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Calcium pentosan polysulfate and sodium pentosan polysulfate may be used to treat intervertebral disc degeneration

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ABSTRACT

Intervertebral disc degeneration (IDD) is a major health problem world-wide, and several spinal disorders are closely associated with it. Although people have invested a great deal of time and effort, how to prevent and reverse the IDD for the researchers is still a difficult and hot issue. Intervertebral disc belongs to cartilage tissue, and IDD also is the cartilage degeneration disease. A large quantity of studies have shown that Calcium pentosan polysulfate (CaPPS) and sodium pentosan polysulfate (NaPPS) possess chondroprotective activities and play an important role in maintaining cartilage integrity. We reasonably hypothesize that NaPPS and CaPPS may be used to treat IDD. The possible mechanism may include that: (1) the significant effects of NaPPS and CaPPS in improving capillary blood flow could maintain nutritional supply to intervertebral disc, and preserve intervertebral disc tissue against degeneration; (2) CaPPS and NaPPS preserve cartilage integrity, proteoglycan synthesis, and improve cartilage biomechanical properties; (3) as the multifaceted exosite inhibitors of proteinases NaPPS and CaPPS strongly impede the activity and production of proteinases; (4) promotion of the balance between proteinases and TIMPs also may be involved in treating IDD; (5) NaPPS and CaPPS exhibit potent anti-inflammatory effects, and then reduce inflammation-induced IDD. If the hypothesis were conformed, the symptoms caused by IDD and its related diseases would be a corresponding alleviation or even disappearance, which could greatly alleviate the suffering of patients from disc degeneration diseases. Certainly, many roles of CaPPS and NaPPS, such as effectiveness, safety and side effects, need to be tested, and further works such as animal model and clinical trial, need to be done to prove this hypothesis.

Background

Intervertebral disc degeneration (IDD) is a major health problem world-wide and can lead to several spinal disorders. For example, low back pain with a high incidence is closely associated with IDD [1,2]. Symptomatic IDD could result in not only significant deterioration of quality of life, but also the increase of chronic disability population and economic burden [3–5]. Furthermore, there is a more frequent episode of IDD in elderly populations. Although people have invested a great deal of time and effort, how to prevent and reverse the IDD for the researchers is still a difficult and hot issue. At present, the main measure of treatment for IDD is either surgery or symptomatic therapy, both of which are limited and do not radically alleviate the underlying degeneration of the intervertebral disc. Recent some advanced biological technologies, including gene therapy, molecular therapy, cell therapy and tissue engineering therapy may be potential treatment strategies for inhibiting or reversing IDD [6–10]. However, the real clinical use

Abbreviations: ADAMTS, adamalysin with thrombospondin motifs; CaPPS, calcium pentosan polysulfate; IDD, intervertebral disc degeneration; IL-1, interleukin-1; MMPs, matrix metalloproteinases; NaPPS, sodium pentosan polysulfate; PPS, pentosan polysulfate; TIMPs, inhibitors of matrix metalloproteinases; TNF-α, tumor necrosis factor-α.

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of these methods will take a long way to go. A simple and effective treatment measure for IDD, therefore, is urgently needed.

Pentosan polysulfate (PPS), has attracted our interest because it is a new chondroprotective agent, exhibits a wide range of pharmacological activities in the treatment of cartilage degeneration [11]. Calcium pentosan polysulfate (CaPPS) and sodium pentosan polysulfate (NaPPS), are the respective forms of calcium salt and sodium salt of chemically sulfated xylosan from beechwood. A large quantity of studies have shown that PPS plays an important role in improving blood flow, reducing proteinases activities and maintaining cartilage integrity [11–14]. Furthermore, anti-inflammatory effect is also involved for cartilage protection [11,15]. Because of the above-mentioned pharmacological activities of PPS, actually PPS has shown chondroprotective activities to treat osteoarthritis in various animal models, and double-blind clinical trials have been launched to treat osteoarthritis which is similar with IDD and belongs to a aging-related cartilage degeneration disease, showing promising outcomes [16,17].

