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Role of anti-β_1 adrenergic antibodies from patients with periodontitis in cardiac dysfunction

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BACKGROUND: The presence of serum autoantibodies against β_1 adrenoreceptors (β_1-ARs) in human gingival fibroblast from patients with periodontitis inhibits primary cell-specific growth and induces over-expression of pro-inflammatory mediators. Serum β_1-AR autoantibodies from patients with periodontitis react with myocardium and modify cardiac contractility. The relationship between the presence of serum β_1-AR autoantibodies and alterations in heart rate variability (HRV) was also studied.

METHODS: An enzyme-linked immunosorbent assay (ELISA) using cardiac and gingival fibroblast membranes or synthetic peptides corresponding to the second extracellular loop of human β_1-AR was used to detect serum autoantibodies. The HRV was assessed from RR interval files generated from 22:00 to 08:00 hours. The autoantibody effects on contractility were measured on spontaneous rat isolated atria.

RESULTS: Circulating autoantibodies from 36 patients with periodontitis and 20 healthy individuals (controls) interacted with fibroblasts, the cardiac surface, and β_1-AR synthetic peptides. The distributions of serum antibodies against gingival and myocardium membranes and β_1-AR synthetic peptide were 88.8%, 77.7%, and 92.8%, respectively. Moreover, 88.5% of patients with periodontitis whose sera were positive against β_1-AR synthetic peptide had decreased HRV. The corresponding affinity-purified anti-β_1-AR peptide IgG displayed partial agonist-like activity modifying the isolated atria contractility.

CONCLUSION: This manuscript describes that patients with periodontitis showed increased levels of serum IgG with reactive activity against β_1-AR. Those patients demonstrated decrease in heart rate, and IgG derived from their sera induced aberrant contractility of heart atrium. We propose that periodontitis increases the risk of cardiovascular diseases, although it increases anti-β_1-AR autoantibody that alters myocardial contractility.

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Keywords: autoantibodies; contractility; heart rate variability; myocardium; peptides

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Introduction

Periodontal diseases are multi-factorial (1, 2). Among patient variables, the stress and local hyperactivation of the autonomic adrenergic system are co-factors that contribute to the prevalence and incidence of disease progression (3).

The pathogenesis of periodontal disease considers essential immunologic factors associated with infections caused by bacteria in sub-gingival plaques (4). Local synthesis of biological products, such as bacteria-specific immunoglobulin (Ig) secretion, soluble inflammatory mediators, tissue degradation products, and enzymes produced by fibroblasts on bone cells, has been included in the pathology of periodontal disease (5–8).

Moreover, disease susceptibility and progression have been associated with autoimmune disorders (9), which consider the role of the host response in regulating the virulence and magnitude of the composition of the local flora and the magnitude of the tissue destruction. Thus, in periodontal disease during the process of combating pathogenic invasion, the immune system may cause localized tissue damage and activate systemic humoral immune responses (9).

Local production of antibodies against granulomatous tissues within periodontal tissues (10) and detection of immunoglobulins against type I collagen in sera and tissues of patients with periodontal disease suggest that autoimmunity may play a role in periodontal disease (11).

On the other hand, periodontitis has been linked to systemic illnesses, such as cardiovascular diseases and stroke. Increasing evidence indicates that periodontal disease is a risk factor for coronary disease (12–14)

through dysfunction of endothelial cells induced by periodontopathic bacteria or their products, or inflammatory mediators derived from infected periodontal tissue (13). It also raises core questions about the effect of other non-thrombotic factors triggering functional alterations in the myocardium, thus inducing the 'remodeling phenomenon' of the heart.

On the basis of an autoimmune hypothesis, we described that serum antibodies with β_1 adrenoreceptor activity were able to interact with gingival fibroblast adrenergic receptors in patients with periodontitis (15, 16). Moreover, antibodies with immune reactivity against β_1 adrenergic receptor activity that modifies the contractility of the myocardium have been described in sera of patients with different myocardiopathies (17–20).

Herein, we considered the possibility that serum antibodies from patients with periodontitis react with gingival fibroblasts and myocardium. We investigated the adrenergic system by screening sera of patients with periodontitis against β_1 adrenoreceptors (β_1-ARs). We determined the frequency of serum antibodies against β_1-ARs and the alterations in heart rate variability (HRV). Moreover, we determined whether the autoantibodies against β_1-AR modify the contractility of the heart *in vitro* toward β_1 adrenergic control as was observed *in vivo* with the HRV of patients with periodontitis.

