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An overview of the dental pulp: its functions and responses to injury

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Abstract

The dental pulp is a unique tissue and its importance in the long-term prognosis of the tooth is often ignored by clinicians. It is unique in that it resides in a rigid chamber which provides strong mechanical support and protection from the microbial rich oral environment. If this rigid shell loses its structural integrity, the pulp is under the threat of the adverse stimuli from the mouth, such as caries, cracks, fractures and open restoration margins, all of which provide pathways for micro-organisms and their toxins to enter the pulp. The pulp initially responds to irritation by becoming inflamed and, if left untreated, this will progress to pulp necrosis and infection. The inflammation will also spread to the surrounding alveolar bone and cause periapical pathosis. The magnitude of pulp-related problems should not be underestimated since their most serious consequence is oral sepsis, which can be life threatening, and hence correct diagnosis and management are essential. Clinicians must have a thorough understanding of the physiological and pathological features of the dental pulp as well as the biological consequences of treatment interventions.

Key words: Dental pulp, pulp disease, inflammation, necrosis.

Abbreviations and acronyms: CGRP = calcitonin gene-related peptides; IL = interleukins; PBF = pulp blood flow; SP = substance P; TTXr = tetrodotoxin-resistant; TTXs = tetrodotoxin-sensitive.

INTRODUCTION

The dental pulp resides in a rigid chamber comprising dentine, enamel and cementum, which provide strong mechanical support and protection from the microbial rich oral environment. However, if this rigid shell loses its structural integrity, the pulp is under the threat of the adverse stimuli from the mouth. Caries, cracks, fractures and open restoration margins provide pathways for micro-organisms and their toxins to enter the pulp. The response of the pulp to irritation is inflammation and, if unattended, this will eventually progress to pulp necrosis. Inflammation may spread to the surrounding alveolar bone and cause periapical pathosis. The magnitude of pulp-related problems should not be underestimated. The most serious consequence of pulp disease is oral sepsis, which can be life threatening.[1,2] If the infection spreads from the maxillary teeth, it may cause purulent sinusitis, meningitis, brain abscess, orbital cellulitis and cavernous sinus thrombosis, whereas infection from the mandibular teeth may cause Ludwig's angina, parapharyngeal abscess, mediastinitis, pericarditis, emphysema and jugular thrombophlebitis. Moreover, the number of teeth that are extracted result in mutilated dentitions, malnutrition and possible emotional problems.

Toothache is a common complaint in the dental clinic, and yet diagnosis of pulp disease is often difficult due to the seemingly unclear symptoms and the inaccessibility of the pulp for clinical tests. This is further complicated by referred toothache originating from the tissues other than the pulp. Improper diagnosis can lead to improper treatment, causing distress to the patient and embarrassment to the practitioner. An understanding of the histophysiology of the healthy pulp and the possible underlying pathological processes in the diseased pulp, careful assessment of the pain history, and appropriate clinical examination and diagnostic tests, should aid the dental practitioner in reaching an accurate diagnosis and a positive treatment outcome.

The dental pulp and its nature

The dental pulp derives from neural crest cells (the ectomesenchyme). Proliferation and condensation of these cells lead to formation of the dental papilla from which the mature pulp is derived. The mature pulp bears a strong resemblance to the embryonic connective tissue, with a layer of highly specialized cells, the odontoblasts, along its periphery.[3] The physical confinement of the dental pulp, its high incidence of sensory nerve innervation and the rich microcirculatory components make the dental pulp a unique tissue. Knowledge of the normal pulp function, its components and their interaction is necessary to provide a framework for understanding the changes that occur in diseased pulps.

Functions of the dental pulp

A fundamental question that needs to be addressed is whether the dental pulp is necessary in a fully formed

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tooth. One can argue that the tooth can continue to function normally after the pulp is removed and replaced with a root canal filling. In such situations, the circulation of the periodontal ligament and the surrounding tissues will support a pulpless or an endodontically treated tooth.

A recent study on the bacterial invasion into dentinal tubules of human teeth with or without viable pulp has shown that teeth with pulps are much more resistant to bacterial invasion into the dentinal tubules than are teeth with root canal fillings.[4] In the latter, bacteria are able to enter teeth and reach the root canal system in a relatively short period of time.[4] Hence, the pulp plays an important role in this defense process. In teeth with pulps, the dentinal tubules are occupied by dentinal fluid and odontoblastic processes, which may behave collectively as a positively charged hydrogel.[5,6] The hydrogel is capable of arresting a great number of the bacteria that enter the pulp. The outward flow of the dentinal fluid is important in the pulp's defense against the entry of harmful substances because it affects the rate at which toxic substances from the mouth diffuse into the dentinal tubules.[7,8] Moreover, antibodies or other antimicrobial agents may be present within the dentinal fluid in response to bacterial infection of the dentine.[3] The possible build-up of immune complexes and the precipitation of high molecular weight plasma proteins, such as fibrinogen, in the dentinal fluid may reduce the functional radius of the dentinal tubules and hence reduce the dentine permeability.[9]

