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Hypothermia-dependent and -independent effects of forced swim on the phosphorylation states of signaling molecules in mouse hippocampus

Yuriko Hayashi [a,b], Shinya Kusakari [a], Miho Sato-Hashimoto [a], Eriko Urano [a], Masahiro Shigeno [c], Tsuneo Sekijima [c], Takenori Kotani [d], Yoji Murata [d], Hirokazu Murakami [b], Takashi Matozaki [a,d], Hiroshi Ohnishi [a,*]

[a] Laboratory of Biosignal Sciences, Institute for Molecular and Cellular Regulation, Gunma University, 3-39-15 Showa-Machi, Maebashi, Gunma 371-8512, Japan
[b] Department of Laboratory Sciences, Gunma University Graduate School of Health Sciences, 3-39-22 Showa-Machi, Maebashi, Gunma 371-8514, Japan
[c] Department of Environmental Science, Graduate School of Science and Technology, Niigata University, 2-8050 Ikarashi, Niigata, Niigata 950-2181, Japan
[d] Division of Molecular and Cellular Signaling, Department of Biochemistry and Molecular Biology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-Cho, Chuo-Ku, Kobe 650-0017, Japan

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ABSTRACT

Forced swim (FS) stress induces diverse biochemical responses in the brain of rodents. Here, we examined the effect of hypothermia induced by FS in cold water on the phosphorylation of FS-sensitive signaling molecules in the mouse brain. As we have shown previously, FS in cold water induced a significant increase in the level of tyrosine phosphorylation of SIRPα, a neuronal membrane protein, in mouse hippocampus, while such effect of FS was markedly reduced in mice subjected to FS in warm water. FS in cold water also induced phosphorylation of mitogen-activated protein kinase kinase (MEK) as well as of cAMP response element-binding protein (CREB), or dephosphorylation of α isoform of Ca^{2+}/calmodulin-dependent protein kinase II (αCaMKII) in the hippocampus. These effects of FS on the phosphorylation of these molecules were also lost in mice subjected to FS in warm water. Genetic ablation of SIRPα did not change the phosphorylation states of these molecules in the brain. Forced cooling of anesthetized mice, which induced a marked increase in the phosphorylation of SIRPα, induced dephosphorylation of αCaMKII in the brain, while the same treatment did not affect the phosphorylation level of MEK and CREB. Hibernation also induced an increase and a decrease of the phosphorylation of SIRPα and αCaMKII, respectively, in the brain of chipmunk. These results suggest that hypothermia is a major element that determines the levels of phosphorylation of αCaMKII and SIRPα during the FS in cold water, while it is not for the phosphorylation levels of MEK and CREB.

1. Introduction

Investigation of biochemical responses in the brain to stress provides valuable clues to understand how stress leads to depressive and other mental illnesses. Forced swim (FS) test is widely used as an animal model of behavioral despair or depression [1]. In this behavioral test, mice or rats placed in water show consistent behavioral responses to the unpleasant environment, active swimming followed by profound immobility. This behavioral immobility is thought to represent a state of despair or depression because it is markedly reduced by treatment with various classes of antidepressant [2,3].

FS is an effective stressor to induce biochemical responses in the animal brain. For example, FS stress induces rapid changes in the activation states of several functional molecules, such as mitogen-activated protein kinase kinase (MEK), cAMP response element-binding protein (CREB), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), in the brain [4–6]. In our previous study, we have shown that FS induced a significant increase in the level of tyrosine phoshorylation of signal regulatory protein α (SIRPα) in mouse brain [7]. SIRPα (also known as SHPS-1, p84, and BIT) is a transmembrane protein that contains putative tyrosine phosphorylation sites in its cytoplasmic region [8,9]. Mice expressing a mutant form of SIRPα that lacks most of the cytoplasmic region manifest prolonged immobility in the FS test, suggesting that tyrosine phosphorylation of SIRPα participates in regulation of the behavioral immobility of mice in the FS test [7]. Recently, we found that a decrease in body temperature during FS in cold water is a major cause of the FS-induced tyrosine phosphorylation of SIRPα in the brain [10]. These results indicate that some parts of biological responses in the brain to FS stress might be induced by hypothermia rather than by psychiatric stress.

