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Research Article

The Emerging Concept of Hormonal Impact on Wound Healing in Feminizing and Masculinizing Genital Surgery

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Abstract

We attempt, within this review, to discuss the effects of hormones for their known impact on the wound healing cascade. Hormone receptors mediate a cellular response; changes in their expression, whether physiologic or pathologic, affect growth and development, and have effects on wound healing. Attempts to measure their distribution have been quite variable in their effectiveness not only between but within a given tissue. Other factors contribute to this variability. These include age, gender, and tissue histology (urinary mucosae, periurethral vessels, muscular layer, and connective tissue). Gene expression and autonomic nervous system receptors have been noted to change in relation to variance in hormonal status. Reduced levels of estrogens and androgen are associated with dramatic alterations in genital tissue structure, including the nerve network, as well as the response to physiological modulators. Estrogen and androgen deficiency is associated with reduced expression of sex steroid receptors. Cutaneous, vascular, and mucosal tissue of the genitalia, may be more sensitive than other tissues to the effects of a variety of hormones with differential effects for mucosal versus cutaneous epithelium, and for male and female derived tissue. We might also imagine that chromosomal variations exhibited in disorders of sexual development could modify the hormonal environment and the response to hormones during wound healing.

Hormonal influence on wound healing is an emerging concept. Androgens, glucocorticoids, estrogens and relaxin have all been studied and shown to have differential effects on wound healing. Receptor labeling within penile tissue may provide an indication of ability to respond to pre or post-operative administration of hormonal therapy.

Keywords

Hypospadias; Hormones; Wound healing

Introduction

Wounding, through surgical incision, as in the case of feminizing genitoplasty and masculinizing surgeries such as hypospadias repair, involves all layers of epithelium from the superficial epidermis of labia, vaginal introitus, clitoris or penis, subcutaneously to the deep layers of the basement membrane, and the vaginal mucosa, urothelium and their deeper layers. Incisional injury and healing of the corporal and spongiosal tissues, as well as that of the pedicalized dartos tissues invariably interposed in the repair, and possibly other tissues such as intestinal, buccal mucosal or epithelial grafts may also be involved. Each, consequently, contributes their molecular roles in the healing process. This complex variation of possibilities that includes surgical technique, surgical flap construction, tissue undercutting and changes to vascularity and innervation, cannot be excluded from consideration for contributions to wound healing parameters.

Current Status of Knowledge

The cutaneous, vascular, and mucosal tissue of the genitalia, are tissue which may be more sensitive than tissues from other sites on the body, to the effects of a variety of hormones [1-3]. There may be differential effects for mucosal vs. cutaneous epithelium, and for male and female derived tissue [4]. Sex divergence in wound healing is multifaceted, being strongly influenced by macrophage inhibition factor (MIF) and seemingly limited by the combined actions of gonadal steroids [5]. We might also imagine that chromosomal variations exhibited in disorders of sexual development could modify the hormonal environment and the response to hormones during wound healing.

It has been notable that hormone receptors are quite variable in their distribution, and their intensity for staining, among tissue types, tissue locations, and for gender differences. Changes in urinary mucosae, periurethral vessels, muscular layer, connective tissue, gene expression, and autonomic nervous system receptors, have been noted in relation to variance in hormonal status [6]. Reduced levels of estrogens and androgen are associated with dramatic alterations in genital tissue structure, including the nerve network, as well as the response to physiological modulators. Estrogens and androgen deficiency is associated with reduced expression of sex steroid receptors [7].

As an example of variability of distribution of the hormonal receptors in the epithelium, presumptive evidence suggests that relaxin receptors are present specifically, and almost exclusively, along the basement membrane [8,9], whereas glucocorticoid receptor staining is more widespread [10]. One reason for differential hormonal effects, therefore, rests with differences in receptor expression in tissue layers or compartments.

We attempt, within this review, to discuss the effects of hormones for their known impact on the wound healing cascade. Wound healing involves a wide variety of cell types and cytokines. Wound healing has been divided into three phases: inflammation, tissue formation, and tissue remodeling [11]. Tissue injury (or incision) begins the inflammation stage of wound healing, beginning with fibrin deposition and platelet degranulation arising from damaged blood vessels. Platelets, along with surrounding damaged tissue release chemokines that attract neutrophils, monocytes, and mast cells to the site of injury. These cells also secrete chemical messengers which produce the classic signs of tissue inflammation [12]. One sentinel growth factor released by platelet degranulation and by infiltrating monocytes is transforming growth factor –beta (TGF-β). Evidence suggests that different TGF-β isoforms can markedly affect the development of a scar during wound healing [13].

