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Research Article

Lactobacillus gasseri NK109 Alleviates Lipopolysaccharide-Induced Cognitive Impairment in Mice by Up-Regulating Inflammation-Mediated BDNF Expression

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Abstract

Exposure to lipopolysaccharide (LPS) causes cognitive impairment (CI). In the preliminary study, *Lactobacillus gasseri* NK109 suppressed LPS-induced expression of proinflammatory cytokines in macrophages. Therefore, the effect of NK109 on LPS-increased CI was investigated in mice. Intraperitoneal injection of LPS caused CI-like behaviors and neuroinflammation. However, orally administered NK109 reduced LPS-increased CI-like behaviors and hippocampal IL-1β and TNF-α expression, whereas LPS-decreased BDNF expression increased. NK109 also reduced LPS-increased colonic myeloperoxidase, IL-1β, and TNF-α expression. The efficacy of NK109 was increased by the combination of soybean embryo ethanol extract (S_E). These findings suggest that NK109 with S_E can improve CI by alleviating inflammation-mediated BDNF expression, thereby being beneficial for dementia therapy.

Keywords

Lactobacillus gasseri NK109, cognitive impairment, lipopolysaccharide.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, which is closely connected with systemic inflammation including neuroinflammation and neurotransmitter imbalance (Cao *et al.*, 2020; Tarawneh and Holtzman, 2012). In particular, neuronal inflammation is known to be deteriorated by the alteration of gut microbiota and overexpression of bacterial toxins such as lipopolysaccharide (LPS) (Busche and Hyman, 2020; Cryan *et al.*, 2020; Jang *et al.*, 2018; Reitz and Mayeux, 2014). Exposure to gut bacteria LPS causes neuroinflammation and gut inflammation in rodents, resulting in cognitive impairment (CI) through the suppression of BDNF expression (Jang *et al.*, 2018). BDNF regulates synapse in the many brain regions including hippocampus for maintaining memory storages (Afonso *et al.*, 2019; Lu *et al.*, 2014).

Approximately 40% of patient with gut inflammation suffer from psychiatric diseases with

gut dysbiosis (Almeida *et al.*, 2020; Fousekis *et al.*, 2021). The breaking of gut microbiota by antibiotics, pathogens, and stresses, causes the overgrowth of harmful bacteria such as *Clostridioides difficile* and toxic substances such as endotoxins (Dodiya *et al.*, 2020; Konstantinidis *et al.*, 2020). Chronic exposure to overproduced endotoxins occurs gut and systemic inflammation, resulting in psychiatric disorder (Jang *et al.*, 2018; Marizzoni *et al.*, 2020). Therefore, the alleviation of gut dysbiosis by probiotics lessens the endotoxin overexpression, leading to the amelioration of gut and systemic inflammation (Angelucci *et al.*, 2019; Gomaa, 2020; Westfall *et al.*, 2017). Gut bacteria lipopolysaccharide (LPS) production-inhibiting *Lactobacillus plantarum* NK151 alleviates CI with gut inflammation in mice (Lee *et al.*, 2021b). Anti-inflammatory *Bifidobacterium longum* NK46 improves CI with colitis in rodents (Lee *et al.*, 2019). IL-1β expression-inhibiting *Lactobacillus gasseri* NK109 also increases cognitive function in aged or *Escherichia coli*-treated mice (Yun *et al.*, 2020; Yun *et al.*, 2023). Anti-inflammatory *Lactiplantibacillus plantarum* C29 increases cognitive function in 5xFAD and aged mice by upregulating inflammation-mediated brain-derived neurotropic factor (BDNF) expression (Jeong *et al.*, 2015; Lee *et al.*, 2018). Based on these findings, up-regulating NF-κB activation-suppressed BDNF expression may be beneficial for the therapy of cognitive impairment. Furthermore, the cognitive impairment-ameliorating effects of probiotics are enhanced by the addition of natural products such as soybean (*Glycine max*), which also improves cognitive impairment (Hwang *et al.*, 2019; Lee *et al.*, 2021a; Lee *et al.*, 2018). Nevertheless, the cognitive impairment-ameliorating action mechanism of NK109 with or without natural products remains elusive.

Therefore, to confirm whether the suppression of NF-κB signaling by probiotics could regulate CI, we examined the effects of *Lactobacillus gasseri* NK109 and its supplement combined with soybean embryo ethanol extract (S_E) on LPS-induced CI in mice.