The pulp's specialized cells, the odontoblasts, and perhaps undifferentiated mesenchymal cells (which may differentiate into dentine-forming cells if stimulated), retain the ability to form dentine throughout life. This enables the healthy pulp to partially compensate for the loss of enamel or dentine caused by dental caries or tooth wear through the formation of a hard tissue barrier that isolates irritants from the remaining pulp tissue. Secondary dentine is deposited circumferentially at a very slow rate throughout the life of a normal tooth. The odontoblasts secrete the dentinal matrix and retreat toward the pulp center. They become crowded and their direction can be altered. The dentine thus produced is "wavier" and contains fewer tubules. Odontoblasts may also form sclerotic dentine, reactionary dentine and reparative dentine in response to adverse stimuli, such as caries or operative procedures. In sclerotic dentine, the dentinal tubules become partially or completely filled with mineral deposits consisting of hydroxyapatite and whitlockite crystals, resulting in a decrease in the permeability of the dentine. However, for sclerosis to occur, viable odontoblast processes must be present within the tubules. In reactionary dentine, the tubules are continuous with the primary dentine and extend down to the odontoblasts. Reparative dentine occurs at the pulp surface of primary or secondary dentine and it will be localized to the site of irritation. It forms proportionally to the amount of primary dentine destroyed. The rate seems to depend inversely on the rate of carious attack; that is, more dentine is formed in response to slowly progressing carious lesions. The tubules in the reparative dentine are irregular or frequently absent, which makes it less permeable to external stimuli. Cells forming the reparative dentine are thought not to be the primary odontoblasts but are derived from the cells deeper in the pulp such as fibroblasts in the cell-rich zone, endothelial cells or pericytes of the blood vasculature which are differentiated upon the stimulation by tissue growth factor-β.[10,11] The reparative dentine, especially at the junctional zone between primary and secondary dentine, has low permeability and may block the ingress of irritants to the pulp.

Pulp is equipped with the cellular components necessary for the initial recognition and the subsequent processing of antigens hence its ability to elicit an immune defense reaction.[12-15] The main immune cells in a normal pulp are peripheral T cells (helper/inducer and cytotoxic/suppressor). The major antigen presenting cells in the dental pulp are the dendritic cells located primarily in the odontoblastic layer.[16] These cells uptake, process, and present foreign antigens as HLA-DR antigens on the cell surface to $CD4^+$ T-lymphocytes. Other antigen-presenting cells are similar to macrophages and are located in the more central portions of the pulp. In rat incisors, Class II antigen activated macrophages are four times more common than the dendritic cells.[14] It is noteworthy that the normal dental pulp does not appear to have B cells.[15]

Pulp is also a sensory organ. Its sensitivity to thermal stimuli is well recognized.[17] Regardless of the nature of the sensory stimuli, such as thermal change, mechanical deformation or trauma, the pulp registers different impulses as a common sensation, i.e., pain. Such pain-registering ability is important as part of the defense mechanisms of the pulp. Patients with an inflamed pulp tend to seek treatment earlier while the injury is confined within the tooth, as opposed to those whose teeth have been root-filled where the pain sensation will not be experienced until substantial damage has occurred in the tissues surrounding the root. In addition, the proprioceptive function of the pulp limits the load imposed on teeth by the masticatory muscles, thus further protecting the tooth from injury.[18,19]

Odontoblasts

The odontoblasts are unique cells. Whilst the cell body of other mineral forming cells is close to the cell process and stays within the calcified matrix, the cell process of odontoblasts extends a considerable distance into the dentine matrix and perhaps all the way to the outer boundary of the dentine in some cases while the cell body remains in the pulp at the inner boundary of the dentine.[20] In other words, the cell process extends some distance from its nutritional and controlling centre. The odontoblastic process is extremely fine and

resides within a dentinal tubule, which is like a capillary tube with a diameter that is much smaller than that of an erythrocyte. Microtubules and microfilaments are the principal components of the process, providing infrastructure for transportation from the cell body to the remote cell process.

In addition to a role in forming dentine, odontoblasts may be involved in sensory transduction.[21] The presence of tight, adhering and gap junctions may imply that these cells communicate with each other; and if one is affected, many others are also affected. Gap junctions exist between and among odontoblasts and nerve fibres,[22,23] and they provide a pathway of low electrical resistance between and among the odontoblasts and nerve fibres. The hydrodynamic effects of fluid displacement within the dentinal tubules or the odontoblasts may activate mechanoreceptors of sensory nerve axons.[24] The odontoblast itself may be capable of mechanotransduction by stretch-activated ion channels in the cell membrane.[25] Odontoblasts are also implicated in the regulation of pulp blood flow and in the development of pulp inflammation. The enzyme NADPH-diaphorase involved in the production of nitric oxide, a potent vasodilator, is present in the odontoblasts.[26,27] Their capacity to synthesize the inflammatory mediator PGI_2 has been demonstrated and this may excite nerves in the vicinity resulting in a brief hyperalgesia.[28]

Although there is abundant information on the structural aspects of odontoblasts, very little is known about the dynamic aspect of these cells, especially in the mature pulp. Forming and maintaining dentine involves active transportation of calcium ions, collagen precursors or components of the extracellular matrix from the pulp proper to the long process,[20] an activity that presumably requires energy and hence oxygen. An *in vitro* respiratory study using the direct method of Warburg has demonstrated significantly higher oxygen uptake in the peripheral regions of bovine molar pulps, indicating that odontoblasts may have a high oxidative metabolism.[29] A study with an *in vitro* culture system has demonstrated that a large amount of oxygen is essential for maintaining proper functions of odontoblasts.[30] Using oxygen-sensitive micro-electrodes, it has been shown that odontoblast cells consume a relatively high amount of oxygen in the rat incisor pulp *in vivo*.[31] The average oxygen consumption rate of the odontoblasts obtained from that study is 3.2mL/O_2/min/100g tissue, which is comparable with that of the brain.[32] Furthermore, a transmission electron microscope study has shown that odontoblasts are the cells most sensitive to ischaemia.[33] Odontoblasts in the pulp horn of rat molars with experimentally-induced hypoxia retain tritiated misonidazole, a marker preferentially labeling cells with hypoxia.[34]

The earliest signs of pulp reaction to insults (such as dental caries) are morphological changes and an overall reduction in the number and size of odontoblast cell bodies.[35] The disruption in the underlying odontoblast cell layer occurs even before the appearance of inflammatory changes in the pulp.[36] An electromicroscopic study on the ultrastructural changes of ischaemic pulps induced experimentally by extraction has shown that distinct cellular changes, such as chromatin clumping, irregular nuclear membrane and swollen mitochondria, appear in odontoblasts as early as one hour after extraction.[37] Although no explanation has been offered for the vulnerability of odontoblasts to insults, it can be speculated that the lack of oxygen due to circulatory disturbance during pulp inflammation may be the main contributing factor.

