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Maturation Phenomenon in Cerebral Ischemia IV

Apoptosis and/or Necrosis, Neuronal Recovery vs. Death, and Protection Against Infarction

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October 30–November 3, 1999
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Preface

The maturation phenomenon, described by Ito et al. in 1975 [2], refers to ischemic changes that develop hours or days following an ischemic insult. The delayed neuronal death of CA1 pyramidal cells of the hippocampus [6] is a classic example. When the intensity of the ischemic insult is increased, the maturation phenomenon of ischemic injuries intensifies in the cerebral cortex, in a continuous manner, from less extensive to more extensive disseminated selective neuronal necrosis (DSNN), and then further to cerebral infarction upon reaching a critical threshold of intensity [1, 3–5].

The report of this phenomenon boosted research in the field as it became evident that ischemic damage is not a sudden event, but a process potentially susceptible to therapeutic intervention. Since then a growing number of studies have improved our knowledge about mechanisms of cell death and recovery.

In September 1990, Ito and collaborators organized the first international symposium on "Maturation Phenomenon in Cerebral Ischemia" in Tokyo [3]. The second symposium was also held in Tokyo, in March–April 1996 [4]. The Third International Workshop on Maturation Phenomenon in Cerebral Ischemia was held in Pozzilli, Italy, in April 1998 [5].

The maturation phenomenon represents a continuing struggle for survival between the acceleration of tissue or neuronal death and the activation of defense mechanisms leading to neuronal recovery. The elucidation of these mechanisms is important for developing the ability to manipulate them during a long-lasting "therapeutic window". This book contains the presentations at the Fourth International Workshop on Maturation Phenomenon in Cerebral Ischemia, held in New Orleans, Louisiana, USA, on 30 October–3 November 1999, with the subtitle "Apoptosis and/or Necrosis, Neuronal Recovery vs. Death, and Protection Against Infarction".

This book outlines the present status of investigations and provides further stimulation for research in this field. In this current publication, the focus is centered on the elucidation of (1) the role of genetic expression and neuronal apoptosis, (2) factors modulating neuronal plasticity and the course of maturation phenomenon in cerebral ischemia (metabolic and inflammatory factors), (3) factors and mechanisms enhancing susceptibility or tolerance (growth factors, etc.), (4) ischemic infarction: threshold, experimental and clinical dynamics and therapeutic designs for prevention or reduction of intensity, and (5) mitochondrial role in ischemic cell death.

Distinct Ischemic Effects on HSC70, HSP72, and c-fos Expression in Young and Adult Gerbils

R. M. McCarron, N. Bertrand, Y. Chen, A.-L. Siren, and M. Spatz

Summary. Young animals were previously shown to be more resistant to ischemia than were adult animals. This difference was attributed to maturation/function of gonads and/or neurons. This study evaluated the existence of age-related changes in transcriptional expression of HSC70, HSP72 and c-fos mRNA in transient global ischemia, and their possible relationship to neuronal cell survival in CA1 hippocampus. The results indicated that ischemic response in young animals compared with that in adult animals showed: (1) more rapid and/or prolonged expression of HSC70, HSP72, and c-fos mRNAs; (2) a marked induction of HSP72 protein; and (3) enhanced pyramidal cell survival. The observed endogenous 'tolerance' of CA1 neurons in young gerbils to ischemia/reperfusion injury may be related to the expression of HSC70, HSP72 and c-fos.

Introduction

Various studies have demonstrated a relative resistance of young (compared with adult) animals to hypoxia and/or ischemic insults [19, 20, 26, 30]. The difference in susceptibility to ischemia was attributed to maturation of gonads that, at sexual maturity, may influence the CBF [22]. Subsequent investigations of ischemic effects on energy metabolism, and monoaminergic and cholinergic systems of the brain in young and adult gerbils, suggested a linkage between neuronal maturation/function and relative resistance of young brain to ischemia [8, 9]. The aim of this study was to determine the existence of age-related changes in transcriptional expression of HSC70, HSP72 and c-fos mRNA in transient global ischemia. A variety of genes (including these) have been studied in ischemia in adult animals, but only limited studies have been reported using young animals [2, 4]. This report briefly summarizes data regarding ischemic effects on gene expression and neuronal integrity in the hippocampal CA1 subfield in young and adult gerbils.

Materials and Methods

Young (3 weeks old) and adult (3 months old) Mongolian gerbils obtained from Tumblebrook Farm (West Brookfield, Mass.) were subjected to bilateral carotid occlusion (15 min) under anesthesia with 1.5% halothane in 70% N_2O/30% O_2 and release (1, 3, 9, 24, or 48 h). Sham-operated animals were also subjected to anesthesia and to all surgical procedures except clamping of the carotid artery. At the

end of each experimental period, gerbils were killed by transcardiac perfusion with 4% paraformaldehyde under pentobarbital anesthesia.

