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Differential modulation of lipopolysaccharide- and zymosan-induced hypophagia by dexamethasone treatment

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ABSTRACT

The treatment of experimental animals with lipopolysaccharide (LPS) induces behavioral depression, in which the central and peripheral inductions of proinflammatory cytokines are proposed to play an important role. We have shown that the intraperitoneal injection of zymosan, composed of insoluble particles prepared from yeast cell walls, can induce behavioral depression assessed as hypophagia in mice, although the role of proinflammatory cytokines in this response has not yet been investigated. We have also shown that the subcutaneous injection of the corticoid, dexamethasone (Dex), a potent inhibitor of cytokine production, is effective in attenuating hypophagia in LPS-treated mice. The attenuated response was associated with the suppression of the gene induction of proinflammatory cytokines (i.e., IL-1β, IL-6 and TNFα) in the brain and liver. In contrast, no significant induction of proinflammatory cytokine genes was observed in the brain or liver during zymosan-induced hypophagia; the subcutaneous injection of Dex did not attenuate zymosan-induced hypophagia but its intraperitoneal injection did. Thus, zymosan-induced hypophagia was less responsive to a subcutaneous injection of dexamethasone than LPS-induced hypophagia, which may be due to the limited role of systemic inflammation in this response. An important role of localized, rather than systemic, inflammation in zymosan-induced hypophagia was suggested, although the role of local proinflammatory cytokines remains to be clarified.

1. Introduction

Peripheral administration of lipopolysaccharide (LPS) induces in animals a pattern of behavioral depression including hypomotility, hypophagia and suppressed exploration (Bret-Dibat et al., 1995; Bluthe et al., 1992; Avitsur et al., 1997). Numerous studies have shown that LPS induces the systemic production of proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor α (TNFα) and IL-6, which have been proposed to play important roles in behavioral depression (Laye et al., 2000; Bluthe et al., 2000a; Swiergiel and Dunn, 1999). These cytokines are thought to act as transmitters of peripheral immune signals to the central nervous system (CNS) (Hopkins, 2007; Konsman et al., 2000; Banks, 2001). Proinflammatory cytokines are also induced in the hypothalamus, cortex, and hippocampus (Eriksson et al., 2000; Turrin et al., 2001), and their central administration results in similar behavioral responses induced by peripheral challenge with LPS (Gonzalez et al., 2006; Bluthe et al., 2000b). These observations suggest that proinflammatory cytokines mediate behavioral responses to LPS.

Glucocorticoids (GCs) inhibit the induction of proinflammatory cytokines mainly by interacting with the intracellular glucocorticoid receptor involved in the activation of nuclear factor kappa B (NFκB) and activator protein-1 (AP-1) (Jonat et al., 1990; Ray and Prefontaine, 1994; Munoz et al., 1996). These effects of GCs explain the primary mechanism by which exogenous GCs exert immunomodulatory and anti-inflammatory actions. The administration of GCs is effective in attenuating LPS-induced behavioral depression (Fishkin and Winslow, 1997; Pezeshki et al., 1996).

We demonstrated that the intraperitoneal injection of zymosan, composed of insoluble particles prepared from yeast cell walls, induces hypophagia in mice (Takenaka et al., 2005; Naoi et al., 2006). Pretreatment with a cyclooxygenase-2 (COX-2)-selective inhibitor, but not with a COX-1-selective inhibitor, also attenuates zymosan-induced hypophagia (Naoi et al., 2006) similar to LPS-induced hypophagia (Johnson et al., 2002; Lugarini et al., 2002; Swiergiel and Dunn, 2002). The expression level of COX-2 was elevated similarly in LPS- and zymosan-treated mice (Naoi et al., 2006). These findings suggest that prostaglandins generated by COX-2 are common mediators of both LPS- and zymosan-induced hypophagia. On the other hand, although zymosan is recognized by toll-like receptor 2 (TLR2) or mannose receptors, it can activate NFκB and induce proinflammatory cytokines similarly to responses to LPS through TLR4 (Deva et al., 2003; Fernandez et al., 2005). Therefore, it can be assumed that zymosan and LPS induce hypophagia through the induction of proinflammatory cytokines and, thus, pharmacological

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Table 1
Primer sequences used in real-time RT-PCR

