Serotonin (or 5-hydroxytryptamine, 5-HT) is synthesized by nerve cells in the central nervous system (CNS), but is mainly synthesized peripherally by intestinal chromaffin cells (1). Because 5-HT cannot cross the blood–brain barrier, peripheral and central 5-HT function distinctly. In peripheral tissues, 5-HT promotes cell proliferation, participates in immune activation and inflammatory processes, and activates itch signals by combining with its receptor on afferent nerve fibres. Patients with psoriasis have a significantly higher risk of depression (2), while depression is associated with a decrease in the availability of monoamine neurotransmitters, such as 5-HT in the CNS (3). The brain–gut axis is a 2-way channel system that links the CNS and gastrointestinal tract, where 5-HT may be a key neurotransmitter for the connection. Because the secretion of 5-HT by intestinal cells can be regulated by the CNS through the brain–gut axis (4), we hypothesized that psychological disorders may modify the association of 5-HT with psoriasis that was reported previously (5). We also hypothesized that intestinal permeability may regulate the secretion of 5-HT by chromaffin cells. The aims of this study were to investigate the effect of modification by comorbid depression or anxiety on the association of serum 5-HT with psoriasis severity, and whether 5-HT mediates the association of intestinal permeability with psoriasis.

Table I. Characteristics of study patients with regard to depression

| Characteristics | Total | Yes (PHQ-9 ≥8) | No (PHQ-9 <8) | ρ-value |
|-----------------|-------|----------------|---------------|---------|
| Total, n (%)    | 113   | 22 (19.5)      | 91 (80.5)     | 0.332   |
| Age, years, mean±SD | 39.6±12.8 | 37.2±11.8 | 40.2±13.0 | 0.314 |
| Women           | 77 (68.1) | 13 (16.9) | 64 (83.1) | 0.701 |
| Men             | 36 (31.2) | 9 (25.0)  | 27 (75.0) | 0.311 |
| Anxiety, n (%)  | 22 (19.5) | 15 (68.3) | 7 (31.7)  | <0.001 |
| BMI, kg/m², mean±SD | 24.0±4.4 | 26.6±3.8 | 23.3±4.3 | <0.001 |
| Course, year, median (IQR) | 5.0 (1.0, 11.5) | 8.0 (3.5, 10.5) | 5.0 (1.3, 12.8) | 0.311 |
| PASI, median (IQR) | 6.7 (3.6, 13.2) | 7.6 (3.7, 17.5) | 6.7 (3.6, 12.4) | 0.770 |
| 5-HT, pg/ml, median (IQR) | 526 (341, 688) | 566 (356, 736) | 525 (336, 686) | 0.701 |
| LPS, pg/ml, median (IQR) | 6.1 (1.8, 6.5) | 8.0 (1.3, 9.7) | 5.7 (1.8, 5.3) | 0.186 |

5-HT: 5-hydroxytryptamine; LPS: lipopolysaccharides; BMI: body mass index; DLQI: Dermatology Life Quality Index; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; PHQ-9: 9-item Patient Health Questionnaire.

Materials and Methods

A total of 113 patients with psoriasis vulgaris were recruited consecutively. Two dermatologists independently assessed the severity of skin lesions with the Psoriasis Area and Severity Index (PASI). The Generalized Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) were used to measure the symptoms of anxiety and depression (6, 7), respectively, both with validated cut-offs of 8 to screen anxiety and depression. Enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of 5-HT and lipopolysaccharide (LPS), an indicator of intestinal permeability. Wilcoxon rank sum test was used to compare medians, and Spearman’s correlation was used to test the effect size and significance. A mediation effect model was established to examine whether 5-HT links the association of LPS with PASI.

The characteristics of the patients with regard to depression is shown in Table I. The prevalence rates of anxiety and depression in the study subjects were both 19.5% (22/113). Age, course of psoriasis, PASI, 5-HT, and LPS were not statistically different between patients with depression and those without. When stratified by depression (Fig. 1), 5-HT was significantly correlated with PASI in patients with symptoms of depression (r = 0.50), but was not associated with PASI in those without depression (r = –0.01). Similarly, 5-HT was significantly correlated with PASI (r = 0.41) only in patients with comorbid anxiety. Interestingly, we found that LPS showed a consistent relationship with 5-HT (r = 0.84 and 0.82) but differential associations with PASI (r = 0.23 and –0.11) in patients with and without depression, respectively. This

Fig. 1. Relationship between 5-hydroxytryptamine (5-HT) and Psoriasis Area and Severity Index (PASI) in patients with and without depression.
indicates that intestinal permeability may regulate the secretion of 5-HT independent from the CNS, but, like 5-HT, it may not affect psoriasis when mental comorbidity was not present. A mediation effect model was then established and it was found that 5-HT significantly mediated ($\beta=8.82, p=0.022$) the correlation between LPS and PASI in patients with anxiety or depression.

