Effect of Ginkgo Biloba Extract on Lipopolysaccharide-induced Anhedonic Depressive-like Behavior in Male Rats

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The peripheral administration of lipopolysaccharide (LPS) induces depressive-like behavior. Anhedonia is a core symptom of depression, defined as a loss of the capacity to experience pleasure. The present study used the sucrose preference test to investigate the influence of Ginkgo biloba extract (EGb 761) on LPS-induced anhedonia in male rats. The animals were randomly divided into four groups: (I) vehicle + saline, (II) vehicle + LPS, (III) EGb 761 + saline, and (IV) EGb 761 + LPS. Saline or LPS (100 μg/kg) was administered intraperitoneally 2 h before the sucrose preference test. Sucrose consumption was recorded 2, 4, 6, 13, and 24 h after 100 μg/kg of LPS or saline injection in the dark phase of the light/dark cycle. Dopamine and serotonin levels in the nucleus accumbens were measured. Our results indicated that the vehicle + LPS group exhibited a significant decrease in sucrose intake compared with the vehicle + saline group. The EGb 761 + LPS group showed more sucrose and food consumption than the vehicle + LPS group. Additionally, compared with the EGb 761 + LPS group, the vehicle + LPS group had less dopamine levels in the nucleus accumbens. Treatment with EGb 761 had no effect on water intake. Our results suggest that EGb 761 may be useful for reducing anhedonic depressive-like behavior. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: EGb 761; anhedonia; sucrose preference test; lipopolysaccharide; rat.

INTRODUCTION

Major depressive disorder (MDD) is a mental disorder characterized by an overall low mood accompanied by a loss of interest or pleasure in normally enjoyable activities, significant weight loss or weight gain, and a decrease or increase in appetite (Martin-Soelch, 2009). The prevalence of the MDD is 8–12% (Andrade et al., 2003; Kessler et al., 2003), and the most common time of onset is between 30 and 40 years of age, with a later peak between 50 and 60 years of age (Eaton et al., 1997).

Research has shown a possible link between the development of MDD and inflammation (Maletic and Raison, 2009; Miller et al., 2009). This theory suggests that stressful life events, such as sickness, may prompt a physical response that actually alters the brain and subsequently brain function. The administration of the bacterial endotoxin lipopolysaccharide (LPS) induces sickness behavior in animals, which resembles depressive-like symptoms, including anhedonia, anorexia, and body weight loss (De La Garza, 2005; Henry et al., 2008; Singal et al., 2006; Yirmiya, 1996). Anhedonia is a core clinical feature of MDD and most likely related to abnormalities in dopamine (DA)-reward pathway (Martin-Soelch, 2009; Wise, 2008). The sucrose preference test is frequently used to measure anhedonia in rodents (Papp et al., 1991; Wang et al., 2009). Rats that receive a microinjection of LPS exhibit a reduction of sucrose intake, with a significant loss of dopaminergic neurons in the substantia nigra (Santiago et al., 2010). The mesolimbic dopaminergic pathway, originating from the cell bodies in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc), is well known for its important role in reward motivation (Di Chiara, 2002; Treadway and Zald, 2011). Depressed patients show a defect in the VTA dopaminergic neurons and commonly displayed anhedonia (Hatzigiakoumis et al., 2011). Deficits in DA transmission in the NAc in rats have been resulted in anhedonic behavior (Roth-Deri et al., 2009). EGb 761, a standardized extract of Ginkgo biloba leaves that contain 24% flavone glycosides (e.g., kaempferol and quercetin) and 6% terpene lactones, has been reported to have beneficial effects on memory, vigilance, cognitive functions related to aging, and dementia (DeFeudis and Drieu, 2000). Ginkgo Biloba exerts effects in the forced swimming test (FST), tail suspension test (TST), and learned helplessness model in rodents, three behavioral models that predict antidepressant efficacy. Ginkgo Biloba extract significantly decreases immobility time in both rats (Kalkunte et al., 2007; Sakakibara et al., 2006) and mice (Rojas et al., 2011; Sakakibara et al., 2006). Rats that were fed Ginkgo Biloba displayed a decrease in the number of escape failures (Kalkunte et al., 2007; Porsolt et al., 1990). As mentioned earlier, these studies focus attention on Ginkgo biloba extract that has antidepressant activity in despair-based behavioral tests (FST and TST).
and learned helplessness rodent model of depression. However, unknown is whether Ginkgo biloba exerts an antidepressant effect on reward-based behavior. In the present study, systemic administration of LPS was used as an experimental tool to investigate the pretreated effect of EGb 761 for 14 days on LPS-induced anhedonic depressive-like behavior in male rats. The current study was performed using the sucrose preference test to determine the effects of EGb 761 on LPS-induced anhedonic depressive-like behavior in male rats, and food intake was also assessed. Because the NAc is part of the mesolimbic dopaminergic reward circuitry playing an important role in anhedonia (Chaudhury et al., 2013; Nestler and Carlezon, 2006), tissue levels of DA and serotonin (5-HT) in the NAc were measured to clarify the possible related mechanism in the present study.

