Original article

Folia Neuropathologica

Systemic administration of lipopolysaccharide impairs glutathione redox state and object recognition in male mice. The effect of PARP-1 inhibitor

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Folia Neuropathol 2009; 47 (4): 321-328

Abstract

Our previous data demonstrated that systemic inflammation evoked by intraperitoneal injection of lipopolysaccharide (LPS; 1 mg/kg b.w.) induces morphological and biochemical changes in the brain, including alterations of poly(ADP-ribose) polymerase-1 (PARP-1) activity and expression of several genes. In this study, the effect of systemic inflammatory response (SIR) on glutathione redox state and on cognition, spatial memory and locomotor activity was evaluated by using spectrophotometric method, object recognition test, Morris water-maze and open-field tests, respectively. The effect of PARP-1 inhibitor was included in this study. Our data indicated that SIR significantly decreases reduced glutathione (GSH) level, enhances its disulfide form (GSSG) and decreases glutathione reductase activity. Moreover, SIR affects the object recognition and locomotor activity but has negligible effect on spatial memory. PARP-1 inhibitor protects against LPS-evoked recognition impairment and significantly improves spatial memory in LPS-treated mice. The effect of PARP-1 inhibitor could be in part connected with lowering of PARP-1 involvement in regulation of transcription of several pro-inflammatory genes. Moreover, PARP-1 inhibitors may modulate glutamatergic receptor signaling that plays an important role in learning and memory.

Key words: *memory, lipopolysaccharide, 3-aminobenzamide, brain.*

Introduction

Endotoxin lipopolysaccharide (LPS), a major component of cell wall of gram-negative bacteria, activates innate mechanisms of immune response, and is responsible for overactivation of immune system in most cases of septic shock. It was presented previously that systemic inflammatory response (SIR) evoked by intraperitoneal injection of LPS evokes morphological and molecular changes in the brain [8,9]. The several groups have shown an increase of cytokine accumulation in the brain [15,27].

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Recently, Johnson et al. demonstrated the presence of fluorescently-labeled LPS in brain sections and in microvessels after systemic administration [14]. Moreover, acute brain ischemic or traumatic damage or several types of tissue stress occurring in neurodegenerative disorders may induce inflammation by activation of the innate response of immune system. In the brain the inflammatory processes are mainly maintained by microglia and astrocytes [43] and may be responsible for the induction of neuronal death [20].

Intraperitoneally injected LPS may affect brain by different ways and mechanisms. LPS can act through Toll-like receptors (TLRs) that could be innate bridges to neuroinflammation [3]. During the last few years a lot of data were published on TLR signaling in the brain indicating several levels and mechanisms of its regulation [18]. The most important events in TLR2 or TLR4 receptor-related cascade is the release of inflammatory cytokines such as IL-1β, IL-6 and TNF-α. The expression of these receptors was observed in the brain mainly in glial cells [3,16,21]. However, they were also found in neurons [41,45].

Inflammasome, 700 kDa multiprotein complex that activates caspase-1 or caspase-5, plays a very important role in proinflammatory signaling. The complex can interact with NF-κB, the transcription factor that is regulated by DNA-bound enzyme poly-(ADP-ribose) polymerase (PARP-1, E.C. 2.4.2.30). Recently, it was demonstrated that this nuclear enzyme plays an important role in release of pro-inflammatory mediators in the brain. Inhibitor of PARP-1 blocked the increase of expression of TNF-α, IL-6, E-selectin and ICAM-1, and reduced neurological symptoms evoked by transient focal brain ischemia [13].

The pro-inflammatory action of PARP-1 has been described previously in peripheral inflammation, as arthritis, colitis, asthma and also in septic shock [7,40]. The inflammatory and immune responses evoked in sepsis may be responsible for molecular and functional brain alterations and for long-term cognitive impairment [29].

Till now little is known about the effect of mild systemic inflammation on memory and locomotor function. Our previous study indicated that systemic inflammation induced in mice by ip. injection of LPS in a dose of 1 mg/kg b.w. leads to expression of TNF-α, COX-2, iNOS, increases nNOS activity, reactive oxygen species (ROS) level, lipid peroxidation and DNA damage [8,9].

