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**What is This?**
Physiological Factors Influencing Salivary Clearance of Sugar and Fluoride

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The salivary clearance of sugar and fluoride is influenced by several physiological factors not yet fully investigated or understood. There are reasons to believe that these factors influence both the acid production by sugar fermentation in the dental plaque and the cariostatic action of fluoride on the enamel surface and its immediate environment. This paper presents theoretical and experimental considerations of physiological factors which influence the kinetics of sugar and fluoride in the oral cavity.


Introduction.

Oral pharmacokinetics has recently been defined as the study of the distribution and elimination of a substance introduced into the oral cavity (Ekstrand et al., 1986). This concept includes all physiological and chemical processes taking place in the oral cavity as a function of time after the intake. Oral pharmacokinetics is of importance in many aspects of oral physiology and pathology, due to the specific functions of the oral cavity as the first part of the alimentary tract.

A soluble substance introduced into the oral cavity is diluted by the freshly secreted saliva and subsequently swallowed, a process very similar to serial dilution. The elimination of a substance from saliva with time is usually referred to as salivary clearance (e.g., Dawes, 1983; Tehrani et al., 1986) or oral clearance (e.g., Lundquist, 1952; Lagerlöf et al., 1985). In the present paper, we use the term salivary clearance, defined as the elimination of a substance from the saliva as a function of time.

The pathogenesis of caries involves dissolution of fermentable carbohydrates, such as sucrose, in saliva. The sucrose is subsequently transported into the dental plaque by diffusion. The rate of transport is proportional to the concentration gradient of the sucrose between saliva and plaque fluid (Dawes and Dibdin, 1986). This implies that the rate of salivary clearance is one of the determining factors for the availability of fermentable substrates to the bacteria in the plaque. As a consequence, importance has been attributed to salivary sugar clearance in the development of dental caries (Lundquist, 1952; Sundström and Ericsson, 1968; Adorjan and Stack, 1976).

There is now abundant evidence that the most important mechanism of the cariostatic action of fluoride is related to the concentration of fluoride in the liquid phase of the enamel and its immediate environment (for review, see Luoma et al., 1986). Furthermore, increased fluoride levels in saliva and dental plaque decrease the acid production of the plaque (Geddes and McNee, 1982; Ekstrand et al., 1985).

In the prevention of dental caries, several dental fluoride preparations (such as dentifrices, rinse solutions, varnishes, and gels) are used topically, resulting in a wide range of concentrations of fluoride in the saliva. Fluoride is then subsequently cleared from the oral cavity at various rates (Aasenden et al., 1968; Bruun et al., 1982). Hence, the availability of fluoride in the deep layers of dental plaque and at the enamel surface will be influenced by the rate of clearance of fluoride from the saliva.

The present paper is a review of recent research on salivary clearance with special reference to sugar and fluoride. Furthermore, a new model for salivary fluoride clearance is presented.

Theoretical models for salivary sugar clearance.

The first theoretical study of the physiological process of elimination of carbohydrates from the oral cavity was made by Swenander-Lanke (1957). She proposed a model in which the oral cavity is represented by an open vessel into which saliva flows at a constant rate. Saliva is swallowed continuously at the same rate. The resulting sugar concentration in the saliva was described by a straight line in a semilogarithmic plot. Her model was further elaborated by Simon (1972), who also included the volume of saliva in the mouth and the salivary flow rate.

An elaborate model for salivary clearance of sugar was proposed by Dawes (1983). The essential features of this model are shown in Fig. 1. The oral cavity is approximated by an

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Fig. 1 — The salivary clearance model of Dawes (1983). Saliva is elicted from the salivary glands (S) at a rate determined by the concentration of sugar (C) stimulating the taste buds (T). The volume of saliva in the mouth increases to a maximum volume (M), which stimulates a swallow (I). The volume swallowed is assumed constant, leaving a residual volume (R) in the mouth.
swallow occurs. Then the volume returns to a residual value, and a new cycle starts. The model was programmed into a computer, and the effects of nine different variables were studied by varying one variable at a time, keeping the others constant. This model, as well as the previously described models, is limited to solutions of sugar, and does not apply to solid foodstuffs. Factors such as salivary stimulation during chewing, quality of the saliva, or food consistency and retentiveness were not included in the model. The results from these calculations showed that the most important variables affecting salivary sugar clearance were the unstimulated salivary flow rate and the volumes of saliva in the mouth immediately before and after swallowing. The amount of sugar taken into the mouth had surprisingly little effect on sugar clearance. This finding was attributed to the salivary-stimulating effect of sugar.

