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Interleukin-1 and IL-1 receptor antagonist in gingival crevicular fluid

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Abstract

Background/aims: This study aimed to investigate the cytokine IL-1β and its receptor antagonist IL-1ra in gingival crevicular fluid (GCF), in patients with adult periodontitis.

Method: A total of 40 GCF samples were harvested from 10 subjects with moderate to severe adult periodontitis and 10 healthy controls. Subjects were selected from both genders, with all the upper anterior teeth present, and with no relevant systemic illness, pregnancy or recent medication. All subjects were non-smokers and had not received any periodontal therapy within the preceding 3 months. Deep bleeding sites, deep non-bleeding sites and healthy sites were investigated in relation to upper anterior teeth. Clinical measurements were recorded for each site, after obtaining a GCF sample. IL-1β and IL-1ra were quantified using new commercially available ELISA kits (Quantikine^{TM}), and could be detected in all samples.

Results: The mean concentration for IL-1β was 0.11 (SD 0.14) pg/μl for bleeding periodontitis sites, 0.04 (0.05) pg/μl for non-bleeding periodontitis sites, and 0.01 (0.03) pg/μl for healthy sites ($p<0.001$). In contrast, the mean concentration for IL-1ra was 6.99 (9.78) pg/μl for healthy sites, 0.59 (0.44) pg/μl for non-bleeding periodontitis sites, and 0.44 (0.36) pg/μl for bleeding periodontitis sites ($p<0.001$, except for comparisons between bleeding and non-bleeding periodontitis sites, $p>0.05$). For healthy sites, a strong inverse relationship was found between IL-1β and IL-1ra levels in GCF.

Conclusions: The results suggest a strong relationship between the severity of adult periodontitis and the increasing GCF levels of IL-1β and decreasing levels of IL-1ra.

Key words: interleukin-1; interleukin-1 receptor antagonist; gingival crevicular fluid

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Interleukin-1 (IL-1) is an important mediator of immune and inflammatory responses (Alexander 1994). IL-1 production may be induced by micro-organisms, microbial products, inflammatory agents, and antigens (Dagmar & Meley 1994), and has wide effects on multiple target cells and tissues. These include increased macrophage cytocidal activity, prostaglandin production, neutrophil chemotaxis and activation, neutrophilia, B lymphocyte proliferation and antibody production. T-lymphocytes are also stimulated to produce lymphokines. Furthermore fibroblast proliferation, collagenase and prostaglandin production, osteoclast formation, bone and cartilage resorption are increased.

2 forms of IL-1 have been identified: IL-α and IL-1β. Both forms are glycoproteins of 17 kDa (Dinarello 1991). Both are structurally related polypeptides that show approximately 25% homology at the amino acid level (Tizard 1995), and have similar pro-inflammatory properties, with IL-β being the more potent (Tatakis 1993). IL-1β is usually produced at 10-to-50 folds higher level than Il-1α (Tatakis 1993) and is usually secreted by cells, while IL-1α usually remains membrane bound (Dinarello 1991). Both types of IL-1 need to bind to specific receptors on certain lymphocytes (specifically Th2 cells) in order allow for signal transduction to occur (Dinarello 1991).

2 receptors for IL-1 (IL-1r) of 68 and 80 kDa have been studied and cloned (Dinarello 1991, Tizard 1995). IL-1rI (80 kDa) is found on T cells, fibroblasts and keratinocytes, whilst IL-1rII (68

kDa) is found on B cells and PMNs. Few IL-1 receptors need to be bound for signal transduction, and biological activity is also controlled by interleukin-1 receptor antagonist (IL-1ra) and by specific soluble receptors (Rose-John & Heinrich 1994, Burger et al. 1995). IL-1ra is a glycoprotein that belongs to the same family as IL-1 and is produced by the same cells, especially macrophages (Seckinger et al. 1987). Its only known function is to bind to IL-1 receptors, blocking IL-1 and preventing signal transduction (Starner 1991).

