STRESS-INDUCED PHOSPHORYLATION OF C-JUN-N-TERMINAL KINASES AND NUCLEAR TRANSLOCATION OF HSP70 IN THE WISTAR RAT HIPPOCAMPUS

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Abstract — Glucocorticoids are key regulators of the neuroendocrine stress response in the hippocampus. Their action is partly mediated through the subfamily of MAPKs termed c-Jun-N-terminal kinases (JNKs), whose activation correlates with neurodegeneration. The stress response also involves activation of cell protective mechanisms through various heat shock proteins (HSPs) that mediate neuroprotection. We followed both JNKs and Hsp70 signals in the cytoplasmic and nuclear compartments of the hippocampus of Wistar male rats exposed to acute, chronic, and combined stress. The activity of JNK1 was decreased in both compartments by all three types of stress, while the activity of cytoplasmic JNK2/3 was elevated in acute and unaltered or lowered in chronic and combined stress. Under all stress conditions, Hsp70 translocation to the nucleus was markedly increased. The results suggest that neurodegenerative signaling of JNKs may be counteracted by increase of nuclear Hsp70, especially under chronic stress.

Key words: Wistar rat, neuroendocrine stress, hippocampus, JNK, Hsp70

INTRODUCTION

The hippocampus (HIPPO) is a part of a mammalian limbic brain that plays a crucial role in the response to neuroendocrine stress by mediating feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis (Sapolsky et al., 1986). Stress hormones adapt and modulate brain functions by changing the structure of neurons, but they may also influence neuronal damage or suppress neurogenesis and cell survival (Czeh et al., 2001). Apart from the glucocorticoid receptor, which is the main molecular regulator of the feedback response, mitogen-activated protein kinases (MAPKs) are also sensitive to stress and activated by it (Meller et al., 2003).

The MAPKs are widely distributed throughout the brain and have important roles in regulation of synaptic plasticity, memory formation, and neurotransmission (Sweatt, 2001). The c-Jun-N-terminal kinase (JNK) subfamily belongs to the MAPKs and is comprised of three isoforms (JNK1, JNK2, and JNK3). In response to external stimulation, activated JNKs phosphorylate numerous transcription factors, including c-jun (Whitmarsh et al., 1996) and activating transcription factor 2 (Gupta et al., 1995), enhancing their transcriptional activity and thereby influencing a wide range of cellular signals. Moreover, activated JNKs have been mainly considered as degenerative signal transducers and efficient activators of apoptosis in the nervous system (Waetzig et al., 2004). The molecular mechanism by which JNKs channel prodegenerative signals is mediated through activation of pro-apoptotic molecules, inactivation of anti-apoptotic molecules, and pathological release of cytochrome c (Putcha et al., 2003; Schroeter et al., 2003).

To prevent cellular damage, cells activate the transcription of heat shock proteins (HSPs) which ensure the coordinated regulation of protein translocation, import, and folding (Clarke, 1996) and limit cellular damage by their ability to prevent protein aggregation and restore the function of denatured proteins (Parsell et al., 1993). As a member of the HSP family, Hsp70 is also activated by stress.

Moreover, Hsp70 mediates neuroprotection, and its overexpression was shown to protect hippocampal neurons from cytotoxic effects of stress (Beaucamp et al., 1998). One of the mechanisms through which Hsp70 prevents cytotoxic stress effects is by its ability to suppress JNK activation (Gabai et al., 1997; Mosser et al., 1997), thus inhibiting the pro-apoptotic signals mediated by JNKs (Tournier et al., 2000).

Considering the opposite roles of JNKs and Hsp70 in regulation of the stress response, we studied expression levels of these proteins and their cytoplasmic-nuclear translocation in the hippocampus of Wistar male rats exposed to acute, chronic, or combined neuroendocrine stress.

MATERIALS AND METHODS

Animal care and treatment

All experiments were performed on adult (3-month-old) Wistar male rats (body mass 330-400 g) housed in four per standard-size cages and offered food (commercial rat pellets) and water *ad libitum*. Light was kept on between 07.00 am and 07.00 pm, and room temperature (RT) was kept at $20 \pm 2°C$. For the stress experiments, animals were divided into four groups: group I consisted of unstressed animals (control group); group II animals were exposed to acute immobilization for 30 min; group III animals were subjected to chronic isolation stress by housing them individually for 21 days; and group IV was exposed to chronic isolation for 21 days, followed by 30-min immobilization.

