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THE MECHANISM OF THE MONOFLUOROPHOSPHATE ACTION ON HYDROXY APATITE AND DENTAL ENAMEL

by

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Fischer, Muhler & Wust in 1954 reported that treatment of powdered dental enamel with 2 per cent Na_2PO_3F solution at pH values from 6.7 to 2.0 maintained a pure apatite structure of the enamel in contrast to treatment with solutions of KF and Na_2SiF_6, which under corresponding circumstances also gave rise to the formation of CaF_2. In a previous report by the present author (1961 a) the observation was made that the pH gradients of the enamel uptake of F^{18} from $Na_2PO_3F^{18}$ and NaF^{18}, respectively, were significantly different. These data indicate that the fluorine uptake in dental enamel from Na_2PO_3F has another mechanism than the corresponding uptake from simple fluorides.

The reaction between simple fluorides and hydroxy apatite depends in the first rank on the concentration of F^- and OH^- ions in the solution and consists partly in an exchange of OH^- against F^- in the apatite, partly — and especially at higher fluoride concentrations — in a disintegration of the apatite structure with formation of CaF_2 and liberation of phosphate (*McCann* 1952). The corresponding reaction with powdered dental enamel seems to be more complicated, *inter alia* involving the formation of CaF_2 through exchange with carbonate ions and MgF_2 through reaction with Mg compounds in the enamel (*McCann & Bullock* 1955).

The formation of pure fluorapatite without contamination by calcium fluoride, which is less stable at physiological pH levels, involves a theoretical advantage of Na_2PO_3F in the field of caries prevention. Other potential advantages are the relatively high solubility of the calcium salt of monofluorophosphate and its low toxicity. Monofluorophosphates have also been shown to reduce the acid solubility of enamel and dentine surfaces (*Burnett* 1955, *Pigman & Newbrun* 1962, *Ericsson* 1963) and inhibit human caries (*Hawes & al.* 1954, *Goaz & al.* 1963, *Finn & Jamison* 1963), and numerous clinical observations indicate a desensibilizing action of these compounds on exposed root surfaces.

It therefore appeared of interest to throw experimental light on the mechanism of action of monofluorophosphates on calcium phosphates and dental enamel. In the present work this was done by the use of synthetic calcium phosphates and powdered dental enamel and to a great extent with solutions of isotope-labelled Na_2PO_3F and NaF.

MATERIAL AND METHODS

Powdered dental enamel for the experiments was produced by crushing and grinding the enamel of intact human teeth from which the dentine had been drilled off in advance. The enamel powder produced was divided into the sieve fractions 24—40 and 40—100 (inner mesh widths of the sieves: 24 = 0.25 mm, 40 = 0.15 mm, 100 = 0.06 mm). The enamel powder was then separated from possible rests of dentine according to the Manly-Hodge technique.

The hydroxy apatite for some of the experiments was synthetized in the laboratory according to a previously described technique (*Ericsson* 1949). In some of the tests an analytically pure commercial product was used as well as analytically pure commercial dicalcium phosphate.

F^{18} for the isotope experiments was produced by neutron irradiation of Li^6-enriched lithium nitrate in the reactor R 1 of Atomenergi Co. in Stockholm. The irradiation gives rise to the formation of H^3, F^{18} and some contaminating activity, mainly Na^{24}. In a water solution of the irradiated salt calcium phosphate was precipitated, which after washing contained the main part of F^{18}

and rests of H^3 but no contaminating activity. By glass distillation with $HClO_4$ of this calcium phosphate, carrier-free F^{18} was obtained as SiF_6 ions, which are practically totally hydrolysed to fluoride ions in neutral water solutions.

P^{32} was obtained as orthophosphate with small quantities of carrier phosphate from the reactor R 2 of Atomenergi Co.

Sodium monofluorophosphate, Na_2PO_3F, was labelled with F^{18} and/or P^{32} according to previously described methods (*Ericsson* 1961 b).

pH determinations were carried out with Radiometer's pH meter No. 22.