Oxidative stress is an important event that may affect glutathione redox state in the brain. Glutathione (GSH) is the most abundant non-protein thiol that buffers ROS in the brain tissue [11]. Inactivation of ROS by GSH in glutathione peroxidases (GP)-catalyzed reaction leads to formation of glutathione disulfide (GSSG). Subsequently, GSH is regenerated by glutathione reductase (GR) using NADPH. When the glutathione redox state is disturbed, the massive oxidative stress could lead to PARP-1 over-stimulation and to accumulation of poly(ADP-ribose), PAR, a regulator of several transcription factors and novel death signaling molecule. The effect of mild systemic inflammation on glutathione redox state on learning and memory was not evaluated till now.

The aim of this study was to investigate the glutathione system in the brain after systemic injection of lipopolysaccharide. Then the effect of LPS-evoked systemic inflammation on cognitive functions was analyzed. Moreover, the influence of PARP-1 inhibitor on LPS-evoked alterations was evaluated.

Material and Methods

LPS (from *E. coli* serotype 055:B5; toxicity 1.5 × 10^6 U/mg) and 3-aminobenzamide (3-AB), DMSO, NADPH and other reagents used for determination of GSH/GSSG level and GR activity were obtained from Sigma (St. Louis, USA).

Animals

All experiments were carried out on male C57BL/6 mice 2.5 month-old (approximately 20 g of body weight). All animals were supplied from the Animal House of Mossakowski Medical Research Centre, PAS, Warsaw, Poland. The animals were maintained under controlled conditions of temperature and humidity with a 12-h light/dark cycle, and free access to food and water. All experiments on animals were accepted by Polish National Ethics Committee, and were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Experimental design

Animals were injected intraperitoneally with LPS (1 mg/kg b.w.) or/and 3-AB (30 mg/kg b.w.). Control animals received 100 µl of saline. Then, animals were returned to their home cage and decapitated after 3,

24 or 48 h. Seven days after the treatment mice were subjected to behavioral tests and after that decapitated. The brains were quickly isolated, than blood vessels were removed and brain parts were quickly isolated and frozen at –80°C for further analysis.

Preparation of brain homogenate

The brain cortex was homogenized in Dounce homogenisator using Tris-HCL buffer pH 7.4 as described previously [35]. The protein content was determined with Lowry method, by using bovine serum albumin, as a standard [19].

Determination of lipid peroxidation

Lipid peroxidation was estimated by measurement of thiobarbituric acid-reactive substances (TBARS) level, as described previously [35], with method of Asakawa and Matsushita [2].

Determination of GSH and GSSG level

Reduced glutathione (GSH) was determined by a kinetic enzymatic method according to a methylglyoxal reaction in the presence of glyoxalase, whereas oxidized glutathione (GSSG) was measured by NADPH oxidation in glutathione reductase reaction as described by Akerboom et al. [1].

Measurement of Glutathione Reductase activity

This enzyme activity was determined by the rate of NADPH oxidation according to the methods described previously [4].

Object recognition test

The test was performed according to the method described by Ennaceur et al. [12] modified by Kosiorek et al. [17]. The apparatus was a wooden box (65 × 45 × 45 cm) placed in a sound-isolated room with a constant illumination of 40 lx at the level of the test box. Throughout the experiment, no cleaning of the box was allowed for saturation with olfactory stimuli. A day before testing, mice were submitted to a habituation session, where they were allowed to explore the apparatus for 5 min. The experimental session consisted of two trials. In the first trial (T1), one object-stimulus, the sample (A), was placed in the box. During the second trial (T2), a new object (B) was added. The object (A') presented during T2 was a duplicate of the sample presented in T1 (A) in order to avoid olfactory traits. The objects had no natural significance for mice and had never been associated with a reinforcement stimulus. At the beginning of each trial, mice were placed at the center of the box, with their heads oriented in the opposite direction to the object. The respective duration of T1 and T2 was 5 and 3 min. T2 started 2 h after T1 began. The basic measurement was the total time spent by mice exploring objects during T1 and T2 trials. Exploration of an object was defined as follows: directing the nose at a distance 2 cm to the object and/or touching it with the nose. From this measure, the following variables were defined:

A = the time spent in exploring the sample during T1, B + A' = the time spent in exploring a duplicate of the familiar object A (A') and a new object (B) during T2. Index of discrimination (ID) was calculated for each animal and expressed as a ratio: time B × 100 / (time B + A'). When ID < 50, it was concluded that the mouse did not recognize the familiar object A', if ID > 50, the mouse was interpreted as remembering the object.

