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Review

Secretory IgA in Saliva can be a Useful Stress Marker

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Abstract

To evaluate secretory immunoglobulin A (sIgA) in saliva as an immunological stress marker, we reviewed the literature on sIgA and its variation caused by psychosocial factors. Among the studies on the effect of academic stress on sIgA secretion, we could distinguish two kinds of stress effects: the immediate stress effect which increases sIgA secretion immediately after stress, and the delayed stress effect which decreases sIgA secretion several days after stress. On the basis of production and secretion mechanisms of sIgA, we also speculated on possible mechanisms that underlie the variations of sIgA caused by stress. Eventually, we concluded that sIgA in saliva can be a useful stress marker if we analyze the delayed stress effect on sIgA separately from the immediate stress effect on sIgA.

Key words: IgA, secretory, marker, stress, saliva

Introduction

Psychoneuroimmunological research has shown that psychosocial factors, including stress, social support, and emotion may affect susceptibility to infectious disease by influencing the immune system[1,2].

Because the immune system is a part of a complex and interactive network formed by the brain, neurotransmitters and neuropeptides, secretory glands, and various types of immune cells, no single measure of 'immune functioning' can fully express immune competence. However, for practical and ethical reasons, only a few immunological parameters can be measured in experimental research dealing with human subjects.

In several studies, secretory immunoglobulin A (sIgA) has been chosen as a measure of resistance to infectious disease, because it plays an important role in the defense mechanism of mucosal membranes.

Besides, psychometric instruments (questionnaires) for measuring stress have been developed. To complement these questionnaires, immunological stress markers would be valuable objective measures.

This article reviews the literature on sIgA and its variations caused by psychosocial factors, speculates on possible mechanisms that underlie the variations of sIgA, and evaluates sIgA, especially salivary IgA, as an immunological stress marker.

General aspects of sIgA

Secretory immunoglobulin A (sIgA) is found in various secretory fluids, including saliva, breast milk, and nasal, gastrointestinal, bronchial, and urogenital secretions at high levels of concentration[3-5].

The secretory process and immunological functions of sIgA have been extensively studied[3-12].

Briefly, the secretory process of sIgA can be summarized as follows. At first, dimeric immunoglobulin A molecules, joined by a glycoprotein named J chain, are produced locally by IgA producing plasma cells in the lamina propria of mucosal membranes or in the connective tissue of glands[6-9]. Some of them diffuse through basement membranes to the basolateral surface of epithelial cells, where they are taken up by the epithelial cells with polymeric immunoglobulin receptors (poly-Ig receptor), then transcytosed to the apical surface of the epithelial cells, and released into secretory fluids in the form of sIgA[6-12]. This secretory process is shown schematically in Fig.1.

The sIgA molecule is composed of a dimeric immunoglobulin A containing the J chain, and another glycoprotein, secretory component (SC), which is a residue of the poly-Ig receptor and binds covalently to the J chain. The SC stabilizes the sIgA molecule and protects it from degradation by bacterial and digestive enzymes in the secretory fluid environment[3-12].

For immunological functions, sIgA antibodies prevent bacteria from forming colonies on mucosal surfaces, kill them directly or activate complements or provide synergism with innate defense mechanisms, e.g. lacto-ferrin, lacto-peroxidase, etc. They also neutralize toxins and enzymes produced by bacteria[3-9]. In addition, sIgA antibodies neutralize pathogenic viruses so as to inhibit their penetration into epithelial cells. Moreover, it is recently reported that even low concentrations of sIgA, which can not prevent influenza A virus from penetrating into cells, inhibit

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their infectivity by damaging their activation process in the cell[13]. It is also reported that dimeric IgA, endocytosed by the poly-Ig receptor, can neutralize the Sendai virus which penetrates into epithelial cells[14].

Besides, the sIgA antibodies prevent allergens and carcinogens[15] from being absorbed through mucosal membranes into the body. Moreover, immune-complexes formed beneath the epithelial cells after antigen absorption are transported out and into secretions by the poly-Ig receptor dependent transport system (or SC dependent transport system)[16].

