Heat shock protein expression protects against cerebral ischemia and monoamine overload in rat heatstroke

YI-LING YANG1 AND MAO-TSUN LIN2
1Department of Physiology, National Cheng-Kung University Medical College, Tainan, Taiwan 701; and 2Department of Physiology, National Yang-Ming University, Medical College, Taipei, Taiwan 11221

Yang, Yi-Ling, and Mao-Tsun Lin. Heat shock protein expression protects against cerebral ischemia and monoamine overload in rat heatstroke. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H1961–H1967, 1999.—This study attempted to ascertain whether the ischemic damage to neurons and monoamine overload in brain that occur during rat heatstroke can be attenuated by heat shock protein (HSP) 72 induction. Effects of heatstroke on mean arterial pressure (MAP), cerebral blood flow (CBF), brain dopamine (DA) and serotonin (5-HT) release, and neural damage score were assayed in rats 0, 16, or 48 h after heat shock (42°C for 15 min) or chemical stress (5 mg/kg sodium arsenite ip). Brain HSP 72 in rats after heat shock or chemical stress was detected by Western blot, and brain monoamine was determined by a microdialysis probe combined with high-performance liquid chromatography. Heatstroke was induced by exposing the animal to a high ambient temperature (43°C); the moment at which MAP and CBF decreased from their peak values was taken as the time of heatstroke onset. Prior heat shock or chemical stress conferred significant protection against heatstroke-induced hyperthermia, arterial hypotension, cerebral ischemia, cerebral DA and 5-HT overload, and neural damage and correlated with expression of HSP 72 in brain at 16 h. However, at 48 h, when HSP 72 expression returned to basal values, the above responses that occurred during the onset of heatstroke were indistinguishable between the two groups (0 h vs. 48 h). These results lead to the hypothesis that the brain can be preconditioned by thermal or chemical injury, that this preconditioning will induce HSP 72, and that HSP 72 induction will correlate quite well with anatomic, histochemical, and hemodynamic protection in rat heatstroke.

Microdialysis; heat shock; chemical stress; dopamine; serotonin

HEATSTROKE, a very serious disease in medical emergency, has been studied extensively by many investigators (34). Our previous studies (8, 14, 33) demonstrated that cerebral ischemia rather than hyperthermia is the main reason for the central nervous system dysfunction that occurs during heatstroke. Evidence has also accumulated to suggest that marked activation of the nigrostriatal dopaminergic (8, 16) or serotoninergic (5, 9) systems is associated with ischemic neuronal damage during heatstroke. Destruction of brain dopaminergic (16) or serotoninergic (9) pathways protects against ischemic neuronal injury in heatstroke in rats.

There is mounting evidence that neurons produce heat shock protein (HSP) in response to a variety of environmental stresses, resulting in protection from subsequent lethal damage (29, 32, 36–38). HSP 72 induction increases the number of surviving neurons in rat hippocampal neuron primary culture as well as the tolerance of hippocampal neurons to ischemic injury (10, 19, 30). This raises the possibility that pretreatment that increases brain HSP 72 content before heatstroke may limit the development of arterial hypotension, cerebral ischemia, cerebral monoamine overload, and neuronal damage that occur during the onset of heatstroke (12).

To address the question properly, in the present study we compared the temporal profiles of mean arterial pressure (MAP), cerebral blood flow (CBF), brain dopamine (DA) and serotonin (5-HT) release, and neuron damage score in rats with or without brain HSP 72 expression in heatstroke.

MATERIALS AND METHODS

HSP 72 induction. HSP expression was induced in male Wistar rats (Animal Resource Center, National Science Council, Taipei, Taiwan, ROC) weighing 250–300 g by either heat shock (39) or chemical stress (28). For heat shock treatment, rats under general anesthesia (1 h after 40 mg/kg pentobarbital sodium ip) were heated gently with an electric pad. The colonic temperature of the heated animals was kept at 42 ± 0.5°C for 15 min. They were returned to room temperature during the recovery period. For chemical stress treatment, the unanesthetized rats were treated with sodium arsenite (5 mg/kg ip). These groups of animals were subjected to heatstroke experiments at 0, 4, 8, 16, or 48 h after the start of heat shock or chemical stress treatment.

