

Serum 5-Hydroxytryptamine is Related to Psoriasis Severity in Patients with Comorbid Anxiety or Depression

Minxue SHEN^{1-5#}, Duling CAO^{1,3,4#}, Yi XIAO^{1,3,4*}, Yehong KUANG^{1,3-5}, Danrong JING^{1,3,4}, Yajia LI^{1,3,4}, Panpan LIU^{1,3,4}, Xiang CHEN^{1,3-5} and Wu ZHU^{1,3-5*}

¹Department of Dermatology, Xiangya Hospital, 87 Xiangya Road, Changsha 410008, ²Department of Social Medicine and Health Management, Xiangya School of Public Health, ³Hunan Engineering Research Center of Skin Health and Disease, ⁴Hunan Key Laboratory of Skin Cancer and Psoriasis, Central South University and ⁵National Clinical Research Center for Geriatric Disorders (Xiangya Hospital), Changsha, China 410008. *E-mails: 421995957@qq.com; zhuwu70@hotmail.com

[#]These authors contributed equally.

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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.

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

Table I. Characteristics of study patients with regard to depression

Characteristics	Total	Depression		p-value
		Yes (PHQ-9 ≥ 8)	No (PHQ-9 < 8)	
Total, n (%)	113	22 (19.5)	91 (80.5)	
Age, years, mean ± SD	39.6 ± 12.8	37.2 ± 11.8	40.2 ± 13.0	0.332
Sex, n (%)				
Men	77 (68.1)	13 (16.9)	64 (83.1)	0.314
Women	36 (31.2)	9 (25.0)	27 (75.0)	
Anxiety, n (%)	22 (19.5)	15 (68.3)	7 (31.7)	< 0.001
BMI, kg/m ² , 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.

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

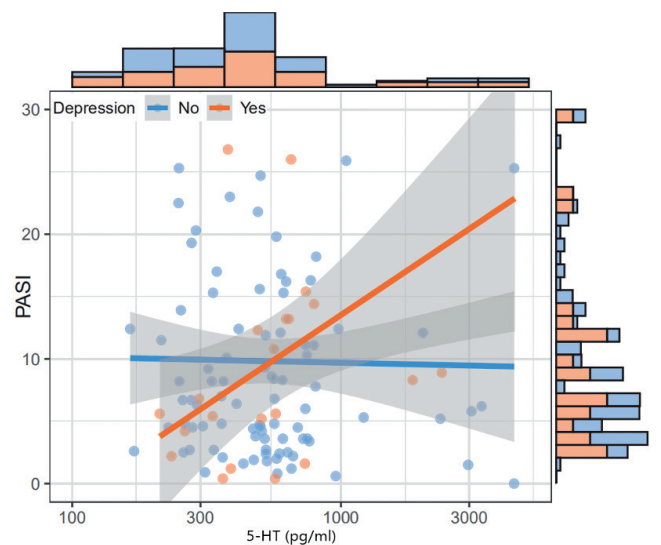


Fig. 1. Relationship between 5-hydroxytryptamine (5-HT) and Psoriasis Area and Severity Index (PASI) in patients with and without depression.

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 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.

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The authors have no conflicts of interest to declare.

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