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Commentary

Adenosine receptor agonists for promotion of dermal wound healing

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ABSTRACT

Wound healing is a dynamic and complex process that involves a well-coordinated, highly regulated series of events including inflammation, tissue formation, revascularization and tissue remodeling. However, this orderly sequence is impaired in certain pathophysiological conditions such as diabetes mellitus, venous insufficiency, chronic glucocorticoid use, aging and malnutrition. Together with proper wound care, promotion of the healing process is the primary objective in the management of chronic poorly healing wounds. Recent studies have demonstrated that A_{2A} adenosine receptor agonists promote wound healing in normal and diabetic animals and one such agonist, Sonedenoson, is currently being evaluated as a prospective new therapy of diabetic foot ulcers. We will review the mechanisms by which adenosine receptor activation affects the function of the cells and tissues that participate in wound healing, emphasizing the potential beneficial impact of adenosine receptor agonists in diabetic impaired healing.

1. Introduction

The mechanisms underlying the normal repair process, cell migration and proliferation, and extracellular matrix deposition and remodelling, have been extensively studied [1–3]. Cellular responses to inflammatory mediators, growth factors, cytokines, and to mechanical forces must be appropriate and precise in order to obtain optimum healing of a cutaneous wound. However, even during the normal process of wound healing complications can occur, including infection, thrombosis, and ischemia [4,5]. More importantly, the orderly progression of the healing process is impaired in chronic wounds, including those due to diabetes.

Impaired wound healing is a major concern for diabetic patients because their wounds do not heal properly and are a source of major suffering and cost. Only two-thirds of diabetic foot ulcers eventually heal and up to 28% may result in amputation [6]. The pathogenesis of diabetic foot ulcers is complex and it is well recognized that a number of contributory factors working together ultimately lead to impaired healing. Several intrinsic factors, such as peripheral neuropathy, foot deformity, peripheral vascular disease and peripheral oedema have been identified as the commonest factors responsible of impaired healing after trauma. In addition, extrinsic factors, such as wound infection, callus formation, and excessive pressure to the site, further aggravate the healing process [7].

Recent studies suggest that nerves play a central role in tissue homeostasis and can orchestrate complex reparative as well as destructive processes. First, an intact nociceptor system of primary afferent sensory nerves is important for

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the initiation of the inflammatory process and successful tissue repair [8]. Apart from the loss of pain perception, which is a key factor in the development of neuropathic foot ulcers, loss of autonomic function and small fibre neuropathy can result in impaired neurogenic control of local microcirculatory blood flow, impaired fluid homeostasis, diminished energy metabolism, oxygen delivery, and inflammatory responses. These processes could render the feet of diabetic patients with neuropathy more susceptible to tissue damage and infection [9].

Given the complexity of the pathogenesis of diabetic foot ulcers, many different interventions have been proposed to accelerate the healing process, but few have been subjected to formal evaluation. Despite the relatively large number of studies of growth factors like PDGF (becaplermin), EGF, basic FGF and other agents modulating aspects of wound physiology, there is currently little evidence to suggest that any of the reported interventions should be adopted in routine practice. Diabetic foot ulcer management is based on the simple principles of eliminating infection, debridement, cleansing and the use of dressings to maintain a moist wound bed, and lastly, becaplermin is the only promoting agent approved for use of those ulcers resistant to simpler interventions [6].

Based in studies carried out in vitro and in experimental animal models, we are proposing a new strategy for the promotion of impaired wound healing, the use of adenosine receptor agonists. We will summarized the biology of adenosine and review its actions on different tissues and cells implicated in the healing of cutaneous wounds, as well as its effect on experimental wounds in animals.

