Neurotransmitters and Dental Stem Cells: Future Pulp Regeneration

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Abstract

Background: Although there have been many studies on stem cells, there are few sources that discuss how neurotransmitters and stem cell proliferation interact to regenerate dental pulp. Dental pulp regeneration is an innovative procedure for reviving the dental pulp, if feasible for entire tooth. Natural dental repair of dental pulp stem cells in injured teeth activates the platelets to release serotonin (5-HT) and dopamine (DA) in bulks. This induced the research on the role of neurotransmitters in increasing the cell proliferation rate of stem cells. In this review, the prospective future treatments for dental pulp regeneration are also covered.

Highlight: This review focuses on the prospective strategies for dental therapy in the future as well as the role of neurotransmitters in promoting stem cell proliferation for tooth pulp regeneration.

Conclusion: The interaction of neurotransmitters with dental stem cells has been discovered, and this review provides hope for the regeneration and repair of the tooth pulp. The evidence points to neurotransmitters as a factor in the increased proliferation of stem cells.

Key Words: Neurotransmitter; Stem cell; Tooth regeneration; Tooth repair; Regenerative dentistry; Dental pulp.

1. Introduction

Tooth loss is typically caused by oral disorders such as dental caries, periodontal disease, and trauma. The mental and physical anguish that might result from being in this predicament can significantly diminish a person's quality of life (QOL) [1]. Maintaining healthy and functional teeth is important not just for enjoying meals and maintaining QOL, but it also helps to prevent dementia since mastication activates the brain [2]. Thus, there is a lot of interest in how teeth can grow back [3].

The discovery of properties of stem cells which is capable of self-renewing and differentiating by Canadian scientists in 1960 sparked interest in stem cell research [4]. Stem cells are undifferentiated cells that can develop into any adult cell type. They are present in all multicellular organisms and may be identified by their capacity to do so [5]. These cells have a regenerative capacity that is unparalleled, and as a result, they are widely used, either alone or in conjunction with scaffolds, to either replace or repair damaged cells [6]. There are two requirements that cells must meet in order to be considered "stem cells." First, in order to generate clones of themselves, stem cells need to be capable of unlimited self-renewal. The proliferation of stem cells is strictly regulated compared to rapidly replicating cancer cells. Importantly, stem cells must be capable of giving rise to a specialised cell type that forms part of the healthy organism [7].

There are two main sources of stem cells used, which are embryonic stem cells (ES) and somatic stem cells, also known as adult stem cells. ES cells are obtained by harvesting the inner cell mass of a pre-implantation blastocyst [8, 9]. These cells have been produced from rodents, primates, and humans. In dentistry, there are views that somatic (adult) stem cells are preferable compared to EC since they are readily available and their usage does not raise

ethical difficulties which involves the destruction of human embryos [10]. The different type of somatic dental stem cell in different location in the mouth are shown in the Figure 1.