HSP 72 detection. The animals were killed by decapitation at the end of the experiment for detection of HSP 72. The brains were quickly removed and stored at 0°C. The corpus striatum was dissected from the brain and placed into Eppendorf tubes. For protein extraction, the samples were weighed, rapidly thawed in 6 vols of homogenizing buffer consisting of 20 mM Tris·HCl (pH 7.6), 100 mM KCl, 5 mM NaCl, 2 mM EDTA, 1 mM EGTA, 0.25 M sucrose, 2 mM dithiothreitol, and 2 mM phenylmethylsulfonyl fluoride at pH 7.2, and then homogenized by a sonicator. After centrifugation at 5,000 g for 15 min at 4°C, the protein assay was carried out by the Bradford method. The samples (40 µg/lane) were incubated for 5 min at 95°C in Laemmli buffer, separated on 10% SDS-polyacrylamide discontinuous gel, and then electrophoretically transferred to a polyvinylidene difluoride membrane. The membrane was blocked for 1 h at room temperature with PBS containing 10% skim milk. Mouse monoclonal antibodies against HSP 72 (Oncogene Science) were used as primary antibodies (1:1,000 dilution). Incubation time with the primary antibody at room temperature was 1 h. Band detection was performed with an enhanced chemilumines-

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ence Western blotting analysis system (RPN 2108; Amer-

sham International, Amersham, UK).

Heatstroke induction. Six groups of animals were used: 1)

rats 0 h after heat shock; 2) rats 16 h after heat shock; 3) rats

48 h after heat shock; 4) rats 0 h after chemical stress; 5) rats

16 h after chemical stress; and 6) rats 48 h after chemical

stress. Under urethane (1.4 g/kg ip) anesthesia, the femoral

terary of these animals was cannulated with polyethylene

tubing (PE-50) for measurement of systemic arterial blood

pressure and heart rate. Pulsatile arterial pressure, MAP,

and heart rate were monitored continuously with a pressure

transducer and a chart recorder (model 2400, Gould). The

animals were then placed in a Kopf stereotaxic frame (Grass)

in the flat skull position. A flow probe was implanted into the

right corpus striatum using the atlas and coordinates of

Paxinos and Watson (24) for measurement of CBF. At the

same time, for measurement of extracellular monoamine

release a microdialysis probe was implanted stereotaxically

into the left corpus striatum. Heatstroke was induced by

exposing these groups of animals to an ambient temperature

of 43°C; the moment in which MAP and CBF began to

decrease from their peak levels was taken as the onset of

heatstroke (8, 16; see Fig. 2). All experimental protocols were

approved by the Animal Research Committee of the Yang-

Ming University School of Medicine. Adequate anesthesia

was maintained in the animals after administration of ure-

thane (1.4 g/kg ip). At the end of the experiments, the animals

were killed for evaluation of neuron damage, HSP 72 detec-

tion, or histological verification of the path of the probes.

CBF measurement. CBF was monitored with a Laserflo

BPM2 laser-Doppler flowmeter (Vasamedic, St. Paul, MN). A

24-gauge stainless steel needle probe (diameter 0.58 mm,

length 40 mm) was implanted into the corpus striatum as

indicated in Heatstroke induction. The Laserflo BPM2 records

at a bandwidth of 30 Hz and a low band pass of 20 KHz. The

display is digital only, collects eight data points per second,

and was set to give a moving average of data every 0.3 s. Blood

perfusion was recorded until the flux value leveled off at a

stable reading, which usually occurred after ~1 min. That

value was then recorded and used as the flux measurement

for the period.

In addition, an autoradiographic technique was used to

quantify CBF in the corpus striatum (31). Approximately 50

µCi of [14C]antipyrine in 1 ml of normal saline were

infused at a constant rate via the femoral venous catheter for

a period of 1 min, during which time arterial samples were

collected on filter paper disks for assay of arterial concentra-

tion. At exactly 1 min, the animal was decapitated and the

brain was removed, frozen, and assayed for [14C] concentra-

tion by the autoradiographic technique. Autoradiographies of

sections from brain tissue were calibrated by dialysis of a known

amount of the

probes.

