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RESEARCH ARTICLE

Predictive value of changes in electroencephalogram and excitatory postsynaptic field potential for CA1 damage after global ischaemia in rats

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Abstract Recordings of the electroencephalogram (EEG) are regularly used to asses the severity of transient global ischaemia in rats. Here, we investigated whether the EEG obtained from electrodes placed in the hippocampus does indeed give valuable information about the consequences of an ischaemic event. Furthermore, we evaluated how evoked synaptic responses from the same electrodes placed in the hippocampal CA1 area changed with time and in relation to damage. We performed transient two vessel-occlusion with hypobaric hypotension in rats to induce selective, delayed neuronal death in CA1. Beforehand, the animals had been chronically implanted with electrodes. Stimulating electrodes had been placed into the Schaffer collaterals and recording electrodes into the CA1 area. EEG was recorded from shortly before ischaemia until up to 40 min post-ischaemia. Field excitatory post-synaptic potentials (fEPSP) were recorded before ischaemia or sham-operation and 2 and 7 days afterwards. We found a significant negative correlation between the duration of the EEG amplitude decrease (flattening) and the number of surviving neurons in CA1, which were quantified by histology after 7 days post-ischaemia. However, substantial neuronal damage was only seen when the time of flattening was more than 12 min and outlasted the time of ischaemia. The impairment of synaptic function, measured as the decrease of fEPSP slope 2 days post-ischaemia correlated with the later maturated structural damage in CA1. The fEPSP remained decreased until day 7 post-ischaemia. Animals with no damage (sham condition) showed a transient decrease of the fEPSP slope. In conclusion, our data show that the duration of EEG-flattening predicts the extent of neuronal damage. However, EEG-flattening just during the period of clamping both common carotid arteries—albeit an essential precondition for substantial CA1 cell loss to occur—is not sufficient to predict damage. The degree of impairment of evoked synaptic function of CA1 neurons (fEPSP) 2 days after ischaemia predicts the final extent of damage with significant probability.

Keywords Hippocampus · Neurodegeneration · Electroencephalogram · Field excitatory post-synaptic potentials · Rat

Introduction

The electroencephalogram (EEG) is a functional readout widely used for evaluating the efficacy of experimental techniques applied to induce ischaemia in rodents (e.g. Smith et al. 1984a; McBean et al. 1995; Kawai et al. 2004). This electrophysiological approach is especially interesting, as results could be useful for developing diagnostic tools. The EEG has also been used for prognostication after resuscitation from cardiac arrest in humans (Bassetti et al. 1996; Rothstein et al. 1991; Scollio-Lavizzari and Bassetti 1987), however, mostly followed by quite elaborate techniques of

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analysis (Geocadin et al. 2000; Scheuer and Wilson 2004). These techniques comprise, for example, power spectrum analysis via fast Fourier transform (Giaquinto et al. 1994; Lin et al. 1995) or linear auto-regressive modelling (Bell et al. 1990; Issakson et al. 1981). In experimental settings, however, for practical reasons, EEG-flattening (low-amplitude EEG) is the simple parameter chosen to decide whether ischaemia was indeed induced or not (Fortuna et al. 1997).

After transient global ischaemia, selective neuronal death appears in the CA1 layer of the hippocampal formation (Kirino and Sano 1984; Smith et al. 1984b; Schmidt-Kastner and Hossmann 1988; Zola-Morgan et al. 1986). This degeneration is delayed and develops—when defined by histological parameters—most obviously from days 2 to 4 post-ischaemia (Kirino 1982; Petito et al. 1987; Pulsinelli et al. 1982). However, current literature suggests that electrophysiological analysis may help to interpret the functional significance of histological data (Aoyagi et al. 1998; Henrich-Noack et al. 2005). In the literature, a few pioneering papers have already shown results from combined in vivo ischaemia and electrophysiological recordings in the CA1 area (Buzsàki et al. 1989; Suyama et al. 1992; Kiprianova et al. 1999; Gillardon et al. 1999), but knowledge about the electrophysiological post-ischaemic changes is far from being complete. More results about electrophysiological function have been published using in vitro or ex vivo preparations. However, our former data have suggested that effects in vitro can differ substantially from in vivo data (Henrich-Noack et al. 2005), and therefore, the latter are essential for a correct interpretation.