MATERIALS AND METHODS

Subjects. Male Wistar rats (8 weeks old) were purchased from the Animal Center of National Science Council, Taipei, Taiwan. The animals were housed in groups of four in a cage (47 × 26 × 21 cm) in a temperature (22 ± 1 °C)-controlled and humidity (55 ± 10%)-controlled room on a 12-h light–dark cycle (lights off at 8:00 PM). All of the rats used for sucrose preference test and food intake test were singly housed in polycarbonate cages. The experimental protocols were approved by the Institutional Animal Care and Use Committee, HungKuang University (10119), and all of the experimental procedures conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experimental protocol and procedure. After 1 week of acclimation, 9-week-old rats were separated into individual cages and divided into two groups that were treated with 50 mg/kg of EGb 761 or vehicle [distilled water (DW)] everyday between 3:00 PM and 5:00 PM by gavage. The present model everyday between 3:00 PM and 5:00 PM by gavage with 50 mg/kg of EGb 761 or vehicle [distilled water (DW)] performed from 9:00 PM to 8:00 AM. The present model everyday between 3:00 PM and 5:00 PM by gavage with 50 mg/kg of EGb 761 or vehicle [distilled water (DW)] was repeated until the response of LPS-treated rats returned to the pretreatment level.

Food consumption and body mass. Food intake (g) and body mass were recorded once daily at the onset of the dark period. Food containers were filled with 100 g of the pelleted rat chow, and food intake was quantified 2 and 24 h after LPS/saline injection. The number of pellets eaten was recorded by subtracting the food remaining in the food container and on the cage floor from the amount of food measured at the preceding time point. Food spillage in the cage was ignored because it has been previously reported to be similar among rats and generally weigh less than 1% of the food consumed (Yirmiya, 1996).

Determination of NAc DA and 5-HT concentrations. The rats were sacrificed by decapitation with CO2 after the last behavioral test, then the brain was rapidly removed and immediately frozen in −20 °C isopentane and stored at −80 °C until analysis. Gietzen and her colleagues have found that values for monoamines and amino acids are stable for 6–9 months, if the preparations are kept at −80 °C (Gietzen et al., 1997). We measured DA and 5-HT levels in tissue punches within 6 months of tissue collection. Serial 180-μm thick coronal sections were prepared using a cryostat at −14 °C. The brain areas of the NAc were microdissected according to Palkovits (1973). Micropunchen tissue samples were obtained bilaterally, homogenized at room temperature in 0.1-N perchloric acid and centrifuged at 10,000 g for 20 min at 4 °C, then the supernatant was assayed for DA and 5-HT by using a DA or a 5-HT ELISA kit (Abnova, Taipei, Taiwan).

Statistical analysis. Statistic 6.0 (StatSoft Inc., Tulsa, OK, USA) was used for statistical analyses. The sucrose preference test and food consumption data were analyzed by two-way repeated measures analysis of variance (ANOVA), with time as the repeated factor and manipulation (DW or EGb 761 and saline or LPS) as the between-subject factor. Changes in body weight and the levels of DA and 5-HT were evaluated by Factorial ANOVA. Fisher’s least significant difference post hoc test was used to establish significance between mean values. Values of p less than 0.05 were considered statistically significant. All of the quantitative data are expressed as mean ± SEM.

