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Research Report

Expression and cellular distribution of transient receptor potential vanilloid 4 in cortical tubers of the tuberous sclerosis complex

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ABSTRACT

Cortical tubers in patients with tuberous sclerosis complex (TSC) are highly associated with intractable epilepsy. Recent evidence has shown that transient receptor potential vanilloid 4 (TRPV4) has direct effects on both neurons and glial cells. To understand the role of TRPV4 in pathogenesis of cortical tubers, we investigated the expression patterns of TRPV4 in cortical tubers of TSC compared with normal control cortex (CTX). We found that TRPV4 was clearly up-regulated in cortical tubers at the protein levels. Immunostaining indicated that TRPV4 was specially distributed in abnormal cells, including dysplastic neurons (DNs) and giant cells (GCs). In addition, double immunofluorescent staining revealed that TRPV4 was localized on neurofilament proteins (NF200) positive neurons and glial fibrillary acidic portein (GFAP) positive reactive astrocytes. Moreover, TRPV4 co-localized with both glutamatergic and GABAergic neurons. Furthermore, protein levels of protein kinase C (PKC), but not protein kinase A (PKA), the important upstream factors of the TRPV4, were significantly increased in cortical tubers. Taken together, the overexpression and distribution patterns of TRPV4 may be linked with the intractable epilepsy caused by TSC.

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal-dominantly inherited, multisystem disorder resulting from mutations of the TSC1 or TSC2 genes (DiMario et al., 2015). Neurological manifestations account for most disabling clinical disease of TSC, including cortical tubers, subependymal nodules, subependymal giant cell tumors and white matter abnormalities (Novegno et al., 2012). Cortical tubers, a typical pathological hallmark of TSC, are focal abnormalities of cortical architecture that exhibit over proliferation of both neurons and glial cells and marked disorganization of cortical lamination (Grajkowska et al., 2010; Moavero et al., 2010). Epilepsy is the most common presenting symptom in TSC patients with cortical tuber, about two thirds of these patients have a poor response to the currently anti-epileptic drugs (Chu-Shore et al., 2010; Pascual-Castroviejo, 2011). Clinically, cortical tubers are often recognized as epileptogenic foci, surgical intervention is another effective treatment.

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To date, most research focused on the function of selective ion channels in seizure (Ermolinsky et al., 2011; Suleiman et al., 2011), and little attention was paid to the potential role of nonselective ion channels. Transient receptor potential vanilloid 4 (TRPV4) is a ligand-gated nonselective cation channel that is permeable to many cations, such as Ca^{2+}, Mg^{2+} (Venkatachalam and Montell, 2007). TRPV4 is widely expressed in central nervous system (Kauer and Gibson, 2009), it can be activated by various stimuli, including hypotonic, warm temperature, lipids downstream of arachidonic acid metabolism (Plant and Strotmann, 2007). Accumulating evidence indicated that TRPV4 plays important role in the brain physiological and pathological processes (Everaerts et al., 2010). Moreover, TRPV4 has been implicated in a variety of neurological disorders, including cerebral neuropathic pain (Hsu et al., 2014), ischemia (Jie et al., 2014) and seizure (Kauer and Gibson, 2009).

Previous studies have reported that TRPV4 might have specific effects on both neurons and glia. Lipids downstream of arachidonic acid metabolism, which could activate TRPV4, increases during seizure activity (Everaerts et al., 2010). In addition, several reports have demonstrated that activation of TRPV4 may disrupt neural excitabilities and modulate synaptic transmission (Li et al., 2013; Ryley Parrish et al., 2013). Actually, protein kinase C (PKC) and protein kinase A (PKA) are involved in the course of epilepsy (Jiang et al., 2015;

Table 1 – Clinical and neuropathological characteristics of patients with TSC.

