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Original Research

Antidepressant Effects of 3-Indolepropionic Acid by Regulating Inflammation Level via Short-Chain Fatty Acids

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Abstract

Background: 3-indolepropionic acid (IPA) is an important gut microbiota-derived metabolite and has anti-inflammatory properties. We have observed the potential antidepressant effects of IPA, and therefore conducted this study to further detect its potential antidepressant effects and search for the possible action mechanisms. **Methods:** Chronic restraint stress (CRS) was used to induce depression-like behaviors (DLBs) in mice, and then IPA was administered to mice with DLBs (double-blind manner, 20 mg/kg, once daily for 10 consecutive days, intraperitoneal injection, ten days). The feces and hippocampus samples were collected to detect gut microbiota compositions, short-chain fatty acids (SCFAs), G protein-coupled receptor 43 (GPR43), and inflammation-related factors. **Results:** Disordered gut microbiota, decreased SCFA levels, decreased GPR43 (SCFA receptors), and increased inflammation levels were observed in CRS-induced depressed mice. After IPA treatment, DLBs in CRS mice were significantly improved, along with the improved gut microbiota and increased SCFA levels, especially acetic acid, propanoic acid, and valeric acid. Meanwhile, we found that IPA could increase the level of GPR43 and decrease the levels of inflammation-related factors in the hippocampus of CRS mice. In addition, close relationships among SCFAs, GPR43, and inflammation-related factors were observed. **Conclusions:** These results suggested that IPA might exert antidepressant effects through gut microbiota modulation, which elevated SCFA levels and subsequently alleviated brain inflammation.

Keywords: depression; 3-indolepropionic acid; short-chain fatty acids

1. Introduction

Depression is a prevalent and debilitating mental disorder, which is characterized by affective symptoms (sad mood, anhedonia, guilt), cognitive symptoms (poor concentration, indecision), neurovegetative symptoms (sleep/appetite changes, fatigue), behavioral symptoms (psychomotor agitation/retardation), and in severe cases, suicidal ideation or behavior [1,2]. In China, an increasing number of people suffer from depression, which is recognized as one of the twenty most important and preventable health problems [3]. According to the World Health Organization, an estimated 280 million people worldwide have depression. This condition affects approximately 5% of the adult population, with a prevalence of 5.7% among adults aged 60 and older. Nowadays, the pathogenesis of depression is still unclear despite various theories that have tried to explain it, such as neurotransmission deficiency and gut microbiota disturbances [4,5,6,7]. This dilemma results in the unsatisfactory response rate to first-line antidepressant drugs in clinical practice [8,9]. Thus, there is an urgent need to further explore the pathogenic mechanisms of depression and develop novel therapeutic approaches.

Much evidence has shown that gut microbiota is closely involved in the onset and development of depression [10,11]. Our previous studies found that gut microbiota compositions were obviously changed in both depressed humans and depression-like cynomolgus macaques [12,13]. As gut microbiota has become a research hotspot, many researchers have attempted to find novel treatment modalities for depression from the intestinal tract. Some studies have found that lactobacilli and bifidobacteria may serve as potential antidepressant probiotics to reduce depressive symptoms [14,15]. Guo et al. [16] reported that Akkermansia muciniphila could relieve depression-like behaviors

(DLBs) in stress-induced depressed mice. These results demonstrate that targeting gut microbiota holds promise for treating depression and warrants further investigation.

The central nervous system (CNS) also plays a vital role in depression. Interestingly, there are close interactions between the gut microbiota and the CNS. Evidence shows that the overgrowth of Gram-negative bacteria producing lipopolysaccharides may increase systemic and central nervous system inflammation [17,18]. In addition, previous studies have extensively explored intestinal permeability as a bidirectional system linking the hypothalamic–pituitary–adrenal axis and the gut microbiota, thereby influencing depressive disorders [19,20]. These findings further demonstrate the links between gut microbiota and depression.

Gut microbiota-derived metabolites, such as neurotransmitters, play key roles in gut–brain crosstalk. Tryptophan metabolism is one of the important metabolic processes in the body. In the gut, gut microbiota can convert tryptophan into 3-indolepropionic acid (IPA) via the indole pathway [21]. IPA exerts protective effects at both the cellular and tissue levels. Previous studies found that IPA could ameliorate gut dysbiosis and serve as a therapeutic target for various diseases [22,23]. IPA enhances tight junctions and barrier integrity by activating the intestinal pregnane X receptor (PXR). This reduces lipopolysaccharide translocation and systemic inflammation, thereby breaking the vicious cycle of dysbiosis and facilitating microbiota restoration. Meanwhile, some researchers have observed that IPA can produce neuroprotective effects by modulating inflammatory responses [24,25]. Considering the close relationships between depression and inflammation response, we hypothesized that IPA might exert antidepressant effects by improving inflammation levels, and therefore conducted this study to validate our hypothesis. Our previous study [26] and other studies [27,28] have provided some evidence to support this statement: we observed that IPA might improve DLBs via aryl hydrocarbon receptor (AhR); Chen et al. [27] found the potential effects of indole acetic acid on alleviating mood disorders; and Abildgaard et al. [28] reported that the antidepressant-like effects of probiotics in rats were associated with a higher plasma level of IPA.