* Corresponding author. Fax: +81 27 220 8894.
E-mail address: ohnishih@gunma-u.ac.jp (H. Ohnishi).

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Here we show that hypothermia induced by immersion in cold water is a major determinant of the levels of phosphorylation of α isoform of CaMKII (αCaMKII), as well as that of SIRPα, in the brain of animals subjected to FS. In contrast, hypothermia is not important for induction by FS of the phosphorylation of MEK and CREB.

2. Materials and methods

2.1. Animals

Eight- to thirty-week-old male C57BL/6 mice were studied. Mice that express a mutant form of SIRPα [11] were backcrossed to the C57BL/6N for >10 generations. Mice were bred and maintained at the Institute of Experimental Animal Research of Gunma University under specific pathogen–free conditions. They were housed in an air-conditioned room at 23 °C with a 12-h-light, 12-h-dark cycle.

Male chipmunks (*Tamias sibiricus*) obtained from ARCLAND SAKAMOTO Co. Ltd. (Niigata, Japan) were housed in an air-conditioned room at 23 °C with a 12-h-light, 12-h-dark cycle. To facilitate hibernation, animals were placed in a totally dark room kept at 5 °C, and the surface body temperature was measured every day between 16:00 and 18:00 for more than one year with the use of infrared thermometer IT-540 (HORIBA Co. Ltd, Kyoto, Japan). Hibernating animals were defined as those, whose surface body temperatures dropped below 10 °C for more than 10 consecutive days before the day of tissue collection. Animals, whose body surface temperature were kept above 10 °C for more than 90 consecutive days before the day of tissue collection, were referred to as cold-adapted awake animals.

All animal experiments performed in this study were approved by the Animal Care and Experimentation Committee of Gunma University (No. 09-064).

2.2. Primary antibodies and reagents

Rabbit polyclonal antibodies (pAbs) specific for tyrosine-phosphorylated SIRPα (anti-pSIRPα) were described previously [7]. Rabbit pAbs to SIRPα were obtained from Upstate Biotechnology (Lake Placid, NY). Rabbit pAbs or a mAb (41G9) to the Ser^{217}/Ser^{221}-phosphorylated (active) form of MEK, rabbit pAbs or a mAb (47E6) to MEK, rabbit pAbs or a mAb (87G3) to the Ser^{133}-phosphorylated (active) form of CREB, and rabbit pAbs or mAb (D76D11) to CREB were from Cell Signaling Technology (Danvers, MA). Rabbit pAbs to the Thr^{286} (α isoform)/Thr^{287} (β isoform) -phosphorylated (active) form of CaMKII were from Promega (Madison, WI), and a mouse mAb to CaMKII was from BD Biosciences (San Jose, CA).

2.3. Forced swim and forced cooling of mice

FS of mice in cold (23 °C) or warm (37 °C) water and forced cooling (FC) of mice were performed as described previously [10].

2.4. Immunoblot analysis

For immunoblot analysis, brain tissues were dissected from mice or chipmunks killed by cervical dislocation immediately after treatments, washed with ice-cold phosphate-buffered saline and stored in liquid nitrogen before preparing the homogenates. Tissues were homogenized and subjected to immunoblot analysis as described previously [10].

2.5. Statistical analysis

All quantitative data are presented as means ± SE and were analyzed by Student's *t* test with the use of Stat View 5.0 software (SAS Institute, Cary, NC). A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Importance of low water temperature for FS-induced acute changes in the phosphorylation of MEK, CREB, and αCaMKII in the brain