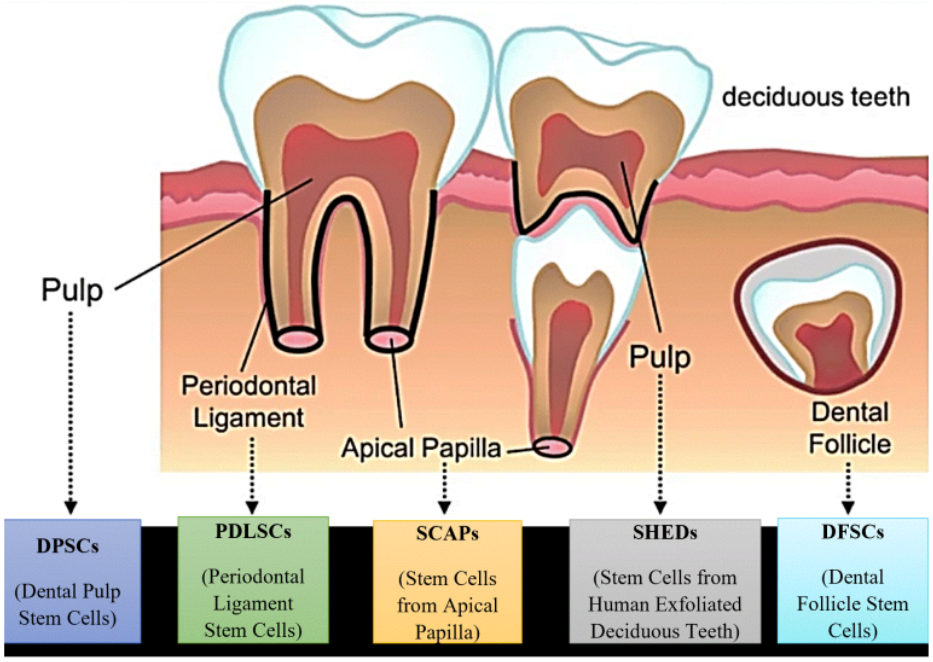

Figure 1 Dental stem cells in different location in the mouth

The location of the stem cell give name to the different type of cell. Dental pulp stem cells (DPSC) are located in the pulp of permanent tooth while stem cells from human exfoliated deciduous teeth (SHED) is located in the pulp of deciduous teeth. Periodontal ligament stem cells (PDLSCs) can be found in periodontal ligament area while stem cell from apical papilla (SCAPs) are located at the apex of the tooth. In the dental follicle, it is known as dental follicle stem cells (DFSCs).

2. Materials and methods

Using the keywords 'neurotransmitter', 'stem cell', 'tooth regeneration', 'tooth repair', 'regenerative dentistry', and 'dental pulp', literature search was performed via PubMed and ScienceDirect from 2001 to 2022. Nine publications reporting neurotransmitters interactions with stem cells were found for tooth and pulp regeneration.

3. Results

Dentin pulp is susceptible to injuries of varied severity. All of these traumas are accountable for dentin-pulp changes [11]. The pulp is a mesenchymal soft tissue that is located between the central chamber and the root tip. The typical healthy dental pulp tissue is composed of layered cells that are able to divide and differentiate [12]. It is also comprised of odontoblasts, fibroblasts, and immunological cells (Goldberg et al., 2008). Tissue repair, regeneration, and the regulated inflammatory response are all under the control of the pulp cells (Eming et al., 2007). It is possible that pulp cells will start an inflammatory response to begin the healing process, albeit this will depend on the kind and severity of the bacterial infection. And this is true regardless of whether or not the bacteria have colonised the whole pulp.

3.1. Neurotransmitters and stem cells

3.1.1. Serotonin

Serotonin, also known as 5-hydroxytryptamine or 5-HT, is a monoamine neurotransmitter that plays a role in the control of neuroendocrine function, modulation of depressive symptoms, regulation of anxiety, and temperature regulation. There are two primary processes involved in the production of 5-HT. The first process involves the formation of 5-Hydroxytryptophan from tryptophan through the action of tryptophan hydroxylase. The second process involves

the conversion of 5-Hydroxytryptophan to 5-HT through the action of the L-aromatic amino acid decarboxylase enzyme [13]. Moreover, 5-Hydroxytryptophan is a necessary precursor for 5-HT found in the cell's cytoplasm [14].

5-HT has a role in dentin repair by modulating the endogenous pulpal stem cell. A robust quantitative measure of dentin restoration was used by Baudry [15] to examine the impact of in vivo pharmacological inhibition of 5-HT and dopamine (DA) receptors on tooth healing at day 30 after pulp damage. Soon after damage, gelatine hydrogel microspheres containing selective 5-HT1D (SB714786), 5-HT2B (RS127445), or 5-HT7 (SB269970) receptor antagonists were implanted inside the pulp of the first rat molar (final concentrations 100 nM). The increase in Ca2+ concentration that normally happens during dentin regeneration was blocked by blocking 5-HT2B and, to a lesser extent, 5-HT7 receptors. Ca2+ accumulation in the mesial pulp was unaffected by antagonistic 5-HT1D receptors. These results validate the presence and activity of 5-HT2B and 5-HT7 receptors on the surface of odontogenic cells as demonstrated *in-vitro* [15].

