INTRODUCTION

Inflammation arising from the summation of the various effects of stimulation of peripheral nerves is referred to as neurogenic inflammation. The hallmark of neurogenic inflammation is increased vascular permeability due to activation of neurokinin 1 (NK1) receptors located on postcapillary venules by substance P (SP) released from sensory nerve fibers. This effect is transient, and participation of sensory nerves in both acute and chronic inflammation is the result of subsequent activation of cells of the immune system (particularly mast cells) and continued stimulation of release of inflammatory mediators or neuropeptides. This process has been reported to affect a variety of organs, including the bladder, skin, gut, lungs, airways, eye, and joints. Antidromic stimulation of unmyelinated
sensory C fibers results in plasma extravasation and accumulation of leukocytes in the bladder and other organs. Various stimuli, such as antigens, cold, heat, bacterial or viral infection, or direct stimulation of nerves can initiate neurogenic inflammation. The concept that sensory nerves participate in amplification of local inflammation is further substantiated by the observation that prolonged blockade of the sciatic nerve with a local anesthetic (bupivacaine) significantly decreased (but did not ablate) carrageenan-induced paw swelling in the rat. Often the effects of neurogenic inflammation remain long after the inciting cause is gone. The processes associated with neurogenic inflammation also play a significant role in the amplification of inflammation to a level that may be disproportionate to the original insult.

Interstitial cystitis (IC) is a puzzling bladder disorder that arises from unknown causes and is characterized by intense suprapubic pain associated with increased urgency and frequency in voiding. Several clinical and experimental studies have suggested that neurogenic inflammation plays a critical role in the pathogenesis of IC, which is an attractive hypothesis, particularly in light of the absence of a clearly identifiable cause for symptoms in most IC patients. It is highly probable that neurogenic inflammation participates in the onset or persistence of a variety of bladder disorders, and various therapeutic strategies directed at preventing or suppressing the participation of the nervous system in cystitis are being investigated. Research to date indicates that peripheral nerves directly participate in the inflammatory process as chemotactic factors, through the action of neuropeptides released from the nerves on the vasculature, or as a result of reciprocal interaction between the nerves, neuropeptides, and other cells, such as mast cells.

NEUROPEPTIDES AND INFLAMMATION

Neuropeptides such as SP, neurokinin A (NKA), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide, and somatostatin (SOM) are located in capsaicin-sensitive primary afferent nerves in the bladder of humans and animals. Tachykinins are a subgroup of neuropeptides that share commonalities in their amino acid sequences. Most of the physiological effects of SP and related neuropeptides (including NKA, neurokinin B [NKB], eleidosin, and physalaemin) depend on their C-