To examine the effect of water temperature on FS stress-induced biological responses in the brain, we analyzed the phosphorylation states of signaling molecules in mouse brain after exposure to FS in two different water temperatures (23 °C and 37 °C). Consistent with our previous observations [7,10], immunoblot analysis with pAbs specific for tyrosine-phosphorylated SIRPα (anti-pSIRPα) revealed that the level of tyrosine phosphorylation of SIRPα in the hippocampus was markedly increased by exposure of mice to FS stress for 10 min in cold water (23 °C), and this effect of FS was markedly reduced in the hippocampus of mice subjected to FS with warm water (37 °C) (Fig. 1A). We further examined the effect of water temperature on the levels of phosphorylation of MEK (Ser^{217}/Ser^{221}), CREB (Ser^{133}), or αCaMKII (Thr^{286}) (Fig. 1B–D). MEK is a component of the MAPK signaling cascade that regulates multiple cellular functions, such as cell proliferation, differentiation, survival, or tumor metastasis [12]. MEK is phosphorylated by Raf family kinases at two serine residues (Ser^{217}/Ser^{221}) and such phosphorylation activates its kinase activity. CREB is a transcription factors that bind to cAMP responsive element (CRE) of promoter sites [13]. Phosphorylation of CREB at Ser^{133} is crucial for the activation of this molecule, and is triggered by a variety of signaling processes, including an increase in intracellular Ca^{2+} or cAMP. CREB plays multiple functions in the central nervous system, including the regulation of synaptic plasticity and memory formation [13]. CaMKII is a serine/threonine kinase that is highly expressed in the brain [14], and a large portion of brain CaMKII consists of the α and β isoforms, which form heteromeric or homomeric complexes [15]. Binding of Ca^{2+}/calmodulin facilitates autophosphorylation of CaMKII at Thr^{286} (in αCaMKII) that is important for sustaining the CaMKII activity in a Ca^{2+}-independent manner [16]. Genetic ablation of this autophosphorylation site resulted in a defective long-term potentiation (LTP)-induction and deficiency in spatial learning [17]. Preceding studies reported that FS stress induced an increase in the phosphorylation of MEK and CREB, but also induced a decrease in the phosphorylation of CaMKII [4–6]. We confirmed such effects of FS in cold water on the phosphorylation of MEK, CREB, and αCaMKII (Fig. 1B–D). Similar to the effect on tyrosine phosphorylation level of SIRPα, exposure of mice to FS stress in warm water (37 °C) did not induce significant changes in the levels of the phosphorylation of all these molecules when compared with those in control animals allowed to stand in warm shallow water (Fig. 1B–D). These results suggest that low water temperature is an important element that induces acute changes in the levels of phosphorylation of MEK, CREB, and αCaMKII in the brain during the FS in cold water. The water temperature also affects the basal phosphorylation levels of MEK, CREB, and αCaMKII, but not that of SIRPα, in the brain of control mice. Phosphoryalation levels of MEK and CREB were increased in control mice standing in warm water when compared with those in cold water, although the differences are not statistically significant for MEK (Fig. 1B and C). In contrast, phosphorylation of αCaMKII in control mice standing in warm and shallow water was markedly decreased