Cryostat sections were used for in situ hybridization, immunocytochemistry and morphological analysis of CA1 hippocampus. Oligonucleotide probes (^{35}S-labeled) were used to assess constitutive HSC70, inducible HSP72, and c-fos mRNA expression. In immunocytochemistry studies, a double immunofluorescent staining was carried out with a murine anti-72 kDa HSP monoclonal antibody (code RPN 1197, Amersham) specific for the inducible form of HSP72, and a rat anti-HSC70 monoclonal antibody (SPA-815, StressGen) specific for the constitutive form of HSP70. Sections were counterstained with hematoxylin.

Regional intensity of in situ hybridization was quantitated on sections, with an automated image analysis system consisting of a video camera and microcomputer based analysis system (MetaMorph@). The appropriate threshold window was chosen and the selected windows were converted to binary images. Data are expressed as the mean ± SEM number of silver grains/μm^2 of CA1 hippocampal area. Cresyl violet staining was used to evaluate neuronal integrity in the CA1 subfield.

Neuronal damage was evaluated by counting surviving neurons in the right and left hemispheres of a 0.36 mm length representative region under a light microscope at ×160 magnitude. The average values of both right and left hippocampi were calculated for each animal; experimental groups consisted of four to seven animals.

Results

The expression of HSC70 mRNA had already been significantly increased in young (but not adult) gerbils after 1 h reperfusion (Fig. 1 A). Young gerbils exhibited significantly higher levels of HSC70 mRNA than adult animals at all reperfusion time points examined. HSC70 mRNA in adult animals was significantly upregulated only at 48 h reperfusion.

The HSP72 mRNA expression in young (but not adult) gerbils was also significantly upregulated at 1 h reperfusion (Fig. 1 B). However, HSP72 mRNA expression in adult animals was significantly elevated at 3, 8 and 24 h of reperfusion. Nonetheless, significantly greater levels of HSP72 mRNA expression were still observed in young animals at most time points.

In sham controls, HSC70 protein expression was considerably higher in young compared with adult gerbils (Fig. 1 C). In adults exposed to ischemia/reperfusion, no consistently significant changes in HSC70 expression in CA1 hippocampus were observed. Interestingly, a significant decrease in HSC70 expression occurred in young gerbils exposed to ischemia followed by 24 h and 48 h reperfusion.

Young animals exhibited significantly higher levels of HSP72 protein than did adults, in all three groups studied (sham, 24 and 48 h of reperfusion) (Fig. 1 D). In addition, significant increases in HSP72 expression were observed at 24 and 48 h of reperfusion; adult gerbils exhibited a slight though significant increase in HSP72 protein expression only after 48 h reperfusion.

The expression of c-fos mRNA in CA1 hippocampus was upregulated in both adult and young gerbils at 1 h of reperfusion (Fig. 1 E). At 8 h of reperfusion, c-fos

