Psychoneuroendocrinology 63 (2016) 217–227

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Structural & functional consequences of chronic psychosocial stress on the microbiome & host

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 2 October 2015
Accepted 2 October 2015

Keywords:
Psychosocial stress
Gut microbiota
Behavior
Immune regulation
Functional metagenome
Chronic social defeat

ABSTRACT

Introduction: Given the lasting impact of psychological distress on behavior, along with the role of the microbiome in neurobehavioral development, we sought to examine the relationship between the microbiota and stress-induced behavioral deficits.
Methods: Male C57BL/6 mice exposed to chronic social defeat were subjected to behavioral analysis and profiling of the intestinal microbiome. Mice were also analyzed for phenotypic and functional immune changes. A computational approach on 16S rRNA marker gene sequences was used to predict functional changes in the metagenome as a consequence of structural shifts in the microbiota.
Results: Chronic social defeat induced behavioral changes that were associated with reduced richness and diversity of the gut microbial community, along with distinct shifts at the level of operational taxonomic units (OTU) across phyla. The degree of deficits in social, but not exploratory behavior was correlated with group differences between the microbial community profile. *In silico* analysis predicted a shift in the functional profile of the microbiome: defeated mice exhibited reduced functional diversity and a lower prevalence of pathways involved in the synthesis and metabolism of neurotransmitter precursors and short-chain fatty acids. Defeated mice also exhibited sustained alterations in dendritic cell activation, and transiently elevated levels of IL-10+ T regulatory cells that were suppressed over time.
Conclusions: This study indicates that stress-induced disruptions in neurologic function are associated with altered immunoregulatory responses and complex OTU-level shifts in the microbiota. It is thus suggested that a dysbiotic state, along with specific changes in microbial markers, may predict the onset of adverse neurocognitive deficits commonly observed following exposure to severe stressors. The data also predict novel pathways that might underlie microbiota-mediated effects on brain and behavior, thus presenting targets for investigations into mechanisms and potential therapy.
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1. Introduction

There is abundant evidence demonstrating the adverse impact of stress on physiology and neurocognitive correlates during development and adulthood: trauma or abuse during early life increase the risk of psychiatric conditions and can impair the development of the stress response (Heim et al., 2008), while inadequate coping behavior contributes to the etiology of diseases such as gastrointestinal disorders and increased risk of depression (Dinan, 2005; Mayer, 2000). Amidst the efforts to elucidate the mechanisms underpinning this association, there has been a growing recognition of the importance of the microbiota to normal development and function of several physiological processes, including metabolism, immunity, and behavior. Indeed, so integral are these symbionts to host function that it has been suggested that almost all animals, including humans, should be viewed as multi-species organisms or "holobionts" (Gilbert et al., 2012).

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http://dx.doi.org/10.1016/j.psyneuen.2015.10.001
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The body of work demonstrating the systemic role of the microbiome, especially in neural development and function, is extensive. Disruption or absence of the microbiome impairs behavior and its development, leading to increased exploration, decreased apprehension, and impaired social behavior (Bercik et al., 2011; Desbonnet et al., 2014). Conversely, chronic administration of *Lactobacillus rhamnosus* (JB-1) alters GABAR expression in the brain, and reduces anxiety-like and depressive behavior (Bravo et al., 2011). Particularly, there is compelling evidence of bidirectional interaction between stress and the microbiome. Exposure to stress alters the structural composition of the intestinal microbiota (Bailey et al., 2011; O'Mahony et al., 2009), while germ-free (GF) status and intestinal colonization alter the developmental trajectory of the stress response (Neufeld et al., 2011; Sudo et al., 2004). Within the context of the holobiont paradigm, the influence exerted by these microorganisms on brain development and behavior is a consequence of the evolution of a multi-species organism. To provide clearer insight into the implications of the concept of the collective "self" for health and disease, and understand the functional relationship between the microbiota and stress-induced alterations, we need greater insight into the mechanisms, pathways, and consequences of communication along the microbiota-gut-brain axis.