Gene	Sequences (5′-3′)	Size (bp)	Accession no.
IL-1β	F: caactgtgaaatgccacc R: gtgacactgcctgcctga	176	NM_008361
IL-6	F: ccacttcacaagtcggaggctta R: gcaagtgcatcatcgttgttcatac	122	NM_031168
TNFα	F: aagcctgtagcccacgtcgta R: ggcaccactagttggttgtctttg	112	NM_013693
β-actin	F: ctggcaccacaccttctaca R: ggtacgaccagaggcataca	171	NM_007393

agents that can suppress the induction of proinflammatory cytokines could affect zymosan-induced hypophagia. We therefore compared the effects of GC administration on hypophagia and proinflammatory cytokine induction in mice challenged with LPS and zymosan.

2. Materials and methods

2.1. Experimental animals and treatments

Male ddY mice at 4 weeks of age (SLC Japan, Shizuoka, Japan) were housed in plastic cages placed in an air-conditioned room (temperature at 23±2 °C and humidity at 55±5%) under a 12 h:12 h light–dark cycle; lights were turned off at 08 00 h. The animals were maintained under the above conditions for 10 days prior to the experiments below. LPS from *Escherichia coli* 055:B5 (Sigma-Aldrich, St. Louis, MO) or zymosan (Zymosan A, Sigma-Aldrich) was dissolved in physiological saline and intraperitoneally (ip) injected at 0.1, 0.25 and 0.5 mg/kg for LPS and at 20, 50 and 100 mg/kg for zymosan. LPS and zymosan were injected at 13 00 h. The concentrations of the LPS and zymosan solutions were adjusted to the doses for injection at a constant injection volume of 10 ml/kg body weight. Dexamethasone (Dex) (Wako Pure Chem, Osaka, Japan) dissolved in dimethylsulfoxide (DMSO, 100%) was subcutaneously or intraperitoneally (ip) injected at 10 mg/kg body weight in a volume of 1 ml/kg, 2 h prior to LPS or zymosan injection. The same volume of 100% DMSO without Dex was subcutaneously or ip injected in the control groups. All the procedures for the animal experiments in this study were performed according to the Guide for Animal Experiment, University of Toyama and approved by the Committee of Animal Care and Experiments of the University of Toyama.

2.2. Assessment of hypophagic response

We assessed hypophagic response as the reduction in the intake of solid milk diet (Naoi et al., 2006) made of agar and sweetened condensed milk diluted with water as follows; agar (Wako Pure Chem) was dissolved in distilled water at 2% (w/v) by heating and then mixed with a same volume of sweetened condensed milk (Snow Brand Milk Products Co., Ltd. Tokyo, Japan) diluted 2-fold with distilled water. A 10-ml aliquot of the mixture was poured into a polystylene plastic vial (25 mm diameter and 40 mm height) and cooled in room. The solid milk diet was prepared daily for each test. The mice were exposed to the milk diet for a short duration (30 min) 2 h after the injection of LPS or zymosan in non-food-deprived mice. The maximum hypophagic responses have been shown at this time point after LPS and zymosan challenges (Naoi et al., 2006).

2.3. Relative levels of proinflammatory cytokine gene transcripts in the brain and liver

Two hours after the injections of LPS (0.25 and 0.5 mg/kg) and zymosan (50 and 100 mg/kg), the mice were sacrificed by cervical dislocation. The brain and liver were harvested, rinsed in ice-cold saline, quickly frozen in liquid nitrogen, and stored at −70 °C. Total RNA was extracted from frozen tissues using RNAiso (Takara Bio, Tokyo, Japan) and dissolved in nuclease-free water. RNA concentration was determined by measuring ultraviolet absorption, and a constant amount (1 μg) of total RNA was reverse-transcribed using Superscript III (Invitrogen, Carlsbad, California) in the presence of random hexamer primers (Invitrogen). The mixture containing first-strand cDNA was diluted with a constant volume of nuclease-free water, and its aliquot was introduced into a real-time polymerase-chain reaction (PCR) system in the presence of SYBR Green using SYBR Green Real-time PCR Master Mix (Toyobo, Osaka, Japan). The sequence of the gene transcript of β-actin, IL-1β, IL-6, or TNFα was amplified using the LineGene real-time PCR system (Bioflux, Tokyo). The primers used to amplify these gene transcripts are listed in Table 1. The PCR conditions were 95 °C for 10 min, followed by 35 (β-actin), 40 (IL-1β and TNFβ) or 45 (IL-6) cycles of 94 °C for 15 s, 58 °C (IL-1β), 60 °C (IL-6 and TNFα) or 61 °C (β-actin) for 15 s and 72 °C for 30 s. A standard curve using serial 1:10 dilutions of pooled cDNA for each target transcript was generated in every PCR experiment to determine the relative amounts of the sequences amplified with the respective primers. The amplified products were verified by checking melting curves after the final cycle of each PCR