Calcium determinations were made complexometrically with EDTA and Eriochrome black with the end point in a known concentration of added Mg, according to a method earlier described in principle (*Ericsson* 1955).

Experiments with shaking of solids and liquids were carried out as short time tests, partly owing to the rapid decay of F^{18}, partly because it could be assumed that the short duration of the intraoral contacts between enamel and fluoride solution was best simulated thereby.

The statistical error of the radiometric determinations was kept below 1 per cent in practically every case. In the triplicate tests with powdered enamel and hydroxy apatite the deviation of the isotope uptake by the single specimen from the average uptake was practically always less than 5 per cent and never exceeded 10 %.

EXPERIMENTS

Uptake by calcium phosphate and powdered dental enamel of F^{18} and P^{32} from solutions of doubly labelled sodium monofluorophosphate

A

In plastic tubes fitting into the well crystal of the scintillation detector triplicate 100 mg portions were weighed up of powdered enamel (sieve fraction 40—100), synthetic hydroxy apatite and anhydrous dicalcium phosphate ($CaHPO_4$), respectively. Into each tube 2 ml 300-mM Na_2PO_3F were pipetted. After shaking of the tubes in an upright position for 15 minutes they were cen-

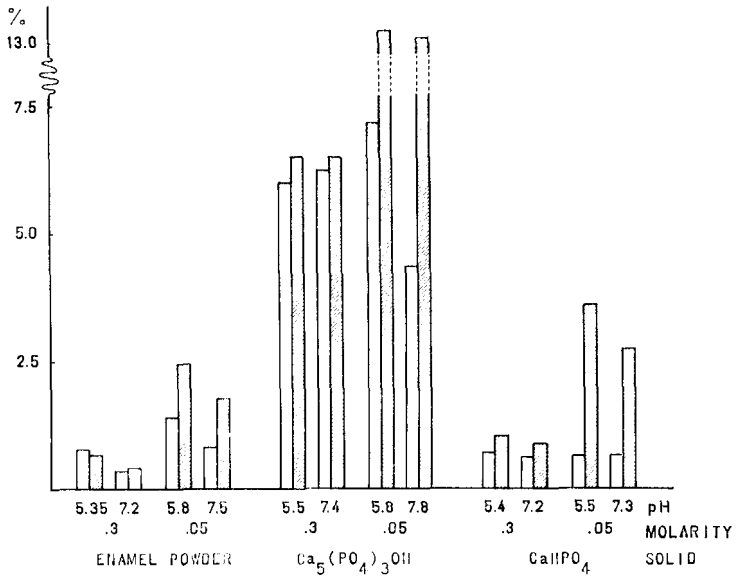

Fig. 1.

F^{18} and P^{32} uptake by different solids from double-labelled Na_2PO_3F.
Ordinates = % of total solution activity.

trifuged for 3 minutes, the supernatant was suctioned off and its pH determined.

The powders were washed in the tubes with 3×4 ml distilled water, after which the activity of the powders was analyzed radiometrically in the well crystal.

The first analysis gave the sum of the annihilation radiation of the F^{18} positrons and the bremsstrahlung of the P^{32} negatrons. A repeated analysis at least 24 hours later, when the F^{18} atoms had disintegrated, gave the P^{32} radiation separately. The F^{18} and P^{32} radiations could then be recalculated to a selected standard time.

Test series with the same solids were also performed with the doubly labelled 300-mM Na_2PO_3F, buffered to pH 4.5 with 100-mM acetate buffer, and with both solutions diluted to 50-mM Na_2PO_3F concentration.

Results

The results appear from Fig. 1. The uptake of F^{18} and P^{32} as percentage of the activities of the solutions was of the same order from the 300-mM solutions, while the P^{32} uptake dominated from the 50-mM solutions. Hydroxy apatite showed the greatest uptake of both isotopes, while dicalcium phosphate took up little more than the enamel powder in spite of its smaller particle size. The pH gradient of the uptake of both P^{32} and F^{18} was fairly small and in some of the tests was absent.

