WHY DO BENIGN PAROXYSMAL POSITIONAL VERTIGO EPISODES RECOVER SPONTANEOUSLY?

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Abstract — It is well known that most episodes of benign paroxysmal positional vertigo (BPPV), even in untreated, recover spontaneously in 2 to 6 weeks. In the present study, we put forward the hypothesis that this is mainly due to the fact that endolymph, owing to its low calcium content (20 μM) is able to dissolve otoconia. To support this, the fate of frog saccular otoconia immersed in normal endolymph (Ca²⁺ content 20 μM) and in Ca²⁺-rich endolymphatic fluids (up to 500 μM) was studied by observing the crystals at regular intervals for 3 weeks. The results demonstrated that normal endolymph can dissolve otoconia very rapidly (in about 20 hours). When the endolymphatic Ca²⁺ content was increased (50 to 200 μM) otoconia dissolution time was slowed down (about 100 to 130 hours, respectively) and completely stopped when the endolymphatic Ca²⁺ content was of 500 μM. The present results therefore suggest that the major process involved in the spontaneous recovery of BPPV episodes is the capability of the endolymph to dissolve dislodged otoconia. © 1998 Elsevier Science Inc.

Keywords — BPPV; otoconia; cupulolithiasis; canalolithiasis.

Introduction

Benign paroxysmal positional vertigo (BPPV), first described by Adler (1) and Barany (2), and then so named by Dix and Hallpike (3), is one of the most common causes of vertigo.

Although the pathophysiological mechanisms of BPPV are still a matter of debate (4), it is generally accepted that this labyrinthine disorder is, with few exceptions (central vestibular dysfunction), mainly due to dislodged otoconia either settling on the cupula (cupulolithiasis) (5) or, concealed with other debris, forming clots free-floating inside a semicircular canal, usually the posterior one (canalolithiasis) (6,7).

From clinical experience, it is also known that BPPV is a transient (benign) phenomenon that, as a rule, recovers spontaneously in about 2 to 6 weeks. Sometimes, however, positional vertigo episodes are recurrent or persistent (8–10). A reliable case-record on a large series of patients is still lacking in the literature.

The processes underlying the remission of BPPV episodes have never been investigated in detail, and only a few contradictory hypotheses have been put forward (4,11).

In the present study, we suggest that the spontaneous remission of BPPV episodes is chiefly due to the fact that endolymph, owing to its low content of ionized calcium (20 μM) (12–14), is able, by itself, to dissolve dislodged otoconia, thus producing a progressive attenuation, up to disappearance, of BPPV symptoms.

To verify this hypothesis, the fate of otoconia immersed in artificial endolymph with normal Ca²⁺ content (20 μM) and in solutions with higher Ca²⁺ content (up to 500 μM) has been investigated.
Methods

Otoconia were removed from the sacculus of the frog (*Rana esculenta* L.) and placed, in small groups, in Petri dishes (capacity 5 ml) filled either with normal artificial endolymph (Ca$^{2+}$ 20 μM) or with endolymphatic solutions with an increased Ca$^{2+}$ content (50, 200, 500 μM). The different media were obtained by adding to a common endolymphatic solution (composition: NaCl 18 mM; KCl 100 mM; NaHCO$_3$ 1.2 mM; NaH$_2$PO$_4$ 0.17 mM; CaCl$_2$ 1 mM; pH 7.3) suitable amounts of ethylenediaminetetraacetic acid (EDTA) (0.98 mM for Ca$^{2+}$ 20 μM; 0.95 mM for 50 μM; 0.80 mM for 200 μM; 0.50 mM for 500 μM). In the same experiments, frog otoconia were placed either in human artificial endolymph (composition: NaCl 16 mM, KCl 150 mM; NaHCO$_3$ 1.2 mM; NaH$_2$PO$_4$ 0.17 mM; CaCl$_2$ from 20 μM to 500 μM; pH 7.3) or in human artificial perilymph (composition: NaCl 160 mM; KCl 5 mM; NaHCO$_3$ 1.2 mM; NaH$_2$PO$_4$ 0.17 mM; CaCl$_2$ from 20 μM to 400 μM; pH 7.3) or in plain water with the same Ca$^{2+}$ content (CaCl$_2$ from 20 μM to 500 μM). Plain water pH was adjusted to 7.3 by adding NaOH.

The results demonstrated that the EDTA-Ca$^{2+}$ buffer system adopted in the present study was very efficient in maintaining Ca$^{2+}$ concentration constant in the different solutions. In fact, Ca$^{2+}$ levels, measured by means of Ca$^{2+}$-sensitive microelectrodes, did not change after the addition of otoconia to the various media. Ca$^{2+}$-sensitive microelectrodes were made according to a procedure already described (15). As ion exchange resin, the calcium ionophore I - Cocktail A (Fluka) was employed.

Criteria for the Evaluation of Otoconia Dissolution Rate

Frog otoconia (Figure 1) constitute a fairly heterogeneous population of crystals, mainly cylindrically shaped (length 1 to 20 μm; diameter 0.5 to 4 μm), that, according to Pote and Ross (16), have a mineral structure mimicking calcite.

![SEM image of the otoconia removed from frog sacculus.](image-url)
For scanning electron microscopy (SEM), otoconia were dried, gold-coated, and observed with a Joel JXA-840A scanning electron microscope. To evaluate the dissolution rate of the different otoconia, when they were immersed in the various endolymphatic solutions, crystals were subdivided by length in 4 classes of 3, 5, 10, and 15 μm, respectively. This was performed by choosing, under microscopic control (Zeiss Universal microscope), an area in the Petri dish where the otoconia were well separated from each other and where the majority of them fell in the desired length class. (The only difficulty was the individuation of 15 μm otoconia, which are relatively rare in the otoconial mass, whereas all the other otoconial classes, that is, 3, 5, and 10 μm, were always well represented).