RESULTS

Effect of EGb 761 on sucrose consumption after LPS treatment

As shown in Fig. 1, a decrease in sucrose consumption was observed after LPS injection. The ANOVA revealed
significant effects of injection ($F_{1,32} = 13.95, p < 0.001$) and significant time × injection ($F_{5,160} = 4.97, p < 0.001$) interactions. The post hoc analysis revealed that rats treated with either DW or EGb 761 exhibited a significant reduction of sucrose intake after LPS injection compared with rats that received saline injection 4 to 13-h post-injection ($p < 0.05$). Rats treated with EGb 761 exhibited an attenuation of the effects of LPS on sucrose intake compared with LPS-injected animals treated with DW 13-h post-injection ($p < 0.01$). Sucrose intake was restored to baseline levels 24 h after LPS injection. No baseline differences were observed between groups.

**Effect of EGb 761 on water consumption after LPS treatment**

No significant differences were found in water intake between groups (Fig. 2).

**Effect of EGb 761 on food consumption and body weight change after LPS treatment**

The ANOVA revealed significant main effects of treatment ($F_{1,32} = 18.40, p < 0.001$) and injection ($F_{1,32} = 50.35, p < 0.001$) and significant time × treatment ($F_{13,396} = 13.75, p < 0.001$) and time × injection ($F_{13,396} = 46.85, p < 0.001$) in food consumption. In the DW-treated group, the animals that received an LPS injection exhibited a significant decrease in food intake compared with animals that received a saline injection 13-h and 24-h post-injection ($p < 0.001$). Similarly, the EGb 761 group that received LPS exhibited a reduction of food consumption compared with rats that received a saline injection at 13 h ($p < 0.05$). However, these two groups were not significantly different with regard to food intake 24 h after the injection. Additionally, EGb 761 treatment mitigated the reduction of food intake caused by LPS 13-h and 24-h post-injection ($p < 0.001$). As shown in Fig. 4, rats that received an intraperitoneal injection of LPS exhibited a decrease in body weight (Fig. 4). The ANOVA revealed significant main effects of treatment ($F_{1,32} = 7.92, p < 0.05$) and injection ($F_{1,32} = 7.56, p < 0.001$) and a significant treatment × injection interaction ($F_{1,32} = 5.33, p < 0.05$). The post hoc analysis revealed that the DW + LPS group exhibited a significant decrease in body mass compared with the DW + saline group ($p < 0.001$). The EGb761 + LPS group exhibited less body weight loss than the DW + LPS group ($p < 0.001$). Furthermore, EGb 761-treated rats injected with LPS exhibited a decline in body mass compared with the EGb 761 + saline group ($p < 0.001$).

**Effect of EGb 761 on the levels of DA and 5-HT in the NAc after LPS treatment**

Fig. 5 shows that both DA (Fig. 5A) and 5-HT (Fig. 5B) levels in the NAc were decreased after LPS injection. For DA (Fig. 5A), ANOVA revealed significant main effects of treatment ($F_{1,32} = 148.25, p < 0.001$) and injection ($F_{1,32} = 319.07, p < 0.001$) and a significant treatment × injection interaction ($F_{1,32} = 77.07, p < 0.001$). The DA levels in the NAc were significantly decreased in the DW + LPS group as compared with the DW + saline group ($p < 0.001$). Pretreatment of rats with EGb 761 significantly attenuated the reduction of NAc DA contents caused by LPS injection ($p < 0.05$). Furthermore, EGb 761-treated rats injected with LPS had higher DA levels than EGb 761 + saline group ($p < 0.001$). For 5-HT (Fig. 5B), only a significant effect of injection ($F_{1,32} = 19.03, p < 0.001$) was observed. The 5-HT levels in the NAc were significantly decreased in the DW + LPS group as compared with the DW + saline group ($p < 0.01$).