MATERIALS AND METHODS

Materials

LPS and MRS were purchased from Sigma (St Louis, MO) and BD (Franklin Lakes, NJ), respectively. A commercial soybean germ ethanol extract (S_E, unprocessed, contained 0.2% soyasaponin Bb) was purchased from Mirae Biotech (Pocheon-shi, Korea).

Culture of NK109

NK109, which was isolated from human feces (female, 34 yrs, Korean) in the previous report (Yun *et al.*, 2020), was cultured in MRS broth at 37°C for 24 h, centrifuged, and freeze-dried.

Culture of macrophages

Macrophage cells (peritoneal macrophages and BV2 cells) were cultured, as previously reported (Jeong *et al.*, 2016; Lee *et al.*, 2017). These cells (1×10^6 cells/mL) were incubated with LPS (100 ng/mL) in the absence or presence of NK109 (N_4, 1×10^4 CFUs/mL; N_6, 1×10^6 CFUs/mL) for 20 h. In the supernatant, proinflammatory cytokine levels were assayed.

Animals

C57BL/6 mice (male, 6 weeks old, 18-20 g) were purchased from Koatech (Pyeongtaek-shi, Korea), maintained under the controlled condition, as previously reported. All experiments were approved by the Committee for the Care and Use of Laboratory Animals at Kyung Hee University (IACC, KHUASP(SE)-21306) and were ethically carried out according to the University Guideline.

Mice with CI were prepared by intraperitoneally injecting LPS (10 μg/kg/day), as previously reported (Hong *et al.*, 2014; Lee *et al.*, 2011). (1) Mice were divided into four groups (NC, LP, N_L, and N_H), intraperitoneally injected with LPS daily for 5 days. Test agents (LP, vehicle alone; N_L, 5×10^8 CFU/mouse of NK109; N_H, 1×10^9 CFU/mouse of NK109) were orally gavaged daily for 5 days next day after LPS treatment. Each group consisted

of 7 mice. (2) Mice were divided into five groups (NC, LP, NL, S_EN_L, and S_EN_H), intraperitoneally injected with LPS daily for 5 days. Thereafter, test agents (LP, vehicle alone; S_EN_L, the mixture of 100 mg/kg/day of SE and 0.5 × 10^9 CFU/mouse/day of NK109; and S_EN_H, the mixture of 100 mg/kg/day of SE and 1 × 10^9 CFU/mouse/day of NK109) were orally gavaged daily for 5 days. NC was treated with saline instead of LPS and test agents. Each group consisted of 7 mice.

Cognitive behaviors were measured in the Y-maze task (YMT), novel object recognition test (NORT), and Barnes maze task (BMT) (Yun *et al.*, 2021; Yun *et al.*, 2023). Mice was killed by exposure to CO_2 in a chamber. Bloods, brains, and colons were collected and stored at − 80°C. The biomarkers were assayed using enzyme-linked immunosorbent assay (ELISA). For the immunostaining, mice were perfused and brain and colon tissues were collected, post-fixed with paraformaldehyde, cytoprotected, freezed, immunostained, and observed using a confocal microscope.

Statistics

Experimental data are described as mean ± S.D. The significance was analyzed using one-way ANOVA followed by Duncan's multiple range test ($p < 0.05$).

RESUTLS

Effect of NK109 on the expression of proinflammatory cytokines in LPS-stimulated macrophages

To understand whether NK109 could mitigate inflammation-involved cognitive decline, we first investigated the effect of NK109 on proinflammatory cytokine expression in LPS-stimulated macrophages (Fig. 1). LPS treatment significantly up-regulated TNF-α and IL-1β expression in peritoneal macrophages and BV2 cells. However, NK109 inhibited aLPS-induced TNF-α and IL-1β expression.

Effect of NK109 on LPS-induced CI and colitis in mice

Next, we investigated the effect of NK109 on LPS-induced CI in mice (Fig. 2). Intraperitoneally injected LPS impaired