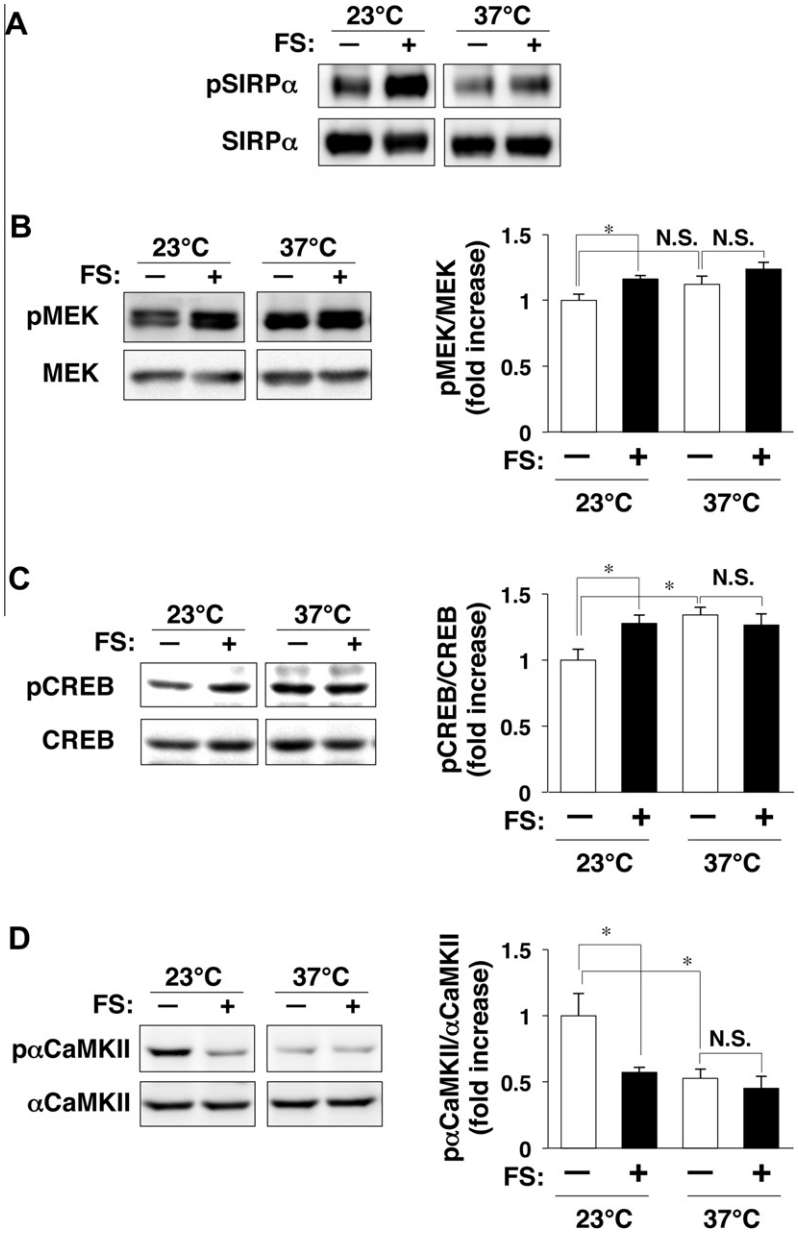

Fig. 1. FS-induced acute changes in the phosphorylation of MEK, CREB, and αCaMKII in the mouse hippocampus. Mice were subjected to the FS stress test (FS+) or allowed to stand (FS−) in cold (23 °C) or warm (37 °C) water for 10 min, after which homogenates of the hippocampus were immediately prepared and subjected to immunoblot analysis with anti-pSIRPα and pAbs to SIRPα (A), Abs to phosphorylated MEK (pMEK) and Abs to MEK (B), Abs to phosphorylated CREB (pCREB) and Abs to CREB (C), or Abs to phosphorylated CaMKII and Ab to CaMKII (D). The ratio of the intensity of the pMEK, pCREB, or phosphorylated αCaMKII (pαCaMKII) band to that of the MEK, CREB, or αCaMKII band, respectively, was determined and the percentage of each value to a summation of the values for four different conditions (±FS at 23 °C, ±FS at 37°C) in the same blotting sheet was calculated. Final data were expressed as fold increase relative to the value for control mice allowed to stand in cold water (right panels). Data are means ± SE for a total of four (MEK and αCaMKII) or six (CREB) mice for each condition. N.S., not significant; $^{*}P < 0.05$ (Student's t test).

when compared with those in cold and shallow water (Fig. 1D). Stress by contact with cold and warm water may have different effects on the phosphorylation levels of MEK, CREB, and αCaMKII.

3.2. Phosphorylation of MEK, CREB, and αCaMKII during FS in the brain of SIRPα mutant mice

Tyrosine phosphorylated SIRPα binds and activates protein tyrosine phosphatase Shp2 in the brain [9]. Preceding studies suggested that Shp2 positively regulates Ras-MAPK signaling pathway [18] that is known to participate in phosphorylation of CREB at Ser^{133} [19]. Thus, we examined the significance of tyrosine phosphorylation of SIRPα for the FS-induced activation of MEK and CREB by the use of SIRPα mutant mice that express a mutant form of SIRPα lacking most of the cytoplasmic region [11]. This mutant SIRPα protein did not undergo tyrosine phosphorylation even after FS treatment in cold water (Fig. 2A) as we have reported previously [7]. In the brain of the mutant mice, either basal or FS-induced phosphorylation of MEK and CREB was comparable to those of wild-type mice (Fig. 2B and C). In addition, no apparent difference was observed in the levels of phosphorylation of αCaMKII between wild-type and SIRPα mutant mice in either basal or FS-stressed condition (Fig. 2D).