2. Purine metabolism and biology

Adenosine is a ubiquitous purine nucleoside produced by stepwise dephosphorylation of ATP by the coordinated action of ecto-apyrase (CD39) and ecto-5′-nucleotidase (CD73) (Fig. 1). While extracellular ATP and other nucleotides (ADP, UTP and UDP) have many biological effects through direct activation of cell surface receptors for adenine nucleotides (seven P2X ionotropic and eight P2Y metabotropic receptor subtypes), adenosine modulates cellular and organ function via occupancy of four specific cell surface receptors (A_1, A_{2A}, A_{2B} and A_3), all members of the large family of 7-transmembrane spanning, heterotrimeric G protein-associated receptors [10,11]. The A_1 and A_3 adenosine receptors coupled with Gi proteins are associated with two effector systems, namely, adenylate cyclase and phospholipase C. The binding of adenosine or its agonists to A_1 and A_3 adenosine receptors either induce inhibition of adenylate cyclase leading to a decrease in intracellular cAMP levels or stimulate phospholipase C and the release of intracellular Ca^{2+}. A_{2A} and A_{2B} receptors are associated with Gs proteins and their activation stimulates an increase in intracellular cAMP. In addition, they couple to mitogen-activated protein kinases (MAPK), which may give them a role in cell growth, survival, death and differentiation [12]. The affinity of selected agonists at the different adenosine receptor subtypes is summarized in Table 1.

Extracellular actions of purines in non-neuronal cells, including fast signalling roles in exocrine and endocrine secretion, platelet aggregation, cardiovascular effects and kidney function, have been known for a long time. More recently, slow purinergic signalling has been implicated in embryological development, wound healing, restenosis, atherosclerosis, ischemia, cell turnover of epithelial cells in skin and visceral organs, inflammation, neuroprotection and cancer [13,14].

More interestingly, purines and pyrimidines have major roles in the activities of neurons. This includes nociceptive mechanosensory transduction, as well as acting as a cotransmitter and neuromodulator in most, if not all, nerve types in the peripheral and central nervous systems [13]. This raises the innovative hypothesis that diabetic patients suffering from peripheral neuropathy will have altered purinergic neurotransmission.

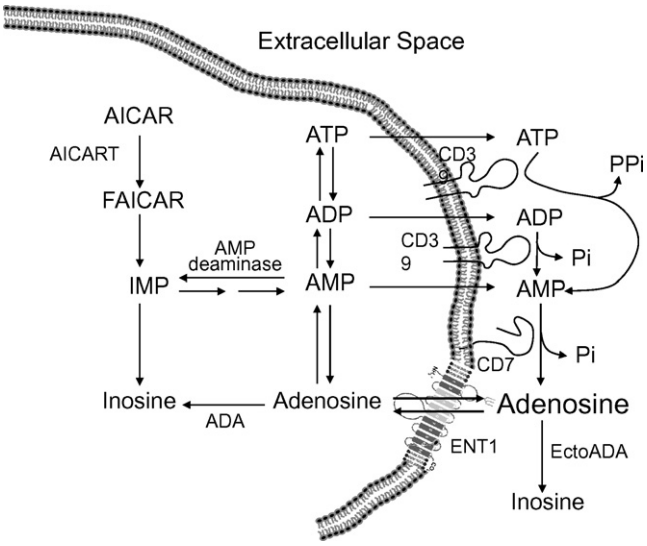

Fig. 1 – Adenosine metabolism. AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AICART, 5-aminoimidazole-4-carboxamide ribonucleotide transformylase; FAICAR, formyl 5-aminoimidazole-4-carboxamide ribonucleotide; ADA Adenosine deaminase; EctoADA Ectoadenosineaminase; CD73 Ecto-5′-nucleotidase; CD39 ecto-nucleoside triphosphate diphosphohydrolase (NTPDase); ENT1 equilibrative nucleoside transporter 1.

3. Could adenosine play a role in normal wound healing?

Under basal conditions, the extracellular adenosine concentration is rather constant (30–300 nM), and held in tight check by the equilibrium between adenosine production/release into the extracellular space and adenosine uptake by cells or catabolism to inosine (Fig. 1). In contrast its concentration can increase dramatically to micromolar or even higher ranges when there is an imbalance between energy use and energy supply, such as in oxygen depletion, or under conditions of cellular or tissue necrosis or stress as a result of ATP catabolism [12].