Here, an anthropomorphic model is used to examine the impact of psychosocial stress on host-microbiota interactions, and the relationship between the microbiome and stress-induced behavioral deficits. We profile the community structure and species-level shifts in the intestinal microbiota, including in the relative abundance of *Akkermancia muciniphilia* and Coriobacteriaceae. These specific taxa have been previously reported to be associated with healthy and stress-exposed microbiome communities, respectively (Bendtsen et al., 2012; Everard et al., 2013). Accordingly, in an effort to investigate the use of specific microbial community markers to predict adverse consequences on the host, we examined whether such alterations are retained, amidst broader shifts in the microbiota, across experimental studies. We also examine the nature of the stress-induced dysbiosis—specifically, the *Firmicutes/Bacteroidetes* ratio, which signals the status of the human gut microbiota in models of obesity and antibiotic-induced dysbiosis (Mariat et al., 2009; Sanderson et al., 2006; Thompson et al., 2015).

Given evidence of immune-mediated signaling along the microbiota-gut-brain axis in the literature (Desbonnet et al., 2010; Forsythe et al., 2010), we profile the immunoregulatory and innate immune phenotype, as well as the function of the peripheral immune system. Moreover, using a computational approach, we address the biological pathways that may be driving the effects of the microbiome on brain and behavior by profiling the predicted functional implications of structural shifts in the microbiome.

2. Methods

2.1. Animals

Male C57BL/6 mice, eight-weeks old, and male CD-1 mice, retired breeders, were acquired from Charles River (Montreal, QC, Canada). All animals were allowed to acclimatize to the housing facility for seven days prior to beginning the experiment. Animals were housed in standard conditions (12-h light–dark (LD) cycle, lights on at 07:00) with ad libitum access to standard rodent chow and water. All experiments followed the guidelines of the Canadian Council on Animal Care and were approved by the McMaster Animal Research Ethics Board.

2.2. Social defeat

Chronic social defeat (CSD) procedures were conducted as previously described (Berton et al., 2006). Defeats were conducted over the course of 10 consecutive days. During each defeat session, intruder C57BL/6 mice were allowed to interact for 5–10 min with a novel resident CD-1 mouse. Intruder mice were carefully observed to ensure the demonstration of subordinate posturing. For 24 h after each defeat session, mice were house in the same cage across a perforated Plexiglas divider to enable the transmission of visual and olfactory cues. Control mice were housed two per cage on either side of a Plexiglas divider while preventing any physical contact.

2.3. Behavioral testing

2.3.1. Open field test (OFT)

Testing was carried out in the dark phase of the LD cycle under dim-light conditions, one day after exposure to the final defeat session (Fig. S1). After a 1-h habituation period in the testing room, mice were singly placed into an 18 × 38 cm clear Plexiglas enclosure for a period of 30 min. Total distance traveled, rearing count, and time spent in the center of the field were recorded *via* photo beam sensors outfitted around the arena (Motor Monitor; Kinder Scientific). The equipment was cleaned between each test.

2.3.2. Three-chambered sociability test

All tests were conducted 2 days after the final defeat session, during the light phase of the LD cycle following a 30-min habituation period in the testing room. The testing apparatus was a three-chambered Plexiglas box, with each chamber possessing the dimensions 24.5 cm L × 44 cm W × 30 cm H. The dividing walls of the chambers possessed small openings that allowed mice access to each chamber. During the habituation phase of the test, a single test mouse was placed in the center chamber—with access to side chambers obstructed—and allowed to freely explore for 5 min. Following this, an unfamiliar sex- and strain-matched conspecific (stranger) was placed within a round, wire cup in one of the side chambers. An identical inverted wire cup was placed in the other side chamber. During the sociability phase, the test mouse was placed in the center chamber and allowed to freely explore all three chambers for a period of 10 min. During each phase, distance moved, time spent in each chamber, and time spent in within-chamber zones were recorded by a video camera positioned directly over the testing apparatus (EthoVision XT; Noldus). Sociability scores were calculated using (time spent in mouse-chamber interaction zone/time spent in empty-chamber interaction zone). The equipment was cleaned and wiped down between test mice.

2.3.3. Aggressor interaction test

Following completion of the three-chambered sociability test, mice were placed for 10 min in a 24.5 cm × 44 cm arena. A novel aggressor CD-1 was placed under a round, wired cage at one end of the arena. Time spent in the aggressor interaction zone and non-interaction zone was calculated for each mouse (EthoVision XT; Noldus).

2.3.4. Light–dark (LD) test

In a separate cohort of mice, on day 3 following the final defeat session, testing was carried out in the dark phase of the LD cycle under dim-light conditions. After a 1-h habituation period in the testing room, mice were singly placed into an 18 × 38 cm clear Plexiglas enclosure containing a black insert at one end for a period of 10 min. Kinderscientific motor monitor software was used to record time spent in the light zone and number of entries into the light

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