Intervertebral disc belongs to cartilage tissue and is similar with articular cartilage in many aspects [18]. And many pathophysiologic changes have appeared in IDD, such as gradual block of nutrition pathway in early degenerative period, catabolism of collagens and proteoglycans within the extracellular matrix, and activity of proteinases and inflammatory mediators [19,20]. PPS, as a new chondroprotective agent, is reported to protect cartilage against degradation and possess cartilage diseases modifying pharmacological effects [11–17].

Hypothesis

The hypothesis is reasonably proposed that NaPPS and CaPPS may be used to treat IDD. It follows that symptoms of correlatived with disc degeneration diseases typically such as low back pain, therefore are alleviated.

Possible mechanism

Given the pathogenesis of IDD and the pharmacological effects of CaPPS and NaPPS, we propose several possible mechanisms of CaPPS and NaPPS treating IDD and its related diseases (Fig. 1).

Improvement of nutritional supply

It has been claimed that the lack of nutritional supply is one of the primary causes of IDD [21]. The supply of nutrition is essential for all cell survival. The nucleus pulposus of intervertebral disc is an avascular tissue in the human body. The adult nucleus pulposus of intervertebral disc is mainly nourished by capillaries that derive from the vertebral bodies, penetrating the subchondral plate and terminating just above the cartilaginous end-plate [19,22]. Then small nutrients such as oxygen and glucose must diffuse from the capillaries through upper and lower end-plate of the cartilage and dense extracellular matrix to the cells of nucleus pulposus [23]. So the nutritional pathway to the nucleus pulposus cells is precarious. A lack in nutrient supply that hinder the transportation of oxygen and lactic acid into and out of the disc leads to a lowering of oxygen tension or of pH, which could thus reduce the living ability of intervertebral disc cells and could ultimately lead to a high occurrence rate of IDD [19,24].

The nutrient supply to the intervertebral disc can be disordered by vascular-related disease such as atherosclerosis [25,26]. In addition, some thrombophilic and hypofibrinolytic diseases also could lead to the block of blood supply to the intervertebral disc [27]. It has been proved that the pharmacological activities of CaPPS and NaPPS on fat metabolism involve increase of the clearing factor and reduction in blood several lipids such as total lipids, triglycerides, and cholesterol [11,28]. In fact, NaPPS has been used to treat thrombosis and improve blood flow condition for many years. PPS has the pharmacological activities of inhibition of factor Xa, thrombin, factor IXa, factor V, factor VIII, and stimulation of fibrinolysis, which results in the decomposition of mini-bolysis and improves the endmost blood flow [11,29]. Furthermore, the activation or release of lipases such as the glycerylester hydrolase system is the mechanism of NaPPS in intravascular lipolysis [12]. It has also been shown that CaPPS and NaPPS could increase the plasma levels of lipases and remold the hemodynamic parameters [11]. Associated with the nutrient mechanism of IDD and the significant effects of PPS in improving capillary blood flow, we reasonably propose that NaPPS and CaPPS could preserve intervertebral disc tissue against degeneration through improving nutritional supply to intervertebral disc.

Increase of biosynthesis of extracellular matrix

The process of disc degeneration involves the destruction of the extracellular matrix such as collagens and proteoglycans. The progressive loss of proteoglycans (e.g. Aggrecan, a large chondroitin sulfate proteoglycan) is one of the most significant biochemical changes in the matrix of intervertebral disc [30]. This loss from the extracellular matrix results in several adverse influences

