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Electroconvulsive seizure induces thrombospondin-1 in the adult rat hippocampus

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ABSTRACT

Synaptic dysfunction has recently gained attention for its involvement in mood disorders. Electroconvulsive therapy (ECT) possibly plays a role in synaptic repair. However, the underlying mechanisms remain uncertain. Thrombospondin-1 (TSP-1), a member of the TSP family, is reported to be secreted by astrocytes and to regulate synaptogenesis. We investigated the effects of electroconvulsive seizure (ECS) on the expression of TSPs in the adult rat hippocampus. Single and repeated ECS significantly increased TSP-1 mRNA expression after 2 h and returned to sham levels at 24 h. Conversely, the TSP-2 and -4 mRNA levels did not change. Only repeated ECS induced TSP-1 proteins. ECS also induced glial fibrillary acidic protein (GFAP) expression. The GFAP expression occurred later than the TSP-1 mRNA expression following single ECS; however, it occurred earlier and was more persistent following repeated ECS. ECS had no effect on the α2δ-1 or neuroligin-1 expressions, both of which are TSP-1 receptors. Furthermore, chronic treatment with antidepressants did not induce the expression of TSP-1 or GFAP. These findings suggest that repeated ECS, but not chronic treatment with antidepressants, induces TSP-1 expression partially via the activation of astrocytes. Therefore, TSP-1 is possibly involved in the synaptogenic effects of ECS.

1. Introduction

Electroconvulsive therapy (ECT) is the most potent treatment for antidepressant-resistant mood disorders. However, the underlying mechanisms of action remain unclear. Therefore, identifying some of the molecular and cellular mechanisms affected by ECT may provide further insight into the pathophysiology of depression and the development of more effective therapeutic strategies.

Synaptic dysfunction has recently received attention for its involvement in mood disorders (Duman and Aghajanian, 2012). In fact, the number of synapses has been reported to decrease in certain brain regions in depressed patients (Kang et al., 2012). Furthermore, the dysregulation of synaptic genes has also been reported in patients with major depressive disorder (MDD) (Duric et al., 2013; Kang et al., 2012; Zhurov et al., 2012). On the other hand, ketamine, a fast-acting and effective agent in MDD patients resistant to traditional antidepressants, induces synaptogenesis and reverses the synaptic deficits caused by chronic stress (Li et al., 2010). Electroconvulsive seizure (ECS), an animal model of ECT, has been reported to increase the total number of synapses in the adult rat hippocampus (Chen et al., 2009). Hippocampal synaptogenesis is considered as one of the theories on how ECT works (Bolwig, 2011). However, the precise underlying mechanism remains unclear.

Glia, especially astrocytes, exist far more abundantly than neurons in the brain. They are often found in close proximity to the pre- and postsynaptic terminal of neurons (Araque et al., 1999). Astrocytes can modulate the efficacy of synapses through the release and uptake of neuroactive substances. Glial reduction has been found in several brain regions in MDD patients (Ongur et al., 1998; Rajkowska and Miguel-Hidalgo, 2007; Takebayashi et al., 2009). In addition, an animal study with the pharmacological ablation of astrocytes suggested that the loss of astrocytes is sufficient to induce depressive-like behavior (Banasr and Duman, 2008). Therefore a certain synaptogenic factor which is secreted by astrocytes may possibly be a therapeutic target for mood disorders.

Abbreviations: ADAMTS-1, a disintegrin and metalloproteinase with thrombospondin motifs 1; BCA, bicinchoninic acid; COMP, cartilage oligomeric matrix protein; ECS, electroconvulsive seizure; ECT, electroconvulsive therapy; EGF, epidermal growth factor; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAP, glial fibrillary acidic protein; MDD, major depressive disorder; SDS, sodium dodecyl sulfate; SPARC, secreted protein acidic and rich in cysteine; TSP, thrombospondin; TSRs, TSP Type 1 repeats.

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Thrombospondins (TSPs) are large, oligomeric multidomain glycoproteins. TSP was originally discovered as a secretory component of platelet α-granules and it has been shown to play a role in platelet aggregation. This protein is now designated as TSP-1, and it remains the best characterized of the five presently known TSP isoforms. The TSP isoforms, including TSP-1, -2, -3, -4, -5/cartilage oligomeric matrix protein (COMP) are divided into two subgroups according to their domain structure. Subgroup A TSPs include TSP-1 and -2, which characteristically contain a procollagen homology domain, three TSP Type 1 repeats (TSRs) and three epidermal growth factor (EGF)-like repeats (Fig. 4A). Subgroup B TSPs include TSP-3, -4 and TSP-5/COMP, which lack a region of the procollagen homology domain and the three TSRs and have four EGF-like repeats instead of three. TSP-5/COMP additionally lacks the N-terminal heparin-binding domain (Adams and Tucker, 2000). They are now known to be involved in a variety of biological functions as a part of the extracellular matrix (Adams and Lawler, 2004; Adams and Tucker, 2000). Recently, TSP-1 and -2 have been shown to be secreted by astrocytes and to regulate synaptogenesis, especially during presynaptic maturation in the developing brain (Christopherson et al., 2005; Crawford et al., 2012). Indeed, TSP-1/2 double null mice have been shown to exhibit a decrease in the number of synapses in the cerebral cortex, although the number of neurons and the expression levels of synaptic proteins are normal, as observed in wild-type mice (Christopherson et al., 2005). The expressions of TSP-1 and -2 which are induced by astrocytes peak at the start of the synaptogenic period in the mouse brain (postnatal days 5–10) and decrease in the adult brain (Christopherson et al., 2005). On the other hand, TSP-4 was found in astrocytes as well as neurons in the adult brain, and it has also been reported to play a role in synaptic organization (Arber and Caroni, 1995; Caceres et al., 2007; Cahoy et al., 2008). In this manner, studies regarding the synaptogenic effects of TSPs have so far been intensively carried in TSP-1, -2 and -4. TSPs act through a number of extracellular matrix proteins and cell surface receptors, such as α2δ-1 (Eroglu et al., 2009) and neuroligin-1 (Xu et al., 2010). TSP-1 has also been reported to play a role in the astrocyte-mediated spine and synaptic pathology of Down's syndrome (Garcia et al., 2010). However, there have been no reports regarding the role of TSPs in the pathophysiology and/or therapeutic strategies of mood disorders.