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Tissue reepithelialization is also controlled by cytokines, and begins with the migration and proliferation of keratinocytes. These activated keratinocytes express specific extracellular molecules that form an orderly matrix [14]. Fibroblasts then migrate to the wound and through interactions between neighboring cells and cytokines begin to exhibit a myofibroblast phenotype and lead to wound contraction [15]. After contraction, the wound is remodeled as collagen is degraded and reformed by a combination of metalloproteinases and inhibitors of metalloproteinases secreted by tissue macrophages, epidermal cells, and fibroblasts [11].

These events represent a balance of both anabolic and catabolic activities that result in wound repair. The balance typically favors collagen accretion and the formation of a scar at the site of the wound. Dysregulation of these activities can arise pharmacologically (chronic medication), geriatrically, endocrinologically (diabetes), or genetically and shift the balance toward extremes of keloid formation or chronic ulceration. Hormones affect stages of the wound healing process in different ways. This may be one of the reasons that we note scar less wound healing in utero [16], in apparent vaginal wounds after scarless sexual trauma in adolescent girls [17], and an increase in fistula/dehiscence in adolescent boys after hypospadias repair [18].

The goal of this paper is an initial attempt to document the effect that specific hormones have on stages of the wound healing process.

Androgens

Evidence from both animal and human studies have implicated androgens as repressors of wound healing, murine wounding studies have shown that androgen ablation affects the mediators of early healing, most especially those involved with inflammation. Abrogating testosterone or dihydroxytestosterone production or signaling causes reductions in leukocytosis with concomitant reductions in tissue levels of Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) and decreased matrix metalloproteinase (MMP) activity [4,5,14,19-21]. Blunted inflammatory effects were seen in local macrophages as well as stromal fibroblasts and represented an early healing (48hr) phenomenon which eventuated in accelerated wound healing. In a study of murine wounding with concomitant trauma-hemorrhage, androgen ablation reduced IL-1, and IL-6, and resulted in a stronger repair [22]. These studies also point to the ubiquitous distribution of androgen receptors in skin, with involvement of keratinocytes, epidermal cells, hair follicles, fibroblasts, and macrophages. Use of knock-out animals has added further evidence for the correlation between androgens, wound-infiltrating macrophages, and TNF-α production [23]. Effects are most pronounced during the early stages of healing and are cell-type dependent.

Other aspects of the wound healing cascade are affected. Androgens influence reepithelialization by increasing expression of beta-catenin, an important inhibitor of wound healing, however; they do not influence the migration and proliferation of dermal fibroblasts [20]. Androgens may affect wound remodeling because they have been shown to inhibit the expression of matrix metalloproteinases: MMP-1, MMP-3, and MMP-7 [24]. Finally, the observation that advanced age exacerbates androgen effects in male keratinocytes helps to explain, in part, why older males experience wound healing difficulties [25].

Estrogens

Estrogen has a profound influence on the body's inflammatory response to tissue wounding. Estrogens decreases the number of Polymorphonuclear Leukocytes (PMN) found within the wound by inhibiting chemotaxis [26] thereby reducing elastase mediated degradation of fibronectin leading to increased collagen deposition [27]. Estrogens down regulate the cytokine macrophage migration inhibitory factor (MIF) [28] which acts as a counter-regulator to the anti-inflammatory cytokines: IL-6, IL-1beta, and IL-8 secreted by monocytes [29]. MIF up-regulates genes associated with muscle contraction, immune response, and adhesion as well as down-regulate virtually all signaling cascades found in the wound environment and many cytoskeletal/epidermal genes leading to dysfunction in the wound healing cascade [30]. Estrogens can decrease the expression of JE/MCP-1 in fibroblast: a major chemoattractant for mononuclear phagocytes [31]. Estrogens increase expression of extracellular matrix components such as type I procollagen, tropoelastin, and fibrillin 1 while decreasing the expression of MMP-1 which has been shown to be mediated via a TGF-beta/Smad signaling pathway [32]. Estrogens also increases the secretion of GM-CSF by kertinocytes at the wound edge [33] leading to increased proliferation and migration of other keratinocytes, endothelial cells, and cells of the immune response which accelerates reepithelialization [34]. Estrogens have been shown to increase collagen deposition while decreasing MMP-mediated collagenolysis [35]. Two estrogen receptors have been studied in wound healing: ER-α and ER-β with the different subtypes being expressed in a wide variety of tissues. These subtypes also have been shown to have differential functions in the wound healing process. In a rat model, ER-α was found to be the chief subtype in the basal epithelium in the glans penis. This study also demonstrated that estrogen's antagonism in neonatal rats block development of the glans epithelium to develop [36]. (ER-α has been shown to promote wound healing by activating angiogenesis [37] and mediate Vascular Endothelial Growth Factor(VEGF) activity [35] ER-β has been demonstrated to be requisite of estrogen mediated epidermal wound healing in a mouse model [38]. In human keratinocytes, both ER-α and ER-β affect migration and proliferation, however, it appears that ER-β stimulation produces these effects without an increase of TGF-β1 [39]. The anti-inflammatory effects mediated by estrogens are believed to involve both subtypes of ER [38]. The known functional and local difference provide reason to study both subtypes of ER in foreskin specimens.

