Brain, Behavior, and Immunity 63 (2017) 115–126

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Special Issue on Perinatal Inflammation

Suboptimal nutrition in early life affects the inflammatory gene expression profile and behavioral responses to stressors

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A R T I C L E I N F O

Article history:
Received 2 September 2016
Received in revised form 6 October 2016
Accepted 14 October 2016
Available online 15 October 2016

Keywords:
Stressor
Perinatal diet
High fat
Low protein
Cytokine
Chemokine
Resilient
Sickness behavior

A B S T R A C T

Nutritional conditions in early life can have a lasting impact on health and disease risk, though the underlying mechanisms are incompletely understood. In the healthy individual, physiological and behavioral responses to stress are coordinated in such a way as to mobilize resources necessary to respond to the stressor and to terminate the stress response at the appropriate time. Induction of proinflammatory gene expression within the brain is one such example that is initiated in response to both physiological and psychological stressors, and is the focus of the current study. We tested the hypothesis that early life nutrition would impact the proinflammatory transcriptional response to a stressor. Pregnant and lactating dams were fed one of three diets; a low-protein diet, a high fat diet, or the control diet through pregnancy and lactation. Adult male offspring were then challenged with either a physiological stressor (acute lipopolysaccharide injection, IP) or a psychological stressor (15 min restraint). Expression of 20 proinflammatory and stress-related genes was evaluated in hypothalamus, prefrontal cortex, amygdala and ventral tegmental area. In a second cohort, behavioral responses (food intake, locomotor activity, metabolic rate) were evaluated. Offspring from low protein fed dams showed a generally reduced transcriptional response, particularly to LPS, and resistance to behavioral changes associated with restraint, while HF offspring showed an exacerbated transcriptional response within the PFC, a reduced transcriptional response in hypothalamus and amygdala, and an exacerbation of the LPS-induced reduction of locomotor activity. The present data identify differential proinflammatory transcriptional responses throughout the brain driven by perinatal diet as an important variable that may affect risk or resilience to stressors.

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1. Introduction

Early life nutrition is a key determinant in proper growth and development. Both deficient (Triunfo and Lanzone, 2015), as well as excess nutrition (Li et al., 2013) (e.g., total calories or specific macro- (fat, protein) or micro- nutrients (iron, vitamins), have been linked to altered growth parameters. Clinically, this can lead to babies being born small-for-gestational age (SGA) or large for gestational age (LGA), respectively. Beyond nutrition, a wide range of pregnancy conditions increase the risk for SGA (maternal infection, hypertension or placental dysfunction (Kramer, 2013) and LGA (gestational diabetes or maternal obesity (Yu et al., 2013). Both SGA and LGA increase the risk for perinatal complications and chronic health conditions (hypertension and obesity (Rosebloom et al., 2001; Ravelli et al., 1976) later in life and have been associated with an increased risk for adverse neurobehavioral disorders, including schizophrenia, and difficulty with emotional regulation (Grissom and Reyes, 2013). Therefore, it is important to define how early life nutrition affects the developing brain.

The role of proinflammatory responses in the brain are increasingly appreciated as contributors to a number of mental health disorders, including depression, anxiety (Ramirez and Sheridan, 2016) and schizophrenia (Esslinger et al., 2016). Both physiological stressors such as an immune challenge (Ziko et al., 2014; Strenn et al., 2015; Kentner et al., 2008; Doremus-Fitzwater et al., 2015) or psychological challenges (Vecchiarelli et al., 2016; Knapp et al., 2016) can induce a proinflammatory response throughout the brain, with cortex, hypothalamus, amygdala and hippocampus being the regions most often examined. Additionally, proinflammatory responses in the brain have been shown to contribute to the behav-

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http://dx.doi.org/10.1016/j.bbi.2016.10.013
0889-1591/© 2016 Published by Elsevier Inc.

ioral changes that accompany both physiological stressors (Konsman et al., 2002; Reyes and Sawchenko, 2002), and psychological stressors (e.g., repeated social defeat (Wohleb et al., 2014) or chronic restraint (Kim et al., 2016).

The goal of the present experiment was to determine whether altered early life nutrition could affect the proinflammatory gene expression profile in the offspring brain. We model SGA and LGA offspring by feeding dams a diet deficient in protein or high in fat, respectively, through breeding and lactation (Grissom and Reyes, 2013; Whitaker et al., 2012; Vucetic et al. 2010a, 2010b). Using this model, we have shown alterations in dopamine and opioid expression in the brain, as well as executive function deficits. The present studies examined a panel of 20 proinflammatory-related genes in response to peripheral LPS administration, a physiological stressor, or 15 min restraint, a psychological stressor (Li et al., 1996). Four brain regions were examined; hypothalamus, a central brain structure in the response to stressors, as well as prefrontal cortex (PFC), amygdala (AMYG), and ventral tegmental area (VTA), structures involved in emotional processing as well as stress responses. The present data support the conclusion that early life nutrition affects proinflammatory gene expression profiles throughout the brain, and these responses differ by brain region, by stressor, and by dietary challenge.