2. Methods and Materials

2.1 Animal Model

Chronic restraint stress (CRS) was used here to induce DLBs in mice. The C57BL/6 mice (male, 6-8 weeks old) were randomly assigned into two groups: CRS group (n = 12) and control (CON) group (n = 12). According to the results of our previous study [26], the sample size in our present study could yield a power of 0.86 at a significance level of 0.05. The housing conditions were displayed in **Supplementary Materials**. We used a computer to generate random numbers to do random allocation. The two groups had similar baseline characteristics. The experimental operator, treatment administrators, and outcome assessors were blinded to group allocation. Group allocation information was replaced with numerical codes. Mice in the CRS group were exposed to CRS by placing them in 50 mL plastic tubes with a few holes, and were under water and food deprivation during the restraint time. Mice in the CON group were normally housed. The total process continued for 28 consecutive days. Mice were euthanized using carbon dioxide (CO_2) asphyxiation (flow rate: 20% of the chamber volume per minute). The CO_2 flow was continued for at least one minute after respiratory arrest, followed by immediate cervical dislocation to ensure death. After decapitation, the brains were removed. Hippocampi were dissected on ice, snap-frozen, and stored at –80 °C. Fecal samples were also collected and stored at –80 °C.

2.2 DLB Evaluation

The following two classical behavioral tests were used to detect the DLBs in the CRS group: the sucrose preference test (SPT) and forced swim test (FST). The procedures of SPT and FST were exactly performed according to our previous studies [26,29]. The sucrose preference (SP) in the SPT was employed to detect anhedonia, and immobility time (IT) in the FST was employed to detect despair in mice. In addition, we conducted an open field test (OFT) to detect anxiety-like behaviors in the CRS group, and the central distance (CD%) was the evaluation index. The experimenters were kept unaware of group assignment (CON vs. CRS). The detailed information of behaviors testing methods was displayed in **Supplementary File 1**.

2.3 Gut Microbiota, SCFAs, and Cytokine Detection

The gut microbiota compositions in the feces were measured using 16S rRNA analysis (Shanghai Bioclouds Biotechnology Co., Ltd, Shanghai, China). The short-chain fatty acids (SCFAs) in the feces were measured using gas chromatography–mass spectrometry (GC-MS) (Shanghai Bioclouds Biotechnology Co., Ltd, Shanghai, China). We performed 16S rRNA and GC-MS according to the routines in our previous research [26,29], and the specific steps were displayed in **Supplementary File 1**. Additionally, we used enzyme-linked immunosorbent assay (ELISA, Jianglai Industry Co., Ltd, Shanghai, China) to detect two SCFA receptors [G protein-coupled receptor 41 (GPR41) (product number: JL23399) and G protein-coupled receptor 43 (GPR43) (product number: JL23395)] and four inflammation-related factors (nuclear factor kappa B, NF-κB; nod-like receptor thermal protein domain-associated protein 3, NLRP3; interleukin-6, IL-6; and interleukin-1β, IL-1β) in the hippocampus of mice. Our previous studies demonstrated that these molecules were closely associated with depression, which prompted us to investigate them [26,29].