Pulp microcirculation

The resilience to noxious insults and the inherent healing potential of the dental pulp is well recognized. Since the pulp is relatively incompressible, the total volume of blood within the pulp space cannot be greatly increased. Hence careful regulation of pulp blood flow is of critical importance and alterations in pulp microcirculation may be the first to occur with the onset of pulp inflammation.[3,34,38]

In general, the pulp microcirculation is supplied through the maxillary artery, which is a branch of the external carotid artery. The maxillary artery leads into the dental artery and enters the tooth via arterioles feeding each individual pulp microvasculature. Pulp vessels are arranged in a hierarchical system:[39-41] the arterioles course up centrally and give off branches to form a capillary network at the periphery of the pulp and the blood drains into venules at the centre of the pulp. The capillary network provides the odontoblasts with a rich source of nutrients. The vascularity of the pulp is comparable with that of the most vascular parts of the brain and the tongue, indicating that the pulp is a highly vascular tissue.[42] One study has shown that pulp vessels are immune to artherosclerosis in monkeys.[43]

The dental pulp has a relatively high blood flow. It is estimated to be 40–50ml/min/100g of pulp tissue in a mature tooth as determined by radioactive microsphere techniques.[44-46] This flow is relatively high, compared to that of other oral tissues and skeletal muscle.[47] Numerous shunt vessels have also been observed in the dental pulp, although their function is less well understood.[39,48] These vessels can be arterio-venous anastomoses, venous-venous anastomoses or U-turn loops. They provide a direct communication between arterioles and venules, hence bypassing the capillary bed. Considerable shunting occurs in the apical half of the pulp.[48] When the intrapulpal pressure rises during inflammation, these shunt vessels may open up to reduce the intrapulpal pressure so that the normal blood flow is maintained.[49]

Special features of the pulp with respect to its circulation

The dental pulp has an unusual combination of features that makes its circulation rather unique.

Firstly, the compliance of the pulp is low because it resides in a rigid, unyielding calcified wall. A near simultaneous increase in pulp tissue pressure has been recorded as a result of vasodilatation.[50] Because capillary dilation and the transudation of fluids that comprise the early stages of acute inflammation increase the volume of tissue, such swelling in the dental pulp is likely to cause a pressure increase that stimulates pulp nerves to register pain. Secondly, the dental pulp is a firm and resilient connective tissue, composed principally of a gelatin-like material, such as proteoglycans and other glycoproteins, reinforced throughout by irregularly arranged and interlaced collagen fibres. The resilient ground substance limits intrapulpal pressures to the site of irritation, and is not transmitted throughout the pulp space.[51] Significant pressure differences have been observed at sites only 1 to 2mm apart.[52] Pressure from the increased tissue fluid collapses the thin-walled veins and venules only in the area of the affected pulp tissue, causing a localized vascular stasis and ischaemia, resulting in local cellular death. The gelated extracellular matrix may also act as a barrier against the spread of micro-organisms and toxic products. However, the inflammatory process and resultant intrapulpal pressure changes may progress apically by increments circumferentially from compartment to compartment. When the structural integrity of the pulp tissue is lost with overwhelming inflammation, the increased tissue pressure can spread with a resultant compression of the blood vessels at the apex and result in total necrosis.[53] Thirdly, although the dental pulp is a rich vascular tissue, terminal arteries supplying it fall within the microcirculatory diameter range.[3] Unlike in most tissues, the pulp circulation lacks a true collateral blood supply. This restricted blood source may presumably limit the blood supply to the dental pulp, making it less capable of overcoming a severe irritant than other better-supplied tissues. Fourthly, because the tooth bridges between the bacteriologically sterile environment of the jawbone and the heavily contaminated environment of the mouth through an oral epithelial membrane, diseases in the pulp will invariably extend through the apical foramen into the surrounding bone causing further problems.

As a consequence of these features, the degree of pulp inflammation does not necessarily need to be severe to cause pulp death, and if left untreated, progression to the surrounding alveolar bone is likely to occur. Hence, careful regulation of the pulp microcirculation seems to be critically important in order to maintain the well-being of the pulp. The fact that most pulps survive life-long exposure to various inimical attacks implies the presence of a well-regulated microcirculation in the pulp.

Functions of the pulp microcirculation

The primary function of the pulp microcirculation, in common with all circulation in the body, is to supply oxygen and nutrients to its constituent cells, as well as providing an exit route for metabolic waste products from the tissue. Blood is brought to the tissue through pulp arterioles. Oxygen, nutrients and wastes are exchanged in capillaries by diffusion, and waste products are removed by pulp venules. In general, blood flow to any organ must be high enough to ensure sufficient oxygen and nutrient supply. On the other hand, an excessively high blood flow level is undesirable as it leads to a waste of energy. Hence, it is plausible that the main purpose of the relatively high blood flow in the pulp is to serve the pulp cells, perhaps the odontoblasts in particular, with important nutrients in an adequately high concentration in the capillary bed.

The pulp microcirculation also acts to maintain an intraluminal pressure within the pulp vasculature in harmony with the pulp tissue pressure. Studies using servo-nulling techniques have demonstrated that the dental pulp has a relatively high tissue pressure but it is considerably lower than the blood pressure inside the vessels.[54] Bulk flow of fluid occurs across the capillary walls for distribution of the extracellular fluid. Positive net capillary filtration pressure leads to bulk flow of fluid out of the capillary into the extraluminal tissue space, which in turn is balanced by an equal lymphatic return.[55,56] Thus, the tissue fluid volume in the pulp remains constant. The relatively high pulp tissue pressure results in an outward flow of fluid in the dentinal tubules, which helps to dilute toxins and wash out bacteria.