Odontogenic stem cells have a dual serotonergic identity, and A4 and H8 pulpal cell lines exhibit significant quantities of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor 1 (IGF-1), all of which are stored in enormous dense-core vesicles [16]. The growth hormones BDNF, NGF, and IGF-1 have all been shown to promote axon guidance and elongation, as well as neuronal survival [17, 18]. Pulp stem cells secrete neurotrophins that may facilitate dentin remineralization, root formation, and tooth restoration. In addition to producing 5-HT and DA, the A4 and H8 pulpal cell lines also display fully functional enzymes necessary for complete 5-HT/DA processing. Included in this group are the rate-limiting enzymes in the biosynthesis of serotonin (5-HT) and dopamine (DA),

tyrosine hydroxylase and tryptophane hydroxylase, and the monoamine oxidases essential for bioamine catabolism.

3.1.2. Dopamine

Dopamine (DA), a catecholamine 3,4-dihydroxyphenethylamine, operates as a neurotransmitter throughout a broad evolutionary span. Dopamine is known to control motor circuits, evaluate sensory stimuli, and mediate reward or reinforcement signals in the mammalian brain [19].

DA take part in the dental repair via D1 and D3 receptors. Early after lesion, the first rat molar pulp was implanted with gelatine hydrogel microspheres containing selective antagonists of D1 (SCH23390) and D3 (S33084) receptors (final concentrations 100 nM). At day 30 after pulp damage, mesial pulpal Ca2+ concentration was used as a reliable quantitative measure of dentin restoration. The increase in Ca2+ concentration that generally takes place during dentin healing was inhibited by blocking D1 and D3 receptors. The findings imply that D1 and D3 receptors are present and active on the surface of odontogenic cells, validating the in vitro findings. These wide data imply that DA and 5-HT co-released by platelets and subsequent activation of all D1, D3, 5-HT2B, and 5-HT7 receptors are necessary for tooth regeneration.

Osteogenic induction of periodontal ligament stem cells (PDLSCs) was established by cultivating cells on Mussel-inspired polydopamine (PDA) film or an uncoated polystyrene surface as a control, according to Lee [20]. In order to determine whether or not PDLSC underwent osteogenic differentiation, intracellular calcium levels and alkaline phosphatase (ALP) activity, as well as the protein expression of osteocalcin (OCN), osterix (OSX), and runt-related transcription factor 2 (RUNX2) were analysed. PDLSCs that were grown on PDA film

had more osteogenic activity than PDLSCs that were grown on the control surface. In addition to this, in comparison to control cells, PDLSCs grown on PDA film revealed greater levels of the integrin adhesion receptors integrin 5 and 1 in their respective proportions. One isoform of the intracellular signalling protein phosphatidylinositol-3-kinase (PI3K), p110, was expressed by PDLSCs on PDA film in a PDA dose-dependent manner. This signalling protein was shown to interact with integrin 1, demonstrating that integrin is required for PI3K activation in response to PDA. Finally, PDA-induced osteogenic activity of PDLSCs was reduced by PI3K inhibition [20].

3.1.3. Acetylcholine

There are insufficient data about acetylcholine in pulp regeneration and dental stem cell. However, acetylcholine play role in the neuronal development. The role of acetylcholine as modulator of fibre outgrowth was studied by Biagioni [21]. In two experimental conditions, the role and importance of acetylcholine as a modulator of neuronal development has been investigated. At first, a choline acetyltransferase construct was transfected into a neuroblastoma cell line, which is unable to synthesise any neurotransmitters. Next was the stimulation of acetylcholine production, which is followed by enhanced expression of neuronal traits. In rat dissociated retinal cell cultures, small amounts of acetylcholine were discovered spontaneously [22]. This discovery corresponds with amacrine cells regulating ganglion cell fibre elongation through the release of acetylcholine.

