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Effect of 710 nm visible light irradiation on neurite outgrowth in primary rat cortical neurons following ischemic insult

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ABSTRACT

Objective: We previously reported that 710 nm Light-emitting Diode (LED) has a protective effect through cellular immunity activation in the stroke animal model. However, whether LED directly protects neurons suffering from neurodegeneration was entirely unknown. Therefore, we sought to determine the effects of 710 nm visible light irradiation on neuronal protection and neuronal outgrowth in an *in vitro* stroke model.

Materials & methods: Primary cultured rat cortical neurons were exposed to oxygen-glucose deprivation (OGD) and reoxygenation and normal conditions. An LED array with a peak wavelength of 710 nm was placed beneath the covered culture dishes with the room light turned off and were irradiated accordingly. LED treatments (4 min at 4 J/cm^2 and 50 mW/cm^2) were given once to four times within 8 h at 2 h intervals for 7 days. Mean neurite density, mean neurite diameter, and total fiber length were also measured after microtubule associated protein 2 (MAP2) immunostaining using the Axio Vision program. Synaptic marker expression and MAPK activation were confirmed by Western blotting.

Results: Images captured after MAP2 immunocytochemistry showed significant ($p < 0.05$) enhancement of post-ischemic neurite outgrowth with LED treatment once and twice a day. MAPK activation was enhanced by LED treatment in both OGD-exposed and normal cells. The levels of synaptic markers such as PSD 95, GAP 43, and synaptophysin significantly increased with LED treatment in both OGD-exposed and normal cells ($p < 0.05$).

Conclusion: Our data suggest that LED treatment may promote synaptogenesis through MAPK activation and subsequently protect cell death in the *in vitro* stroke model.

1. Introduction

Visible light (VIS) has various known biological effects: vasodilation [1,2], acceleration of wound healing [3,4], pain relief [5,6], cognition [7,8], circadian rhythm maintenance [9,10], modulation of depressive symptoms [11,12], and immune modulation [13]. Near-infrared light (NIR) via light-emitting diode (LED) treatment promotes wound healing in humans and animals [14]. Recently, increasing evidence has suggested that NIR-LED is therapeutic to neurons injured by toxins in primary cultured neurons. It upregulates cytochrome oxidase activity and ATP content in primary cultures of rat visual cortical neurons functionally inactivated by tetrodotoxin, potassium cyanide (KCN), or sodium azide (NaN_3) [15]. Photobiomodulation is therapeutic to rat retinal neurons poisoned by methanol-induced formate, a reversible inhibitor of cytochrome oxidase [16].

Neurite outgrowth is an important aspect of neuronal plasticity and regeneration in neuropathological conditions and neural injury. Neurite outgrowth is also essential for neuronal pathfinding and the establishment of synaptic connections during development [17]. Activation of the ERK and PI3K/Akt signaling pathways has been reported to regulate neuronal differentiation [18,19]. Collectively, these data suggest that both ERK and PI3K/Akt signaling are involved in neurite outgrowth [17]. Recent studies support a role of JNK in the regulation of neurite outgrowth during development. JNKs are also implicated in axonal regeneration of adult dorsal root ganglion neurons, as their specific inhibition *in vitro* dramatically reduces neuritogenesis without affecting neuronal survival [20]. p38 mitogen-activated protein (MAP) kinase plays

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multiple roles in neural functions, including migration, survival, synaptic function, and endocytosis. In addition, p38 MAP kinase is essential for neurite outgrowth; a p38-specific inhibitor blocks neurite outgrowth in several nervous systems [21].

Synaptophysin, a major integral membrane protein of synaptic vesicles, generally co-localizes with axon terminals [22]. Growth associated protein (GAP43), a neuron-specific, membrane-associated phosphoprotein, is dramatically elevated during neuronal development and regeneration. GAP43 is among the most abundant proteins in neuronal growth cones. GAP43 overexpression in transgenic mice produces spontaneous axonal sprouting and enhances induced remodeling in several neuron populations [23]. The postsynaptic density (PSD), a macromolecular signaling assembly embedded in the postsynaptic membrane of neurons, contains receptors, scaffold molecules, and cytoskeletal elements and is the primary postsynaptic site for signal transduction and signal processing [24]. PSD95, the best characterized protein member of the PSD95 family, was abundantly expressed in the PSD of excitatory synapses.