Control of pulp blood flow

There has been some disagreement as to whether the pulp microcirculation is capable of functional regulation. Pulp blood flow in anaesthetized animals is dependent on alterations in systemic blood pressure.[57] Stealing perfusion of the surrounding tissues has been implicated in the paradoxical decrease in pulp blood flow in response to arterial infusion of well-known vasodilators in other circulations.[58] "Stealing" of the blood supply to the dental pulp is thought to occur when vasodilation of the neighbouring tissues reduces the perfusion pressure to the pulp, thus producing a decrease in the blood flow to the pulp.[58] However, the passive view of pulp microcirculation has been challenged by a body of *in vivo* data: topical application or close intra-arterial bolus injection of various vasoactive substances alter pulp blood flow while systemic blood pressure is unaltered.[38,59-62] Pulp blood flow in anaesthetized animals of several species is under the influence of local nerve impulses unrelated to systemic haemodynamics.[63] Perivascular sympathetic nerve fibres liberate noradrenaline and possible neuropeptide Y causing a reduction of pulp blood flow,[64-67] whereas intradental sensory nerves liberate neuropeptides causing an increase in pulp blood flow.[50,68-71] Reflex excitation of the sympathetic nervous system causes pulp vasoconstriction and a reduction in pulp blood flow.[72] Reflex activation of sensory axons causes pulp vasodilatation spreading beyond the site stimulated as

a result of branching of sensory axons.[73] Beaded nerve terminals are found in intimate association with smooth muscle in the walls of arterioles and venules. The peri-vascular nerve endings are adrenergic post-ganglionic fibres containing noradrenaline, or somatosensory nerve fibres containing substance P or calcitonin gene-related peptides.[74,75] These nerve fibres appear to participate in the regulation of the pulp blood flow by affecting vascular smooth muscle tone, thereby changing vessel diameter. Pulp blood flow is hence considered to be predominantly under neural control.[63]

The possible existence of a local vascular regulation in the pulp has been proposed recently.[76-79] It is important in the confined and restricted circulation that microvascular tone is modulated locally to match the nutrient flow and tissue demands. Using an isolated pulp arteriole preparation combined with *in vivo* measurement of pulp blood flow and pulp oxygen tension, it has been demonstrated that the pulp vasculature is capable of responding to a range of vasoactive mediators and the pulp microcirculation may be controlled locally by endothelium-related factors, metabolic (tissue-related) factors, as well as humoral (blood-borne) factors.

It is important to study the pulp microcirculation because of its brave but limited success in dealing with injury in a restricted low compliance environment. Studies of oxygen tension in the tissue and the individual properties of the pulp vessels will help to understand the mechanism that leads to necrosis in hypoxia and anoxia following vessel collapse after progressive spread in raised interstitial fluid pressure. Two practical outcomes of this understanding would be the discovery of therapeutic agents and strategies that could help the pulp survive, and the developments of techniques for measuring pulp blood flow clinically such that a true diagnosis of the presence and extent of pulp inflammation could be made. Both outcomes may enable practitioners to diagnose and treat pulp diseases at an early stage.

Pulp nerves

The dental pulp contains both sensory and autonomic nerves to fulfill its vasomotor and defensive functions.[75,80-84]

Sensory nerves

The sensory nerves, which are involved in pulp pain perception and transduction, are branches of the maxillary and mandibular divisions of the trigeminal nerve. The small branches enter the apical foramina and progress coronally and peripherally following the route of the blood vessels, and they branch extensively subjacent to the cell-rich zone, forming the plexus of Raschkow. The plexus contains both large myelinated A-δ and A-β fibres (2–5μm in diameter) and the smaller unmyelinated C fibres (0.3–1.2μm). At about the level of the cell-rich zone, myelinated fibres lose their myelin sheath. In the cell-free zone, they form a rich network of free nerve fibres that are specific receptors for pain. From there, the free nerve terminals may enter the odontoblastic layer, and penetrate into the predentine zone or to the inner dentine next to the odontoblastic cell process, but not every dentinal tubule will contain nerve endings. Myelinated nerves do not reach their maximal development and penetration into the pulp until the tooth is fully formed, which may explain why young teeth are less sensitive than adult teeth. The branching of nerve axons has been observed not only within the pulp but also occurs in the periapical region where these axons may branch to supply the pulps of adjacent teeth just prior to entering the pulp.[85]

It has been postulated that the A-δ and A-β fibres produce the initial rapid sharp pain in response to external stimuli without the presence of tissue injury because of their peripheral location, low threshold of excitability and fast conduction. On the other hand, the smaller C fibres cause a slow, dull and crawling pain related to pulp tissue damage and the inflammatory process due to their much higher threshold of excitability and slow conduction. Almost all of the A-δ fibres are located in the coronal portion of the pulp, with the greatest nerve density in the pulp horns. In contrast, C-fibres are located in the pulp proper, extending most likely into the cell-rich zone.[86]

Pulp usually responds to various stimuli as one sensation, i.e., pain. However, the exact mechanism that transmits the stimuli through the dentine to initiate pain is largely unknown.

Several hypotheses about dental pain transmission have been proposed including hydrodynamic mechanism, odontoblastic transduction and dentine innervation.