From these sIgA functions, it may be expected that high proper sIgA secretion would prevent infections by various microorganisms in the mucosal membranes effectively. In fact, a review article concluded that the relatively high levels of sIgA in saliva is related to the lower incidence of upper respiratory tract illness, with the average effective size r = 0.25[17]. In addition, it is recently reported that transient salivary IgA-deficiency, which may permit various allergens to penetrate through the mucosal membranes, in the first year of life is a risk factor for the subsequent development of bronchial hyper reactivity[18]. Moreover, in children with a history of recurrent colds and flu, not only elevated psychosocial stress was observed but also lower sIgA/albumin ratios in saliva were detected[19].

Effect of psychosocial factors on sIgA

Various psychosocial factors, including academic examination[20-27], daily hassles[28], negative mood[29], desirable and undesirable daily events[30], work demand[31], and various relaxing factors[32-36] were investigated as a possible sIgA modifier. Results of those studies are shown briefly in Tables 1 to 3. In all of those studies, salivary IgA was chosen as a sIgA, because it is not only

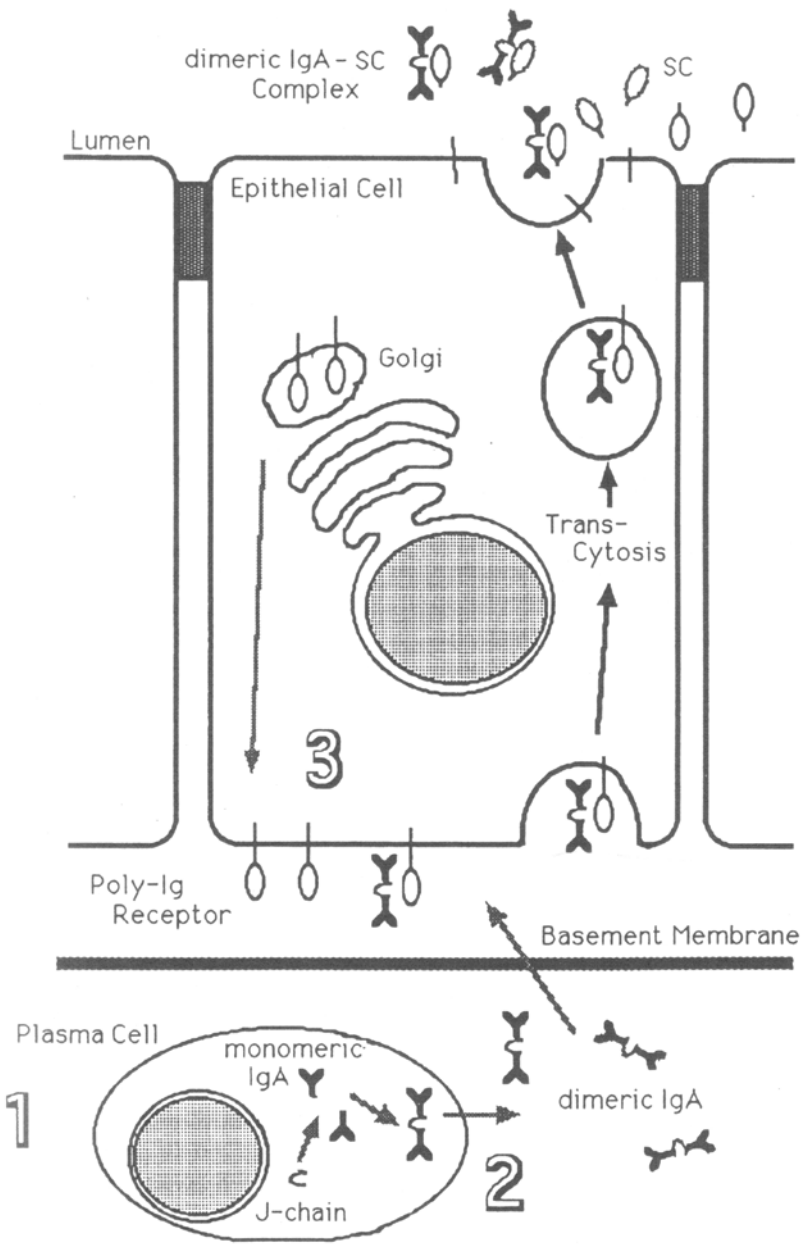

Fig.1 **Selective transport system of IgA into external secretions.**
Psychosocial factors could affect sIgA response at the following three steps in the SC-dependent transport system: 1. number of plasma cells, 2. immunoglobulin producing activity of plasma cells, 3. expression of polyIg receptors or SCs.

important for defense against upper respiratory tract infectious diseases as mentioned previously, but it also can be collected easily.

However, current literature does not show much agreement about the determinant of a sIgA response, except for the relaxing factors. Studying academic stress, as shown in Table 1, a decrease in sIgA level[20-23], as well as no alterations[24], or an increase[25-27] have been reported. Studying other kinds of stressful events as shown in Table 2, the sIgA response was also not simple[28-31]. On the other hand, all of the relaxing factors shown in Table 3 had positive effects on the sIgA response.

To explain the disagreement on the stress effect mentioned above, we tried to determine some rules which control the sIgA response to psychosocial factors. For simplifying the problem, we concentrated our attention on the studies on the academic stress effect as shown in Table 1. When we inspected the difference of methods of those studies, we noticed some interesting facts as follows. The sIgA levels decreased when it was determined several days or a few weeks after academic stress[20-23]. Whereas the sIgA levels increased when determined immediately after academic stress[25-27]. (Refer to sIgA variation and sampling time in Table 1.) We may call those opposite sIgA responses after stress as a delayed stress effect on the sIgA response and an immediate stress effect on sIgA response, respectively. The immediate stress effect seems to fade away in a short time after stress is relieved, resulting in a return of increased sIgA to its initial level[25,27].