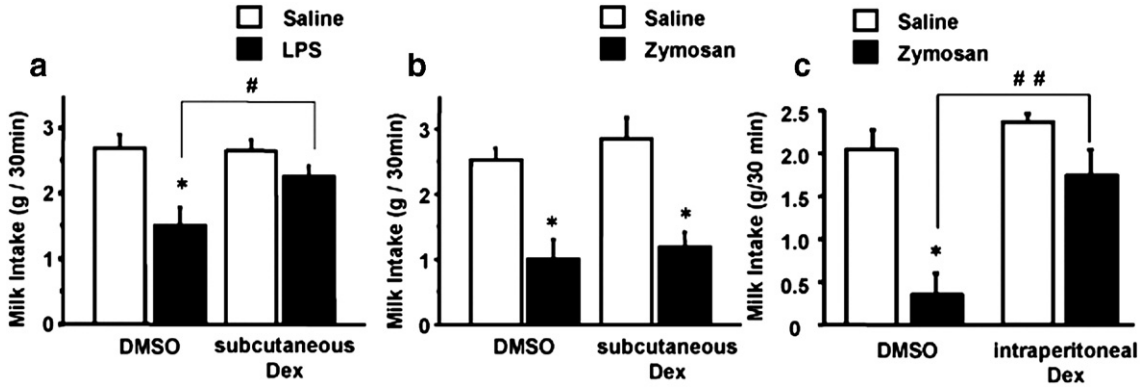

Fig. 1. Effect of dexamethasone treatment on LPS- and zymosan-induced hypophagia. Dexamethasone (Dex) was subcutaneously injected 2 h before the intraperitoneal injection of LPS (0.25 mg/kg body weight) or zymosan (50 mg/kg body weight). Fourteen and 7 mice were used in each group in the experiments for LPS (a) and zymosan (b), respectively. In addition, Dex was intraperitoneally injected 2 h before the intraperitoneal injection of zymosan (c). Nine mice were used in each group in this experiment. Milk intake for 30 min was evaluated 2 h after the LPS or zymosan challenge. Values represent means±SEM. Two-way ANOVA revealed a significant interaction [$F(1, 52)=4.4$, $p<0.05$] between LPS and subcutaneous Dex treatments but no significant interaction between zymosan and subcutaneous Dex treatments [$F(1, 24)=0.066$]. However, a significant interaction [$F(1, 32)=6.074$, $p=0.0193$] between zymosan and intraperitoneal Dex treatments was observed. Statistically significant differences between DMSO- and Dex-treated groups in LPS-treated and zymosan-treated mice were observed in the post hoc test followed by a one-way ANOVA (# and ## at $p<0.05$ and $p<0.001$, respectively). Asterisk (*) indicates the significant effect of LPS or zymosan ($p<0.05$) compared with that in the saline-treated groups in each DMSO- or Dex-treated group.

