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Serotonin system and autoimmunity

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Considering both, our results and available literature reports, it seems that decresed platelet serotonin level (PSL) is a general finding in inflammatory rheumatic disorders including including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective tissue disese (MCTD) and primary Sjogren's syndrome (pSS), signifying the role of the *5-HT* in the pathogenesis of autoimmune rheumatic disorders including pSS. This could partially reflect increased *5-HT* secretion during platelet activation in the acute stage of the disease. An inverse correlation between PSL and clinical disease activity was found in SLE, the lowest levels occurring in active stage of the disease. Absence of correlation between decreased PSL and increased release of other platelet granule constituents in RA and SLE, was reported. We have documented no correlation between magnitude of PSL reduction and clinical disease activity, indicating different biochemical , and/or genetic features of pSS, as pSS patients demonstrate a systemic inflammatory reaction of low-grade intensity. It is well known that the actions of *5-HT* are primarily terminated by the membrane *5-HT* transporter (5-HT*T*), and that *5-HTT* gene (SLC6A4) could be a common genetic modulator of *5-HT* transport. Overall, significant heterogeneity was observed among studies investigating the effects of the *5-HTT* polymorphisms on PSL in healthy subjects and thus did not support the hypothesis that the *5-HTT* variants have direct effect on PSL. In reviewing the literature, no data was found on the influence of the *5-HTTLPR, rs 25531* and *5-HTTVNTRin2* polymorphisms of *5-HTT* gene on PSL in patients with pSS. Our results corroborate the findings of a great deal of the previous work, which did not demonstrate association between *5-HTTLPR* variants and platelet *5-HT* concentration in the group of healthy individuals. Potential functional consequences of both promoter and intronic 2 VNTR polymorphisms of the *5-HTT* gene on PSL in pSS patients and healthy individuals, was documented. Significant association between PSL and *5-HTT* gene variants was found, indicating that *5-HT* system may play important role in the pathogenesis of pSS. Furthermore, reduction in pSL in a group of pSS patients with frequent episodic tensoion-type headache (FETH) correlated with number of white matter signal hyperintensities in pSS patients as compared to healthy controls, signifying a more widespread cerebral vasculopathy in pSS patients than in healthy individuals. We demonstrated here that additional mechanisms, such as impaired *5-HT* transport can contribute to PSL reduction. However, absence of association between *5-HTT* gene polymorphisms and PSL in healthy controls and the presence of the specific genotype *5-HTTVNTRin2* ss cannot provide the sole explanation for lower PSL. Reduced PSL may also be a consequence of activation of kynurenine-pathway-enzymes by proinflammatory cytokines, which then redirect tryptophan metabolism and affect *5-HT* synthesis. *5-HT* released by platelets helps drive the persistent vascular permeability via *5-HT* elsewhere. Adequate level of vitamin D may be required to activate the transcription of the *5-HT*-synthesizing gene tryptofan hydroxylase 2 (*TPH2*) in the brain and supresses the transcription of TPH1 in peripheral tissues, where when found in excess it promotes inflammation. Although DCs expressing *5-HT* receptors are considered to play an important role in immune activation, the role of *5-HT* system in modulating pDC function in the context of pSS inflammation remains to be determined. Thereby, altered *5-HT* uptake by platelets can be a prerequisite for the decreased PSL, imlying that antidepressants (SSRI) used to treat depression by targeting *5-HTT* may also target PSL in pSS.

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