The present study was designed to examine the predictive value of changes in the EEG and field excitatory postsynaptic potentials (fEPSP) for CA1 damage after transient global ischaemia. For this purpose, we implanted electrodes into the hippocampus, as it was shown that no significant correlation between EEG and histological scores exists with the exception of the hippocampal areas (Mariucci et al. 2003).

Materials and methods

Surgical preparations for electrophysiology

Preparations were performed according to Manahan-Vaughan and Reymann (1997). Ten-week-old male *Wistar* rats were ordered and kept at least 1 week in the animal facilities for adaptation. For electrode implantation the animals were anaesthetized with sodium pentobarbitone (ca. 50 mg/kg) and placed into a stereotactic unit. Bregma and the midline were exposed. Two stainless-steel screws were inserted without piercing the dura, into the skull. The screws were attached via silver wire to a socket connector. One served as ground electrode. The other was used as reference electrode. A Teflon-coated stainless-steel recording electrode (0.1 mm diameter) was placed in the stratum radiatum of the CA1 region (0.3 mm posterior to bregma; 2.8 mm lateral to midline). A bipolar stimulating electrode (Teflon-coated stainless steel, 0.1 mm diameter wire) was placed in the Schaffer collaterals of the ipsilateral dorsal hippocampus (4.0 mm posterior to bregma; 3.8 mm lateral to midline). Recordings of evoked field potentials through the electrodes were obtained during electrode implantation to confirm their correct placement. The entire electrode assembly was then fixed to the skull using cyanoacrylate glue and dental cement. The animals were allowed at least 8 days to recover before further electrophysiological recordings started.

Measurement of evoked potentials

Throughout, each experiment the animals could move freely, as the implanted electrodes were attached permanently to a socket, which in turn, was connected by a flexible cable through swivel contacts to a stimulation unit and an amplifier. Field EPSPs were evoked in the stratum radiatum by stimulating at low frequency (0.025 Hz) with single biphasic square wave pulses of 0.1 ms duration per half wave, generated by a constant current isolation unit. The fEPSP slope function was measured as the maximal slope on the first negative deflection of the potential. Input/output (I/O) curves were generated by increasing stimulation intensities stepwise up to 400 μA.

EEG recordings

The EEG was recorded during surgery from the same implanted recording electrode. The signal from the electrode passed through a high-impedance miniature amplifier placed close to the rat's head to the EEG recorder (Philipps PM 3335) and then printed on paper. The frequency band of the recorded signal was restricted to 20 Hz by the mechanical capacities of the ink printer.

Induction of ischaemia

At least 10 days after electrode implantation, we induced transient global ischaemia under normothermic conditions as described by Dirnagl et al. (1993) in rats weighting in average 356 ± 47.4 g (mean ± SD). After initial anaesthesia with 3–4% halothane (Sigma, MO, USA), the rats were intubated and connected to a small animal ventilator (Sachs Electronic, March, Germany) that delivered 1% halothane in a nitrous oxide/oxygen mixture. Both common carotid

arteries were isolated and the tail artery was cannulated (tube rinsed with 50 IU heparin; Ratiopharm, Ulm, Germany) for the measurement of blood gases (Radiometer, Copenhagen, Denmark) and blood pressure (Foehr Medical Instruments, Seeheim, Germany). The lower body of the animal (excluding the thorax) was housed in a negative pressure chamber, which was connected to a vacuum pump. Ischaemia was induced by transiently clamping both common carotid arteries and reducing the mean arterial blood pressure to 35–40 mm Hg by controlled negative pressure simultaneously (venous pooling). Selective damage was induced by 7, 10 and 12 min ischaemia. Fifteen minutes of transient global ischaemia induced significantly increased mortality and unselective brain damage. Therefore, only up to 12 min ischaemia was used for the current study of selective neuronal CA1 damage. The animals were removed from the respirator as soon as they regained spontaneous respiration and kept for 90 min under 30°C environmental temperature.

The principles of laboratory animals care (NIH publication No. 86-23, revised 1985) were followed as well as the current version of the German laws on The Protection of Animals.

