

MECHANISMS OF ACTION OF FLUORIDE IN DENTAL CARIES

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INTRODUCTION

The benefits of using fluoride to prevent caries have been known for many years but a complete understanding of this mechanism is still researched'. Scientists have proposed that fluoride have several functions. A predominant part of the cario-static activity of fluoride is a function of its concentration in the fluid environment of the tooth². Fluoride works best when a constant, low level of this mineral is maintained in the oral cavity³. The most important caries inhibitory role of fluoride is topical or post eruptive, although a pre-eruptive role continue to be suggested^{1,4,5,6}.

Fluoride's action in preventing dental caries is multi-factorial; it promotes remineralisation of incipient lesions; increases resistance to acid demineralisation; interferes in the formation and functioning of dental plaque micro-organisms; increases the rate of post eruptive maturation; and alters tooth morphology.

Three principal mechanisms by which fluoride is considered to inhibit dental caries have been identified'.

It reduces the enamel solubility in acid by pre-eruptive incorporation into the hydroxyapatite crystal.

It promotes remineralisation and inhibits demineralisation of early carious lesions. It inhibits glycolysis, the process by which cariogenic bacteria metabolises fermentable carbohydrates.

Pre-eruptive Systemic Effects

From the very beginning of research into fluoride and its relationship with dental caries, it was assumed

that the caries inhibitory action of fluoride was dependent upon the pre-eruptive incorporation of the mineral in the developing dental enamel thereby reducing its solubility in the demineralising acids⁸.

Early fluoridation studies found that caries reduction was greater in children who were born as fluoridation began, when compared to those for whom fluoridation began after birth^{9,10}. At the same time it was also noted that there was caries inhibition in the teeth which had erupted or were erupting when fluoridation began^{11,12}.

By the mid-seventies, it had become evident that the incorporation of fluoride ion in the developing enamel could not by itself explain the reduction in dental caries to the extent that was being claimed¹³. The concentration of fluoride in enamel was actually shown to be very low and poorly correlated with the water fluoride levels¹⁴. From a depth of 2.0 micron, the enamel fluoride level averaged 1700 ppm in non-fluoridated areas, 2200-3200 ppm in optimally fluoridated areas and as high as 4800 ppm in areas where the fluoride level in drinking water ranged between 5-7 ppm¹⁴.

Sub-surface sound enamel generally contain fluoride at levels of about 20-100 ppm depending on the fluoride ingestion during tooth development. Teeth, which develop in a fluoridated drinking water area, have a fluoride content toward the higher end of this range. The outer few micrometers of enamel can have F levels of 1000-2000 ppm¹⁵. Several investigators have shown that fluoride in the solution surrounding the carbonated apatite crystals is much more effective at inhibiting demineralisation than fluoride incorporated into the crystals at the levels found in enamel¹⁶. Featherstone and co-workers^{17,18} found no measurable reduction in synthetic carbonated apatite (3% CO₃ by

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weight, comparable to dental enamel mineral) solubility with about 1000 ppm F incorporated. Very importantly, this means that fluoride incorporated during tooth mineral development at normal levels of 20-100 ppm (even in fluoridated drinking water areas or with the use of fluoride supplements) does not alter the solubility of the mineral. Even at higher levels such as 1000 ppm in the outer few micrometers of enamel there is no measurable benefit against acid induced dissolution.

Only when fluoride is concentrated into a new crystal surface during remineralisation is there a sufficient quantity to alter the solubility of enamel beneficially. However, in laboratory experiments as little as 1 ppm in the acid solution reduced the dissolution rate of carbonated apatite to that equivalent to hydroxyapatite¹⁸. Further increases in fluoride in the acid solution in contact with the carbonated apatite mineral surface decreased the solubility rate logarithmically. These results indicate that if fluoride is present in the solution surrounding the crystals it is adsorbed strongly to the surface of carbonated apatite (enamel mineral) crystal acting as a potent protection mechanism against acid dissolution of the crystal surface. So, if fluoride is present in the plaque fluid at the time that the bacteria generate acid it will travel with the acid down into the sub-surface of the tooth, adsorb to the crystal surface and protect it against being dissolved.

