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·*Original Article*·

Sperm lipid peroxidation and pro-inflammatory cytokines

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Abstract

Aim: To investigate if interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interferon-gamma (IFN-γ) or tumor necrosis factor-alpha (TNF-α) are able to stimulate the level of lipid peroxidation of sperm membranes, either alone or in the presence of leukocytes. **Methods:** Semen samples from normozoospermic donors were prepared by density gradient. The sperms were exposed to the indicated cytokines, at physiological and infection-inflammation concentrations, in the absence or presence of leukocytes. Lipid peroxidation of the sperm membranes was determined by measuring malondialdehyde (MDA) and 4-hydroxialkenals (HAE) formation. **Results:** TNF-α, IL-8 and IFN-γ increased the level of sperm membrane lipid peroxidation when tested at physiological concentrations. At infection-inflammation concentrations, only IL-8 was able to produce a higher effect. When assayed in the presence of leucocytes, IL-8 and TNF-α showed a higher effect at infection-inflammation concentrations than at physiological concentrations. Finally, IL-8 showed a higher effect in the presence of leukocytes than in their absence at both physiological and infection-inflammation concentrations. TNF-α also showed a higher effect when assayed in the presence of leukocytes than in their absence, but only at infection-inflammation concentrations. There was no effect of IL-6 or IL-10 in any of the tested conditions. **Conclusion:** Several pro-inflammatory cytokines at physiological concentrations increase the level of lipid peroxidation of sperm membranes, which could be important for the sperm fecundation process. However, infection–inflammation concentrations of some cytokines, such as IL-8 and TNF-α, either alone or in the presence of leukocytes, could drive the lipid peroxidation of the spermatozoa plasma membrane to levels that can affect the sperm fertility capacity. *(Asian J Androl 2007 Jan; 9: 102–107)*

Keywords: interleukin-6; interleukin-8; interleukin-10; tumor necrosis factor-alpha; interferon-gamma; lipid peroxidation; spermatozoa; infection-inflammation

1 Introduction

Experimental evidence shows that low and controlled concentrations of reactive oxygen species (ROS) play an important role for the sperm acquisition of fertilizing ability. Thus, low amounts of free radicals in human semen enhances the spermatozoa ability to bind the zona pellucida. Also, the incubation of sperm with low concentrations of hydrogen peroxide has been shown to stimulate sperm capacitation, hyperactivation, acrosome reaction and oocyte fusion [1].

Cytokines are regulatory peptides produced and secreted by leukocytes and other cells, and they have been

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implicated as growth and differentiation factors. The seminal plasma contains significant levels of several cytokines [2], which are normally present in the male genital tract. It has been proposed that they are released by germ cells, Leydig cells and Sertoli cells, epididymis and prostate and that their expression is modulated during the seminiferous epithelium cycle [2]. It has also been proposed that the most important interleukins appearing during inflammatory diseases of the genital tract are interleukin-6 (IL-6) and interleukin-8 (IL-8), in a clear relationship with leukocytospermia.

There is clear evidence indicating the effects of cytokines on spermatozoa functions. It has been found that: i) IL-1 alpha, IL-1 beta and tumor necrosis factor-alpha (TNF-α), stimulate sperm peroxidation by increasing ROS generation [3]; ii) there is a positive correlation between IL-6 levels in seminal plasma and membrane sperm lipid peroxidation [4]; iii) interferon-gamma (IFN-γ) and TNF-α have been shown to decrease the motility of spermatozoa [5, 6]; iv) infertile patients with varicocele show elevated levels of IL-6 and ROS, and decreased levels of total antioxidant capacity [7]; and v) mean levels of IL-6, IL-8 and IL-11 are higher in the seminal plasma of patients with genital infection and oligo-teratoasthenozoospermia than those in seminal plasma of normal fertile men [8].

Leukocytes are often present in normal semen and, as it is well known, inflammatory-infectious processes in the male genital tract increase the number and the secretion of cytokines. The enhanced production of ROS can result in an enhanced level of membrane sperm lipid peroxidation which, in turn, can affect the fertilizing capacity of the spermatozoa. In this regard, infertile males positive for IgA antibodies to *Chlamydia trachomatis* show an abnormally high level of lipid peroxidation [9].

Excessive ROS can have major destructive effects on sperms and their membranes, which are rich in polyunsaturated fatty acids. Thus, by increasing the level of membrane lipid peroxidation, they diminish the membrane fluidity and functions. They also reduce the linear velocity of spermatozoa in men and can exert major destructive effects on sperm DNA.

The aim of the present study was to investigate the capacity of IL-6, IL-8, IL-10, IFN-γ and TNF-α to act directly on the level of lipid peroxidation in sperm, either at physiological or at infection-inflammation concentrations, and to determine if the addition of leucocytes further increases their effects.