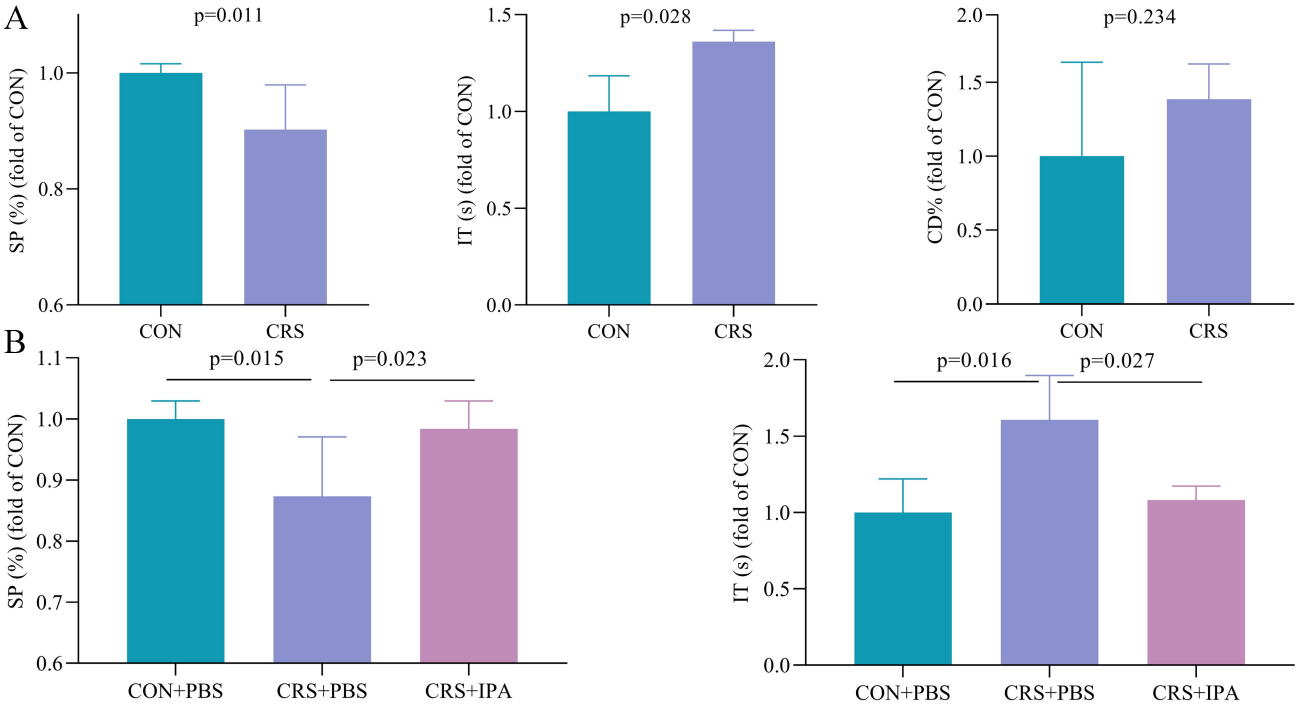

Fig. 1. IPA significantly improved CRS-induced depression-like behaviors. (A) Mice in the CRS group had lower SP, higher IT, and similar CD% compared to mice in the CON group; (B) after IPA intervention, the decreased SP and increased IT in the CRS group were significantly improved. SP, sucrose preference; IT, immobility time; IPA, 3-indolepropionic acid; CON, control; CRS, chronic restraint stress; CD, central distance; PBS, phosphate-buffered saline.

2.4 IPA as Intervention Agent

According to our previous study [26], IPA was dissolved in vehicle (5% dimethyl sulfoxide (DMSO)) at a dosage of 20 mg/kg. After the depression model was built, we randomly divided the CRS mice into two groups: one group receiving phosphate-buffered saline (PBS) mixed with 5% DMSO, and the other group receiving IPA. The CRS+PBS group and CRS+IPA group had similar body weight (BW) and SP before intervention. The mice in the CON group (CON+PBS group) received PBS mixed with 5% DMSO. The method of administration was intraperitoneal injection. After ten days, we conducted tests to evaluate the DLBs in mice and collect samples.

2.5 Statistical Analysis

Student's *t*-test, Mann–Whitney non-parametric test, or one-way analysis of variance (ANOVA) test was used to assess the differences between the groups, when appropriate. The Kolmogorov–Smirnov test was used to assess the normality of the data. If a difference was identified in the one-way ANOVA test, we performed the post-hoc analysis to further determine which two groups differed significantly. We conducted Spearman correlation analysis to assess the correlations between differential variables. The alpha diversity and beta diversity were evaluated using three parameters (ACE, Shannon, and phylogenetic diversity) and principal coordinate analysis (PCoA), respectively [30]. The linear discriminant analysis (LDA) effect size (LEfSe) was conducted to explore differential genus, which were significantly affected by IPA [31]. Benjamini and Hochberg False Discovery method was used to correct for multiple comparisons. All the analyses were conducted using R software 4.0, and statistical significance was defined as a *p*-value less than 0.05.

3. Results

3.1 IPA Treating CRS-induced DLBs

Before the CRS procedure, the two groups had similar SP and BW. After CRS procedure, the significantly lower SP (p = 0.011, Mann–Whitney non-parametric test), significantly higher IT (p = 0.028, Student's t-test), and similar CD% (p = 0.234, Mann-Whitney non-parametric test) were observed in the CRS group than in the CON group (Fig. 1A), suggesting that CRS successfully induced DLBs, but not anxiety-like behaviors, in mice. After IPA treatment, the decreased SP in mice with DLBs was significantly improved (p = 0.023, effect size = 1.407, CRS+PBS vs. CRS+IPA), and the increased IT in mice with DLBs was also significantly improved (p = 0.027, effect size = 0.920, CRS+PBS vs. CRS+IPA) (Fig. 1B). The CON+PBS and CRS+IPA had similar SP and IT, and the CON+PBS group had significantly higher SP (p = 0.015) and lower IT (p = 0.016) compared to the CRS+PBS group (Fig. 1B). These findings indicated that IPA might yield antidepressant ef-

fects in mice with CRS-induced DLBs.