Materials and methods

Patients

The study group consisted of 36 male adult patients with periodontitis (group I) who were attending the Periodontology Clinic from the metropolitan area of Buenos Aires. The mean age was 41 years, with a range of 32–50 years. Healthy subjects (group II) were used as controls (20 male subjects) with a mean age of 38 years and a range of 30–46 years. The assessment of clinical parameters was carried out by a calibrated periodontist following the criteria on the basis of clinical parameters and the severity and the periodontal tissue destruction (21). The characteristic clinical signs of periodontitis included the following: loss of clinical attachment, horizontal or/and angular alveolar bone loss, periodontal pocket formation, and gingival inflammation. To be included in the study, at least six sites with ongoing periodontal disease were required. Clinical measurements on patients with periodontitis included sites with alveolar bone loss >2 mm and a pocket depth >5 mm with bleeding and attachment loss >3 mm. In the healthy subjects (control group), the probing depth was <3 mm and the attachment loss was <2 mm. Moreover, probing pocket depth and clinical attachment level were assessed at six sites per tooth and bleeding on probing at four sites per tooth. None of the subjects (patients in group I and controls in group II) had systemic illnesses and they were never-smokers. The patients with periodontitis had not received periodontal treatment or antibiotics within the preceding 5 months or any anti-inflammatory drugs 3 weeks prior to the study.

The clinical characteristic of the study population as well as healthy subjects (control) referring especially body mass index (BMI; kg/m^2), lipid profile (cholesterol, low-density lipoprotein (LDL; mg/dl), high-density lipoprotein (HDL; mg/dl)), and blood pressure (mm Hg) are described in Table 1. Additionally, pocket probing depth (PPD) and clinical attachment loss (CAL) are shown in Table 2. All of the patients consented to participate in the study, and the investigation was conducted according to the tenets of the Declaration of Helsinki of 1975 as revised in 2000.

Heart rate variability (HRV)

The patients with CP and the healthy subjects were studied according to a previous report (22). The heart rate (HR) was recorded using an Oxford Medilay 2-24 miniature analogue tape recorder (Oxford Medical Systems, Abinydonn, UK). The recording speed was 2 mm/s. The HRV was assessed from RR interval files generated from 22:00 to 8:00 hours and analyzed in hourly epochs. The summary time domains statistical measures of the calculated HRV included the long-term HRV standard deviations of all NN (SDNN) index that represent variability over cycles, while the rms SD are short-term HRV measured estimating a high-frequency variation in HR (22).

Table 1 Characteristic of the study populations

Demography and risk factors	*Periodontitis patients Group I (n = 36)*	*Healthy subjects Group II (n = 20)*
Gender		
Male	30	18
Female	6	2
Education level		
Elementary school	32	17
High school	4	3
BMI (range kg/m^2)	19–24	18–21
Measure blood pressure (mmHg)		
Measure SBP (mean ± SD)	132 ± 19	115 ± 12
Measure DBP (mean ± SD)	77 ± 11	68 ± 10
Laboratory examination		
Cholesterol total (mean ± SD), mg/dl	170 ± 31	168 ± 21
LDL (mean ± SD), mg/dl	118 ± 16	115 ± 11
HDL (mean ± SD), mg/dl	28 ± 11	26 ± 17

BMI, body mass index (range ≥27 kg/m^2); SBP, systolic blood pressure. DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2 Periodontitis Selection Index

Parameters	*Numerical ranges*
PPD	≥5 mm
CAL	≥4 mm
BP	positive

PPD, pocket probing depth; CAL, clinical attachment loss; BP bleeding on probing.

Human sera and IgG purification

Sera and the corresponding IgG were obtained from patients with periodontitis (group I) and normal individuals (group II). Six milliliters of blood was obtained by venipuncture and allowed to clot at room temperature, and the serum was separated by centrifugation at 2000 *g* and stored at −20°C until used in assays. The IgG was obtained by precipitation with ammonium sulfate at 50%, followed by three washes and re-precipitation with 33% ammonium sulfate. The resulting precipitate was submitted to chromatography on DEAE-cellulose, equilibrated with 10 mM phosphate buffer (pH 8). The eluted peaks were concentrated by ultrafiltration to 10 mg protein/ml. Control immune electrophoresis with goat anti-human total serum and goat non-specific anti-human IgG showed only one precipitin line.