2 Materials and methods

2.1 Preparation of sperm

Fresh semen samples were obtained from healthy normozoospermic volunteers at the Laboratory of Animal Reproduction and Development, Universidad Simón Bolivar, by masturbation after a minimum of 2 days of sexual abstinence. Informed consent was obtained from all subjects. The semen samples were processed by Isolate density centrifugation gradient (two layers: 40% and 90%) (Irvine Scientific, Santa Ana, CA, USA). The resulting pellet was resuspended in original Biggers, Whitten and Whittingham's medium, washed by centrifugation (300 × *g* for 10 min) and diluted to give 10 million spermatozoa/mL. This final sample was evaluated by the peroxidase test to guarantee the absence of leucocytes.

2.2 Preparation of white blood cells

Fresh venous blood samples were obtained from healthy adults. Human peripheral leucocytes were isolated from the whole heparinized blood, using a double gradient centrifugation for both mononuclear and granulocyte cells (Histopaque 1077 and 1119; Sigma, St. Louis, MO, USA). The gradient was centrifuged at 700 × *g* for 30 min at room temperature. Mononuclear and granulocyte cell layers were harvested from the respective interfaces and then pooled. After two washes with Biggers, Whitten and Whittingham's medium at 200 × *g* for 10 min, the cell pellets were finally diluted to a concentration of 5×10^6 cells/mL.

2.3 Experimental protocol

Sperm aliquots were treated for 2 h at 37ºC with the tested different cytokines at two different concentrations, denominated here as physiological and infection–inflammation concentrations, which were determined as the mean of several values taken from several authors [8, 10–16]. The physiological concentrations used were: IL-6 (25.0 pg/mL), IL-8 (50.0 pg/mL), IL-10 (7.8 pg/mL), IFN-γ (127.1 pg/mL) and TNF-α (1.6 pg/mL). The infection-inflammation concentrations were: IL-6 (125.0 pg/mL), IL-8 (100.0 pg/mL), IL-10 (3.9 pg/mL), IFN-γ (508.5 pg/mL) and TNF-α (17.0 pg/mL). In a second group of experiments, similar incubations were carried out, but now in the presence of leukocytes (5×10^6/mL). For the first group, the control consisted of sperm cells in culture medium; for the second group, the control consisted of sperm cells in culture medium plus the indi-

cated amount of leukocytes.

2.4 Lipid peroxidation measurement

After the incubations, the cell membranes were assayed for lipid peroxidation level, using the LPO-586 assay kit (LPO-586; Bioxytech SA, Bonneuil sur Marne, France) according to the manufacturer's instructions. This assay was based on the reaction of a chromogenic reagent, N-metil-2-phenylindole with malondialdehyde (MDA) and 4 hidroxyalkenals (HAE) at 45ºC. One molecule of either MDA or HAE reacts with two molecules of chromogenic reagent to yield a stable chromophore with maximal absorbance at 586 nm. The samples (200 μL triplicate) were mixed with the chromogenic reagent (650 μL) and methanelsulfonic acid (150 μL). The preparations were incubated at 45ºC for 60 min, and then centrifuged at 15 000 × *g* for 10 min. The supernatants were transferred to cuvettes and their absorbance was measured at 586 nm. MDA and HAE values were calculated using an MDA standard curve. The detection limit for the assay was 0.1 nmol/mL in the final reaction medium.

2.5 Statistical analysis

Statistical analysis was carried out by the paired *t*-test. All results were expressed as mean ± SE. $P \leq 0.05$ was accepted as statistically significant.

3 Results

3.1 Cytokines at physiological or infection-inflammation concentrations

As shown in Table 1, only three of the tested cytokines, TNF-α, IL-8 and IFN-γ, when present in the incubation medium at physiological concentrations, were able to significantly raise the level of lipid peroxidation of the sperm membranes. IL-6 and IL-10, under these conditions, did not show any significant effect. When utilized at infection-inflammation concentrations, only IL-8 was able to further raise the level of the membrane lipid peroxidation. The other cytokines tested under these conditions did not produce any significant effect over that produced when they were utilized at physiological concentrations.

3.2 Cytokines at physiological or infection-inflammation concentrations plus leukocytes

As shown in Table 2, when leukocytes were present in the incubation medium, only IL-8 at a physiological concentration was able to significantly raise the level of lipid peroxidation of the sperm membranes over the level produced when incubated in the absence of leukocytes. Also, IL-8 and TNF-α showed a higher effect at infection–inflammation concentrations than at physiological concentrations. Finally, comparison between Tables 1 and 2 shows that at infection-inflammation concentrations, TNF-α and IL-8 produced a higher effect in the presence of leukocytes than in their absence ($P < 0.05$ for both).

