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Research report

# Leptomycin B ameliorates vasogenic edema formation induced by status epilepticus via inhibiting p38 MAPK/VEGF pathway

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ABSTRACT

The blood-brain barrier (BBB) disruption during brain insults leads to vasogenic edema as one of the primary steps in the epileptogenic process. However, the signaling pathway concerning vasogenic edema formation has not been clarified. In the present study, status epilepticus (SE) resulted in vascular endothelial growth factor (VEGF) over-expression accompanied by loss of BBB integrity in the rat piriform cortex. Leptomycin B (LMB, an inhibitor of chromosome region maintenance 1) attenuated SE-induced vasogenic edema formation. This anti-edema effect of LMB was relevant to inhibitions of VEGF over-expression as well as p38 mitogen-activated protein kinase (MAPK) phosphorylation. Furthermore, SB202190 (a p38 MAPK inhibitor) ameliorated vasogenic edema and VEGF over-expression induced by SE. These findings indicate that p38 MAPK/VEGF signaling pathway may be involved in BBB disruption following SE. Thus, we suggest that p38 MAPK/VEGF axis may be one of therapeutic targets for vasogenic edema in various neurological diseases.



## 1. Introduction

Status epilepticus (SE, a prolonged seizure activity) is one of the neurologic emergencies that lead to death or permanent neurologic defects. In epilepsy patients, SE is one of the undesirable conditions due to insufficient dosage or withdrawal of anti-epileptic drugs (AEDs). In addition, SE is a high risk factor of developing acquired epilepsy, since SE causes 3–5% of symptomatic epilepsy (~35% of epileptic syndromes; Hesdorffer et al., 1998; Temkin, 2001; Jacobs et al., 2009). Although the mechanisms underlying the epileptogenic process are not well understood, blood-brain barrier (BBB) disruption leading to vasogenic edema is one of the possible mechanisms for the development of acquired epilepsy following SE. This is because serum-protein extravasation (leakage of blood serum components into the brain parenchyma) during vasogenic edema formation contributes to neuronal hyperexcitability, astroglial loss/dysfunction and impairment of potassium homeostasis, which lead to epileptogenesis and progression of epilepsy (Cacheaux et al., 2009; David et al., 2009; Friedman et al., 2009; Ivens et al., 2007; Seiffert et al., 2004; van Vliet et al., 2007; Kim et al., 2013, 2010). Thus, the prevention of vasogenic edema formation is one of the major therapeutic strategies, which help to alleviate life-threatening complications and to inhibit epileptogenesis following SE.

Recently, we have reported that SE impairs BBB integrity via endothelin B ($ET_B$) receptor activation, which disrupts BBB elements by reactive oxygen species, nitric oxide and/or matrix metalloproteinase (MMP)-9. Indeed, $ET_B$ receptor antagonism effectively alleviates SE-induced vasogenic edema (Kim et al., 2013, 2015; Y.J. Kim et al., 2014). Similarly, $ET_B$ receptor antagonists attenuate the formation of vasogenic edema by inhibiting MMP-9 and vascular endothelial growth factor (VEGF) expressions following cold injury (Michinaga et al., 2015). Although VEGF has neuroprotective functions in vivo (Wang et al., 2005; Bellomo et al., 2003; Sun et al., 2003; Hayashi et al., 1997; Hayashi et al., 1998), it results in unfavorable vascular responses including hemodynamic steal phenomena and increase in vascular permeability (Wang et al., 2005; Kilic et al., 2006). Considering up-regulation of VEGF in neurons and glia induced by SE (Nicoletti et al., 2008), thus, it is likely that VEGF would be involved in vasogenic edema formation induced by SE, but not be fully clarified.

Leptomycin B (LMB) is an inhibitor of chromosome region maintenance 1 (CRM1) that is one of the nuclear protein exporters (Scaffidi et al., 2002; Faraco et al., 2007). In addition, LMB has a potent anti-tumor (Lu et al., 2012), anti-inflammatory (Loewe et al., 2002) and neuroprotective effects (Hyun et al., 2016). Interestingly, LMB inhibits VEGF expression in human meningioma