**DISCUSSION**

The present study confirmed previous reports that LPS can induce depressive-like behavior, such as anhedonia, anorexia, and body weight loss in rats (Kentner et al., 2010; Pitychoutis et al., 2009; Singal et al., 2006; Yirmiya, 1996). We found that pretreatment with EGb 761 for 14 days corrected the diminishment of sucrose intake, food consumption, and body weight loss caused by LPS administration in male rats, suggesting that EGb 761 had a protective effect on LPS-induced anhedonic depressive-like behavior.

The sweet taste of sucrose is strongly rewarding for animals, including rodents and primates (Bachmanov et al., 1997; Berridge, 2000; Levine et al., 2003). Central
DA plays a critical role in the subjective pleasure associated with positive rewards (Wise, 2008), and the mesolimbic dopaminergic system is the key role in the regulation of reward-related behavior, such as sucrose and food in the present study (Stricker and Zigmond, 1984; Wang et al., 2001; Wise, 2006; Wise et al., 1978). Several studies have demonstrated that DA can reverse the reduction of sucrose intake in rats subjected to chronic mild stress (Bekris et al., 2005; Muscat et al., 1992; Papp et al., 1993; Papp et al., 1994; Willner et al., 1994). Researchers theorize that anhedonia may be associated with dysfunction of DA transmission in the reward circuit (Bressan and Crippa, 2005). Bilateral 6-hydroxydopamine (6-OHDA) lesions of the VTA decreased sucrose intake in rats (Shibata et al., 2009; Shimura et al., 2002) and mice (Martinez-Hernandez et al., 2006). Furthermore, licking sucrose increases DA release in the NAc in rats. Moreover, microinjections of the DA reuptake inhibitor nomifensine into the NAc significantly enhanced DA release, and this phenomenon was diminished by centrally administering a DA receptor antagonist (Hajnal and Norgren, 2001). No significant change in DA activity in the NAc is observed during licking of water (Hajnal and Norgren, 2001). Water consumption is unaffected by dopaminergic lesions of the VTA (Martinez-Hernandez et al., 2006; Shibata et al., 2009; Shimura et al., 2002). Rats that received intracerebroventricular 6-OHDA exhibited a dramatic impairment of feeding with subsequent body weight (Zigmond and Stricker, 1972). Our present study found that EGb 761 + LPS group displayed more sucrose (Fig. 1) and food consumption (Fig. 3) and had lower body weight loss (Fig. 4) than D/W + LPS group. Pretreatment with EGb 761 for 14 days diminished the reduction of DA levels in the NAc caused by LPS injection (Fig. 5). EGb 761 has no effect on water intake after LPS injection (Fig. 2). These results indicate that sucrose/food intake and not water consumption depends on the VTA-NAc DA link in rodents, suggesting that mesolimbic dopaminergic activity plays an important role in hedonia.

Figure 3. Effect of EGb 761 administration on food consumption after LPS treatment. The data are expressed as mean ± SEM. (a) EGb 761 + LPS versus EGb 761 + saline; (b) DW + LPS versus DW + saline; (c) EGb 761 + LPS versus DW + LPS. **p < 0.01, ***p < 0.001.

Figure 4. Effect of EGb 761 administration on body weight changes 24 h after LPS treatment. The data are expressed as mean ± SEM. (a) EGb 761 + LPS versus EGb 761 + saline; (b) DW + LPS versus DW + saline; (c) EGb 761 + LPS versus DW + LPS. ***p < 0.001.

Figure 5. Effect of EGb 761 administration on NAc DA (A) and 5-HT (B) levels after LPS treatment. The data are expressed as mean ± SEM. (a) EGb 761 + LPS versus EGb 761 + saline; (b) DW + LPS versus DW + saline; (c) EGb 761 + LPS versus DW + LPS. *p < 0.05, **p < 0.01, ***p < 0.001.