3.2 IPA Improving Gut Microbiota Compositions

The alpha diversity in the CRS+PBS group was significantly different compared to the other two groups; however, the alpha diversity was similar between the CON+PBS group and CRS+IPA group (Fig. 2A). Meanwhile, the results of PCoA showed that the beta diversity in the CRS+PBS group was significantly different compared to both the CON+PBS group (p = 0.004) and CRS+IPA group (p = 0.003) (**Supplementary Fig. 1**). These results indicated that IPA might improve gut microbiota compositions in the CRS mice. As shown in Fig. 2B, at the genus level, the relative abundances of gut microbiota varied significantly among the three groups. To find out the genera that could be significantly affected by IPA, LEfSe was further performed. The results showed that IPA might significantly affect 36 differential genera, most of them (n = 19) belonged to phylum Firmicutes, while eight belonged to phylum Bacteroidota (Fig. 2C). Additionally, close relationships among these differential genera were observed.

3.3 Effects of IPA on SCFA Levels

In total, eight SCFAs were successfully identified in the feces of mice. We observed that mice in the CRS group had decreased levels of SCFAs (CRS+PBS vs. CON+PBS), and IPA treatment might restore these levels in the CRS mice (CRS+IPA vs. CRS+PBS) (Fig. 3A). Further analysis showed that the levels of acetic acid (p = 0.002), propanoic acid (p = 0.036), and valeric acid (p = 0.028) were significantly decreased in the CRS+PBS group than in the CON+PBS group (Fig. 3B). After IPA intervention, the levels of these three SCFAs in the CRS mice were significantly restored (acetic acid, p = 0.032, effect size = 1.432; propanoic acid, p = 0.045, effect size = 2.832; valeric acid, p = 0.011, effect size = 3.733; Fig. 3B). These findings showed that IPA might have positive effects on SCFA levels. In addition, we found that there were close relationships between acetic acid/propanoic acid/valeric acid and 20 differential genera (Fig. 3C), indicating that these differential SCFAs were mainly related to genera under Firmicutes and Bacteroidota.

3.4 Effects of IPA on Inflammation Levels

Two SCFA receptors and four inflammation-related factors in the hippocampus of mice were assessed here. GPR41 and GPR43 were the receptors of SCFAs. Finally, we observed that GPR43 level was significantly lower in the CRS+PBS group relative to the CON+PBS group (p = 0.022), but significantly improved after IPA treatment (CRS+PBS vs. CRS+IPA, p = 0.002, effect size = 2.462), whereas no difference was found between the latter two groups, and GPR41 level was similar among the three groups (Fig. 4). Meanwhile, we found that the CRS+PBS group had the significantly higher levels of NF-κB (p = 0.001), NLRP3 (p = 0.0002), IL-1β (p = 0.011) and IL-6 (p = 0.0003) relative to the CON+PBS group; after IPA treatment, the increased inflammation levels were significantly restored (CRS+IPA vs CRS+PBS; NF-κB, p = 0.001, effect size = 0.649; NLRP3, p = 0.001, effect size = 0.906; IL-1β, p = 0.004, effect size = 0.622; IL-6, p = 0.004, effect size = 0.991; Fig. 4). These results indicated that IPA positively influenced inflammation levels in the hippocampus of CRS mice.

3.5 Correlation Analysis Between SCFAs and Inflammation Factors

SCFAs may exert anti-inflammatory effects by regulating NF-κB. Here, Spearman correlation analysis was conducted to assess the potential relationships between the significantly changed SCFAs and GPR43. We found that there were close correlations between GPR43 and the three SCFAs (acetic acid, r = 0.656, p = 0.007; propanoic acid, r = 0.741, p = 0.001; valeric acid, r = 0.618, p = 0.012) (Fig. 5). Meanwhile, we found that NF-κB was negatively correlated with GPR43 (r = –0.533, p = 0.035) and positively correlated with NLRP3 (r = 0.700, p = 0.003) (Fig. 5). In addition, the level of IL-1β was found to be significantly positively correlated with the level of NLRP3 (r = 0.850, p = 0.00003) (Fig. 5). Considering the relationships among these molecules, our findings indicated that IPA might yield antidepressant effects by modulating the inflammation level in the hippocampus of CRS mice via SCFAs.

4. Discussion

In the present study, we found that IPA might significantly improve DLBs in the CRS mice. To explore the potential mechanism of action, we assessed the effects of IPA on gut microbiota compositions, and observed that IPA might improve the disordered gut microbiota compositions and restore the decreased levels of SCFAs in the feces of CRS mice. Secondly, we focused on the inflammation levels in the hippocampus of mice, and found that IPA might reduce the elevated levels of NF-κB, NLRP3, IL-6, and IL-1β via regulating GPR43 level in the hippocampus of CRS mice. In addition, we observed the close relationships between differential SCFAs and inflammation-related factors. Our findings suggested that IPA might hold promise as a candidate target for depression treatment.