B

Since the ratio (F^{18}-uptake): (P^{32}-uptake) was much closer to unity for 300-mM solution than for 50-mM solution, the concentration difference might be thought to be the cause. For this reason the tests with powdered enamel and hydroxy apatite were repeated in two series, one with a 600-mM Na_2PO_3F solution, the other with the same solution buffered to pH 4.5 with 100-mM acetate buffer.

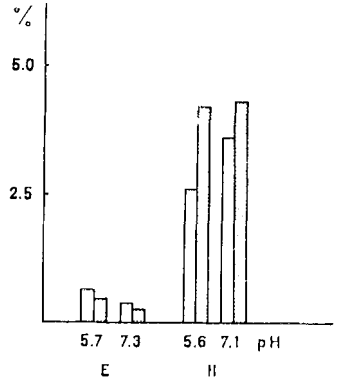

Fig. 2.

F^{18} and P^{32} uptake by enamel powder (E) and hydroxy apatite (H) from double-labelled Na_2PO_3F.

Ordinates = % of total solution activity.

F^{18} P^{32}

Results

The results appear from Fig. 2, which shows some dominance of the F^{18} uptake in the enamel powder but still considerable dominance of the P^{32} uptake in the pure hydroxy apatite.

Comparative tests on the uptake by synthetic hydroxy apatite and powdered dental enamel of P^{32} from labelled orthophosphate solutions and F^{18} from labelled sodium fluoride or sodium monofluorophosphate solutions

A. Simultaneous uptake by hydroxy apatite of P^{32} from labelled orthophosphate buffer and F^{18} from labelled sodium fluoride

Into each of three plastic counting tubes were weighed up 100 mg of the same synthetic hydroxy apatite as was used in the previous series. Into each tube was pipetted 3 ml of a solution of 50-mM P^{32}-labelled phosphate buffer pH 7, at the same time 50-mM as regards F^{18}-labelled NaF. After shaking in an upright position for 15 minutes the tubes were centrifuged for 3 minutes. The supernatant was suctioned off and its pH value determined. Each powder was centrifuge-washed with 3×4 ml distilled water and its activity analyzed immediately and after 24 hours.

The same experiment was carried out with a solution where the P^{32}-labelled phosphate buffer had the pH value 5.0 but the same content of F^{18}-labelled NaF.

Results

The results appear from Fig. 3, where the corresponding results with doubly labelled 50-mM Na_2PO_3F solution from Fig. 1 have also been entered. One finds that the uptake of P^{32} and F^{18} from the combined orthophosphate and fluoride solution was about the same in contrast to the uptake of these isotopes from the doubly labelled Na_2PO_3F solution. The pH gradient in the range 5.5—8 was in both cases greatest for the F^{18} uptake.

B. Uptake by powdered enamel and hydroxy apatite of P^{32} from labelled orthophosphate, with or without the presence of fluoride or monofluorophosphate ions

Into each of 9 counting tubes were weighed up 100 mg enamel powder, sieve fraction 40—100. To three of these tubes was added 2 ml of a neutral solution of P^{32} as orthophosphate, practically

