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Maternal care modulates the febrile response to lipopolysaccharide through differences in glucocorticoid receptor sensitivity in the rat

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ABSTRACT

Early life adversity increases the risk for later infection. The febrile response is a potent mechanism to combat infection. We found that variations in maternal care influence the febrile response to 50 μg/kg lipopolysaccharide (LPS) challenge in adult male rats. Offspring from low-licking/grooming (LG) mothers had an increased febrile response compared to offspring from high-LG mothers challenged with LPS. Low-LG offspring had reduced plasma IL-6 at one and two hours post challenge compared to high-LG offspring. IL-6 gene expression in the anterior hypothalamus was induced following LPS challenge in low-LG offspring but not in high-LG offspring at two hours post challenge. Occupancy of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) to the IL-6 promoter region in the anterior hypothalamus was greater in low-LG offspring treated with LPS than in high-LG offspring. These findings suggest greater activation of thermoregulatory neurons in the anterior hypothalamus of low-LG compared to high-LG offspring following LPS challenge. Low-LG offspring had greater plasma corticosterone levels following LPS challenge and they had enhanced glucocorticoid receptors (GR) in the spleen compared to high-LG offspring. Enhanced glucocorticoids and glucocorticoid receptor sensitivity associated with reduced IL-6 induction early post challenge in low-LG offspring. Challenge with RU-486 prior to LPS challenge eliminated differences in the febrile response between offspring of high and low-LG mothers. Individual differences in GR sensitivity may modulate differences in the febrile response to LPS challenge, exerting a long-term influence on the capacity to recover from infection.

1. Introduction

Inflammation is the primary response of the body to both physical injury and exposure to infection. Psychological stressors have also been shown to increase the inflammatory response (Glaser and Kiecolt-Glaser, 2005). The link between psychological stress and inflammation can have adaptive value in that increased psychosocial stress is often accompanied by increased risk of physical injury and infection following wounding. Early life adversity (ELA) including emotional neglect, abuse and parental loss are linked with an increased risk for the development of diseases with an inflammatory basis in adulthood. Some of these diseases include major depressive disorder, certain cancers, asthma, diabetes, obesity and cardiovascular disease (Miller et al., 2011; Nusslock and Miller, 2016). These inflammation-based diseases create a tremendous burden both at the societal level and at the level of the individual in terms of health care costs, lost productivity and reduced physical and emotional wellbeing. Determining the factors early in life that increase the risk for these inflammation-based diseases would aid in identifying individuals at risk. These individuals could then be targeted with intervention programs early in life that would reduce their risk of suffering from the increased morbidity and reduced longevity associated with inflammatory-based diseases.

The level of inflammation in the body is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. The endocrine system and the immune system are mutually regulatory. The end product of the HPA axis, cortisol in humans and corticosterone in rodents is a potent anti-inflammatory agent (Berkenbosch et al., 1987; Sapolsky et al., 1987; Besedovsky et al., 1986). Glucocorticoid feedback inhibition of immune-related genes that initiate inflammation is considered the central physiological mechanism in the prevention of inflammation (Slavich and Irwin, 2014).

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Early life adversity increases the neuroendocrine response to acute stress. Exposure to an immune challenge with the endotoxin, lipopolysaccharide (LPS) in early life increases the neuroendocrine response to acute stress in adult rats (Shanks et al., 1995). Similarly, rats that received less mothering behaviour including licking/grooming (LG) and arched backed nursing in early life also show an enhanced neuroendocrine response to acute stress as adults (Liu et al., 1997; Weaver et al., 2004). Prolonged exposure to stressors leads to a condition termed glucocorticoid resistance or glucocorticoid insensitivity wherein immune cells become less sensitive to the anti-inflammatory effects of glucocorticoids due to their prolonged secretion in the presence of chronic stress (Schleimer, 1993). While the ensuing increased release of glucocorticoids following stress may serve several adaptive functions including the ability to mount defensive responses to threat (Cameron et al., 2005), they also create a cost in the form of an increased risk of persistent inflammation.

Highly adverse environments often present with an increased risk of injury and infection. The first line of defense against invading pathogens is the innate immune response (Takeda et al., 2003; Medzhitov, 2007). Organisms that were exposed to early life adversity may show an enhanced innate immune response to infection in order to combat increased exposure to wounding and invading pathogens (Slavich and Irwin, 2014). Over-activation of the innate immune response can lead to septic shock which can be deadly though (Abbas et al., 2014). A key function of glucocorticoids is to restrain the degree of innate immune system activation, thereby reducing neuro-inflammation (Bellavance and Rivest, 2014).