4 Discussion

The objective of the present study was to investigate the capacity of IL-6, IL-8, IL-10, IFN-γ and TNF-α to act directly on the sperm membrane lipid peroxidation level, either at physiological or at infection-inflammation concentrations, and to determine if the addition of leucocytes could further enhance their effect. The study was carried out considering several aspects. The sperm

Table 1. Effect of cytokines at physiological or infection-inflammation concentrations on lipid peroxidation of sperm membranes. Data were represented as mean ± SE. LPO, lipid peroxidation (malondialdehyde [MDA] plus 4-hydroxialkenals [HAE]); Sp, spermatozoa; ns, not significant.

Experimental conditions	Physiological (LPOs, μm/10^7 Sp, $n = 8$)	*P* values *vs.* control	Infection-inflammation (LPOs, μm/10^7 Sp, $n = 8$)	*P* values *vs.* physiological concentrations
Sp (control)	0.792 ± 0.071	–	–	–
Sp + IL-6	0.791 ± 0.081	ns	0.909 ± 0.077	ns
Sp + TNF-α	1.333 ± 0.122	< 0.001	1.382 ± 0.118	ns
Sp + IL-8	1.284 ± 0.112	< 0.001	2.300 ± 0.228	< 0.001
Sp + IFN-γ	1.077 ± 0.099	< 0.01	1.156 ± 0.128	ns
Sp + IL-10	0.856 ± 0.070	ns	0.840 ± 0.084	ns

Table 2. Effect of cytokines at physiological or infection-inflammation concentrations plus leukocytes, on lipid peroxidation of sperm membranes. Data were represented as mean ± SE. LPO, lipid peroxidation (malondialdehyde [MDA] plus 4-hydroxialkenals [HAE]); Leu, leukocytes; Sp, spermatozoa; ns, not significant.

Experimental conditions	Physiological (LPOs, μm/10^7 Sp, n = 8)	P values *vs.* physiological concentrations (– leukocytes)	Infection-inflammation (LPOs, μm/10^7 Sp, n = 8)	P values *vs.* physiological concentration (+ leukocytes)
Sp + Leu (control)	0.867 ± 0.084	ns	–	–
Sp + Leu + IL-6	0.898 ± 0.087	ns	0.943 ± 0.079	ns
Sp + Leu + TNF-α	1.509 ± 0.127	ns	1.965 ± 0.180	< 0.05
Sp + Leu + IL-8	2.471 ± 0.150	< 0.001	2.992 ± 0.290	< 0.05
Sp + Leu + IFN-γ	1.187 ± 0.122	ns	1.239 ± 0.115	ns
Sp + Leu + IL-10	0.916 ± 0.102	ns	0.868 ± 0.087	ns

preparations included a density centrifugation gradient in order to obtain homogeneity and low reactive species production. The white blood cells preparations included a double gradient centrifugation, in order to obtain both, mononuclear and granulocytes cells. This aspect is very important, because the predominant leukocytes in semen are granulocytes (50–60%), followed by macrophages (20–30%) and by T lymphocytes (2–5%). Granulocytes are the major producers of ROS, followed by macrophages. In order to get a better resolution, the level of lipid peroxidation of the sperm membranes was determined by measuring formation of MDA and HAE. The cytokines quantities chosen for the present study are those present in the male genital tract *in vivo*, either at physiological or at infection-inflammation conditions (picograms) [8, 10–16] and not nanograms, as utilized in many other studies on this subject.

At physiological concentrations (Table 1), TNF-α, IL-8 and IFN-γ were able to increase the level of lipid peroxidation of the sperm membranes in about 60–70%. In contrast, at infection-inflammation concentrations, only IL-8 was able to further raise the lipid peroxidation of the membranes, reaching a value that was 80% higher than that reached at physiological concentration. Interestingly, most of the IL-8 concentrations reported during genital infections are higher than those used in the present study. When the incubations were carried out in the presence of leukocytes (Table 2), IL-8 at physiological concentration, increased in about 90% the level of lipid peroxidation over that produced when incubated in the absence of leucocytes, being the only tested cytokine that was able to produce any extra effect under these conditions. Also, at infection-inflammation concentrations, TNF-α and IL-8 in the presence of leukocytes produced a higher effect on the level of lipid peroxidation than when they were at physiological concentrations. Finally, IL-8 and TNF-α when tested in the presence of leukocytes, showed a higher effect at infection-inflammation concentrations than at physiological concentrations (Tables 1 and 2).