Recently, increasing evidence suggested that low level infrared laser irradiation (808 nm) protects brain neuronal cells after stroke. Transcranial infrared laser therapy improved clinical rating scores and motor function after embolic strokes in rabbits [25,26], and low-energy laser irradiation improved neurological deficits in rats following acute stroke [27]. Moreover, we previously reported that 710 nm LED has a protective effect through cellular immunity activation in the stroke animal model [28]. Noninvasive intervention of low level laser therapy issued 24 h after acute stroke may provide a significant functional benefit with an underlying mechanism, possibly through the induction of neurogenesis [29]. In this context, quantitative evaluation of LED irradiation induced neuronal outgrowth and synaptogenesis in neurons suffering ischemic injury is needed to excavate the possible mechanism on cellular as well as molecular level. The purpose of this study is to ascertain the effects of 710 nm visible light irradiation on synaptogenesis and neuronal protection in an *in vitro* model of ischemic stroke.

2. Materials and methods

2.1. Primary cortical neurons culture

Primary cortical neurons were collected from embryonic day 18 Sprague–Dawley rat embryos and cultured at 37 °C in a humidified atmosphere containing 95% N_2 and 5% CO_2 with Neurobasal medium with B27 supplement with antibiotics at a density of 1×10^6 cells/ml as described previously [6] with some modifications. All experimental procedures were in accordance with the Guide for Care and Use of Laboratory Animals and approved by the Medicine Animal Studies Committee of Konkuk University. Detailed procedures are described in the Supplemental Methods.

2.2. OGD exposure

Primary cortical neurons were collected from embryonic day 18 Sprague–Dawley rat embryos. On DIV 6, the culture medium was replaced with a glucose-free, serum free MEM medium, and cells were put into an anaerobic incubator ($pO_2 < 2$ mm Hg; Forma Anaerobic Systems, Thermo Electron, USA) with an atmosphere of 95% N_2 and 5% CO_2 and 98% humidity at 37 °C for 1 h. OGD was terminated by removing the cultures from the anaerobic incubator, changing the medium, and returning them to normoxic conditions. Control cultures were exposed to serum-free MEM containing glucose for the same duration in normoxic conditions.

2.3. Irradiation procedure

An LED array (25 cm × 10 cm) with a peak wavelength of 710 nm (QRAY, Inc. Seoul, Korea) was placed beneath covered 60 mm culture dishes with the room light turned off, and the dishes were irradiated accordingly. LED treatments (710 nm for 4 min at 4 J/cm^2 and 50 mW/cm^2) were given once, twice, thrice, or four times within 8 h at 2-h intervals for 7 days.

2.4. Total RNA extraction and RT-PCR analysis

Total RNA was extracted from primary cultured cortical neurons using Trizol reagent (Invitrogen, Carlsbad, USA). Detailed procedures are described in the Supplemental Methods.

2.5. Western blot analysis

Protein extracts from primary cortical neurons (20 μg) were separated by sodium dodecyl sulfate–polyacrylamide gels using Tricine buffer and were subsequently transferred to nitrocellulose. The blots were probed with anti- GAP43, PSD95, synaptophysin, pErk, Erk, pJNK, JNK, pp38 or β-actin. HRP conjugated anti-rabbit IgG or anti-mouse IgG (vector, 1:2000) was used as a secondary antibody, and the blots were then developed by enhanced chemiluminescence (LAS 3000, Fujifilm, Japan).

2.6. Immunocytochemistry

Immunocytochemistry against MAP-2 was performed. Detailed procedures are described in the Supplemental methods.

2.7. Capturing images and analysis

Images were captured and analyzed with Axio Vision software using a CCD camera attached to inverted light microscope with a 40× objective (Carl Zeiss, USA). Five or more randomly captured images were analyzed for each group. Detailed procedures are described in the Supplemental Methods.

2.8. Statistical analysis

Data are expressed as percentages of values obtained in control conditions and are presented as mean ± S.E.M. of at least three experiments in independent cell cultures. Statistical analysis was performed using a one-way ANOVA followed by Newman-Keuls Multiple Comparison Test. Values of $p < 0.05$ were considered significant.