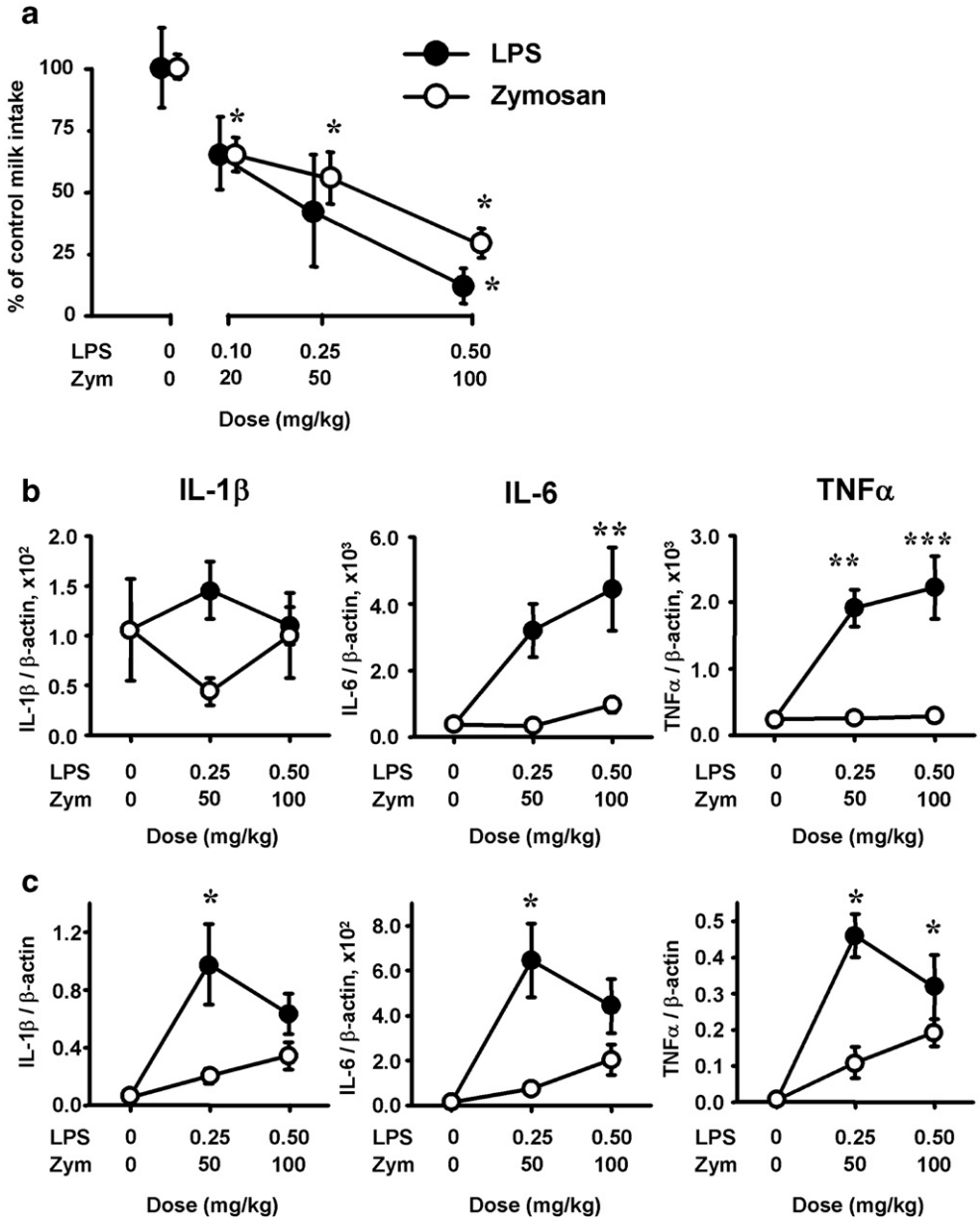

Fig. 2. Hypophagia and induction of proinflammatory cytokine gene transcripts in the brain and liver of LPS- or zymosan-challenged mice. Mice were ip injected with LPS at 0 (n=4), 0.10 (n=5), 0.25 (n=5) and 0.5 mg/kg (n=5) or zymosan at 0 (n=5) 20 (n=6), 50 (n=6) and 100 (n=5) mg/kg in panel a. Milk intake was evaluated 2 h after LPS or zymosan challenge. The levels of the gene transcripts of IL-1β, IL-6 and TNFα in the brain (b) and liver (c) of the mice treated with the vehicle (n=4), LPS at 0.25 (n=6) and 0.5 mg/kg (n=7) or zymosan at 50 (n=6) and 100 mg/kg (n=7) were determined by an RT-PCR technique, as described in Materials and methods. The relative expression levels of the gene transcripts were standardized to those of β-actin. Values represent means ± SEM. Statistically significant difference compared with the control groups was estimated by a one-way ANOVA followed by a post hoc test (*p<0.05, **p<0.01, ***p<0.001).

experiment. The amounts of the gene transcripts were expressed as the relative value standardized to that of β-actin in each sample.

2.4. Statistical analysis

Two-way analysis of variance (ANOVA) was used to analyze the effects of LPS or zymosan and Dex, and their interaction on milk intake and gene expression. The comparison among individual groups was carried out by one-way ANOVA and Bonferroni's post hoc test.