Histology

For histological processing, the brains were removed, fixed by immersion (ethanol/paraformaldehyde/glacial acid; Merck, Darmstadt, Germany) and embedded in paraffin. Life/death staining was performed on 10 µm hippocampal slices with toluidine blue/fuchsin acid (Sigma). Slightly blue-stained neurons with distinct round nuclei were evaluated as morphologically intact neurons and were counted in the CA1 region and the dentate gyrus of both hemispheres in a blind manner. Data are given as number of healthy neurons within a 500 µm area in the CA1 region (mean ± SEM). The electrode position was confirmed in each animal on slices stained with toluidine blue.

Statistics

For checking the correlation between the number of surviving cells and time of EEG flattening during surgery, we applied a calculation of the two-tailed Spearman correlation coefficient. This correlation coefficient was also calculated for the comparison of cell loss and fEPSP slope at different intensities of stimulation on second and seventh day post-ischaemia. For comparison of I/O curve points between groups of rats, we used the Mann–Whitney *U*-test and for comparison data on different days in one group, we used the Wilcoxon test for related samples.

Results

Histology

As cell death in CA1 is completed on day 7 post-ischaemia, we determined neuronal density in this area after 7 days post-ischaemia in animals from which electrophysiological data were obtained. These animals from which we recorded electrophysiological responses comprised three groups: control animals (sham condition), animals with partial damage in CA1 and animals with almost complete damage in CA1. In control animals (sham condition) where no cell death could be detected with toluidine blue/fuchsin acid staining and where also no cell damage was discoverable as dark neurons or irregularly shaped cells, the neuronal density in the CA1-subfield was 100.3 ± 17.1; $n = 6$ (neurons per 500 µm; values are always given as mean ± SEM). Several animals developed a partial damage after ischaemia. The average neuronal density in CA1 in this group with sporadic cell death and damage was 82.4 ± 24.7; $n = 11$. The third group which comprised rats which suffered from a CA1-selective, but almost complete cell loss showed a neuronal density of 7.2 ± 7.1; $n = 7$.

In an extra experimental series using rats which were not tested for electrophysiological responses, the histological outcome was evaluated at earlier post-ischemic times, reflecting the delayed neuronal degeneration in CA1. One day after the interruption of blood flow for 12 min, 98.3 ± 5.9 ($n = 4$) neurons were still viable along a 500 µm CA1 band. On day 2 this number was decreased, however, we still found a neuronal density of 69.9 ± 16.1 per 500 µm ($n = 5$).

EEG—correlation with histology

In 44 rats, we recorded EEG during surgery from shortly before ischaemia until animals were disconnected from artificial ventilation. For these rats, the number of surviving cells in CA1 was counted. The duration of substantial EEG amplitude decrease (i.e. flattening, which was defined as an at least threefold decrease of peak to peak EEG maximal deflections) was quite different between animals. The time of flattening differed from 0 to 37.3 min (mean value 13.87 ± 11.9 min). Records with different times of flattening in relation to cell counts are presented in Fig. 1 b. In 23 rats, the time of flattening exceeds the maximum time of 12 min carotid clamping, while in the other 21 rats it was shorter. In six rats, flattening lasted more than 30 min. Figure 1a provides examples of original EEG traces. In the upper panel (A) a recording is shown where the time of ischaemia and the time of significant EEG decrease match. In the middle (B) an example is provided where the time of EEG flattening exceeds by far the time of ischaemia and the