As a result of this research, we have become able to understand, at least in part, the effect of other psychosocial stressors on sIgA secretion, as shown in Table 2. We may say it is a case of the delayed stress effect on the sIgA response that daily hassles caused a decrease in salivary IgA secretion after 4 weeks[28]. We may also say it is a case of immediate stress effect on the sIgA response that the work demand of air traffic controllers caused an increase in salivary IgA secretion[31].

However, it may not be appropriate to explain by the idea mentioned above that desirable and undesirable daily events correlate positively or negatively to salivary IgA secretion respectively[30], or that a negative mood showed a positive correlation to salivary IgA levels[29]. We must have some other ideas to explain those emotional effects on salivary IgA secretion.

All of the relaxing factors shown in Table 3 had positive effect on the sIgA response[32-36]. We may call those phenomena a relaxation effect on sIgA response.

Table 1 Effects of academic stress on salivary IgA[20-27].

Auther	Stress	Change	Sampling time	Note
Jemmott (1983)	Exam	--(p<.025)	Five times over one year (Sept, Nov*, April*, June*, July)	Higher sIgA secretion in RAS group (p<.06). No recovery in IPS group.
Jemmott (1988)	Exam	--(p<.0001)	Three occasions (1st: 5days before exam, 2nd*: on day of exam, 3rd: 14 days after exam.)	Higher sIgA concentration in adequate social support group (p<.05).
Mouton (1989)	Exam	--(p<.01) (at the most contrast, April-Sept)	Four occasions over 2 academic years (March, April*, Sept, Oct*)	A weak negative correlation (between stress level and sIgA secretion: r=-.25, stress level and sIgA concentration: r=-.36)
Deinzer (1998)	Exam	--(p<.01) weeks arround exam	25 days before exam, and every day for 2 weeks arround exam	Saliva was taken every morning immediately after awakening. No relationship between sIgA and URT symptoms.
Kiegolt-Glaser (1984)	Exam	+-	Two occasions (1st: one month before exam, 2nd*: on the first day of exam week)	Plasma IgA increased.
McClelland (1985)	Exam	+ (p<.06) (right after exam) +- (one and 3/4 hr later)	Three occasions (1st*: right after exam, 2nd*: one and 3/4 hr later, 3rd: several days later)	Rise of sIgA right after exam was followed by a drop one and 3/4 hr later. Lower sIgA, steeper drop of sIgA, and greater increase of NE in stronger n power group.
Evans (1994)	presentation for a science module	+(p<.l) (immediately after presentation)	ln 2 consecutive weeks during the same scheduled hours (9: 30, 10: 30, 11: 30, 12: 30), and immediately after presentation.	lncrease in cortisol.
Spangler (1997)	Exam	++ (p<.05) (5 and 15 mim after exam)	15 min before and 5 and 15 min after exam	SIgA also increased after the control situation.

