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Sulfate-reducing bacteria impairs working memory in mice☆

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HIGHLIGHTS

- Increased sulfate-reducing bacteria (SRB) abundance affects cognition in mice.
- SRB administered to mice impairs radial arm maze and Morris water maze performance.
- Impaired maze performance is correlated with increased cecal hydrogen sulfide.

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ABSTRACT

The ability of gut microbes to bi-directionally communicate with the brain and vice versa form the basis of the gut microbiome-central nervous system axis. It has been shown that inoculation with pathogenic gut bacteria alters the behavior of mice; however, it is not known whether or not non-pathogenic resident microbes have similar effects. In this study, we tested the hypothesis that the administration of sulfate-reducing bacteria (SRB), a specific group of resident gut bacteria that generate hydrogen sulfide (H_2S), impair learning and memory performance in mice tested in an 8-arm radial maze and Morris water maze. We found that mice spent more time in the center of the maze when they were gavaged with live SRB as compared to mice given saline (control), lactulose + mannitol (L/M), or killed SRB. SRB-gavaged mice were also tested using the Morris water maze and were found to take longer to complete the test, spend more time further from the platform, and have a longer path length to reach the platform. This effect of SRB on maze performance was associated with a higher concentration of H_2S in the small intestine and cecum. We conclude that SRB, a specific resident gut bacterial species, could impair cognitive function in mice.

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1. Introduction

The gut microbiome is important to both homeostasis and health of the host. The human microbiota consists of ~100 trillion microbes that live in and on us, the vast majority of which reside in the large intestine. Comparatively, the microbiome includes 10-fold more cells than the human body and over 100-fold more genes than the host [1,2]. The contribution of the gut microbiota to the physiology of the host is substantial with a collective metabolic activity of a virtual organ inside the intestinal lumen [3]. Multiple levels of mutualism take place between host and microbes and within the microbial community itself with potential for metabolic effects on the human host and vice versa [4–7]. A change in the gut microbiota such as represented by an increase in the concentration of just one specific resident species may, therefore, have far-reaching effects on the host.

Food constituents that have not been assimilated before reaching the microbes in the large intestine are fermented. Hydrogen is the major metabolic byproduct of fermentation, which is then consumed by another group of microbes that utilize hydrogen, or hydrogenotrophs, as an energy source for their metabolism [8,9]. There are three groups of hydrogenotrophs in the human gut: sulfate-reducing bacteria (SRB), methanogens, and acetogens. Proportionally, the two most common groups of hydrogenotrophic microbes are hydrogen sulfide (H_2S)-producing SRB and methane (CH_4)-producing archaeal methanogens [10] with acetogens frequently outcompeted by the other groups [11–13]. The relative

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dominance of the metabolic activity of SRB is suggested by the finding that ~30% of the UK population harbor significant methanogen numbers in the large intestine [14, 15]. The type of gas excreted is governed by an individual's microbiota that will show preference towards one pathway or the other [16].

SRB are anaerobic gram-negative bacteria that use sulfate as their terminal electron acceptor and convert hydrogen (H_2) to hydrogen sulfide (H_2S), which is known to be a highly toxic gas. Survivors of accidental H_2S exposure from industry or environment have reported depression, impaired concentration and impaired memory [17, 18]. H_2S is also generated endogenously by the host in minute amounts by enzymes cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) and is a gaseous neurotransmitter similar to carbon monoxide (CO) and nitric oxide (NO). In addition to vasodilation and smooth muscle relaxation, H_2S is required for long-term potentiation of hippocampal neurons, the experimental equivalent of the formation of memory [19, 20]. In contrast, resident SRB in the intestine are capable of producing much larger quantity of H_2S. It is not known, however, whether increasing the number of H_2S-generating SRB could affect cognitive functions that are dependent on learning or memory. In this study, we hypothesized that administering SRB into the gut by oral gavage may increase luminal H_2S and impair the learning maze performance of mice.

2. Results

2.1. Experiment I. Between subject comparison of live SRB, saline, lactulose/mannitol (L/M), and killed SRB in radial eight-arm learning maze

Mice treated with live SRB required a greater number of arm entries (18.0 ± 2.8 arm entries) to collect eight baits than mice treated with Saline (10.0 ± 1.5), lactulose/mannitol (L/M; a fermentable substrate added to increase hydrogen availability) (8.3 ± 0.3), or Killed SRB (8.7 ± 0.5) ($P < 0.05$) (Fig. 1a). Live SRB generated the greatest number of errors (10.7 ± 2.7 errors) compared to Saline (2.0 ± 1.5), L/M (0.3 ± 0.3), or Killed SRB (0.8 ± 0.5) ($P < 0.05$) (Fig. 1b). There was no significant difference in the total time to complete the maze across the different test groups [Saline (190.5 ± 36.2 s), L/M (162.0 ± 22.9 s), SRB (189.7 ± 26.8 s), Killed SRB (165.8 ± 25.0 s)]. Mice given live SRB spent more time in the center of the maze (38.8 ± 7.7 s) than Saline (22.2 ± 7.1 s), L/M (16.5 ± 3.0 s), or Killed SRB (18.5 ± 4.1 s) ($P < 0.05$) (Fig. 1c). Greater time in the center of the maze indicated that the animal spent more time selecting the next arm.