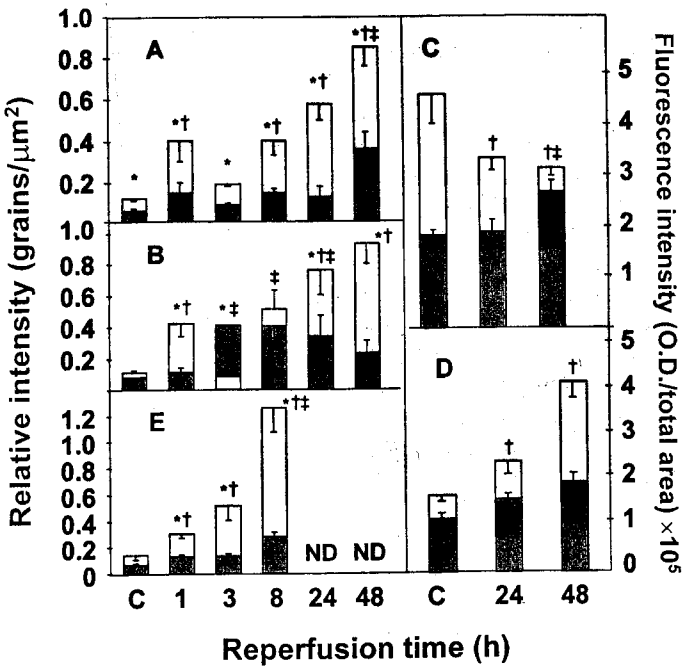

Fig. 1. Effect of ischemia/reperfusion on HSC70, HSP72 and c-fos mRNA and protein expression. Relative intensities of expression are displayed for **A** HSC70 mRNA, **B** HSP72 mRNA, **C** HSC70 protein, **D** HSP72 protein, and **E** c-fos mRNA, in the CA1 subfields of hippocampus in young (*open bars*) and adult (*dark bars*) gerbils which were sham-operated (Ctrl) or subjected to 15 min of cerebral ischemia followed by indicated times (1–48 h) of recirculation. Each point represents the intensity of in situ hybridization, expressed as the mean ± SEM number of silver grains/μm^2 in three to five animals per reperfusion period. Statistically significant differences in mRNA expression were assessed by ANOVA followed by post-hoc Newman-Keuls test ($P<0.05$). * $P<0.05$ vs adult; † $P<0.05$ vs control of the young group; ‡ $P<0.05$ vs control of the adult group

mRNA levels continued to increase in both young and adult animals. At all times studied, young gerbils expressed higher levels of c-fos mRNA than did identically treated adults.

Considerably fewer CA1 pyramidal cells were observed in adults compared with young gerbils after 24 and 48 h of reperfusion; sham-operated young and adult gerbils had similar numbers of neurons (294 ± 33 and 277 ± 26 neurons/mm^2, respectively). The average neuronal densities after 15 min of ischemia followed by 48 h or 7 days of recirculation in the CA1 subfield of young animals (72 ± 8% and 79 ± 9% of control, respectively) were not significantly different from sham-operated controls. In adult gerbils subjected to the same period of ischemia and reperfusion, extensive neuronal damage in the CA1 subfield was observed at both 48 h or 7 days of recirculation (34 ± 9% and 26 ± 4% of control, respectively). A photomicrograph depicts the neuronal loss in adult compared with young CA1 hippocampus following ischemia (15 min) and 7 days reperfusion (Fig. 2).

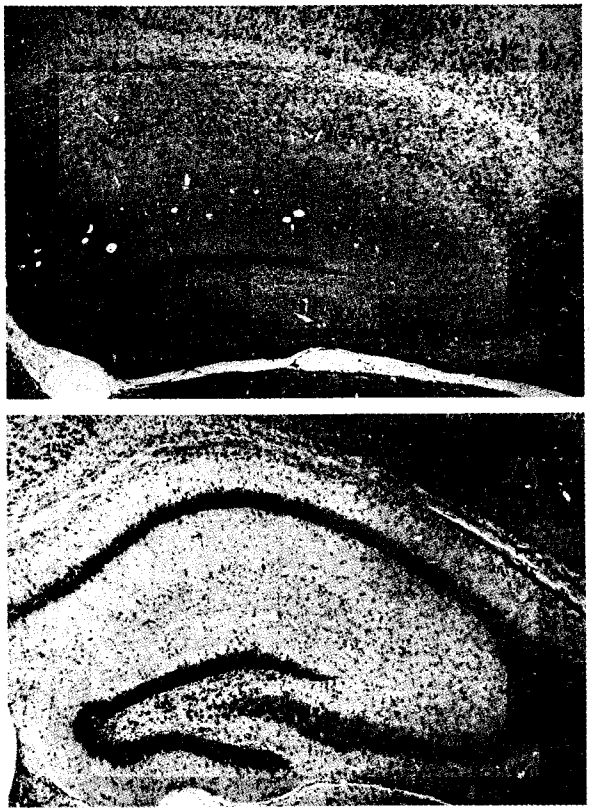

Fig. 2. Effect of ischemia/reperfusion on neuronal integrity of hippocampal CA1 in young and adult animals. Animals were subjected to ischemia (15 min)/reperfusion (7 days) as described in Materials and Methods. The photomicrograph shows a marked loss of neurons in adult CA1 hippocampus (*upper panel*) and no significant loss of neurons in young CA1 hippocampus (*lower panel*)

Discussion

The results of this study clearly indicated that the overall induction of HSC70, HSP72 and c-fos mRNA expression in the CA1 subfield of the hippocampus was greater in young gerbils than in adult gerbils subjected to identical insults. In addition, a more rapid and prolonged expression of HSC70 and HSP72 mRNA was observed in young animals; c-fos mRNA expression was also more prolonged in young animals. This response to ischemia was associated with a marked induction of HSP72 protein and survival of pyramidal cells.