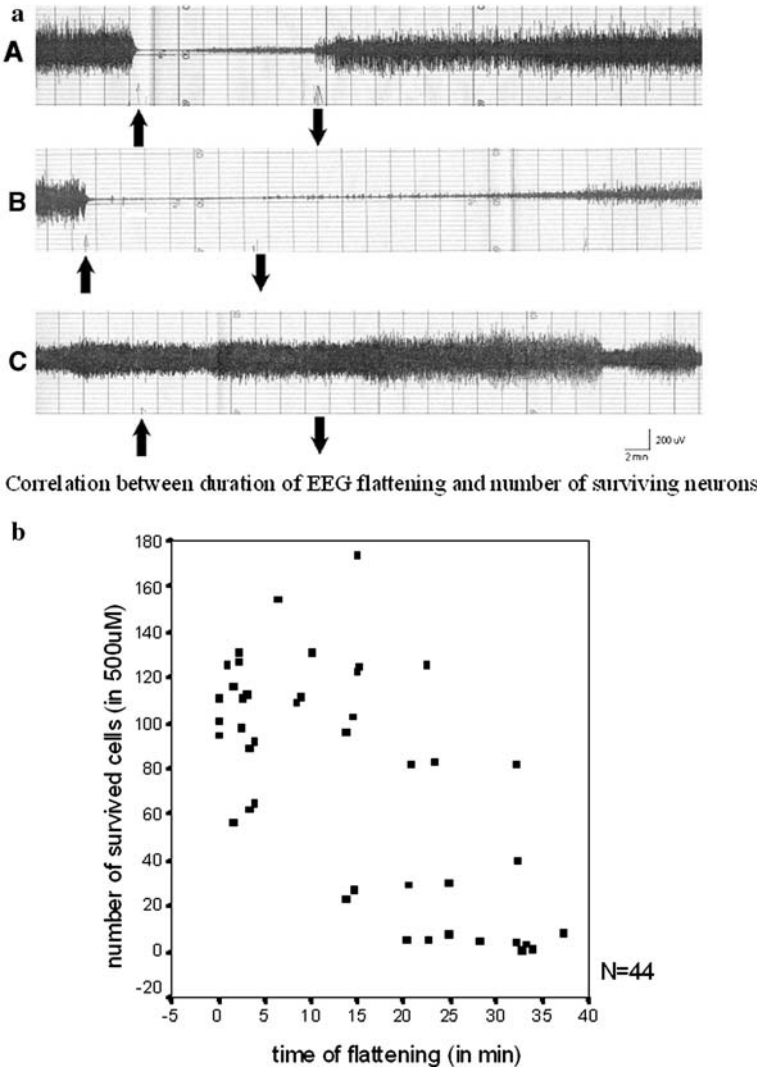

Fig. 1 In **a** original EEG traces are presented as examples of an animal with (*A*) an isoelectric EEG only during the period of ischaemia (the ⇑-symbol indicates beginning of ischaemia, ⇓ indicates onset of reperfusion). In (*B*) the substantial EEG decrease outlasts by far the period of clamping both common carotid arteries and in (*C*) we did not detect any significant changes in the EEG although, the standard technique of interruption of blood flow was applied. In **b** numbers of surviving cells, as quantified by histological evaluation after 7 days post-ischaemia, are plotted against duration of EEG flattening after clamping both common carotid arteries. Electrodes were located in the CA1 area of the right hemisphere

lower part (C) of Fig. 1a demonstrates that in some animals no flattening could be detected at all. In some animals the recording was continued after halothane was switched off. We did not see any influence on the recorded EEG.

Spearman's correlation coefficient was calculated for comparison of EEG flattening and the number of surviving cells in the hippocampus. The value was −0.61 for the right hippocampus, where electrodes were placed ($P < 0.001$). So, the number of surviving cells was highly negatively correlated to the time of EEG flattening.

fEPSP—correlation with histology

We recorded I/O curves before, on days 2 and 7 after ischaemia or sham condition in 24 rats. Representative examples of original traces from rats, which underwent 12 min of ischaemia are shown in Fig. 2 a, b. Due to histological criteria, they were divided into three groups (see section Histology). Averaged I/O curves at different time points for the group of rats with no signs of cell death in the hippocampus are shown in Fig. 3a. The data for the group with partial cell loss is presented in Fig. 3b and for the group with almost total cell loss in Fig. 3c.

When analysing changes with time inside groups, a decline of responses was seen on day 2 in the group with no cell loss (Fig. 3a) and with restoration of the responses on day 7 (responses on 150, 300 and 400 µA currents were smaller on day 2 than on day 7 and before ischaemia, Mann–Whitney *U*-test, $P < 0.05$). Instead, both groups with clear cell loss (Fig. 3b, c) did not change significantly until day 7 after the decline of responses on day 2.