Figure 1, top, shows that heat shock (42°C body

temperature for 15 min), in the presence of an increase

in body temperature, induced HSP 72 expression in the

striatum that was detected 4 h after treatment, peaked

between 8 and 16 h, and returned to baseline by 48 h. In

this series of experiments, heat shock was conducted in

rats 1 h after intraperitoneal administration of pento-

barbital sodium. Normothermic control rats receiving

the same dose of pentobarbital sodium did not express

HSP 72 in the corpus striatum. Chemical stress (so-

dium arsenite injection), in the absence of an increase

in body temperature, also induced HSP 72 expression

in the corpus striatum that was detected 4 h after

injection, peaked between 8 and 16 h, and returned to

baseline by 48 h (Fig. 1, bottom). Every animal in the

sysis, Stockholm, Sweden), and a microbore reversed-phase

column was filled with Inertsil ODS-2 (GSK-C18, 5-mm OD,

150 × 1.0-mm ID). The performance of each microdialysis

probe was calibrated by dialysis of a known amount of the

standard mixture, and recovery of all analyses was then

determined. Brain concentrations of 5-HT and other mono-

amines were calculated by determining each peak height

ratio relative to the internal standard and were also corrected

by each probe performance. The internal standard 3-methoxy-

tyramine and standard mixtures were prepared fresh daily.

The mobile phase was prepared by adding 60 ml of acetoniti-

trile, 0.42 g of SDS (2.2 mM), 200 g of sodium citrate (30 mM),

10 mg of EDTA (0.027 mM), and 1 ml of diethylamine in

double-distilled water. The solution was adjusted to pH 3.5 by

concentrated orthophosphoric acid, and its final volume was

adjusted to 1 liter. We filtered the mixture with a 0.22-µm

nylon filter under reduced pressure and degassed it by

pumping helium gas for 20 min. The flow rate was 0.05–0.06

ml/min, maintaining column pressure at ~7.6 mPa.

In vitro tests were run to determine the recovery of 5-HT or

other monoamines in the dialysis solution at the flow rate

used. At room temperature, dialysis probes were immersed

in dialysis solution containing 5-HT or DA. At a flow rate of 1.35

µl/min, the relative recovery was 14 ± 1.4% (n = 8). Basal

monoamine levels were considered stable after observation of

four consecutive samples with no upward or downward trend.

These basal values were averaged, and all samples were

expressed as a percentage of the mean baseline to avoid large

variations in the abscissa values.

Evaluation of neuron damage and probe placement. In

separate experiments, 5 min after the onset of heatstroke rats

were killed, and brains were perfused, fixed in 10% neutral

Formalin, and embedded in paraffin blocks. Coronal sections

(6 µm) through the striatum were stained with hematoxylin

and eosin for microscope evaluation. Neuronal damage was

graded from the grading system of Pulsinelli et al. (26, 27) in

which 0 = normal, 1 = few neurons damaged, 2 = many

neurons damaged, and 3 = all neurons damaged. All probe

placements were in the regions of the corpus striatum as

verified by microscopic evaluation.

Statistics. The numerical values cited are means ± SE.

Repeated-measures analysis of variance was used for factori-

al experiments, whereas Duncan’s multiple-range test

(multi-time point experiments) was used for post hoc multiple

comparisons among means. Student’s t-test was used when

only two groups were compared. The criterion for statistical

significance was set at P < 0.05.

RESULTS

Figure 1, top, shows that heat shock (42°C body

temperature for 15 min), in the presence of an increase

in body temperature, induced HSP 72 expression in the

striatum that was detected 4 h after treatment, peaked

between 8 and 16 h, and returned to baseline by 48 h. In

this series of experiments, heat shock was conducted in

rats 1 h after intraperitoneal administration of pento-

barbital sodium. Normothermic control rats receiving

the same dose of pentobarbital sodium did not express

HSP 72 in the corpus striatum. Chemical stress (so-

dium arsenite injection), in the absence of an increase

in body temperature, also induced HSP 72 expression

in the corpus striatum that was detected 4 h after

injection, peaked between 8 and 16 h, and returned to

baseline by 48 h (Fig. 1, bottom). Every animal in the

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In the present study using a well-described rat model (12), we induced thermal or chemical preconditioning and clearly demonstrated production of HSP 72 in the brain at 16 h that returned to baseline at 48 h. Using preconditioned animals, we induced heatstroke to find that prior heat shock or chemical stress conferred significant protection against heatstroke-induced hyperthermia, arterial hypotension, striatal ischemia, striatal DA and 5-HT overload, and striatal neuronal damage. These results are consistent with previous findings that HSP 70 expression can alter the resistance of the heart (42) and the brain (4) to subsequent ischemic or nonischemic injury. With the loss of HSP 72 observed at 42 h, no further protection was induced in the preconditioned animals in our studies, this raises questions of hyperthermic insults, including the induction of other HSP as well as diverse physiological changes (32). Because the thermal insult is attenuated in the preconditioned animals in our studies, this raises