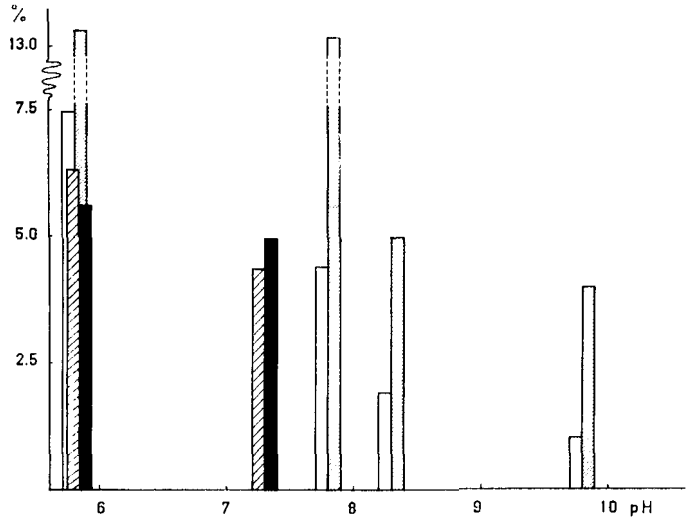

Fig. 3.

F^{18} and P^{32} uptake by hydroxy apatite from double-labelled Na_2PO_3F and from mixture of P^{32}-labelled orthophosphate and F^{18}-labelled NaF (all 50-mM).

Ordinates = % of total solution activity.

F^{18} uptake from Na_2PO_3F
P^{32} „ „ „
F^{18} „ „ NaF
P^{32} „ „ orthophosphate.

carrier-free. To three other tubes was added the same quantity of the same P^{32} solution, which at the same time was 50-mM as regards sodium fluoride. To the remaining three tubes was added the same P^{32} solution containing at the same time 50-mM Na_2PO_3F.

The tubes were stoppered and shaken in an upright position for 15 minutes. After centrifugation for 3 minutes the supernatants were suctioned off and their pH determined.

The tubes with the P^{32}-exposed enamel powders were centrifuge-washed with 3×4 ml distilled water, after which the P^{32} uptake was determined radiometrically.

The same experimental series was carried out with pure synthetic hydroxy apatite.

Results

The results appear from Fig. 4. It is seen that the NaF-containing solutions have given somewhat higher final pH values and a somewhat lower P^{32} uptake than the control solution, while the addition of Na_2PO_3F has given either the same or clearly lower final pH values than the control solution and a strongly reduced P^{32} uptake in the powders.

This can possibly be interpreted as a result of a competition between PO_3F ions and orthophosphate ions for the free positions in the apatite structure.

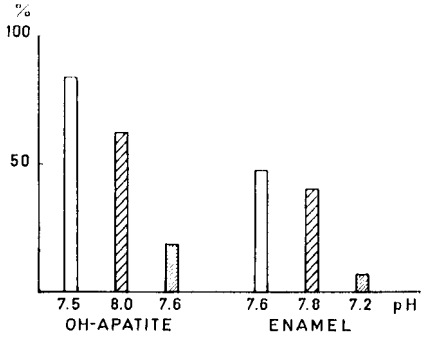

Fig. 4.

Influence of F and PO_3F ions on P^{32} uptake from labelled low-carrier orthophosphate by hydroxy apatite and powdered enamel.
Ordinates = % of total solution activity.

Uptake in absence of interfering ions.
„ „ presence of NaF.
„ „ „ „ Na_2PO_3F.

C. Uptake by powdered enamel and hydroxy apatite of P^{32} from labelled orthophosphate solution, with or without fluoride ions or monofluorophosphate ions

Experiment B was repeated with the change that 50-mM P^{32}-labelled orthophosphate buffer pH 7.0 was used instead of carrier-free P^{32} solution.

Results

The results appear from Fig. 5. On a percentage basis the P^{32} uptake is much lower than in the previous experiment with carrier-free solution, which should be a normal consequence of the competition between radioactive and inactive phosphate groups for the exchange positions in the apatite structure. In this test sodium fluoride has increased the P^{32} uptake in both solids, while monofluorophosphate has clearly reduced this uptake.

Just as in the previous experiment the last-mentioned effect may be interpreted as a competitive influence on the orthophosphate uptake in the apatite structure.