Glucocorticoids have been shown to modulate several aspects of the neuroimmune response including the febrile response to LPS (Morrow et al., 1993; McClellan et al., 1994; Ellis et al., 2005). Administration of the glucocorticoid receptor antagonist, RU-486, has been shown to both increase bioactivity of the circulating pyrogen IL-6 and the magnitude of the febrile response (Morrow et al., 1993; McClellan et al., 1994). Infection is often followed by the elicitation of a febrile response. Fever is a phylogenetically ancient mechanism that allows an organism to reduce bacterial load by increasing core body temperature (Ellis et al., 2005; Jiang et al., 2000). Following exposure to LPS, several pro-inflammatory cytokines are released from immune cells and increase fever as an adaptive mechanism to recover from infection (Blatteis, 2000; Roth and Blatteis, 2014; Harden et al., 2015). Immune challenge leads to peripheral cytokine release from immune cells that is followed by central cytokine release. IL-6, a key pro-inflammatory cytokine involved in mediating the febrile response is increased in the periphery and is transcribed by the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and increases in a region of the brain that mediates the febrile response, the anterior hypothalamus following LPS challenge (Klir et al., 1993, 1994). While inhibition of the febrile response increases the risk for mortality from infection, an overactive innate immune response to infection can also increase the risk for septic shock (Jiang et al., 2000; Kluger et al., 1998). Glucocorticoids and anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA) constrain the magnitude and duration of the febrile response and protect against septic shock (Coelho et al., 1992; Ashdown et al., 2007; Roth and Blatteis, 2014).

Variations in early life maternal care program the development of the hypothalamic-pituitaryadrenal (HPA) response to stress in adult offspring (Liu et al., 1997). Glucocorticoids are a critical modulator of the innate immune response to infection including the elicitation of the febrile response (Coelho et al., 1992; Morrow et al., 1993; McClellan et al., 1994). Based on these findings, we hypothesize that variations in early life maternal care will lead to individual differences in the innate immune response to LPS challenge, particularly in the magnitude of the febrile response. The mechanism through which early life maternal care may program the innate immune response may involve circulating glucocorticoids or glucocorticoid receptor sensitivity. We hypothesize that reduced maternal licking/grooming (LG) in early life will increase the neuro-immune response to bacterial mimetic challenge in adulthood. Prolonged over-activation of the innate immune response to infection and the neuroendocrine response to stress in adverse environments with multiple sources of infection may increase the risk for neuro-inflammation, in turn increasing the risk for the development of diseases with an inflammatory basis (Maes et al., 2009).

2. Methods

2.1. Subjects and housing

Adult male Long-Evans hooded rats derived from litters born in our colony at the Douglas Mental Health University Institute were used in these experiments. The dams and their pups were housed in 46 × 18 × 30 cm clear 'Plexiglas' cages. Food and water were provided *ad libitum* throughout the study with a 12:14 h light: dark schedule (lights on at 09:00). The animals underwent routine cage maintenance beginning on postnatal day 7 (p7). The litters were otherwise not manipulated until weaning on day 22 at which time animals were paired with a littermate in same-sex pairs and remained pair-housed in 46 × 18 × 30 cm clear 'Plexiglas' cages until p120 in a room with a 12:12 h light:dark schedule. The ambient temperature of the colony housing and testing rooms was 22 ± 1 °C and the relative humidity levels were approximately 50%. All procedures were performed according to guidelines developed by the Canadian Council on Animal Care with protocols approved by the McGill University Animal Care Committee.

2.2. Observations of maternal behaviour

Natural variations in maternal care were observed using a procedure similar to the method first described by Myers et al. (1989). Maternal behaviour of dams was observed in the home cages over the first 6 days postpartum. Observations occurred at regular intervals each day with three periods during the light phase (10:00, 13:00, 17:00 h) and two periods during the dark phase (07:00 and 20:00 h). During the dark phase, the room was illuminated with dim red lighting that allowed a clear view of maternal pup interactions. Each observation session lasted 75 min during which time the behaviour of each dam was scored every 3 min for the presence of pup licking/grooming (LG) behaviour. Both whole body and anogenital licking were included, but were not distinguished from each other. Observers of maternal behaviour were trained using videos of maternal behaviour until they reached high inter-observer reliability scores for the presence or absence of LG and other maternal behaviours. The frequency score for pup LG for each dam was thus based on a total of 750 observations (25observations/session × 5 sessions/day × 6 days = 750 observations/dam) and was expressed as a percentage (number of LG occurrences/750 × 100). High-LG litters were defined by dams whose LG frequency scores were greater than 1 standard deviation (SD) above the cohort's mean. Low-LG mothers were defined as females whose LG frequency scores were greater than 1 SD below the cohort mean (Champagne et al., 2003). Only male offspring were used in all of the following experiments.

2.3. Recordings of core body temperatures using remote biotelemetry

At postnatal day (p) 120, male offspring from high and low-LG mothers were anesthetized with isoflurane gas. Under aseptic con-