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Review

Psoriasis: A review of the role of serotonergic system

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Psoriasis, a chronic inflammatory skin disease, is not yet curable, and its precise causes remain unclear. Nevertheless, several lines of evidence support that psoriasis is a multifactorial disease. Because psoriasis occurs in connection with stress and mood disorders, the genes in serotonergic system may be involved in psoriasis with regard to etiology and pathogenesis. Such molecular impacts supported by scientific evidence on serotonergic gene expression changes and genetic polymorphisms have been increasingly highlighted. The serotonergic system has also received considerable attention as a potential target for the therapy of psoriasis. Here, we summarize the current knowledge about role of genes in serotonergic system in psoriasis and point out possible directions of future studies.

Key words: Psoriasis, serotonergic system, gene expression, genetic polymorphism.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease affecting about 3% of the population worldwide (Schon and Boehncke, 2005; Lowes et al., 2007). It is thought to be a multigenic disease, the expression of which is dependent on certain external triggering factors (Henseler, 1998). It is also an autoimmune disease in which the role of T cells in pathogenesis has primarily been highlighted (Uyemura et al., 1993; Prinz, 2003; Bos et al., 2005). Consistently, lymphocyte subsets in peripheral blood of psoriatic patients have been found to be varied depending on disease severity (Langewouters et al., 2008; van Lingen et al., 2008). To support the immune hypothesis, novel immune regulatory molecules have been identified in peripheral blood mononuclear cells from psoriatic patients when analyzed using gene expression profiling (Kunz et al., 2004; Koczan et al., 2005). In the omics era, such omics techniques as functional genomics and proteomics have also been proved useful in finding new molecules possibly responsible for mechanisms underlying pathogenesis of psoriasis (Trcka and Kunz, 2006). For instance, certain immune molecules have been discovered in serum samples of psoriatic patients using the proteomics technique (Liu et al., 2007). It is noteworthy that these particular data are intriguing although they are preliminary. Still, more studies with respect to preclinical and clinical settings should be carried out to verify the pre-existing data.

Oxidative stress in keratinocytes is considered a factor in an aetiopathogenic concept which considers psoriasis as a typical inflammatory process described by increased antioxidant activity and overexpression of apoptotic receptors (Dimon-Gadal et al., 2000; Shilov and Sergienko, 2000). Oxidative stress is subsequently emphasized and evidently proved to associate with pathogenesis of psoriasis (Relhan et al., 2002; Trouba et al., 2002; Rocha-Pereira et al., 2004; Okayama, 2005; Sezer et al., 2007; Toker et al., 2009; Zhou et al., 2009). For this reason, antioxidant strategies have proven to be beneficial therapeutics. For example, pharmacological behavior of avarol-3'-thiosalicylate, a promising antipsoriatic agent, has been experimentally demonstrated to possess antioxidant properties, thus suppressing the inflammatory process (Amigo et al., 2007). Since diet has also been suggested to play a role in the aetiology and pathogenesis of psoriasis, various dietary factors showing such beneficial effects as anti-inflammatory and antioxidant properties are of great interest in the present decade (Wolters, 2005;

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Abbreviations: 5-HT, 5-Hydroxytryptamine (serotonin); **5-HTT,** serotonin transporters; **NICE,** neuro-immuno-cutaneous-endocrine; **TPH,** tryptophan hydroxylase; **5-HTR2A,** serotonin 2A receptor; **SNPs,** single nucleotide polymorphisms; **LD,** linkage disequilibrium; **EMSA,** electrophoretic mobility shift assay; **5-HTTLPR,** 5-HTT linked polymorphic region.

Kharaeva et al., 2009). It has been well docu-mented that a number of patients with psoriasis show an elevated sensitivity to gluten, a food allergen. Thus, treatment using gluten-free diet is considered one of the alternative therapeutic approaches for patients with psoriasis (Wolters, 2005).