*: stressful period RAS: the relaxed affiliative motive syndrome IPS: the inhibited power motive yndrome URT: upper respiratory tract

Possible mechanisms of variation of sIgA secretion caused by psychosocial factors.

As already shown in Fig.1, sIgA in saliva is produced locally by plasma cells in the salivary gland, and transported from the basolateral site of aciner cells or ductal cells of the salivary gland to their luminal site by the mechanism of SC dependent transport[3-12].

In the process of production and secretion of sIgA, we can point out three steps where psychosocial factors would affect a variation of sIgA secretion. In Fig.1, those steps are indicated by the large numerical characters, 1, 2, and 3.

The step shown by the character '1' in Fig.1 is the amount of plasma cells of the salivary gland. The number of plasma cells, expected to correlate positively with the level of IgA secretion in saliva, is in the balance with the continuous recruitment of plasma cells and the loss of them.

The plasma cells in the salivary gland will be recruited continuously to the gland in the following way. The precursor cells, B lymphocytes, are activated in mucosal associated lymphoid tissue (MALT), and induced switching to IgA. MALT includes gut associated lymphoid tissue (GALT), bronchial associated lymphoid tissue (BALT), and tonsil. The activated B lymphocytes migrate from MALT through lymphatic vessels into the blood circulation, then reach and stay in the salivary gland afterwards[37]. Several days will pass before the B lymphocytes maturate into plasma cells in the salivary gland.

At the same time, the plasma cells are lost continuously from the salivary gland, depending on the life span of the plasma cells. The average life span of plasma cells is thought to be less than 20 days, relating to the site of B cell activation, e.g. spleen, lymph nodes, lamina propria, and bone marrow[38].

Without the recruitment of precursor cells, continuous loss of plasma cells will result in a reduction of the number of plasma cells, and, consequently, in a decrease of sIgA secretion. In the salivary gland, rapid turnover of plasma cells was indicated in the case of chronic lymphocytic leukemia given an extracorporial blood irradiation therapy, and showing a significant decrease of circulating lymphocytes, which means a reduction in the supply of precursor cells of plasma cells, followed by a rapid decrease in salivary IgA levels[39].

Favorably, in meta-analytic studies, it is concluded that psychological stress affects T and B lymphocytes in the blood so as to inhibit the number and functions of the lymphocytes[40,41]. Stress hormones, cortisol and catecholamines, may be responsible for this stress effect on lymphocytes[42].

Since the effect of psychological stress on blood lymphocytes resembles that of extracorporial blood irradiation, it is expected that psychological stress decreases salivary sIgA secretion in the same manner as extracorprial blood irradiation, through a reduction in the recruitment of precurcer cells of plasma cells to the salivary gland.

The decrease of sIgA secretion will happen gradually, depending on the reduction rate of the supplying precursor cells and the half life of plasma cells. It is tempting to think this speculated mechanism of a decrease in sIgA may underlie the delayed stress effect on the sIgA response, mentioned previously, meaning a decrease of sIgA secretion several days after stress.