Among these hypotheses, the hydrodynamic theory enjoys the most popularity.[7] The free nerve endings at the periphery of the pulp are exquisitely sensitive to sudden pressure changes and fluid movement. The dentine contains thousands of capillary-like tubules that are filled with water-like dentinal fluid. A stimulus such as cold or compressed air will extract tubular fluid from its outer surface and cause an outward flow whereas other stimuli, such as heat or chewing pressure on a loose filling, will drive the tubular fluid inward towards the pulp. This rapid fluid movement, either inward or outward, exerts a direct mechanical deformation on the low-threshold A-δ fibres within the tubules or in the subjacent pulp tissue. The fluid movement may also cause a concomitant movement of odontoblasts, which may in turn deform nerve fibres in contact with their process or cell body. The deformed nerve membrane increases its permeability to Na^+ ions. The rapid inward movement of the sodium depolarizes the A-δ fibre membrane, and an action potential (pain impulse) is initiated.

The dentine innervation theory postulates that nerve endings penetrate dentine and extend to the dentino-enamel junction. Direct mechanical stimulation of these nerves will initiate an action potential. Free nerves have

been demonstrated to penetrate into the dentine, but these nerves are confined to the inner one-third of dentine. Moreover, pain producing substances such as bradykinin fail to induce pain when applied to dentine, and bathing dentine with local anesthetic solutions does not prevent pain.

The transduction theory states that odontoblasts can transduce a mechanical stimulus and transfer that signal to a closely opposed nerve terminal. Odontoblasts are derived from the neural crest and their cellular processes extend into the dentinal tubules which extend to the dentino-enamel junction. Odontoblasts communicate with each other via gap junctions, and are closely associated with nerve terminals. Nonetheless, odontoblasts are matrix-forming cells and hence they are not considered to be excitable cells, and no synapses have been demonstrated between odontoblasts and nerve terminals. That is, they have no means of chemical transmission.

Dental pain is also modulated and influenced by the higher centres in the body. It is a subjective experience and to a great extent depends on psychological phenomena. The precise mechanism for the transmission of pain and the specific pathway to the higher centre is not completely understood. The gate control theory has been proposed but it is still speculative.[87] This theory suggests that there is a gating mechanism in the substantia gelatinosa of the spinal cord and brainstem on which both peripheral nerve fibres and descending central influences exert their effect in the pain experience.[88] Depending on the degree of activity in large diameter and small diameter afferent nerve fibres, the gating mechanism either inhibits or facilitates transmission of impulses: the large diameter fibres are activated by non-noxious stimuli and close the gate, whereas the small diameter fibres are activated by noxious stimuli and open the gate. Descending control mechanisms from higher central nervous centres, such as cognitive, motivational and affective processes, also modulate the gate. Ascending pain pathways, the sensory-discriminative pathway, allows localization of pain and reticular information pathway deals with the unpleasant, aversive and emotional aspects of pain.

Sympathetic nerves

A sympathetic adrenergic vascular control exists in the dental pulp.[89] Mediators presently known are noradrenaline and neuropeptide Y. The sympathetic nerve fibres originate from the cervical sympathetic ganglion, and after joining the trigeminal nerve at its ganglion, most of them follow the course of the sensory nerves to the teeth, or they possibly travel via the blood vessels. Sympathetic vasoconstriction is typically activated by stress stimuli and by painful stimuli directed at almost any part of the body. Sympathetic vaso-constriction may modulate the excitability of the sensory nerves. In the compromised pulp, sympathetic vaso-constriction is attenuated. Local sensory vasodilation becomes predominant, which may contribute to further progression of pulp inflammation.[63]

Neurogenic inflammation

Activation of sensory nerves in the pulp (either by electrical stimulation of the inferior alveolar nerve or directly on the tooth crown) induces a long-lasting blood flow increase in the pulp and increased vascular permeability. Furthermore, excitation of A-δ fibres seems to have an insignificant effect on pulp blood flow (PBF), whereas C fibre activation causes an increase in PBF. Neurogenic inflammation is thought to be mediated by neuropeptides released from sensory nerves, such as substance P (SP) and calcitonin-gene-related-peptides (CGRP), and possibly the reactive oxygen species at the site of inflammation.[59,63,79,90,91] However, little is known about the correlation between the symptoms and levels of neuropeptides in the pulp except that the amount of

Table 1. Common causes of pulp disease

Group	Type	Examples or reasons
Microbial	Coronal ingress	Caries, marginal breakdown of restorations, fractures, cracks
	Radicular ingress	Advanced periodontal disease, cracks, fractures, breakdown of root canal fillings, advanced external invasive resorption
Traumatic	Accidental	Fractures, concussion, luxation, avulsion, traumatic occlusion
	Physiological	Attrition, abrasion, traumatic occlusion
Iatrogenic	Cavity preparation	Heat, deep cavity, dehydration, pulp exposure
	Restoration procedures	Insertion, fracture, cementing, polishing
	Accumulative	Area of dentine cut
	Prosthetic manipulation	Fixed and removable prosthodontics
	Orthodontics	Tooth movement
	Periodontics	Treatment of deep pockets
	Radiation	Radiotherapy for carcinoma
	General anaesthesia	Trauma during intubation procedures
	Surgery	Rhinoplasty, Caldwell-Luc, dento-alveolar surgery, oral surgery
	Electrical	Galvanic reaction
	Local analgesia	Reduced blood flow due to vasoconstrictors
	Smoking	Reduced blood flow
Chemical	Restorative materials	Material toxicity
	Erosion	Various acids, foods
Others	Ageing	Blood supply reduced
	Systemic diseases	Hypophosphataemia
	External invasive resorption	Advanced cases – pulp may be exposed, or plaque enters through the defect