IL-1β is important in periodontal diseases due to its potency in inhibiting bone formation and enhancing bone resorption (Dinarello 1991, Mundy 1991, Stashenko et al. 1991), stimulating the production of prostaglandin E2, collagenase, and proteinase (Dinarello 1990, 1991). IL-1β has been shown to have a dual function in collagen digestion. It inhibits the intracellular phagocytic pathway, but at the same time strongly promotes extracellular digestion by inducing the release of collagenolytic enzymes such as collagenase (Nakaya et al. 1997, Van der Zee et al. 1997). Previous studies have reported that IL-1β is usually found in significant amount in GCF samples taken from patients with adult periodontitis (Masada et al. 1990, Wilton et al. 1992). Recently, IL-1ra has also been identified in GCF (Kabashima et al. 1996, Ishihara et al. 1997).

To date few studies have investigated the relationship between IL-1β and IL-1ra in GCF. The aims of this study were to investigate further the cytokine IL-1β and its receptor antagonist IL-1ra in GCF. The objectives for this study were: (1) To investigate GCF IL-1β and IL-1ra concentrations in periodontally healthy and in adult periodontitis sites. (2) To investigate the relationship between GCF IL-1β and IL-1ra in GCF.

Materials and Methods

Subject and site selection

Full ethical approval was obtained for this study and written, informed consent was obtained from each subject. Patients were chosen at random from those attending the Periodontology and the Restorative Clinics at the Charles Clifford Dental Hospital, Sheffield.

Diseased subjects had moderate to severe adult periodontitis with the following sites present in each subject: (1) a healthy site having a probing depth $\leqslant$3 mm, with no bleeding on gentle probing, (2) a non-bleeding site having a probing depth $\geqslant$6 mm, and (3) a bleeding site having a probing depth $\geqslant$6 mm.

Subjects were selected from both genders, with all the upper natural anterior teeth present, and with no relevant systemic illness, pregnancy or recent medication. Patients had not used mouthrinses or pulsed oral irrigators on a regular basis. All subjects were non smokers and had not received any periodontal therapy within the preceding 3 months.

Age and gender matched subjects with healthy periodontal tissues having sulcus depths $\leqslant$3 mm, no bleeding on gentle probing, and with no clinical signs of inflammation were also selected from amongst patients attending the Restorative Clinic, to act as a second group of healthy controls. The 3 sites in each subject with periodontitis and the 1 site from each periodontally healthy subject were selected to investigate the concentrations of IL-1β and IL-1ra in gingival crevicular fluid (GCF).

Measurements

All patients refrained from rinsing, drinking or eating, 30 min prior to investigations. Measurements were taken in the following order: (1) GCF samples; (2) probing depth (to the nearest mm) at each studied site (PTD Sensor Periodontal Probe Type US; (C)), (3) the presence or absence of bleeding from the sites measured; (4) loss of attachment (the distance between the cement-enamel junction to the base of the pocket). Only upper anterior teeth were included in the study to improve the access for sampling and reduce the risk of salivary contamination during sampling.

GCF sampling procedures

Each sample site was carefully isolated using cotton wool rolls and saliva ejector, to avoid saliva contamination, since saliva contains both IL-1β and IL-1ra. Supragingival plaque and saliva were removed with cotton pellets. A Periopaper strip (Periopaper®, Interstate Drug Exchange, Amitiville NY 11701–1130) was inserted gently avoiding any irritation, 0.5 mm into the gingival crevice at each of the chosen sites, and left in place for 30 s. The first sample was discarded (since it contained a sample of the previously accumulated GCF). A second Periopaper® strip was inserted gently 0.5mm into the same selected site after an interval of 10 s, and left in place for 3 min to ensure collection of an adequate sample was obtained. The GCF volume was measured immediately using a calibrated Periotron 6000™ (HARCO Electronics). After recording the readings obtained from the Periotron 6000™, they were converted into GCF volumes using a calibration graph.

Laboratory procedures

The GCF samples were placed in a transport medium containing 1 ml of phosphate buffered saline and bovine serum albumin (Sigma, St Louis, MO) immediately after the recording of the Periotron readings. After sonicating the capsules using an ultrasonic bath (L & R 2014) in order to ensure adequate eluting of GCF components from the paper strips, 150 μl amounts were transferred from each sample (1 ml transport medium and a Periopaper® strip containing a known amount of GCF), to a new labelled vial. This procedure was repeated four times in total in order to obtain 4 labelled vials into each of which 150 μl had been transferred from the original 1 ml vial. The remaining 400 μl and the periopaper strip were then discarded.