Another step, shown by character '2' in Fig.1, is the IgA producing ability of plasma cells. There is no direct evidence that a psychological stress or relaxation modulates IgA production by plasma cells yet. However, psychological stress or relaxation may possibly modulate plasma cell activity through stimulation of nerves, cytokines, and hormones. This is considered because a histopathologic study showed that plasma cells in the lamina propria were associated with nerve fibers[42,43]. Also, some studies reported that several cytokines, including interleukin-1 (IL-1), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), erythropoietin, and nerve growth factor[44-51], and hormones, including growth hormone, insulin-like growth factor-I, insulin-like growth factor-II, and insulin[52], influence the immunoglobulin production by plasma cells.

The remaining step which psychosocial factors might affect, shown by character '3' in Fig.1, is the SC dependent transport of

Table 2 Effect of other psychosocial factors on salivary IgA[28-31].

Auther	Factor	Change or Relation	Sampling time	Note
Farne (1992)	Variation of daily hassles	--(p<.01) (4 weeks after)	Three times with a 4 week interval.	
Evans (1993)	Negative mood	Positive correlation (r=.39, p<.006)	Each evening up to 2 weeks	Between subjects, 'net' desirable events positively correlated with sIgA (r=.56, p<.028).
Stone (1994)	Desirable daily events	Positive correlation (r=.11, p<.01)	At the end of each day, for 12 weeks	Secretory IgA antibody activity to rabbit albumin was assayed.
	Undesirable daily events	Negative correlation (r=-.17, p<.05)		
Zeier (1996)	Work of air traffic controllers	++ (p<.001)	Before and after 100 min working session	Increase in salivary cortisol concentration (p<.001)

IgA by epithelial cells. The production of a secretory component by epithelial cells can be regulated by various kinds of immunological, endocrinary, and neural factors. These factors include interferon-γ[54,55], IL-4[55], tumor necrosis factor-α[56,57], IL-1-α[56,57], IL-1-β[58], estradiol[59] and androgens[60], cholinergic agonist[57,58] and beta-adrenergic agonist[57,58], prostaglandin E2[57,58], vasoactive intestinal peptide[57,58], and somatostatin[58]. However, it should be noted that the mode of effect of those factors is rather organ specific[58]. Cholera toxin, 8-bromoadenosine 3':5'-cyclic monophosphate (bcAMP), and 8-bromoguanosine 3':5'-cyclic monophpsphate (bcGMP) significantly increased the secretory component production by submandibular acinar cells[57,58]. This result implies that, in the salivary gland, sIgA transport by the SC dependent system can be affected by psychological stress or relaxation through neural and/or endocrine mechanisms which vary intracellular cAMP or cGMP.

Can sIgA be a useful immunological stress marker?

As shown previously, current literature showed a favorable (positive) agreement in the effect of relaxing factors, whereas it showed a disagreement in the effect of stress on the sIgA response.

Stone et al[61] attributed the inconsistency of the sIgA response to a negative correlation between sIgA concentration and salivary flow[62] and to a possible degradation of sIgA by proteases in whole saliva. Moreover, they proposed their original method of measuring specific sIgA antibodies in parotid saliva as a measure of immunocompetence, in place of measuring total sIgA in whole saliva[61].

In opposition to the opinion of Stone et al[61], Jemmott et al [17] suggested that the negative correlation between the sIgA concentration and salivary flow is weak and not so problematic when unstimulated saliva is used, and taking salivary flow into account when measuring sIgA levels, e.g. assessing sIgA secretion rate, the problem of the negative correlation between sIgA concentration and salivary flow will be solved. Jemmott et al[17] also suggested that the measurement of sIgA concentration in whole saliva is highly reproducible and stable over time. Finally, they concluded that sIgA is a useful measure of resistance to infectious diseases[17].

It is true that Jemmott et al[20,21] have successfully showed that academic stress inhibits the sIgA secretion rate. In addition, they showed personality characteristics differentiated patterns of sIgA secretion rate[20] and a positive effect of social support on sIgA levels[21]. (Refer notes in Table 1.)