Psoriasis can also be provoked or exacerbated by a variety of diverse environmental factors, particularly infections and drugs. Several lines of evidence have been linked to altered immune responses associating with psoriasis, especially in predisposed individuals. These include bacteria (*Streptococcus pyogenes*, *Staphylococcus aureus*), fungi (*Malassezia*, *Candida albicans*), and viruses (papillomaviruses, retroviruses, endogenous retroviruses) although precise mechanisms caused by some of these microorganisms remain to be elucidated (Fry and Baker, 2007; Prinz, 2009). As far as medications are concerned, the use of various drugs, such as lithium, *β*-blockers, antimalarial agents, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors, has also been associated with induction or worsening of disease in psoriatic patients (Abel et al., 1986; Fry and Baker, 2007). In fact, there may be a growing literature of drugs that can aggravate existing psoriasis or induce it for the first time.

In the present time, studies on molecular mechanisms underlying psoriasis are not only concerned with genetics, but also epigenetics; that is the study of differences in phenotype in the absence of variation in the genetic code. Epigenetics is associated with the pathogenesis of various skin diseases including psoriasis (Millington, 2008). Such example as hypomethylation has been well demonstrated in psoriasis (Ruchusatsawat et al., 2006). Still, there may be other trigger factors with regard to psoriasis in addition to a genetic and immunogenic background, thus supporting psoriasis as a multifactorial disease. It is noteworthy that precise mechanisms underlying pathophysiology of psoriasis are ambiguous. Such mediator as serotonin (5-hydroxytryptamine, 5-HT) should be further investigated with respect to psoriasis since serotonin has been revealed to essentially connect all three systems closely together referred to as neuro-immuno-cutaneous system (Misery, 1997). In fact, addition of another system has been subsequently evident, thus establishing a model known as neuro-immuno-cutaneous-endocrine (NICE) (O'Sullivan et al., 1998; Locala, 2009). Herein, we review the up-to-date knowledge about potential role of serotonergic genes regarding their expression changes and genetic polymorphisms in psoriasis and point out possible directions of future studies.

ROLE OF SEROTONERGIC GENE EXPRESSION IN PSORIASIS

Because psoriasis occurs in connection with stress and mood disorders (Peters et al., 2000; Griffiths and Richards, 2001) and occasionally has been reported to be induced in patients after treatment with antidepressants (Barth and Baker, 1986; Osborne et al., 2002; Tan Pei Lin and Kwek, in press), the pathophysiological role of such monoamine as serotonin acting as a neuromediator in the central and peripheral nervous systems (Azmitia, 1999; Kema et al., 2000), has received considerable attention. Serotonin was first isolated about sixty years ago and identified to be the vasoconstrictor compound contained in serum (Rapport et al., 1948). It was subsequently identified as a neurotransmitter synthesized in the central nervous system (Jacobs and Azmitia, 1992). Regarding serotonin biosynthesis and its related metabolic pathways (Figure 1), the first step in the biosynthesis of serotonin is catalyzed by tryptophan hydroxylase (TPH), which is the rate-limiting enzyme of the pathway. It is encoded by two genes: the well characterized *tph1* gene (Darmon et al., 1986) and a subsequently identified *tph1* gene. The expression of *tph1* is non-neuronal while that of *tph2* is neuronal (Cote et al., 2003; Walther et al., 2003). Degradation of serotonin is controlled by the enzymatic activities of monoamine oxidase. In the pineal grand, tryptophan is the precursor of melatonin biosynthesis via serotonin. The significance of serotonin in neuronal and peripheral physiology has been interestingly discussed (Cote et al., 2004). From that particular review, it is noteworthy that the functions of serotonin are closely connected regardless of its biosynthetic sources. Serotonin is not only produced by enterochromaffin cells of the gut and the serotonergic neurons of the brain, but also other cells including lymphocytes (O'Connell et al., 2006). It is stored in the blood by platelets and released at sites of inflamemation (Geba et al., 1996), thus signifying its crucial role in chronic inflammatory disorders.