Samples were stored at -80°C. A maximum of 4 h elapsed between sampling and freezing. Commercially available Enzyme Linked Immunosorbent Assays (ELISA) were used subsequently to quantify the IL-1β and IL-1ra in the GCF samples (Quantikine, R&D systems, Minneapolis, MN) in accordance with the manufacturers instructions. After the colour development was stopped, optical density was measured using a microtiter plate computerised reader, set to wavelength of 540 nm.

Statistical analysis of the data

GCF volumes (μl), IL-1β and IL-1 ra concentrations (pg/μl), probing depth and attachment loss (mm), bleeding on probing (bleeding/non-bleeding) were transferred to a spreadsheet programme on a personal computer. Also, the data were analyzed using 2 statistical packages (Minitab, version 9.2 for windows and SPSS for Windows, version 6.0) for statistical analysis. Initially, the means,

Table 1. Clinical data for periodontitis subjects and periodontally healthy controls

	Probing depth (mm) mean (±SD)	Attachment level (mm) mean (±SD)	GCF (μl) mean (±SD)
bleeding sites	6.8±0.8	6.3±1.9	2.6±0.9
non-bleeding sites	6.3±0.7	4.9±1.6	1.4±1.2
healthy sites (periodontitis subjects)	2.5±0.5	1.6±0.5	0.5±0.9
healthy sites (periodontally healthy subjects)	2.3±1.3	1.3±0.5	0.5±0.9

Table 2. Mean IL-1β (pg/μl) and IL-1ra (pg/μl) in GCF for healthy and diseased sites

	IL-1β (pg/μl) mean (SD)	IL-1ra (pg/μl) mean (SD)
bleeding sites	0.11 (0.14	0.44 (0.36)
non-bleeding sites	0.04 (0.05)	0.59 (0.44)
healthy sites (periodontitis subjects)	0.01 (0.03)	6.99 (9.78)
healthy sites (periodontally healthy subjects)	0.01 (0.01)	9.65 (12.90)

IL-1β
$p=0.005$ bleeding versus non-bleeding periodontitis sites, $p=0.005$ bleeding periodontitis sites versus healthy sites in subjects with adult periodontitis.
$p=0.007$ non-bleeding versus healthy sites in subjects with adult periodontitis.
IL-1ra
$p=0.005$ bleeding versus healthy sites in subjects with adult periodontitis, $p=0.005$ non-bleeding versus healthy sites in subjects with adult periodontitis.
IL-1β and IL-1ra
$p=0.002$ inverse relationship. The concentration of IL-1β was high and the concentration of IL-1ra was low at disease sites. The concentration of IL-1β was low and the concentration of IL-1ra was high in GCF from healthy sites.

the standard deviations and ranges were calculated for the quantitative data.

Anderson Darling tests were carried out to establish if the data were normally distributed. Thereafter, Mann-Whitney tests, for non-parametric data, were used to compare each of IL-1β and IL-1ra concentrations respectively, between healthy sites in healthy subjects and healthy sites in diseased subjects. Friedman's two way analysis of variance test was used to investigate the differences in GCF IL-1β and IL-1ra concentrations respectively, according to site. The differences in GCF IL-1β and IL-1ra concentrations between groups were investigated using Wilcoxon matched pair tests. Bonferroni correction for multiple testing was taken into account where appropriate (Altman 1991). Finally, the Spearman test for ranked non-parametric data was used to study the correlations between IL-1β and IL-1ra concentrations for all sites. *P*-values of less than 0.05 were taken to indicate statistical significance.

Results

Subjects and sites

20 subjects were included in this study, 10 of whom had a healthy periodontal status (as controls) and 10 of whom had adult periodontitis. The mean age of the diseased subjects was 42.9 (range 35–53 years, SD±6.5) whereas the mean age for the controls was 41.5 (range 35–51 years, SD±5.7). The diseased group was comprised of 4 males and 6 females, and the controls comprised of 5 males and 5 females. Of the 40 sites, 10 sites bled on gentle probing.

Mean GCF, pocket depth and attachment loss were calculated for healthy and diseased sites of diseased subjects and for healthy sites of control subjects (Table 1).