However, Mouton et al[22] suggested that assaying salivary IgA to measure stress may not be as useful in psychophysiological

Table 3 Effect of relaxing factors on salivary IgA[32-36].

Auther	Factor	Change	Sampling time	Note
Dillon (1985)	Humorous videotape	++ (p=.026)	Before and after videotape (30 min long)	
	Didactic videotape	+-		
Green (1987)	Relaxation response	++ (p<.05)	Before and after treatment (20 min long)	No significant change in salivay cortisol.
	Guided visualization	++ (p<.05)		
	Massage	++ (p<.01)		
	Lying down	+-		
	Touching control	+-		
Jasnoski (1987)	Relaxation	++ (p<.025) (vs vigilance task control)	Before and after protocol (1 hr long)	Negative correlation (r=-.39, p<.05) between sIgA and saliva norepinephrine.
Green (1988)	Relaxation	++ (p<.001)	Before and after 20-min relaxation practice	Increase of serum IgA (p<.001), IgG (p<.001), IgM (p<.05) over a 3 week practice period.
		++ (p=.014) (22nd day vs 1st day)	On the 22nd day of relaxation practice	
Olness (1989)	Self-hypnosis	+-	Before and after self-hypnosis (25 min long)	Children (6-12 yr old) were recruited.
	Self-hypnosis + specific suggestions	++ (p=.007)		

research as expected. It was because, in their academic stress study enrolling dentistry students on four occasions over a period of 8 months, they observed a significant difference in the level of salivary IgA only for the most polarized contrast, i.e., between final exam and end of summer vacation, and they also observed a weak negative correlation between the level of salivary IgA and the stress rating only at the final exam[22].

In our opinion, the sIgA response to psychological stress can be rather complex because of the following. The delayed stress effect, which decreases sIgA secretion in saliva gradually, must be superimposed with the immediate stress effect, which increases sIgA secretion in saliva immediately. Thus, an inhibition of the sIgA response caused by stress experienced several days previously can be cancelled at the time of saliva sampling by an increase in the sIgA response caused by another stress experienced only several hours before saliva sampling.

Therefore, when the delayed and inhibitory effect of some stress on the sIgA response is concerned, it is necessary to remove immediate and increasing effect of other stresses from the sIgA response. Deinzer, et al.[23] successfully solved the problem by sampling saliva every morning immediately after awakening and before doing anything else.

Reversely, when the immediate and increasing effects of some stress on the sIgA response is concerned, the delayed and the inhibitory effect of other stresses would not affect the result, because the delayed stress effect would be almost constant during the short experimental period. From this point, sIgA in saliva can be said to be a more suitable immunological marker for the immediate stress effect than for the delayed stress effect.

Complexity of sIgA response to stress may be seen only in human. Interestingly, it is reported that salivary IgA can be a marker of social stress in rats[63]. Male rats housed singly showed stable sIgA levels with little variation, while those housed separately with a female showed an initial decrease in sIgA followed by a steady increase. Males housed in a group (n=6) showed a steady decline in sIgA levels[63].

In their study of air traffic controllers, Zeier, et al.[31] suggested that positive emotional engagement is responsible for the observed sIgA increase. They also suggested that measuring sIgA response may be a valuable tool for differentiating between positive and negative stress effects or between successful and unsuccessful adaptation or coping with situational demands[31].

Miletic, et al.[64] reported an interesting fact that elderly persons who were excited by social events over the weekend days (friends or family member visits, worship and social events in churches, etc.) showed an increase in their sIgA secretion during the weekend days.

In summary, sIgA in saliva is a promising candidate as a stress marker which may be able to differentiate between positive and negative stress effects. However, some additional studies will be necessary to establish proper methods to separate the immediate stress effect and the delayed stress effect on sIgA response, and to elucidate mechanisms of sIgA variation caused by psychosocial factors.

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