Saliva: does it provide protection against Sudden Infant Death Syndrome

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Abstract

Historically it has been theorised that saliva, or at least the excessive production of saliva, may be a risk factor for SIDS. Also, until comparatively recently the main functions of saliva have been considered to be as an aid to digestion and protection against caries.

However, more recent work has shown that saliva contains many extremely useful substances including antimicrobial agents and antifungals. Indeed, work on saliva assays, as an alternative to blood tests to detect and predict health problems, is an increasingly promising area of research. In addition various degrees of “dry mouth” have been shown to lower the body’s defences against infection.

Whilst not suggesting that xerostomia is a precursor of SIDS, it is clear that saliva production is at its lowest ebb during sleep. Therefore it is hypothesised that saliva could have a protective effect against SIDS either due to anti-infection agents or to the production of saliva inducing swallowing and possibly triggering brain activity and the ability to arouse from sleep.

This theory is discussed in relation to some of the factors that have been suggested to provide protection against SIDS, for example pacifier use. Conversely, known risk factors for SIDS, such as sleeping, sleeping position, overheating, and tobacco smoke are considered in relation to saliva production.

It is therefore considered that saliva, may be a useful and profitable area for future research.
Introduction

During the past 15 years, the reduction of the rate and the incidence of Sudden infant death syndrome (SIDS) in most developed countries have been startling. In the United Kingdom for example during the period 1989 to 2002 the incidence of SIDS has fallen from 1407 to 342 and the rate from 1.81 to 0.48 deaths per 1000 live births.

Much of this reduction has been ascribed to the publicising and parental adoption of preventative measures such as “Back to Sleep” and “Feet to Foot” campaigns and advice regarding the maintenance of equitable nursery and cot temperatures.

Clearly such reductions, which have been mirrored in most countries, are a triumph for careful reproduced epidemiological research. However, it would appear that the research community is no closer in solving the key fundamental questions – for example:

- What causes SIDS?
- What is the underlying mechanism(s) that has made the SIDS prevention campaigns so successful?
- Why, in most countries has the SIDS rate stabilised in more recent years?

Numerous theories have been postulated. More recent research has focused on a single cause of SIDS with toxic, infective, metabolic, nutritional, endocrine, cardiac, respiratory and neurologic disorders being blamed. However, Byard and Krous in their textbook suggest that the ‘syndrome’ is most likely a heterogeneous entity, with not all the previous proposed causes playing significant roles.

They further suggest that studying the complexities of infant physiological and pathologic responses to a variety of intrinsic and extrinsic factors is an appropriate way forward for researchers and that each factor that is identified may hold clues to the further understanding of mechanisms of infant death.

In the light of these comments, a novel theory has been formulated – that is the role of saliva – in an attempt to add one further factor to the debate and to explain a number of epidemiological findings.
The Functions of Saliva

Until comparatively recently the main functions of saliva have been considered to be as an aid to digestion and as a protection against caries. However in the past 15 years research has shown that saliva has far wider dimensions and functions, particularly in relation to the body’s defences.

These may be summarised as follows:

Table 1. Functions of saliva

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Fluid/Lubricant</td>
<td>Coats mucosa and helps to protect against mechanical, thermal and chemical irritation. Assists smooth air flow, speech and swallowing</td>
</tr>
<tr>
<td>Ion reservoir</td>
<td>Solution supersaturated with ions facilitates remineralisation of the teeth</td>
</tr>
<tr>
<td>Buffer</td>
<td>Helps to neutralise plaque pH after eating, thus reducing time for demineralisation</td>
</tr>
<tr>
<td>Cleansing</td>
<td>Clears food and aids swallowing</td>
</tr>
<tr>
<td>Antimicrobial actions</td>
<td>Specific (eg sIgA) and non specific (eg Lysozyme, Lactoferrin and Sialoperoxidase) anti-microbial mechanisms help control oral microflora. Sustained IgA secretion is likely to protect suckling infants from microbial infection</td>
</tr>
<tr>
<td>Antiviral/fungal agent</td>
<td>Mucins and proteases have been proposed as a barrier to viruses (and some carcinogens), preventing their access to epithelial cell surfaces. MUC7 16-mer (residues 36-51 of human salivary mucin, MUC7) and histatin 5 possess potent in vitro antifungal activity</td>
</tr>
<tr>
<td>Epidermal Growth Factor</td>
<td>EGF, produced naturally in human saliva has been shown to reduce the symptoms of ulcerative colitis</td>
</tr>
<tr>
<td>Agglutination</td>
<td>Aggregation and accelerated clearance of bacterial cells</td>
</tr>
<tr>
<td>Pellicle formation</td>
<td>Protective diffusion barrier formed on enamel from salivary proteins</td>
</tr>
<tr>
<td>Digestion</td>
<td>Due to the presence of the enzyme amylase, starchy food debris on the teeth is broken down</td>
</tr>
<tr>
<td>Taste</td>
<td>Saliva acts as a solvent thus allowing interaction of foodstuff with taste buds facilitate taste</td>
</tr>
</tbody>
</table>
| Excretion                 | As the oral cavity is technically outside the body, substances which are secreted in saliva are excreted. This is a very
inefficient excretory pathway as reabsorption may occur further down the intestinal tract.