Preparation of cytoplasmic and nuclear extracts

Animals were sacrificed by rapid decapitation and the hippocampus (HIPPO) area was removed and immediately frozen in liquid nitrogen until further preparation. Frozen tissues were weighed and homogenized (1: 2 = tissue mass:vol) in ice-cold 20 mM Tris-HCl (pH 7.2) buffer containing 10 % glycerol, 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 2 mM DTT, and protease inhibitors (20 mM Na_2MoO_4, 0.15 mM spermine, 0.15 mM spermidine, 0.1 mM PMSF, 5 µg/ml antipain, 5 µg/ml leupeptin, 5 µg/ml aprotinin, 10 µg/ml trypsin inhibitor, and 3 mM benzamidine) and phosphatase inhibitors (20 mM

β-glycerophosphate, 5 mM $Na_4P_2O_7x10H_2O$, 2 mM Na_3VO_4, and 25 mM NaF) by 20 strokes of a Potter-Elvehjem teflon-glass homogenizer. Samples were centrifuged for 10 min at 2,000 g at 4°C, the supernatants were ultracentrifuged for 1 h at 105,000 g and the final supernatants were used as the cytoplasmic fraction. Pellets were washed (three times) in 0.5 ml of homogenization buffer and centrifuged for 10 min at 2,000 g at 4°C. The final pellets were weighed, resuspended (1: 1 = mass: vol) in the same buffer supplied with 0.5 M KCl, incubated for 1 h in an ice-bath (with frequent vortexing), and centrifuged for 10 min at 8,000 g at 4°C. The supernatant was used as a nuclear extract (Spencer et al., 2000).

Corticosterone assay

Blood from each animal was collected at the time of sacrifice. Serum was prepared by 15-min centrifugation at 3,000 rpm. The corticosterone (CORT) level was determined using the OCTEIA Corticosterone EIA kit according to the manufacturers' instructions (American Laboratory Products Co.). Absorbance at 450 nm (reference 650 nm) was determined with a microplate reader (Wallac, VICTOR² 1420, PerkinElmer). The CORT concentration (ng/ml) was determined using a standard curve.

Western blot detection of JNKs and their phosphorylated isoforms

Protein concentration in cytoplasm and nuclear fraction was determined by the method of Lowry et al. (1951). The samples were mixed with denaturing buffer according to Laemmli (Laemmli, 1970) and boiled for 5 min at 100°C, after which 60 µg of protein was subjected to electrophoresis on 7.5% sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE). Subsequently, proteins were transferred onto a PVDF membrane (Immobilon-P membrane, Millipore) using a blot system (Transblot, BioRad) and further probed with appropriate antibodies. The signal was developed using an enhanced chemiluminescence reagent (ECL, Pierce) and exposed to X-ray film. Anti-human JNK1/JNK2 monoclonal antibody (BD, PharMingen) was used to detect total JNK, phospho-SAPK/JNK (Thr183/Tyr185) antibody (Cell Signaling) to detect phosphorylated

JNK, and Hsp70 (N27F3-4) antibody (Santa Cruz Biotechnology) to detect Hsp70. β-actin, which was used as a loading control, was detected using rabbit polyclonal anti-β-actin (ab8227, Abcam). Densitometry of protein bands on X-ray film was performed using Image J Analysis PC software.

Statistical analysis

Data are presented as means ± SEM from four to six independent measurements. Data were analyzed by one-way ANOVA followed by the Tukey *post hoc* test. Values were considered statistically significant if the p value was less than 0.05.

RESULTS

Corticosterone level in different stress conditions: Given that the level of corticosterone (CORT) in the blood serum is the major determinant of the stress response of the HPA axis, we measured its concentration in each of the Wistar male rats subjected to different stress conditions using a commercial CORT kit (Table 1). As expected, acute (30-min) exposure to high-intensity physical-emotional-psychosocial stress such as that caused by immobilization resulted in a significant increase of serum CORT levels. Contrary to this, chronic isolation for 21 days (low-intensity but long-term psychosocial stress) led to a significant decrease of CORT serum levels. When the chronically stressed animals were subsequently subjected to acute immobilization (i.e., combined stress), serum CORT increased to a level similar to that observed after acute stress (Table 1). The results shown in Table 1 indicate that acute and combined stress result in a major increase, whereas chronic stress led to a significant decrease of CORT concentration in the blood serum.