3. Results

A two-way ANOVA reveals that LPS and subcutaneous Dex treatments interact in changing milk intake [F (1, 52)=4.4, p<0.05] (Fig. 1a). In addition, a significant difference was shown by a one-way ANOVA among the groups [F (3, 52)=7.919, p=0.0002], and a post hoc test also revealed that milk intake was significantly enhanced by Dex pretreatment in LPS-treated mice (p<0.05). In contrast, no significant interaction between zymosan and subcutaneous Dex treatments was observed [F (1, 24)= 0.066, NS] (Fig. 1b). Thus, subcutaneous Dex treatment was effective in attenuating LPS-induced hypophagia but not zymosan-induced hypophagia (Fig. 1a and b). However, we cannot exclude the possibilities that subcutaneous Dex treatment did not reach the peritoneum to inhibit inflammatory responses induced by ip injected zymosan, thereby leading to the failure of this treatment to attenuate zymosan-induced hypophagia. When Dex was injected ip prior to zymosan injection, a significant interaction between zymosan and Dex treatments in changing milk intake was observed [F (1, 32)=6.074, p=0.0193] (Fig. 1c). The one-way

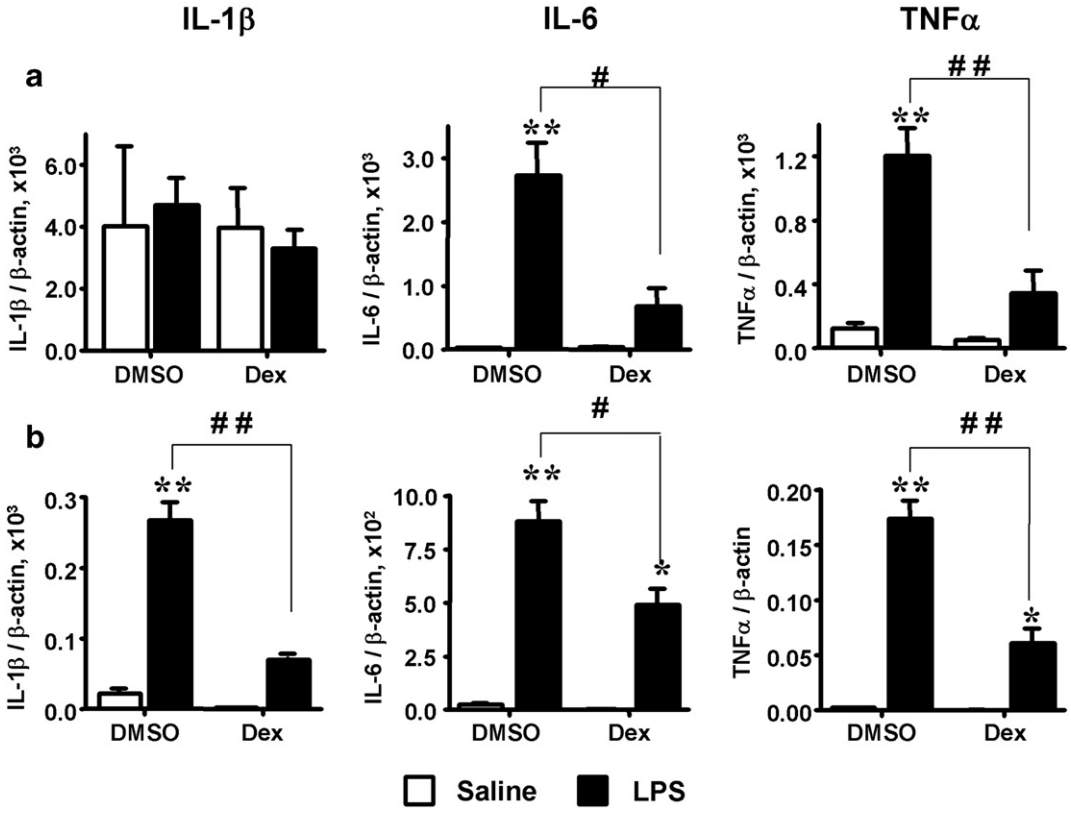

Fig. 3. Effect of Dex on induction of proinflammatory cytokine gene transcripts in the brain (a) and liver (b) of LPS-treated mice. Dexamethasone (Dex) was subcutaneously injected 2 h before the intraperitoneal injection of LPS (0.25 mg/kg body weight). The levels of the gene transcripts of IL-1β, IL-6 and TNFα in the brain and liver were determined by an RT-PCR technique, as described in Materials and methods. The relative expression levels of the gene transcripts were standardized to those of β-actin. Values represent means ± SEM for 5 mice in DMSO × saline, 10 mice in DMSO × LPS, 5 mice in Dex × saline and 10 mice Dex × LPS. Statistical significant difference among the individual groups was estimated by a post hoc test followed by a one-way ANOVA between the DMSO- and Dex-treated groups in the LPS-treated mice (# and # # at $p<0.01$ and 0.001, respectively). Asterisks (* and **) indicate significant effects of LPS compared with the saline-treated groups in the DMSO- or Dex-treated group (*$p<0.05$ and **$p<0.001$, respectively).

ANOVA followed by a post hoc test revealed that Dex treatment significantly augmented milk intake compared with DMSO treatment in the zymosan-treated mice ($p<0.001$).

The increasing doses of LPS and zymosan induced similar hypophagic responses ranging from 40 to 90% reduction in milk intake compared with the control values [$F(7, 33)=6.339$, $p<0.001$ in one-way ANOVA and $p<0.05$ in a post hoc test) (Fig. 2a). The two higher doses of LPS (0.25 and 0.5 mg/kg body weight) and zymosan (50 and 100 mg/kg body weight), which induced similar hypophagic responses (Fig. 2a), were used to compare the abilities of LPS and zymosan to induce proinflammatory cytokine