3.3. Importance of hypothermia for the induction of acute changes in the phosphorylation of CaMKII in the brain

We next examined the effect of forced cooling (FC) of anesthetized mice on the levels of phosphorylation of MEK, CREB, and

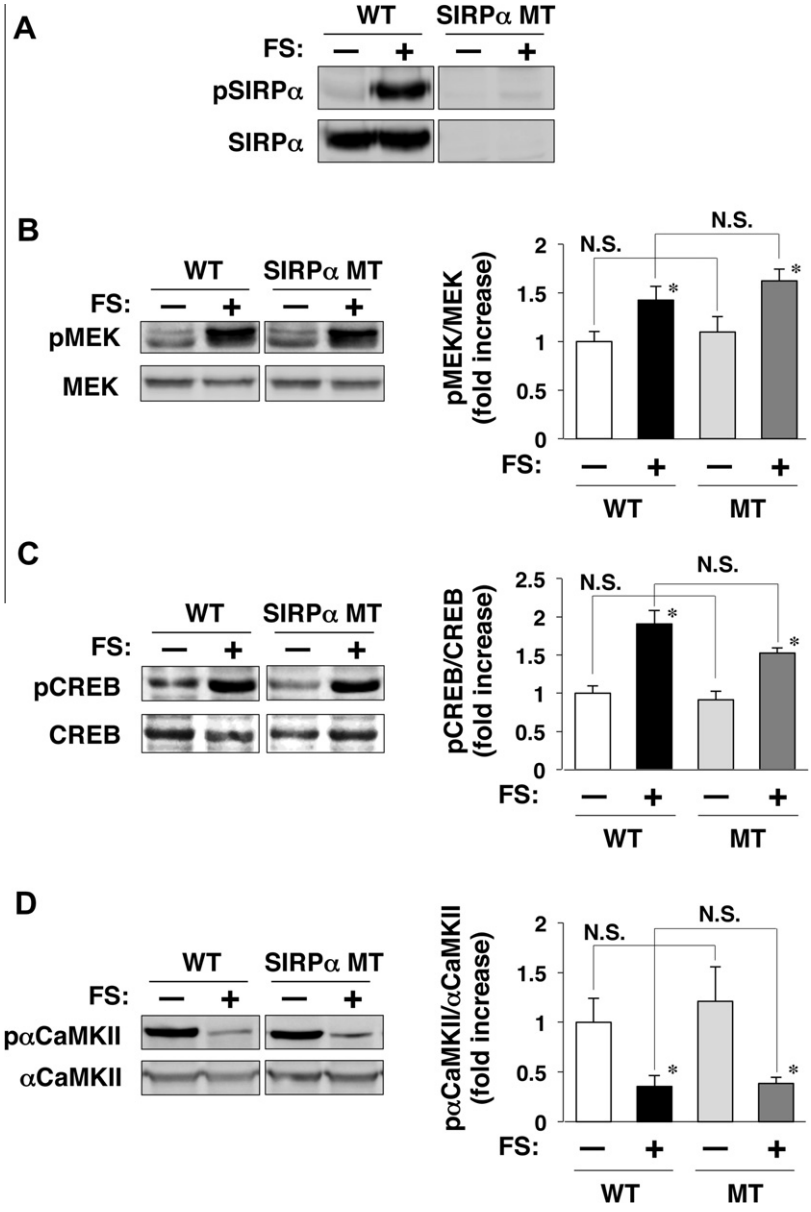

Fig. 2. Phosphorylation of MEK, CREB, and αCaMKII in the hippocampus of SIRPα mutant mice. Wild type or SIRPα mutant mice (MT) were subjected to the FS stress test (FS+) or allowed to stand (FS−) in cold (23 °C) water for 10 min, after which homogenates of the hippocampus were immediately prepared and subjected to immunoblot analysis to evaluate the levels of phosphorylation of SIRPα (A), MEK (B), CREB (C), or αCaMKII (D) as in Fig. 1. The level of the phosphorylation of MEK, CREB, or αCaMKII was quantified as in Fig. 1 (right panels). N.S., not significant for indicated comparison; $^{*}P < 0.05$ between ±FS (Student's t test). Data are means ± SE for a total of three (MEK and αCaMKII) or four (CREB) mice for each condition.

