

Brief report

Activation of extracellular signal-regulated kinase signaling by chronic electroconvulsive shock in the rat frontal cortex

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Abstract

The effects of chronic electroconvulsive shock (ECS), given daily for 1, 5 and 10 days, on the activation of extracellular signal-regulated kinase (ERK) were studied in the rat frontal cortex. The phosphorylation of MEK1/2 and ERK1/2 increased through 5 days of ECS. Thereafter, a plateau was achieved. The expression of brain-derived neurotrophic factor was continuously increased for 10 days. Our data show that the effect of ECS on ERK1/2 signaling is increased with chronic treatment.

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1. Introduction

Electroconvulsive shock (ECS), an animal model for electroconvulsive therapy (ECT), is a strong depolarizing stimulus that affects various signal transduction pathways in neurons. The therapeutic effect of ECT requires multiple treatments, a finding that suggests an accumulation of partial effects over the course of repeated treatments. Therefore, to understand the therapeutic mechanism of electroconvulsive therapy, it would be helpful to investigate the accumulated effects

of a series of repeated ECS administrations, which would not necessarily be apparent in the acute effect of a single ECS.

Chronic antidepressant treatments activate signaling related to brain-derived neurotrophic factor (BDNF) in the hippocampus of experimental animals or human subjects (Duman et al., 1997; Chen et al., 2001; Altar et al., 2003). The extracellular signal-regulated kinase (ERK) pathway is an important cascade that transmits neurotrophin signals, and ERK activation results in cellular proliferation and differentiation (Seger and Krebs, 1995). We previously reported a single ECS-induced transient activation of ERK1/2 in the rat hippocampus and cerebral cortex (Kang et al., 1994; Jeon et al., 1998). Since chronic ECS has been reported

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to induce neurogenesis in the hippocampus and cellular proliferation in the frontal cortex (Madsen et al., 2005, 2003), it is plausible that chronic ECS has a long-term effect on the ERK signaling pathway. Little is known, however, about the effect of chronic ECS on ERK expression or phosphorylation. Chronic treatment with the antidepressant drug fluoxetine resulted in either increased (Tiraboschi et al., 2004) or decreased phosphorylation (Fumagalli et al., 2005) of ERK, a mixed result in terms of the total activity of the ERK signaling cascade.

In this study, we examined the effect of chronic daily ECS on the expression and phosphorylation of ERK1/2 in the rat frontal cortex. We also observed MEK (mitogen-activated protein kinase-kinase) and brain-derived neurotrophic factor and (BDNF) as upstream signaling molecules of ERK1/2.

2. Methods

2.1. Preparation of animals and samples

Animals were treated in accordance with National Institutes of Health (NIH) *Guide for the Care and Use of Laboratory Animals*. Male Sprague–Dawley rats (150–200 g) were housed for 2 weeks before the experiment and maintained under 12 h light/12 h dark conditions with food and water available ad libitum. Rats were divided into four groups and at least four rats were used per group. Each group was given the following treatments, respectively: only sham treatment for 10 days (sham), sham treatment for 9 days and ECS on the 10th day (E1X), sham treatment for 5 days and then ECS for 5 days (E5X), and daily ECS for 10 days (E10X). Electroconvulsive shock (130 V, 0.5 s) was administered via earclip electrodes. Rats were sacrificed by decapitation 24 h after the last treatment and the frontal cortices were dissected.

2.2. Immunoblot analysis

Tissue was homogenized in 10 v/w of ice-cold homogenization buffer (50 mM Tris, pH 7.4, 1% Triton X-100, 0.5% deoxycholate, 150 mM NaCl, 1 mM EGTA, 1 mM EDTA, 1 mM Na_3VO_4 , Complete Mini Protease Inhibitor Cocktail (Roche Diagnostics, Switzerland), 1 mM DTT, 1 mM PMSF). Homogenates were centrifuged and supernatants were boiled with Laemmli's sample buffer. The samples were then separated by SDS-PAGE and immunoblotted with antibodies against phospho-ERK1/2 (Thr202/Tyr204),

phospho-MEK1/2 (Ser217/221) (Cell Signaling Technology, Beverly, MA), BDNF (Santa Cruz Biotech, Santa Cruz, CA), MEK1 (BD Biosciences, San Jose, CA) and β -actin (Sigma-Aldrich, Steinheim, Germany). Signals were detected by the enhanced chemiluminescence method.

2.3. Statistical analysis

Immunoblot signals were quantified with TINA program version 2.10G (Raytest, Germany). To ensure statistical power, at least four independent experiments were done. Statistical analysis was performed by Mann–Whitney *U*-test. The level of significance was set at $P < 0.05$.

3. Results

Total phosphorylations of ERK1 and ERK2 were increased over the course of repeated ECS in the rat frontal cortex. Both signals showed the same pattern. Phosphorylation increased after a single ECS (E1X), and further increased in the E5X and E10X groups, with a significant difference from sham in all groups: $131.1 \pm 23.3\%$ (mean $\pm$ S.D.) from control, $150.5 \pm 20.8\%$ and $150.8 \pm 13.3\%$ for the E1X, E5X and E10X groups, respectively (see Fig. 1A). The total protein level was unchanged after repeated ECS treatment in the rat frontal cortex.

The phosphorylation of MEK1/2, the upstream regulator of ERK1/2, showed a similar pattern: $127.5 \pm 49.5\%$, $175.0 \pm 33.0\%$ and $170.4 \pm 54.0\%$ for E1X, E5X and E10X, respectively (see Fig. 1B). Statistical significance was detected in the E5X and E10X groups. The total amount of MEK1 was unchanged by repeated ECS.

We next investigated changes in the protein level of BDNF. As shown in Fig. 1C, we found a significant and continuous increase of BDNF after ECS ($151.3 \pm 22.4\%$, $235.1 \pm 24.4\%$ and $327.5 \pm 12.5\%$ for the E1X, E5X and E10X groups, respectively). Statistical significance compared with the sham group was observed for all treated groups.

4. Discussion

The phosphorylation of ERK1/2 was increased after a single administration of ECS, and increases accumulated over five consecutive daily treatments (E5X) before reaching a plateau with more prolonged treatment (E10X). A corresponding change in the basal (24 h after the last stimulus) activity of ERK1/2 was expected.

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