D. Uptake by powdered enamel and hydroxy apatite of F^{18} from labelled NaF, with or without the presence of PO_3F ions or orthophosphate ions

Into each of 12 counting tubes was weighed up 100 mg enamel powder, sieve fraction 40—100. To each of 3 of these tubes was added 2 ml of an F^{18}-labelled 50-mM NaF solution; to 3 tubes was added each 2 ml of the same solution, buffered to pH 7.0 with 50-mM veronal buffer; to each of 3 tubes was added 2 ml of the same NaF solution, being at the same time 50-mM Na_2PO_3F; to the last 3 tubes was added each 2 ml of the NaF solution, simultaneously containing 50-mM phosphate buffer pH 7.0.

The tubes were stoppered, shaken in an upright position for 15 minutes and centrifuged for 3 minutes. The supernatant was

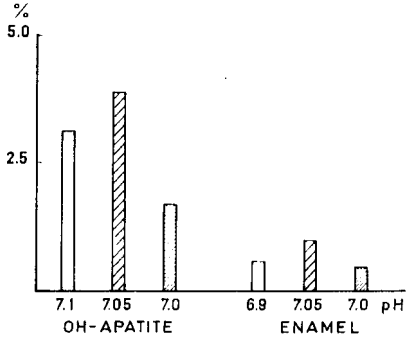

Fig. 5.

Influence of F and PO_3F ions on P^{32} uptake from labelled 50-mM orthophosphate by hydroxy apatite and powdered enamel.

To be read as Fig. 4.

suctioned off and the pH determined. The powders were centrifuge-washed with 3×4 ml distilled water and analyzed radiometrically.

The same experimental series was carried out with synthetic hydroxy apatite instead of enamel powder.

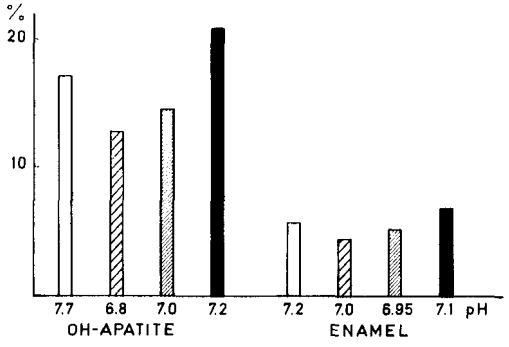

Fig. 6.

Influence of PO_3F ions, orthophosphate ions and presumably indifferent buffer ions (Veronal) on F^{18} uptake from labelled 50-mM NaF by hydroxy apatite and powdered enamel.

Ordinates = % of total solution activity.

Uptake in absence of interfering ions.
„ „ presence of Na_2PO_3F
„ „ „ „ orthophosphate.
„ „ „ „ Veronal.

Results

The results appear from Fig. 6. One finds that the veronal buffer has increased the F^{18} uptake in both enamel powder and hydroxy apatite, while the phosphate buffer and still more so the monofluorophosphate have reduced the uptake of the solid phases.

A plausible interpretation of these results might be that fluorine from the PO_3F ions has competed, by some mechanism, with fluoride ions for positions in the apatite lattice, while orthophosphate ions may have counteracted the apatite disintegration by a common ion effect.

E. Uptake by powdered enamel and hydroxy apatite of F^{18} from labelled Na_2PO_3F, with or without the presence of fluoride ions or orthophosphate ions

This experiment was conducted in the same way as D with the exception that F^{18}-labelled Na_2PO_3F solution, 50-mM, substituted the NaF solution which was instead included among the interfering substances.

Results

The results appear from Fig. 7. The phosphate buffer decreased the F^{18} uptake from Na_2PO_3F to a clearly greater extent than the same buffer influenced the corresponding uptake from labelled NaF in experiment D. The fluoride ions reduced the F^{18} uptake from $Na_2PO_3F^{18}$ much more dramatically than the reverse interaction Na_2PO_3F—NaF^{18} in the previous experiment.

It appears thus that fluoride ions enter the apatite lattice more easily than monofluorophosphate ions and in some way block the positions that may be occupied by monofluorophosphate groups.