Fluoride present in solution at low levels amongst the enamel crystals can markedly inhibit dissolution of tooth mineral by acid¹⁸. This fluoride comes from "topical" sources such as drinking water, and other fluoride products. The fluoride incorporated developmentally into the normal tooth mineral is insufficient to have a measurable effect on acid solubility¹⁹.

The most revealing study to confirm the above mentioned findings was the Tiel-Culemborg Fluoridation study of Netherlands'. There were lesser carious lesions at the dentine level in the fluoridated Tiel after fifteen years of fluoridation than in the non-fluoridated Culemborg; there was no difference between these communities in the initial enamel lesion. This shows that although fluoride in enamel does not prevent the initial enamel lesion, however fluoride in the drinking water does prevent these initial lesions in progressing into dentinal lesions. The findings of

this study clearly show that fluoride in the oral cavity inhibits further demineralisation of the initial lesion and promotes its remineralisation.

Post-eruptive Systemic Effects

The systemic involvement of fluoride in protection of the enamel does not stop once the tooth has erupted; consumed fluoride is excreted through the saliva and can aid in tooth protection throughout the lifetime¹⁵.

As the saliva flows over the plaque its buffering components (bicarbonate, phosphate and peptides) neutralise the acid produced by the bacteria and the pH rises back towards neutral, at least when there is normal salivary function. This slows down and stops the sub-surface dissolution of the mineral.

Further, the saliva is "supersaturated" with calcium and phosphates providing a driving force for mineral to go back into the tooth²⁰. If the chemistry is right at the partially demineralised crystal surface within the lesion then a new surface grows on the crystal. The partially dissolved crystals act as "nucleators" for remineralisation. Fluoride acts to speed up this remineralisation process by adsorbing to the surface and attracting calcium ions. The newly formed veneer will preferentially take up fluoride from the solution surrounding the crystals and exclude carbonate¹⁹. Consequently this "veneer" will have a composition somewhere between hydroxyapatite and fluorapatite. Fluorapatite contains approximately 30 000 ppm F. The new surface will be "fluorapatite-like" in its properties so that the crystal will now behave like low solubility fluorapatite rather than the high solubility carbonated apatite of the original crystal surface¹⁸. Fluoride speeds up this process, acting to bring calcium and phosphate ions together, and is preferentially included in the chemical reaction that takes place, producing a lower solubility end product.

Post-eruptive Topical Effects

It is well established that fluoride in drinking water reduces dental caries, but does not eradicate it. The role of systemically incorporated fluoride is of very limited value as providing fluoride only before tooth eruption does not afford maximum protection against caries. In fact, topical mechanisms are now considered the primary means by which fluoride imparts protection to teeth^{20,21}.

Topical fluorides are important in caries prevention independent of the provision of systemic fluorides. Fluoride in the drinking water provides fluoride at levels in the mouth, which can inhibit demineralisation and enhance remineralisation, and tip the caries balance towards protection, provided the challenge is not too great. The mechanism of action of fluoride in the drinking water is therefore more important as a topical delivery system. There is considerable evidence that the cariostatic effects of fluoride are, in part, related to the sustained presence of low concentrations of ionic fluoride in the oral environment which decrease the rate of enamel demineralisation and enhance the rate of remineralisation^{19,22,23,24}.

The post eruptive beneficial effect of fluoride likely occurs primarily from the presence of fluoride in the fluid around the tooth surface. Fluoride is responsible for decreasing demineralisation when the tooth is exposed to organic acids and for increasing the rate of remineralisation¹.

The frequency of fluoride exposure to the tooth surface is of prime importance to maintain the high fluoride concentration that is necessary in the fluid around the enamel surfaces to prevent caries and enhance the remineralisation of early carious lesions^{2,21,22}.