Open field test

This test was performed according to protocols established by Winnicka et al. and Kosiorek et al. [17,44]. Locomotor (crossings of squares) and exploratory (rearings) activity was measured in an open field, which was a 60 cm × 60 cm square floor divided by eight lines into 25 equal squares and surrounded by a 47 cm high wall. The animals were placed in the center of the open field box and crossings of squares and rearings were counted during 5min.

Morris water-maze Test

The test was performed according to the procedure described by Morris [24] with some modifications [34]. Experimental apparatus consisted of a circular water tank (100 cm in diameter and 60 cm high). An invisible platform (10 cm in diameter) was placed 1 cm below the surface of the water, at a temperature of 27°C. The titan whiteness was added to the water in order to cover the bottom of the tank.

Above the tank the source of light and the camera were set. Spatial learning was tested toward the end of the study because the neurorestorative processes require certain time periods to be clinically evident. 5 groups consisting of 7 animals and one group consisting of 9 animals were subjected to 3 training trials every day during 3 days. Two starting points were set, named W and B. At the start of a trial, the mouse was placed at W point and allowed to swim for 120 seconds or until it found the platform. Secondly, after all mice were tested, the mouse was placed at the B starting point and finally the last testing started from the W place. The platform was located in a constant position throughout the trial. If the animal found the platform, it was allowed to remain there for 2 seconds before being returned to its cage. If the animal was unable to find the platform within 120 seconds, the experiment was terminated and a maximum score of 120 seconds was assigned. On 4th day 2 test-trials were performed. Test-trial was performed similarly to training trial except it was lasting 60 sec and there was no platform in the tank. During all trials animals were video-tracked using the Noldus EthoVision System.

Statistical analysis

The results were expressed as mean ± standard error of means (S.E.M.). For statistical comparison, results were analyzed using GraphPad Prism software, by Student's *t*-test or one-way ANOVA followed by Newman-Keuls post hoc test, p values < 0.05 were considered statistically significant.

Results

Effect of systemic inflammation on free radical-mediated lipid peroxidation

It was found that systemic inflammation induced by LPS enhances the level of aldehydes and ketones, the end-products of lipid peroxidation. These compounds, among them mainly malondialdehyde, were determined as thiobarbituric acid-reactive substances (TBARS). The statistically significant increase of TBARS level was found previously in the brain hemispheres 48 hours after LPS injection, it reached the value 122.00 ±4.92%, comparing to control. Inhibitor of PARP-1, 3-aminobenzamide (3-AB) protected the brain against LPS-evoked lipid peroxidation [9]. In the present study the increase of TBARS level was observed in brain cortex 4 days after LPS administration. PARP-1 inhibitor protected against LPS-evoked lipid peroxidation.

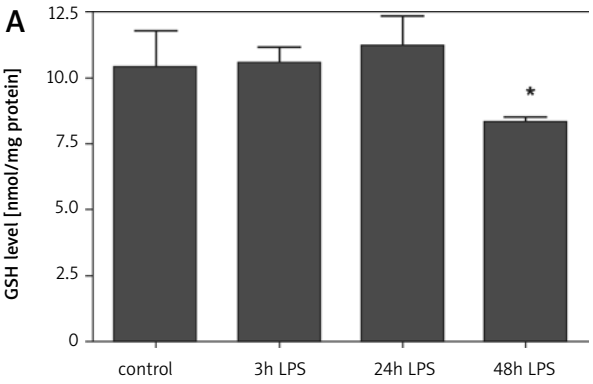
The glutathione redox state in the brain cortex of mice subjected to LPS-evoked systemic inflammation