αCaMKII in the brain, because body temperature is an important determinant of the FS-induced tyrosine phosphorylation of SIRPα [10]. Mice were anesthetized and cooled as described in Materials and methods. Tyrosine phosphorylation of SIRPα was markedly increased in the hippocampus of cooled mice, compared with that in warmed control mice as observed previously [10] (Fig. 3A). Immunoblot analysis revealed that the phosphorylation of MEK or CREB in the hippocampus was not affected significantly by FC (Fig. 3B and C). In contrast, the level of phosphorylation of αCaMKII in the hippocampus was markedly decreased by FC (Fig. 3D). These results suggest that a decrease in body temperature is important for dephosphorylation induced by FS in cold water of αCaMKII in the brain, while it is not for the induction of phosphorylation of MEK and CREB.

3.4. Effects of hypothermia on the phosphorylation of αCaMKII and SIRPα in the brain of chipmunks during hibernation

We further examined the effect of hypothermia on the phosphorylation of αCaMKII and SIRPα in the brain under a more physiological condition. For this purpose, we prepared brain homogenates from hibernating or awake chipmunks, both of which were housed under dark condition at 5 °C. In the hippocampus of hibernating animals, whose body surface temperatures were less than 10 °C (data not shown), the level of tyrosine phosphorylation of SIRPα was markedly increased, compared with that apparent with awake animals, whose surface body temperatures were more than 10 °C (data not shown) (Fig. 4A). Immunoblot analysis of the same samples revealed that the phosphorylation

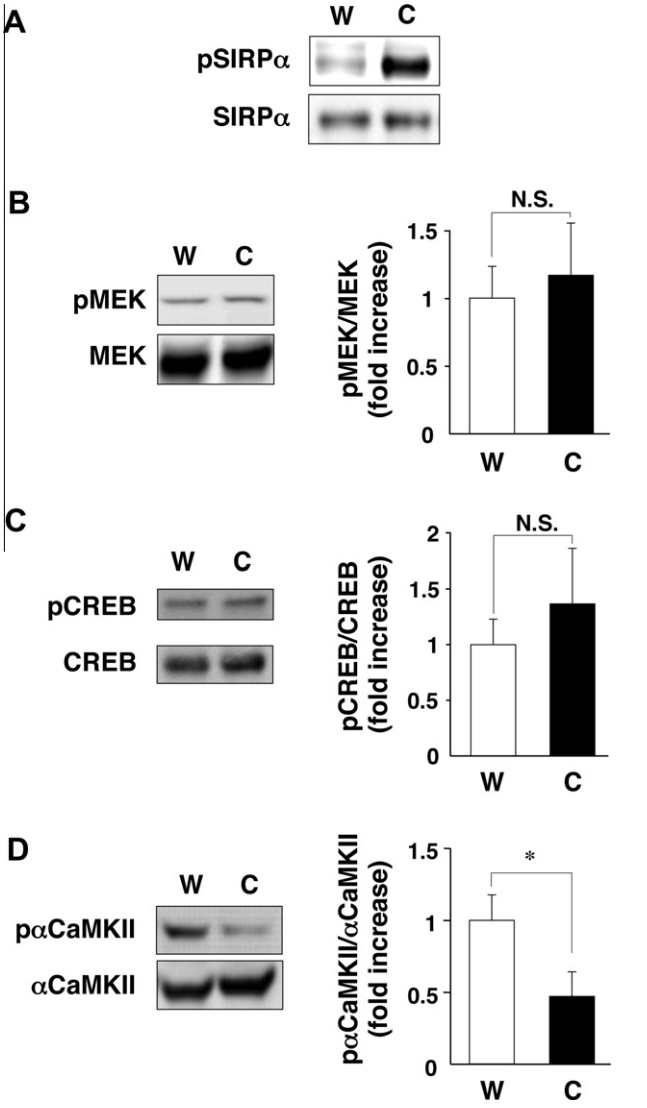

Fig. 3. Effect of hypothermia on phosphorylation of MEK, CREB, and αCaMKII in the hippocampus. Anesthetized mice were cooled (C) or warmed (W). Homogenates of hippocampus were prepared and subjected to immunoblot analysis to evaluate the levels of phosphorylation of SIRPα (A), MEK (B), CREB (C), or αCaMKII (D) as in Fig. 1. The ratio of the intensity of the band for phospho-specific antibody to that for pan-antibody was expressed as fold increase relative to the value for warmed mice (right panels). N.S., not significant; $^{*}P < 0.05$ (Student's t test). Data are means ± SE for a total of four mice for each condition.