Purification of anti-peptide antibodies by affinity chromatography

The IgG fraction of group I and group II patients was independently subjected to affinity chromatography on the synthesized peptide covalently linked to Affi-Gel 15 gel (Bio-Rad, Richmond, CA, USA). The IgG fraction was loaded on the affinity column equilibrated with PBS, and the non-peptide fraction was eluted with the same buffer. Specific anti-peptide autoantibodies (anti-β1-AR peptide IgG) were then eluted with 3 M KSCN and 1 M NaCl, followed by immediate extensive dialysis against PBS. The IgG concentration of both non-anti-peptide antibodies and specific anti-β_1-AR peptide antibodies was determined by radial immunodiffusion assay, and the immunologic reactivity against the β1-AR peptide was evaluated by ELISA (16, 17).

Membrane preparation

Rat cardiac and fibroblast culture of human gingival cell (16, 18) membranes were prepared, as previously described (17, 18). In brief, the cells or atria were homogenized in an Ultraturrax at 4°C in six volumes of potassium phosphate buffer, 1 mM $MgCI_2$, 0.25 M sucrose (pH 7.5) supplemented with 0.1 mM phenylmethyl sulphonyl fluoride (PMSF), 1 mM EDTA, 5 μg/ml leupeptin, 1 μM bacitracin, and 1 μM pepstatin A. The homogenate was centrifuged twice for 10 min at 3000 *g*, then at 10 000 and 40 000 *g* at 4°C for 15 and 90 min, respectively. The resulting pellets were suspended in 50 mM phosphate buffer fortified with the same protease inhibitors (pH 7.5). By cumulative concentration of ^{3}H-DHA binding to cardiac and fibroblast membranes, it was demonstrated that they expressed β_1-AR being the maximum number of binding site (B_{max}) = 206 ± 12 and 180 ± 15 fmol/10^5 cells and the fmol/mg protein dissociation constant (K_d) = 3.6 ± 0.4 nM and 2.3 ± 0.2 nM for cardiac and fibroblast membranes, respectively. The ^{3}H-DHA binding was performed as previously described (18).

ELISA

Fifty milliliters of peptide solution (20 μg/ml) or cardiac or gingival fibroblast-purified membranes (50 μg/ml) in 0.1 M Na_2CO_3 buffer (pH 9.6) was used to coat microtiter plates at 4°C overnight. After blocking the wells with 2% bovine serum albumin in PBS for 1 h at 37°C, 1/30 dilution of sera from groups I and II was added in duplicate and allowed to react with the peptide for 2 h at 37°C. After thoroughly washing the wells with 0.05% Tween 20 in PBS, 100 μl of 1:6000 goat anti-human IgG alkaline phosphate-conjugated antibodies were added and incubated for 1 h at 37°C. After extensive washing, *p*-nitrophenylphosphate (1 mg/ml) was added as the substrate and the reaction was stopped after 30 min. Optical density (OD) was measured at 405 nm with an ELISA reader. As a negative control, non-antigen-paired wells with M_1 cholinergic peptide and wells with no primary antiserum were also conducted. The results for each sample were expressed as the mean ± SEM of duplicate values.

Contractile study

Rats were decapitated and atria were removed quickly and placed in a glass chamber containing Krebs Ringer bicarbonate (KRB) solution (pH 7.4) that was gassed with 5% CO_2 in oxygen at 30°C. After a stabilization period of 30 min, spontaneous tension and frequency were recorded using a force transducer coupled to an ink-writing oscillograph, as previously described (18). Then, the preparations were paced by means of a bipolar electrode using a SK4 Grass stimulator, with stimuli duration of 2 ms and a voltage that was 10% above threshold. The constant resting tension applied to the atria (preload tension) was 750 mg. The contractility (dF/dt) was assessed by recording the maximum rate of isometric force development above the externally applied resting tension. To obtain the maximum IgG effect, different concentrations of IgG were added to normal rat atria every 15 min. Control values (equal to 100%) referred to the dF/dt before the addition of different IgG concentrations.