Acetylcholine production begins early in motor neuron development, and its potential function in regulating subsequent processes of neuron differentiation and interaction with target cells has been investigated [23]. The initial activation of choline acetyltransferase (ChAT) in development and the availability of quantifiable levels of acetylcholine, and the presence and localization of muscarinic acetylcholine receptors (mAChRs) imply that activation of acetylcholine production in dorsal root ganglia (DRG) might be associated to its ability to regulate neurite elongation, presumably in combination with neurotrophic factors. The ChAT

transfected neuroblastoma clones greatly proposed that acetylcholine acts as a modulator of fibre development [24-26].

3.2. Potential of Dental Stem Cells for Future Pulp Therapy

Angiogenesis and tissue mineralization is the key for formation of new dentin or pulp-like tissue [27]. It is essential for the longevity of tissue-engineered implants that there be a quick recovery of blood flow to the transplant locations. This blood supply acts as a conduit for the transfer of nutrients, the delivery of oxygen, and the removal of metabolic waste. This explanation applies to dentin and pulp regeneration because the opening at the root apex is too tiny for intracanal blood infusion [28]. Long-term engraftment of stem cells may be less effective as a therapy if nutrients and oxygen are not given on time. There is also a chance that transplanted cells could die from lack of oxygen, which is called hypoxia-induced apoptosis.

In the past, it was common practise to wait for access to the transplanted replacement within the canal region and the ingrowth of new vasculature. However, if this technique develops to a dense, multicellular structure that restricts blood flow, it may not be effective. Furthermore, because the host-derived vascular networks take a long time to set up, which consists of the initial migration and proliferation of endothelial cells, the angiogenic sprouting of new blood vessels, and the ultimate phase of vascular stabilisation, it is likely that the bioengineered replacement grafts are likely to fail from ischemia and necrosis before they integrate with host tissue [29]. Pre-vascularization has become an option for treating this problem. With the help of the vessel plexuses made ahead of time, the bioengineered grafts may be able to connect to the vascular system of the host faster after being transplanted.

3.2.1. Hypoxia for Angiogenesis

Hypoxia is a normal occurrence in both pathological and nonpathological circumstances involving tooth pulp tissue. Dental pulp cells (DPCs) are often vulnerable to ischemia when surrounding vascular bundles are extensively damaged in traumatic injuries. In addition, because of their unique anatomical structure, which consists of being surrounded by tough dentin and having a small opening at the apices, they are vulnerable to having their blood supply cut off during the restoration process. This occurs when vasoconstrictors found in local anaesthetics reduce the microcirculation of blood flow. Ischemia disrupts the tooth pulp's oxygen equilibrium by reducing the amount of oxygen that can reach the pulp from the circulation. Furthermore, dental caries' rising inflammatory reactions typically elevate intracanal pressure, forcing the oxygen out. The root canal area has a high oxygen tension even in the absence of pathology. Whereas ex vivo pulp cell growth and expansion are regularly observed, approximately 3% seems to be lower than in ambient air. Consequently, a number of studies have sought to simulate pulp hypoxia in order to examine how DPCs react to low oxygen levels.

Amemiya [30] made the observation that when canine DPCs were subjected to hypo oxygenation circumstances, they formed more formazan and expanded quicker than pulp cells that were cultured in normoxic conditions. Following that, many studies on human dental pulp cells (hDPCs) discovered that those grown in hypoxic settings exhibited higher rates of proliferation, higher proportions of side populations, stronger angiogenic potential, and higher in vitro erythropoietin expression compared to normal conditions [31, 32]. The odontogenic capacity of hDPCs was proven in vitro and in vivo when they were efficiently isolated by Iida [33] from inflamed teeth of elderly adults exposed to hypoxia. Recent research discovered extensive vessel-like networks emerging in a stem cells from apical papilla (SCAP)-

human umbilical vein endothelial cells (HUVEC) coculture group under hypoxic settings, as well as that the created hypoxic environment drastically boosted the production of hypoxia-inducible factor-1 (HIF1), ephrinB2, and vascular endothelial growth factor (VEGF) [29]. Hypoxia may be a practical and efficient technique for priming the reparative pulp tissue angiogenic potential of dental pulp stem cells and regeneration and improving the possibility of separating healthy DPCs from pulp tissue that has been destroyed or replaced.