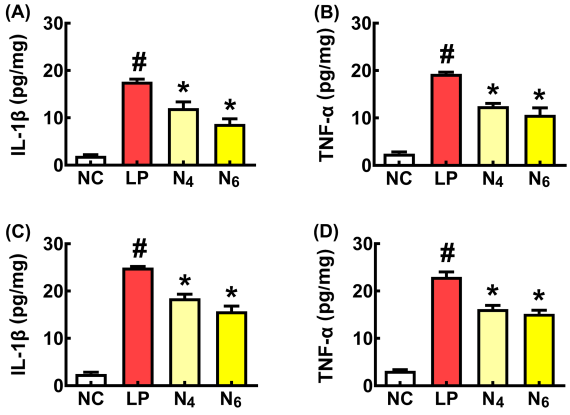

Fig. 1. The effects of NK109 on the TNF-α and IL-1β expression in LPS-stimulated macrophages. Effect on the TNF-α (A) and IL-1β expression (B) in peritoneal macrophages. Effect on the TNF-α (C) and IL-1β expression (D) in BV2 cells. Cells were incubated with NK109 (N_4, 1 ´ 10^4 CFU/mL; N_6, 1 ´ 10^6 CFU mg/mL). NC was treated with vehicle (PBS). Data values were described as mean ± S.D. (n = 4). $^{\#}p<0.05$ vs NC group. $^{*}p<0.05$ vs LPS group.

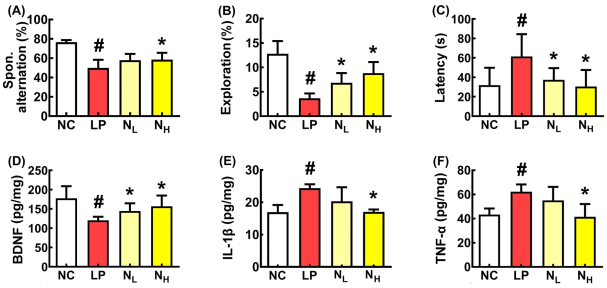

Fig. 2. The effect of NK109 on the LPS-induced CI in mice. Effects on CI-like behaviors in the YMT (A), NORT (B), and BMT (C). (B) Effects on hippocampal BDNF (D), IL-1β (E), and TNF-α (F) levles. NC was treated with vehicle (saline) instead of LPS and test agents. Test agents (LP, vehicle alone; N_L, 0.5 × 10^8 CFU/mouse of NK109; N_H, 1 × 10^9 CFU/mouse of NK109) were orally gavaged in mice daily for 5 days. Data values are as mean ± SD (n = 7). $^{\#}p<0.05$ vs NC group. $^{*}p<0.05$ vs LP group.

cognitive behaviors in the YMT to 65.2% of normal control (NC) mice. However, oral administrations of NK109 improved LPS-impaired cognitive function. NK109 at a dose of 50 mg/kg (N_L) restored LPS-impaired cognitive

function to 89.8% of NC mice. However, LPS or NK109 did not significantly affect average values of the arm entry numbers in the YMT. LPS treatment also reduced exploration in the NORT to 28.9% of NC mice and increased the escape time (on the third day) in the BMT to 192.8% of NC mice. However, NK109 alleviated exploration and latency. N_L treatment increased LPS-impaired exploration time to 58.9% of NC mice and decreased LPS-induced escape time to 115.1% of NC mice. The CI-ameliorating effect of N_H was higher without significance than that of N_L. Furthermore, NK109 suppressed IL-1β and TNF-α expression in the brain, whereas BDNF expression increased. NK109 also decreased LPS-induced myeloperoxidase, IL-1β, and TNF-α expression in the colon (Fig. 3).

The combined effects of NK109 with SE on LPS-induced CI and colitis in mice

Oral administration of NK109 and heat-processed SE mix increased cognitive function in aged mice (Yun *et al.*, 2023). Therefore, to investigate whether SE could increase the CI-ameliorating effect of NK109, we investigated the effects of N_L, S_EN_L, and S_EN_H on LPS-induced CI in mice (Fig. 4). N_L, S_EN_L, and S_EN_H all alleviated LPS-induced CI-like behaviors (Fig. 4A-C). They suppressed IL-1β and TNF-α expression and NF-κB$^+$Iba1$^+$ cell number in the brain, whereas BDNF expression and BDNF$^+$NeuN$^+$ cell number increased (Fig. 4D-H). They also decreased LPS-induced myeloperoxidase, IL-1β, and TNF-α expression