Once located, the area was photographed (Nikon A1 camera) every 3 hours during the first 2 days and every 8 hours for the following 18 days. Dissolution time of each otoconial class was determined by observing the time at which otoconia disappeared.

To avoid evaporation, which might alter the ion composition of the solutions and therefore the efficiency of the Ca²⁺ buffer system, the Petri dishes were closed by covers that were removed only during the time required for taking pictures. Petri dishes, containing otoconia, were always kept at room temperature (about 22°C).

All experiments were performed in accordance with the guidelines of the Declaration of Helsinki.

**Results**

A representative example of the fate of otoconia immersed in Ca²⁺ 50 μM endolymphatic solution is depicted in Figure 2. It may be seen

![Figure 2. Time course of the dissolution of otoconia when immersed in a 50 μM Ca²⁺ endolymphatic fluid.](image)

<table>
<thead>
<tr>
<th>Ca²⁺</th>
<th>20 μM</th>
<th>50 μM</th>
<th>200 μM</th>
<th>500 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 μm</td>
<td>5.2 ± 1.5</td>
<td>68 ± 10</td>
<td>100 ± 10.3</td>
<td>&gt;480</td>
</tr>
<tr>
<td>5 μm</td>
<td>9.7 ± 1.5</td>
<td>78 ± 4</td>
<td>108 ± 4.6</td>
<td>&gt;480</td>
</tr>
<tr>
<td>10 μm</td>
<td>14.2 ± 2.8</td>
<td>84 ± 4.6</td>
<td>118 ± 7.6</td>
<td>&gt;480</td>
</tr>
<tr>
<td>15 μm</td>
<td>19.5 ± 3</td>
<td>98 ± 4</td>
<td>128 ± 6.5</td>
<td>&gt;480</td>
</tr>
</tbody>
</table>

Table 1. Otoconia Dissolution Time (hours) versus Their Dimensions and Endolymphatic Ca²⁺ Content (N = 4)
that this medium is able to dissolve otoconia, even the largest ones, in about 100 h. Figure 2 also shows that, as expected, dissolution was a progressive process, affecting at first small otoconia (3 to 5 μm; 60 to 70 hours) and then increasingly larger ones. After about 100 h, all of the otoconia were completely dissolved.

The results of the whole series of experiments (n = 4) are summarized in Table 1. It may be noted that otoconia dissolution time was clearly dependent on Ca\textsuperscript{2+} endolymphatic content. In fact, dissolution was very rapid (about 20 h for the largest ones) in normal endolymph (Ca\textsuperscript{2+} content 20 μM), quite slower in Ca\textsuperscript{2+} 50, 200 μM solutions (100 to 130 hours, respectively), and completely absent (>480 h irrespectively on otoconia dimensions) when the endolymphatic Ca\textsuperscript{2+} content was of 500 μM.

Similar results were observed when frog otoconia were placed either in human endolymph (n = 2) or in human perilymph (n = 1) or in plain water (n = 2) with the same Ca\textsuperscript{2+} content (data not shown).

**Discussion**

The present results clearly demonstrate that otoconial dissolution rate is strictly dependent on the Ca\textsuperscript{2+} concentration of the medium in which crystals are immersed and not on its electrochemical composition. In fact, under the same Ca\textsuperscript{2+} level, an artificial human endolymph, an artificial human perilymph, or plain water had the same capacity to dissolve otoconia.

Our results have also shown that a medium with a Ca\textsuperscript{2+} content similar to that of a normal endolymphatic fluid (20 μM) can rapidly dissolve otoconia (about 20 h for the largest ones).

The experimental conditions adopted in the present study are, in all probability, the most favorable ones for otoconial dissolution (few, well separated otoconia immersed in a very large (5 ml) Ca\textsuperscript{2+}-buffered volume). It is in fact presumable that, in physiological conditions, both in the case of cupulolithiasis (“heavy cupula,” that is, otoconia attached or trapped in the cupula) and of canalolithiasis (free-moving clots formed by otoconia and other debris), otoconial dissolution rate is strongly slowed, due either to the presence of diffusion barriers (cupula or clots) or to the small (few μl) endolymphatic volume.

Moreover, it can’t be excluded that in physiological conditions, notwithstanding the very low protein content of the endolymph (17), some biochemical (enzymatic) factors might affect the dissolution of the otoconia. The results show that the otoconia dissolution did take place, although in a longer time, even if the endolymphatic Ca\textsuperscript{2+} content was 10 times higher (200 μM) than that present in normal conditions (12–14). This suggests that the endolymph is endowed, in regard to otoconia dissolution process, with a high safety factor.

One aspect that cannot be ignored in this discussion is that our results give an acceptable explanation only for the spontaneous resolution of single positional vertigo episodes, but do not explain recurrent or persistent cases. It may be tentatively suggested that recurrent positional vertigo episodes are chiefly due to an imbalance between production and absorption of otoconia that, recurrently, cause a spillover of crystals into canal organs (18). Persistent positional vertigo might be due either to an increase in endolymphatic Ca\textsuperscript{2+} levels (about 500 μM) or to otoconia deeply trapped in the cupula or embedded in Ca\textsuperscript{2+}-impermeable structures that, as suggested by Hall and colleagues (19), might prevent dislodged otoconia from dissolution.

Future experiments will be devoted to clarifying these points.

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**REFERENCES**

3. Dix R, Hallpike CS. The pathology, symptomatology