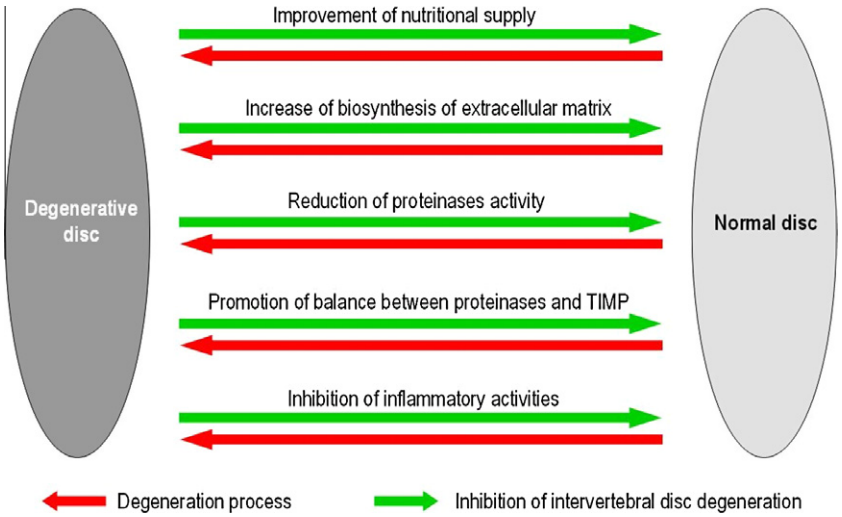

Fig. 1. The possible mechanisms of CaPPS and NaPPS treating IDD.

including loss of hydration, reduction of movement of molecules into and out of the disc, and decline of ability of resisting mechanical compression, which alter the environment and metabolic behavior of intervertebral disc [21,31]. Previous studies suggested that CaPPS could promote the proteoglycans synthesis of animal and human chondrocytes and lead to the accumulation of large proteoglycans [11]. In osteoarthritic joint, CaPPS is capable of resulting in the production of large molecular weight proteoglycans aggregates in the cartilage matrix [11]. Therefore, CaPPS and NaPPS preserve cartilage integrity, proteoglycan synthesis, and improve cartilage biomechanical properties.

Inhibition of proteinases activity

It is generally agreed that proteinases activity, principally such as aggrecanases and matrix metalloproteinases (MMPs), contributes to disorders of proteoglycans and collagens of intervertebral disc [32,33]. The adamalysin with thrombospondin motifs (ADAMTS) family, such as ADAMTS-4 (also called aggrecanase-1) and ADAMTS-5 (aggrecanase-2), are the main enzymes responsible for aggrecan (a large chondroitin sulfate proteoglycan) breakdown in intervertebral disc [34,35]. The MMPs belong to a family of extracellular zinc-dependent proteinases, divided into four main subfamilies including collagenases, gelatinases, stromelysins and membrane-type MMPs [36]. A large number of studies have shown that the MMPs, particularly the collagenases and gelatinases, are mainly responsible for the destruction of the collagens in intervertebral disc matrix [32,33]. The fibrillar collagens, such as type II collagen, provide tensile strength to the intervertebral disc and limit escapement of proteoglycans within the nucleus pulposus. Type II collagen degradation increases with degeneration and contributes to human IDD [37,38]. Therefore, the regulation of these enzymes activity is considered to be a possible future therapeutic target for the treatment and prevention of IDD and its related diseases [33,39].

In fact, NaPPS and CaPPS are considered as the multifaceted exosite inhibitors of proteinases, strongly impede many of these proteinases activity, and downregulate their production by chondrocytes and even other cells [11,13]. In degenerative cartilages of animals administered CaPPS or NaPPS, activities of MMPs not only could be inhibited directly, but also may be influenced by these agents through alternative pathways [11]. Furthermore, it also was shown that NaPPS and CaPPS could enter chondrocytes and bind to promoter proteins, and ultimately downregulate gene expression of MMPs [11]. CaPPS, as a chondroprotective agent, interacts with the C-terminal ancillary domain and directly inhibits the ADAMTS-4 activity [14]. And there is a similar finding that CaPPS protects cartilage against degeneration and directly blocks activity of ADAMTS-4 and ADAMTS-5 through interaction with the noncatalytic spacer domain of ADAMTS-4 and the cysteine-rich domain of ADAMTS-5 [13]. So we consider that CaPPS and NaPPS inhibiting proteinases activity may be one of important mechanisms to treat IDD which belongs to the cartilage degeneration disease.