Stress and stress-related hormones increase serotonin synthesis (Azmitia and McEwen, 1969; Azmitia et al., 1993). Interestingly, circuitry of the stress cascades has been thoroughly reviewed by Lechin et al. (2006). In particular, serotonergic neurons, which are distributed in both dorsal raphe and median raphe, function in responding to various types of stress, thus leading to an increase in cortisol production. Subsequently, cortisol released from adrenal grand crosses the blood-brain barrier and acts on cortisol receptors located at dorsal raphe serotonergic neurons, but not median raphe serotonergic ones. For this reason, prolongation of all types of stress triggers exhaustion of only dorsal raphe serotonergic neurons. The large spectrum of behavioral and physiological functions, e.g., in stress and mood, influenced by serotonin is mediated via various receptor subtypes (Glennon, 2003), and these have been classified based on their structural and transductional properties (Barnes and Sharp, 1999; Verge and Calas, 2000).

The serotonergic system which consists of serotonin molecules, serotonin receptors and serotonin transporters

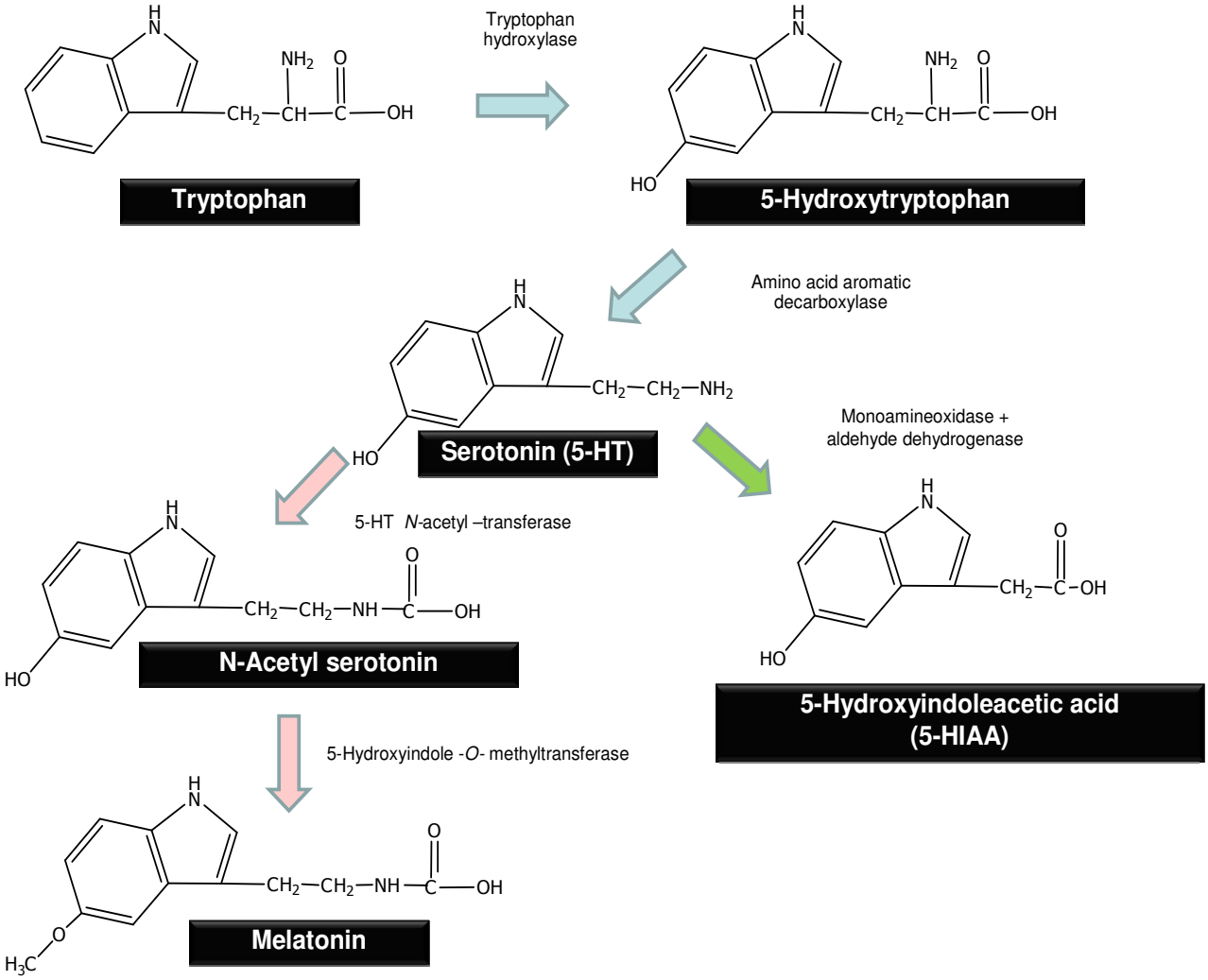

Figure 1. The schematic presentation of serotonin metabolism in humans. Serotonin is synthesized by a pathway analogous to that of the catecholamines. Prior to enzymatic catalysis of tryptophan hydroxylase, the neuronal uptake of tryptophan is considerably vital for serotonin biosynthesis in the central nervous system. Metabolism of serotonin is primarily through monoamine oxidase yielding the principle metabolite, 5-hydroxy indole acetic acid. In the pineal grand, melatonin is synthesized from serotonin by the sequential action of two enzymes.