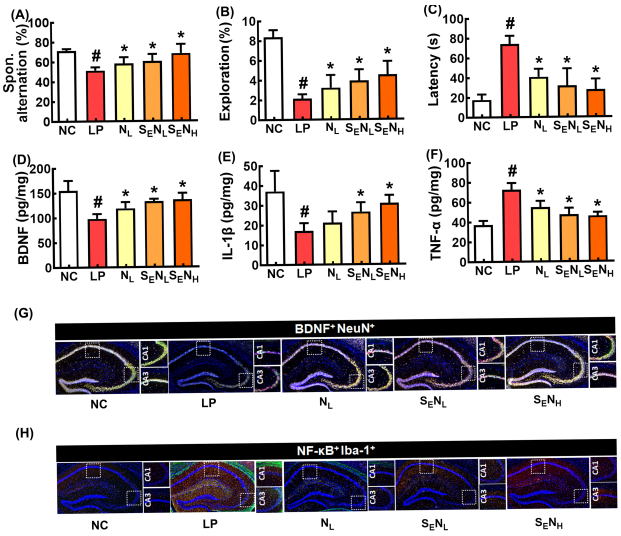

Fig. 4. The effects of S_EN_L and S_EN_H on LPS-induced CI in mice. Effects on CI-like behaviors in the YMT (A), NORT (B), and BMT (C). Effects on hippocampal BDNF (D), IL-1β (E), and TNF-α (F) levels and BDNF$^+$NeuN$^+$ (G) and NF-κB$^+$Iba1$^+$ cell numbers (H) NC was treated with vehicle (saline) instead of LPS and test agents. Test agents (LP, vehicle alone; N_L, 0.5 × 10^9 CFU/mouse of NK109; S_EN_L, [S_E (100 mg/kg/day of SE) plus N_L (0.5 × 10^9 CFU/mouse of NK109)]; and S_EN_H, [S_E (100 mg/kg/day of SE) plus N_H (1 × 10^9 CFU/mouse of NK109)]) were orally gavaged in mice daily for 5 days. Data values are as mean ± SD (n = 7). $^{\#}p$<0.05 vs NC group. $^{*}p$<0.05 vs LP group.

and NF-κB$^+$CD11c$^+$ cell number in the colon (Fig. 5). Of these, S_EN_H most potently alleviated CI-like behaviors, down-regulated proinflammatory cytokine expression in the brain and colon, and up-regulated BDNF expression in the hippocampus, followed by S_EN_L and N_L. However,

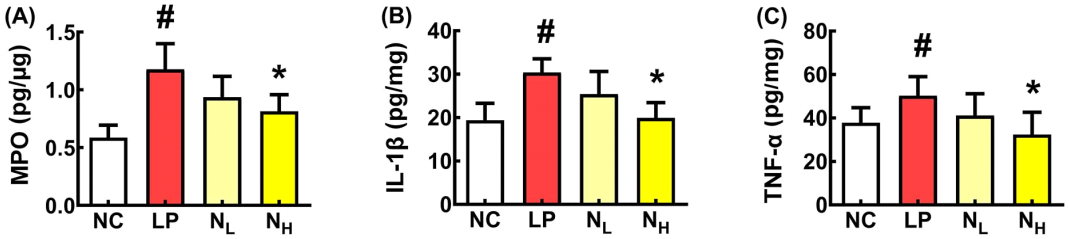

Fig. 3. The effect of NK109 on the LPS-induced colitis in mice. Effects on myeloperoxidase (MPO) (A), IL-1β (B), and TNF-α (C) levels in the colon. NC was treated with vehicle (saline) instead of LPS and test agents. Test agents (LP, vehicle alone; N_L, 0.5×10^8 CFU/mouse of NK109; N_H, 1×10^9 CFU/mouse of NK109) were orally gavaged in mice daily for 5 days. Data values are as mean ± SD (n = 7). $^{\#}p$<0.05 vs NC group. $^{*}p$<0.05 vs LP group.

