Dermatologic therapy with cardiotonic digitalis?

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The use of the cardiotonic steroids known as digitalis to treat cardiac disease dates back to Hippocrates. Although the use of digitalis to treat heart disease has decreased considerably, it appears that this agent still plays a role in modern cardiology. The mechanism of action of digitalis has, for many years, been assumed to depend on its capacity to inhibit the plasmalemmal Na-K-ATPase. This inhibition would increase cytosolic sodium and, through alterations in Na/Ca exchange, effect an increase in cytosolic calcium, which in turn would render the primary physiological effect of this agent, increases in cardiac inotropy (2). Recently, this classical ionic signaling pathway has been challenged. The cardiotonic steroids appear to initiate a signal transduction pathway through the plasmalemmal Na-K-ATPase that does not depend on its ability to inhibit the enzymatic function of the pump. Rather, the inotropic effect of the interaction of cardiotonic steroids with the Na-K-ATPase appears to depend on the assembly of a macromolecular complex or Na-K-ATPase signalsome, consisting of the proteins caveolin-1, Src, and the epidermal growth factor receptor (EGFR) with the Na-K-ATPase (1, 3, 11). In fact, analogous to receptor tyrosine kinases, the binding of cardiotonic steroids appears to induce endocytosis of this signalsome in a clathrin-independent manner (10). A variety of cellular and systemic physiological effects has been ascribed to the activation of either the classic ionic pathway or signalsome pathway in vivo, including regulation of cell proliferation, blood pressure, and renal sodium excretion (1, 6, 7). Elevations in endogenous digitalis-like compounds have been associated with hypertension, congestive heart failure, and the cardiomyopathy seen with experimental renal failure (8).

It is the presence of substantial fibrosis that accompanies the pathological cardiac hypertrophy which prompted the present study by El-Okdi et al. (5) in the Journal of Applied Physiology. The previous studies from this laboratory reported that the circulating concentrations of the cardiotonic steroid marinobufagenin correlated with the amount of cardiac fibrosis seen with experimental renal failure (8, 9). Moreover, this group demonstrated that the direct treatment of cultured cardiac fibroblasts with a variety of cardiotonic steroids induced substantial increases in collagen production in a manner that clearly involved signaling through the Na-K-ATPase signalsome but did not involve increases in transforming growth factor-β or Smad proteins (4, 9). In an effort to further investigate this phenomenon, in the present study El-Okdi and associates (5) exposed human dermal fibroblasts to relatively low concentrations of cardiotonic steroids and found marked increases in collagen production, molecular phenotypical alterations, as well as accelerated wound healing in an in vitro model. In what must be considered still rather preliminary experiments, they successfully extended this wound-healing observation to a rat model of surgical wounding. The authors go on to speculate that there may be other applications of this phenomenon. It seems obvious that even cosmetic applications might be possible.

These are exciting possibilities. However, one must exercise caution in interpreting these findings. First, it is surprising that given the authors’ findings, alterations in wound healing and/or sclerotic skin disorders have not been seen (or rather recognized) with the therapeutic use of digoxin. Perhaps this is related to the in vivo dose-response curve. Patients treated for heart disease with digoxin typically achieve plasma concentrations of ~1 nM, whereas the authors employed 30 nM digoxin in the olive oil carrier. That said, there is some discordance with the in vitro experiments where accelerated healing of the wounded human dermal fibroblasts occurred with digoxin at 1 nM concentration. Next, it should also be said that while the demonstrated alterations in the molecular phenotype of the human dermal fibroblasts were impressive, the authors have a long way to go to fully characterize the changes in dermal fibroblasts that result from exposure to cardiotonic steroids. Perhaps most importantly, although the in vivo responses may be valid and are certainly consistent with the in vitro data, it may be that the applicable logical expression is: “true-true-unrelated”. Although fibroblast production of collagen is certainly an important aspect of wound healing, the topical digitalis might work through many other mechanisms, including the recruitment of additional fibroblasts from either stem cells, induction of epithelial mesenchymal transformation, increased proliferation of fibroblasts, and/or mechanisms involving other cells that might modulate the function of fibroblasts resident in the dermis. Clearly, the authors have just begun to investigate this important and complex area.

These concerns stated, the authors (5) are to be commended for this work. They have delineated a novel mechanism by which fibroblasts can be stimulated to produce more collagen, and they have also identified that dermal fibroblasts are particular sensitive to stimulation through this pathway. This is an exciting observation. Moreover, they have demonstrated that this pathway may be exploited to effect a therapeutic response in terms of wound healing. Certainly, further studies to address the specific molecular mechanisms involved with dermal fibroblasts, as well as the potential dermatological therapeutic potential, are warranted. If the authors of this study are correct in their conclusions, digitalis may, after all, end up to be a dermatological rather than cardiac medication.

REFERENCES