Table 2. Common reactions of the dental pulp to stimuli

Type of stimulus	Examples	Pulp reaction	Outcome if not treated
Short-term	– Cavity preparation procedures such as cutting dentine, heat produced, drying, etc – Trauma without luxation	Acute inflammation	Healing and recovery (since the stimulus is not continuous or it is removed)
Long-term	– Dental caries – Restoration breakdown – Erosion, attrition – Chemical irritation (i.e. loss of coronal tooth structure or its integrity)	Chronic inflammation	a) Necrosis b) Then infection of the pulp space – bacterial pathway of entry created by the loss of tooth structure c) Once infected, the tooth will eventually become pulpless
Trauma	– Luxation – Avulsion (i.e. any injury that severs the apical blood vessels)	Necrosis	a) Infection of the pulp space if a pathway for bacterial entry is present b) Once infected, the tooth will eventually become pulpless

SP increases with the progression of caries. Furthermore, its expression is significantly higher in painful pulp with large carious lesions than in asymptomatic pulps with similar size carious lesions.[92] Excitatory amino acids have been suggested to activate sensory nerves to release CGRP.[93]

Neuropeptides may also have some modulatory role in the pulp immune defense system.[94] Pulp dendritic cells may interact with T lymphocytes by the generation of cytokines, which up regulate the expression of adhesion molecules on vascular endothelial cells to facilitate immune-cellular infiltration. They may induce transendothelial migration of immunocompetent cells, such as $CD43^{+}$ cells during acute neurogenic inflammation.[95]

Diseases of the pulp

The dental pulp may be exposed to a number of irritants that are noxious to the health of the pulp and jeopardize the functions of the pulp. They may be either constant irritants or specific events that interfere with the pulp blood supply (Table 1). Irritants can be classified as being short-term, long-term or due to trauma. Each type of irritant or injury will have a different effect on the pulp – in general, the effects will be acute inflammation, chronic inflammation or necrosis (Table 2). Short-term irritants will usually cause acute inflammation which will then be followed by resolution of the inflammation and repair of the tissue since the irritant does not persist or is no longer occurring. Common examples of short-term irritants are the cutting or drying of cavities during their preparation and traumatic injuries that have not displaced the tooth so the apical blood supply has not been disrupted. In contrast, typical long-term irritants are dental caries, restorations breaking down, cracks, erosion and chemical substances which all lead to the loss of tooth structure. Long-term irritation will cause chronic inflammation of the pulp and, if left for long enough, pulp necrosis which will then be followed by infection of the pulp space since bacteria will have a pathway by which they can enter the tooth. In these situations, the pathway of entry for the bacteria will be where the tooth structure has been lost. Trauma that causes displacement (luxation or avulsion) of the teeth will result in severing of the apical blood vessels. In teeth with fully developed roots, these blood vessels will often not be able to heal and revascularize the pulp. Therefore, in these cases, the response of the pulp to the injury is immediate necrosis. Subsequently, the necrotic pulp may become infected but this requires that there be a pathway for bacterial entry such as through a crack or fracture. A crack or a fracture may have been created during the same traumatic incident that displaced the tooth so infection is not unusual in these cases. No matter what the cause, once a pulp has necrosed and become infected, in all such cases the bacteria within the root canal system will digest and remove the necrotic pulp so the tooth then becomes pulpless.

Bacteria

Bacterial infection is the most frequent cause of pulp and periapical diseases.[96-101] Bacteria may enter the tooth via caries,[102-105] dental anomalies (e.g., dens invaginatus, deep lingual and palatal grooves), exposed lateral canals or damaged cementum as a result of periodontal diseases,[106,107] tooth cracks or fractures,[108,109] and marginal breakdown at the restoration-tooth interface.[110-113]

Bacterial infections of the pulp space consist of mixed microbial and predominantly anaerobic flora.[114-117] It has been found that *Streptococcus mutans* by itself will not induce pulp inflammation.[114,115] Although several species of bacteria have been identified, there is no absolute correlation with clinical signs and symptoms; and it is noteworthy that the pulp may become inflamed long before the bacteria physically reach the pulp.[103] Superficial caries in pits and fissures may cause pulp inflammation.[118] Substances such as bacterial toxins, enzymes, antigens, chemotoxins, organic acids and products of tissue destruction may diffuse through the dentinal tubules to cause pulp irritation.[99]

The response of pulp to bacteria depends on many factors, such as the speed of bacterial ingress and the speed of progress of caries, which can be slow, rapid or completely inactive (caries tends to be an intermittent

process, with periods of rapid activity alternating with periods of quiescence). Caries progresses quickly through demineralized enamel, but will progress more slowly in demineralized but more organic dentine.[119] In young teeth, bacteria may cause the early death of odontoblasts, and those dentinal tubules devoid of odontoblast cell processes become dead tracts. These tracts are highly permeable, and therefore they are a potential threat to the integrity of the pulp. Fortunately, the healthy pulp responds by depositing a layer of reparative dentine over its pulp surface, thus walling it off. The pulp response is also related to the thickness and degree of calcification of the remaining dentine, since dentine permeability can be reduced by dentinal sclerosis and reparative dentine formation.[104] If the distance between the caries and the pulp is 1.1mm or more, pulp inflammation may be negligible. When the caries reaches within 0.5mm of the pulp, there is a significant increase in the extent of inflammation, but the pulp becomes acutely inflamed only when the reparative dentine is invaded by irritants such as bacteria or their toxins.

Bacterial entry via periodontal pockets is less likely to cause pulp inflammation unless the main apical foraminae are involved in the pocket which contains bacterial plaque.[120]

Trauma

Trauma from accidents or bruxism may cause pulp inflammation. Crown fractures may provide a pathway for microbial invasion[108] which can lead to pulp necrosis and infection of the root canal system. Root fractures affect the pulp differently since they may disrupt the pulp vascular supply within the portion of the tooth that is coronal to the fracture line and this can lead to necrosis of the pulp in that segment of the tooth. However, the rate of survival of the pulp following root fractures is high and the pulp can initiate a callus-like form of healing at the fracture site, especially in immature teeth. Impact trauma may squash the blood vessels at the apex of tooth and cause temporary disruption of blood flow, resulting in vascular stasis with subsequent development of hypoxia and ischaemia. However, a young tooth with a wide apical foramen may recover by re-establishing blood flow. Severe impact (such as intrusion) may destroy the pulp vessels at the apical foramen and lead to pulp necrosis. However, depending on the severity of the impact, the age of the patient and the prior health status of the pulp, revascularization may occur, especially in immature teeth. This usually results in calcification of the root canal in the longer term but occasionally internal resorption has been observed.