Table 1. Effects of heatstroke on colon temperature, mean arterial pressure, heart rate, striatal DA and 5-HT release, striatal blood flow, and survival time in rats with or without heat shock protein induction in striatum

<table>
<thead>
<tr>
<th>Groups</th>
<th>T&lt;sub&gt;co&lt;/sub&gt;, °C</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>DA, % baseline</th>
<th>5-HT, % baseline</th>
<th>SBF, % baseline</th>
<th>ST, min</th>
<th>HSP 72 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermic control rats</td>
<td>0 min before testing</td>
<td>36.5 ± 0.2</td>
<td>86 ± 2</td>
<td>331 ± 13</td>
<td>100 ± 4</td>
<td>100 ± 5</td>
<td>100 ± 4</td>
<td>&gt;300</td>
</tr>
<tr>
<td></td>
<td>80 min after testing</td>
<td>36.4 ± 0.2</td>
<td>83 ± 3</td>
<td>325 ± 17</td>
<td>101 ± 5</td>
<td>102 ± 4</td>
<td>98 ± 3</td>
<td></td>
</tr>
<tr>
<td>Rats 0 h after heat shock</td>
<td>70 min before HS onset</td>
<td>36.3 ± 0.3</td>
<td>90 ± 5</td>
<td>355 ± 19</td>
<td>100 ± 6</td>
<td>101 ± 7</td>
<td>102 ± 5</td>
<td>18 ± 6</td>
</tr>
<tr>
<td></td>
<td>10 min after HS onset</td>
<td>43.0 ± 0.3</td>
<td>45 ± 4</td>
<td>555 ± 22</td>
<td>636 ± 23</td>
<td>440 ± 39</td>
<td>32 ± 6</td>
<td></td>
</tr>
<tr>
<td>Rats 16 h after heat shock</td>
<td>70 min before HS onset</td>
<td>36.8 ± 0.7</td>
<td>88 ± 7</td>
<td>340 ± 21</td>
<td>108 ± 7</td>
<td>105 ± 9</td>
<td>103 ± 6</td>
<td>&gt;300†</td>
</tr>
<tr>
<td></td>
<td>10 min after HS onset</td>
<td>41.5 ± 0.7</td>
<td>85 ± 3</td>
<td>575 ± 40</td>
<td>106 ± 9</td>
<td>110 ± 10</td>
<td>106 ± 8</td>
<td></td>
</tr>
<tr>
<td>Rats 48 h after heat shock</td>
<td>70 min before HS onset</td>
<td>36.2 ± 0.5</td>
<td>96 ± 7</td>
<td>350 ± 21</td>
<td>105 ± 7</td>
<td>109 ± 9</td>
<td>105 ± 8</td>
<td>20 ± 8</td>
</tr>
<tr>
<td></td>
<td>10 min after HS onset</td>
<td>42.8 ± 0.4</td>
<td>42 ± 3</td>
<td>560 ± 35</td>
<td>648 ± 25</td>
<td>432 ± 40</td>
<td>35 ± 8</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE of 10 rats/group; nos. in parentheses denote no. of rats with heat shock protein (HSP) induction over total no. of rats tested. T<sub>co</sub>, colon temperature; MAP, mean arterial pressure; HR, heart rate; DA, dopamine; 5-HT, serotonin; SBF, striatal blood flow; ST, survival time; HS, heat stroke. *P < 0.05, significantly different from corresponding control values (70 min before HS onset), ANOVA; †P < 0.05, significantly different from corresponding control values (rats without HSP 72 expression), ANOVA.
Table 2. Effects of heatstroke on colon temperature, mean arterial pressure, heart rate, striatal DA and 5-HT release, striatal blood flow, and survival time in rats with or without striatal HSP 72 induction