Assay for cyclic adenosine monophosphate (cAMP)

Rat atria (10 mg) were incubated in 1 ml KRB for 30 min, and the anti-β_1-AR peptide IgG were added in the last 15 min. When blocker was used, they were added 25 min before the addition of the antibody. After incubation, atria was homogenized in 2 ml of absolute ethanol and centrifuged at 6000 *g* for 15 min at 4°C. Pellets were then re-homogenized in ethanol–water (2:1). Supernatant was collected and evaporated to dryness as described earlier. Cyclic AMP in the residue was dissolved in 400 μl of 0.05 M sodium acetate buffer (pH 6.2). For determination of the nucleotide, we used ELISA employing the protocol of production of cAMP from Amersham Biosciences (Piscataway, NJ, USA). Results were expressed in pico moles per milligram of wet weight of tissue (pmol/mg tissue ww).

Drugs

Stock solutions of atenolol were freshly prepared before each experiment. The β_1 peptide corresponds to the sequence of the second extracellular loop of the human β_1-AR (HWWRA ESDEA RRCYN DPKCC DFVTN

RC). A control, unrelated peptide derived from the second extracellular loop of the human M_2 cholinoreceptor (VRTVE DGECY IQFFS NAAVT FGTA) was used. Radioactive material, synthetic peptides, and β adrenergic antagonists were from Dupont/New England Nuclear (Boston, MA, USA), Sigma Genosys (St. Louis, MO, USA), and Sigma Chemical Company (St. Louis, MO, USA), respectively.

Statistical analysis

A Student's *t*-test for unpaired values was used to determine the levels of significance. Analysis of variance (ANOVA) and a *post hoc* test (Dunnett's method and Student–Newman–Keuls test) were employed when pair-wise multiple comparison procedures were necessary. The differences between means were considered significant at a $P < 0.05$.

Results

ELISAs were performed to demonstrate whether there is a relationship between serum IgG from patients with periodontitis against gingival fibroblasts and cardiac membranes. (Fig. 1) shows the optical density (OD) values for sera from patients with group I and healthy subjects (group II) using human gingival fibroblasts (A) and rat cardiac (B) membranes as coating antigens. The OD values obtained with the group I sera were always >2 SD from those of healthy individuals. Additionally, Table 3 shows the distribution of autoantibodies from patients with periodontitis that had high levels of OD values. It can be seen that 88.8% and 77.7% of the sera reacted positively against gingival fibroblasts and cardiac membranes, respectively.

To determine the molecular interaction between IgG and human β_1-ARs, OD values for each of the 28 patients with periodontitis (that reacted positively on cardiac membranes) were evaluated using β_1 synthetic peptides as coating antigens. The scatterogram in (Fig. 2A) shows the immunoreactivity of sera from patients in group I was significantly higher than that of the control individuals (group II; $P < 0.001$). On the other hand, when unrelated synthetic peptide (M_2 cholinoreceptor peptide) was used as a coating antigen, both IgG from groups I and II yielded negative results (Fig. 2B). Additionally, Table 1 shows that the 92.8% of sera that reacted positively against cardiac membrane were positive against β1 adrenergic synthetic peptide.

Table 3 Distribution of serum autoantibodies against gingival, myocardium, and β_1 adrenoreceptors synthetic peptide from periodontitis patients

Coating antigen	*Optical density (mean ± SEM)*	*Positive/total number*	*Positive (%)*
Gingival fibroblast	0.75 ± 0.03	32/36	88.8
Myocardium	1.26 ± 0.09	28/36	77.7
β_1 adrenergic peptide	1.28 ± 0.07	26/28	92.8

Immunoreactivity of serum autoantibodies against human gingival fibroblast membranes, rat cardiac membranes, and human β_1 adrenergic synthetic peptide. Sera (1/30 dilution) was assayed on sensitized microplates with 50 μg/ml of purified membranes or 20 μg/ml human β_1 adrenergic synthetic peptide.

It is known that β_1-ARs are involved in regulating various cardiac parameters, including HR and heart rate variability (HRV), and the alterations in these functions are considered risk factors for the development of cardiovascular disease (23). Thus, we evaluated the HRV in 23 patients with periodontitis from whom sera reacted positively against β_1 synthetic peptide and from 20 healthy individuals as controls. Table 4 shows the differences between patients with periodontitis and healthy subjects for the HRV with respect to the long-term (SDMM) index and short-term (rms SD) index. These data show a significant decrease in HRV in patients with periodontitis in comparison with the control group. Moreover, 88.5% of the patients with periodontitis whose sera were positive for β_1 adrenergic synthetic peptide showed a decrease in HRV.