genes. The one-way ANOVA revealed that the levels of the gene transcripts of IL-6 [$F(4, 25)=6.044$, $p=0.0015$] and TNFα [$F(4, 25)=12.97$, $p<0.0001$] but not IL-1β [$F(4, 25)=1.308$, $p=0.294$] in the brain significantly differed among the control, LPS and zymosan groups (Fig. 2b). The post hoc test indicated that a high dose of LPS significantly elevated the expression level of the IL-6 gene in the brain compared with that in the control group ($p<0.01$). Both low and high doses of LPS significantly elevated the expression levels of the TNFα gene in the brain compared with those in the control group ($p<0.01$ and $p<0.001$). In the liver, the expression levels of all the three genes significantly differed among the groups [$F(4, 25)=5.086$, $p=0.0039$ for IL-1β, $F(4, 25)=5.960$, $p=0.0016$ for IL-6 and $F(4, 25)=7.657$, $p=0.0004$ for TNFα]. However, a lower LPS dose induced significant ($p<0.05$) and stronger responses in the inductions of the IL-1β, IL-6 and TNFα gene transcripts than a higher LPS dose (Fig. 2c). These results suggest that the maximal responses were induced by the lower dose of LPS in inducing these cytokine genes, although we did not test much lower doses of LPS. In contrast, the expression levels of proinflammatory cytokine genes were not significantly elevated in the brain of the mice treated with the two doses of zymosan compared with those in the control groups ($p>0.05$) (Fig. 2b), despite a similar degree of hypophagia being induced (Fig. 2a). Similarly, no significant elevation in the expression levels of these gene transcripts was induced in the liver of the zymosan-treated mice compared with that in the control groups ($p>0.05$) (Fig. 2c).

The two-way ANOVA revealed a significant interaction between LPS and subcutaneous Dex treatments in changing the expression levels of the IL-6 and TNFα genes [$F(1, 26)=5.905$ for IL-6, $p=0.022$ and $F(1, 26)=5.937$ for TNFα, $p=0.022$]. The one-way ANOVA followed by a post hoc test also indicated that the elevated expression levels of the IL-6 and TNFα genes were significantly lowered by Dex treatment ($p<0.01$ and $p<0.001$, respectively) (Fig. 3a). Similarly, significant interactions between LPS and Dex treatments were shown with the change in the expression levels of the IL-1β and TNFα genes in the liver [$F(1, 26)=20.33$ for IL-1β, $p<0.001$ and $F(1, 26)=5.937$ for TNFα, $p=0.022$] (Fig. 3b). As regards the expression level of the IL-6 gene in the liver, the interaction between LPS treatment and Dex pretreatment was not significant [$F(1, 26)=3.554$, $0.05<p<0.1$]. However, when a one-way ANOVA followed by a post hoc test was used, the elevated expression levels of all the three genes in the liver from the LPS-treated mice were found to be significantly decreased by Dex pretreatment ($p<0.001$ for IL-1β, $p<0.01$ for IL-6 and $p<0.001$ for TNFα).