Liberation of hydroxy ions and hydrogen ions on shaking calcium phosphate with solutions of NaF and Na_2PO_3F, respectively

The above reported experiments with labelled orthophosphate and monofluorophosphate solutions had indicated that orthophosphate and monofluorophosphate ions could compete for certain positions in the apatite structure. These positions should primarily be PO_4 groups, since the PO_3F ion is isomorphous with the PO_4 ion. However, if the PO_3F ion enters a PO_4 position in the apatite lattice, the electroneutrality is upset, since the former ion is bivalent and the latter trivalent. This has to be compensated by some mechanism, for example by exchange of an F atom from the PO_3F group with an O atom from a neighbouring OH group, with simultaneous extrusion of the proton. If this occurred, there was the theoretical possibility that extruded protons could measurably lower the pH value of the solution.

A

The following experiment was carried out to test this possibility.

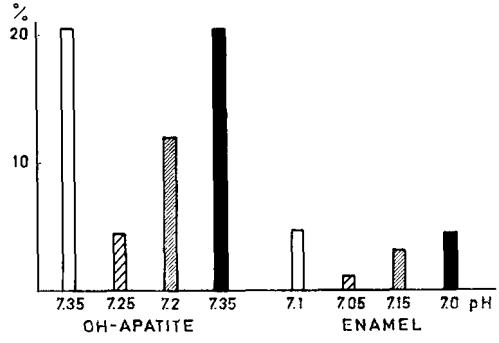

Fig. 7.

Influence of F ions, orthophosphate ions and presumably indifferent buffer ions (Veronal) on F^{18} uptake from labelled 50-mM Na_2PO_3F by hydroxy apatite and powdered enamel.

Ordinates = % of total solution activity.

- Uptake in absence of interfering ions.
- „ „ presence of NaF.
- „ „ „ „ orthophosphate.
- „ „ „ „ Veronal.

In a centrifuge tube 600 mg hydroxy apatite were shaken with 20 ml 50-mM Na_2PO_3F for 30 minutes. For comparison the same apatite was shaken in the same way with a 50-mM NaF solution. After centrifugation the supernatants were suctioned off, their pH determined and titrated back to the original pH values of the solutions, using 0.01-N HCl and 0.01-N NaOH, respectively.

Results

The results appear from Table 1. The NaF solution has, as expected, increased the pH value of the solution by the liberation of OH ions and proton-combining PO_4 groups. The pH value of the Na_2PO_3F solution has instead decreased on shaking with apatite. This should mean a liberation of a relatively great quantity of protons from the apatite since other ions which are simultaneously liberated (Ca, PO_4) have a pH-increasing influence.

B

The liberation of protons through the action of Na_2PO_3F on hydroxy apatite could be expected to have a pH gradient and the resulting pH change of the solution should be related to the quantity of simultaneously liberated calcium and phosphate ions. In order to test this theory the previous experiment was repeated

Table 1

Liberation of hydroxy ions and hydrogen ions on shaking hydroxy apatite with solutions of NaF and Na_2PO_3F, respectively.

Solution	Initial pH	Final pH	Quantity of 0.01-N HCl or NaOH required for titration to initial pH
NaF	6.36	7.26	0.950 ml HCl
		7.21	0.925 „ „
		7.19	0.978 „ „
Na_2PO_3F	6.90	6.55	0.527 ml NaOH
		6.49	0.502 „ „
		6.53	0.500 „ „

and expanded with the following changes: the Na_2PO_3F solution was from the beginning given different pH values between 5.40 and 8.50 by the addition of HCl or NaOH. After shaking, the resulting pH and the dissolved calcium quantity were determined, while back-titration was not carried out.

