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Rhein: A potential biological therapeutic drug for intervertebral disc degeneration

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ABSTRACT

Intervertebral disc degeneration (IDD) is regarded as an important cause of low back pain, which continues to be a common disability. IDD is thought to involve sequential changes of intervertebral disc that lead to the reduction of disc cells and the extracellular matrix. In addition, inflammation is crucially involved in IDD. Currently, there is urgent need to develop biological therapies for IDD that can both relieve symptoms and directly reverse the process of degeneration. Rhein (RH) is an anthraquinone molecule with the abilities of enhancing the synthesis of matrix components and inhibiting inflammatory response. Recently, the metabolic precursor of RH called diacerein has been demonstrated to have significant effects on pain relief and function improvement in the treatment of osteoarthritis. Given the occurrence of matrix degeneration and involvement of inflammation in IDD, we propose that RH might be a promising biological therapeutic drug for IDD due to its bioactivities. In addition, we hypothesize that the underlying mechanisms might be that RH has the ability to diminish interleukin-1 (IL-1) induced apoptosis and inhibit IL-1 induced secretion of MMPs and aggrecanases.

Introduction

Intervertebral disc degeneration (IDD) is a public health problem. IDD is generally regarded as an important cause of low back pain [1], which continues to be a common disability that reduces patients' quality of life and increases health care expenditures [2–4]. IDD is thought to involve sequential changes of intervertebral disc (IVD) that lead to the reduction of disc cells and the extracellular matrix, which is made predominantly of proteoglycans, collagens, and noncollagenous proteins [1,5–7]. In addition, inflammation has been shown to contribute to IDD [6,8,9]. However, current clinical treatments of IDD mainly focus on the clinical symptoms of IDD, and no attempt has been tried to interfere with the biochemical and pathophysiologic processes of degeneration for effective prevention and therapy of IDD [5,10–12].

Rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) (RH) is an anthraquinone molecule derived from the rhizome of Rheum palmatum and related species [13]. The anti-inflammatory and -tumor activities of RH have been well-documented [13–15]. Recently, diacerein, a metabolic precursor of RH, has been used in the treatment of osteoarthritis (OA) and demonstrated significant effects on pain relief and function improvement [16,17]. Two main abilities of RH have been validated to be responsible for the effects: anti-inflammatory activity and enhancing the synthesis of matrix components, such as types I, II collagen and aggrecan [18–20].

However, up to now, no reported studies have examined the therapeutic effects of RH for IDD. Given the occurrence of matrix degeneration and involvement of inflammation in IDD, we hypothesize that RH might be a potential biological therapeutic drug for IDD.

Evidences and possible mechanisms

RH is an anthraquinone molecule found in plants of Rheum palmatum and related species. It is traditionally used in the treatment of constipation and jaundice [13]. Recently, the anti-inflammatory activity and enhancing the synthesis of matrix components effects of RH have been studied intensively [18–20]. Diacerein, which is metabolized into RH in humans, has been used in the treatment of OA and there are significant evidences that diacerein has both clinical efficacy and a structural effect on cartilage [16,17,21].

OA is a common joint disorder characterized by the destruction of cartilaginous matrix of the articular joint [22,23]. Accumulating evidence has shown that pro-inflammatory cytokines play important roles in cartilage degradation in OA [24,25]. One of these cytokines is interleukin-1 (IL-1) which stimulates the degradation process and suppresses cartilage-matrix synthesis [26]. RH can directly inhibit the synthesis and activity of IL-1β, and diminish IL-1β induced secretion of matrix metalloproteinases (MMPs) and aggrecanases, thereby preventing the breakdown of cartilage [27,28].

The disc cells regulate the homeostasis of IVD tissues through maintaining the balance between the anabolism and catabolism [29]. This balance is modulated by a variety of biochemical substances, including cytokines, growth factors, acting in a paracrine or/and autocrine fashion [30,31]. IL-1 family members are critical

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regulators of IVD cell function and the biological effects of IL-1 are balanced by the synthesis of IL-1 through IL-1 converting enzyme (ICE) and the inhibition of IL-1 function by IL-1 receptor antagonist (IL-1Ra) [7,32–34]. In IDD, increased production of IL-1 by disc cells was observed which was associated with a failure of up-regulating IL-1Ra [1]. It is thought that IL-1 induces the production of MMPs and aggrecanases, but does not influence the secretion of tissue inhibitors of metalloproteinase (TIMP) [7,32]. This unbalanced change in metabolic enzymes would contribute significantly to the degradation of the extracellular matrix of the IVD. It is also reported that IL-1β can promote the apoptosis of native IVD cells and play an important role in IDD [35].

Based on the above, we hypothesize that RH could slow the progression of IVD by diminishing IL-1 induced apoptosis of IVD cells, and inhibiting IL-1 induced secretion of MMPs and aggrecanases, and thus may be a potential biological therapeutic drug for IDD.

Testing

We suggest the following approaches to test the hypothesis:

(1) Rat nucleus pulposus disc cells are isolated and cultured in monolayer and alginate culture systems following the method previously described [36]. Cells will be respectively treated with IL-1β; RH and IL-1β; IL-1β and IL-1Ra. In addition, an animal model of IDD will be established following the method we recently published [37]. One hundred and eighty rats will be randomized into four groups and receive needle-puncture at tail discs; needle-puncture plus RH injection; needle-puncture plus saline injection; surgical exposure only (exposed control), respectively.

(2) In monolayer culture system, Annexin V-FITC/PI double staining will be employed to quantify the apoptotic incidences by using flow cytometry. In alginate culture system, real-time polymerase chain reaction (PCR) will be used to evaluate the expression of MMPs, TIMPs, and ADAMTS (a well-known aggrecanase family) following the method described previously [38]. The expression level of MMPs, TIMPs, and ADAMTS at protein level will be measured by Western blot as previously described [39], and the amount of MMPs, TIMPs, and ADAMTS in the conditioned media will be quantified by enzyme-linked immunosorbent assay (ELISA) following the method of Niu et al. [40]. Finally, [^{35}S]-sulfate incorporation into newly synthesized proteoglycan in the cellular pool and the corresponding culture medium will be measured as previously described [29].

(3) In animal model, the discs will be harvested 1, 2, and 4 weeks later. The disc height on molybdenum target digital radiographs, biochemistry (water content, glycosaminoglycans, and hydroxyproline), and histology will be evaluated following the methods we recently published [37].

(4) Analyze whether RH diminishes IL-1 induced apoptosis, the expression of MMPs and ADAMTS, and proteoglycan losses and whether RH prevents or reverses IDD in animal model by statistical analysis.

Conclusion

RH has the ability to diminish IL-1 induced apoptosis of IVD cells, as well as inhibit IL-1 induced secretion of MMPs and aggrecanases, which together will contribute to the inhibition of the progression of IDD. If our hypothesis is supported by further experiments, RH will be applied as a potential biological therapeutic drug for IDD.

Conflict of interest

None declared.

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