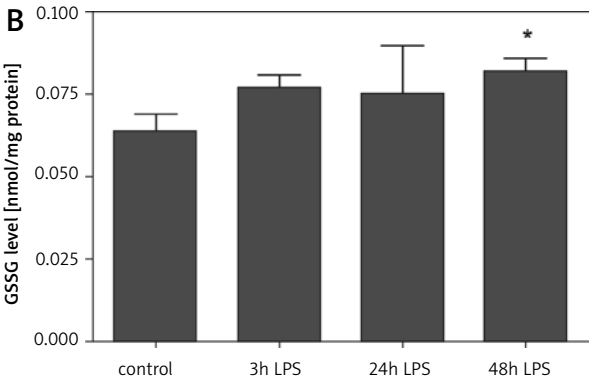
The observed enhancement of oxidative stress in brain of mice injected with mild dose of LPS leads to significant lowering of GSH level in brain cortex 48 h after LPS administration (Fig. 1A) (similar changes were observed also in other brain parts, data not shown). Concomitantly, the concentration of glutathione disulfide GSSG was enhanced and the ratio of GSH/GSSG was significantly decreased 48 h after LPS administration (Figs. 1B, 1C). Moreover, the activity of glutathione reductase (GR) was analyzed after LPS injection. The activity of this enzyme was significantly reduced 3 h and 48 h after LPS administration, comparing to control (Fig. 2).

Cognition function and locomotor activity in mice subjected to systemic inflammation

We have used object recognition test to study cognition function in mice 4 days after lipopolysaccharide-evoked systemic inflammation and to evaluate the action of PARP-1 inhibitor, 3-AB. Our study indicated significant decrease of cognition function 4 days after systemic injection of LPS. Moreover the object recognition was significantly improved in mice subjected to systemic inflammation after administration of PARP-1 inhibitor, 3-AB at a dose of 30 mg/kg of body weight (Fig. 3). PARP-1 inhibitor in control mice decreased memory function because under physiological condition this enzyme is involved in memory formation and it should not be inhibited.

To study the locomotor activity in mice the open field test was used. PARP-1 inhibitor had no effect on total and on internal crossing squares by control animals. LPS-evoked systemic inflammation had also no affect on this locomotor activity and on exploratory activity. However. the data indicated that PARP-1 inhibitor, 3-AB significantly increased locomotor and exploratory activity in mice subjected to systemic inflammation evoked by LPS (Fig. 4).





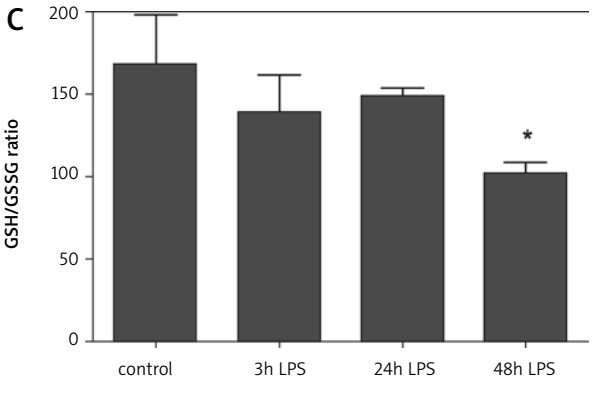


Fig. 1A-C. Effect of systemic inflammation on glutathione redox state in mice brain cortex. Mice were injected with LPS (1mg/kg b.w. ip.) and after 3, 24 or 48 h brain cortex was prepared. The levels of reduced glutathione (GSH) (A), glutathione disulfide (GSSG) (B), and GSH/GSSG ratio (C) were measured, as described in material and methods. Data are the means ± SEM from 4 animals in each group. *p < 0.05, comparing to the control group.

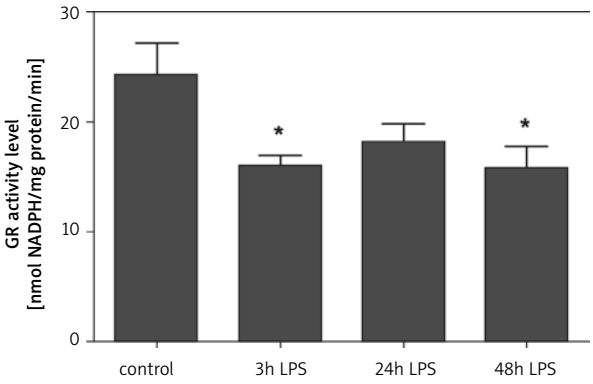


Fig. 2. Effect of systemic inflammation on activity of glutathione reductase (GR) in brain cortex of mice injected with LPS. Mice were injected with LPS (1 mg/kg b.w. ip.) and after 3, 24 or 48 h brain cortex was prepared. Activity of glutathione reductase was measured, as described in material and methods. Data are the means ±SEM from 4 animals in each group. *p < 0.05, comparing to the control group.