3. Results

3.1. 710 nm light irradiation in primary cortical neurons promotes neurite outgrowth

We first determined whether neuronal growth might be altered in primary cortical neurons that have been irradiated with 710 nm light. Primary cultured rat cortical neurons were exposed to LED irradiation for 7 days from day *in vitro* (DIV) 6. LED treatments were given once, twice, thrice, or four times within 8 h a day. We found that 710 nm light irradiation significantly promotes neurite density and fiber diameter in comparison with non-treated groups, which was confirmed by images captured following MAP2 immunocytochemistry staining and analyzed by the Axio Vision software (Fig. 1A and B). LED treatment once and twice a day significantly increased the mean neurite density and diameter. After LED treatment once and twice a day, mean neurite density increased by

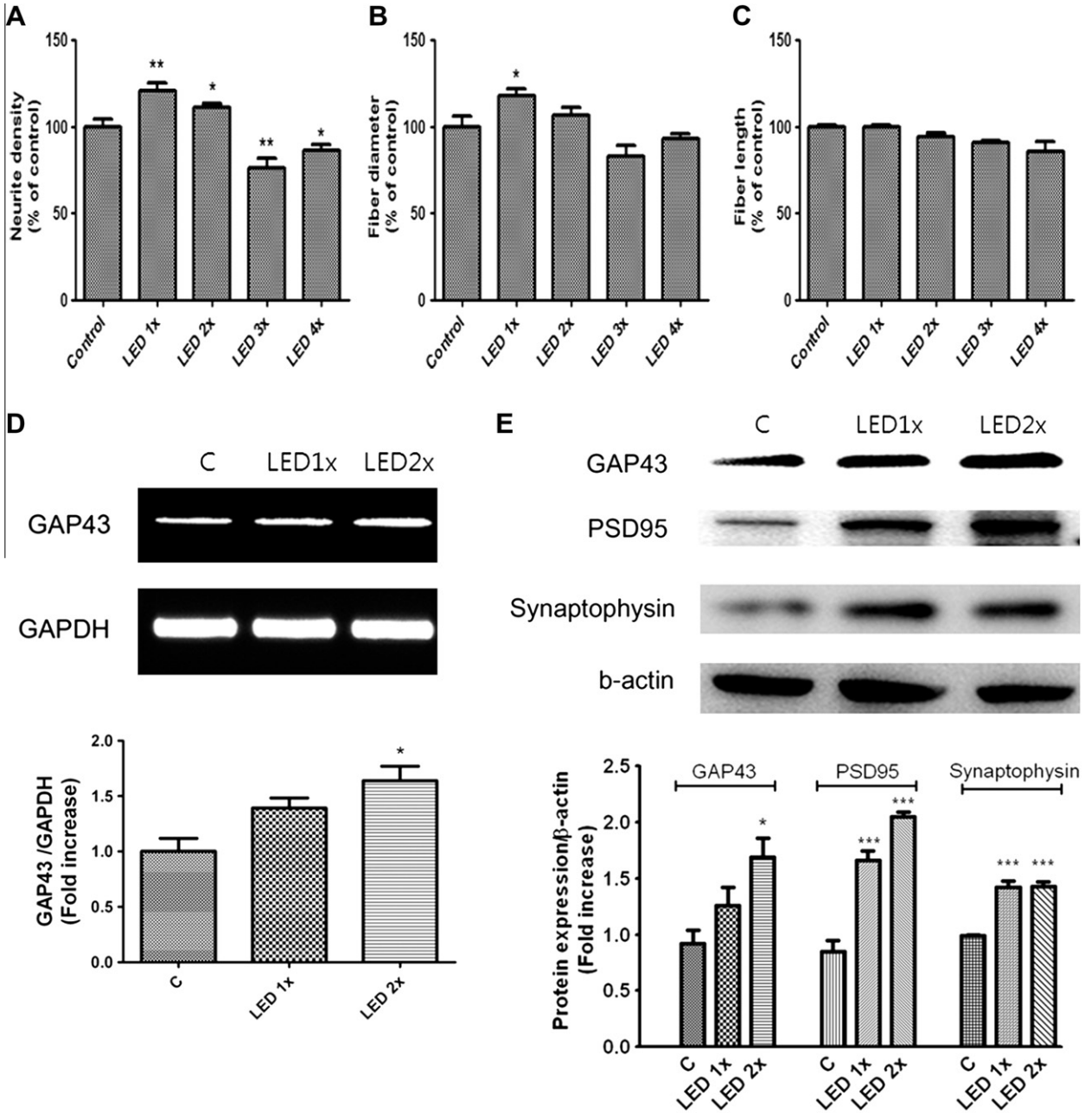

Fig. 1. 710 nm light irradiation in primary cortical neurons promotes neurite outgrowth. Cortical neurons were treated with LED once (LED1x), twice (LED2x), thrice (LED3x), or four times (LED4x) within 8 h at 2-h intervals for 7 days. The mean neurite density (A), mean fiber diameter (B) and total fiber length (C) were measured by software at 40× magnification with an inverted light microscope. $^{*}p < 0.05$ and $^{**}p < 0.01$vs control. (D) Representative photomicrographs of RT-PCR against GAP43 after 7 days of LED irradiation on primary cortical neurons. $^{*}p < 0.05$ vs control. (E) Representative photomicrographs of Western blots of the synaptogenesis markers GAP43, PSD95, or synaptophysin after 7 days of LED irradiation on primary cortical neurons. $^{*}p < 0.05$ and $^{***}p < 0.001$ vs control. (D, E) The intensity of each band was determined densitometrically and normalized against GAPDH or β-actin. Expression levels are depicted as fold increase relative to the corresponding untreated control.

20.73 ± 4.65% ($p < 0.01$) and 11.08 ± 2.62% ($p < 0.05$), respectively. However, LED treatment three and four times a day significantly decreased the mean neurite density by 26.7 ± 5.31% ($p < 0.01$) and 13.8 ± 3.76% ($p \leqslant 0.05$), respectively. It may be due to biphasic dose response effects of LED light on primary cortical neurons [30]. Mean neurite diameter significantly increased by 18.21 ± 4.65% ($p < 0.01$) after LED treatment once a day. To see whether LED treatment can effectively alter synaptogenesis, we checked the levels of synaptic markers, such as GAP43, PSD95, and synaptophysin, by RT-PCR and Western blot analysis. GAP43 mRNA expression was increased by LED treatment once or twice a day for 7 days in cultured cortical neurons (Fig. 1D). The levels of GAP43, PSD95, and synaptophysin expression significantly increased after LED treatment once or twice a day for 7 days (Fig. 1E).

3.2. Mitogen-activated protein kinase (MAPK) activation by 710 nm light irradiation is involved in neurite outgrowth

MAPK signals are known to be important in neurite outgrowth. Therefore, we examined whether the neurite-promoting effect of 710 nm light irradiation was due to activation of specific MAPK signals, including ERK, JNK, and p38. Light irradiation increased activation of ERK, JNK, and p38 kinases as determined by their phosphorylation measured at day 7 of LED treatment (Fig. 2). We