The heart is a major tissue of β_1-AR expression where β_1-AR mediates the organ's response to changes in circulating catecholamine levels, i.e., increased

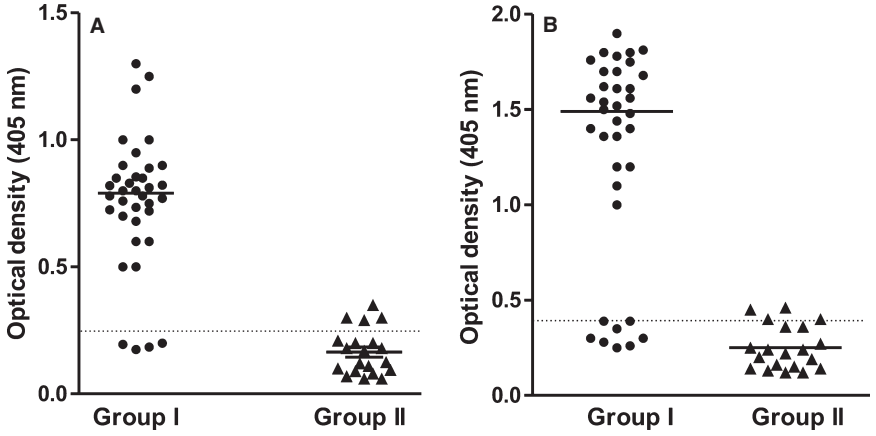

Figure 1 Immunoreactivity of circulating IgG antibodies against fibroblast membrane (A) or against cardiac membrane (B). The individual optical density (OD) for each serum sample (1/30 dilution) from 36 periodontal patients (group I) or 20 normal individuals (group II) were evaluated by duplicate. Cut-off values of OD 0.220 and 0.380 for anti-fibroblast membranes and anti-cardiac membranes, respectively.

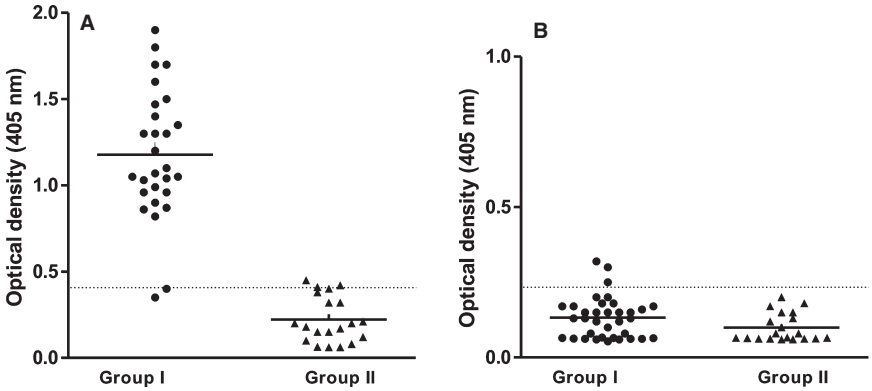

Figure 2 Immunoreactivity of circulating IgG antibodies against β_1 adrenoreceptors (β_1-AR) synthetic peptide (A) or against M_2 mAChR synthetic peptide (B). The individual optical density (OD) for each serum sample (1/30 dilution) from 36 patients with periodontitis (group I) and 20 healthy subjects (group II) were evaluated in duplicate. Cut-off values of OD 0.450 and 0.210 for anti-β_1-AR peptide and anti-M_2 mAChR synthetic peptide, respectively.

Table 4 Time domain heart rate variability parameters in periodontitis patients and normal subjects

Subjects	*SDNN index*	*rms SD index*	n
Normal	91 (11)	69 (13)	20
CP	68 (10)*	40 (12)*	23

Data are the mean ± standard deviation.
n, number of patients tested, SDNN, standard deviations of all NN. Statistics related to comparison with parallel normal subjects. $^*P < 0.05$ vs. normal.

myocardial contractility, resulting in positive inotropic and chronotropic effects. Because we have observed that patients with periodontitis have an enhanced cardiac rate (or decreased HRV) *in vivo,* which may reflect profound alteration of sympathetic activity, we tested whether or not autoantibodies from sera of CP patients lead to β_1-AR activation in the atria. For this purpose, we selected the 23 patients with periodontitis that had a decrease in HRV and whose sera were positive against β_1 adrenergic synthetic peptide in the ELISA. The IgG fraction was independently subjected to affinity chromatography and eluted from the column covalently linked to β_1 adrenergic synthetic peptide (anti-β_1-AR peptide IgG). Increasing concentrations of anti-β_1-AR peptide IgG were applied to spontaneously beating isolated rat atria, and changes in the magnitude of contractility (d*F*/d*t*) were measured (Fig. 3).

