Research Article

Developing a novel hypothesis to enhance mental resilience via targeting Faecalibacterium prausnitzii in gut-brain axis

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Highlights

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Short-chain fatty acids especially Butyrate can increase resilience in stress conditions.

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Faecalibacterium prausnitzii is a kind of butyrate producing probiotic.

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As a hypothesis, the composition of probiotics can be engineered to yield more butyrate.

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As a hypothesis, in stress conditions, engineered *Faecalibacterium prausnitzii* can produce much butyrate.

Abstract

Social stress (SS) can lead to mental disorders (MD) in some people, such as depression and anxiety, while others who are resilient can handle SS without showing signs of mental illness. Resilience is characterized by human capacity to adapt to life's adverse events without losing function or developing a mental disorder. Exploring molecular processes can help elucidate resilience mechanisms that counteract the pathophysiology of depression. Gut microbiome plays an essential role in the homeostasis of human body, especially the central nervous system (CNS). Therefore, it may support the counterbalance of certain disorders, such as depression, through the microbiota-gut-brain (MGB) axis. Short-chain fatty acids (SCFAs) produced by the gut microbiota, such as butyrate, increase the transmission activity of neurotransmitters, brain-derived neurotrophic factor (BDNF) expression and the regulation of microglia maturation enhances resilience in response to stress. Probiotics can be engineered to yield more butyrate. However, the overproduction of

SCFAs is not necessarily beneficial and may lead to known side effects, such as intestinal dysbiosis or metabolic dysfunction. Herein, as we hypothesized the potential effect of the microbiome in resilience promotion, we have designed a cortisol-sensitive operon that allows gut microbiota to regulate the production of SCFAs according to the environmental demands which produces butyrate only when responding to stress. Amongst gut bacteria, *Faecalibacterium prausnitzii* (*F. prausnitzii*) has large amounts of butyrate and can be manipulated by designed plasmid, a process which makes it a suitable candidate to be translated into clinic.

Introduction

Mental disorders (MD) contribute to 7.4 % of the global burden of disease (GBD) [1]. Amongst a plethora of MD, depression and anxiety are one of the leading causes of disability globally [2]. The yearly cost of depression in the United States is almost 326 billion dollars, with substantial social and economic ramifications [3]. Since almost 70 % of depressed patients receiving first-line antidepressants do not respond adequately to treatment, it is crucial to investigate alternate mechanisms, like resilience. Susceptibility to MD, such as depression, is primarily influenced by genetic factors, as well as early-life and ongoing exposure to physical and psychological stressors, such as financial difficulties, divorce, and tragic life events [4].

Resilience is defined as human capacity to adapt to life's adverse events. This capacity to recover quickly or maintain normal function succeeding the hardship as a defense mechanism against the development of MD plays a crucial role in response to stress and subsequently reduces insults to mental health [5]. Given the increasing focus on the influence of gut microbiota on bodily functions, numerous studies have indicated a bidirectional relationship between gut microbiota and the brain. These findings indicate that gut microbiota may modify both brain function and its response to stressors.

The complex multi-organ bidirectional communication system known as the “microbiota-gut-brain” or MGB axis is critical in maintaining mental well-being [6]. It is shown that mental disturbances such as stress can alter the intestinal flora through certain physiological factors like cortisol hormone, secreted by the adrenal gland, highlighting the potentially substantial effect of gut composition on brain physiology [7].

The gut microbiota produces several functionally significant metabolites such as bile acids, branched-chain amino acids, short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), and catecholamines. Additionally, the gut microbiota can produce and induce the secretion of various neurotransmitters. These metabolites are secreted directly or

indirectly by the gut microbiota and interact with the central and enteric nervous systems [8].

SCFAs, the primary products of microbial fermentation in the gut, exert positive modulatory effects on different aspects of host health such as immune system functionality, mental health, neural development, and even preventing the development of inflammatory bowel disease [9]. Among the SCFAs, butyrate plays a significant role in reducing gut inflammation, thus affecting the brain by modulating the components of the gut-brain axis [10].

Faecalibacterium prausnitzii (*F. prausnitzii*) is one of the "next-generation probiotics" (NGP), which is abundantly (about 5–15 %) found in the human gut. *F. prausnitzii* is a primary source of butyrate production in the gut microbiome and is recognized for its ability to improve intestinal healing [11]. Butyrate produced by this bacterium increases the expression of the Brain-Derived Neurotrophic Factor (BNDF), a potent neuromodulator with direct effects on stress regulation [12]. Studies have demonstrated a positive correlation between butyrate produced by *F. prausnitzii* and cortisol levels, ultimately affecting mental health [13].