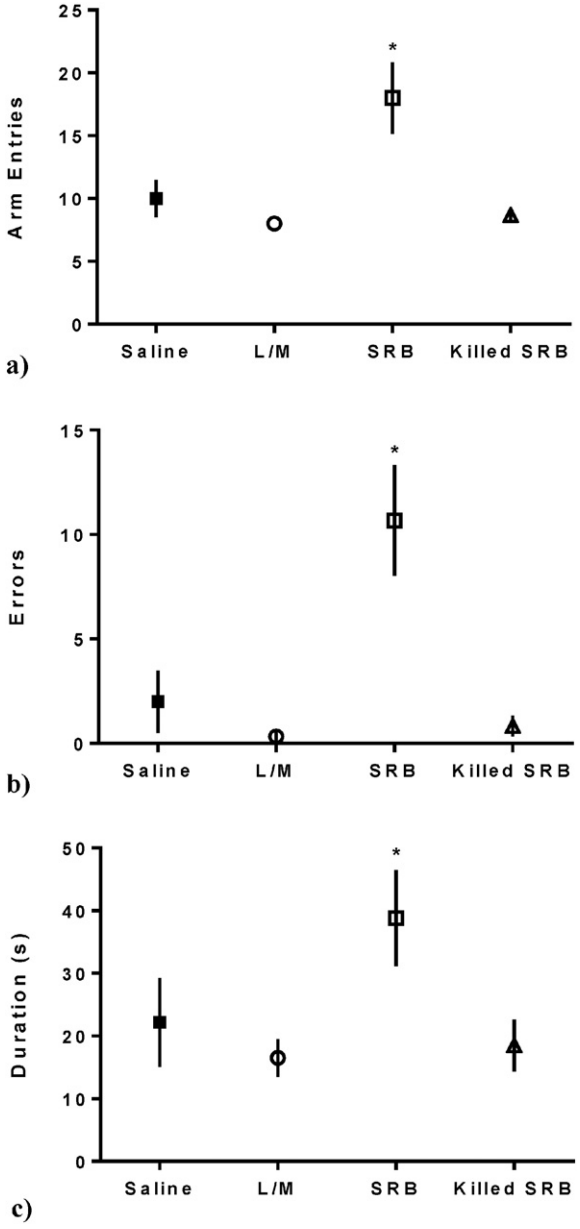

Fig. 1. Eight-arm radial maze results for Experiment I. a) Number of times mice entered maze arms to retrieve bait in Experiment I for mice administered Saline, lactulose/mannitol (L/M), live sulfate-reducing bacteria (SRB), and killed sulfate-reducing bacteria (Killed SRB). Data are mean with standard error. *$P < 0.05$. b) Number of errors mice made in the maze in Experiment I for mice administered Saline, lactulose/mannitol (L/M), live sulfate-reducing bacteria (SRB), and killed sulfate-reducing bacteria (Killed SRB). Data are mean with standard error. *$P < 0.05$. c) Time spent in the center of the eight arm radial maze in Experiment I for mice administered Saline, lactulose/mannitol (L/M), live sulfate-reducing bacteria (SRB), and killed sulfate-reducing bacteria (Killed SRB). Data are mean with standard error. *$P < 0.05$.

2.2. SRB functional genes

Hydrogen is converted to H_2S by SRB via the enzymatic products of dissimilatory sulfite reductase (DSR) genes that together form one functional DSR complex. *DsrB*, the catalytic subunit of the DSR complex in SRB, was used to assess SRB distribution. DNA was extracted from the mucosa of the cecum and relative expression levels of *dsrB* were measured by qPCR. When compared to Saline (1.7 ± 0.8), *dsrB* gene expression in the cecum was highest in live SRB (Mean fold change = 857.3 ± 178.7) ($P < 0.005$), followed by killed SRB (507.7 ± 190.6) ($P < 0.05$) and L/M (7.8 ± 4.1) (N.S.) (Fig. 2).

2.3. Luminal concentrations of hydrogen sulfide

The cecal concentration of H_2S in parts per billion (ppb) was highest in the live SRB-treated group (1101 ± 244.4 ppb), which was associated with the worst maze performance ($P < 0.001$) compared to Saline 75.0 ± 12.3 ppb, L/M 100.2 ± 12.3 ppb (N.S.), and Killed SRB 114.0 ± 46.1 ppb (N.S.) (Fig. 3). Hydrogen sulfide concentrations in the small intestine were significantly lower in the saline administered mice (7.8 ± 5.3 ppb) ($P < 0.0005$) compared to all other groups: live SRB (61.2 ± 50.0 ppb), L/M (66.7 ± 9.6 ppb), and Killed SRB (42.0 ± 29.5 ppb).

2.4. Experiment II. Within subject comparison of saline, fecal slurry, and SRB in radial eight-arm learning maze

The Saline, fecal slurry (FS), and SRB groups all underwent testing with and without the addition of lactulose and mannitol (L/M). There was no intragroup difference whether or not L/M was added, therefore data from individual groups of Saline, FS, and SRB were combined for further analysis. The average time spent in the center platform of the learning maze was significantly greater for mice gavaged with live SRB

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