4. Discussion

There are many lines of evidence supporting the role of brain proinflammatory cytokines in behavioral responses induced by LPS as

well as by other bacterial and viral components (Fernandez et al., 2005; Cunningham et al., 2007). As shown in our study, there are close relationships between the inductions of proinflammatory cytokine genes (i.e., IL-6 and TNFα, but not IL-1β) in the brain and hypophagia in LPS-treated mice (Figs. 1 and 2), suggesting that these gene products play an important role in LPS-induced hypophagia. However, there are some data that do not support the role of proinflammatory cytokines in LPS-induced hypophagia; that is the administration of neutralizing antibodies against IL-1, IL-6 and TNFα was ineffective in modulating LPS-induced hypophagia (Teeling et al., 2007). The peripheral administration of these antibodies might be less effective in neutralizing proinflammatory cytokines expressed in the brain but may be more effective in neutralizing peripheral cytokines. Peripherally injected antibodies against proinflammatory cytokines might not cross the blood–brain barrier and might be inactive to inhibit their actions in the brain. In contrast, there is a study showing the attenuation of LPS-induced behavioral responses by the administration of neutralizing antibodies against IL-6 (Harden et al., 2006). In addition, two independent groups have demonstrated conflicting effects of the genetic disruption of IL-6 on LPS-induced hypophagia (Bluthe et al., 2000a; Swiergiel and Dunn, 2006). It is possible that the role of proinflammatory cytokines differs depending on the intensity of behavioral depression induced by various doses of LPS. We also suppose that a single proinflammatory cytokine cannot fully account for LPS-induced hypophagia. The inhibition of the actions of multiple proinflammatory cytokines might be effective in attenuating LPS-induced hypophagia (Swiergiel et al., 1997; Swiergiel and Dunn, 1999). As shown in our study, Dex treatment attenuated the induction of multiple proinflammatory cytokines in the brain and liver (Fig. 3), which may be the basis for the preventive effects of this agent on LPS-induced hypophagia. On the other hand, anti-inflammatory cytokines such as IL-10 may play a protective role in LPS-induced hypophagic response (Bluthe et al., 1999), although the effects of their neutralization or gene deletion have not yet been examined.

There are reports indicating that hypophagia is induced by peripheral challenge with various bacterial and viral components other than LPS such as muramyldipeptides (MDP) or polyinosinic: cytidic acid (polyI:C), a synthetic mimetic of viral double-stranded RNA (Fortier et al., 2004; Gayle et al., 1998). Under these experimental conditions, the induction of proinflammatory cytokine genes (Gayle et al., 1998) and their protein products (Fortier et al., 2004) seems to be a common response associated with hypophagia. In contrast, we found that the administration of zymosan at the doses required to induce hypophagia does not significantly induce the expression of the IL-6 or TNFα gene in the brain. (Figs. 1 and 2). The levels of the IL-6 and TNFα gene transcripts in the liver of the mice treated with a higher dose of zymosan (100 mg/kg) did not significantly change (Fig. 2c). However, these levels tended to be higher than those in the saline-treated group when a less conservative post hoc test was used ($0.05<p<0.1$ in Fisher's PLSD), suggesting that a higher dose of zymosan could induce the inflammatory responses in the liver. Although we have not determined the concentration of these cytokines in the brain or liver, we have confirmed that the concentration of plasma IL-6 measured by enzyme-linked immunosorbent assay was not significantly elevated in the mice treated with the behaviorally active doses of zymosan (unpublished observations). These results suggest that systemic responses to zymosan in inducing proinflammatory cytokines are weakened compared with LPS responses. Importantly, we also demonstrated that intraperitoneal Dex treatment attenuates zymosan-induced hypophagia (Fig. 1c). Thus, zymosan-induced hypophagia seems to be a unique experimental condition of hypophagia associated with local inflammation rather than systemic inflammation. The differential location of inflammation induced by LPS and zymosan challenge is possibly due to the nature of these immune activators; LPS could easily penetrate circulation after its ip injection, but ip injected zymosan localizes in the peritoneal cavity. It is also suggested that proinflammatory cytokines generated in the local site play an important role in zymosan-induced hypophagia.

