 2000). The increased immunoreactivity of FosB, including in the Ammon's horn, 8 weeks after pilocarpine-induced SE may reflect the accumulation of an isoform of ΔFosB that may be responsible for late response to cellular damage, e.g. delayed apoptosis.

Alterations in the parvalbumin containing neuronal population

The parvalbumin containing neuronal population has been examined in earlier works that deal with 4-AP induced seizure (Mihály et al., 1997, 2001). PV expressing neurons are fast-spiking GABAergic interneurons that mediate mainly perisomatic inhibition, alteration of their function is linked with either hippocampal and neocortical seizure activity (Silva et al., 2002; Sloviter, 1991). Long-lasting seizures cause neuronal damage that has been reported to occur even in the dentate gyrus among parvalbumin-positive interneurons (Kobayashi and Buckmaster, 2003).

PV-positive cells in the rat hippocampus express protein subunits of the delayed rectifier K channel, and the neurons are sensitive to low concentrations of 4-AP (Du et al., 1996). Long-lasting seizures have been shown to induce heat-shock protein expression in hilar neurons, as an indication of cellular injury (Sloviter and Lowenstein, 1992). However, no change in the PV mRNA content was detected in the hippocampus and neocortex after 12 days of 4-AP treatment (Vizi et al., 2004). The present study revealed no significant reduction in the number of PV immunopositive neurons and the increased immunopositivity of FosB in this neuronal subpopulation could be regarded as indicating the persistent, and probably adaptive, changes in the function of the inhibitory circuits after repeated 4-AP seizures.

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