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Editorial

Pain — Skin Deep at Times?

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In recent years it has become apparent that the skin is not merely a static organ with barrier functions. Skin is an extremely dynamic organ that participates in multiple homeostatic and other functions. Furthermore, there is a growing appreciation of the skin's key role in contributing to certain persistent nociceptive processes (1). Petersen and colleagues (2) have suggested a contributing nociceptive role of skin in certain patients with postherpetic neuralgia since surgical excision of painful skin resulted in immediate reduction in pain and analgesic use.

Skin incision alone appears sufficient to result in primary mechanical, thermal, or chemical hyperalgesia. However, incised deep tissue is necessary for the development of guarding pain and increased spontaneous activity of dorsal horn neurons (3,4). Kang and Brennan (4) demonstrated that one day after a skin incision, C-fibers located within 2 mm from the incision exhibited greater chemosensitivity to pH 6.0 lactic acid compared to control.

Wei et al (5) using a tibia fracture rat model found that fracture chronically increased the expression of endothelial and keratinocyte neurokinin-1 (NK-1) receptors in the injured limb. Also, subcutaneous and intravenous substance P-evoked extravasation responses are augmented in the ipsilateral hindlimb post-fracture (5). Substance P, activating upregulated NK-1 receptors in the injured limb, may promote keratinocyte proliferation (5).

In epidermal keratinocytes nerve growth factor (NGF) production facilitates neuropeptide release (6). After the release of neuropeptides by a nociceptive stimulus, an upregulation of the expression of NGF and an increase in NGF secretion from keratinocytes is induced (7). Interleukin-1B (IL-1B) may directly activate sensory neurons and also upregulates nerve growth factor (NGF) expression in keratinocytes (8). Anti-NGF therapy inhibits hyperalgesia (8). NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels (9). NGF may lower the activation threshold induction of pain (9,10). Kawamata et al suggested a close interaction between TRPV1 and ETA (11) during ET-1-induced thermal hyperalgesia. Activation of the ETA-protein kinase C pathway may result in sensitization of TRPV1 activity which is needed for ET-1-induced thermal hyperalgesia (11).

Keratinocytes and Nociception

Keratinocytes may be intimately involved in the modulation of certain nociceptive processes via multiple mechanisms. It is possible that in certain painful conditions keratinocytes may contribute to modulation of nociceptive processes by an increase or decrease in the number and/or function of specific ion channels (e.g. sodium channels [NaV], transient receptor potential vanilloid [TRPV] ion channels) as well as by an increase or decrease in the amount of specific mediator release from keratinocytes (e.g. opioids, prostaglandins, adenosine triphosphate [ATP]) (Fig. 1).

The antinociceptive effects of the CB(2) receptor-selective agonist AM1241 were prevented in rats when naloxone or antiserum to beta-endorphin was injected

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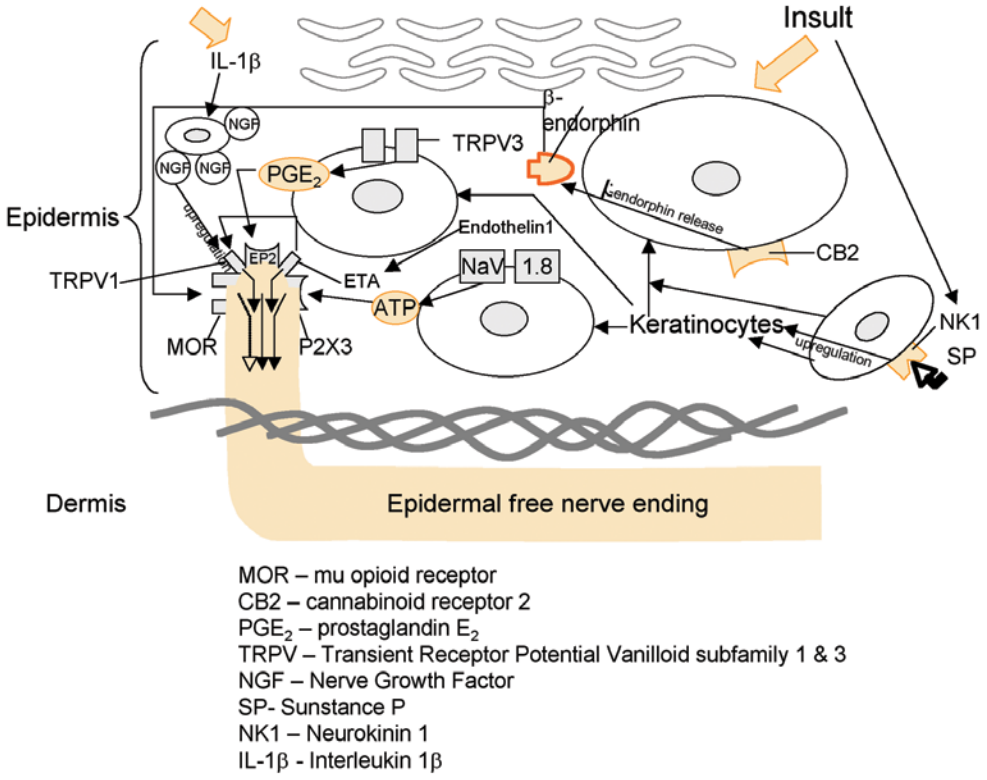