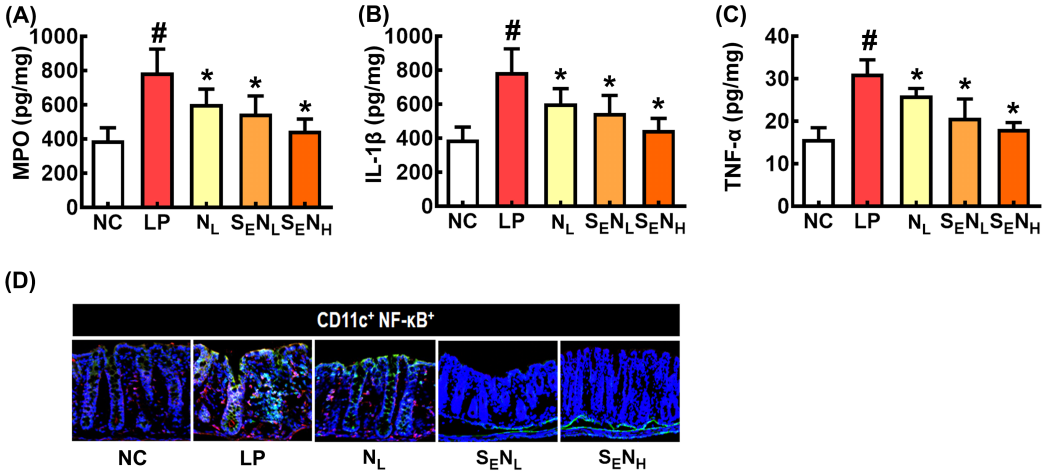

Fig. 5. The effects of S_EN_L and S_EN_H on LPS-induced colitis in mice. Effects on myeloperoxidase (MPO) (A), IL-1β (B), and TNF-α (C) levels and NF-κB$^+$CD11c$^+$ cell number (D) in the colon. NC was treated with vehicle (saline) instead of LPS and test agents. Test agents (LP, vehicle alone; N_L, 0.5 × 10^9 CFU/mouse of NK109; S_EN_L, [S_E (100 mg/kg/day of SE) plus N_L (0.5 × 10^9 CFU/mouse of NK109)]; and S_EN_H, [S_E (100 mg/kg/day of SE) plus N_H (1 × 10^9 CFU/mouse of NK109)]) were orally gavaged in mice daily for 5 days. Data values are as mean ± SD (n = 7). $^{\#}p<0.05$ vs NC group. $^{*}p<0.05$ vs LP group.

there were not significant differences between them.

DISCUSSION

Brain and gut are at the bidirectional cross-talks through neural, immune, and endocrine networks (Cryan *et al.*, 2019; Maqsood and Stone, 2016). Gut inflammation significantly increased the occurrence of dementia (Jang *et al.*, 2018). The attenuation of gut inflammation by probiotics or drugs alleviates CI and depression (Park *et al.*, 2020; Sakurai *et al.*, 2022; Yang *et al.*, 2020; Yun *et al.*, 2021). Anti-inflammatory *Limosilactobacillus mucosae* NK41 mitigated LPS-impaired cognitive function and gut inflammation in mice (Lee *et al.*, 2019). *Lactiplantibacillus plantarum* C29 and DW2009, a C29-fermented soybean, increased cognitive function and alleviated colitis in 5xFAD mice (Lee *et al.*, 2018). They also alleviated CI and gut inflammation in mice treated with LPS or D-galactose (Lee *et al.*, 2021a; Woo *et al.*, 2014). Furthermore, DW2009 improved cognitive function in patients with mild CI (Hwang *et al.*, 2019). These results suggest that anti-inflammatory probiotics may alleviate CI as well as gut inflammation *in vivo* through the activation of gut-brain axis.

In the present study, NK109 improved LPS-impaired CI, neuroinflammation, and colitis in mice. In particular, NK109 suppressed proinflammatory cytokine expression and NF-κB-positive immune cells in the colon and brain. In the previous study, NK109 attenuated *Escherichia coli*-induced CI and depression in mice by regulating NF-κB activation and gut microbiota dysbiosis and cognitive function in aged mice (Yun *et al.*, 2020). These findings suggest that NK109 may attenuate CI by suppressing inflammatory response.

When NK109 was combined with SE, the combinations also alleviated LPS-impaired cognitive behaviors, suppressed NF-κB-positive cells and proinflammatory cytokine in the brain and colon, whereas BDNF level and BDNF-positive cells increased. Moreover, S_EN_H more potently alleviated CI than S_EN_L or N_L. Although the efficacy of S_EN_H against cognitive impairment was not significantly different to that of NK109 or S_EN_L, the combination of NK109 and SE additively alleviated CI and colitis. In addition, NF-κB activation-induced neuroinflammation suppresses BDNF expression in the brain (Carreño *et al.*, 2011; Kairisalo *et al.*, 2009; Lee *et al.*,

2021a; Marini *et al.*, 2004; Ying *et al.*, 2002). These results suggest that the combination of NK109 and SE may strongly alleviate CI by suppressing inflammatory responses and inducing BDNF expression. Moreover, the combination of probiotics with natural products may be beneficial for improving their efficacies.

In conclusion, heat-processing may increase the efficacy of SE on CI. The combined treatment of SE and NK109 may additively mitigate CI by the regulation of NF-κB-mediated BDNF expression.

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Conflicts of Interest

The authors declare no conflict of interest.

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