Lipopolysaccharide does not affect acoustic startle reflex in mice

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Abstract

Bacterial endotoxin (lipopolysaccharide; LPS) evokes in rodents an adaptive sickness behavior. It also produces changes in stress hormones secretion and activity of brain serotonergic and noradrenergic systems that have been implicated in stress responses, fear, and anxiety. Acoustic startle reflex (ASR) is regarded as a protective behavioral response that is enhanced in threatening situations or following an aversive event, and it can be modulated by physiological and emotional state of an animal. Effects of intraperitoneal injections of LPS on ASR, prepulse inhibition (PPI), locomotor activity in open field, and blood plasma corticosterone concentration were studied in lines of mice that display high (HA line) or low (LA line) swim stress-induced analgesia and also differ in emotional behaviors, including the magnitude of ASR. In both lines LPS produced robust sickness behavior, as evidenced by a decrease in locomotion and body weight, and an increase in corticosterone concentration. However, in neither line LPS injections affected responses to acoustic stimuli as assessed by the ASR and PPI magnitudes. The findings suggest that in sickness behavior induced by LPS the protective responses to salient environmental stimuli are not impaired. The significance of this finding for the concept of sickness behavior is discussed.

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1. Introduction

Lipopolysaccharide (LPS) is an endotoxin that is a major component of the outer cell wall of Gram-negative bacteria. Peripheral administration of LPS evokes sickness behavior that is characterized by hypophagia or anorexia, body weight loss, a decrease in locomotion, a decrease in exploration and social interactions, behavioral despair, anhedonia, and fever (Dunn and Swiergiel, 2005; Hart, 1988; Larson and Dunn, 2001; Swiergiel et al., 1999; Swiergiel and Dunn, 2001). LPS also increases activity of brain serotonergic and noradrenergic systems (Dunn, 1992; Lacosta et al., 1999; Linthorst and Reul, 1998), and it stimulates release of stress hormones (Kakueska et al., 1993; Turnbull and Rivier, 1999; Wiecezorek et al., 2005). These neurotransmitters and hormones have been implicated in stress response, fear and anxiety (Millan, 2003), and may mediate effects of LPS. In fact, it has been shown that LPS exerts anxiety-like effects in mice tested in light-dark box and elevated plus-maze tests (Lacosta et al., 1999; Swiergiel and Dunn, 2007).

The acoustic startle reflex (ASR) is a single oligosynaptic motor reflex, elicited by strong acoustic stimuli, which can be modulated by physiological and emotional state of an animal. The startle response is a protective behavioral response and is enhanced in threatening situations or following an aversive event. It is used as a model in the studies of mechanisms of anxiety-like and emotional behaviors
Acoustic startle reflex (ASR) and prepulse inhibition (PPI) were measured with an ASR test system (Coulbourn Instruments, Allentown, PA). Each mouse was inserted into a 180 × 85 × 90 mm plastic cage covered with an aluminum grid and four such cages were then placed in a ventilated double-walled sound-attenuating chamber, each cage on a separate force-sensitive platform. The signal produced by the vertical reactive force of each animal’s startle, was amplified, rectified, passed through a low-band 40 Hz filter, and digitized at 1 kHz. The maximum ASR amplitude, base to peak, was computed off-line during a 200-ms sample window.

2.5. Acoustic startle reflex apparatus

The apparatus was a 60 × 60 cm arena painted matte black and surrounded by a 30 cm high wall. A 40 W white bulb that was directed towards the ceiling of the observation room dimly illuminated the arena. A black/white video camera, connected to PC computer with a frame grabber, was mounted above the arena. A mouse was injected with LPS (0.5, 1, and 5 μg/mouse, ip) or saline, 2 h later placed in the central part of the arena, and its behavior scored automatically using an EthoVision 3.1 video analysis system (Noldus).

2.3. Open field test (OF)

The apparatus was a 60 × 60 cm arena painted matte black and surrounded by a 30 cm high wall. A 40 W white bulb that was directed towards the ceiling of the observation room dimly illuminated the arena. A black/white video camera, connected to PC computer with a frame grabber, was mounted above the arena. A mouse was injected with LPS (0.5, 1, and 5 μg/mouse, ip) or saline, 2 h later placed in the central part of the arena, and its behavior scored automatically using an EthoVision 3.1 video analysis system (Noldus).

2.4. Corticosterone assay

Two hours after the LPS (0.5, 1, and 5 μg/mouse, ip) or saline administration, mice were killed by decapitation and blood collected in 1.5 ml Eppendorf tubes containing EDTA, centrifuged and plasma corticosterone concentration determined using a high-performance liquid chromatography (HPLC) method. Briefly, corticosterone was extracted with ethyl acetate (betamethasone as internal standard) from 0.1 ml plasma samples, the extraction medium centrifuged, and the supernatants washed with sodium hydroxide (0.1 M) and water (Ling and Jamali, 2003). After an overnight evaporation of ethyl acetate, the dried samples were dissolved in the HPLC mobile phase. They were analyzed using an isocratic HPLC system (UV detector set at 250 nm, RP-C18 analytical column (250 × 4.6 mm) kept at 40 °C, acetonitrile/water mobile phase (35:65 v/v), flow rate of 0.5 ml/min). The extraction efficiency was above 90% and the detection limit was about 1 ng/ml of plasma, using 0.1 ml plasma sample.

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2.5.1. Startle and prepulse inhibition testing

Two hours (LPS: 1 μg/mouse, or saline) or 30 min (MK-801: 1 mg/kg, or saline) after the ip injections mice were tested for ASR and PPI. All animals were tested in random order during one experimental session, and in identical conditions. The startle session started with a 5 min habituation period with background noise level of 70 dB that was maintained throughout the session. The acoustic prepulses (PP) consisted of wide-band noise bursts of 79 dB and were 20 ms in duration. The acoustic startle pulses (SP) were 10 ms in duration. The interval between the PP and the SP was 100 ms. Each session lasted about 23 min and consisted of seven blocks of five trials. Each block included five different trial types: one stronger SP of 108 dB alone, one weaker SP 98 dB alone, one PP of 108 dB alone, one weaker SP 98 dB alone, and the detection limit was about 1 ng/ml of plasma, using 0.1 ml plasma sample.
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