I34. SENSORY–IMMUNE INTERACTIONS AND THE ROLE OF NEUROPEPTIDES IN A SERUM TRANSFER INDUCED MOUSE MODEL OF INFLAMMATORY ARTHRITIS

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Objective: The serum-transfer arthritis is a widely-used translational mouse model of RA, in which the immunological components have thoroughly been investigated. In contrast, little is known about the role of sensory neural factors, neuropeptides and the complexity of neuro-immune interactions. Therefore, we analysed the involvement of capsaicin-sensitive peptidergic sensory nerves, and the neuropeptides pituitary adenylyl-cyclase activating polypeptide (PACAP), as well as the tachykinins substance P/neurokinin A (SP/NKA) and haemokinin-1 (HK-1). These peptides are expressed in sensory neurons and immune cells, and they are known to modulate vascular and cellular inflammatory mechanisms.

Methods: Polyarthritis was induced by i.p. injection of the arthriticogenic K/BxN serum. Resiniferatoxin (RTX) pretreatment was performed to inactivate capsaicin-sensitive nerves. Gene-deficient mice (Tac1−/−, where SP/NKA are missing; Tac4−/−, where HK-1 is absent; or PACAP−/−) were used to analyse the roles of the respective peptides. Oedema, touch sensitivity, noxious heat threshold, joint function and clinical arthritis severity scores were determined repeatedly throughout two weeks. Micro-CT to detect bone morphological alterations, in vivo optical imaging to quantify MMP and neutrophil-derived MPO activities, semiquantitative histopathological scoring and radioimmunoassay to measure somatostatin in the joint homogenates were also performed.

Results: In RTX-pretreated mice, autoantibody-induced joint swelling, arthritis severity score, and MMP and MPO activities, as well as histopathological alterations were significantly greater. Self-control quantification of the bone mass revealed decreased values in intact female mice, but significantly greater pathological bone formation after RTX pretreatment. Mechanical hyperalgesia from day 10 was smaller, and although thermal hyperalgesia did not develop, noxious heat threshold was significantly higher following defunctionalization of the capsaicin-sensitive peptidergic nerves. Somatostatin-like immunoreactivity elevated in the tibiotarsal joints in non-pretreated, but not in RTX-pretreated mice. There was no change in any arthritic symptoms in Tac1−/− animals. In Tac4−/− mice joint swelling, hyperalgesia and histopathological alterations were significantly smaller compared with WT animals, but MPO activity was not altered. In PACAP−/− mice, clinical score and oedema were significantly reduced, mechanical hyperalgesia and motor impairment were absent, metabolic activity and superoxide production were significantly less, MPO activity was significantly lower in the early, but greater in the late phase. Synovial hyperplasia was significantly greater and progressive bone spur formation was only observed in PACAP-deficient mice.

Conclusion: Although capsaicin-sensitive sensory nerves mediate mechanical hyperalgesia in the later phase of autoantibody-induced chronic arthritis, they play important anti-inflammatory roles at least partially through somatostatin release. Although the tachykinins SP/NKA are not involved in this immune arthritis model, HK-1 is an important mediator of joint inflammation and the consequent pain. PACAP increases swelling, vascular leakage, hyperalgesia and early inflammatory cell accumulation, but decreases immune cell functions and bone neoformation in the late phase. Identification of their targets and the receptor mechanisms can open novel perspectives in arthritis therapy.

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