(5-HTT) may play a significant role in psoriasis. To support this hypothesis, our previous study demonstrated comparable serotonin levels in serum of psoriatic patients and healthy controls, but platelet serotonin concentrations were significantly decreased in the patients (Tencomnao et al., 2007). Also, immunohistochemical techniques showed that expression of serotonin was significantly stronger in the prickle cells, sweat gland cells, sebaceous gland cells, and hair roots of the lesions in the progressive stage of psoriasis than in the static stage, while there was no expression of serotonin in the specimens of normal skin (Huang et al., 2004). Recently, serotonin has been considered one of the mediators of pruritus in psoriasis in addition to opioid system, prostanoids, interleukin 31 and proteases (Reich and Szepietowski, 2007), thus pointing out possible directions of future studies aiming the psoriasis pathogenesis. Also, as it is known that serotonin is largely stored in platelets, platelet functions in such dermal diseases as urticaria, atopic eczema/dermatitis sysdrome and psoriasis have been reviewed with respect to associations between changes in platelet activity and reactivity and pathogenic mechanisms (Kasperska-Zajac et al., 2008). For this reason, modulation of serotonin levels in psoriasis may reflect certain changes in genes encoding enzymes crucial for serotonergic metabolism.

In addition to serotonin, a few genes in the serotonergic system have been studied with respect to their expression in psoriasis. For example, it was demonstrated that expression of serotonin 2A receptor (5-HTR2A), a mediator of the downstream effects of serotonin, was significantly higher in involved and noninvolved psoriatic skin than

that of normal skin as involved psoriatic skin having the highest 5-HTR2A level (Nordlind et al., 2006), thereby corroborating its molecular role in promoting cell proliferation (Azmitia, 2001). The 5-HTR2A has been shown to be present in activated T cells (Stefulj et al., 2000; Leon-Ponte et al., 2007). As a result, the 5-HTR2A has received much attention since the molecular involvement of 5-HTR2A in psoriasis has not been fully understood.

