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Herpes simplex virus-mediated overexpression of metenkephalin in sensory neurons

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Keywords

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Context

Although the underlying cause of rheumatoid arthritis (RA) has not been determined, studies in animal models have identified several contributing factors. Notably, it has been observed that numerous physiological changes occur in both the peripheral and central nervous system during the onset of disease. Among these are the spinal and supraspinal release of endogenous opioids, such as met-enkephalin (ME). These peptides have been shown to be involved in the control of pain and can inhibit inflammatory processes. In previous work, it has been shown that following infection of sensory neurons with recombinant herpes simplex virus (HSV), the virus undergoes retrograde transport to the nucleus of the neuron in the dorsal root ganglion (DRG). Following infection of the footpad of rats with recombinant HSV containing the ME coding region, ME expression was detected in the DRG and in the peripheral fibers. In this study, the authors wanted to determine if overproduction of ME in the sensory neurons of rats could block pathologies of adjuvant-induced arthritis.

Significant findings

The ME coding region was inserted into HSV under control of the latency-associated transcript promoter (HSVLatEnk), which enables high level transgenic expression during the latency phase of HSV infection. Three weeks after the injection of HSVLatEnk into the hind footpads of adjuvant-induced polyarthritic rats, ME transgene expression was detected in the L4-L5 lumbar DRG, but not in adjacent ganglia or in the spinal cord. ME delivery in this manner reduced hyperalgesia and improved spontaneous mobility of the animals. Furthermore, the joint pathology was clearly improved, as demonstrated by a diminution of the joint diameter and radiological amelioration of osseous lesions of both tarsus and metatarsus.

Comments

Most RA gene therapy studies have focused on the inhibition of classical inflammatory mediators or on immunomodulation. However, the importance of neurogenic inflammation in arthritis has been firmly established, and this study reminds us that neural mediators are potential therapeutic targets. Indeed, this type of approach might be an interesting alternative or adjunct to the protection of diseased tissues without depletion or disruption of the immune system. Despite their natural pathogenicity for humans, HSV-based vectors are well suited for neuronal gene delivery. The large size of the HSV genome enables insertion of multiple genes and complex regulatory domains, and because of their capacity to establish a longstanding latent infection within neurons, they have an interesting potential for persistent transgene expression.

Methods

HSV, adjuvant-induced arthritis, radiography, pain-related behaviour, in situ hybridization, radioimmunoassay, immunohistochemistry, RT-PCR

Additional information

References

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