Glucocorticoids

Corticosteroids have long been used as an anti-inflammatory medical therapy in specific autoimmune diseases, inflammatory syndromes, and transplant rejection. They disrupt the inflammatory stage of wound healing by inhibiting the transcription of an important monocyte-selective chemotatic factor: MCP-1 [40] and by decreasing the expression of the pro-inflammatory cytokines IL-1 and IL-6 [41,42]. Glucocorticoids with beta-catenin affect keratinocyte migration by synergistically suppressing keratins K6 and K16 thus altering cytoskeleton needed for migration [43]. Furthermore, gluccocorticoids can decrease matrix deposition causing a delay in wound healing [44]. Gluccocorticoids inhibit the expression of cytokines TGF-beta, and IGF-1, leading to a decrease in collagen deposition which in turn decreases anchoring fibril formation thereby lengthening wound healing [45,46]. Finally, gluccocortoids affect wound remodeling through suppression of macrophage-specific metalloelastase, TGFbeta1 and 2 and MMPs 1, 2, 9, and 10; and by inducing TIMP-2 [47,48]. Glucocorticoids exert a deleterious effect on the wound healing process, which has been suggested to result from the anti-inflammatory action of these steroids. Glucocorticoids regulate the expression of various genes at the wound site which are likely to encode key players in the wound repair process. Beer

et al demonstrate that the proinflammatory cytokines interleukin-1 alpha and –beta, tumor necrosis factor alpha, keratinocyte growth factor, transforming growth factors beta 1, beta 2, and beta 3 and their receptors, platelet-derived growth factors and their receptors, tenascin-C, stromelysin-2, macrophage metalloelastase, and enzymes involved in the generation of nitric oxide are targets of glucocorticoid action in wounded skin. These results indicate that anti-inflammatory steroids inhibit wound repair at least in part by influencing the expression of these key regulatory molecules [49]. Glucocorticoids (corticosteroids) cause dehiscence of surgical incisions, increased risk of wound infection, and delayed healing of open wounds. They produce these effects by interfering with inflammation, fibroblast proliferation, collagen synthesis and degradation, deposition of connective tissue ground substances, angiogenesis, wound contraction, and re-epithelialization [50]. Corticosteroids may lower transforming growth factor-beta (TGF-beta) and insulin-like growth factor-I (IGF-I) levels and tissue deposition in wounds [51].

Relaxin

Relaxin is a 6-kD pleiotropic, polypeptide hormone and a member of the insulin-like growth factor family. Data suggest it can modulate inflammatory and immune responses. Relaxin has been shown to inhibit porcine mast cell degranulation [52], human neutrophil activation [53] and combats mitogen-induced airway sensitivity reactions in vivo [54]. Other data show that relaxin promotes leukocyte adhesion and migration *in vitro* [55].

As well, relaxin also influences fibroblast function, suggesting a modulatory role in extracellular matrix production during wound healing. *In vitro*, relaxin dosing studies using dermal fibroblasts demonstrated reductions in collagen and increases in collagenase production [56,57]. It has been linked to tissue vascularization via induction of vascular endothelial growth factor.

On the tissue level, histology studies of ligament biopsies have shown that fibroblasts from these tissues selectively bind relaxin [58-60]. Murine studies have shown decreases in foreign body fibrosis and lung fibrosis following relaxin administration [57,61]. More recently, it has been noted that age-related cardiac and pulmonary fibrosis in homozygous relaxin knock-out mice has been reversed by continuous relaxin infusion [62,63]. Others have also observed abrogation of fibrosis in models of hepatic and renal injury [64,65], as well as reduced scar formation in the lacerated skeletal muscle of mice following relaxin administration [66]. Some of these physiological effects are potentiated by either estradiol or TGFβ.

Other considerations

The foregoing discussion suggests that the use of estrogens and relaxin would promote wound healing by limiting inflammation, reducing collagen deposition, enhancing matrix remodeling enzymes, and improve vascularity. These same attributes that prompt interest in hormone therapy are also ones that act deleteriously in the case of neoplasms. While androgen and estrogens are widely-recognized risk factors for the development of prostate, breast, and cervical cancers, relaxin has also been linked to these disease processes [67-70]. That future clinical trials must account for this risk reflects prudent, responsible investigation.

Conclusion

Hormonal influence on wound healing is an emerging concept. Androgens, Glucocorticoids, estrogens, and relaxing, have all been studied and shown to have differential effects on wound healing. Receptor labeling within penile, clitoral, vaginal, and labial tissue may provide an indication of ability to respond to pre or post-operative administration of hormonal therapy.

Conflict of interest

No conflict of interest.

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Ethical Approval

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