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Influence of stress on secretory IgA: is it a possible stressmarker in animals?

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Abstract
The concentration of secretory immunoglobulin A (sIgA) in the saliva can be affected by several different factors. One such factor is stress, which is well known to increase the susceptibility to infections. Since stress is difficult to clearly define and it can vary between individuals what is percieved as stress, it would be valuable to have a biological marker. Such a marker could be a helpful tool in assessing well-being in laboratory animals. Secretory IgA is one candidate that has been studied. In this mini-review, the effect of stress on the amount of sIgA, mainly salivary IgA, is discussed. It is concluded that sIgA is a potential stress marker in humans as well as in animals. However, more detailed studies are needed to further evaluate this.

Introduction
It is well known that stress affects the immune system and may increase the susceptibility to infections (*Solomon GF., et al.* 1974. *Plaut SM., SB. Friedman* 1981). This may be due to suppression of components of the immunologic defense. The field of psychoimmunology has rapidly expanded and various parameters have been evaluated as potential measures of immunocompetence in relation to psychological factors (*Calabrese JR., et al.* 1987). One of these parameters is secretory immunoglobulin A (sIgA), which has been studied in association with e.g. recurrent upper respiratory tract infections, secretory otitis media and oral antigens (*Drummond PD., B. Hewson-Bower* 1997. *Hess M., J. et al* 1991. *Bosch JA., et al.* 1996). Stress is difficult to objectively define, and therefore a biological marker would be of great value in many cases, e.g. to assess well-being in laboratory animals. In the present mini-review one of the potential stress markers, sIgA in the saliva, is discussed.

Secretory IgA
IgA is the dominant immunoglobulin isotype on all mucosal surfaces. It acts as a first line of defense, by opsonization of foreign invaders and blockade of their infectivity *(Miletic ID., et al.* 1996). Secretory IgA is found in saliva, urine, tears and other mucosal fluids. A polypeptide (J-chain) links two IgA molecules to form a dimer, to which also a polypeptide secretory component is linked. This component is responsible for an increased resistance to proteolysis. Secretory IgA has a short half-life (3-6 days) and a high synthesis rate (66 mg/kg/day) (*Islam KB.,et al.*,1994).
Saliva is attractive for psychophysiological studies because it can easily be collected by a non-invasive method, and therefore, sampling can be performed several times every day. Another reason for using a salivary protein as a stress-marker is the fact that salivary secretion is regulated by the autonomic nervous system (ANS) *(Mandel ID., S. Wotman,* 1976). Several different types of physical and psychological stressors have been shown to give an ANS response, with effects on target organs due to activation of adrenergic receptors. There is also a possible direct action of stress hormones on specific receptors in the salivary glands.

Physiological modifiers of sIgA concentrations

Physical stress
The immune system responds to increased physical activity and it is claimed that exercise results in a better resistance to infections (*Nash HL.*,1987). In contrast, intense physical training

may cause immune suppression (*Pedersen BK., et al.*,1996). It is difficult to determine an exact level where the physical activity turns into harmful stress for the body. So far most studies have investigated intense training over a long period of time. In elite athletes, decreases in salivary IgA levels have been observed following intense endurance exercise (*Tomasi TB., et al.*, 1982). For elite swimmers, a significant decrease in salivary IgA levels was recorded both pre and post exercise over an eight months training period *(Gleeson M., et al.*,1995). This indicates a chronic, local immune suppression associated with intensive exercise. Long distance running can also alter IgA levels in saliva. Participants in a marathon race and in a 31 km race all showed significant reductions in IgA concentrations in the saliva (*Muens G., et al.*, 1989). These levels returned to normal after three days. Cross-country skiing is another sport in which a reduction in salivary IgA occurs after a race (*Tomasi TB., et al.*, 1982). Two hours intense ergometer cycling gave a similar result with a 70% decrease in salivary IgA (*McKinnon LT., et al,*. 1987). Pregnancy and parturition are events that fall between physical and psychological stress and may contain a part of both. At parturition a significant drop in salivary IgA occurs *(Annie CL., M. Groer,* 1991).