It should be noted that IL-8 alone, at infection-inflammation concentration or at any of the two concentrations used, produced a very high level of lipid peroxidation when tested in the presence of leucocytes. This level was much higher than those produced by any of the other tested cytokines. TNF-α also produced a high level of lipid peroxidation when tested in the presence of leukocytes.

It is difficult to explain why IFN-γ, a clear pro-inflammatory cytokine, shows a much lower effect than IL-8 and TNF-α when tested at physiological concentrations. It will be necessary to determine the presence and the characteristics of the respective receptors. In this regard, two receptors associated with a protein G and PLC signalization have been described for IL-8 in different immune cells [17]. However, it is still necessary to investigate if IL-8 receptors are present in human spermatozoa.

In apparent contradiction with our results, a recent study [18] showed that there is no correlation between IL-8 seminal plasma level and the outcome of *in vitro* fertilization, and also, that there is no correlation between IL-8 level and MDA in semen. This apparent contradiction could be as a result of the fact that these authors measured MDA in seminal plasma containing the contribution of MDA by immature and genital tract cells, and not just in the spermatozoa, as we did. Also, it is important to point out the fact that under *in vitro* conditions, we are eliminating the effects of vitamins and antioxi-

dant enzymes that could keep the balance of the oxidative stress *in vivo*.

Cytokines probably play a physiological role in local regulation of sex hormones and in paracrine control of reproduction processes, including spermatogenesis. For example, IL-6 affects spermatogonial proliferation, germ cells differentiation, Sertoli cells stereidogenesis and protein secretion, whereas TNF-α controls the survival of germ cells and Leydig cells stereidogenesis [19]. However, increased concentrations of some cytokines produced during infection-inflammatory processes could increase the level of spermatozoa plasma membrane lipid peroxidation, as shown by the present study, thus interfering with the sperm quality. Additionally, interleukins could amplify the production of certain cytokines by leukocytes during genitourinary inflammation, further increasing ROS production and, consequently, spermatozoa plasma membrane lipid peroxidation. Buch *et al.* [3], studying the effect of several cytokines on sperm peroxidation, observed that TNF increases the production of MDA by the sperm; however, because the leukocytes were not removed from the preparation, the author could not test the possibility of a direct effect of the cytokine by itself in the absence of leukocytes. In another study [20], it was found that TNF-alpha decreases sperm motility.

In vitro studies, using several cellular lines, have shown that cytokines are able to induce ROS production. Thus, TNF-α and IL-1, were found to be able to increase the production of hydroxyl radicals and lipid peroxidation in mouse tumorigenic fibroblast cells and mesanglial cells [21]. Other authors [22] have shown that IFN-γ, IL-1β and TNF-α can stimulate the expression of inducible nitric oxide synthase (NOS) by mouse, rat and human osteoblast-like cells. Additionally, it was found that cytokine-stimulated NOS expression in human kidney epithelial cells involves activation of tyrosine kinases including JAK2, PKC, p38 MAPK and NF-kappa B [23].

Even when, as shown in recent studies, IL-6 is able to increase protein tyrosine phosphorylation (JAK) in the spermatozoa, thus indicating the presence of intracellular signaling machinery to respond to this cytokine [24], we did not find any effect of this cytokine on sperm membrane lipid peroxidation. Perhaps the concentrations utilized in our experiments were too low to activate the corresponding receptors. In contrast, IFN-γ, which is also able to enhance tyrosine phosphorylation (STAT1) in the sperm [25], increased the sperm membrane level of lipid peroxidation in the present study.

In the present study, the different effects of the cytokines on the level of sperm membrane lipid peroxidation could be the result of differential modulating effects of anti-inflammatory and pro-inflammatory molecules. Thus, for example, the increased production of IL-10 by the epididymis during cryptorchid crypteepididymis suppresses T-cell pro-inflammatory responses, contributing to the protection of spermatozoa from immune destruction [16].

In conclusion, the present study shows that some cytokines can act directly on spermatozoa to enhance their level of lipid peroxidation, indicating a direct reactive oxygen species production by the spermatozoa. The way in which cytokines can stimulate ROS production by the spermatozoa is not clearly understood. Two receptors for cytokines have been identified in human sperm, IFN-γ receptors [26] and IL-6 receptors, both specific ligands for the binding of the gp80 subunit (IL6-Rα) [24] and for the signal transducing protein gp-130 (IL-6Rβ) [27].

Because *in vivo* there is always more than one cytokine present, it is very difficult to determine which of them could be responsible for one or another effect, particularly if it is considered that some cytokines can be inhibitory or synergistic on the action of other cytokines [22]. Consequently, conclusions regarding the effect of any particular cytokine, when tested alone, must be considered with caution.

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