There was a significant correlation between the changed fEPSP slope at higher stimulation intensities (more than 200 µA) on day 2 post-ischaemia and the final damage category as defined later by quantification of surviving neurons in CA1 and histological evidence of cell damage and debris ($P < 0.005$; Spearman's correlation coefficient = 0.572–0.883). At this time point, there was no significant correlation

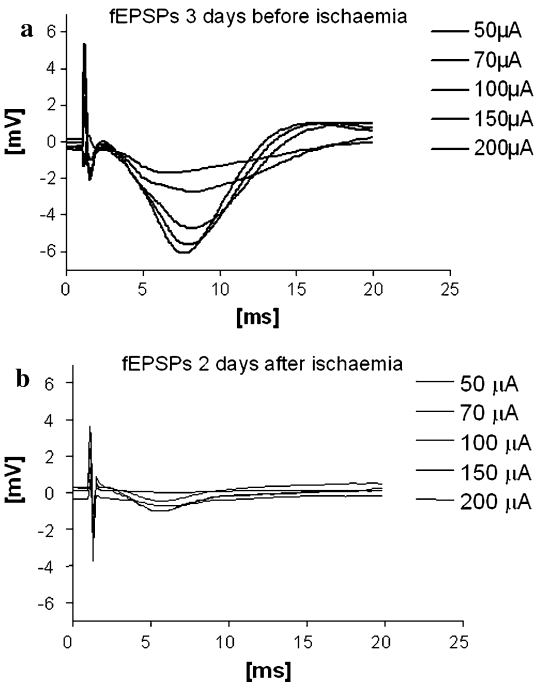

Fig. 2 Representative original traces of fEPSP curves from an individual animal are shown. In **a** the responses at different stimulation intensities are shown when the rat was tested before ischaemia. The traces in **b** illustrate the strongly reduced fEPSP response. The histological analysis revealed later an almost complete damage in CA1

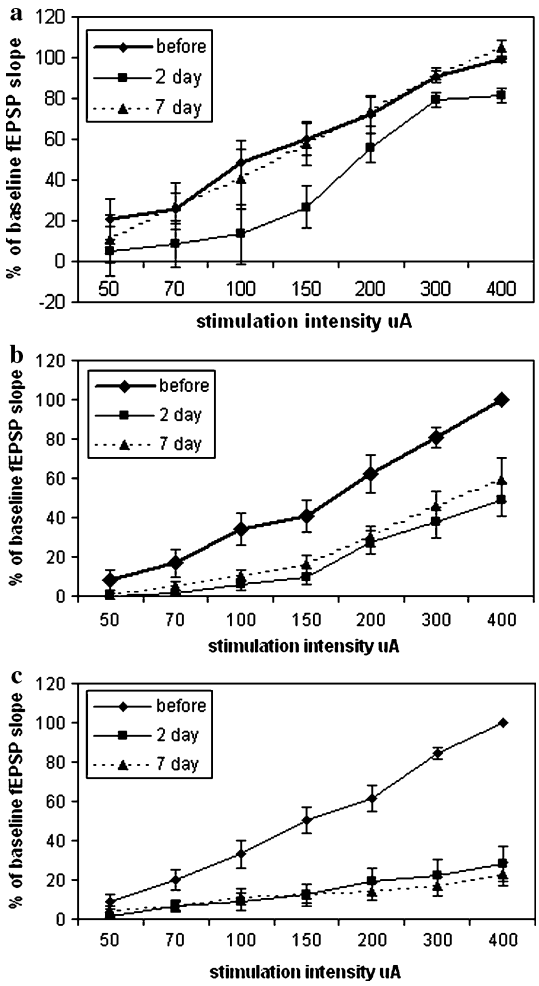

Fig. 3 Temporal profile of the changes in the fEPSP I/O curves after transient global ischaemia values are given as percentage of fEPSP slope in response to 400 µA in control. In **a** the minor influence of sham-condition on fEPSP is demonstrated. Only on day 2, a reversible decrease at lower stimulation intensities was detectable. In contrast, the changes in animals which suffered from partial CA1 cell loss (**b**) were more pronounced and irreversible. In rats, which developed an almost complete damage in the CA1 area, we revealed the biggest decrease in the fEPSP response, which was also already completed on day 2 post-ischaemia

between the fEPSP slope and the number of finally survived neurons. For day 7 post-ischaemia the correlation between fEPSP slope and damage category was even stronger and started at evoked activity with 150 µA stimulation intensity ($P < 0.001$; Spearmann's correlation coefficient = 0.628–0.830). On the seventh day, we found also correlation between number of finally survived cells and fEPSP slope at 200, 300 and 400 µA stimulation intensity ($P < 0.01$; Spearmann's correlation coefficient = 0.524–0.559).

