Degree of Saturation of Blood Plasma in Vertebrates
with Octocalcium Phosphate


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In previous papers it has been shown that octocalcium phosphate OCP occurs in bone mineral of vertebrates. Although this compound is not stable, there is a continuous new-formation of OCP due to bone turnover. Literature data of the calcium and phosphate concentrations in the blood plasma of vertebrates were collected and the degree of saturation with OCP was calculated. The results show that blood plasma of vertebrates is almost saturated with OCP. This fact indicates that OCP is the solubility controlling phase in the mineral of vertebrates. Further it verifies the expectation based on physicochemical theory that the interaction between body fluids and bone mineral is important in the calcium and phosphate homeostasis.

Introduction

In addition to the main components calcium and phosphate the mineral in bone contains also considerable amounts of the minor components carbonate, sodium and magnesium. In the past several authors have proposed that bone mineral contains several calcium phosphates rather than one [1–3]. On the basis of experimental observations [4] and theoretical predictions based on the thermodynamics of solid solutions [5] the occurrence of different mineral phases in bone is indeed more likely than that of a simple apatite solid solution. In a previous paper [6] it was proposed that the sodium content of bone mineral is representative for the amount of an apatite phase with the stoichiometry

$$\text{Ca}_{8.5}\text{Na}_{1.5}(\text{PO}_4)_4(\text{CO}_3)_3\text{CO}_3$$ (1)

This compound is known from in vitro synthesis [7]. Further, it was proposed [6] that the magnesium content is representative for the amount of a whitlockite phase with the stoichiometry

$$\text{Ca}_9\text{Mg}(\text{HPO}_4)(\text{PO}_4)_6$$ (2)

This compound is known as a mineral [8]. On the basis of these assumptions and using the chemical composition of over 100 bone samples reported in the literature it could be shown [6, 9, 10] that the inorganic phase of mature bone of vertebrates can be explained if one assumes that it is composed of compounds (1) and (2) in addition to an apatite “rest” phase with the composition

$$\text{Ca}_6(\text{PO}_4)_{3.3}(\text{CO}_3)_{1.6}(\text{OH})_{1.5}$$ (3)

This apatite is also known from in vitro synthesis [11]. Variations in the Ca, P, Na, Mg and CO$_3$ content of bone mineral occurring in the samples of mature bone considered could be explained with this three phase model by assuming variations in the relative amounts of the phases (1), (2) and (3). When similar considerations were applied to the mineral of dentin [4] and to arterial-wall and heart-valve calcifications [12] it was found that they probably contained the same phases (1), (2) and (3).

Recently, the data on the chemical composition of young and developing bone have been analyzed in the same way [13]. It was found that these bones probably contained in addition a considerable amount of a fourth mineral phase, i.e. octocalcium phosphate OCP with the stoichiometry

$$\text{Ca}_6(\text{HPO}_4)_2(\text{PO}_4)_{2.5}\text{H}_2\text{O}$$ (4)

The data indicated that OCP was the precursor phase of bone mineral and that it was transformed in the body fluids within about one month into a mixture of the phases (1), (2) and (3). This is in accordance with earlier suggestions [14] that OCP is the precursor phase of bone mineral.

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During life there is continuous turnover of bone, including the mineral. This means that the bone mineral becomes never completely exempt of OCP. For this reason it was proposed to introduce the complete analysis of bone mineral as a method to determine the rate of turnover of bone [15].

Hoppenbrouwers et al. [16] determined the rate of dissolution of dentin mineral in buffers having different values for the logarithm of the ionic activity product of OCP which is defined as

$$\log I_{OCP} = 8 \log a(Ca) + 2 \log a(HPO_4) + 4 \log a(PO_4).$$  \hspace{1cm} (5)

In this formula $a(X)$ represents the activity of ion $X$ in the aqueous solution. They found that this mixture of phases (1), (2) and (3), which is also found in bone mineral, is in equilibrium with aqueous solutions that have a $\log I_{OCP}$ value of $-75 \pm 1$. This value is much lower than the values calculated for human blood plasma which vary from $-69.2$ to $-71.3$ [4].

The solubility product of OCP is known from a few studies. Moreno et al. [18] found a value of $-68.6$ for the logarithm of the solubility product of finely dispersed OCP, which might be considered as a measure for the formation product. Shyu et al. [19] found a value of $-73.3$ for coarse grained OCP whereas Verbeeck et al. [20] found a value of $-70.9$ for well crystalline and very pure OCP. As the range for human blood plasma [17] was between that of the formation product and the real solubility product for well crystalline and very pure OCP, it was suggested that in man OCP is the solubility controlling phase of bone mineral and that the tendency to maintain its solubility product is of great importance for the calcium and phosphate homeostasis [17]. The present paper was intended to investigate whether this might also be valid for other vertebrates.

