



ADVANCING HEALTH EDUCATION & RESEARCH

AVA Research Reviews provides AVA members with recent published, peer-reviewed articles in a broad array of violence and abuse topics. The goal is to highlight and disseminate violence and abuse research in a timely fashion, and to enhance healthcare providers' practice by fostering the educational mission of AVA

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AVA Research Review

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Review Title: Delay in Wound Healing and Potential Connection to Violence Experiences

Reviewer: : Marie Christensen, MD, Plastic Surgeon, Park Nicollet Clinic, Minneapolis MN
Clinical Professor of Surgery, University of Minnesota Schools of Medicine & Dentistry, MPLS MN

Article: Hanna KR, Katz AJ. An Update on Wound Healing and the Nervous System. *Annals of Plastic Surgery* 2011;67: 49-52.

Article Summary:

Brief Overview
Impaired wound healing is a significant clinical, economic, and social problem. There is a growing body of research over the past several decades that support the importance of neuropeptides and neurotransmitters in wound healing. The purpose of this

article is to review current translational research that supports the role of the nervous system in normal wound physiology and the current state of clinical application.

The authors reminded us that the association between the nervous system and tissue integrity was first recognized by Jean-Martin Charcot in 1877. While his theory fell out of favor to the concept that delayed wound healing (specific to decubitus ulcer healing) was the result of unrelieved pressure), the current research has re-embraced his concept of the nervous system being indispensable in skin health and wound healing. In this review of the existing literature by Hanna and Katz on this subject, they included 600 articles specifically related to neuropeptide and wound healing. Given the common issue of delayed wound healing in the diabetic

population, while they were interested in what mechanisms may be specific to the diabetic, they included articles specific to diabetes as well as wound healing articles that did not include this specific disease. The articles from the past 30 years were culled: most involved tissue culture and animal model (murine).

Relevant findings

Normally innervated skin enjoys a vasomotor (conduction that controls the constriction and dilation of blood vessels), sudomotor (conduction that controls the activity of sweat glands) and pilomotor (conduction that controls the activity of erector muscles of hair) homeostasis because of neurotransmitters and neuropeptide substances produced at efferent nerve endings. Their action is influenced by a host of other peptides including Neuropeptide Y (NPY), ACTH, norepinephrine, nerve growth factor (NGF), substance P (SP), Calcitonin gene-related peptide (CGRP), and vocative intestinal peptide (VIP). Keratinocytes rely on ACTH for skin viability. The local afferent sensory system also has a clinical function involving additional neuropathies resulting in pain, vasodilatation and neurogenic inflammation. As one can glean from this very brief

description, the cascade of relevant regulators is complex, sensitive, highly interdependent and not completely understood. Physical trauma produces neuropeptide release, as do the chemicals produced by inflammation. Most wound healing research has been focused on the allergic-inflammatory response, with mast cell degradation, prostanoids and bradykinins as the most commonly studied and recognized inflammatory contributors to the process of wound healing.

Specific results that were described include the following noteworthy findings. Gibran's work with diabetic mice showed that absence of afferent nerve fibers at the wound site was associated with prolonged wound healing, and improved healing time. Ekstrand used mice without NPY receptors, and found that their delayed healing time could not be improved by NPY but the control group had even better healing time. They determined that the role of the NPY neuropeptide appeared to have an antigenic rather than inflammatory effect in wound healing properties. Prohan et al suggests that CGRP aids in endothelial growth & angiogenesis, in addition to its role as an inflammation reducer. NGF stimulates neuronal sprouting in the skin

and may play a role in increased production of neuropeptide by increasing the number of nerve endings.

The authors point out that the delicate homeostasis of the wound healing cascade. Its complexity is sensitive and, if that homeostasis is significantly altered, further problems with skin integrity may result. Some neuropeptide substances are detrimental if in excess and may be responsible for scar hypertrophy (SP, VIP, CGRP), keloid (SP), psoriasis (CGRP), rosacea (SP), and hyperesthesia's (NGF).

Authors Conclusions:

The current knowledge of the interactions between wound healing and the nervous system have "come full circle" from when it was first described by Charcot in 1877. Today's scientific community embraces both the contribution that neuropeptides and neurotrophic factors are important in wound healing. The authors state that, with this current knowledge, therapies are lagging, and this offers opportunity for future interventions to address wound healing.

Reviewer's Comment:

So, what does this body of research have to do with violence and abuse? As a

surgeon, I am puzzled by wounds that “don’t heal right”: delayed healing, unstable scar, keloid scar, pain syndromes and reflex sympathetic dystrophies,- especially in patients who have no obvious reason for healing issues, like tobacco abuse, diabetes, vascular insufficiency, malnutrition or steroid use. As we glean from an emerging body of literature on the pathophysiology of chronic stress, and the complex cellular, neural-endocrine response provoked by exposure to violence and abuse, could there be a connection to wound healing and the chronic stress of ongoing violence exposure? In the context of our clinical practice, when there is a dilemma in reconciling the lack of “known” risk factors for delayed wound healing, should we consider the environmental stress of a patient as a potential contributor to what we are observing clinically? While the conclusion I am drawing regarding a potential clinical application to this article is not based, per se, on this article, the science of this article may, in fact, be missing a key element: the impact of environmental stress on wound healing. My take away is that we should include these physiologic distortions of neurotransmitters and neural pathways in our treatment of

acute and chronic wound recovery, and probe into the other potential causative factors that may aid in the healing of our patients.