Taken together, the importance of resilience is highlighted by previous studies showing that not everyone who suffers from childhood abuse or other traumatic events develops psychopathology [4]. In this study, we proposed a bioengineering strategy to recruit *F. prausnitzii* to enhance mental resilience by manipulating bacteria for better response to cortisol levels by secreting functionally significant products, such as SCFAs, and specifically butyrate.

There are few investigations targeting the administration of engineered bacteria as probiotic supplements to enhance mental resilience. Therefore, it is essential to investigate the potential effects of this strategy on mental health improvement.

Section snippets

The hypothesis

In order to improve mental function and resilience, we hypothesize using genetically engineered *F. prausnitzii* containing TetR and NR3C1 (intracellular glucocorticoid receptor of cortisol) chimeric peptide, as well as manipulating the acetyl-CoA pathway that can

increase the production of short-chain butyrate fatty acids in response to increased cortisol content. In our quest for designing this personalized and environment-sensitive treatment, we hypothesized an on/off switch for the butyrate

Evolution of hypothesis

The test of our hypothesis would be conducted into *in vitro* and *in vivo* methods.

Consequences of hypothesis

Stress susceptibility is associated with biological factors like glucocorticoids, sex hormones, the activation of the immune system both centrally and peripherally, and responsiveness of the stress response system. The inability to induce considerable adversity in human subjects in controlled experimental conditions and the paucity of research on human molecular processes and brain circuits have made it challenging to elucidate the neurobiological mechanisms driving resilience. However, the

Limitations and future perspectives

Based on the available empirical data, our hypothesis seems to possess a fair degree of plausibility. Nevertheless, it is imperative to address and deliberate on the issues concerning this hypothesis. The primary obstacle is ensuring the bacteria's sustainability, aiming to achieve optimal efficacy. The viability of probiotic bacteria is a matter of concern due to their exposure to challenging conditions during various stages of preparation and consumption, such as processing, storage, and

Conclusion

Our hypothesis is mainly based on the bidirectional interaction between the gut microbiome and the brain, as we have approached changing the gut microbiota population by designing a genetically modified probiotic supplement. As mentioned earlier, *F. prausnitzii* is abundantly found in the healthy human gut as flora. Due to its predominance in abundance and health-promoting qualities, *F. prausnitzii* has been suggested as an intestinal health indicator. Its decreased abundance has been correlated

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CRediT authorship contribution statement

Mohammad Rahmanian: Writing – original draft, Investigation, Conceptualization. **Mobina Fathi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Mahya Eftekhari:** Conceptualization. **Kimia Vakili:** Writing – original draft. **Niloofar Deravi:** Writing – original draft. **Shirin Yaghoobpoor:** Writing – original draft. **Hosein Sharifi:** Writing – original draft. **Ramin Zeinalddin:** Writing – original draft. **Amirhesam Babajani:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References (58)

- C. Hammels *et al.*

Defeat stress in rodents: from behavior to molecules

Neurosci Biobehav Rev

(2015)

- J. Zhang *et al.*

A key role of the subdiaphragmatic vagus nerve in the depression-like phenotype and abnormal composition of gut microbiota in mice after lipopolysaccharide administration

Transl Psychiatry

(2020)

- S. Wang *et al.*

Ingestion of Lactobacillus intestinalis and Lactobacillus reuteri causes depression-and anhedonia-like phenotypes in antibiotic-treated mice via the vagus nerve

J Neuroinflammation

(2020)

- S. Wang *et al*.

Ingestion of Faecalibaculum rodentium causes depression-like phenotypes in resilient Ephx2 knock-out mice: A role of brain–gut–microbiota axis via the subdiaphragmatic vagus nerve

J Affect Disord

(2021)

- C. Gubert *et al*.

Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases

Neurobiol Dis

(2020)

- K. Zhang *et al*.

Abnormal composition of gut microbiota is associated with resilience versus susceptibility to inescapable electric stress

Transl Psychiatry

(2019)

- S. Wang *et al*.

Antibiotic-induced microbiome depletion is associated with resilience in mice after chronic social defeat stress

J Affect Disord

(2020)

- A. Farzi *et al*.

Gut Microbiota and the Neuroendocrine System

Neurotherapeutics

(2018)

- V. Behringer *et al*.

Non-invasive monitoring of physiological markers in primates

Horm Behav

(2017)

- J.M. Sasso *et al.*

Gut Microbiome-Brain Alliance: A Landscape View into Mental and Gastrointestinal Health and Disorders

ACS Chem Nerosci

(2023)

View more references