Effect of stress on JNK activity: We estimated JNK1 (46 kDa) and JNK2/3 (54 kDa) activity by following their phosphorylation at residues Thr183/Tyr185, which are crucial for activation of these kinases in the cytoplasmic and nuclear fractions of the HIPPO under stress (Figs. 1a and 1b). The ratio of pJNK1 to (total) tJNK1 (pJNK1/tJNK1) indicates that cytoplasmic and nuclear JNK1 phosphorylation was low in all types of stress in relation to the control. Only in the case of acute stress was the phosphorylation of nuclear JNK1 not significantly changed (Figs. 1b and 1d). In contrast, the activation of cytoplasmic JNK2/3 was markedly increased in acute stress, while it was unaltered or lower in other types of stress (Figs. 1a and 1c).

Effect of stress on Hsp70: In parallel with JNK activity, we investigated cytoplasmic and nuclear levels of Hsp70 in acute, chronic, and combined stress. The cytoplasmic level of Hsp70 was significantly decreased under all stress conditions (Figs. 2a and 2c). Increase in the nuclear level of Hsp70 indicated its cytoplasmic-nuclear translocation in all three types of stress, the most prominent elevation occurring under chronic stress (Figs. 2b and 2c).

DISCUSSION

It has been postulated that regulation of the adaptive vs. the maladaptive CNS response to stress involves multiple cellular signaling pathways (Chrousos et al., 2007). Activation and feedback at the level of the HPA axis are crucial steps in the response to

Table 1. Stress-induced changes in serum corticosterone level of Wistar males: The total number of animals in each experimental group [control (Ctrl), acute (A), chronic (C) or combined stress (C+A)] is indicated above, while means ± SEM for serum corticosterone are given below. Differences are statistically significant at **p<0.01 and ***, ###p<0.001 (* stress vs. control, # acute vs. chronic or combined).

Treatment → Parameter ↓	Control (Ctrl)	Acute (A) immobilization	Chronic (C) isolation	Combination C+A
Number of animals	15	15	15	15
Corticosterone (*ng/ml*)	136.8 ± 9.5	626.9 ± 25.9***,###	64.7 ± 6.9**	601.2 ± 20.1***,###

a

Cytoplasm

Control   Acute   Chronic   Combined

pJNK

tJNK

ß-actin

b

Cytoplasm

Control   Acute   Chronic   Combined
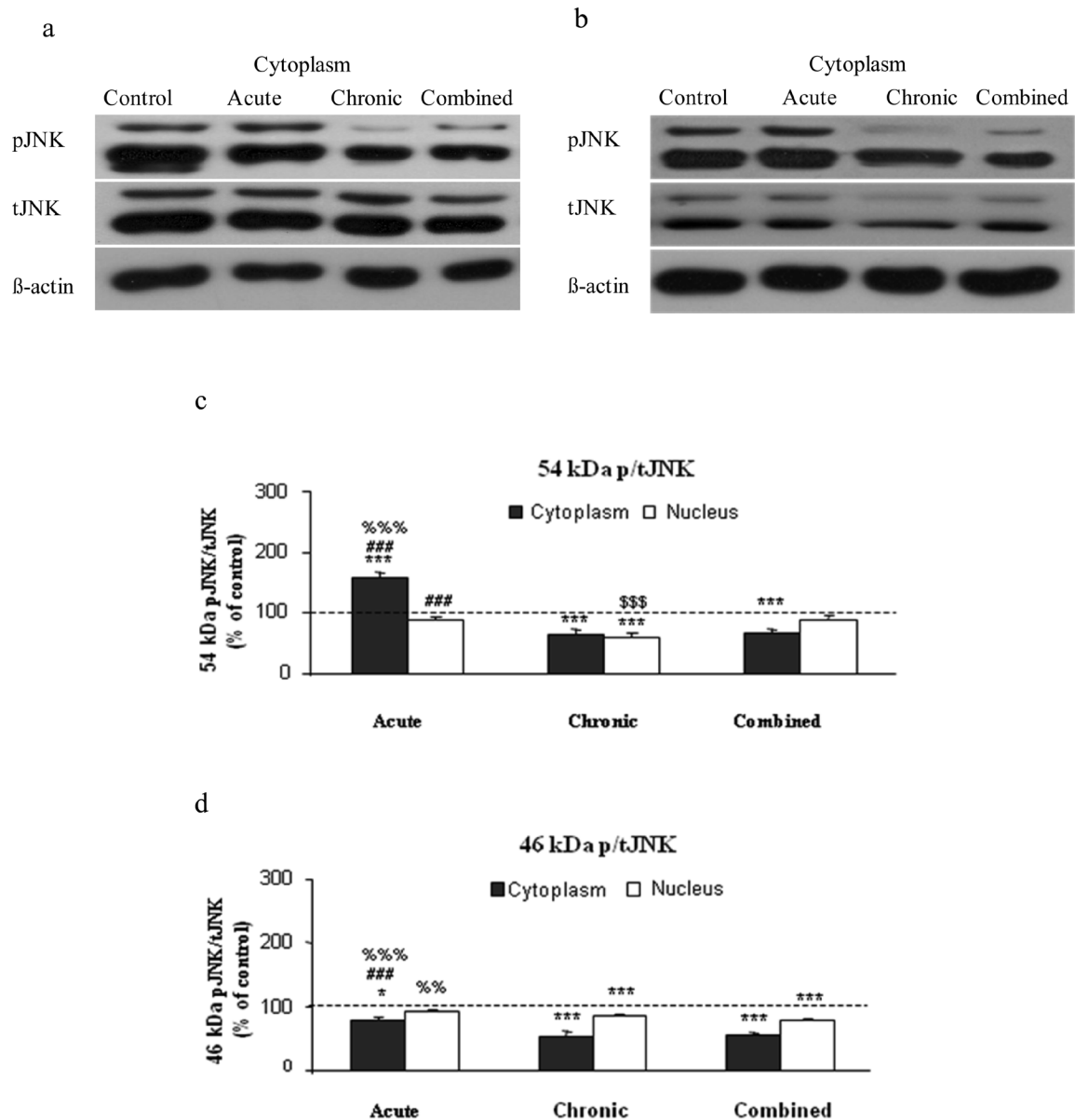
pJNK