Gut microbiota plays a vital role in maintaining the health of the host. Evidence has shown that the disturbances of gut microbiota are closely related to many diseases [32,33]. Some researchers thought that the disordered gut microbiota might be the cause of some complicated diseases [34,35]. Our previous studies found that both depression patients and mice with DLBs had obviously different gut microbiota compositions compared to controls [36,37]. Thus, targeting gut microbiota may be a promising method for treating depression. In recent decades, many researchers have developed novel methods to treat depression

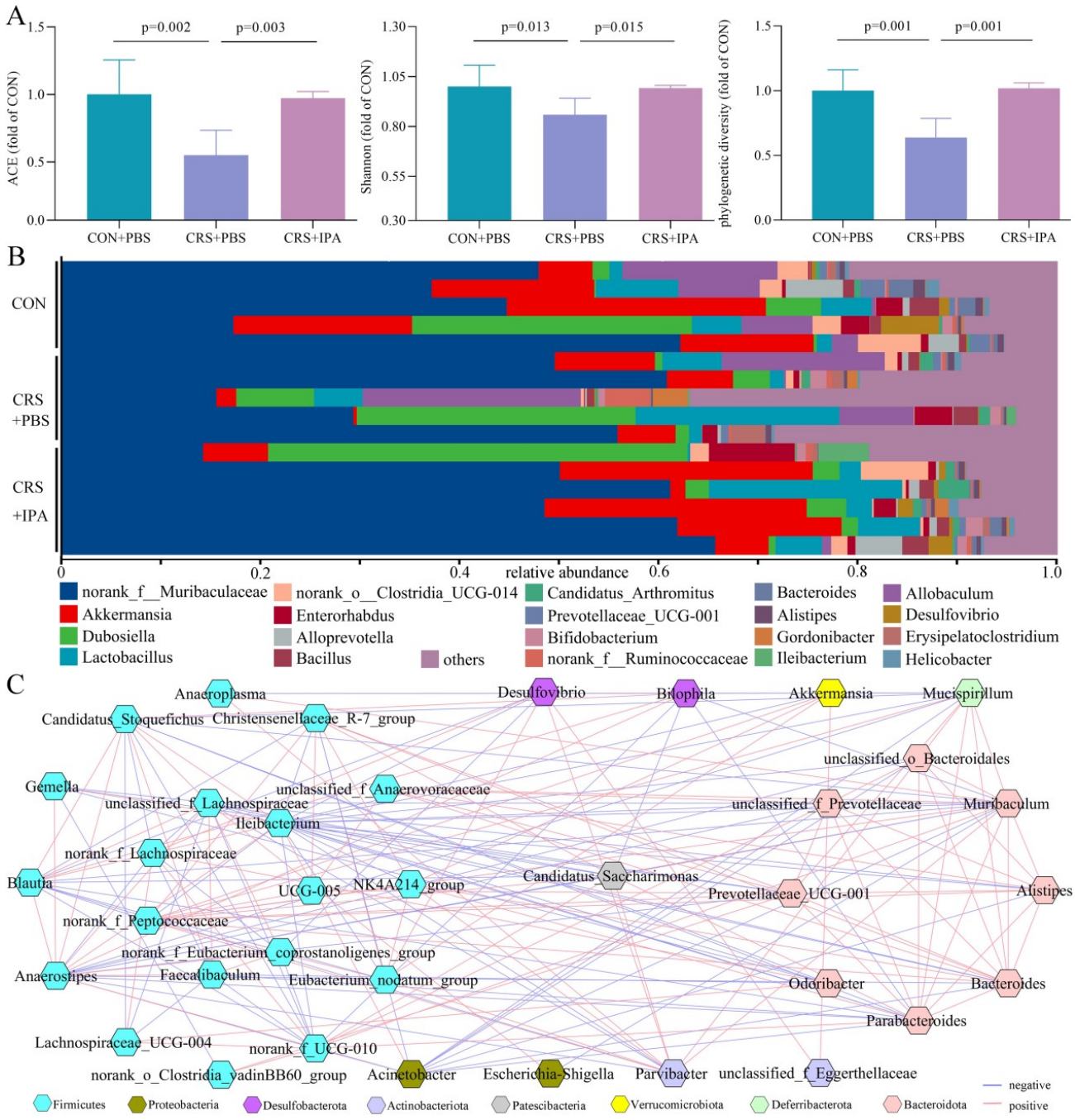

Fig. 2. IPA improved the disordered gut microbiota compositions. (A) alpha diversity in the CRS+PBS group was significantly different compared to the other two groups; (B) the relative abundances of genera (top 20) in the three groups; (C) there were close relationships among the identified 36 differential genera.

via targeting gut microbiota, including probiotics, postbiotics, and fecal transplantation [38]. Here, we found that IPA might recover the gut microbiota compositions in mice with DLBs. Our present findings suggested that IPA might effectively alleviate DLBs by ameliorating gut microbiota disturbances.