IL-1β and IL-1ra concentration

The IL-1β and IL-1ra concentrations for healthy and diseased sites are presented in Table 2. No statistical differences could be demonstrated between IL-1β concentration in healthy sites of diseased patients and healthy sites in healthy controls. Thus, analyses were confined to diseased subjects only. From Table 2, it can be seen that the mean concentration for IL-1β was the highest in the bleeding periodontitis sites, intermediate in the non-bleeding periodontitis sites, and the lowest in the healthy sites. However, the variability of the IL-1β concentrations was greatest for the bleeding periodontitis sites (SD 0.14), intermediate for the non-bleeding sites (SD 0.05), and the lowest for the healthy site (SD 0.03). All comparisons between groups reached statistical significance.

Means of IL-1ra concentrations were calculated for the healthy and the diseased sites of the diseased subjects group, and for the healthy sites of the controls group. These results are presented in Table 2. No statistical differences could be demonstrated between IL-1ra concentration in healthy sites of diseased subjects and healthy sites of controls. Thus, analyses were confined to diseased subjects.

IL-1ra concentration in the healthy sites was significantly different from those in the bleeding and non-bleeding periodontitis sites ($p<0.01$). Whereas, no statistical differences could be found between IL-1ra concentrations in bleeding sites versus non-bleeding sites. However, there was a trend in IL-1ra concentrations from non-bleeding sites to bleeding periodontitis sites.

IL-1β and IL-1ra

A significant correlation was found between IL-1β and IL-1ra concentrations ($p<0.01$). As IL-1β concentrations increased, IL-1ra concentrations decreased.

Discussion

In this study IL-1β and IL-1ra were detected in all GCF samples from healthy and diseased sites. These findings for periodontally diseased sites are in agreement with previous studies. However, our findings contrast to Masada et al. (1990) and Wilton et al. (1992) who reported that IL-1β, and Kabashima et al. (1996) who reported that IL-1ra were not detected in GCF from healthy sites. An explanation for this finding might be that assays employed in earlier studies were less sensitive and could not detect low levels of IL-1β and IL-1ra, if present at healthy sites. In addition, earlier assays may not have been specific for IL-1β (Lotz et al. 1988). Nonetheless, using a more sensitive and specific immunoassay, Ishihara et al. (1997) found that IL-1β was present in all GCF samples from all adult periodontitis sites, but not in samples from healthy sites.

IL-1β in GCF may originate from plasma, and may also be found in GCF samples as a result of saliva or blood

contamination. Although we could not rule out the contribution derived from plasma, this probably was not a factor in our study, because none of the patients had medical conditions such as rheumatoid arthritis, where IL-1β has been reported in plasma (Eastgate et al. 1988). Non-inflamed sites are also usually infiltrated by inflammatory cells that could be the origin of IL-1β detected in GCF samples from healthy sites. Samples of GCF may also be contaminated with IL-1β from blood in bleeding sites or saliva during collection (Dinarello 1991, Tizard 1995). However, care was taken to avoid contamination by collecting samples before measurement of probing depth, that may evoke bleeding. Salivary contamination was avoided by isolating sites with cotton rolls, using a saliva ejector and taking samples from anterior teeth.

The sampling method and collection time, have also been found to be of great importance. These two variables may influence the composition of GCF samples (Eley & Cox 1997a,b,c). Collection of GCF samples using small precut strips for a relatively short time is a valuable, reproducible and reliable collection technique (Lamster 1997). However, collection of GCF for 30 s is not enough time for collecting some cytokines in detectable amounts (Reinhardt et al. 1994). Therefore, a collection time of 3 min was selected for the collection of GCF. Irritation of periodontal tissue such as may be caused by repeated collections was also avoided, since this may evoke bleeding or increase the flow of the GCF and stimulate the release of various cytokines (Lee et al. 1995).

