

**A Topical Niacin Prodrug Enhances Wound Healing by Stimulation of Leptin Secretion**

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Leptin, the *ob* gene product, has been characterized as a satiety-regulating cytokine that is predominantly expressed by adipocytes. Recent studies indicate that leptin exerts numerous protective effects including the enhancement of skin re-epithelialization following wounding. The purpose of this study was to test the hypothesis that niacin and prodrugs of niacin designed for topical delivery could stimulate leptin release and thereby accelerate wound healing. A prodrug of niacin was designed and synthesized with physical properties that allow transdermal delivery to the skin at an optimal rate to release niacin while avoiding the vasodilation observed following oral or topical delivery of niacin. The efficacy of delivery was demonstrated by increases in the active form of niacin, NAD, in skin samples taken from the site of application. Safety testing of this compound on human volunteers showed that it did not cause irritation or any other adverse effects following topical application. The niacin prodrug stimulated leptin release when applied to the skin of mice. That niacin also stimulates leptin release in humans was demonstrated by the observation that niacin increased leptin secretion from cultured human adipocytes. In contrast, the same levels of niacinamide did not have any effect on leptin secretion. Studies on wound healing in mice showed that the topical niacin prodrug decreased wound diameter by greater than 60% relative to vehicle control at 8 days following wounding ( $p = 0.014$ ). Assessment of the niacin prodrug in human volunteers revealed that it enhanced resistance of the epidermal barrier to environmental stresses and resulted in significant improvement in skin texture. These data support the hypothesis that niacin derivatives designed for topical delivery will provide therapeutic benefit for wound healing.