SCFAs are the main metabolites of gut microbiota, and their disturbances are closely related to many diseases. Researchers have reported the decreased levels of SCFAs in depression patients [39]. Using an animal depression model, we found significantly decreased levels of acetic acid, propanoic acid, and butyric acid in the depressed mice [22,36]. Meanwhile, some studies reported that SCFAs might be directly or indirectly involved in the onset of depression [40,41], and a folk medicine was found to be effective in alleviating DLBs through SCFAs [42]. Here, we also identified the lower SCFA levels in the CRS-induced depression mice; moreover, we found that IPA intervention

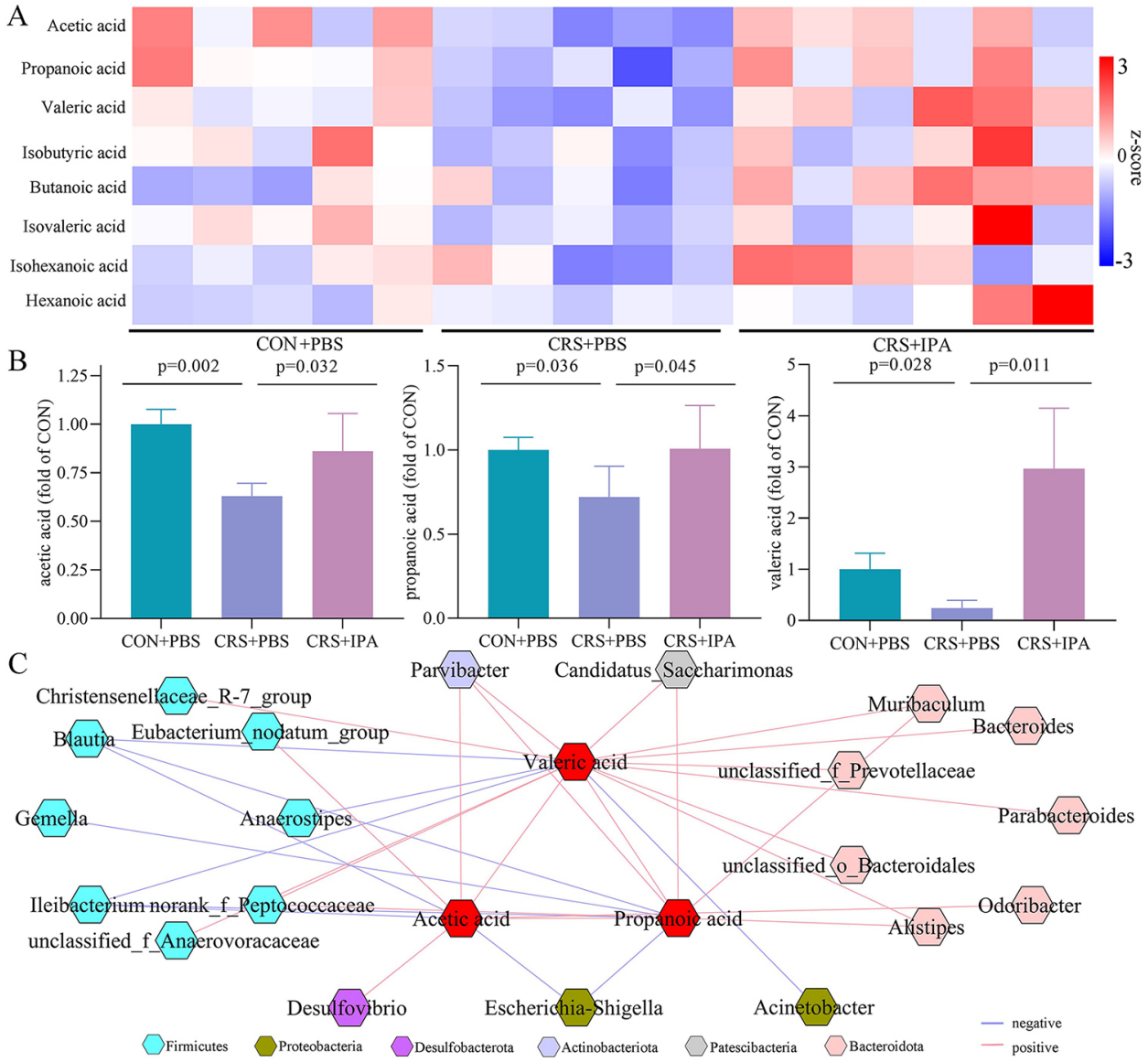

Fig. 3. IPA improved the SCFA levels in the feces of CRS mice. (A) SCFA levels were decreased in the CRS mice, and IPA treatment might increase SCFA levels; (B) IPA showed the positive effects on acetic acid, propanoic acid, and valeric acid; (C) Differential genera under Firmicutes and Bacteroidota were mainly correlated with acetic acid, propanoic acid, and valeric acid. SCFA, short-chain fatty acids.

might recover the decreased SCFA levels in the depressed mice, especially acetic acid, propanoic acid, and valeric acid. Our findings suggested that SCFAs might serve as the critical mediators in the antidepressant action of IPA.