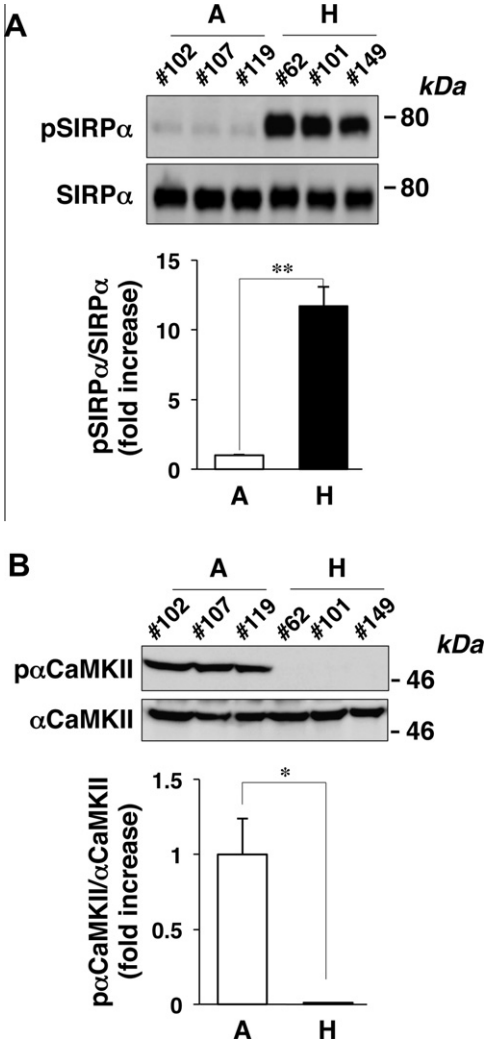

Fig. 4. Effect of hibernation on the phosphorylation of αCaMKII and SIRPα in the brain of chipmunks. Hippocampus was dissected from chipmunks during hibernation (H) or arousal (A). Homogenates were prepared and subjected to immunoblot analysis with anti-pSIRPα and pAbs to SIRPα (A), or pAbs to phosphorylated CaMKII and mAb to CaMKII (B). Identification numbers for each animal are indicated at the top of each lane. The ratio of the intensity of the pSIRPα or pαCaMKII band to that of the SIRPα or αCaMKII band is expressed as fold increase relative to the value for animals in arousal state. Data are means ± SEM from three chipmunks for each condition. $^{*}P < 0.05$, $^{**}P < 0.01$ (Student's t test).

level of αCaMKII was markedly decreased and almost undetectable in the hippocampus of hibernating animals, while substantial phosphorylation of the same molecule was easily detectable in awake animals (Fig. 4B). These results suggest that physiological hypothermia during hibernation induces remarkable changes in the levels of phosphorylation of αCaMKII and SIRPα in the brain of chipmunks.

4. Discussion

Our present data suggest that water temperature is an important determinant of the FS-induced changes in the phosphorylation levels of MEK, CREB, and αCaMKII in the brain. Difference in water temperature also affects the basal phosphorylation levels of MEK, CREB, and αCaMKII, but not that of SIRPα, in control mice that were allowed to stand in shallow water. In these animals, sensation of cold and warm water may have different effects on the phosphorylation of MEK, CREB, and αCaMKII, but not that of SIRPα, even in the absence of FS stress.

Our previous data suggest that tyrosine phosphorylation of SIRPα contributes to the reduction of the behavioral immobility in the FS test [7]. Similarly, signaling molecules examined in this study may also participate in the regulation of the behavioral immobility during FS-test in cold water. Tyrosine phosphorylated SIRPα binds and activates protein tyrosine phosphatase Shp2 [9]. In addition, Shp2 positively regulates Ras-MAPK signaling pathway [18] that participates in phosphorylation of CREB at Ser^{133} [19]. Thus, we hypothesized that tyrosine phosphorylation of SIRPα participates in the regulation of FS-induced activation of MEK and CREB. However, a lack of SIRPα signaling in SIRPα mutant mice did not affect the FS-induced phosphorylation of MEK and CREB in the brain. FS-induced dephosphorylation of αCaMKII was not affected in these mice either. Thus, SIRPα signal is not involved in the regulation of the phosphorylation of MEK, CREB, and αCaMKII in the brain during FS.