Results

The results appear from Fig. 8. It is seen that the pH value of Na_2PO_3F solutions with original pH above about 6.2 has been lowered by shaking with calcium phosphate. The pH decrease has

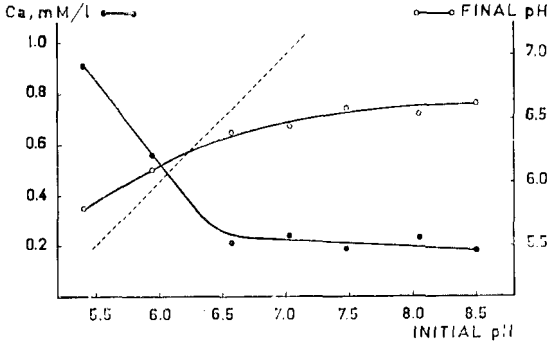

Fig. 8.

Final pH and concentration of dissolved calcium after shaking hydroxy apatite with Na_2PO_3F solution.

Dashed line indicates where unchanged pH values would have been located.

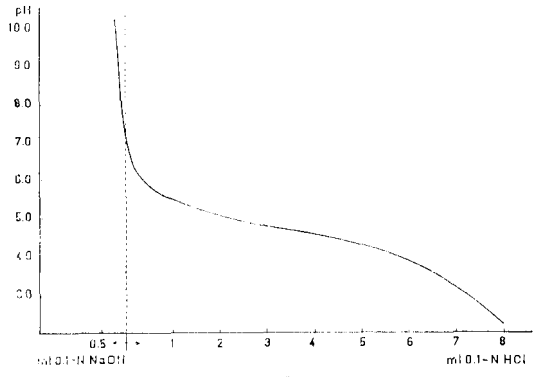

Fig. 9.

Buffer curve of monofluorophosphate.
15 ml 50-mM Na_2PO_3F titrated with 0.1-N NaOH and HCl.

been numerically greater the higher the original pH of the solution, and the final pH appears to approach 6.6—6.7 asymptotically. This agrees well with the fact that the uptake in hydroxy apatite of fluorine and phosphorus from Na_2PO_3F has a low pH gradient, that the calcium dissolution according to the diagram has shown little change in this region and that the buffering power of monofluorophosphate is weak in this pH area (Fig. 9).

Below pH about 6.2 the pH value of the monofluorophosphate solution has been increased by shaking with calcium phosphate. Protons have probably been liberated to at least the same degree in this region also, but the liberation of other ions (see the calcium curve) has dominated here.

DISCUSSION

The reported investigations strongly indicate that the reaction between PO_3F ions and hydroxy apatite or dental enamel is primarily an exchange with PO_4 groups of the crystal structures accompanied by an intracrystalline transposition according to the scheme $PO_3F^{2-} + OH^{1-} \rightarrow PO_4^{3-} + F^{1-} + H^{1+}$, with extrusion of the proton. The proton extrusion as well as the exchange competition between PO_3F ions and orthophosphate ions in the same solution are at any rate established.

This probable reaction mechanism contributes to explain why calcium fluoride is not formed in hydroxy apatite or dental

enamel through the influence of monofluorophosphate solutions. It also agrees with the observation that the pH gradient of the fluorine uptake in dental enamel is much lower for monofluorophosphate solutions than for e.g. sodium fluoride solutions: the proton extrusion should be counteracted by a low pH value at the same time as this enhances the exchange in other ways.

If the PO_3F uptake takes place essentially according to the assumed mechanism in hydroxy apatite and dental enamel it is possible that this also occurs to some extent in the skeleton after peroral ingestion of monofluorophosphate. While it has previously been shown (*Ericsson & collab.* 1961) that the PO_3F ion must be split in the body to a great extent, the low acute toxicity of this ion compared to that of the F ion (*Shourie & collab.* 1950) appears on the other hand difficult to explain if not through a certain retardation of this physiological hydrolysis (*Ericsson & collab.*, loc. cit.). Unhydrolysed PO_3F ions would then be able to react with the skeletal apatite.