As shown in Fig. 3, the anti-β_1-AR peptide IgG behaved as a partial β_1 adrenergic agonist; increasing the d*F*/d*t* at low concentrations and at higher concentrations, the autoantibodies decreased the d*F*/d*t*. Both the stimulatory and inhibitory effects were almost abolished by pre-treating atria with 1×10^{-7} M atenolol (a β_1-AR antagonist) and 1×10^{-5} M β_1 adrenergic synthetic peptide. The IgG from normal subjects and the non-peptide fraction gave negative results in the study system (data not shown).

To demonstrate that anti-β_1-AR peptide IgG induces atria signaling acting on post-synaptic membrane β_1-AR, we determine cAMP production in the presence

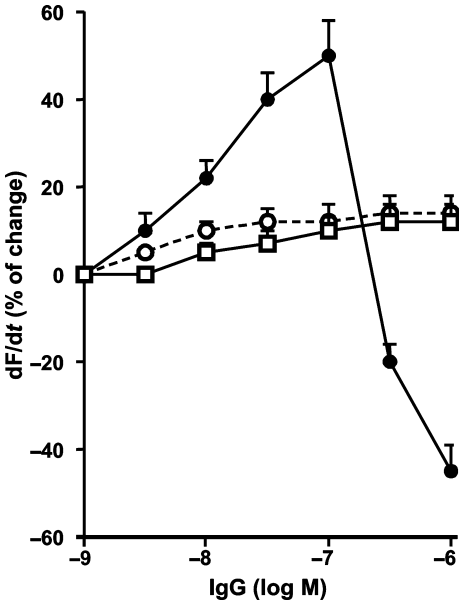

Figure 3 Effect of increasing concentration of anti-β_1 adrenoreceptors (β_1-AR) peptide IgG on contractility (d*F*/d*t*) of rat isolated atria. The effects of anti-β_1-AR peptide IgG alone (•-•) or in the presence of 1×10^{-7} M atenolol (○-○) or 1×10^{-5} M β_1 adrenergic synthetic peptide (□-□) was evaluated in duplicate. Values are the mean ± SEM of 36 patients with periodontitis in each group.

of increasing concentrations of the antibodies. In Fig. 4. we can see a significant increase in cAMP production which is impaired by atenolol (β_1-AR antagonist) and anti-β_1 synthetic peptide. Control IgG from healthy individuals was ineffective in the study system (Fig. 4).

Discussion

An increased prevalence of cardiovascular and autoimmune diseases in periodontitis has been reported (24, 25). Herein, we have demonstrated an association between periodontal infections and an increased risk of cardiovascular disease, pointing to the role of

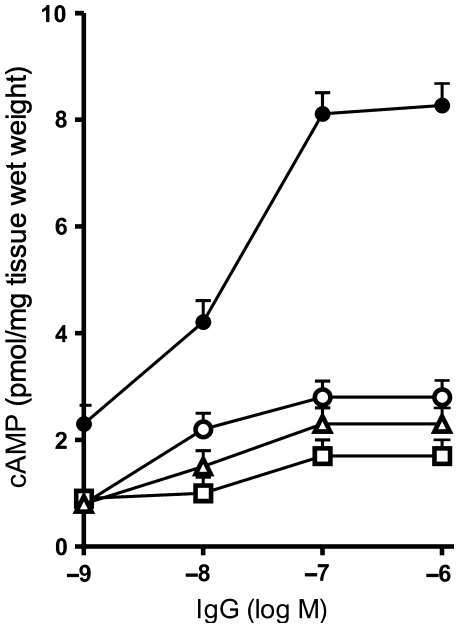

Figure 4 Concentration–response curve of anti-β_1 adrenoreceptors peptide IgG alone (•-•) and normal IgG (control) (Δ-Δ) on the production of cyclic adenosine monophosphate in rat atria. Influence of 1×10^{-7} M atenolol (□-□) or 1×10^{-5} M β_1 adrenergic synthetic peptide (○-○). Values are the mean ± SEM of 36 patients with periodontitis in each group.

anti-β_1-AR antibodies in the serum of patients with periodontitis.

