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Introduction

Nociception provides a means of neural feedback that allows the central nervous system (CNS) to detect and avoid noxious and potentially damaging stimuli in both active and passive settings. e sensation of pain divides into four large types: acute pain, nociceptive pain, chronic pain, and neuropathic pain. is article will consider the categories of acute and nociceptive pain together. Acute noxious stimuli (e.g., heat, cold, mechanical force, or chemical stimulation) trigger nociceptors. Acute pain becomes in ammatory pain when the noxious stimulus persists long enough to allow nociceptive neurons to release their pro-in ammatory markers and sensitize or activate responsive cells in their local environment [1]. Nociceptive pain arises from tissues damaged by physical or chemical agents such as trauma, surgery, or chemical burns, while neuropathic pain arises from diseases or damage mediated directly to sensory nerves, such as diabetic neuropathy, shingles, or post herpetic neuralgia [2]. Di erentiating acute and nociceptive pain from neuropathic pain aids in understanding the broader study of pain; however, neuropathic pain will not be evaluated further in this article.

Regarding active settings, stimulated nociceptive neurons convey high-threshold noxious stimuli to the CNS. e nociceptive signal may either get redirected immediately in a spinal re ex loop, producing a rapid and re exive withdrawal or transported to the areas of the brain responsible for integrating the information with higher-ordered sensations such as pain [3]. In addition to spinal a erent transmission to the CNS, nociceptive neurons are also capable of responding to noxious stimuli by secreting chemical signals from their peripheral nerve endings. Local actions on nearby neuronal and non-neural cells undergo mediation through the release of vesicles containing preformed pro-in ammatory cytokines and growth factors.

Description

Depending on the speci c monomial sensitivity of a previously inactive nociception, speci c noxious stimuli are detected by expressed receptors that open their action channels in response to activation. e open action channels on the nociceptive neurons depolarize the nociception, inducing vesicle fusion and cytokine release. e cytokines are pro-in ammatory, and once released, they elicit and propagate a matched release of pro-in ammatory cytokines from local epithelial, endothelial, and lymphoid cells. e responding cells may then migrate or otherwise disseminate their pro-in ammatory signals that go on to sensitize or activate surrounding nociceptors originally outside of the primary nociceptive eld [4] .

e spread of nociception-induced in ammation occurring over an area greater than that of the original nociception(s) involved is referred to as neuroin ammation. e propagation from nociceptive neurons to the surrounding cells, which may in-turn sensitize nearby nociceptive neurons, is why neuroin ammation is considered to be a self-reinforcing phenomenon. Not only do the released pro-in ammatory molecules activate local in ammatory cells, but they are also capable of directly activating other nociceptive nerve endings because almost all nociceptive nerve endings possess receptors for all of the pro-in ammatory markers they are capable of releasing.

e pro-in ammatory molecules released from a directly stimulated nociceptive neuron are capable of binding to and activating a local nociceptive neuron entirely una ected by the original stimulus. As with direct activation, the pro-in ammatory molecules bind the receptors

Cellular

RT-PCR has provided the means to discover and classify nociceptive neurons based on the speci c receptors they possess, which are sensitive to noxious stimuli. Nociceptors in the skin and other peripheral organs form highly complex and interconnected networks with each other. Schwann cells are peripheral glial cells that envelop these networks everywhere except where the terminal axons project through the basement membrane of the epidermis and the nerve endings become ‘free' or ‘naked' (i.e., unmyelinated). Unfortunately, the complex and sequestered nature of nociceptors in vivo has made them di cult to study, and much of what researchers know about the activity, gene expression, and important factors present in nociceptors has been discovered by studying nociceptive neurons grown in culture [5]. While nociceptors grown in culture have been found to possess many of the same molecules found in vivo, it is not currently possible to discern the absence of any in vivo molecules that only receive the necessary signals produced when the nociceptive neuron is fully imbedded in cutaneous tissue.