Effects of topical fluoride on oral bacteria

In addition to its direct mineralising effect on enamel, fluoride may affect oral plaque bacteria. These bacteria secrete acids onto tooth surfaces (the by-products of carbohydrate fermentation), which initiates tooth demineralisation. The entry of fluoride into the bacterial cell interferes with acid production, thus reducing potential enamel destruction²⁵. This, however, is not considered to be an important determinant of fluoride's beneficial effect in reducing caries.

Several workers have investigated the possible effects of fluoride on oral bacteria^{22,26,27}. Perhaps the most significant findings in several laboratories are that fluoride cannot cross the cell wall and membrane in its ionised form (F⁻), but can rapidly travel through the cell wall and into the cariogenic bacteria in the form of hydrofluoride^{22,26,27}. Hydrofluoride (HF) forms from H⁺ and F⁻ ions as the bacteria produce acids

during the metabolism of fermentable carbohydrates. So, as the bacteria produce acid the pH falls. A portion of the fluoride present in the plaque fluid then combines with hydrogen ions and rapidly diffuses into the cell, effectively drawing more HF from the outside and so on. Once inside the cell the HF dissociates again, acidifying the cell and releasing fluoride ions which interfere with enzyme (enolase) activity in the bacterium. Under these circumstances fluoride is trapped in the cell and the process becomes cumulative²⁸.

Therefore, fluoride from topical sources is taken up by the bacteria when they produce acid, thereby inhibiting essential enzyme activity. This is the third 'topical' mechanism of action of fluoride against the progression of dental caries²². Recent evidence demonstrates a direct effect of fluoride on the ability of caries-causing streptococci to colonise tooth enamel surfaces. Streptococci that cause caries bind glucan on tooth enamel surfaces by means of glucan-binding molecules called lectins. Fluoride interferes with this specific binding and thus inhibits bio-film formation by the streptococci that demineralise enamel²⁹. The fluoride ion also inhibits chain formation (growth) in streptococci and effects the physiological capabilities of the micro-organism to metabolise sucrose⁰. However, these effects manifest only at high fluoride concentrations, making the role of fluoride in remineralisation the likely process for caries reduction.

The role of low levels of fluoride in saliva and plaque

Over 20 years ago Brown and co-workers predicted that low concentrations of fluoride would enhance remineralisation³¹. Laboratory studies using a pH-cycling model that simulates the demineralisation and remineralisation aspects of the caries process showed that when levels of 0.03 ppm fluoride or higher were incorporated in the mineralising solution (artificial saliva in the model) remineralisation was enhanced^{18,32}. This laboratory model was developed to mimic caries progression around orthodontic brackets in vivo³³. As the fluoride concentration increased remineralisation increased with an optimum being achieved at about 0.08 ppm or above in the calcium phosphate mineralising solution. Further, the relationship between the logarithm of the fluoride concentration in the mineralising solutions and the degree of

protection afforded against caries-like attack was linear. The clinical implication of this finding is that small increase in the background level of fluoride in saliva and plaque fluid could provide important caries protection via enhancement of remineralisation³⁴.

Studies have shown that when fluoride products including dentifrice, rinse and gels are used they cause an initial high concentration of fluoride in the saliva and that this falls off with time as the fluoride is cleared from the mouth^{35,36}. Very importantly, fluoride can be retained at concentrations in the saliva between 0.03 and **0.1** ppm for 26 hours depending on the product and the individual subject^{35,36}. In the case of xerostomic subjects, because of very low saliva flow, elevated levels of fluoride are maintained in the mouth for many hours³⁷. Studies by Zero and co-workers showed that a 0.05% sodium fluoride mouth rinse (225 ppm F) used for 1 min could give elevated fluoride levels in saliva for 2-4 hours and in plaque for much longer times³⁶. O'Reilly and Featherstone showed that demineralisation around orthodontic brackets in vivo could be completely eliminated by the combination of a fluoride-containing dentifrice and a 0.05% NaF rinse daily³³, and Meyerowitz and co-workers found the 0.05% NaF rinse very effective in xerostomic subjects³⁸.