Comparing the three different groups, we noticed that there is no difference in pre-ischaemic I/O curves and quite substantial changes between groups on days 2 and 7 after ischaemia (e.g. see curves from day 2 in Fig. 4). At high intensities of stimulation (more than 150 µA) evoked responses were the highest in the group with no cell loss (Mann–Whitney *U*-test $P < 0.05$). For the highest intensity of stimulation on day 2, there was also a difference in the responses between groups with partial and total cell loss (Mann–Whitney *U*-test $P < 0.05$; Fig. 4). These differences increased until the seventh day after ischaemia. Responses in the group with no cell loss returned to pre-ischaemic values, while curves in other two groups (partial damage group and substantial damage group) developed only very slight changes from days 2 to 7 post-ischaemia. A statistically proven difference from the sham-condition was obtained from 200 µA intensity and was higher at day 7 post-ischaemia (Mann–Whitney *U*-test $P < 0.05$).

Discussion

Flattening of the EEG (isoelectric EEG) is the parameter of choice to evaluate whether ischaemia has been induced or not (Stevens et al. 1986; Fortuna et al. 1997) in experimental settings as it is an easy, simple and fast method. In the current study, we revealed a significant correlation between the length of EEG-flattening and the later evaluated histological CA1 damage (Fig. 1b). However, interestingly, substantial morphological damage occurred only in these

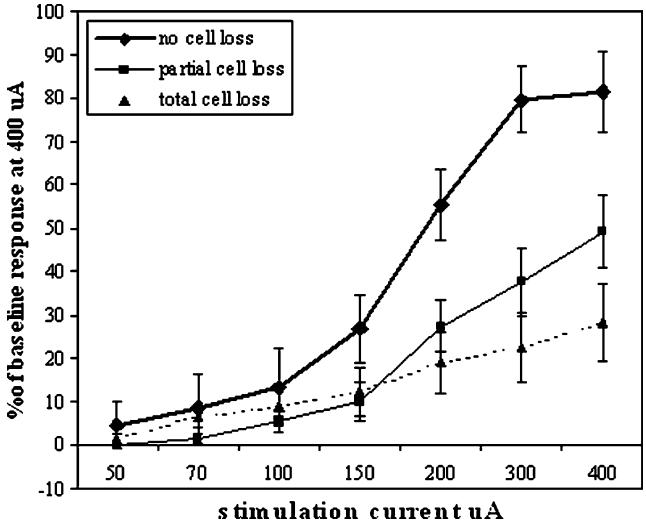

Fig. 4 Comparison of the three differently damaged groups of rats. The graph illustrates the differences in the fEPSP I/O curves from the three histologically distinct groups: rats with no cell death in CA1, rats with partial cell loss in CA1 and rats with almost complete loss of the CA1 pyramidal neurons develop different degrees of fEPSP impairments on day 2 post-ischaemia

animals, which showed significantly extended flattening beyond the period of carotid clamping. Therefore, an isoelectric EEG only during the period of ischaemia does not predict substantial damage, as also indicated by results from neuroprotection research (Braida et al. 2000). However, observing *no* isoelectric EEG during the period of clamping both common carotid arteries indicated that probably no complete ischaemia had been induced and it predicted neuronal survival. Therefore, it is useful to apply the criteria of a preserved intra-ischaemic EEG amplitude as an exclusion parameter for animals in which probably no ischaemia was induced. When the period of EEG flattening extended the time of 12 min ischaemia, the majority of animals developed severe cell loss in the CA1-subfield. However, interestingly, there were at least four outlayers, i.e. animals which showed more than 20 min of EEG flattening but still had a majority of their CA1 neurons surviving (Fig. 1b). From this, we conclude that all animals with severe CA1 damage show extended EEG flattening but not all animals, which show extended EEG flattening develop severe CA1 damage. This result and the literature data are in line with the assumption that isoelectric EEG is a by-product of the ischaemic pathophysiology, but does not play a causal role for neuronal damage. Moreover, the following arguments and data from literature lead to the speculation that a flat EEG could even promote survival and in some cases may be a part of a successful neuronal defence against cell death: Recovery of EEG implies recovery of neuronal activity. However, this demands energy metabolism (Aiello and Bach-y-Rita 2000) from cells that are possibly still impaired. Therefore, too early EEG recovery may have detrimental consequences for significantly challenged neurons. Moreover, results from Raffin et al. (1991) indicated that EEG suppression spares oxygen and Freund et al. (1989) showed that oxygen tension drops dramatically after recovery of electrical activity. This suggests that, it may be an advantage for survival if neurons keep their silent state and flat EEG for a prolonged time. As more severely challenged neurons would need to keep this silent state longer, the duration of EEG flattening, although beneficial, would correlate with the extent of damage as shown in the current study.