<table>
<thead>
<tr>
<th>Groups</th>
<th>T_co °C</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>DA, % baseline</th>
<th>S-HT, % baseline</th>
<th>SBF, % baseline</th>
<th>ST, min</th>
<th>HSP 72 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats 0 h after chemical stress</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 min before HS onset</td>
<td>36.6 ± 0.4</td>
<td>87 ± 8</td>
<td>331 ± 24</td>
<td>106 ± 7</td>
<td>101 ± 6</td>
<td>100 ± 6</td>
<td>20 ± 4</td>
<td>Negative (0/6)</td>
</tr>
<tr>
<td>10 min after HS onset</td>
<td>42.7 ± 0.3*</td>
<td>47 ± 6*</td>
<td>568 ± 29*</td>
<td>609 ± 30*</td>
<td>450 ± 41*</td>
<td>34 ± 5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats 16 h after chemical stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 min before HS onset</td>
<td>36.7 ± 0.2</td>
<td>91 ± 5</td>
<td>338 ± 22</td>
<td>101 ± 6</td>
<td>102 ± 7</td>
<td>98 ± 5</td>
<td>&gt;300†</td>
<td>Positive (6/6)</td>
</tr>
<tr>
<td>10 min after HS onset</td>
<td>41.2 ± 0.4*</td>
<td>82 ± 5†</td>
<td>548 ± 23*</td>
<td>110 ± 7†</td>
<td>114 ± 6†</td>
<td>148 ± 9†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats 48 h after chemical stress</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
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<td>70 min before HS onset</td>
<td>36.6 ± 0.2</td>
<td>88 ± 7</td>
<td>351 ± 24</td>
<td>102 ± 8</td>
<td>100 ± 6</td>
<td>101 ± 6</td>
<td>19 ± 3</td>
<td>Negative (0/6)</td>
</tr>
<tr>
<td>10 min after HS onset</td>
<td>42.2 ± 0.4*</td>
<td>48 ± 7*</td>
<td>553 ± 27*</td>
<td>580 ± 26*</td>
<td>462 ± 39*</td>
<td>36 ± 5*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE of 6 rats/group; nos. in parentheses denote no. of rats with HSP induction over total no. of rats tested. *P < 0.05, significantly different from corresponding control values (70 min before HS onset), ANOVA; †P < 0.05, significantly different from corresponding control values (rats without HSP 72 expression), ANOVA.

the possibility that the resulting pathology would be less. Although tissue injury was formerly attributed to hyperthermia itself, it has recently been observed that normal volunteers heated passively and cancer patients treated with whole body hyperthermia can endure a rectal temperature of 41-42°C with no, or minimal, tissue injury (3, 25). Heatstroke can occur when the rectal temperature increases to only 40°C (1, 2).
Moreover, tissue injury continues to develop after cooling to normal body temperature in 25% of heatstroke patients (2, 7, 20, 34). Our previous results (5, 8, 9, 12, 14, 16, 33) further demonstrated that cerebral ischemia and overloading of DA and 5-HT in the brain, rather than hyperthermia, is the main reason for heatstroke formation in animals.

It has been shown that both intracranial hypertension (because of cerebral edema and cerebral vascular congestion) and arterial hypotension result in a reduction in cerebral perfusion pressure in animals with heatstroke (15, 33). Reduction of cerebral perfusion pressure to below the autoregulatory level will induce cerebral ischemia in animals with heatstroke (14). Our recent results (15) also showed that a decline in stroke volume or ventricular depolarization resulting from an increased plasma level of interleukin-1 is an important mechanism signaling arterial hypotension in rat heatstroke. Indeed, the heatstroke-induced arterial hypotension, intracranial hypertension, cerebral ischemia, cerebral DA and 5-HT overload, and cerebral neuronal damage were significantly attenuated by blockade of interleukin-1 receptors in rats (12, 18). Other lines of evidence showed that heat shock and chemical stress with heavy metal salts or sulfhydryl reagents, all of which induce the expression of HSP 70, concomitantly inhibit the production of interleukin and other cytokines in human monocytes and mouse macrophages activated by lipopolysaccharide (6). Putting these observations together, it seems that induction of brain HSP 72 by prior heat shock or chemical stress reduces the augmented production of interleukin-1 and other cytokines in the plasma and results in protection against heatstroke-induced arterial hypotension, cerebral ischemia, cerebral monoamine overload, and cerebral neuronal damage in rats.