3.2.2. Scaffoldless Delivery Approach with Cell Sheet Technology (CST)

Stem cells are often pre-mixed with foreign scaffold materials to create a 3D built structure before being implanted into target areas. Due to poor cell migration and retention inside the supporting scaffolds, which exacerbates the issues associated with biomaterials, this well-known method has been questioned for quite some time. The presented biomaterials cannot, in general, mimic native extracellular matrix (ECM) or implanted device surfaces. Using a 3D in vitro culture method, Iohara [34] created DPCs over a decade ago. This method just requires one round of centrifugation to remove cell pellets or aggregates, which is a significant improvement over the prior methods. Odontogenic differentiation and extracellular matrix (ECM) accumulation were both significantly higher in the 3D pellet than in the monolayer culture. DPC pellet transplantation with recombinant human bone morphogenetic protein-2 (rh-BMP2) therapy effectively promoted dentin synthesis in canine tooth pulp following amputation [34]. Since the centrifugation stage may add extra force that changes how cells behave, Syed-Picard [35] came up with a self-assembly method where cells can build and keep their preferred 3D microenvironment on their own. This three-dimensional, self-assembled device was implanted into the canal space of human tooth root segments, where it proceeded to create vascularized dental pulp-like tissue in SCIDM [35].

Cell sheet technology (CST), a comparable but distinct novel "scaffold-free" technique created for regenerative medicine has lately been a main focus of current periodontal tissue development research [36-38]. Thermoresponsive polymers, such as poly (ethylene glycol), are the basis of CST, which is a non-invasive technique (N-isopropylacrylamide) (PIPAAm). Unlike conventional methods of cell separation, which often include the use of dissociative enzymes or mechanical forces, this method does not compromise cell viability in the process. Just a small temperature shift is required to remove cells that have been grown in a continuous monolayer while maintaining their structure and extracellular components on a PIPAAm-treated surface [39, 40]. However, necrosis is likely to occur in the graft if ECM is not deposited and nutrients are not acquired, as cell sheets in such a restricted tubular space are difficult to manipulate. Na et al. successfully regenerated pulp tissue throughout a complete empty tooth canal by transforming a cell sheet structure into a more malleable 3D pellet system using a cell sheet derived pellet (CSDP) and ectopic implantation into SCIDM [41]. While these findings are intriguing, a more in-depth in-vivo study of the scaffoldless administration strategy in big animal models is still needed.

3.2.3. Dentin and pulp tissue regenerate locally after pulpotomy.

According to Shimizu [42] and Julovi [43], hyaluronic acid (HA), a glycosaminoglycan that is found in large amounts in the human body, is known to play important roles in maintaining shape and reducing inflammation. It is also a good material for tissue engineering [44]. They conducted in vitro and in vivo investigations to determine if HA sponge is beneficial as a scaffold for dentin-pulp complex regeneration treatment and discovered that it has all of the required properties [45]. Local regeneration of the dentin-pulp complex following pulpotomy in older teeth may be challenging, in contrast to young teeth, which have plentiful blood supply and

cells. Nonetheless, establishing the optimum growth factor combination and developing a delivery mechanism for growth factors and cell scaffolds will boost dentin-pulp complex regeneration treatment after pulpotomy [46].