Earlier studies prior to the universal use of fluoride dentifrice reported differences in salivary fluoride concentrations between fluoridated and non-fluoridated communities with values in the range of 0.005-0.01 ppm of fluoride. Clinical studies conducted in the late 1980s which investigated possible caries risk factors in 7-12 years old children in the United States reported mean baseline fluoride concentrations in saliva of 0.02-0.04 ppm in both fluoridated and non-fluoridated drinking water areas with the fluoride concentration being related to caries status rather than drinking water concentration³⁹. Subsequent similar studies in the 1990s again reported no differences between mean salivary fluoride levels in 7-12-year old children living in fluoridated and non-fluoridated communities, with means of about 0.05 ppm F in each community⁴⁰. In the same study, in which the caries status of the subjects was assessed every 6 months, it was reported that after 2 and 4 years, in this longitudinal caries risk assessment study "children with high individual salivary fluoride (0.075 ppm) were more frequently caries free ($P < 0.02$)⁴⁰.

Remineralisation of early lesions also requires calcium and phosphate, which are primarily derived from saliva and plaque fluid. Several laboratory studies have indicated that the driving force for remineralisation is the degree of supersaturation of the mineralising fluid (saliva in the mouth) with respect to fluoroapatite, hydroxyapatite or both^{19,23,24,41}, and that this is related to the fluoride concentration in the oral fluids.

SUMMARY

The topical effects of fluoride are over-riding and the systemic incorporation of fluoride in the tooth mineral is unfortunately not of major benefit^{19,42}. The frequency of fluoride exposure to the tooth surface is of prime importance to maintain the high fluoride concentration that is necessary to prevent caries. The mechanism of action of fluoride in the drinking water is therefore more important as a topical delivery system².

Fluoride can be provided topically to teeth via rinses, dentifrice, or gels at home, at school, or in the dental office. Fluoridated water and chewable dietary fluoride supplements also provide notable topical benefit. Thus, people of all ages benefit from the topical effects of fluoride, whether or not they consumed fluoridated water or fluoride supplements as children⁴³.

Topical fluoride may be particularly important in the prevention of root caries, a progressive lesion of the root surface, affecting adults with gingival recession; coronal caries, and tooth loss in adults and the elderly. Older adults experience more problems with gingival recession than any other age group, resulting in an increase of root caries. This is in large part due to the fact that people are retaining more teeth and living longer. Older people tend to take more prescription drugs, and many of this effect salivary function and enhance the likelihood of oral disease^{44,45}. Studies have demonstrated that fluoride is incorporated into the structure of the root surface, making it more resistant to decay should it become exposed as a result of gum line recession^{46,47,48}.

In summary, free fluoride ion has direct effects on the ability of the tooth enamel to resist decay in erupted teeth. These effects can be categorised as:

A reduction of the acid solubility of the enamel;

Promotion of remineralisation of incipient enamel lesion at ultra-structural level;

Increasing the deposition of mineral phases of plaque, which may under acidic conditions increase remineralisation and retard demineralisation of the enamel surface; and

Fluoride is incorporated into the hydroxyapatite in the tooth enamel to increase the proportion of fluoroapatite, which is less-easily dissolved by mouth acids than is hydroxyapatite, and therefore more resistant to decay.

Thus, evidence exists for several mechanisms by which free fluoride ion can prevent or retard dental caries. It is apparent that the use of fluoride in multiple measures has a significant impact upon the prevention of dental caries. These measures involve public health benefits of water fluoridation, professional fluoride treatment in dental offices, and the home use of effective fluoridated dentifrice, with the use of fluoride rinses and gels when needed⁴⁹. A predominant part of the cario-static activity of fluoride is a function of its concentration in the fluid environment of the teeth. Fluoride releasing devices, such as fluoride releasing restorative material, may serve to maintain the fluoride levels in saliva and plaque required to prevent caries, especially in high risk patients^{22,50}. Tropical application of a fluoride varnish two to three times a year can result in caries reduction¹.

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