tJNK

ß-actin

c

d

Fig. 1. Western blot experiment demonstrating the effects of acute, chronic, or combined stress on the total level of JNKs (tJNK1 at 46 kDa and tJNK2/3 at 54 kDa) and their respective phosphoisoforms (pJNKs) in the cytoplasm (a) and nucleus (b) of the Wistar rat hippocampus. Immunoreactivities of JNKs are quantified and given as the 54 kDa pJNK/tJNK (c) or 46 kDa pJNK/tJNK (d) ratio, presented as means ± SEM (n=4-6). Differences are statistically significant at *p<0.01, **p<0.01, and ***p<0.001 (* stress vs. control, # acute vs. chronic, $ chronic vs. combined, % acute vs. combined).

stress, and adrenal glucocorticoids (GCs) are important effectors in this system (Munck et al., 1984). The action of GCs are coordinated with the activity of several other stress-sensitive systems, such as mitogen-activated protein kinases (MAPKs) (Meller et al., 2003) and heat shock proteins (HSPs) (Parsell et al., 1993). For example, members of the subfamily of MAPKs termed JNK1 and JNK3 kinases – which are associated with CNS development or neuronal apoptosis and degeneration, respectively (Waetzig et al., 2004) – are both of great importance for GC signaling under stress (Adžić et al., 'under review').
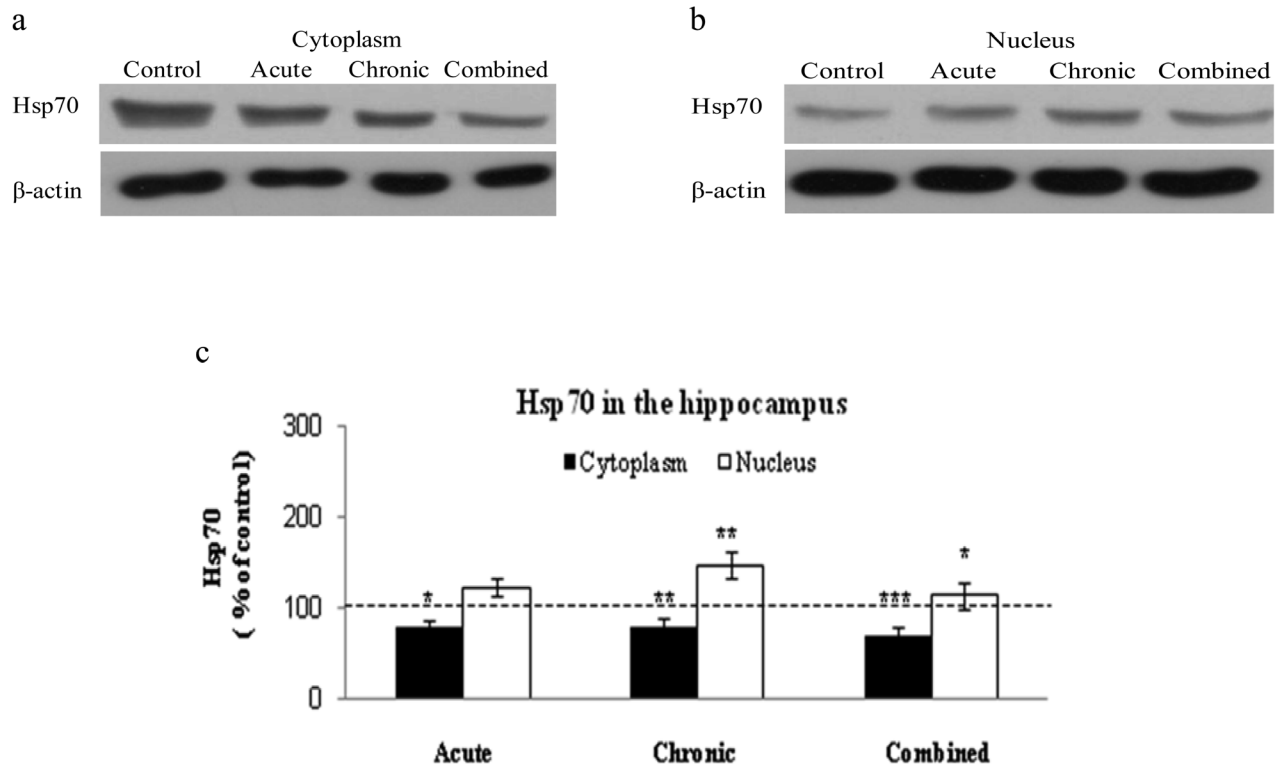
Fig. 2. Western blot experiment demonstrating the effects of acute, chronic, or combined stress on the level of Hsp70 in the cytoplasm (a) and nucleus (b) of the Wistar rat hippocampus. Immunoreactivity of Hsp70 is quantified (c) and presented as means ± SEM (n=4-6). Differences are statistically significant at *$p<0.01$, **$p<0.01$, and ***$p<0.001$ (* stress vs. control).

In response to stress, cells also rapidly activate heat shock proteins (HSPs)**, among which Hsp70 has been associated with inhibition of cell death** by apoptosis (Beere et al., 2001). The interactions between these two opposing pathways, the JNKs and the HSPs, can be viewed as determinants of the biological consequences of stress, i.e., adaptation vs. maladaptation.