The 70 kDa HSPs family consists of constitutive and inducible members that have multiple roles. They act as molecular chaperones and have been implicated in protein synthesis, degradation, and transport [5, 7, 12, 23, 29, 32]. Under normal physiological conditions, the cognate HSC70, unlike the inducible HSP72, is not expressed in the mammalian brain. Both HSC70 and HSP72 can be induced by

cerebral ischemia, seizures and hyperthermia [14, 21, 33]. Interactions between HSP72 and HSC70 have been implicated in neuronal protection against ischemic injury [1, 13, 28]. Although both HSC70 and HSP72 mRNAs and their respective proteins have been extensively studied following focal and global ischemia [21, 25, 27], their precise functions in the post-ischemic brain remain controversial. Early in vivo studies suggested that the induced HSP72 protein might be considered a putative marker of neuronal injury [31]. Other in vivo experiments indicated that HSP72 protein is involved in ischemic tolerance induced by sublethal ischemic preconditioning [3, 4]. The observations described here show that neuroprotection is associated with HSP72 and/or HSC70 proteins. This indicates that these factors may contribute to the apparent tolerance of young animals to ischemia. In particular, the observed shift in HSP72 mRNA induction in the CA1 hippocampus to an earlier period of reflow in young gerbils may indicate its important role in ischemic resistance. These findings are supported by reports that an accelerated induction of HSP72 mRNA was seen in gerbil hippocampal neurons made tolerant to ischemia by preconditioning [3, 4, 16].

A slight decrease in the HSP72 mRNA expression in adult gerbils was observed at the same time as the increased expression in young gerbils (i.e., 48 h of reperfusion). This may indicate that the CA1 neurons of young, but not adult, gerbils still had transcriptional capabilities. Ischemic resistance of young CA1 neurons might therefore be attributed to the enhanced ability of young CA1 neurons to synthesize HSP72 proteins. This may or may not have been associated with the more pronounced induction of HSP72 mRNA.

In addition to HSP72 mRNA, HSC70 mRNA might be involved in the induction of ischemic tolerance observed here. The constitutive expression of HSC70 mRNA (and HSC70 protein) was greater in young gerbils than in adult gerbils. In addition, a strong induction of HSC70 mRNA was observed in young gerbils, following ischemia. Interestingly, this was associated with a significant decrease in HSC70 protein synthesis. The great difference between these responses and those seen in adults (slight increase in both mRNA and protein levels) suggests that HSC70 may be an important element in age-dependent tolerance.

The proto-oncogene c-fos was one of the first immediate early genes discovered. It belongs to multigene families that are known to mediate gene regulation to a wide variety of stimuli (e.g., neurotransmitters, trophic signals, oxidative stress, etc.) [18]. Cerebral ischemia is also a well-known stimulator of c-fos, which has been demonstrated in animals subjected to either focal or global arrest of blood flow to the brain [15, 24]. The ischemic induction of c-fos mRNA was demonstrated in both vulnerable and resistant regions and its localization depended on the model of ischemia. Nevertheless, there is a consensus regarding the temporal and spatial detection of c-fos mRNA in the hippocampus following transient global ischemia in adult animals [15]. These studies demonstrated that the highest level of c-fos mRNA expression at 1 h of recirculation was seen in the dentate gyrus followed by CA3 and CA1 subfields. A decline in c-fos gene expression was seen at 3 h, and expression returned to control levels at subsequent time points of investigation following transient global ischemia (5 min) and reperfusion [15]. The data presented here concerning the transcription of c-fos in the hippocampal CA1 subfield are in agreement with the above reported studies (results of other sub-

fields are not shown here). On the other hand, adult rats subjected to four-vessel occlusion showed the highest level of c-fos mRNA in CA1 at 3 h of recovery, with subsequent decline and return to basal level at 12–24 h [24]. This discrepancy is most likely due to differences in the ischemic models. Likewise, the comparison of the present results observed in young gerbils to those reported in the literature is rather difficult since most of those results were obtained in neonatal brains of rats subjected to hypoxia/ischemia [10]. Blumenfeld et al. [6] studied age-dependent changes in c-fos and HSP72 in hypoxia and unilateral ischemia of immature rats. They described an occasional delayed increase of c-fos in CA1 of adult hippocampus accompanied by strong HSP72 mRNA expression in the entire hippocampus area ipsilateral to carotid artery occlusion in 23-day-old rats. Nonetheless, the continuous rise of c-fos mRNA up to 8 h as demonstrated here has not been previously reported. Most importantly, the results here underline the different response (i.e., significantly greater increase) of c-fos mRNA expression to transient ischemia in CA1 of young and adult gerbils.

In summary, an earlier expression of HSC70 and HSP72 mRNA (and sustained expression of these as well as c-fos mRNA) was observed in young animals' responses to ischemia. These findings were associated with a marked induction of HSP72 protein and pyramidal cell survival. The observed endogenous 'tolerance' of CA1 neurons in young gerbils to ischemia/reperfusion injury may be related to the expression of these genes.

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