**DISCUSSION**

We first identified that 5-HT is related to PASI in psoriatic patients with comorbid anxiety or depression, but not in those without psychological conditions, indicating an effect modification by CNS. It was then found that intestinal permeability may regulate the peripheral secretion of 5-HT, as supported by the strong correlation between serum 5-HT and LPS. Finally, we observed that 5-HT links the association of LPS with PASI in psoriatic patients with anxiety or depression. These findings support an involvement of brain–gut axis in the regulation of psoriasis. However, longitudinal investigation is needed to determine whether 5-HT can be used as a practical predictor for PASI needs. In summary, the current study identified a specific patient subgroup, in which peripheral 5-HT may be involved in the development of psoriasis.

Previous studies have reported the role of 5-HT in psoriatic patients with psoriasis. The peripheral serum 5-HT in psoriasis was elevated, but decreased after treatment (8). A recent study showed that the level of 5-HT was imbalanced in acute psoriasis, and was elevated only in patients with anxiety (5). Expression of 5-HT and its receptors in psoriatic skin lesions were upregulated compared with normal skin, which facilitates the development of psoriasis by promoting the proliferation of keratinocytes and acting as an inflammatory mediator (9, 10).

Expression of serotonin transporter (SERT) on inflammatory cells, such as dendritic cells in the psoriatic epidermis is also increased, and there is a positive correlation between the severity of psoriasis and the number of SERT-positive dendritic cells, which indicates that the regulation of SERT may play a role in psoriasis (11). A population-based cohort study showed that the use of antidepressant selective 5-HT transporter inhibitors (SSRIs) can reduce the systemic use of medication in patients with psoriasis (12). Another study showed that major depression is an independent risk for psoriasis, while long-term treatment with SSRIs can reduce the risk of major depression complicated with psoriasis (13, 14), indicating that SSRIs have a protective effect on psoriasis. In summary, previous studies recognized the important role of the 5-HT energy system in psoriasis, and the current study further identified an effect modification of psychological disorders.

**ACKNOWLEDGEMENTS**

This work was supported by the Ministry of Science and Technology of the People’s Republic of China (2018YFC0117004), the National Natural Science Foundation of China (81974479, 81773329, 81573049, 81830096), and the Department of Science and Technology of Hunan Province (2018SK2082, 2018SK2086) and China Postdoctoral Science Foundation (2020M672518). The funders did not participate in this study. This work was reviewed and approved by the institutional research ethics boards of Xiangya Hospital, Central South University, Changsha, China. Written informed consent was received from all participants.

The authors have no conflicts of interest to declare.

**REFERENCES**

1. Banskota S, Ghia JE, Khan WJ. Serotonin in the gut: blessing or a curse. Biochimie 2019; 161: 56–64.
2. Cohen BE, Martires KJ, Ho RS. Psoriasis and the risk of depression in the US population: National Health and Nutrition Examination Survey 2009–2012. JAMA Dermatol 2016; 152: 73–79.
3. Bluer P, El Mansari M. Serotonin and beyond: therapeutics for major depression. Philos Trans R Soc Lond B Biol Sci 2013; 368: 20120536.
4. O’Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF, Sertotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res 2015; 277: 32–48.
5. Matushchenko V, Kutasevych Y, Jafferany M. Neurotransmitter imbalance in serum of psoriatic patients in exacerbation stage with comorbid psychoemotional disorders. Dermatol Ther 2020; 33: e13337.
6. Ye X, Shu HL, Feng X, Xia DM, Wang ZQ, Mi WY, et al. Reliability and validity of the Chinese version of the Patient Health Questionnaire-9 (C-PHQ-9) in patients with psoriasis: a cross-sectional study. BMJ Open 2020; 10: e033211.
7. Vallieres A, Bastien CH, Ouellet MC, Morin CM. Cognitive-behaviour therapy for insomnia associated with anxiety or depression. Sleep 2000; 23: 1–11.
8. Huang JG, Li GM, Lan YF. Determination of serum 5-hydroxytryptamine in patients with psoriasis. Chin J Dermatol 2000; 33: 118.
9. Younes SF, Bakry OA. Immunohistochemical evaluation of role of serotonin in pathogenesis of psoriasis. J Clin Diagn Res 2016; 10: EC05–EC09.
10. Martins AM, Ascenso A, Ribeiro HM, Marto J. The brain-skin connection and the pathogenesis of psoriasis: a review with a focus on the serotonergic system. Cells 2020; 9: 796.
11. Thorslund K, Amatyba B, Dufva AE, Nordlund K. The expression of serotonin transporter protein correlates with the severity of psoriasis and chronic stress. Arch Dermatol Res 2013; 305: 99–104.
12. Thorslund K, Svensson T, Nordlund K, Ekbom A, Fored CM. Use of serotonin reuptake inhibitors in patients with psoriasis is associated with a decreased need for systemic psoriasis treatment: a population-based cohort study. J Intern Med 2013; 274: 281–287.
13. Chen YH, Wang WM, Li IH, Kao HH, Yeh CB, Kao LT. Major depressive disorder increased risk of psoriasis: a propensity score matched cohort study. J Affect Disord 2021; 278: 407–412.
14. Tzeng YM, Li IH, Kao HH, Shih JH, Yeh CB, Chen YH, Kao LT. Protective effects of anti-depressants against the subsequent development of psoriasis in patients with major depressive disorder: a cohort study. J Affect Disord 2020; 281: 590–596.