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LETTER TO THE EDITOR

Promising role of D-amino acids in irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is an important health care concern. Alterations in the microbiota of the gut-brain axis may be linked to the pathophysiology of IBS. Some dietary intake could contribute to produce various metabolites including D-amino acids by the fermentation by the gut microbiota. D-amino acids are the enantiomeric counterparts of L-amino acids, in general, which could play key roles in cellular physiological processes against various oxidative stresses. Therefore, the presence of D-amino acids has been shown to be linked to the protection of several organs in the body. In particular, the gut microbiota could play significant roles in the stability of emotion *via* the action of D-amino acids. Here, we would like to shed light on the roles of D-amino acids, which could be used for the treatment of IBS.

Key Words: Irritable bowel syndrome; D-amino acid; Gut microbiota; Colitis; Probiotics; Fecal microbiota transplantation

Core Tip: The potential efficacy of D-amino acids for the treatment of irritable bowel syndrome is shown here.

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TO THE EDITOR

With great interest, we have read the article by Mamieva *et al*[1]. As irritable bowel

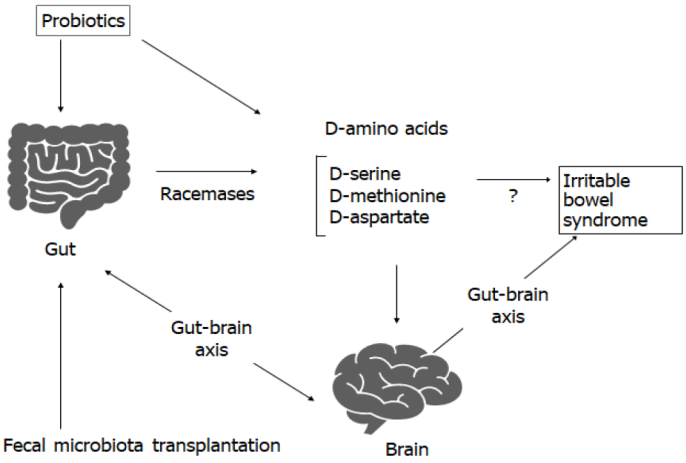

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Figure 1 Gut microbiota could contribute to the production of D-amino acids, which might play key roles in irritable bowel syndrome *via* direct action on the gut and/or indirect action through the gut-brain axis with emotional stability. Fecal microbiota transplantation consists of fecal microbiota infusion from a healthy donor into a recipient subject, which has been also shown to be a promising therapy for irritable bowel syndrome. Arrowheads mean stimulation and/or augmentation whereas hammerheads represent inhibition. Note that some critical events such as reactive oxygen species production, immune activation, and/or cytokine-induction have been omitted for clarity.

syndrome (IBS) could exacerbate the patients' quality of life, it is a considerable health care concern. Although the underlying pathophysiological mechanisms are not clear, the role of low-grade inflammation and mucosal immune activation appears to be obvious in the signs of IBS. IBS is a functional gastrointestinal disorder, and some probiotic supplementation may reduce the symptoms[2]. In addition, fecal microbiota transplantation expects recommendations for the treatment of IBS, suggesting that alterations in the gut microbiota-brain axis are linked to the pathophysiology of IBS (Figure 1). It has been revealed that some cytokines and neurotransmitters as well as several microbial metabolites including short chain fatty acids (SCFAs) such as acetate, lactate, butyrate, and propionate produced by the bacteria in the gut could modulate the integrity of brain function[1]. The bidirectional communication between the gut microbiota and the brain is well-known as the gut-brain axis, which could play an important role in the stability of emotion[3]. As shown in the article by Mamieva *et al*[1], the microbiota could influence the pathogenetic factors of IBS through the production of several microbial metabolites. Here, we would like to add the efficacy of D-amino acids for the alteration of IBS condition.

Mice treated with D-serine prior to the induction of colitis exhibited a reduction in the colonic inflammation that was not seen in mice fed L-serine[4]. In addition, D-serine efficiently suppressed the progression of chronic colitis. Therefore, D-serine might have effective properties as a preventive strategy and/or a treatment for colitis[4]. In addition, several studies have shown the significance of D-amino acids in clinical usage[5]. For example, D-methionine protects against the intestinal damage through anti-oxidative and anti-inflammatory effects, which could improve the gut microbiome imbalance by enhancing the growth of beneficial bacteria[6]. Protective effects of low-dose D-serine have been also shown to suppress the renal damage, which may promote the proliferation of kidney epithelial cells[7]. In addition, D-cysteine administration could defend the kidney from ischemia-reperfusion injury, which may be beneficial for the treatment of several renal diseases[8]. Gastroprotective effect with D-cysteine but not with L-cysteine has been shown *via* the effects of decreasing cellular damage, edema, and epithelium loss[9]. Treatment with D-aspartate may bring positive effects in the nervous system[10]. Furthermore, D-cycloserine is a glutamatergic N-methyl-D-aspartate receptor agonist which has been revealed to support the stability of emotion[11]. Furthermore, the activity of ovarian development with D-tryptophan is more effective than that with L-tryptophan[12]. These data suggest that D-amino acids could have beneficial and/or protective effects on various tissues, which might be favorable to the treatment of IBS (Figure 1). In particular, the emotional stability *via* the action of D-amino acids seems to be important[13], because it has been shown that different types of physiological and/or psychological stressors are known to contribute to the development, maintenance, and exacerbation of IBS[14].

The gut microbiota has a large genetic capacity to produce D-amino acids which are utilized as nutrients to support bacterial growth[15]. D-amino acids are essential elements of peptidoglycans in the cell wall of bacteria. Hence, higher levels of D-amino acids have been basically related to the mass of the gut microbiota[16]. Many bacterial species encode specific racemases that can convert L-amino acids to D-amino acids, which are frequently present in the peptidoglycan-containing bacteria in the gut microbiota[17]. Accordingly, the lumen of the gastro-intestinal tract in mammals may be rich in free D-amino acids that might be derived from such bacteria or fermented foods. Probably, the source of D-

amino acids in mammals may mostly be from their gut microbiota. For example, D-alanine production is linked to the relative abundance of bacterial species such as *Enterococcus* and *Lactobacillus* in the gut microbiota[18]. Therefore, the metabolism of D-amino acids in the body might be modified by the alteration of gut bacterial communities affecting the host health and/or homeostasis[19]. Reduction of the amount of several D-amino acids may promote senescence through the increase of reactive oxygen species production[20,21].

FOOTNOTES

Author contributions: Ikeda Y and Matsuda S contributed equally to this work; Ikeda Y, Taniguchi K, Sawamura H, Tsuji A, and Matsuda S designed the research study and wrote the manuscript; and all authors have read and approved the final manuscript.

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