Phosphorylation of MEK or CREB in the brain was not affected by FC in anesthetized mice. Thus, psychiatric or physiologically sensible stress, such as discomfort associated with the immersion in cold water, is probably important for the phosphorylation of MEK and CREB. In contrast, changes in the levels of the phosphorylation of SIRPα and αCaMKII were induced by FC even in anesthetized mice. In addition, similar changes in the phosphorylation of SIRPα and αCaMKII were also observed in hibernating chipmunk with low body temperature. Hypothermia induced in animals during FS, FC, or hibernation was, thus, important for the induction of an increase and a decrease of phosphorylation of SIRPα and αCaMKII in the brain, respectively. In contrast, mental stress was not important for such changes in the phosphorylation of SIRPα and αCaMKII. Indeed, our previous study suggests that an increase in tyrosine phosphorylation of SIRPα is directly induced in cultured hippocampal neurons by lowering the temperature of the culture medium [10]. Hypothermia-dependent changes of the phosphorylation of these molecules may be adaptive responses of the brain to low temperature rather than those to psychiatric stress. In contrast to SIRPα and αCaMKII, hypothermia itself does not affect the phosphorylation states of MEK or CREB in the brain, suggesting that the hypothermia-dependent changes in the levels of phosphorylation are characteristics of SIRPα and αCaMKII, rather than a general biological response in the brain to hypothermia.

Difference in the sensitivity to the low temperature between protein kinases and phosphatases contributes to the low temperature-induced dephosphorylation and phosphorylation of SIRPα and αCaMKII, respectively. Such mechanism was previously proposed for the low temperature–induced phosphorylation of tau [20], a neuronal microtubule-associated protein. Exposure to a low temperature directly induces hyperphosphorylation of tau in mouse brain slices, with the suppressive effect of the low temperature on the enzymatic activity of tau phosphatases, PP2A or PP2B, being much greater than that on the activity of tau kinases, GSK-3β, JNK, MAPK, or Cdk5 [20]. In contrast, hypothermia-induced dephosphorylation of αCaMKII (Thr^{268}) may be attributable to the dominant suppressive effect of low temperature on the kinase activity of αCaMKII. Another possible mechanism for the hypothermia-induced dephophorylation of αCaMKII may be the suppressive effect of low temperature on neuronal excitability [21], because the first step of the auto-phosphorylation of αCaMKII largely depends on the intracellular Ca^{2+} concentration that is highly correlated with neuronal excitability [22].

The physiological significance of FS-induced changes in the phosphorylation levels of MEK, CREB, αCaMKII, and SIRPα in regulation of the depression-like behavior remains unknown. Among these molecules, phosphorylations of MEK and CREB were not induced by FC in anesthetized mice or by hibernation, suggesting that psychiatric or physiologically sensible stress is more important for these reactions. Psychiatric stress-induced phosphorylation of MEK and/or CREB thus may be implicated in the modulation of the brain functions during the state of despair or depression. Consist with this idea, exposure of rats to chronic stress by mild foot shock induced a pronounced and persistent hyperphosphorylation of ERK1/2, downstream targets of MEK [23]. In contrast, another study reported that the exposure of rat to elevated platform stress reduced the phosphorylation of $Ser^{217/221}$ of MEK in frontal cortex, and acute treatment with an antidepressant, tianeptine or imipramine, or mifepristone (a Type II glucocorticoid receptor antagonist), reversed the stress-induced reduction of phosphorylated MEK [24,25]. Furthermore, mild foot shock stress induced a reduction of phosphorylated CREB in rat cortical and subcortical regions [23]. Exposure of rat to social isolation stress also decreased CREB activity in the nucleus accumbens shell [26], and treatment of rats with an antidepressant, fluoxetine, increased nuclear phosphorylation of CREB in hippocampus and prefrontal cortex [27]. So far, it remains unclear whether activation of MEK/ERK and CREB pathway produces pro- or anti-depressant action in the brain. Further studies are required to elucidate the physiological functions of these signaling pathways in regulation of depression-related pathology.

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