Prostaglandins generated by COX-2 play an important role in LPS-induced hypophagia (Johnson et al., 2002; Lugarini et al., 2002; Naoi et al., 2006; Swiergiel and Dunn, 2002), although the inter-relationship between COX-2 and proinflammatory cytokine has not been understood well. Several proinflammatory cytokines can induce COX-2 and prostaglandin generations during LPS stimulation (Hoozemans et al., 2001; Dunn et al., 2006), suggesting that prostaglandins generated by COX-2 act downstream of proinflammatory cytokines in mediating LPS-induced hypophagia. It is also possible that prostaglandins generated by COX-2 induce proinflammatory cytokine induction in the brain upon LPS challenge. (Kagiwada et al., 2004). However, there are several reports showing that proinflammatory cytokine generation is not modulated by the administration of COX inhibitors despite the attenuation of LPS-induced behavioral changes (De La Garza et al., 2005; Johnson et al., 2002). These observations do not support the role of COX-2 and prostaglandins upstream of proinflammatory cytokines in LPS-induced hypophagia. Since Dex is effective in inhibiting COX-2 induction through its effects on NFκB activation of Pistritto et al. (1999), this pathway may explain the attenuation of LPS-induced hypophagia by this agent. However, additional explanations are required why zymosan can induce hypophagia through COX-2 activation (Naoi et al., 2006), because this response is not associated with proinflammatory cytokine gene induction and is attenuated by ip treatment but not by subcutaneous Dex treatment (Figs. 1 and 2). We suppose that zymosan can activate prostaglandin generation within the peritoneum through the induction of COX-2, which might be directly suppressed by intraperitoneal Dex treatment. In addition, COX-2 induction within the peritoneum upon ip zymosan treatment might depend on the generation of local proinflammatory cytokines. The modulation of these responses within the peritoneum upon ip zymosan by ip Dex treatment can be associated with the attenuation of zymosan-induced hypophagia by this treatment. Further studies are necessary to examine the effects of ip zymosan and Dex treatments on the induction of COX-2 and proinflammatory cytokines in the peritoneum.

Zymosan is an activator for inducing proinflammatory cytokine generation *in vitro* (Sanguedolce et al., 1992; Hartman et al., 1995) and in the peritoneal cavity following ip injection (Fantuzzi and Dinarello, 1998), although relatively larger amounts of zymosan can elicit systemic cytokine generation (Volman et al., 2004; Zhang et al., 2007). Under such conditions, the peak cytokine release is observed at 9 days and behavioral depression is supposed to be prolonged similarly. It is of great interest whether or not Dex treatment is effective for behavioral depression under prolonged inflammatory responses induced by large amounts of zymosan. Furthermore, the prolonged inflammation may involve wide varieties of inflammatory mediators other than proinflammatory cytokines such as lipid-derived mediators (Bulger et al., 2003; Cuzzocrea et al., 2004; Damas and Prunescu, 1993) and nitric oxide (Cuzzocrea et al., 1997). These inflammatory mediators should be considered when the effect of Dex treatment on behavioral depression is examined under the above conditions. On the other hand, we examined the effect of Dex treatment on zymosan-induced hypophagia using relatively limited numbers of mice ($n=7$ or 9) compared with those in the LPS experiment ($n=14$) (Fig. 1). This might affect the conclusion for the differential Dex effects on LPS- and zymosan-induced hypophagia; the differential effects of Dex on LPS- and zymosan-induced hypophagia should be further examined using a sufficient number of animals and under different doses of zymosan.

Numerous studies have suggested the efficacy of the pharmacological modulation of proinflammatory cytokine generation for the modulation of behavioral depression mainly using LPS-treated animals. Our results strongly suggest that zymosan induces hypophagia by utilizing processes distinct from those utilized in LPS-induced hypophagia by showing the differential modulation of these responses

by Dex treatment through different routes and the diminished induction of gene transcripts of proinflammatory cytokines in the brain and liver of zymosan-treated mice. Therefore, the zymosan-induced hypophagia model may be useful for investigating the mechanism of behavioral responses to localized inflammation rather than systemic inflammation. However, the direct role of the local induction of proinflammatory cytokines in the attenuation of zymosan-induced hypophagia by Dex treatment remains to be investigated.

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