Psychological stress

Psychological stress is more difficult to define than physical stress. It is very much up to each individual what is perceived as stress. However, one situation that is considered to be generally stressful is academic examinations. Several studies have been performed on students before and after examination periods *(Mouton C., et al.*, 1989. *Jemmot JB., K. Magloire,* 1988. *Jemmot JB., et al.*, 1983. *Kiecolt-Glaser JK., et al.*, 1984. *McClelland DC., et al.*, 1985). In one study there was no significant difference (*Kiecolt-Glaser JK., et al.*,1984) but most of them show decreased salivary IgA levels in the most stressful periods. Those who were most aroused adrenergically by the examination (with high norepinephrine levels in the saliva) had the greatest decrease in salivary IgA levels (*McClelland DC., et al.*, 1985). Students that reported substantial social support had higher levels of salivary IgA than the students with less support (*Jemmot JB., K. Magloire,* 1988). Additionally, students displaying what was called the "inhibited power-motive syndrome" (basically, a personality type in which the drive for power is high but must be inhibited because of circumstances) had lower IgA levels (*Jemmot JB., et al.*, 1983).

Work can also be a social stressor depending on the nature of the tasks and the environment. The National Institute for Occupational Safety and Health has been interested in salivary IgA as a biomarker of occupational stress (*Henningsen GM., et al.*, 1992). In air traffic controllers the working session caused an increased secretion rate of salivary IgA, which was opposite to what was expected *(Zeier H., et al.*, 1996). The cortisol levels in the saliva were also increased. Similar results were found in soccer coaches during a match (*Kugler J., et al.*, 1996). Perhaps this is a form of positive stress or arousal, where positive emotions counteract the negative effects of stress.

Isolation is another form of social stress. In a study of an isolation period of 60 days the salivary IgA levels was reported to vary in a cyclic manner (*Hennig J., P. Netter,* 1996).

Mood and humour

Anxiety and mood can influence the level of sIgA. For example anxiety has been shown to decrease the secretion of salivary IgA. (*Graham NMH, et al.*, 1988). People that are frequently anxious have significantly lower levels than those who are only occasionally anxious. A positive mood has been shown to result in a higher antibody response to a novel antigen compared to negative mood (*Stone AA., et al.*, 1987). On the other hand, negative mood has been shown to be associated with higher secretion rate of salivary IgA on an individual basis, but not when different groups were compared. (*Evans P., et al.*, 1993). The stress level for an individual does not seem to affect the salivary IgA concentration (*Kubitz KA., et al.*, 1986).

Humour and laughter might be a way to attenuate the adverse effects of psychosocial stress. It has been reported that sIgA levels are correlated with scores on the Coping Humour Scale (*Dillon KM.,*

et al.,1985*)*. The subjects that were presented a humourus film also displayed greater increase in sIgA concentrations than those watching a non humourus film. One explanation for this is that individuals that perceive some humorous aspects in a situation is less likely to appraise the situation as stressful or threatening (*Martin RA., JP. Dobbin,* 1988). It is also possible that pleasant emotions associated with humour may counteract emotions engendered by stress.

Relaxation

Relaxation can be regarded as the opposite of stress. Daily relaxation for 20 minutes may significantly increase the secretion rate of salivary IgA (*Green ML., et al.,* 1988). There is also a longer-term training effect. Individuals who have practised relaxation for three weeks show a higher increase than those who do it for the first time. Combining relaxation and mental imagery gives the same result *(Janoski ML., J. Kugler*, 1987). Salivary IgA is also negatively correlated with salivary norepinephrine. It is proposed that relaxation may be a self-regulating strategy affecting both humoral and cellular divisions of the immune system. (*Green ML.,et al.,* 1988). One study has been performed to evaluate the effectiveness of therapeutic touch in reducing the immunological effects of stress in students. In that report differences in IgA levels between treated and non treated students were observed (*Olson M., et al.,* 1997).