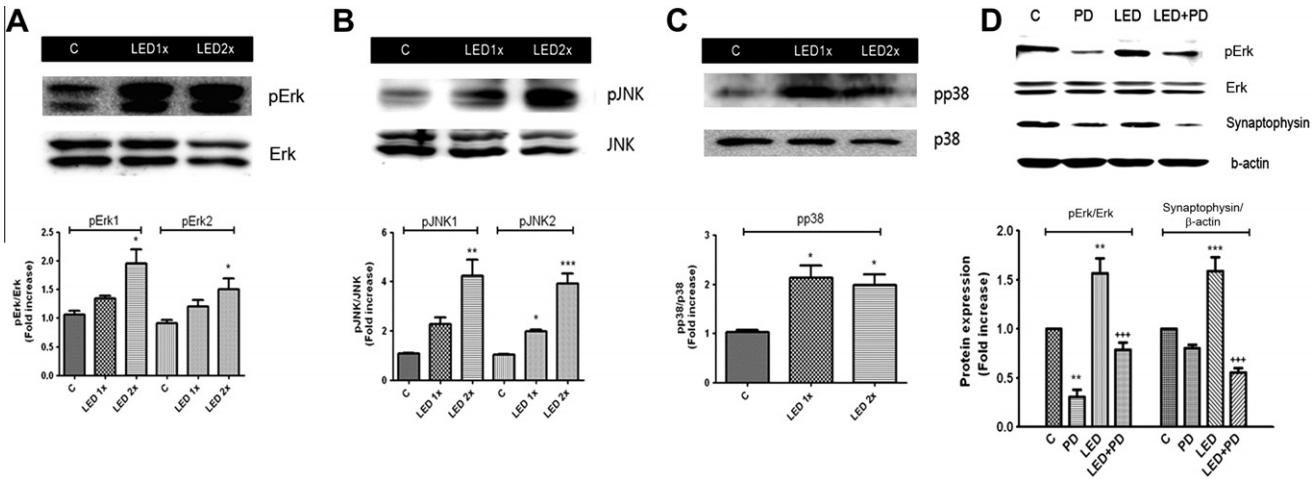

Fig. 2. 710 nm light irradiation induces MAPK activation. Representative photomicrographs of Western blots of pErk (A), pJNK (B), and pp38 (C) after 7 days of LED irradiation on primary cortical neurons. (D) Increased synaptophysin expression by LED treatment was reduced after MEK inhibitor treatment. Representative photomicrographs of Western blots of pErk and synaptophysin after 7 days of LED irradiation with PD 98059 on primary cortical neurons. The intensity of each band was determined densitometrically and normalized against β-actin or Erk. Expression levels are depicted as fold increase relative to the corresponding untreated control. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ vs control; $+++p < 0.001$ vs LED treatment.

used a MEK-specific inhibitor, PD98059 to clarify the role of MAPK pathways in synaptic protein expression and found that inhibition of the ERK pathway with PD98059 (50 μM) significantly suppressed the level of synaptophysin expression in LED-treated cortical neurons ($p < 0.001$; Fig. 2D). These results suggested that MAPK phosphorylation and pERK are associated with the expression of synaptophysin in 710 nm LED -treated cells.

3.3. Post-ischemic LED treatment promotes neurite outgrowth

To determine the effect of LED treatment in neurite outgrowth after OGD, cortical neurons exposed to OGD condition for 1 h were examined after 7 day - LED treatment. We found that 7 day-LED treatment markedly promoted neurite outgrowth and arborization in comparison with non-treated groups, which was confirmed by images captured following MAP2 immunocytochemistry staining and analyzed by the Axio Vision program (Fig. 3). Differences in the mean neurite density (μm^2) and total fiber length (μm) were found in LED-treated groups after OGD. Our findings showed that on DIV 13, the neuronal network was reduced by 48.89 ± 1.41% after OGD plus reoxygenation in non-treated group ($p < 0.001$; Fig. 2A and B). LED treatment increased mean neurite density (82.13 ± 5.87%) and total fiber length ($p < 0.001$; Fig. 3).

3.4. LED treatment via MAPK activation promotes the expression of synaptic markers after OGD

To determine whether LED treatment can effectively restore synaptogenesis after OGD, we checked levels of GAP43, PSD95, and synaptophysin at day 7 of LED treatment. Both GAP43 mRNA and protein expression increased in LED treated group as compared with non-treated cells after OGD ($p < 0.001$; Figs. 4A and B). Moreover, LED treatment significantly increased expression of PSD95. Synaptophysin expression was markedly reduced after OGD plus reoxygenation in non-treated group (0.67 ± 0.54-fold of control), while LED treatment recovered its expression to 1.01 ± 0.09-fold of control (Fig 4B). We also examined whether enhanced expressions of synaptic proteins by 710 nm light irradiation were due to activation of specific ERK signals after OGD plus reoxygenation.

We found that inhibition of the ERK pathway with PD98059 (50 μM) significantly reduced the level of synaptophysin and GAP43 expression in LED-treated cells after OGD ($p < 0.01$;