Promotion of the balance between proteinases and TIMPs

The imbalanced level between proteinases and tissue inhibitors of matrix metalloproteinases (TIMPs) has been considered to lead to the occurrence of IDD [13,39,40]. Normally, there is minor excess of inhibitor over proteinases, whereas in degenerative disc, the increase of TIMPs did not parallel to the same extent as the proteinases [13,39,40]. For example, TIMP-3 is a endogenous inhibitor of the aggrecanases (e.g. ADAMTS-4) [41,42]. Although the cell positive frequency of ADAMTS-4 was increased with disc degeneration, the imbalance between ADAMTS-4 and TIMP-3 still lead to the destruction of the intervertebral disc matrix [13,40]. In vitro and in vivo experiments confirmed that CaPPS could prevent degradation of cartilage extracellular matrix through enhancing TIMP-3 level in cartilage [13,43]. The reason for this increase is that endocytosis of TIMP-3 regulated by lowdensity lipoprotein receptor-related protein is blocked by CaPPS [13]. CaPPS also improve the efficacy of TIMP-3 through increase of binding capacity of TIMP-3 for ADAMTS-4 and ADAMTS-5 [13]. Based on above mentions and the cartilaginous structure of intervertebral disc, CaPPS is reasonably considered to promote the balance between proteinases and TIMP-3 and alleviate degeneration of the intervertebral disc.

Inhibition of inflammatory activities

Inflammation has also been involved in the pathogenesis of IDD and discogenic pain [44]. Increasing evidences imply that inflammatory mediators regulate the catabolic process of intervertebral disc [45]. For example, tumor necrosis factor-α (TNF-α), as a member of the TNF ligand cytokine family, closely associates with the degree of disc degeneration [46,47]. An in vitro model of TNF-α-induced degeneration of intervertebral disc showed that TNF-α could decrease expression of matrix genes and macromolecules, increase activity of matrix degrading enzymes, and induce ADAMTS dependent proteoglycan degeneration [48]. Interleukin-1 (IL-1) has also been proposed as a key inflammatory molecule in the process of disc degeneration [49]. The expression of IL-1 is increased with the degeneration of intervertebral disc. Importantly, IL-1 induces an imbalance between intervertebral disc matrix of catabolism and anabolism, which result in the matrix degenerative changes of disc [49,50]. Therefore, inhibiting inflammatory reaction has been considered to be an effective therapeutic strategy for preventing and reversing IDD [50].

Previous studies suggest that NaPPS and CaPPS exhibit potent anti-inflammatory effects [11,15,51]. The activities of inflammation mediators are efficiently decreased by NaPPS and CaPPS [11]. CaPPS and NaPPS decrease the level of IL-1 and TNF-α, and switch chondrocytes from IL-1- and TNF-induced catabolism to anabolism, so maintaining cartilage homeostasis [11,52]. In addition, the potent and wide anti-inflammatory effects of CaPPS and NaPPS are possibly due to improvement of the microcirculation stimulated by the agents in the inflammatory tissue [11,51], which could associate with forementioned function of improving blood flow of degenerative intervertebral disc.

Conclusions

Associated with the current evidences and possible mechanisms, it is conceivable that CaPPS and NaPPS could aim at various pathogenesis of IDD to preserve intervertebral disc tissue against degeneration. Consequently, we reasonably believe that NaPPS and CaPPS could be used pharmacologically to treat IDD. Meanwhile, the symptoms caused by IDD and its related diseases will be a corresponding alleviation or even disappear, which could greatly alleviate the suffering of patients from disc degeneration diseases. In addition, several administration methods such as oral and intramuscular injection are available, which is beneficial to a wide range of applications. Certainly, many roles of CaPPS and NaPPS, such as effectiveness, safety and side effects, need to be tested, and further works such as animal model and clinical trial, need to be done to prove this hypothesis.

Disclosure

The authors have no financial interests or other intentions in any of the products, devices, or drugs in this article.

Conflict of interest statement

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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