In contrast to the EEG parameter, evoked responses in the post-ischaemic CA1 area in vivo have not been intensively investigated so far. We found already on day 2 post-ischaemia a nearly complete loss of synaptic transmission, indicated by the significantly reduced fEPSP, in the group of animals which later developed a nearly complete deletion of the CA1 band (Fig. 3c). This result differs from outcome measurements using other techniques, like Nissl-staining. In the current work, we analysed the histological outcome also at early post-ischaemic times. By this we revealed, in accordance with the literature (Kirino 1982; Petito et al. 1987) that due to delayed neuronal degeneration, on day 2, a significant proportion of the CA1 pyramidal cells is still intact by morphological criteria. However, at that time sub-cellular changes in the postsynaptic structures most probably have already taken place, but cannot be detected by standard histological methods. It can be speculated that these sub-cellular changes are responsible for the early loss of electrophysiological synaptic responses. This view is supported by results from Pei et al. (2001), who found specific alterations regarding the postsynaptic densities 24 h after transient global ischaemia and it is supported by experiments indicating selective dendritic damage in the CA1 area (Hori and Carpenter 1994). The current electrophysiological results of a pronounced and fast decrease in synaptic function in the CA1 subfield are different from the electrophysiological impairments in the morphologically undamaged dentate gyrus (Henrich-Noack et al. 2005). Although, the action potential firing, measured as population spike amplitude, decreased quickly and intensely in the

dentate gyrus post-ischaemia, there was no significant change in the fEPSP. The pronounced decrease in fEPSP, as seen in the current study may be therefore more closely associated with the development of neuronal destruction than the pure loss of somatic function.

Interestingly, animals which developed only partial CA1 cell loss also developed only partial loss of fEPSP function (Fig. 3b). This correlation can be interpreted in a way that the neurons destined to die loose their synaptic function and surviving neurons preserve their synaptic function. This partial decay was completely developed as early as day 2 after the insult. Therefore, early post-ischaemic fEPSP recordings can be used for predicting the final damage, which is morphologically completed only after day 5 post-ischaemia. In the literature, there are hints that electrophysiological responses in CA1 are impaired after transient global ischaemia (Suyama 1992; Buzsàki et al. 1989). However, in these experiments the CA1 region was indirectly stimulated by electrodes in the perforant path. As the function of the input structure dentate gyrus is also decreased (Henrich-Noack et al. 2005), no specific conclusion could be drawn regarding the Schaffer collateral—CA1 synapses. Although, our data suggest that the basic synaptic function of the surviving neurons is intact, it does not exclude that other electrophysiological features are impaired, as for example plastic abilities like long-term potentiation, as shown by Gillardon et al. (1999) and Kiprianova et al. (1999).

In the group of animals, which did not show any signs of morphological damage in any part of the hippocampal formation (sham condition), we also detected an impairment of synaptic function in the CA1 area (Fig. 3a). However, this decrease in the fEPSP slope was only small and transient. Seven days after the insult the function was fully restored again.

In conclusion, our data showed that flattening of EEG only during the period of ischaemia did not predict whether or not cell death occurs in the CA1 band after transient global ischaemia, but non-flattening of the intra-ischaemic EEG indicated that no damage was induced. However, by measuring intra-ischaemic and post-ischaemic EEG, we revealed a significant negative correlation between the time of flattening and the number of surviving CA1 neurons. A decrease in synaptic transmission on day 2 post-ischaemia, measured as fEPSP slope in the CA1 area, was correlated with the final extent of cell damage. This means that the impairment of basic synaptic function was completely developed before histologically detectable neuronal death appeared. The fEPSP-responses were also decreased in animals, which underwent only sham-conditions. However, this decrease was detected only on day 2 post-ischaemia, and not on day 7 post-ischaemia anymore.

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