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# Potential Ciliary Neurotrophic Factor Application in Dental Stem Cell Therapy

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# Potential Ciliary Neurotrophic Factor Application in Dental Stem Cell Therapy

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## Abstract

Neurotrophic factors have long been considered growth factors that promote survival and growth of various neuronal tissues. Recent studies showed that neurotrophic factors are also present in dental pulp and periodontal ligament. This paper reviews the literature about the ciliary neurotrophic factor (CNTF), a member of the neurotrophic factor family, and indicates the potential clinical application of CNTF in dental stem cell therapy.

## Introduction

Neurotrophic factors have been shown to have the potential to promote survival and regeneration of neurons. The three major groups of neurotrophic factors are subcategorized into neurotrophins, glial- cell derived neurotrophic factor family ligands (GFLs), and neurocytokines. Neurotrophins include nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and others, such as neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). GFLs also belongs to the transforming growth factor beta (TGF-β) family, and GFLs consist of GDNF, neurturin, artemin and persephin [1]. Neurocytokines include ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF). Similar to other neurotrophic factors, CNTF has been shown to play an important role in promoting survival and inducing differentiation of nerve cells. CNTF was first isolated from chick embryonic ciliary ganglionic neurons [2]. It belongs to the interleukin (IL) 6cytokine family which includes IL-6, IL-11, oncostatin M, cardiotrophin 1 and LIF [3]. The IL-6 type cytokines share a common gp130 receptor subunit, and signal principally through the Janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT) pathway [4-6]. CNTF is widely expressed in the brain, spinal cord and ciliary ganglia [7]. CNTF deficient mice develop normally and thrive. When the sciatic nerve was damaged in a sciatic nerve crush experiment, the CNTF knockout mice which underwent sham surgery had no change in walking compared to the wild type animals. However, the recovery from the sciatic nerve injury was significantly impaired in the CNTF knockout mice. These results suggest that CNTF is not essential for neural development but acts in response to injury [8].

Exogenous CNTF is shown to be neuroprotective and it improves neuronal regeneration. There are many clinical trials studying the therapeutic use of CNTF in neurodegenerative diseases. The majority of the trials are treating different types of retinal neurodegeneration [9-11]. CNTF has also been implicated in treating Huntington's disease [12] and amyotrophic lateral sclerosis (ALS) [13,14]. Since the half-life of CNTF is only a couple of minutes, researchers have also investigated different delivery methods, such as including encapsulated cell intraocular implants [15], in order to enhance the effect of CNTF in patients. Human Dental Pulp Stem cells (DPSCs) were first isolated from the third molars [16]. DPSCs are mesenchymal cells in origin. They are able to form single colonies in culture, self-renewal *in vivo*, and demonstrate osteoblastic, chondroblastic, odontoblastic, cementoblastic, adipogenic, angiogenic and neurogenic differentiation potentials [17-19]. The proliferation rate of DPSCs are higher than bone marrow derived mesenchymal stem cells, making them a potential source for tissue regeneration [20].DPSCs have been shown to promote functional recovery of a completely transected spinal cord [21], induce chemo-attraction of host avian trigeminal ganglion axons[22], and when differentiated into supportive glial cells, have been shown to secrete significantly higher levels of neurotrophic factors[23]. Many reports have shown that dental pulp cells from murine and human both produce neurotrophic factors [21,24]. Specifically the mRNA of, NGF, BDNF, GDNF, NT3 and NT4/5 were seen in the inner dental epithelium and dental follicle cells in developing human teeth [25-28].

Every time a tooth is prepared for a filling, there is inflammation and thermal trauma which

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can lead to death of the nerve in the pulp space of the tooth. If CNTF can reduce inflammation post injury to the tooth, it could reduce the need for further treatment. Nerve damage and spontaneous necrosis of a tooth ultimately requires a root canal therapy treatment in order to stabilize and fix the problem. If we can harness the potential nerve survival and regeneration through the use of neurotrophic factors when nerve damage is sustained, it could decrease the necessity for root canal treatment. When orthognathic jaw surgery, periodontal surgery, and oral surgery is done, a potential risk is permanent loss of sensory innervation to that area because of the nerve damage that is done. DPSC therapies along with neurotrophic factors such as CNTF have the potential to be good candidates for neuroregenerative therapy and to be able to give natural sensory feeling back to the patient to increase the quality of life. The biggest challenge to nerve regenerative treatment in the sensory nervous system is that it is extremely difficult to quantify if an animal has lost and regained feeling in an area with sensory nerve damage. Many of the other studies regarding neuroregeneration using neurotrophic factors have looked at motor neuron degenerative diseases that give us quantifiable measurements.

The potential application with regenerative therapy utilizing stem cells for regenerative dentistry could potentially have a lasting impact on the future of dentistry. DPSCs are slowly becoming increasingly studied due to the potential of their regenerative effects. CNTF as a neurotrophic factor has also been studied for its use in neurodegenerative diseases. Characterization of the effects of up regulating CNTF in DPSCs as well as seeing its effect on inflamed DPSCs would be the first step in determining the overall effects of CNTF and DPSC use for regenerative dentistry. Due to the fact that CNTF has already been studied in clinical trials for neurodegenerative diseases and DPSCs have been studied for neuroregeneration in animal models, they are both promising candidates for regenerative dentistry.

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