Taking into account that the hippocampus, as a part of the brain "limbic system", is included in regulation of HPA axis activity and presents the primary neuronal target for the GC feedback reaction (also involving the JNK and HSP pathways), we characterized the effects of brief (acute immobilization), prolonged (21-day isolation), and combined stress on corticosterone (CORT) levels in the blood

serum and on activation of JNK1, JNK2, JNK3, and Hsp70 in the cytoplasm and nucleus of the rat hippocampus.

Our results showed that acute immobilization induces a 4.5-fold increase in the level of blood serum CORT, which is considered as a 'normal' CNS stress response (McEwan, 1998) (Table 1). Long-term social isolation was used as a possible maladaptive chronic stress, and we found a low level of CORT in the blood serum of isolated animals. This finding is in accordance with other authors' published observations showing HPA axis hypoactivity in stress conditions caused by isolation (**Malkesman et al., 2006**). Finally, the ability to retain 'normal' stress signaling after chronic stress was approached by a combination of the two models mentioned

above. We found increased CORT in combined stress, which indicated that HPA axis activity was not terminally compromised by the previous experience of chronic stress and could be resumed after subsequent acute stress (Table 1).

In this respect, our results showed reduced JNK1 activity in both cytoplasmic and nuclear compartments of the HIPPO in chronic and combined stress (Fig. 1). This finding is consistent with the notion that JNK activity is negatively regulated by high CORT levels in the above-mentioned treatments. However, we also observed induction of JNK2/3 activity in HIPPO under acute stress, which is in agreement with recently published reports indicating activation of JNK in these conditions (Shen et al., 2004). In chronic stress, despite low levels of CORT, JNK function is diminished, indicating that other pathways may regulate JNK, perhaps through Akt signaling and reactive oxygen species (ROS).