The means of IL-1β concentrations found in this study were 0.11 pg/μl from the bleeding periodontitis sites, 0.04 pg/μl from the non-bleeding sites, and 0.01 pg/μl from the healthy sites. It is difficult to compare these results with most of the previous studies, due to variations in experimental methodology and mathematical treatment of results. Hou et al. (1995) and Ishihara et al. (1997) reported IL-1β concentrations of 51.26–242.8 pg/site and 4.03–511.12 pg/site respectively. Reinhardt et al. (1994) reported IL-1β concentration of 23–92 pg / 30 seconds which are also difficult to compare with our results. On the other hand, few studies have reported higher amounts of IL-1β in GCF samples such as Wilton et al. (1992), Dagmar & Meley (1994), and Lee et al. (1995) who reported IL-1β concentration of (12.38–420.90 pg/μl), (22.8–882.2 ng/ml), and (433.33–633.12 pg/ml) respectively. These high figures however, may be due to the use of assay kits that may not have been specific for IL-1β.

Our findings for IL-1β concentration in GCF for diseased sites are in general agreement with previous studies reporting a correlation between the severity of the inflammation and the increasing amounts of IL-1β (Dagmar & Meley 1994, Lee et al. 1995, Ishihara et al. 1997). Although there was a wide range in the values of IL-1β detected in our GCF samples, the levels of IL-1β in bleeding periodontitis sites were up to 10 times greater than in samples from healthy sites.

The within-group variation in IL-1β concentrations may be due to minor differences in the degree of inflammation at the time of sampling that are difficult to evaluate by clinical indices (Greenstein 1997). The variability of IL-1β was greatest for the bleeding sites, intermediate for the non-bleeding sites, and lowest for the healthy sites. Previous reports have suggested the IL-1β levels in GCF reflect the severity of the inflammation in the sites studied, even within sites that show similarities in the degree of clinical inflammation (Dagmar & Meley 1994, Lee et al. 1995, Ishihara et al. 1997).

No statistical difference could be found between IL-1ra GCF concentration from healthy sites of diseased subjects and healthy sites of periodontally healthy subjects. The IL-1ra concentrations in healthy sites however, were significantly different from those in the diseased sites. Increased production of IL-1β and suppression of IL-1ra production, in inflammatory periodontal diseases may contribute to tissue destruction, whereas the reverse may result in the suppression of IL-1β mediated tissue destruction (Kabashima et al. 1996). This may explain our findings of raised IL-1β concentrations and low IL-1ra concentrations in GCF from deep bleeding sites compared with healthy sites, and the reverse for healthy sites. This theory is supported by previous studies suggesting the relationship between IL-1ra and IL-1 (including IL-1β and IL-1α) is a natural control mechanism in most clinical situations (Kabashima et al. 1996, Ishihara et al. 1997). IL-1ra may also bind to IL-1α, which is also elevated in inflammation (Dinarello 1991). Other mechanisms have also been reported by which the IL-1 activity could be altered, such as the presence of the specific soluble receptors that bind to the IL-1β molecule itself (Rose-John & Heinrich 1994, Burger et al. 1995), and the release of other cytokines such as IL-4, which has been found to suppress both types of IL-1, as reported by Kabashima et al. (1996).

Since IL-1ra has been shown to inhibit the IL-1 β activity by binding and blocking the specific receptors for IL-1β found on the target cells (Dinarello, 1991), this study investigated whether there is a correlation between IL-1ra levels and IL-1β levels in GCF of subjects with adult periodontitis. A strong correlation was found between IL-1β and IL-1ra concentrations at both the diseased and the healthy sites ($p<0.05$). However, further research and longitudinal studies are required to investigate more closely the relationships between IL-1β and other cytokines including IL-1α, IL-4, IL-1ra and IL-1 soluble receptors, in subjects with known disease activity.

Zusammenfassung

Interleukin-1 und IL-1-Rezeptorantagonist in Sulkusflüssigkeit

Einleitung: Diese Studie hatte das Ziel, das Zytokin IL-1β und seinen Rezeptorantagonisten IL-1ra in Sulkusflüssigkeit (SF) bei Patienten mit Erwachsenenparodontitis zu untersuchen.