Monoamine oxidase inhibitors (MAOIs) have a long history of use as medications prescribed for the treatment of depression. Patients treated with MAOIs present an increase in body weight (Cantu and Korek, 2015).
MAO-B inhibitor properties of induced anhedonia, which may be associated with the vehicle + LPS group, suggesting that EGb 761 increases consumption were higher in EGb 761 + LPS group than in and the amounts of sucrose (Fig. 1) and food (Fig. 3) consumption were diminished in the reduction of substantia nigra pars compacta with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-OHDA dramatically decrease TH neurons expression in rodents, and these animals do exhibit significant motor dysfunction (Ahmad et al., 2005; Rojas et al., 2008). Animals pretreated with EGb 761 exhibited an attenuation of MPTP-induced and 6-OHDA-induced neurodegeneration of the nigrostriatal system (Ahmad et al., 2005; Rojas et al., 2008). Our previous study found that EGb 761 treatment significantly increased neuronal TH-IR in the VTA and DA contents in the NAc (Yeh et al., 2011). Kaempferol, one of the major constituents of Ginkgo biloba extract, is a potent MAO-B inhibitor (Sloley et al., 2000). A previous study reported an increase in MAO-B expression following LPS challenge in vitro (Ekuni, et al., 2009). Research has shown that EGb 761 decreased MAO-B activity in the corpus striatum in mice (Rojas et al., 2004). In the present study, pretreatment with EGb 761 for 14 days diminished the reduction of DA levels in NAc caused by LPS injection (Fig. 5), and the amounts of sucrose (Fig. 1) and food (Fig. 3) consumption were higher in EGb 761 + LPS group than in vehicle + LPS group, suggesting that EGb 761 increases mesolimbic dopaminergic activity and ameliorates LPS-induced anhedonia, which may be associated with the MAO-B inhibitor properties of Ginkgo biloba.

Besides MAOIs, serotonin–NE reuptake inhibitors (SNRIs) are a class of antidepressant drugs used in the treatment of major depression and other mood disorders. Duloxetine is a dual SNRI for treatment of MDD. Peripheral administration of LPS induced depressive like behavior in FST and TST in male mice, and the levels of 5-HT and NE were decreased. Pretreatment of duloxetine was shown to be effective in increasing the concentrations of 5-HT and NE in LPS-induced mice and attenuated LPS-induced depressive-like behavior (Ji et al., 2014; Ohgi et al., 2013). Rats given administration of duloxetine significantly elevated DA and 5-HT levels in the NAc (Muneoka et al., 2009). These results mentioned earlier indicate that duloxetine exhibiting its antidepressant effect in LPS-induced depressive-like behavior may be associated with increases in monoamine neurotransmitter action in the NAc (Ossewaarde et al., 2011). Our results showed that EGb 761 treatment did not influence NAc 5-HT levels in LPS-injected rats (Fig. 5B), suggesting that EGb 761-restored LPS-induced anhedonia may not be associated with 5-HT contents in the NAc.

Accumulating evidence suggests that inflammation may play a role in the pathophysiology of MDD (Maletic and Raison, 2009; Miller et al., 2009; Ohgi et al., 2013; Patel, 2013). The proinflammatory cytokines tumor neurosis factor-α (TNF-α) and interleukin-6 are increased in serum of depressed patients (Dowlati et al., 2010). Mice receiving systemic TNF-α administration displays less sucrose consumption than vehicle-treated controls, Kaster et al. (2012) indicates that increased TNF-α levels is important for inflammation-induced anhedonia. Research has demonstrated that LPS-induced TNF-α level in mice can be suppressed by pretreatment with EGb 761 (Wadsworth et al., 2001). Quercetin, another main flavonoid ingredient of EGb761, has been shown to significantly decrease TNF-α level in LPS-challenged rats (Sah et al., 2011). The present study found that EGb 761 diminished LPS-induced reduction in sucrose consumption may be related to antiinflammatory properties of quercetin in extract of Ginkgo biloba.

In summary, rats that were administered LPS exhibited significant decreases in sucrose intake, food consumption, body weight, and DA contents in the NAc. As mentioned earlier, all decreases caused by LPS were diminished by pretreatment with 50 mg/kg EGb 761. Our results demonstrated that EGb 761-reversed depressive-like symptoms in rats might be associated with its MAO-B inhibitor property (DA agonist). Our results suggest that EGb 761 may provide a beneficial role in the treatment of anhedonic depressive-like behavior. Further studies should be performed to elucidate the precise mechanisms of the anti-anhedonic effects of Ginkgo biloba extract.

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Conflict of Interest

The authors declare no conflict of interest.

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