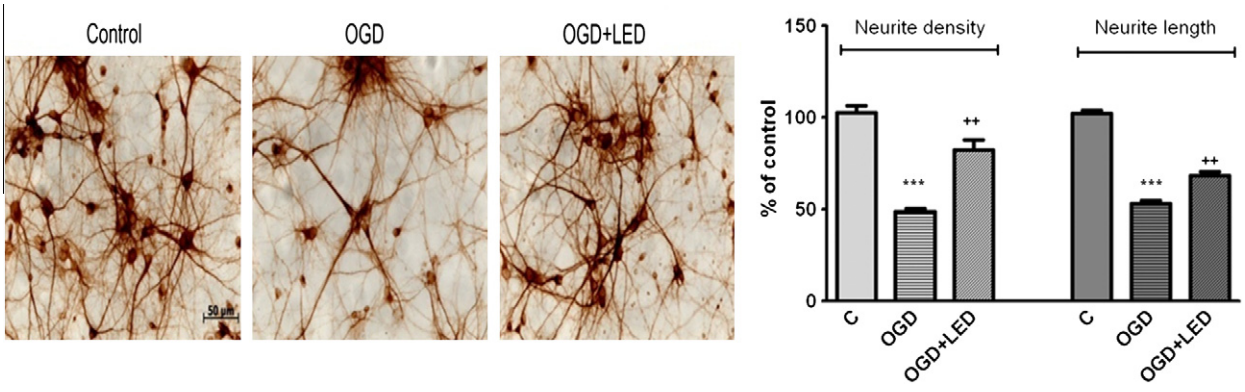

Fig. 3. Post-ischemic LED treatment promotes neurite outgrowth. Representative images showing MAP2 immunocytochemistry results of different groups. After 1 h OGD on DIV 6, cells were treated with or without 710 nm light LED irradiation twice a day for 1 week. Neurite outgrowth levels are depicted as percent increase relative to the corresponding untreated control. $^{***}p < 0.001$ vs control; $++p < 0.01$ vs OGD.