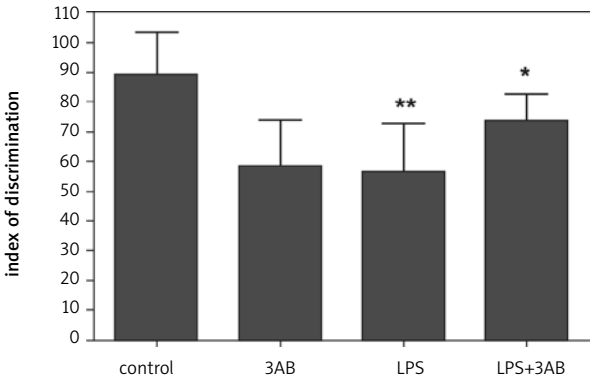


Fig. 3. The influence of LPS and 3-aminobenzamide (3-AB) on cognition function in mice. Mice were treated with LPS (1 mg/kg b.w. ip.) or/and 3-AB (30 mg/kg b.w. ip.) Seven days later object recognition test was performed, as described in material and methods. Results are means ± SEM from 7 animals in each group *p < 0.05, **p < 0.01, comparing to control.

To evaluate the effect of systemic inflammation on spatial memory the Morris water-maze test was applied in the study. LPS slightly impairEd this type of memory but PARP-1 inhibitor 3-AB significantly improved spatial memory in LPS treated animals (Fig. 5).

Discussion

Our results indicated for the first time that mild systemic inflammatory response (SIR) evoked by i.p. injection of lipopolysaccharide (LPS; 1 mg/kg b.w.) induces not only alteration of expression of several genes as COX-2, TNF-α iNOS in the brain, as described previously by us [8-10], but also affects significantly glutathione redox state and cognition function. This mild SIR leads to significant decrease of object recognition memory but it has only negligible effect on spatial memory and locomotor function. Semmler et al. [29,30] described long-term cognitive impairment, significant memory deficit in the radial maze and changes in open field exploratory patterns, but unaffected inhibitory avoidance learning in rat model of sepsis evoked by high dose of LPS (10 mg/kg). The results of Semmler et al. [29] presented that three months after complete recovery from sepsis animals showed memory deficit, neuronal loss and reduced cortical cholinergic innervations. In this study, by using animal PET, it was observed that systemic administration of high dose of LPS decreased regional cerebral blood flow and glucose uptake in brain cortex, and decreased alpha activity of the electroencephalography. Moreover, in this animal model LPS injected ip. affected amount of neuronal cells in brain cortex and hippocampus [30,31]. In our previous studies, mild systemic inflammation-evoked morphological and ultrastructural alterations in the brain were described [8-10]. We have observed activation of free radical dependent lipid peroxidation, significant changes of mitochondria and other intracellular organelles, and different types of programmed cell death as apoptosis and authophagy. We have found enhancement of oxidative/nitrosati-