Table 3. Effects of heatstroke on striatal neuronal damage score and striatal HSP 72 expression in rats pretreated with heat shock or chemical stress

<table>
<thead>
<tr>
<th>Groups</th>
<th>Striatal Neuronal Damage Score (0–3)</th>
<th>SBF, ml·100 g⁻¹·min⁻¹</th>
<th>HSP 72 Expression in Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermic controls 0 h after heat shock</td>
<td>0 (10)</td>
<td>138 ± 6 (10)</td>
<td>Negative (10)</td>
</tr>
<tr>
<td>16 h after heat shock</td>
<td>2.7 ± 0.2 (10)</td>
<td>18 ± 2 (10)</td>
<td>Negative (10)</td>
</tr>
<tr>
<td>48 h after heat shock</td>
<td>1.0 ± 0.3* (10)</td>
<td>160 ± 4* (10)</td>
<td>Positive (10)</td>
</tr>
<tr>
<td>0 h after chemical stress 16 h after chemical stress</td>
<td>2.5 ± 0.3 (10)</td>
<td>22 ± 3 (10)</td>
<td>Negative (10)</td>
</tr>
<tr>
<td>48 h after chemical stress</td>
<td>2.4 ± 0.4 (6)</td>
<td>20 ± 3 (6)</td>
<td>Negative (6)</td>
</tr>
<tr>
<td>0 h after chemical stress</td>
<td>1.2 ± 0.2* (6)</td>
<td>146 ± 16* (6)</td>
<td>Positive (6)</td>
</tr>
<tr>
<td>48 h after chemical stress</td>
<td>2.6 ± 0.4 (6)</td>
<td>24 ± 4 (6)</td>
<td>Negative (6)</td>
</tr>
</tbody>
</table>

Values are means ± SE for no. of rats in parentheses. *P < 0.05, significantly different from corresponding control values (rats without HSP 72 expression), ANOVA.

It should be stated that, after the onset of heatstroke, ischemic injury or monoamine overload was observed to occur in different brain structures including the corpus striatum, hypothalamus, cortex, and thalamus (8, 9, 17). In addition, prior heat shock was shown to induce...
HSP 72 induction in different brain structures (including corpus striatum, hypothalamus, cortex, and thalamus), liver, heart, and kidney (39, 40). In the present study, the corpus striatum was chosen as a representative region for measurement of HSP 72 induction, blood flow, and neuronal damage in rat heatstroke. However, it can be inferred from the present results that in addition to the corpus striatum, the mechanisms existing in other brain structures (such as the hypothalamus, cortex and thalamus) and vital organs are also responsible for these physiological consequences of preconditioning.

In fact, the processes involved in cell injury during ischemia and reperfusion are complex. The generation of free radicals, hydrogen peroxide, and cellular calcium overload are implicated in the process of ischemic neuronal damage (11, 23, 41). In this regard, many investigators demonstrated that HSP 70 induction by either heat shock or immobilization protects the rat or rabbit heart against the calcium overload triggered by calcium depletion-repletion (21, 22, 35). In a rat myocyte culture model, heat shock is capable of inducing acquired thermotolerance and limiting myocyte injury on subsequent H2O2 exposure (35). However, it is not known whether the same mechanisms can be applied to ischemia and reperfusion in the brain. The present results show that heat shock and chemical stress, which induce the expression in brain during heatstroke.

In summary, the present results show that heat shock and chemical stress, which induce the expression of HSP 72 in the brain, concomitantly inhibit the shock and chemical stress, which induce the expression in brain during heatstroke.

This work was supported by grants from the National Science Council of the Republic of China (NSC86-2745-B-010-005) and the Veterans’ General Hospital-National Yang-Ming University joint research program (VTY 88-p5–43), Tsou’s Foundation, Republic of China.

Address for reprint requests and other correspondence: M.-T. Lin, Dept. of Physiology, National Yang-Ming University Medical College, Taipei, Taiwan 11221 [E-mail: mtlin@ym.edu.tw].

Received 21 September 1998; accepted in final form 25 January 1999.

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