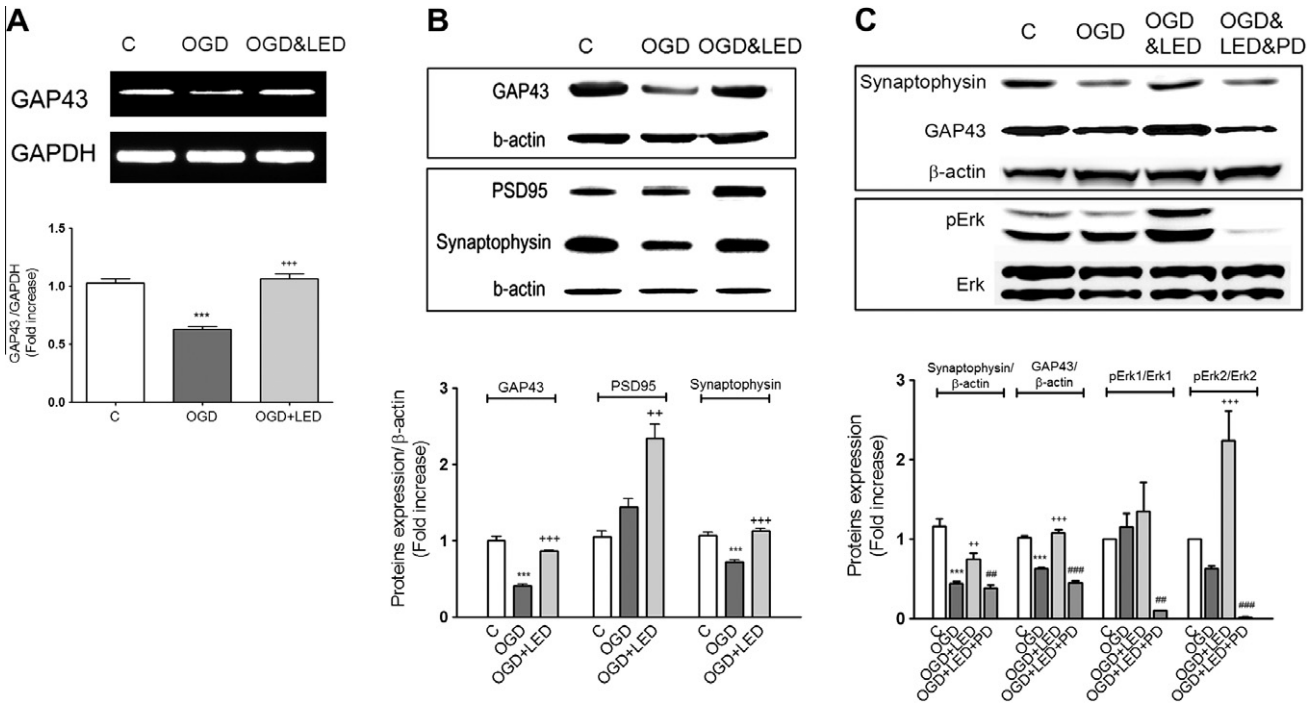

Fig. 4. LED treatment promotes expression of synaptic markers after OGD. (A) Representative photomicrographs of RT-PCR against GAP43 after 7 days of LED irradiation on OGD-exposed primary cortical neurons. The intensity of each band was determined densitometrically and normalized against GAPDH. ***$p < 0.001$ vs control; +++$p < 0.001$ vs OGD. (B) Representative photomicrographs of Western blots of the synaptogenesis markers GAP43, PSD95, or synaptophysin after 7 days of LED irradiation on OGD-exposed primary cortical neurons. ***$p < 0.001$ vs control; ++$p < 0.01$ and +++$p < 0.01$ vs OGD. (C) Representative photomicrographs of Western blots of pErk, synaptophysin and GAP43 after 7 days of LED irradiation with PD 98059 on OGD-exposed primary cortical neurons. ***p < 0.001 vs control; ++$p \leqslant 0.01$ and +++$p < 0.001$ vs LED treatment; ##$p < 0.01$ and ### $p < 0.001$ vs OGD plus LED treatment. (B, C) The intensity of each band was determined densitometrically and normalized against β-actin or Erk. Expression levels are depicted as fold increase relative to the corresponding untreated control.

Fig. 4C). These results indicated that ERK activation is related to the expressions of synaptophysin and GAP43 in 710 nm LED-treated cells after OGD plus reoxygenation.

4. Discussion

In the present study, we demonstrated that 710 nm light irradiation promotes neurite outgrowth of rat cortical neurons in normoxic and ischemic culture conditions. This is the first study suggesting that activation of MAPK by 710 nm irradiation promotes neurite outgrowth in the neurons. Some previous studies have suggested that low level light (LLL, 810 nm wavelength light) irradiation enhances axonal growth and nerve regeneration in both rat spinal cord [31,32] and peripheral nerve injuries [33]. The studies of NIR-LED and LLL on primary cortical neurons have demonstrated that light follows a biphasic dose response effects [30,34]. They suggested that the low level laser irradiation may be responsible for the beneficial stimulatory effects in primary cortical neurons. However, high level light may be responsible for the damaging effects in cellular level. In our results, while LED treatment once or twice a day significantly increased neurite outgrowth and expression of synaptic proteins as compared with non-LED treated ones, but LED treatment thrice or four times a day decreased neurite density in cortical cells.

