SYMPATHETIC MECHANISMS IN SYNOVIAL INFLAMMATION

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The analysis and understanding of the intraarticular influence of nerve fibers on the inflammatory process in human arthritis is far from complete due to the complex nature of this matter. It is widely accepted that substance P, a neurotransmitter of the sensory afferents, is proinflammatory (1). With respect to the sympathetic nervous system and its transmitters, the situation is not as uniform as with substance P. Since norepinephrine (NE) or adenosine, which are colocalized in vesicles of the sympathetic nerve terminal, are ligands of different receptor subtypes with opposing intracellular signal transduction pathways (2), completely different effects may arise depending on the local concentration.
Sympathetic nerve fibers can be measured by fluorescence immunohistochemistry with an antibody against the key enzyme tyrosine hydroxylase, which is responsible for conversion of tyrosine to L-dopa (first step of catecholamine synthesis). Sympathetic nerve terminals are located not only along arteries but are also present in the surrounding tissue. It was demonstrated that there are less sympathetic nerve fibers in inflamed tissue of patients with RA than in those with OA or trauma patients (3, 4). At present, it is not known whether nerve fiber repulsion or low expression of tyrosine hydroxylase is responsible for the observable decrease in nerve fiber density. Nevertheless, these findings indicate that the function of sympathetic nerve fibers is altered. Interestingly, this is not the case for sensory nerve fibers that store substance P (5). During the course of chronic inflammation, neurotransmitters of the sympathetic nervous system (noradrenaline, adenosine, and endogenous opioids) have antiinflammatory effects when concentrations are high (via β-adrenoceptors, A2 adenosine receptors and μ-opioid receptors). Thus, during the course of a chronic inflammatory process, the loss of sympathetic nerve fibers in relation to sensory nerve fibers probably contributes to a proinflammatory situation. In contrast, healthy controls and patients with OA show a similar number of sympathetic and sensory nerve fibers (4). Moreover, the loss of sympathetic nerve fibers in patients with RA is correlated to an increase in the degree of inflammation. Despite the loss of sympathetic nerve fibers in RA patients, a high amount of norepinephrine (NE) is still secreted from synovial tissue. Further studies demonstrated that probably TH-positive synovial cells are the source of the secreted NE (4).
These findings should demonstrate new ideas for a better understanding of hormonal and neuronal factors in the pathophysiology of RA. During the last 5 to 10 years, this new scientific approach was largely intensified, and it becomes more and more evident that RA pathophysiology can only be explained under consideration of multiple mechanisms beyond the immune system.