3.2.4. Cell homing strategy for pulp regeneration

Activation of stem/progenitor cells from the periapical tissue around the apical region of the root facilitates cell homing. Growth factor-impregnated scaffolds are placed into root canals through an enlarged apical foramen to encourage endogenous stem/progenitor cells situated close to the root apex to migrate, multiply, and differentiate [47]. Since it is not necessary to identify or manipulate stem cells in vitro, cell homing may be simpler to implement in clinical settings than cell transplantation [47]. Adult teeth, unlike embryonic teeth, lack pluripotent dental papilla cells. This strategy may rely on the development of novel techniques for producing stem cells surrounding the root apex, including periodontal ligament stem cells [48].

3.2.5. Potential role of NETs (Neutrophil Extracellular Traps)

Lately, neutrophil extracellular traps (NETs) were revealed as a new bacterial killing mechanism that involves reactive oxygen species signalling and resulting in cellular DNA extrusions, leading to microbial entrapment and death [49]. The assessment of their levels inside diseased pulp might be used to target the implementation of innovative disease management techniques. They may be useful in managing pulpal infections. More study is needed to determine how these structures affect the pulp's vitality and healing responses [50].

3.2.6. Low-intensity pulsed ultrasound (LIPUS) treatment

LIPUS treatment may activate mesenchymal stem cells (MSCs) in dental tissues, providing a therapeutic method for promoting dental tissue regeneration. [51]. The process is not entirely understood; however it is thought to be due to non-thermal biomechanical effects. LIPUS, in particular, may impact the cytoskeleton and cell membrane to initiate downstream signalling processes via acoustic microstreaming and physical radiation. As a result, this simple and low-cost method may give an appropriate treatment in the dental clinic for the dental tissues regeneration [52].

4. Discussion

In this review, we chose articles that contained important information about the relationship between neurotransmitters and stem cells for the future dental pulp regeneration. Only a few studies were investigating the role of neurotransmitters on the regeneration of dental pulp, and we had to include studies related to the interaction of neurotransmitters on stem cells proliferation.

Baudry, Alleaume-Butaux [15] demonstrated the presence of serotonin (5-HT) and dopamine (DA) autoreceptors in pulpal stem cells, indicating a dual bioaminergic identity. It was discovered that to mobilise endogenous stem cells for tooth healing, active blood platelets in injured pulp must produce both 5-HT and DA. Further research revealed that systemic 5-HT and DA signals are required for the development of stem cells containing 5-HT and DA receptors, which are essential for tooth repair in vivo. Lee, Yi [20] proposed that PDLSCs cultivated on PDA film may have increased cell proliferation and osteogenic potential due to an interaction between integrins and PI3K. Dopamine polymerization at alkaline pH circumstances led to the formation of the PDA coating, which was then linked to the simultaneous adsorption of several biomolecules and the attachment of cells.

Furthermore, Rim [53] showed that human MSCs cultivated on PDA-coated poly (L-lactide) (PLLA) fibres showed greater osteogenic differentiation than MSCs cultured on non-coated PLLA fibres. Research on the function of acetylcholine in embryonic stem cell survival, proliferation, and death by Landgraf, Barth [24] claimed that ACh increased the survivability of embryonic stem cells but inhibited cell proliferation. They demonstrated that ACh might regulate cell death and proliferation by attaching to particular receptors on stem cells.

From the three neurotransmitters written in this review, both 5-HT and DA are capable in enhancing cell proliferation while ACh decreases the proliferation. Thus, further studies focusing on dental pulp regeneration with 5-HT and DA can be conducted in the future. Overall, additional studies in the field of regenerative dentistry should continue in order to achieve significant accomplishment on dentin and pulp regeneration.

5. Conclusion

Dental stem cell research is emerging and progressing significantly as a promising tool for tooth regeneration in regenerative dental medicine. From this review, the discovery of the interaction of neurotransmitters with dental stem cells raise expectations for tooth pulp repair and regeneration. The data suggests that neurotransmitters contribute to the increase in stem cell proliferation. Neurotransmitters and dental stem cells may hold the key to improving dental treatment in the future, although further study is needed to determine this.

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