Levels of GAP43, PSD95, and synaptophysin were increased by 710 nm light irradiation in normoxic and ischemic culture conditions in this study. Neuronal damage and plasticity can be identified by synaptic proteins, such as synaptophysin, GAP43, and PSD protein after Alzheimer's disease [35,36], Pick disease [35], and stroke [37,38], as well as normal physiological conditions [39,40]. In the pathological state, synaptophysin-like immunoreactivity decreased in the hippocampus and the entorhinal cortex in patients with definite and possible Alzheimer's disease [36]. In an experimental stroke model, synaptophysin immunoreactivity is reflecting increase in synapses in the cortex surrounding an area of infarction. Changes in the level of synaptophysin presumably reflect those in synaptic vesicles, and it thus follows that such changes are an indicator of synaptic plasticity [41,42]. The selective expression of neuronal structural proteins (MAP-2 in dendrites and GAP43 in axons) in neurons observed in the boundary zone to the ischemic core is suggestive of compensatory and reparatory mechanisms in ischemia-damaged neurons after transient focal cerebral ischemia [23,38]. Synaptic ultrastructural analysis showed that environmental enrichment after middle cerebral artery occlusion increased the thicknesses of PSD in the parietal cortex and hippocampus, accompanying improved performance in spatial memory tasks [43]. The reduction in neurite density, neurite length, and levels of GAP43, PSD95, and synaptophysin caused by OGD exposure was recovered by 710 nm light irradiation. Our data suggest that 710 nm visible light irradiation may promote synaptogenesis and subsequently protect cell death in the *in vitro* stroke model. Therefore, 710 nm light irradiation might be a possible therapeutic modality to use after stroke.

A recent report indicated that laser irradiation stimulates NGF-induced neurite elongation on a laminin-collagen coated substrate and protects PC12 cells against oxidative stress [44]. These data are compatible with our findings that 710 nm light irradiation protects cell culture viability in ischemic conditions. It also stimulates neurite outgrowth, and this effect could also have positive implications for axonal protection. In conclusion, our data suggest that 710 nm visible light irradiation may promote neurite outgrowth and synaptic protein expression through MAPK activation and protect against ischemic damage in the *in vitro* stroke model.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.04.147.

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