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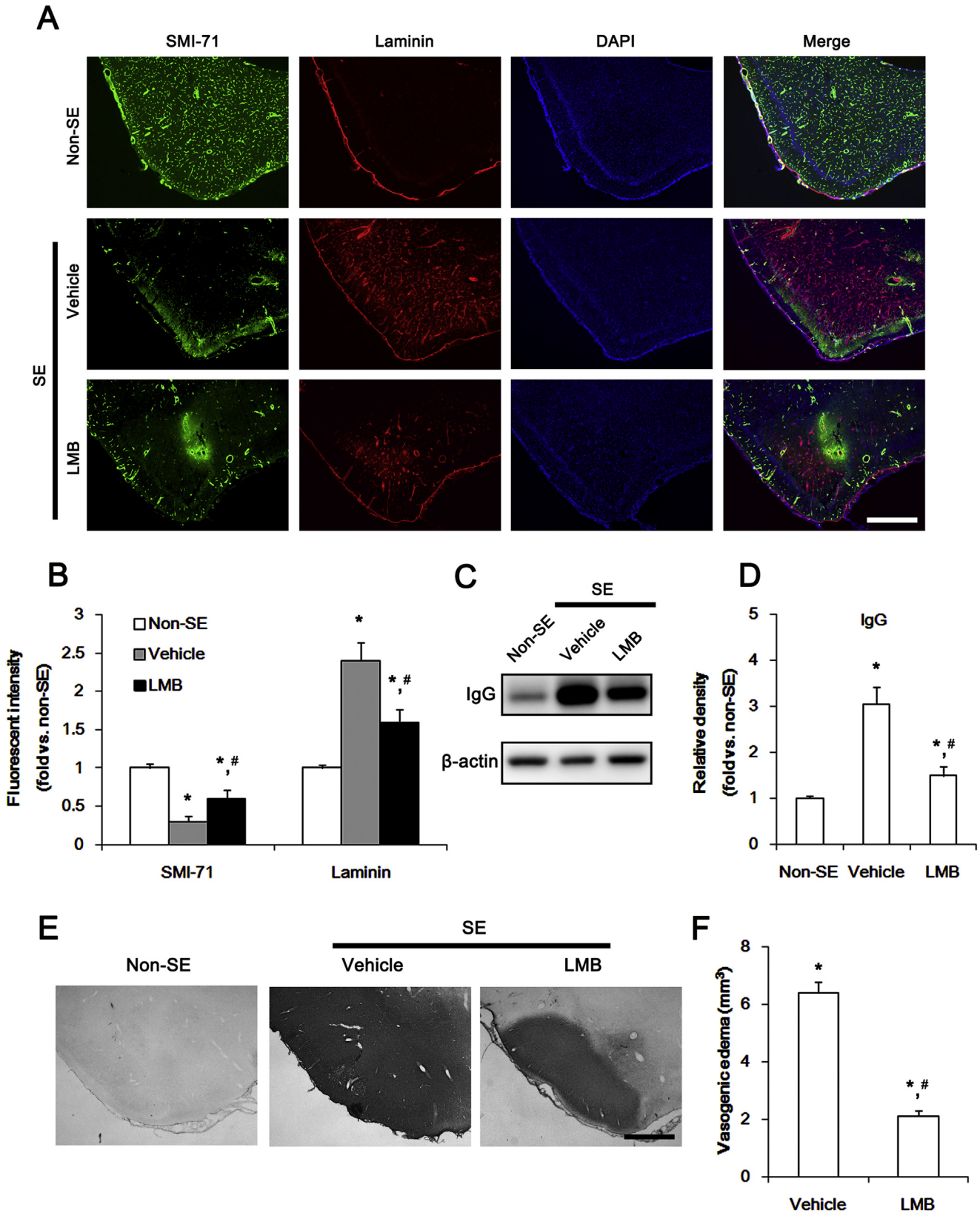


**Fig. 1. Effect of LMB on vasogenic edema induced by SE.** (A) Representative photographs of SMI-71 and laminin expression following SE. Bar = 400 μm. As compare to vehicle, LMB effectively ameliorates the reduction in SMI-71 expression and laminin over-expression induced by SE. (B) Quantitative values (mean ± S.E.M) of the fluorescent intensities of SMI-71 and laminin (n = 7 per each group). Significant differences are $^{*}p < 0.05$ vs. non-SE animals and $^{\#}p < 0.05$ vs. vehicle, respectively. (C) Western blot image for serum extravasation following SE. As compare to vehicle, LMB effectively abolishes serum extravasation induced by SE. (D) Quantitative values (mean ± S.E.M) of the western blot data concerning serum extravasation induced by SE (n = 7 per each group). Significant differences are $^{*}p < 0.05$ vs. non-SE animals and $^{\#}p < 0.05$ vs. vehicle, respectively. (E) Representative photographs of vasogenic edema lesion following SE. Bar = 400 μm. (F) Quantitative values (mean ± S.E.M) of the vasogenic edema lesion (n = 7 per each group). Significant differences are $^{*}p < 0.05$ vs. non-SE animals and $^{\#}p < 0.05$ vs. vehicle, respectively.