Trauma from occlusion can play a role in the initiation and progression of pulp inflammation, however the inflammatory changes tend to be transient.[121,122]

Iatrogenic factors

Paradoxically, the very dental treatment designed to repair the tooth may do harm to the dental pulp. Cavity preparation is a common cause of pulp inflammation. High-speed cutting is superior to low-speed even when air and water coolant are used but some degree of pulp irritation will still occur. Heat, cutting depth (within 0.5mm of the pulp) and dehydration cause damage to the pulp. Pin insertion can crack dentine and predispose the tooth to bacterial infection. Large restorations may cause cracks in teeth when under load. Pressure from condensing restorative materials may intensify pulp responses induced by the cutting procedure. Acid etching, a common procedure in adhesive dentistry, removes the smear layer and this may allow bacteria to enter the dentinal tubules.[123,124] Orthodontic movement, periodontal curettage, and prosthodontic manipulation may also cause pulp inflammation.

Medical procedures, such as rhinoplasty, may damage pulps adjacent to the surgical area or they may interfere with the blood supply to the pulp. The Caldwell-Luc surgical technique, which involves removal of the lining of the maxillary antrum, may also cause pulp inflammation, necrosis or anaesthesia.

Chemical

Most of the current restorative materials are relatively inert. However, it is usually bacteria penetrating the restoration margins which causes pulp inflammation, rather than the chemicals themselves.[113]

Others

Pulps age! With age, nerve and blood supply to the pulp tends to decrease, and the pulp becomes more fibrous and less cellular.[125] As a result, the pulp may become less equipped to mount a defensive reaction to injuries. However, dentine permeability reduces with age as a result of a progressive reduction in tubular diameter and an increase in the formation of peritubular dentine. This provides a more protective environment for the pulp.

The dental pulp usually remains walled off by a thin layer of dentine and predentine until late in the disease process of external invasive resorption. Secondary invasion of micro-organisms into the pulp will elicit pulp inflammation when enough dentine has been destroyed.[126]

Some systemic diseases have dental anomalies. In hereditary hypophosphataemia, the size of the pulp horns tends to increase and dentine is more susceptible to bacterial ingress. Patients with sickle cell anaemia tend to have more frequent toothache which may be due to abnormal blood flow to the pulp.[127,128]

Pathogenesis

Mild and moderate injury to the odontoblast cell processes may produce tubular sclerosis and reparative dentine, but prolonged or severe irritation can cause the death of the odontoblasts and initiation of an inflammatory response. The dynamics of pulp inflammation is not different to that of inflammation in

the periapical and other tissues. Depending on the severity and duration of the irritants, the pulp response ranges from reversible to irreversible pulpitis, then to partial necrosis which leads to total necrosis. This may occur without pain.[129] The dental pulp may also respond to irritation with a range of degenerative changes including fibrosis and calcification.

Inflammation

The initial inflammatory cell infiltrate consists principally of lymphocytes, plasma cells and macrophages. A wide range of non-specific mediators of inflammation such as histamine, bradykinin, serotonin, interleukins (IL) and arachidonic acid metabolites are released in response to bacterial invasion and tissue injury.[130] In addition, many neuropeptides, e.g., substance P (SP) and calcitonin gene-related peptide (CGRP), are also involved and may interact with the mediators produced during inflammation.

The IL-1 and IL-2 producing cells are located within the connective tissue stroma of pulps.[131] Mast cells, which are the main source of histamine, are found in inflamed pulp. A fourfold increase can be found in pulp histamine levels within 30 minutes of thermal injury, suggesting that histamine may play a role in the initial stages of pulp inflammation.[132] Platelets aggregated in the vessels release serotonin, which along with the other inflammatory mediators induce a state of hyperalgesia in the pulp nociceptors. Plasma or tissue kallikreins contact kinogens leading to the production of bradykinin and other kinins to produce many signs and symptoms of inflammation. Phospholipase A_2 causes release of arachidonic acid from cell membranes, resulting in the formation of various prostaglandins, thromboxanes, and leukotrienes.

Immune defense system

In addition to non-specific inflammatory reactions, immunologic responses may also initiate and perpetuate pulp disease. It has been reported that in patients with hereditary combined immunodeficiency, deep caries only produces a mild inflammation and relatively little destruction of the pulp despite the presence of a large number of bacteria.[133] In mild to moderate inflammation, the cell-mediated immunity predominates.[105] In severe inflammation, the appearance of B cells and plasma cells indicates local antibody production, hence the predominance of humoral immunity.[134,135] Specific IgG has been found in pulp with deep caries.[136] Bacterial substances may trigger the complement system via the antigen and antibody complex, which become chemotactic for poly-morphonuclear leukocytes. There is a distinct ratio difference between T-helper and T-suppressor lymphocytes in reversible and irreversible pulpitis. The predominant T-suppressor cells are able to suppress the inflammatory process and reverse the condition in the pulp.