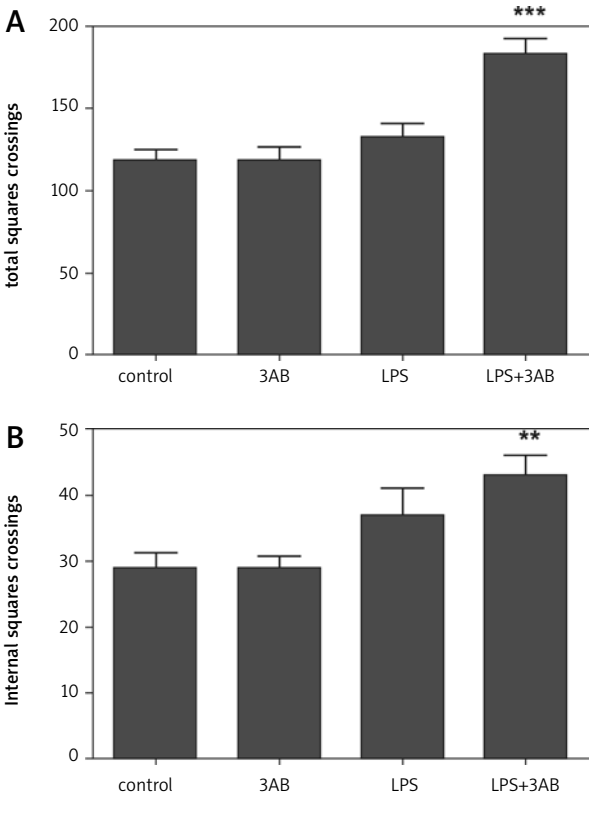


Fig. 4A-B. The influence of LPS and 3-aminobenzamide (3-AB) on locomotor activity in mice. Mice were treated with LPS (1 mg/kg b.w. ip.) or/and 3-AB (30 mg/kg b.w. ip.) Seven days later open field test was performed, as described in material and methods. Total (A) and internal (B) squares crossings were counted. Results are means ±SEM from 7 animals in each group **p < 0.01, and ***p < 0.005, comparing to control.

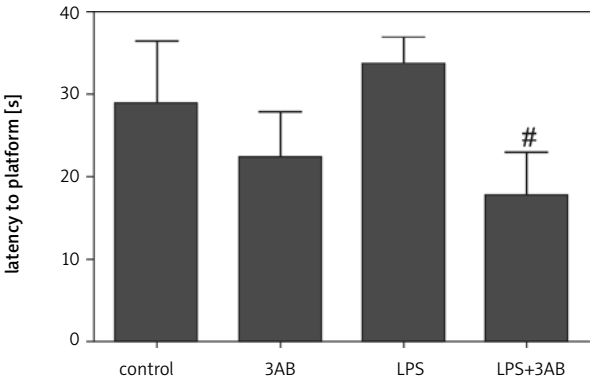


Fig. 5. The influence of LPS and 3-aminobenzamide (3-AB) on spatial memory in mice.Mice were treated with LPS (1 mg/kg b.w. ip.) or/and 3-AB (30 mg/kg b.w. ip.) Seven days later Morris water-maze test was performed, as described in material and methods. Results are means ±SEM from 6-7 animals in each group. # p < 0.05 compare to LPS group.

ve stress and accumulation of poly(ADP-ribose), the product of DNA-bound enzyme PARP-1. This enzyme is the nuclear target for different types of stress and signaling pathways. PARP-1 plays a crucial role in regulation of many transcription factors, including p53 and NF-κB, and more then 40 other nuclear proteins. It is a key enzyme in DNA repair machinery and is engaged in many other physiological processes in the cells [5,6,35]. However, under massive stress and other pathological conditions it could be overactivated and involved in cell death by different mechanisms including activation of proinflammatory gene expression or modulation of NMDA and cholinergic receptor signaling [35,39]. Our data presented that inhibitors of PARP-1 decrease the level of GSK-3 in aged brain and protect it against molecular, morphological and ultrastructural alterations evoked by ischemia–reperfusion injury [32,36-39]. Moreover, several studies reported that inhibition of PARP-1 attenuates the severity of inflammatory processes in different organs [23,25,28,33,40]. In spite of the big interest in the field of neuroinflammation during the last years, no satisfactory therapy exist to protect the brain against biochemical and fuNctional alterations evoked by SIR and sepsis. Recently published data presented a protective effect of selected compounds as N-acetylo-S-cysteine or sulforaphane, acting by enhancement of endogenous level of glutathione in cells [26,42]. For a long time CDP-choline (citicoline) offers neuroprotective action in several central nervous system injuries. The last study of Matyja et al. confirmed the ameliorating effect of CDP-choline [22]. This compound should be also taken into consideration for the treatment of neuroinflammation.

In present study we have indicated that PARP-1 inhibitor (3-AB) protected mice against object recognition memory deficit evoked by systemic inflammation. 3-AB had also positive effect on spatial memory in LPS-treated animals. Moreover, it improved the locomotor activity in male mice subjected to systemic inflammation. Summarizing, our data suggest that PARP inhibitors offer novel therapeutic strategy for brain protection against SIR.

Acknowledgments

The work has been supported by MSHE Scientific Network 28/E-32/BWSN-0053/2008.

Special thanks to Dr Katarzyna Domek -Lopacinska and Mss Magdalena Kudlik for THEIR assistance and help at this behavioral study.

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