Case No.	Gender	Genotype	Age at surgery (year)	Seizure type	Tubers location	Epilepsy duration (year)	Seizure frequency (per month)	PO	Application in the present study
1	F	TSC2	1.5	PS	O	0.6	5	I	WB;IHC
2	M	NMI	1.7	PS; IS	P	0.8	25	I	WB;IHC
3[a]	M	TSC2	2.1	GTCS	FR	0.9	15	II	WB;IHC
4	M	TSC1	2.5	IS	FR	1.5	10	I	WB;IHC
5	M	TSC2	2.6	PS; Tonic	P	1.2	20	I	WB;IHC
6	F	TSC2	4.2	PS	O	2.5	20	II	WB;IHC
7	M	NMI	4.6	Tonic	T	3.2	35	I	WB;IHC
8[a]	F	TSC2	4.8	GTCS	T	4.0	20	III	WB;IHC
9	F	TSC1	5.4	PS; GTCS	FR	3.5	110	I	WB;IHC
10	F	TSC2	6.6	IS	P	4.5	15	I	WB;IHC
11[a]	M	TSC1	7.8	PS	T	5.8	10	I	WB;IHC
12	F	TSC1	8.3	PS	O	6.3	10	IV	WB;IHC
13[a]	F	TSC1	9.6	GTCS	FR	6.5	25	I	WB;IHC
14	F	TSC2	10.2	PS; IS	P	8.2	30	I	WB;IHC
15	M	TSC2	11.3	PS	P	8.0	5	I	WB;IHC
16[a]	F	TSC1	11.5	Tonic	FR	4.5	20	I	WB;IHC
17[a]	F	TSC2	11.5	IS	O	3.5	10	I	WB;IHC
18	M	TSC2	11.9	GTCS; Tonic	FR	7.5	15	II	WB;IHC

Abbreviations: TSC=tuberous sclerosis complex; NMI=no mutation identified; M=male; F=female; PO=postoperative outcome (Engel's class); PS=partial seizure; GTCS=generalized tonic–clonic seizure; IS=infantile spasm; FR=frontal; P=parietal; O=occipital; T=temporal; WB=Western Blot; IHC=immunohistochemistry (including immunofluorescence).
[a] TSC that contained sufficient amounts of perilesional zone (PZ), which has normal-appearing cortex/white matter adjacent to the lesion.

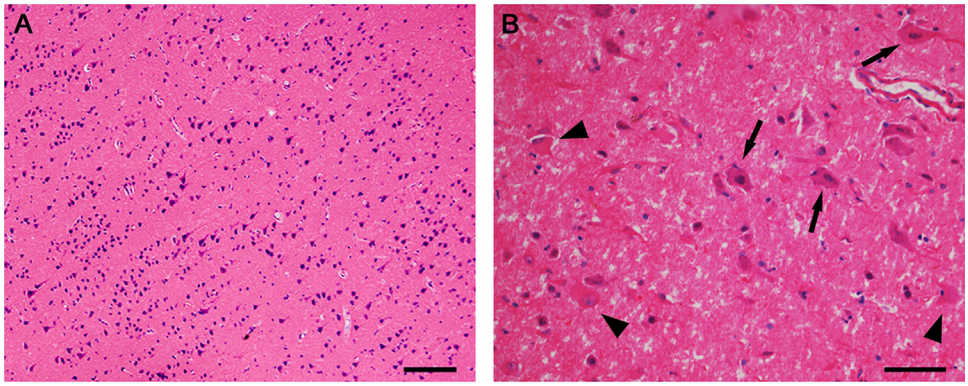

Fig. 1 – Histopathological findings in normal control cortex (CTX) and tuberous sclerosis complex (TSC). (A) Hematoxylin and eosin (H&E) staining of CTX. (B) Representative photomicrographs of TSC showing areas of cortical disorganization containing different cell types, including dysplastic neurons (DNs, arrows) and giant cells (GCs, arrowheads). The bars indicate (A) 100 μm; (B) 50 μm.