EFFECT OF GENETIC POLYMORPHISMS IN SEROTONERGIC SYSTEM ON PSORIASIS

Regarding the human 5-HTR2A gene, it is located on chromosome 13q14-21 (Erdmann et al., 1996), and it consists of three exons spanning more than 20 kilobases (kb) (Saltzman et al., 1991; Chen et al., 1992). Recently, genetic variations in the 5-HTR2A have been discovered to associate with rheumatoid arthritis, a chronic and systemic autoimmune disorder (Kling et al., 2008), thus highlighting the role of SNPs in serotonergic system in chronic inflammatory disorders. In deed, two single nucleotide polymorphisms (SNPs) of this gene have been commonly studied in psychiatric disorders: -1438A/G (rs6311) in the promoter region (Collier et al., 1997) and 102T/C (rs6313) in the exon 1 (Warren et al., 1993). Functional studies have recently sought to identify the molecular mechanism underlying various genetic studies and have focused on both SNPs. Since they are in complete linkage disequilibrium (LD) (Ono et al., 2001; Ohara et al., 1999), studies investigating one polymorphism also provide information about the other. The latter SNP does not directly influence the gene expression because it does not involve the substitution of an amino acid (Bray et al., 2004). In contrast, the former SNP was shown to transcriptionally modulate the 5-HTR2A gene expression (Parsons et al., 2004; Myers et al., 2007). In addition, *in silico* analysis of -1438A/G allelic variants revealed the A allele containing a consensus binding site for the transcription factor Th1/E47, and electrophoretic mobility shift assay (EMSA) successfully demonstrated allele-specific binding to support the bioinformatics prediction (Smith et al., 2008). The biological importance of this SNP with respect to diseases is also underscored based on numerous association studies such as seasonality (Lee et al., 2006), tardive dyskinesia (Boke et al., 2007) and metabolic syndrome (Halder et al., 2007). The divergences in disease susceptibility may be a reflection of the altered density of the receptor crucial for neurotransmitter mechanisms, thus making this SNP a promising candidate for an association study. Therefore, a case-control design should be carried out to investigate the possible involvement of the -1438A/G SNP in psoriasis.

In addition, this review with regard to psoriasis should address another noteworthy component of the serotonergic system, 5-HTT. The expression and function of 5-HTT, which is responsible for the uptake of 5-HT into cells thus removing 5-HT from the extracellular space, is a key factor in the regulation of 5-HT-mediated effects in the central nervous system and the immune system (Mossner and Lesch, 1998). The expression of 5-HTT is regulated by a repeat length polymorphism in the 5-HTT linked polymorphic region (5-HTTLPR). The long (high activity) allele of this polymorphism is associated with a superior number of 5-HTT molecules on lymphocytes (Lesch and Mossner, 1998). The biological relevance of the 5-HTTLPR polymorphism is highlighted by several research findings including an association with primary pulmonary hypertension (Eddahibi et al., 2001), the detected impact on the development of depressive symptoms in individuals afflicted by a negative life event as well as on suicidal behavior (Li and He, 2007), the observed interaction with attachment security on electrodermal reactivity (Gilissen et al., 2008), the noticed effect on the symptomatic profile of panic disorder (Lonsdorf et al., 2009), the risk of sporadic Parkinson's disease (Albani et al., 2009) and the endocrine stress response in newborns (Mueller et al., 2010). Interestingly, 5-HTT has been recently demonstrated to play a role in regulating apoptosis in inflammatory cells associated with psoriasis, in which case this protein might constitute a valuable therapeutic target (Thorslund et al., 2009). Although it has been lately reported no association between 5-HTTLPR and psoriasis in German Caucasian sample; in their finding, 20% of patients with psoriasis suffering from at least mild depression, should be noted (Mossner et al., 2009). Since 5-HTTLPR allele frequencies have been noticeably different with respect to ethnicity, association studies in various populations should be conducted in order to gain insights into mechanism underlying psoriasis.

CONCLUSION

Psoriasis appears to be characterized by stress-induced chronic inflammation, and it has been well documented that stress and stress-related hormones are associated with serotonergic system. In the present work, the author addressed the molecular role of serotonergic genes on psoriasis. Their molecular impacts, obtained from studies on serotonergic gene expression and polymorphism in psoriasis, have been increasingly emphasized. In addition to the addressed polymorphisms in 5-HTR2A gene and 5-HTT gene, other functionally relevant genetic variations of the serotonergic system may play a part in the etiology of psoriasis, and therefore exploring their functional significances is highly encouraged. In clinical practice, finding or developing drugs influencing the serotonergic system might be a simpler mission because these types of agents are commercially available for therapeutic purposes. For instance, drugs such as selective serotonin reuptake inhibitors are popularly utilized to maintain the circulating levels of serotonin. In contrast, medications such as tianeptine act by enhancing serotonin uptake by

platelets and serotonergic axons at the central nervous system as previously described (Lechin et al., 2004). The bottom line is that the circulating serotonin concentrations can be regulated by appropriate therapeutic agents if they are found imbalanced.

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