Odontoblasts

As mentioned above, the earliest sign of pulp inflammation is disruption of the odontoblastic layer. Even before the appearance of inflammatory changes in the pulp, there is an overall reduction in the number and size of odontoblast cell bodies. The nuclei of the cells may be aspirated into the dentinal tubules due to the outward flow of tubular fluid, or the cells may be irreversibly damaged which results in the release of tissue injury factors affecting neigbouring odontoblasts and underlying connective tissue. Cells may undergo vacuolization, ballooning degeneration of mitochondria, and reduction in the number and size of the endoplasmic reticulum. However, it is still unknown whether odontoblasts die of apoptosis or necrosis.

Disease progression

The two key components in pulp inflammation are the microcirculation and the sensory nerve activity.[137] Injury to the pulp may activate the intradental sensory nerves to release neuropeptides, which in turn cause alteration of microcirculatory haemodynamics.

The response of sensory nerves to stimuli depends upon the severity of the pulp injury and the stages of inflammation. Within the first few minutes of injury, destruction and disruption of nerve fibres in the injured dentine and pulp occurs, followed by hypersensitivity of the surviving nerve fibres and the release of neuropeptides into the pulp. Inflammatory mediators, such as bradykinin and the prostaglandin E_2, may also evoke the neurosecretion of CGRP.[138]

These neuropeptides cause vasodilatation and increased vascular permeability, hence the neurogenic inflammation. The tissue becomes oedematous as a result of filtration of serum proteins and fluid from the vessels. In the low-compliant environment of the pulp, the increase in both interstitial fluid volume and blood volume leads to an increase in the tissue pressure, which in turn causes compression of the thin-walled venules, resulting in a decrease in blood flow and an increase in flow resistance in the venules. The flow stasis causes an aggregation of red blood cells and an elevation of blood viscosity. It also produces tissue hypoxia or ischaemia, which suppress cellular metabolism in the affected area of the pulp. This results in tissue necrosis. An increase in carbon dioxide and a decrease in pH levels alter the local micro-environment, and may lead to vasodilatation in the adjacent area and the gradual spread of inflammation.

However, it should be remembered that pulp is capable of localizing the inflammation and the tissue adjacent to the inflammatory lesion may be completely normal.[139] If healing is favourable, the increase in tissue pressure may open the shunt vessels and subsequently redirect the blood before it reaches the inflamed region of the pulp.[140] This prevents a further increase in blood flow and tissue pressure. Also the increase in tissue pressure may initiate increased lymph flow and absorption of fluid into capillaries in nearby non-

inflamed tissue.[53,56,139] All these factors will transport fluid away from the affected area and out of the tooth which will consequently lower the tissue pressure. Furthermore, increased tissue pressure will promote outward flow of fluid through exposed dentine tubules and thereby help to protect the pulp against the entry of harmful substances.

Sprouting of sensory nerve terminals and up-regulation of the neuropeptides may also occur.[141,142] It would be expected that sensory nerves participate in the inflammatory process by an increased release of the neuropeptides. The nerve growth factor produced by pulp fibroblasts may mediate the nerve sprouting reactions.

Should the irritant be eliminated or become inactive, tissue granulation becomes predominant as it replaces inflammation and nerve sprouting subsides when reparative dentine covers the injury site. There is a proliferation of small blood vessels and fibroblasts together with the deposition of collagen fibres.

Alternatively, if the irritant overwhelms the pulp's defense ability, blood flow to the area ceases and the injured tissue undergoes necrosis. Neutrophils in the area degenerate and release intracellular lysosomal enzymes to digest the surrounding tissue, forming necrotic tissue. Pulp microcirculation may also be adversely affected by accidental injury or any event that causes long-term interruption of the blood supply to the pulp.[143]

As time progresses, necrotic pulp tissue will become infected by oral micro-organisms penetrating into the root canal system via caries, cracks or marginal break-down of restorations. The microbes will migrate apically through the tooth root and digest the pulp tissue which renders the tooth pulpless.

Thrombi in pulp blood vessels and collagen sheaths around vessel walls may become nidi for mineralization, resulting in pulp calcification. Pulp canal calcification is a protective mechanism to trauma, or other continual stimuli (such as caries). It may be also a normal physiologic response to ageing and genetic predisposition may play a role.

During the transition from pulpitis to necrosis of the pulp, the inflammation in the pulp may transform it into a vascularized inflammatory tissue and this could initiate resorption of adjacent hard tissue by the formation and activation of dentinoclasts. These cells are believed to be derived from undifferentiated reserve connective tissue cells in the pulp stroma or they may be recruited from blood in the general circulation. These cells fuse to form the multinucleated clastic cells that resorb the dentinal wall, advancing through the dentine from the root canal wall towards the periphery until perforation of the root occurs.

Pain

Pain will be present when tissue damage or inflammation is occurring, not after the damage is done.[144] Inflammatory mediators lower the sensory nerve threshold. The increased tissue pressure acts directly on sensory nerve receptors. An increase in pulp blood flow causes excitation of both A-δ and C fibres via an increase in tissue pressure, whereas reduction in blood flow has an inhibitory effect on A-δ fibres due to hypoxia, but no discernible effect on C fibre activity. As a consequence, the gate remains open and stimuli that were not noxious to a normal pulp (such as heat and cold) trigger a more painful response because of the small-fibre activity (unmyelinated C fibres).

During neurogenic inflammation, sodium channel expression shifts from tetrodotoxin-sensitive (TTXs) to tetrodotoxin-resistant (TTXr), leading to hyperalgesia of C fibres.[145] These TTXr sodium channels are relatively resistant to local anaesthetics compared with TTXs channels. In this situation, bupivicaine may be the anaesthetic of choice because it is found to be more potent than lidocaine in blocking TTXr channels.[146]

CONCLUSION

The dental pulp is a unique tissue and its importance in the long-term prognosis of the tooth is often ignored by clinicians. While pursuing technical excellence in endodontics, it is important that clinicians also have an awareness and understanding of the physiological and pathological features of the dental pulp as well as the biological consequences of treatment interventions.

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