**In vitro studies on salivary sugar clearance.**

An artificial mouth was designed by Lagerlöf et al. (1984) in order to estimate the effect of variation of the salivary parameters on the pH decrease in an artificial plaque consisting of a pure culture of *Streptococcus mutans*. The variable with the largest effect on the pH drop was the unstimulated salivary flow rate. A low salivary flow rate (0.1 mL/min), giving a very slow rate of sugar elimination from the saliva, depressed the pH more extensively than did a salivary flow rate of 1.0 mL/min (Fig. 2). Furthermore, the volume of saliva before and after swallowing had significant influence on the magnitude of the pH depression. Other factors — such as the maximum salivary flow rate, the delay between start of stimulation and maximum flow, the volume of saliva in the mouth at the start of the experiment, and the taste threshold for sucrose — were of lesser importance. This study indicated that the pH depression in the dental plaque is not only determined by the amounts of sugar and bacteria, but is also related to several factors affecting salivary clearance of sugar.

The same artificial mouth was used to investigate the effects of the sucrose concentrations at the start of the experiment on the pH changes in an artificial plaque (Lagerlöf et al., 1985). The pH fall was correlated to the sucrose concentrations over the range 0-10%. At higher concentrations no correlation was found. A maximum correlation between the pH depression in the plaque and the sugar concentration in the surrounding li-
quid was found at two minutes after the start of the experiment. Furthermore, clearing the mouth of sucrose instantaneously at different time points after the start of the experiments showed that exposure of the bacteria to sucrose for as short a period as two minutes gave a nearly maximum fall in pH. Therefore, rinsing the mouth with, e.g., water more than two minutes after consumption of sucrose in a liquid form will have little effect on reducing the pH fall in dental plaque. As already stated, the rate of diffusion of sucrose into the plaque is dependent on the concentration gradient between the saliva and the plaque, which is largest immediately after the sugar intake. It therefore seems likely that the concentrations in these two compartments very soon are equal, whereas the concentration in the plaque will be higher due to the fast dilution of sucrose in the salivary reservoir. Therefore, it may be postulated that the first minutes of salivary sugar clearance will be critical for the availability of sugar to the bacteria of the dental plaque.

**In vivo studies on salivary sugar clearance.**

Many studies on salivary clearance of sugar have been conducted, using different methods. Several of these studies have assessed elimination of carbohydrate-containing foodstuffs from the oral cavity. These are mainly concerned with the qualities of the foodstuff, such as stickiness and solubility, and will not be reviewed in the present paper (for review, see Imfeldt, 1983). A few studies relate to physiological factors influencing salivary sugar clearance. Swenander-Lanke (1957) studied the influence of salivary flow rate on oral sugar clearance by sampling saliva 10 min after intake. She found the salivary sucrose concentration to decline exponentially. This led to the assumption that the clearance time, e.g., the time-span during which sucrose could be detected in the saliva, is an important property of the clearance curve. However, 10 min after intake the salivary flow rate is close to the unstimulated level. The influence of the salivary stimulating properties of the sugar was not detectable in this model, and may explain why only one exponential phase in the sugar clearance curve was found. A few studies report contradictory findings on the correlation between clearance time and caries experience. Keene et al. (1966) and Sundström and Ericsson (1968) found no correlation in contrast to Adorjan and Stack (1976), who found a correlation in boys but not in girls. As illustrated in Fig. 3, the clearance time is presumably of minor importance. The Fig. shows the differences between sugar clearance curves with three different clearance times, but with the same initial concentrations. The difference in sugar concentration between two clearance curves reaches a maximum in from one to two minutes, after which it decreases rapidly. From the Fig., it may be concluded that for the transport of sugar by diffusion into the dental plaque, the first minutes are decisive.

More recently, the clearance of glucose and sucrose from saliva was investigated by Sreebny et al. (1985). They found the clearance of these substances to consist of two exponential phases. The initial rapid phase lasted about six min, after which a slower phase was seen between six and 20 min. They explained this biphasic appearance of the sugar clearance curve to be caused by a more rapid salivary flow rate during the initial period. They also observed that the salivary flow rate did not return to its resting flow level until about one hr after the start of the experiments. This may be explained by an adaptation of the taste threshold for sugar to a lower level.

