The application of polydeoxyribonucleotides in the treatment of diabetes

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Abstract. Polydeoxynucleotides (PDN) are a particular kind of DNA fragment found in the sperm liquid of the salmon. PDN is so close to the human DNA, over 98%. It's very, very important for science and medicine. PDN is a A2A receptor agonist that can help to stop the effect of inflammation, and it's used for different kinds of inflammatory sicknesses.The main functions can be classified as promoting tissue repair, wound healing, treating angiogenesis, anti-inflammation and immune regulation, as well as anti-ischemic effects. And it is also proved to promote the cell proliferation and vascular regeneration, so it hasobvious effects in tissue repair and anti-ischemia. PDN is also involved in diabetes.With the development of synthetic biology and delivery technology, the application prospects of PDRN will be even broader, and it is expected to become an important drug in the treatment of diabetic complications This article will explore the medicinal value of PDRN, current research, and breakthroughs in clinical applications.

Keywords: Polydeoxyribonucleotides; medicine; diabetes.

1. Introduction

1.1. Diabetes

Diabetes Mellitus (DM) is also one of the common diseases that is also increasing as a result of the increasing rate and length of life of the people in this period of time [1], it is expected to be 2.8% in 2000 and it is expected to be 4.4% in 2030. And the estimated number of adult people with DM in the world is more than 415 million, and this number is increasing [2], and it is estimated that more than 640 million adults will be diagnosed with DM by 2040 [3]. Diseases arise as a consequence of body cells not producing much insulin, and there being a glitch in the insulin processing process. It is classified as Type I, Type II and Gestational Diabetes. Causes: it's because some of your genes and your surroundings cause the pancreas islets not to work properly or to make too little insulin, which means that your body doesn't use or store blood sugar well. Hyperglycemia raises the chance of problems for lots of organs [4]. Disease taking it's course, high blood sugar, lower leg, worst case scenario, cutting off your leg.

Wound recovery is thought to be 4 different things. First is hemostasis or vascular contraction then thrombus formation and clotting. And then the next thing is inflammation and that's also good for us. That's like a biological defense mechanism. And then the next one is cell production, so this is how the study makes tissue. Finally, the process of completion of wound healing through tissue reconstruction. But the diabetics with the higher blood sugar are going to have much more serious inflammation. And it's also during the hemostasis that it can become hypercoagulable and poor skin function. Disrupted inflammatory markers and GFs make for worse chronic wound inflammation. Keratinocyte proliferation is decreased and thus there is not enough skin re-epithelialization and fibroblasts do not fully contribute to ECM synthesis, assembly and remodeling [5-8]. Lastly, DM changes immune response, so people with DM are more susceptible to all kinds of infections leading to diabetic wounds in different ways [9, 10]. At present, in terms of the controlled use of dRNAs as a therapeutic agent for diabetes related skin wounds, it can be observed that they have some potential, but they are still not fit for use in this field. This is a review of the current use of pdrn in diabetes and other areas of medicine.

1.2. PDRN

Polydeoxyribonucleotides (PDRN), once derived from human placentas as low-molecular-weight, linear polynucleotides, are now obtainable from the sperm of salmon and trout [11-12]. This patent and registered DNA derivative drugs contain different kinds of deoxyribonucleotides with different molecular weights, mostly 80 - 200 kda, the molecular weight of deoxyribonucleotide fragments is mainly 50 - 1500 kda, the peak of Gaussian distribution of deoxyribonucleotide fragments is 132 kDa . PDRN is significantly bigger than defibrinated polynucleotides (16.5±2.5 kda) . Defibrinylated polynucleotides are from porcine intestinal mucosal DNA. That's something to remember. The high-temperature extraction and purification of PDRN can extract more than 95% of active ingredients, and it destroys protein, peptides, so the product is safe, no immune side effect. For raw material: DNA is from sperm cells - it is the best source of extremely pure DNA without any peptide impurities but contains proteins and lipids of somatic cells . PDRN has only a few therapeutic effects such as tissue repair, anti-ischemic, anti-inflammatory. Very important for continuous delivery and release behavior. That is, it may have some use to make skin grow again in a sore foot of a weak sick person. Both in-vitro and in-vivo studies have shown that PDRN's mechanism is related to adenosine A2A receptors. And PDRN is also binding with the A2A Receptor and it gives like the nucleosides, Nucleotides, and this is repair pathway. PDRN's adenosine A2A receptor binding seems to be connected to its DNA, the size it is when made, and how it is made. In this case, PDRN is an innovation on the drug. Adenosine and dipyridamole, which are nonspecific adenosine receptor agonists that produce adverse side effects and regadenoson, the only other A2A receptor agonist that is available for stress with pharmacologic stress in myocardial perfusion imaging. In conclusion, DPN is also a kind of oligo mixtures, different MW and DNA origins. It has different wound healing promoting effects from PDRN. Some of the more common uses include diabetics, foot ulcers, vascular occlusions, and non-antibiotic eye drops.