Fig. 1. *Schematic of multiple potential mechanisms whereby keratinocytes may modulate nociceptive processes in the skin.*

in the hindpaw where the noxious thermal stimulus was applied, suggesting that beta-endorphin is necessary for CB(2) receptor-mediated antinociception (12). However, AM1241 did not inhibit nociception in mu-opioid receptor-deficient mice (12). Hindpaw injection of beta-endorphin was sufficient to produce antinociception. AM1241 stimulated beta-endorphin release from rat skin tissue and from cultured human keratinocytes (12). This stimulation was prevented by AM630, a CB(2) cannabinoid receptor-selective antagonist and was not observed in skin from CB(2) cannabinoid receptor-deficient mice (12). These data suggest that CB(2) receptor activation stimulates release from keratinocytes of beta-endorphin, which acts at local neuronal mu-opioid receptors to inhibit nociception (12). Furthermore, CB(2) immunolabeling was detected on beta-endorphin-containing keratinocytes in stratum granulosum throughout the epidermis of the hindpaw (12).

Keratinocytes appear to be able to act as thermal receptors via TRPV1 (13). The study of Wilder-Smith et al (13) suggests that in human painful distal small nerve fiber neuropathies, epidermal TRPV1 expression is mainly in keratinocytes. Huang and colleagues (14) generated and characterized transgenic mice that overexpress TRPV3 in epidermal keratinocytes under the control of the keratin 14 promoter. Compared with wild-type controls, keratinocytes overexpressing TRPV3 exhibited larger currents as well as augmented prostaglandin E(2) (PGE(2)) release in response to 2 TRPV3 agonists, 2-aminoethoxydiphenyl borate (2APB), and heat. Upon selective pharmacological inhibition of TRPV1 with JNJ-17203212 (corrected), however, the keratinocyte-specific TRPV3 transgenic mice showed increased escape responses to noxious heat relative to their wild-type littermates (14). Coadministration of the cyclooxygenase inhibitor, ibuprofen, with the TRPV1 antagonist decreased inflammatory thermal hyperalgesia in transgenic but not wild-type animals (14). The results of Huang et al (14) reveal a mechanism for keratinocyte participation in thermal

pain transduction through keratinocyte TRPV3 ion channels and the intercellular messenger PGE(2).

Zhao et al (15) examined whether keratinocytes may contribute to human pain states, by analyzing sodium channel expression in human skin biopsies from subjects with complex regional pain syndrome Type 1 (CRPS) and post-herpetic neuralgia (PHN) using immunohistochemistry. Control skin exhibited immunolabeling for Na(v)1.5, Na(v)1.6, and Na(v)1.7 (15). In contrast, painful skin from CRPS and PHN subjects displayed Na(v)1.1, Na(v)1.2, and Na(v)1.8 immunolabeling, in addition to substantially increased signal for Na(v)1.5, Na(v)1.6, Na(v)1.7. These observations lead Zhao and colleagues (15) to propose that pathological increases in keratinocyte sodium channel expression may contribute to pain by increasing epidermal ATP release, resulting in excessive activation of P2X receptors on primary sensory axons. Consistent with this hypothesis, animal models of neuropathic pain exhibit increases in subcutaneous ATP release and activity of primary sensory neurons; also peripheral administration of P2X antagonists have been shown to reduce neuropathic pain in humans (15). Thus, it appears that skin possesses an extensive and complex array of nociceptive modulating systems that may cause pain in certain circumstances.

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