Inflammation level is closely related to health, and the increased inflammation level is observed in many diseases, such as autism and depression [43,44]. Depression is closely associated with inflammatory response and has itself been viewed, in some cases, as a kind of inflammatory disease [45,46]. As pro-inflammatory mediators, both IL-6 and IL-1β play crucial roles in the inflammation response. Previous studies found that the increased levels of IL-6 and IL-1β had close relationships with the onset of DLBs [47]. The levels of IL-6 and IL-1β are related to NLRP3 inflammasome activation, which can activate caspase-1 to produce inflammatory cytokines [48,49]. And, NF-κB, an important transcription factor, is an important regulator in activating the NLRP3 inflammasome [50]. In addition, GPR43 is one of the SCFA receptors, and evidence shows that the increased level of GPR43 can inhibit the NF-κB signaling pathway [51,52]. Here, we found that CRS mice had significantly lower GPR43 levels and higher levels of NF-κB, NLRP3, IL-6, and IL-1β, whereas the levels of these molecules were restored after IPA intervention. Therefore, our results indicated that IPA might exert antidepressant effects by modulating inflammation levels via SCFAs.

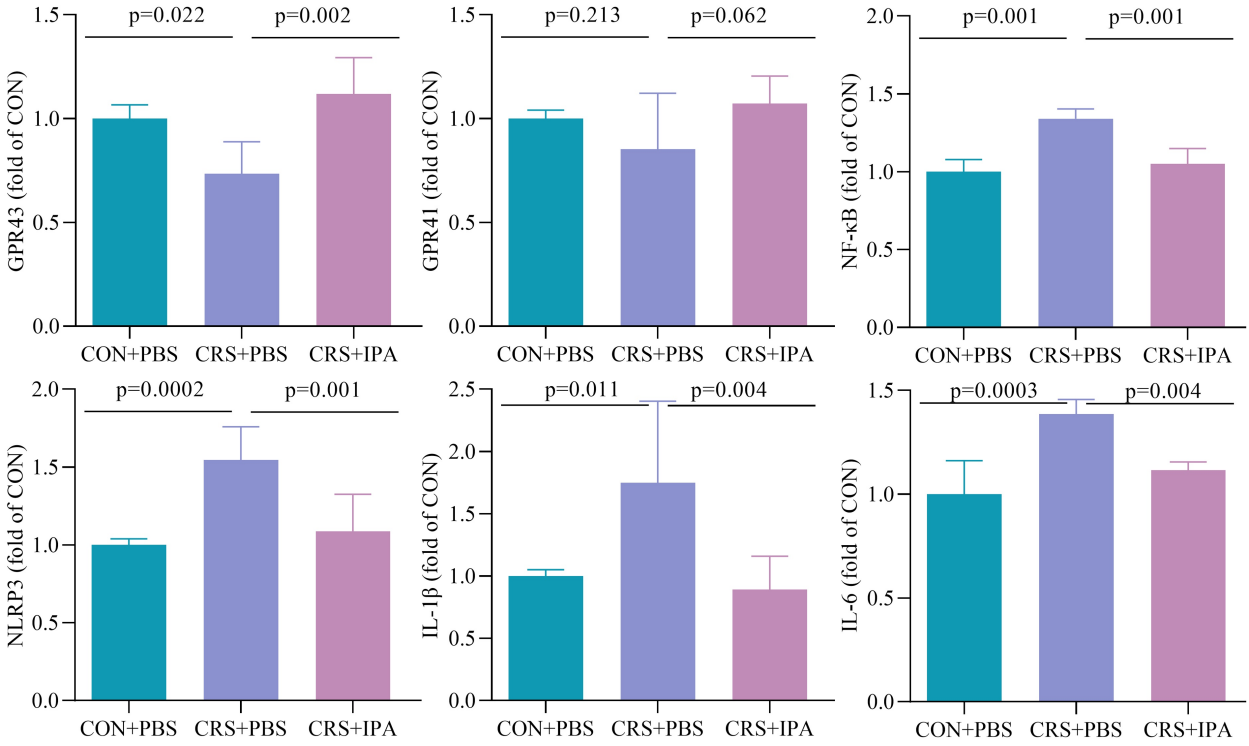

Fig. 4. IPA regulated inflammation levels in the hippocampus of CRS mice. The CRS+IPA group and CON+PBS group had similar levels of GPR43, NF-κB, NLRP3, IL-1β, and IL-6 in the hippocampus, whereas both groups had significantly higher GPR43 levels and lower levels of NF-κB, NLRP3, IL-1β, and IL-6 relative to the CRS+PBS group. GPR41 level was similar among the three groups. GPR43, G protein-coupled receptor 43; NF-κB, nuclear factor kappa B; NLRP3, nod-like receptor thermal protein domain-associated protein 3; IL-1β, interleukin-1β; IL-6, interleukin-6; GPR41, G protein-coupled receptor 41.