2. Medical treatment

2.1. The pharmacological effects of PDRN

2.1.1 Promote tissue repair, wound healing, and angiogenesis

PDRN is a Polypurine Nucleotide which can directly stimulate the proliferation and migration of human dermal fibroblasts and keratinocytes, and cell proliferation increased 2 - 3 times compared to the control group when the concentration was 10 - 50 μg / ml. To reduce the over-expression of MMPs, to prevent collagen from being broken down, and to help the skin deposit more types I and III, and PDRN stimulates adenosine A2a receptors to increase the expression of various growth factors, such as VEGF, bFGF, to stimulate the formation of new capillaries (in diabetic mice, VEGF was about 9 times higher), (animals) To improve the microcirculation and promote the local blood supply of blood oxygen for the wound, in the patients' local blood oxygen supply for wounds in the test, it can be seen that the skin and soft tissue oxygen pressure of the wound in the wound is the wound. The wound healing rate increases with the increase of the percutaneous oxygen pressure of the skin and soft tissue of the wound >50mmHg.

In terms of clinical application, PDRN is highly effective for thermal injuries such as deep second-degree burns and diabetic wound repair. As for deep 2nd degree burns of mice, PDRN treatment speeds up the re-epithelization process and makes things better quicker, which improves the therapy. It can reduce the serum TNF-α content in a systemic manner, but it can increase the expression of VEGF and the production of NO in the wound. And those healing qualities might be able to do something for cell cycles too. Diabetic environment, PDRN stimulates the process of cell cycle protein through granulation tissue growth and inhibit p15 and p27.

2.1.2 Anti-inflammatory and Immune-regulating Effects

PDRN acts through one mechanism via adenosine A2A Receptors: Core pathway: activation of A2A adenosine receptor to inhibit pro-inflammatory pathways (NFkB, MAPK) through the cAMP/PKA pathway to regulate cytokines. Tissue repair, it can promote angiogenesis by increasing VEGF and stimulating cell proliferation by releasing EGF/FGF, thus accelerating the renewal of damaged tissues; chronic inflammatory diseases are also closely related to A2A receptors, and PDRN specifically activates the receptor, so there is a dual "anti-inflammatory + repair" strategy for this disease. In the treatment of diseases such as rheumatoid arthritis, periodontitis, and inflammatory bowel disease, new therapies can be considered, and all its functions and receptors are “star molecules” for the study of inflammation. Future Applications: Formulation Optimization (Oral Microspheres, Topical Gels) Clinical Application: Phase 1/2 Studies for Rheumatoid Arthritis, Periodontitis, and Combined Therapy with TNF-α Inhibitors. that way which can be changed from a lab place into a doctors office type of place, to help the sick people get better, and do it safer.