Some factors in the computer model of Dawes (1983) were investigated by Lagerlöf and Dawes (1984). They found the residual volume in the mouth after swallowing to range from 0.38 to 1.73 mL (mean, 0.77 mL), and the maximum volume before swallowing to range from 0.52 to 2.14 mL (mean, 1.07 mL). In a later study, they varied the maximum volume before swallowing by altering the swallowing frequency and the resting salivary flow rate (Lagerlöf and Dawes, 1985). The results confirmed the predictions from the theoretical model by Dawes (1983) that with higher unstimulated flow rates and lower volumes before swallowing, less time is required for sugar clearance. They also showed that an increased volume before swallowing caused a greater pH fall in an intra-oraly applied artificial plaque. The model of Dawes (1983) predicted only a slight effect of the initial sugar concentration on the salivary clearance of sugar. This prediction was contradicted in a recent study (Goulet and Brudevold, 1984). These investigators found, in contrast to Sreebny et al. (1985), the salivary clearance process to be a one-phase process from approximately one min following the intra-oral exposure. Therefore, the model of Dawes (1983) has been amended to include the effect of taste adaptation on the salivary flow rate (Dawes and Watanabe, 1986).

It seems likely that the clearance of sugar may be different in different parts of the oral cavity. Kellaway (1960) seems to be the only investigator who has been concerned with sugar clearance from interdental spaces. His work did not involve clearance from saliva, but he found the shapes of the clearance curves for sugar from the interdental spaces to be similar to those reported by Swenander-Lanke (1957) on saliva. Recently, the clearance of glucose from saliva was compared with that from spaces located in an intra-oral appliance (Goulet et al., 1985). It was found that the rate of glucose clearance was consistently slower from the spaces than from bulk saliva. The clearance curves were rectilinear when the logarithms of the concentrations were plotted against time. However, the time-span for the experiment was only eight min. Therefore, bimodal curves could not be expected, since the break point seems to appear after six min (Sreebny et al., 1985).

The sucrose clearance from four different sites was recently compared to the sucrose clearance from the bulk saliva (Britse
and Lagerlöf, 1986). Ten subjects rinsed with a 0.3 mol/L sucrose solution for 10 sec. Small foam pads were applied for 30 sec to four different sites at four time points. From each foam pad approximately 10 μL of saliva was recovered, which was subsequently analyzed for sucrose by an enzymatic technique. It was shown that the sugar clearance was most rapid from the lower incisor region, followed by that from the lower lateral area (Fig. 4). It was also shown that the clearance rates from all sites investigated and from bulk saliva were significantly correlated to the unstimulated salivary flow rates of the 10 subjects studied.

**In vitro studies on salivary fluoride clearance.**

The model of Dawes (1983) for salivary sugar clearance was recently adapted for salivary fluoride clearance (Ekstrand et al., 1986). This revised model takes into account the excretion of fluoride via the salivary glands after systemic intake of fluoride (Fig. 5). Based on in vivo experiments, it was assumed that 0.3% of an ingested fluoride dose was recovered in the saliva (Oliveby et al., 1986). The model also included an optional tastant in the fluoride vehicle, which was soluble at a pre-determined rate. By programming the model into a computer, we estimated the effect of a number of variables with a possible influence on salivary fluoride clearance. In these simulations, all but one of the variables were kept constant.

In Fig. 6, clearance curves produced by computer simulation of the model are shown. Variation of the unstimulated salivary flow rate in the range from 0.1 to 1.2 mL/min had a large effect on the salivary clearance of fluoride (Fig. 6a). At the high flow rate, a trough in the clearance curve was observed after 10 min, followed by an increase in the fluoride concentration. The residual volume of saliva in the mouth after swallowing in the normal range (Lagerlöf and Dawes, 1984) influenced the fluoride clearance curve to some degree during the second exponential phase (Fig. 6b). After 10 min, the fluoride concentration in saliva at a residual volume of 1.0 mL saliva after swallowing is approximately 40 times higher than...
that at a low residual volume (0.4 mL). The volume in the mouth before swallowing (Fig. 6c) had an effect similar to that of the residual volume. Some effect on the clearance pattern of fluoride was also found by varying the maximum salivary flow rate elicited by the tantast as stimulus (Fig. 6d). This effect was most pronounced during the first minutes. The amount of fluoride taken into the oral cavity influenced the fluoride clearance to a higher degree (Fig. 6e) than did that found for the clearance of sugar (Dawes, 1983). The additional stimulus exerted by the tantast was constant and independent of the amount of fluoride, whereas stimulation by sugar is concentration-dependent. The solubility rate of the fluoride vehicle influenced the clearance pattern of fluoride to a high degree (Fig. 6f). After the fluoride vehicle had dissolved completely, the fluoride clearance curve paralleled that of instant dissolution. Between 15 and 30 min after the fluoride intake, the concentration levels differed by approximately 100-fold. It could be concluded that the solubility properties of the fluoride vehicle have a pronounced effect on the salivary clearance of fluoride.