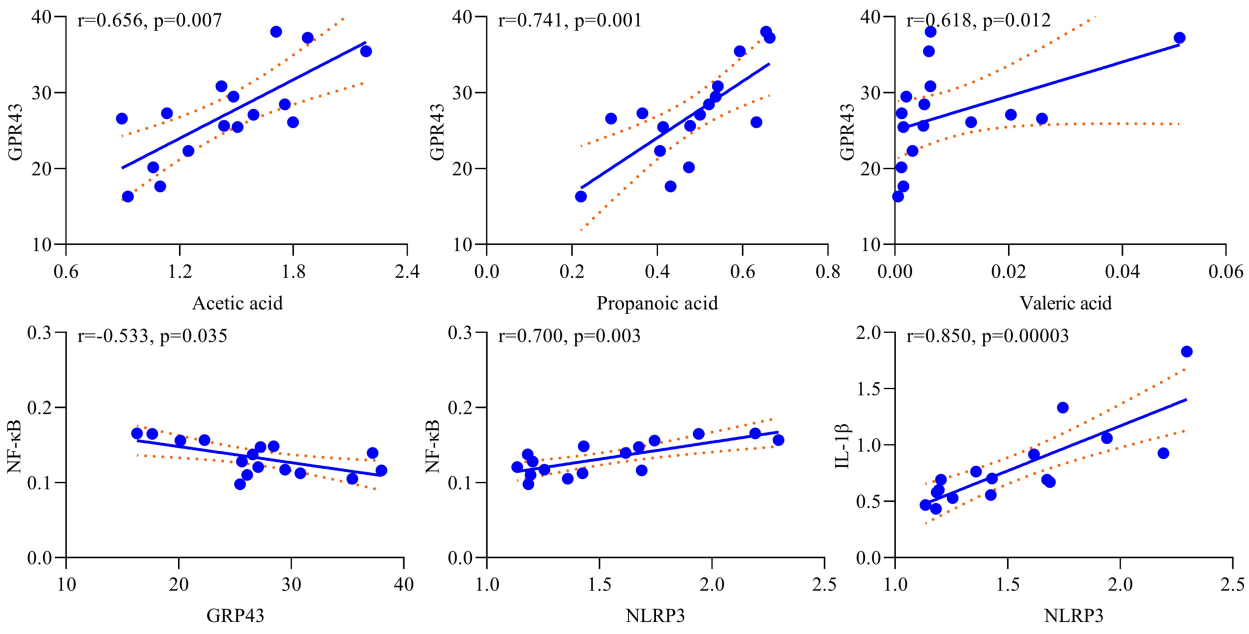

Fig. 5. Close relationships among SCFAs, GPR43, and inflammation levels.

5. Limitations

Several limitations of our study should be mentioned here. Firstly, our conclusion was based on a small sample size, and a strong conclusion could not be drawn; future studies should include more mice to validate and support our conclusion. Secondly, no causal intervention was performed in this study to provide mechanistic evidence that

IPA produces antidepressant effects via SCFAs. Hence, future studies should incorporate experimental approaches to validate this mechanism, such as GPR43 antagonism or knockout, SCFA depletion, fecal microbiota transplantation, or antibiotic-induced microbiota depletion. Third, the robustness of the results could be improved by using additional tests, such as the tail suspension test and novelty-suppressed feeding. However, the number of tests performed should be carefully considered, as more tests may cause greater distress to the mice. Fourthly, our previous study found that IPA could exert antidepressant effects via AhR [26], whereas the present study did not experimentally distinguish the direct effects of IPA from those mediated by the gut microbiota.

6. Conclusions

In conclusion, our previous work indicated that IPA might improve DLBs through AhR to inhibit neuroinflammation [26]. Here, we provided another potential pathway. Our present study found that mice with DLBs had disordered gut microbiota, decreased SCFA levels, and increased inflammation levels compared to control mice. After IPA intervention, the DLBs in the CRS mice were improved, along with the improved gut microbiota compositions. The altered levels of SCFAs, GPR43, and four inflammation-related factors in the CRS mice were also recovered. These results suggested that IPA might yield antidepressant effects via the "SCFAs-GPR43-inflammation" pathway. Our results further indicated that IPA might represent a promising candidate for depression treatment.

Availability of Data and Materials

All data analyzed and generated by the institute are included in this document and are available from the corresponding author upon reasonable request.

Author Contributions

JX and JJZ: Conceptualization, Writing-original draft, Animal modeling, Investigation, Methods, Review & Editing. YZZ, FH and JLW: Animal modeling, Investigation, Methods, and Analysis. KX and JJC: Project Administration, Investigation, Methods and Analysis. YW and PX: Conceptualization, Funding acquisition, Supervision, Review & Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was designed, conducted, and reported in accordance with the Animal Research Reporting *In Vivo* Experiments (ARRIVE) guidelines. All experiments involving mice were conducted according to the ethical policies and procedures approved by the Ethics Committee of Chongqing Medical University (IACUC-CQMU-2025-0138). All mice were maintained in accordance with the Animal Welfare Act and Guide for the Care and Use of Laboratory Animals: Eighth Edition.

Acknowledgment

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL52570.

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