2. Methods

C57BL/6 J females and DBA/2 J males were ordered from Charles River (Wilmington, MA) and bred. B6D2F1/J mice were used in all studies as a hybrid background is more similar to the heterogeneity observed in humans as opposed to a pure inbred strain, and hybrid vigor can lead to robustness (e.g., increased litter size, and resiliency (Davis and Lamberson, 1991; Anisman, 1975). Breeding pairs were randomly assigned to one of three diet conditions, and diets were fed from the onset of breeding, through pregnancy and lactation. Experimental diets were purchased from Test Diet (Richmond, IN, USA); control: #5755, 4.09 kcal/g with 18% of total energy calories from protein, 22% from fat, and 60% from carbohydrate; low protein: #5769, 4.13 kcal/g with 8.5% of total energy calories from protein, 22% from fat, and 69.5% from carbohydrate; high fat: #58G9, 5.21 kcal/g with 18% of total energy calories from protein, 60% from fat, and 22% from carbohydrate (see Table 1). The source of fat across the diets was the same (although the quantities differed), with an increase in mostly lard, and to a smaller extent corn oil in the high fat diet. The maternal diets do not differentially affect litter size or composition, and, pups born to dams fed the low protein diet have significantly lower birth weights (Vucetic et al., 2010a), while those born to high fat fed dams are significantly heavier at birth (Vucetic et al., 2010b). Male offspring were weaned at 21 days of age and fed standard chow (Lab Diet 5001), and housed in groups of 5 in housing rooms with an ambient temperature of 22-23° C. Only one animal per litter was used in any specific experiment. Gene expression experiments were conducted when animals were 8 weeks of age, behavioral experiments were conducted when animals were 4.5 months of age.

Stress paradigms

Table 1
Composition of formulated diets used in the present experiments.

	Control diet	Low protein diet	High fat diet
Test diet number	5755	5769	58G9
% energy from Fat	22.1	21.8	59.9
% energy from Carbohydrate	59.6	70.1	21.4
% energy from Protein	18.3	8.1	18.6
Energy (kcal/g)[2]	4.07	4.12	5.21
Sucrose (% of ingredients)	15	27	6.4

For the gene expression experiments, animals (n = 5–6) were sacrificed either under basal conditions or 2 h after the onset of either a physiological stressor (lipopolysaccharide (LPS) administration, IP), or a psychological stressor (15 min restraint) (Reyes et al., 2003). Samples were collected between 1200–1400, with lights on at 7am. Because animals were group housed, all animals in a given cage were subjected to the same stress condition. Animals from which basal samples were collected were left undisturbed in their home cage in the vivarium housing room adjacent to the procedure room until the time of sample collection. Animals in the LPS condition received 10ug LPS (serotype 055:B5, Sigma) IP, and were returned to their homecage in the housing room. Animals in the restraint condition were placed in a clean Decapicone (Braintree Scientific, Braintree, MA) and secured by taping the rear opening closed. Restraint lasted 15 min, at which point animals were returned to their cage and the cage was returned to the housing room.

2.1. Nucleic acid extraction and gene expression

RNA extraction occurred as previously described (Grissom et al., 2015a). Briefly, at the time of sacrifice, brains were rapidly extracted, placed in RNAlater and stored at -20C. The hypothalamus, prefrontal cortex, amygdala, and ventral tegmental area were dissected as previously described (Vucetic et al., 2010a; Grissom et al., 2015a,b). RNA was extracted using Qiagen AllPrep DNA/RNA Mini kit. 100ug/ul cDNA was synthesized using Applied Biosystems High Capacity Reverse Transcriptase kit.

2.2. Gene expression and cluster analysis

Gene expression was assayed (n = 5–6) using Taqman primers on custom high-throughput OpenArray real-time PCR plates (Life Technologies) assaying housekeeping genes (GAPDH, ACTB) and 20 genes of interest, including chemokines/receptors (CCL2, CCR2, CXCL10), proinflammatory cytokines/receptors (IL-1, IL-18, IL-1R, IL-6, TNF-α), proinflammatory signaling molecules (COX2, NOS, PGES, SOCS3, TLR4, NFκB, IkBα), and neuron/glia signaling (MR, GR, GFAP, GAD1, β-adrenergic receptor (ADRB1; see Table 2). In the PFC, one sample was lost in each of the following conditions due to assay failure; SC-basal, HF-basal, SC-restraint, LP-restraint.

Table 2
Gene ID and assay ID used for qRT-PCR experiments.

Gene	Assay ID
ACTB	Mm00607939_s1
ADRB1	Mm00431701_s1
CCL2	Mm00441242_m1
CCR2	Mm00438270_m1
COX2	Mm00478374_m1
CXCL10	Mm00445235_m1
GAD1	Mm04207432_g1
GAPDH	Mm99999915_g1
GFAP	Mm01253033_m1
GR	Mm00433832_m1
IkBalpha	Mm00477798_m1
IL-18	Mm00434225_m1
IL-1β	Mm01336189_m1
IL-1R	Mm00434237_m1
IL-6	Mm00446190_m1
MR	Mm01241596_m1
NFkB (p65)	Mm00501346_m1
NOS	Mm00440502_m1
PGES	Mm00452105_m1
SOCS3	Mm00545913_s1
TLR4	Mm00445273_m1
TNFα	Mm00443258_m1

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