The results provide evidence that components of the serum IgG fraction from patients with periodontal disease recognize gingival fibroblasts and cardiac membranes. Most of the sera that reacted positively against the surface of rat cardiac membranes showed positive immune reactivity to human β_1-AR peptide. In this sense, using synthetic peptide with an identical amino acid sequence of the second extracellular loop of human β_1-AR, we established that the β_1-AR is the target for the anti-rat cardiac autoantibodies described in patients with periodontitis. Knowing that the amino acid sequences of rodent and human β_1-AR peptides have strong homology (26), we study the β_1-AR-mediated effect of autoantibodies from patients with periodontitis on rat cardiac tissue.

It is generally accepted that the heart is a major site of β_1-AR expression when it mediates the positive chronotropic effect on the heart. Because we observed that serum from patients with periodontitis contains autoantibodies against cardiac and human gingival fibroblast membrane β_1-AR, we tested the HRV in patients with periodontitis from whom sera had positive immunoreactivity to cardiac membranes and β_1-AR synthetic peptide.

We demonstrated that those patients in whom sera contain anti-cardiac and anti-β_1-AR peptide antibodies had a decrease in HRV. This is an important consideration with respect to the likely *in vivo* effects of the autoantibodies, because aberrant β_1 sympathetic receptor expression may result in a decrease in HRV and it is a risk factor for the development of cardiovascular disease, including heart failure, myocardial infarction, and hypertension (23).

This observation is in agreement with the results obtained *in vitro* study. Herein, we demonstrated that the autoantibody was not only able to interact with human β_1-AR at the molecular level, but also displayed partial agonist activity, requiring a lower concentration to trigger an increase in contractility and at higher concentrations to decrease contractility. It is important to note that the level of serum anti-β_1-AR IgG does not correspond to the level of periodontal lesion. However, we postulated that the level of serum anti-β_1-AR IgG should correspond to the degree of the inflammatory processes. Also, serum IgG titers from selected periodontal bacteria species, combined with demographic and behavioral characteristic, resulted in a moderate classification of periodontal status in epidemiologic studies (27). The coupling of the anti-β_1-AR peptide IgG on β_1-AR in atria permits the transduction of one signaling pathway as cAMP elevation. Both of these effects were modulated by antagonists of β_1-AR. It is interesting that the partial agonist activity of the autoantibodies observed *in vitro* mimicked the action on HRV of a partial β_1 adrenergic agonist (celiprolol) described *in vivo* (22).

Therefore, on the basis of our results, we suggest the possibility that the decrease in HRV in patients with periodontitis is caused by antibody fixation and activation of the cardiac β_1-AR.

In the previous work, we demonstrated that patients with periodontal disease have functional serum IgG fixing the β_1-ARs of gingival fibroblasts, resulting in primary cell-specific growth inhibition (15) and induced PGE_2 generation and CD40 over-expression (16) that facilitated the inflammatory process of the disease.

In fact, it has been proposed that during sympathetic hyperactivity, there is a deregulation of the pro- vs. anti-inflammatory cytokines and T helper (Th1) vs. TH2 lymphocyte balance. Thus, catecholamine and PGE_2 up-regulated TH2 lymphocytes, associated with an increase in humoral immunity and a decrease in TH with down-regulation of cell-mediated immunity (28). Then, β_1-AR autoantibodies could exacerbate the course of the disease by altering the focus of immune function with up-regulation of its own production and suppression of cell-mediated immunity.

It is important to note that patients with periodontitis might develop the anti-β_1-AR autoantibodies as a result of molecular mimicry by bacterial pathogens acting on cardiac β_1-AR as a result of receptor alteration and/or degradation during the inflammatory response. The microbial challenge and inflammatory response in the periodontium via a similar mechanism could be causing increased risk for myocardium diseases. Also, these neoantigens from cardiac β_1-AR tissue may be a pivotal key to generate these autoantibodies (anti-β_1-AR peptide IgG) as a clinical manifestation of autoimmunity.

The pathogenic properties of anti-β_1-AR antibodies have been ascribed to their potency to continuously stimulate the sympathetic system. Thus, β_1-AR

autoantibodies could trigger the following two important mechanisms: autoantibodies by targeting cardiac β_1-AR altering the physiologic behavior of the myocardium and exacerbating or maintaining a chronic inflammatory process in periodontitis disease through the induction of a suppressed immune response (16).

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Conflict of interest

There are no conflicts of interest.