Other factors

Both age and gender can influence the concentration of IgA in the saliva. Saliva flow and salivary IgA secretion rate are significantly lower in old people than in the young (*Miletic ID., et al.,* 1996). Age also affects the effects of stress on the immune system (*Pariante CM., et al.,* 1997). In one study on stress and salivary composition male patients had higher rates of IgA secretion in the saliva than female patients (*Somer E., et al.,* 1993). Dietary factors can also influence the concentration of sIgA in the saliva (*Chandra RK..,* 1991). The flow rate is another important factor that is needed to take into consideration. It can be altered by a lot of different factors and thereby change the salivary concentration of individual proteins (*Gleeson M, et al.,* 1995).

Mechanisms linking stress and immunity

In a study on stress in students the decrease in salivary IgA was significantly related to levels of norepinephrine (*McClelland DC., et al.,* 1985). Similarly, a negative relationship was found between salivary IgA and epinephrine in individuals who were frustrated and stressed *(McClelland DC., et al.,* 1980). These findings suggest that the immunosuppressive effects may be due to the action of adrenal hormones, which are elevated during stress. Both adrenergic and cholinergic drugs in culture have effects on lymphocyte functions (*Cohen JJ.,* 1987). Corticosteroids have been shown to block humoral antibody production by binding to specific cytoplasmic receptors in the lymphocytic cells (*Siegel HS.*, 1987). The steroid receptor complex passes into the nucleus altering the enzymatic activity and influences nucleic acid metabolism. This would then interfere with the synthesis of immunoglobulins. Corticosteroids also cause death of immature lymphocytic cells by apoptosis. An alternative pathway involves the association of stress with specific behaviours that modulate the immune response (*Herbert TB., S. Cohen,* 1993). Distressed persons sleep less, exercise less, have poorer diets, smoke more and use alcohol and other drugs more often than non distressed people (*Conway TL., et al.,* 1981). For example smoking has been shown to suppress the secretion of salivary IgA (*Tamura A., et al.,* 1995).

Secretory IgA as a stress-marker in animals

Prolonged stress, if reliably assessed in a non-invasive manner, may be a useful tool to assess animal welfare. When working with laboratory animals avoiding stress is essential ensuring maximum well-being. One problem is that many methods that may be used to measure stress require sampling techniques that are themselves stressful. Collecting saliva is a relatively simple and non stressful method. Rats for example can easily be conditioned for saliva sampling (*Guhad FA., J. Hau,* 1996).

Salivary IgA has been tested as a stress marker in police and army dogs in training (*Skandakumar S., et al.*, 1995). The stress determined by behavioural assessment was associated with increased cortisol levels and decreased IgA levels in the saliva.

For rats, crowding as well as isolation is known to result in stress and immune suppression (*Brain P.*, 1975). This fact has been used to evaluate salivary IgA as a stress marker in rats (*Guhad FA., J. Hau,* 1996). Male rats housed in groups (n=6) showed a decrease in IgA while there were stable levels in singly housed males. In poultry another kind of secretory IgA, lacrimal IgA, has been studied as a potential stress marker (*Florence BD., et al.*, 1995). No significant difference in IgA production could be found, but all groups showed high corticosterone levels, suggesting that all groups already were stressed.

Conclusions

Many factors may influence the concentration of IgA in the saliva. The results on the influence of stress are heterogenous. Both lower, higher and unchanged levels have been reported, although the majority of them support the hypothesis that stress decreases the concentration of IgA in the saliva. One problem might be that so many factors are involved that it is hard to study only one and avoid all confounding factors. The saliva flow is one example, it can itself be changed by stress and thereby indirectly change the concentration of salivary IgA (*Gleeson M, et al.*, 1995). The opposite effect, with increased secretion after mental relaxation, is better supported in the litterature. In conclusion, secretory IgA may be a stress marker but it has to be further studied in more detail.

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