The preferential formation of the stable fluorapatite might explain why clinical tests have given the good results as regards caries inhibition that were referred to in the introduction in spite of the fact that less fluorine is taken up by the dental enamel from Na_2PO_3F than from the often applied compounds SnF_2 and NaF (*Ericsson* 1961 a). If stable fluoride compounds are formed also in the skeleton this should — in combination with the lower acute toxicity of monofluorophosphate — form a clear indication for therapeutic trials with Na_2PO_3F as well as with NaF in cases of osteoporosis, e.g. Paget's disease.

SUMMARY

Tests with F^{18}- and/or P^{32}-labelled Na_2PO_3F, NaF and orthophosphate solutions in contact with powdered dental enamel or synthetic hydroxy apatite indicated, among other things, that PO_3F ions and orthophosphate ions can compete for certain positions in the apatite lattice, probably PO_4 groups.

In a corresponding exchange competition between PO_3F and F ions the latter are preferentially taken up by the apatite.

Other tests demonstrated that protons are liberated from hydroxy apatite by the action of PO_3F ions.

The theory is therefore put forward that the reaction between PO_3F ions and hydroxy apatite or dental enamel is primarily an exchange with PO_4 groups of the crystal structure accompanied by an intracrystalline transposition according to the scheme $PO_3F^{2-} + OH^{1-} \rightarrow PO_4^{3-} + F^{1-} + H^{1+}$, with expulsion of the proton.

This would explain the previously reported formation of pure fluorapatite on treatment of dental enamel with Na_2PO_3F solutions.

RÉSUMÉ

LE MÉCANISME D'ACTION DU MONOFLUOROPHOSPHATE SUR L'HYDROXYAPATITE ET L'ÉMAIL DENTAIRE PULVÉRISÉ

Des solutions de Na_2PO_3F, de NaF et d'orthophosphate, marqués de F^{18} et/ou de P^{32}, ont été agitées avec de l'émail dentaire pulvérisé ou de l'hydroxyapatite. On a trouvé, entre autres choses, que les ions PO_3F et l'orthophosphate peuvent concourir pour certaines positions dans la maille d'apatite, probablement les positions de PO_4.

D'autres expériences ont démontré que des protons sont libérés de l'hydroxyapatite par l'influence des ions PO_3F.

La théorie est donc présentée que la réaction entre les ions PO_3F et l'hydroxyapatite ou l'émail dentaire est premièrement un échange avec des ions PO_4 de la structure cristalline, accompagné par une transposition intracristalline qui forme de la fluorapatite et dégage des protons suivant le schéma $PO_3F^{2-} + OH^{1-} \rightarrow PO_4^{3-} + F^{1-} + H^{1+}$.

ZUSAMMENFASSUNG

DIE WIRKUNGSWEISE DES MONOFLUORPHOSPHATES AUF HYDROXYLAPATIT UND ZAHNSCHMELZ

Untersuchungen mit Lösungen von Na_2PO_3F, NaF und Orthophosphat, mit F^{18} und/oder P^{32} gemerkt, die mit pulverisiertem Zahnschmelz oder synthetischem Hydroxylapatit geschüttelt wurden, gaben u. a. zu erkennen, dass PO_3F-Ionen und Orthophosphationen mit einandern um gewisse Stellungen im Apatitgitter, vermutlich PO_4-Positionen, konkurrieren können.

Andere Teste zeigten, dass Protonen durch die Einwirkung von PO_3F-Ionen vom Hydroxylapatit freigemacht werden können.

Die Theorie ist daher vorgelegt, dass die Reaktion zwischen PO_3F-Ionen und Hydroxylapatit oder Zahnschmelz zuerst ein Austausch mit PO_4-Gruppen der Kristallstruktur ist, und dass dieser Austausch durch eine intrakristalline Umlagerung begleitet ist, wobei gemäss dem Schema $PO_3F^{2-} + OH^{1-} \rightarrow PO_4^{3-} + F^{1-} + H^{1+}$ Fluorapatit gebildet und Protonen ausgestossen werden.

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