**Water balance**
Under conditions of dehydration, salivary flow is reduced, dryness of the mouth and information from osmoreceptors are translated into decreased urine production and increased drinking (integrated by hypothalamus).

**Diagnostic tool**
Increasingly saliva is being investigated as a diagnostic tool for many diseases, such as diabetes, HIV, recurrent breast cancer and for insights into the body’s immune response.

The concentration of many of the constituents of saliva vary with the rate of salivary flow.

**Saliva in infants**

Most of the knowledge of salivary composition and functions has been derived from adults and children, and much less is known about saliva in infants. This is partly due to the difficulty in standardising sampling from the very young. In addition, the effect of stimulating salivation in infants on the composition of their saliva is little understood.

Unlike other species, the development of the salivary glands in humans appears to be substantially complete at birth. Thus by 4-12 months the composition of saliva is approximately within the range found in adults.

Salivary amylase appears in the amniotic fluid at around 18 weeks in utero, rising to high levels at term. Neonatal salivary amylase concentrations are moderately low but rise to adult levels by 1 year. It has been suggested that the development of adult amylase levels is associated with the change of diet at weaning.

Infant amylases have different molecular structures than adult forms, in particular in relation to their carbohydrate moieties. This may indicate an antibacterial function as the side chains of glycoproteins are involved in bacterial recognition. These differences are due to post-translational changes as the catalytic and ion-binding sites of the infant and adult enzymes are similar.

As has been mentioned, there appears to be little research on the unstimulated or stimulated saliva production in infants and very young children. Therefore most of the research work has been carried out on 5 year-olds or upward. In 5 year old children, unstimulated salivary flow is about half that of adults. It would appear that in the past most commentators were agreed that in very young children unstimulated salivary flow is much lower than this, but without giving precise data.

However, recently Seidel and colleagues have managed to measure unstimulated flow rates in newborn infants 6 to 24 hours old. They found an average flow from
awake children just after bathing and 4 hours after feeding of 0.036 ml/hr - about 9 times lower than in healthy adults.

There are a number of factors that effect the flow of unstimulated saliva relevant to newborn babies and infants. When standing, an individual secretes more unstimulated saliva than when seated. However when lying down saliva secretion falls to below the rate for both standing and when seated. This of course is the situation with young babies.

Unstimulated salivary flow decreases significantly in the dark or when the eyes are closed as in sleep\(^\text{15}\). At the same time the flow of unstimulated saliva is not constant during a 24-hour period. It is greatly effected by biological rhythms. Thus when sleeping, unstimulated saliva flow falls to at least half of that experienced when awake. This is demonstrated in Figure 1.

The dashed line illustrates the clinically very important finding of Schneyer and colleagues\(^\text{17}\) that salivary flow rate is greatly decreased during sleep. Salivary protein and electrolyte concentrations also show circadian rhythms of high amplitude\(^\text{18}\).

Thus, we can conclude that when the baby or infant is sleeping, unstimulated saliva is at its lowest ebb from both a quantitative and qualitative point of view.

Similarly, many factors influence the flow of stimulated saliva. Of these, mechanical stimuli – whether chewing or sucking - in the absence of any taste, will stimulate salivation. It is also considered that mastication (and possibly sucking) also serves to mix the contents of the mouth, thus increasing the distribution of the different types of saliva around the mouth\(^\text{20}\).
The importance of mechanical stimuli for eliciting salivary flow cannot be over emphasised, particularly if it is considered that a neonate produces perhaps 0.04 ml unstimulated saliva per minute when awake and only 0.01 ml/min when asleep. If the baby sleeps for 20 hours per 24, then a total unstimulated saliva volume of about 20 ml results. This compares with estimates for a healthy adult of between 500 and 1500 ml per 24 hours \(^{20}\) and for 5-year-old children of 500 ml per day \(^{21}\). Clearly some of the imbalance will be made up with stimulated saliva when feeding, but the major stimulus is normally from non-nutritive sucking.

**Saliva and IgA**

The main factor affecting the composition of saliva is the salivary flow rate: as the flow rate increases, the concentration of some constituents rises, for example, protein, chloride, sodium, bicarbonate, while others fall, for example, phosphate, magnesium. As a generalisation, the “poorest” quality of saliva is produced during sleep \(^{16}\).

The quality of saliva is obviously much easier to accurately measure in young children than quantity. Therefore some useful work has been done in this area. For example, the level of immunoglobulin class A (IgA) has been measured. IgA is an antibody concerned with protection against virus and other infections, especially in the respiratory and digestive systems.

Seidel et al \(^{14}\) found low levels of secretory IgA (sIgA) in newborns. Furthermore they showed that concentrations of sIgA are significantly correlated with saliva flow, as has been shown in adolescents \(^{21}\). However the saliva flow rate found by Seidel and his colleagues was 15 times lower compared to adolescents in other studies and therefore directly affecting the active secretion of sIgA into the oral cavity \(^{22}\).