2.1.3 Anti-ischemic effect

Microcirculation and cell survival in PDRN (polydeoxyribonucleotide)- treated ischemic tissues are improved by many targets. PDRN first activates adenosine A2A receptors, and then promotes the expression of VEGF (vascular endothelial growth factor) and eNOS (endothelial nitric oxide synthase). Increase the production of NO in endothelial cells to dilate blood vessels and produce new capillary blood vessels in ischemic tissues, thereby improving blood perfusion in ischemic tissues when the blood flow in animals increases by about 30%-50% in animals, reduce tissue hypoxia, for example, reduce the size of myocardial ischemic infarction area by 25%, etc., to achieve an anti-ischemic effect of vascular regeneration and microcirculation improvement. And it lessens inflammation by preventing NF-kB and lessening how many pro-inflammatory things go out of the body. This includes TNF-a, IL-1beta. (>40% decrease in TNF-a levels in ischemic colitis models). it can also relieve oxidative stress-induced cell injury by scavenging ROS, protecting mitochondrial function, and reducing lipid peroxidation products such as MDA, and it has anti-inflammatory and antioxidant effects, and finally reduces pdrn ischemia-induced apoptosis by regulating the ratio of apoptosis proteins such as Bax/Bcl-2 and reducing the activity of Caspase-3, for example, it can reduce 50% of the neuronal apoptosis of cerebral ischemia models. Promote ATP synthesis, maintain cellular energy metabolism and energy supply to improve the survival of ischemic tissues. Cell protection, anti-ischemia effect.

PDRN counter ischemia effects have wide-ranging clinical medical applications. Not only acute ischemia like myocardial ischemia and stroke but also chronic ischemic like Intermittent Claudication in peripheral arterial disease. Route: iv, around isotic tissues, oral. Future studies may combine PDRN and thrombolytics (rt-PA) or antiplatelet. It reaches its anti-ischemia effect by means of three separate ways of acting, namely, encouraging the growth of new blood vessels (angiogenesis), hindering the inflammation and oxidation reactions, and stopping cells from dying. It gives a new treatment plan for ischemia. more clinical trials need to be done to prove that it is good and go to the next step of using it in clinics.

A clinical study by 2023 on a subsidiary of Nature Magazine, topical injection of PDRN promotes the healing of diabetic foot ulcers in a randomized controlled trial of 120 patients, with a wound healing rate of 78% (45% in the control group) and an average healing time of 42 days (68 days in the control group), without any adverse reactions. Dermatological application: The University of Insubria in Italy said so in Plastic and Reconstructive Surgery - 40 people who had face-lift surgery got postoperative PDRN injection, their healing time dropped by 30% and their Vancouver Scar Scale scores were notably cut down ($P<0.05$).

3. Future and Prospects

It is a brand-new type of biological active substance that is multifunctional. It will grow quickly in the areas of technological development, large-scale use, and standardization of the market due to its many functions, such as anti-inflammatory, repair tissue, and resist ischemia. This change might turn it into an ordinary and commercial product that can be used for medicine. On technological side, industry would like to go for synthetic bio to break the bottleneck on biological extraction. A big one is Regime Bios global first synthetics PDRN production, no more old salmon testicular extracts and 10x better efficiency, way better purity/stability. Future synthetic techs lowering costs more so that PDRN can shift from hi-end med-aesthetics to mass-market skincare & med devices: "composite hydrogel delivery systems", "layered microsphere controlled-release techs" had already hit exact transdermal penetration and release. Industry is getting smarter about delivery to increase local tissue concentration and testing new formulations for oral and ophthalmic applications.

4. Conclusion

Polydeoxyribonucleotides (PDRN), these are some special parts of DNA that come from salmon germ cells, they look like our DNA and are great for making medicine: PDRN can turn on something called A2A receptors, this helps reduce swelling and encourages the growth and creation of new blood vessels, so tissues get better faster PDRN is extra good for people with diabetes since it can help heal wounds caused by having too much sugar in the blood. It manages chronic wounds such as diabetic foot ulcers by stimulating the growth of fibroblasts, collagen deposits, and VEGF. It also has an anti-ischemic effect and a regulatory role on the immune system, reducing damage to the tissue and promoting recovery. As the technology of synthetic biological & Delivery advance, the use of PDRN will be better. it will be considered as the best therapy agent for diabetes complication.

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