In vivo studies on salivary fluoride clearance.

An elevation of the fluoride concentration in saliva and thus in the plaque fluid may give sufficient caries protection when intermittent pH alterations take place (Luoma et al., 1986). The fluoride concentration in saliva after oral exposure to fluoride preparations for topical use is therefore of considerable interest.

The fluoride concentration in ductal saliva follows the plasma curve very closely, with the mean saliva/plasma ratio reported to be 0.64 (Ekstrand et al., 1977). These authors also found that 30 min following intake of a fluoride dose, ranging from 1.5 to 10.0 mg, a peak in the excreted salivary fluoride concentration was found, ranging from 4 to 26 μmol/L. Therefore, after systemic intake of a fluoride dose, there will be a certain contribution to the salivary fluoride level in the mouth.

Salivary fluoride clearance has been studied by a few investigators, but none of these studies seem to have taken into account all the variables affecting the clearance as discussed in the previous section of this paper. The most extensive study on salivary fluoride clearance was reported by Bruun et al. (1982), who monitored the fluoride concentration in mixed saliva after different topical fluoride treatments and found three distinctly different fluoride clearance curves: (i) a short-term elimination curve after the use of fluoride-containing toothpaste, tablets, or chewing gum; (ii) a long-term elimination curve after topical application of 1.23% F or 2% NaF solution; and (iii) an intermediate elimination curve arising from mouth-rinsing with 0.2% NaF solution. In the first group, the salivary fluoride had initial levels ranging from 1352 to 4472 μmol/L but was back to normal levels within one to two hr. After application of 1.23% F or 2% NaF, the saliva levels were about 520 μmol/L after one hr and remained elevated until 11 hr after treatment. The 0.2% NaF rinse experiment resulted in elevated fluoride levels lasting about three hr.

Aasen and et al. (1968) followed the clearance of fluoride from saliva after different topical fluoride treatments. They reported the time required for total elimination of fluoride to be one week after topical treatment with an acidulated phosphate fluoride (APF) solution containing 1.2% F. When plotting their data, they found a linear relationship between the logarithm of the concentration of fluoride and the logarithm of the time interval after fluoride treatment. They also reported that the rate of fluoride clearance decreased rapidly during the first few hours after fluoride exposure and then very slowly as normal levels were approached.

The in vitro model for salivary fluoride clearance previously mentioned has recently been adapted for some in vivo studies (Oliveby et al., 1987). In particular, the influence of salivary flow on fluoride clearance was studied. Long-term experiments were conducted on volunteers with stimulated salivary flow rates ranging from 0.5 to 2.0 mL/min. In order to maintain an elevated steady-state level of fluoride in saliva, fluoride gels containing 0.25 mg fluoride as sodium fluoride were given repeatedly eight times, i.e., every second hour during the day-time. This dosage schedule lasted for one week. Saliva samples were taken one hr after each gum was chewed. The results showed that there was a statistically significant correlation between calculated steady-state levels and salivary flow rates. This is demonstrated in Fig. 7, which shows the salivary steady-state level in two subjects during nine days. In the subject with a low salivary flow rate, the fluoride concentration remained high but fluctuated during all experimental days. This was in great contrast to the saliva curve seen in the subject with the high salivary flow rate who only had a slight elevation of the steady-state level. This experiment illustrates that although the oral cavity was exposed daily to the same amount of fluoride, great individual variation in the salivary fluoride levels may result due to different salivary clearance patterns.

Conclusions.

The present review has focused on the salivary clearance of sugar and fluoride, substances both related to dental caries. It is evident that physiological and pharmacokinetic factors influence the clearance rates of these substances and may have a greater impact on both the dynamics of the caries process and its prevention than hitherto believed. At the present stage, it may be concluded that important variables for salivary clearance of sugar and fluoride are the salivary flow rate and the volumes of saliva in the mouth before and after swallowing. In order to design optimal prophylactic measures, investigators require detailed knowledge of these parameters.

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