Because JNK2/3 isoforms are activated in hippocampal formations that play a critical role in learning and memory (Eichenbaum, 2001), it is possible that the JNK signaling pathway may also be involved in the formation of emotional memory, which is especially associated with acute stress. The rapid activation of JNK2/3 isoforms in response to acute stress could be explained by non-genomic effects of GCs through corticosteroid membrane receptors that activate a PKC-dependent signaling mechanism and phosphorylation of MAPK family members (Tasker et al., 2006). On the other hand, the low JNK activity under chronic stress may reflect activation of genomic effects of GCs through the GR, which transcriptionally regulates MAPK phosphatase-1 (MKP-1) (Clark et al., 2003), or through non-transcriptional mechanisms mediated by direct GR-JNK interactions (Bruna et al., 2003). The changes in activity of JNK2/3 isoforms in the hippocampus correlates with blood serum CORT variations, which indicates that these changes could be either cause or consequence of CORT variations, suggesting possible mutual regulation of hippocampal JNK2/3 phosphorylation and the serum CORT level.

These reports prompted us to investigate in addition to JNK, Hsp70 as a possible protective element and its subcellular distribution in the HIPPO in response to stress. Our results indicated that hippocampal cytoplasmic Hsp70 was decreased by all three stresses in a stress-type–independent manner. Contrary to this, nuclear Hsp70 in the HIPPO revealed stress-type dependence, since under low CORT its level was significantly elevated. The prevalence of Hsp70 in the nuclear compartment obtained in our experiments could indicate specific nuclear roles for it, roles such as **possible** regulation of steroid receptor (i.e., glucocorticoid receptor) binding to the promoter or removal from it and enhancement of nuclear mobility of steroid receptors, thus influencing transcriptional activity (Stavreva et al., 2004; Elbi et al., 2004). These results are in accordance with observations from our laboratory indicating elevated GR phosphorylation at serine 232, which activates transcriptional activity of the GR in the nuclear compartment of the HIPPO under chronic stress, implying the possibility of its stabilization at GREs by HSPs (Adžić et al., 'under review'). Considering the fact that GR transcriptionally regulates MAPK phosphatase-1 (MKP-1) and that low activity of JNK2/3 isoforms is found under chronic stress, it seems that the mechanism of downregulation of JNK2/3 may possibly involve stabilization of the GR with Hsp70 in the nuclear compartment of the HIPPO.

To sum up, decreased activity of almost all JNK isoforms in both cell compartments under all types of stress could lead to interruption of JNK signaling, which may influence neurodegeneration or neural cell remodeling (neural plasticity), especially in response to chronic stress. On the other hand, nuclear translocation of Hsp70 could represent a possible adaptive mechanism countering JNK action in stress situations.

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ФОСФОРИЛАЦИЈА C-JUN-ТЕРМИНАЛНИХ КИНАЗА И НУКЛЕАРНИ ТРАНСПОРТ HSP70 ПРОТЕИНА У ХИПОКАМПУСУ WISTAR ПАЦОВА ИЗЛОЖЕНИХ СТРЕСУ

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Глукокортикоиди су кључни регулатори одговора хипокампуса на неуроендокрини стрес. Њихово деловање је повезано са активацијом подфамилије митоген-активираних киназа (MAPK), названом c-Jun-N-терминалне киназе (JNK) чија активација корелише са појавом неуродегенерације. Одговор на стрес такође укључује активацију ћелијских протективних механизама преко чланова протеина топлотног шока (HSP) који су медијатори неуропротекције. У овом раду пратили смо сигнале JNK и Hsp70 у цитоплазми и једру хипокампуса Wистар пацова који су излагани акутном, хроничном или комбинованом стресу. Активност JNK1 смањивала се у оба ћелијска компартмана под деловањем сва три стреса, али је активност JNK2/3 у цитоплазми расла у акутном стресу и била је или непромењена или снижена у хроничном и комбинованом стресу. Истовремено у условима сва три стреса запажена је значајно повишена транслокација Hsp70 у једро. Наши резултати указују на могућност да је пронеуродегенеративна сигнализација JNK у наведеним стресним условима уравнотежена присуством повећане количине Hsp70 у једру ћелија хипокампуса, што је нарочито испољено у хроничном стресу.