**Methods**

Literature data were collected about the calcium and inorganic phosphate content and the pH of blood plasma of vertebrates, as far as they are determined in the same sample. When the pH was not measured, it was assumed to be 7.4. When not the ionized or ultrafilterable calcium, but only the total calcium was given, it was assumed that 50% of the calcium was ultrafilterable.

For the calculation of $\log I_{OCP}$ known complexation constants [4] were used and activity coefficients were approximated by the extended Debye-Hückel formula [21], using the ion size parameters as reported by Kielland [22].

**Results**

The results as derived from the analytical data for blood plasma samples of normal healthy vertebrates are given in Table I. The fact that the ultrafilterable calcium can vary from 40 to 60% of the total calcium [31, 32, 40] and that the pH can vary from about 7.37 to 7.43 introduces an error of ±0.6 in the data derived from total calcium analyses and from an assumed pH of 7.4.

**Table I. Logarithm of the ionic activity product for OCP in blood plasma of normal healthy vertebrates.**

<table>
<thead>
<tr>
<th>Species</th>
<th>$-\log I_{OCP}$</th>
<th>n</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killifish</td>
<td>68.5–69.6</td>
<td>2</td>
<td>[23]</td>
</tr>
<tr>
<td>Eel</td>
<td>71.1–71.4</td>
<td>5</td>
<td>[24]</td>
</tr>
<tr>
<td>Lizard</td>
<td>70.0–71.3</td>
<td>2</td>
<td>[25]</td>
</tr>
<tr>
<td>Chicken</td>
<td>69.8–70.5</td>
<td>6</td>
<td>[46]</td>
</tr>
<tr>
<td>Mouse</td>
<td>69.7</td>
<td>1</td>
<td>[26]</td>
</tr>
<tr>
<td>Rat</td>
<td>68.6–71.0</td>
<td>71</td>
<td>[27–31]</td>
</tr>
<tr>
<td>Rabbit</td>
<td>69.6–70.1</td>
<td>4</td>
<td>[45]</td>
</tr>
<tr>
<td>Pig</td>
<td>70.8–71.6</td>
<td>3</td>
<td>[33]</td>
</tr>
<tr>
<td>Dog</td>
<td>68.5–70.8</td>
<td>65</td>
<td>[34–40]</td>
</tr>
<tr>
<td>Lamb</td>
<td>69.5–69.9</td>
<td>2</td>
<td>[41]</td>
</tr>
<tr>
<td>Cow</td>
<td>68.8–70.8</td>
<td>24</td>
<td>[42]</td>
</tr>
<tr>
<td>Pony</td>
<td>70.5–71.6</td>
<td>6</td>
<td>[43]</td>
</tr>
<tr>
<td>Baboon</td>
<td>68.9–69.4</td>
<td>6</td>
<td>[44]</td>
</tr>
<tr>
<td>OCP</td>
<td>68.6–70.9</td>
<td>phases (1), (2) and (3)</td>
<td>74 –76</td>
</tr>
</tbody>
</table>

**Discussion**

Table I indicates that blood plasma of vertebrates is probably in/near-to equilibrium with OCP and not with a mixture of phases (1), (2) and (3). This suggests that the earlier data derived for man [13] apply to vertebrates in general. Hence, the calcium and phosphate concentration in body fluids and, especially, in blood plasma is 2 to 3 times larger than expected, when a mixture of phases (1), (2) and (3) would be solubility controlling [13]. Hence, bone turnover whereby new OCP is formed, probably provides the living cells in vertebrates with concentrations of calcium and phosphate ions in their surrounding fluids, which are the maximum possible on physicochemical grounds. This might be important for vital functions like energy metabolism, muscular function, nerve function, etc. [43–45].
At the moment, the general notion is that calcium and phosphate homeostasis is regulated only by hor-
mones like parathyroid hormone, calcitonin and vita-
mion D metabolites which influence intestinal absorp-
tion and renal excretion predominantly. The present
data indicate that another process, *i.e.* the physico-
chemical equilibrium between bone extracellular
fluid and OCP from the bone mineral, is probably
important in conjunction with these hormonally regu-
lated processes of intestinal absorption and renal excretion. In following studies it will be investigated,
how these processes are coupled.

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