Taking the above into consideration, we focused on TSPs which promote synaptogenesis, as a novel therapeutic target for mood disorders. We subsequently investigated the effects of ECS and antidepressants on the expression of TSPs in the adult rat hippocampus.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (250–300 g) (Charles River Laboratories Japan, Inc., Yokohama, Japan) were group-housed (three per cage) in a treatment-controlled environment under a 12-hour light/dark cycle (lights at 8 AM) with free access to food and water and were given a one-week acclimatization period prior to the experimental manipulations (described below). All animal procedures were approved by the Hiroshima University Animal Care and Use Committee and Kure Medical Center Animal Care and Use Committee.

2.2. ECS

Following acclimatization, the rats received ECS treatment, as previously described (Segawa et al., 2013). Briefly, bilateral ECS was administered via spring-loaded ear clip electrodes using a pulse generator (ECT Unit 7801; Ugo Basile, Comerio, VA, Italy; frequency = 100 pulses/s; pulse width = 0.5 ms; shock duration = 0.5 s; current = 55 mA). This procedure consistently induced a generalized *grand mal* seizure with characteristic clonic and tonic convulsions. The animals received either a single shock or 10 shocks (once daily) during 9 to 10 AM, respectively. In the sham rats, no shocks were delivered via the ear clip electrodes. In order to examine the temporal changes in the mRNA and protein levels of TSP-1 and other TSPs, the rats were killed at several time points, including 1, 2, 4, 8, 16 and 24 h after the last ECS treatment in the single ECS experiments (Fig. 1). In the repeated ECS experiments, the hippocampi were collected at 1, 2 and 24 h after the last ECS administration. The collected hippocampi were frozen immediately in liquid nitrogen and stored at −80 °C until use.

2.3. Chronic antidepressant treatment

Following acclimatization, the rats received antidepressant treatment. Desipramine hydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan; 10 mg/kg) or paroxetine semi-hydrochloride (LKT Laboratories, Inc., St. Paul, MN, USA; 10 mg/kg) were administered i.p. once a day for 21 days. Two hours after the last injection, the rats were sacrificed and the hippocampi were collected.

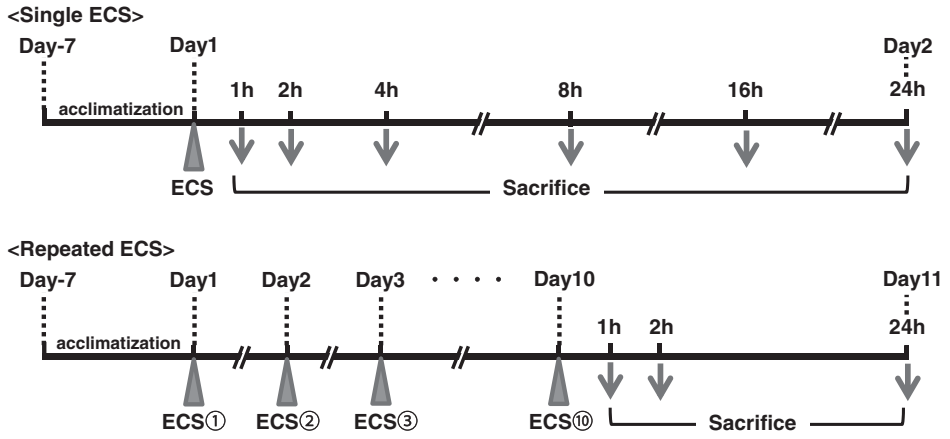

Fig. 1. Schematic depiction of the time course of the ECS study. Rats were given a one-week acclimatization period prior to the experimental manipulations. In the single ECS experiments, the rats were killed at several time points: 1, 2, 4, 8, 16 and 24 h after the single ECS treatment. In the repeated ECS experiments, the rats received 10 shocks (once daily). The hippocampi were collected at 1, 2 and 24 h after the last ECS administration.