However significantly, they found a relatively high concentration of sIgA (175 µg/ml), which is comparable to adult levels in saliva.

They comment that their results suggest that the influence of saliva flow on secretion of sIgA in newborn infants has to be considered when evaluating the sIgA-mediated immune response not only against microbiol invasion but also with respect to vaccination and effector functions during allergic inflammation.

In addition, a number of researchers have suggested that IgA might have a protective effect against sudden infant death syndrome. These research groups have considered IgA from different standpoints. For example, if bacterial toxins do play a role in precipitating a SIDS death, the presence of IgA antibodies to toxins in breast milk, (but not in infant formula) might contribute to the protective effect of breast feeding in relation to SIDS \(^{21}\). Siariakas et al \(^{24}\) also considered the role of IgA in combating bacterial toxins, whereas El Kaissouni et al \(^{25}\) considered that the infants who had died of SIDS had immature IgA producing cells at birth. Stoltenberg et al \(^{26}\) suggested that the mucosal immune system is stimulated by SIDS and found that SIDS victims had lower IgA cell numbers than victims of infectious diseases.
The standard pediatric textbooks make it clear that IgA is important in the protection of the mucosal barriers and its absence predisposes to recurrent respiratory infection.

Accordingly the saliva flow rate as an influence on the secretion of protective IgA, as suggested by Seidel et al, could be a factor in SIDS, and anything that improves the salivary flow rate – such as non-nutritive sucking – might be beneficial against this tragedy.

**Saliva production and swallowing**

The stimulation of saliva by non-nutritive sucking for example produces an important reflex – namely swallowing. Ingram presumed that “the act of sucking produces saliva and the very sucking act throws back the saliva into the reflexogenic zone for the swallowing reflex”. However the control of swallowing is far more complex than this simple statement would suggest.

Indeed, it has been argued that the swallow is not a reflex but rather a programmed response which is only initiated given the right combination of cortical and peripheral sensory cues to the medulla. Recently, Amirili and colleagues have shown in rats and cats that a poorly understood neural circuit in the brain stem controls swallowing. In addition they found that a region in the rostral-medial medulla contains the central pattern generator (CPG) for swallowing, although the exact location of the CPG was never pinpointed.

The importance of receptor stimulation by saliva for the elicitation of the swallowing reflex in man has been investigated by testing the capacity for repeated dry swallowing at maximum frequency in two controlled series: one with stimulated and one with inhibited secretion of saliva. A positive correlation was found between the secretion of saliva and the capacity for repeated dry swallowing. It was concluded that the swallowing reflex in man is dependent on an adequate stimulus - saliva. The evidence that the rate of spontaneous swallows is influenced directly by the volume of saliva produced has been confirmed more recently.

The complexity of swallowing increases when it is considered that it must interact with respiration so that a swallow causes minimal or no disturbance of continual respiration.

In normal newborn infants sucking, swallowing and breathing rhythms are co-ordinated, thus permitting a synchronised performance of these functions.

Jeffery et al has shown that during prone sleep the swallowing rate of newborn term infants is reduced significantly and there is no compensatory increase in arousal, when compared to the supine position. Bearing in mind that prone sleeping is a known risk for SIDS, they conclude that this may be a mechanism for increased risk in SIDS.


Saliva and SIDS

There are very few references to saliva in the SIDS literature. What there is, has generally suggested that saliva could be a cause of SIDS. For example it has been postulated that excessive salivation coupled with an immature swallowing reflex may cause choking. In addition, apnoea, bradycardia and cardiac arrhythmia may result if the infant lay prone with his nares in a pool of saliva.

None of these theories have shown any promise when considered in the light of scene and autopsy evidence.

An adequate supply of saliva, both quantitatively and qualitatively is clearly essential for the health and well being of the infant; the current paper has demonstrated the many functions and beneficial effects of saliva.

It is hypothesised that saliva is beneficial in “defending” against SIDS, but that when the child is sleeping both the salivary flow and the concentration of defensive agents, as has been demonstrated with IgA, is very low.

This might help to explain why the vast majority of SIDS incidences occur when the child is sleeping.

As an adjunct to this hypothesis it has been shown that the production of saliva promotes swallowing which in turn stimulates neural activity. The corollary can therefore be considered in that when saliva production, for whatever reason, is low, the swallow reflex is also at low ebb.

Although there is also no evidence that xerostomia is a precursor to SIDS, the saliva hypothesis could partly explain other known factors for the SIDS matrix:

1. Elevated temperatures reduce salivary flow
2. Exposure to tobacco smoke may result in hyposalivation
3. Pacifier use promotes saliva production, which may partly explain their protective effect on SIDS.

Not surprisingly, there are no clinical studies investigating salivary flow with sleeping position (prone v supine) in young children.

Conclusions

It is hypothesised that the reduced production of saliva in some sleeping infants may increase the risk of SIDS. It is considered that this might be a profitable area for future research.
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References