Methoden: Insgesamt wurden bei 10 Patienten mit moderater bis schwerer Erwachsenenparodontitis und 10 gesunden Kontrollprobanden 40 SF-Proben gewonnen. Es wurden Personen beiderlei Geschlechts ausgewählt, die alle Frontzähne im Oberkiefer aufwiesen, unter keinen relevanten Allgemeinerkrankungen litten, in letzter Zeit keine Medikamente eingenommen hatten und nicht schwanger waren. Alle Personen waren Nichtraucher und hatten keinerlei Parodontalbehandlung in den letzten 3 Monaten vor der Untersuchung durchlaufen. Tiefe auf Sondierung blutende wie auch nicht blutende und gesunde Stellen der Oberkiefer-Frontzähne wurden untersucht. Klinische Parameter für jede Stelle wurden erhoben, nachdem SF-Proben entnommen worden waren. IL-1β und IL-1ra wurden mittels eines neuen kommerziell erhältlichen ELISA-Tests (Quantikine) bestimmt und wurden in allen Proben nachgewiesen.

Ergebnisse: Die mittlere Konzentration von IL-1β lag bei 0.11 ± 0.14 pg/μl an blutenden parodontal erkrankten Stellen, bei 0.04 ± 0.05 pg/μl an nicht blutenden Stellen mit Parodontitis und 0.01 ± 0.03 pg/μl an gesunden

Stellen ($p<0.001$). Im Gegensatz dazu lag die mittlere Konzentration von IL-1ra bei 6.99 ± 9.78 pg/μl an gesunden, bei 0.59 ± 0.44 pg/μl an nicht blutenden und bei 0.44 ± 0.36 pg/μl an blutenden Parodontitisstellen ($p<0.001$; mit Ausnahme des Vergleichs zwischen blutenden und nicht blutenden Stellen mit Parodontitis: $p<0.05$). An gesunden Stellen wurde eine starke reziproke Beziehung zwischen den SF-Konzentrationen von IL-1β und IL-1ra beobachtet.

Schlußfolgerungen: Die Ergebnisse legen den Schluß nahe, daß eine starke Beziehung zwischen dem Schweregrad der Erwachsenenparodontitis und steigenden SF-Konzentrationen von IL-1β bzw. abnehmenden Konzentration von IL-1ra besteht.

Résumé

L'interleukine 1 et le récepteur antagoniste de l'interleukine 1 dans le fluide gingival

Cette étude avait pour but d'étudier, chez des patients atteints de parodontite de l'adulte, la cytokine IL-1β et son récepteur antagoniste IL-1RA dans le fluide gingival. Un total de 40 échantillons de fluide gingival ont été récoltés chez 10 sujets atteints de parodontite modérée à sévère et chez 10 sujets sains contrôles. Les sujets étaient selectionnés dans les deux sexes, avec toutes les dents antérieures supérieures présentes, sans maladie systèmique, grossesse ou traitements médicamenteux récents. Tous les sujets étaient non-fumeurs et n'avaient pas reçu de traitement parodontaux lors des 3 mois précédant l'étude. Des sites profonds présentant un saignement, des sites profonds sans saignement et des sites sains étaient étudiées en relation avec les dents antéro-supérieures. Des mesures cliniques étaient enregistrées pour chaque site, après le prélèvement de l'échantillon de fluide gingival. IL-1β et IL-1RA furent quantifiés en utilisant un nouveau kit Elisa disponible dans le commerce (Quantikine^{TM}), et purent être détectés dans tous les échantillons. La concentration moyenne d'IL-1β était de 0.11 (S.D. 0.14) pg/μl pour les sites atteints avec saignement, 0.04 (0.05) pg/μl pour les sites atteints et ne présentant pas de saignement et 0.01 (0.03) pg/μl pour les sites sains ($p<0.001$). A l'inverse, la concentration moyenne pour l'IL1-RA était de 6.99 (9.78) pg/μl pour les sites sains, 0.59 (0.44) pg/μl pour les sites atteints ne présentant pas de saignement et 0.44 (0.36) pg/μl pour les sites atteints présentant un saignement ($p<0.001$, sauf pour la comparaison entre sites atteints présentant ou non un saignement, $p<0.05$). En ce qui concerne les siste sains, une forte corrélation inverse était trouvée les niveau d'IL-1β et d'IL-1RA dans le fluide gingival. Ces résultats suggèrent l'existence d'une forte relation entre la sévérité de la parodontite de l'adulte, l'augmentation du niveau d'IL-1β et la diminution d'IL-1RA dans le fluide gingival.

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