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Residual bodies and IL-1α stimulate expression of mRNA for IL-1α and IL-1 receptor type I in cultured rat Sertoli cells[1]

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Abstract

The cytokine interleukin (IL)-1α may be produced both by Sertoli cells and immature male germ cells from rat and is thought to play a role in autocrine and/or paracrine regulation of the spermatogenesis. The localization of IL-1 receptors in seminiferous tubules is unknown. In this study we found a constitutive expression of IL-1 receptor type I (IL-1 RI) mRNA in cultured Sertoli cells and peritubular cells from rat, whereas no such transcripts were observed in immature germ cells (pachytene spermatocytes and round spermatids). An autostimulation of IL-1α mRNA synthesis has previously been described in other cell types. Stimulation of Sertoli cells with recombinant IL-1α for 0–7 h resulted in a rapid increase in both IL-1α and IL-1 RI mRNA. When Sertoli cells were cultured with residual bodies for 0–48 h, mRNA levels for both IL-1α and IL-1 RI were increased in a biphasic manner. We suggest that phagocytosis of residual bodies triggers an autocrine IL-1α loop in Sertoli cells where both IL-1α and one of its receptors are stimulated.

Keywords: Interleukin-1α; Interleukin-1 receptor type I; mRNA; Residual bodies; Sertoli cells; Rat testis

1. Introduction

In addition to endocrine regulation by follicle stimulating hormone (FSH) and testosterone, the spermatogenesis is regulated within the seminiferous tubules through cell-cell interactions. Previous studies have shown that Sertoli cells influence developing germ cells through secretion of paracrine factors and vice versa that germ cells affect Sertoli cell activity (Parvinen, 1982; Bellvé and Zheng, 1989; Skinner, 1991; Jégou, 1993).

The cytokine IL-1α may be produced both by Sertoli cells and immature germ cells from rats (Gérard et al., 1991; Haugen et al., 1994). The function of IL-1α within the testis is unknown. However, it has been suggested to function both as a spermatogonial growth factor (Khan et al., 1987; Pöllänen et al., 1989; Söder et al., 1991; Parvinen et al., 1991), as well as an activator of Sertoli cell functions (Okuda et al., 1995; Hoeben et al., 1996). Little is known concerning regulation of IL-1α in the testis. In other cell types IL-1α is transcribed as an early response gene (Fenton et al., 1987; Libby et al., 1986) and is involved in an activation cascade of other cytokines. In Sertoli cells increased IL-1α bioactivity in the medium has been reported when Sertoli cells are cocultured with residual bodies (Gérard et al., 1992; Syed et al., 1995). Whether this increase in activity is caused by de novo synthesis or is solely due to increased secretion of IL-1α has not been determined.

The fact that Sertoli cells may not only produce IL-1α, but also be a cellular target for this cytokine, prompted us to study the expression of IL-1 receptor type I in the seminiferous tubules. Furthermore, since

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an autostimulation of IL-1α synthesis has been found in other cell types (Dinarello et al., 1987; Warner et al., 1987; Kumar et al., 1992; West-Mays et al., 1995), the effect of IL-1α on its own gene expression in primary Sertoli cell cultures was studied. Moreover, to further examine the hypothesis that phagocytosis of residual bodies is the physiological trigger for IL-1α synthesis in Sertoli cells (Gérard et al., 1992), we determined the levels of the IL-1α mRNA in Sertoli cells cultured for varying periods of time with residual bodies.

2. Materials and methods

2.1. Cell preparations

Peritubular cells were prepared from 19-day-old Sprague-Dawley rats (Møllegaards Breeding Centre, Denmark) by the method of Hutson and Stocco (1981). The cells were confluent after 8–10 days and were harvested for RNA extraction on day 10 after plating.

Germ cell preparations (pachytene spermatocytes and round spermatids) were obtained from 32-day-old rats. The fractionation of the germ cells was carried out in bovine serum albumin (BSA) gradients at unit gravity in a velocity sedimentation cell separator (STA-PUT) according to Grootegoed et al. (1977).

Residual bodies were prepared from 55-day-old rats by centrifugal elutriation (Meistrich et al., 1981), employing a JE-5.0 elutriator with a 5 ml standard chamber. Microscopic examination of the fraction enriched in residual bodies revealed a mixture of residual bodies (Rb) and cytoplasts from elongating spermatids (CES). Staining with haematoxylin/eosin showed less than 5% cells in the Rb/CES fraction.

Primary Sertoli cell cultures were prepared from testes from 19-, 35- and 45-day-old rats, essentially as described by Dorrington et al. (1975). Crude cell fractions obtained by trypsinization were plated on petri dishes (Nunc, Denmark) and incubated at 34°C in a humidified atmosphere of 5% CO_2 in air. On the third day after plating in Eagle's Minimal Essential Medium (MEM, Gibco, Grand Island, NY) supplemented with penicillin, streptomycin, fungizone and 10% fetal calf serum (FCS) (Gibco), most of the remaining germ cells in the cultures from 35- and 45-day-old rats were removed by hypotonic shock treatment with 10% MEM in water for 2.5 min. The cell cultures were then incubated further in serum free medium, with change of medium after 24 h. Differential counting with light microscopy revealed that the contamination of germ cells in the Sertoli cell cultures from 19-day-old rats were $< 2\%$. In the Sertoli cell cultures from 35- and 45-day-old animals, this contamination was $\approx 10\%$.

2.2. Incubation of Sertoli cells with residual bodies, recombinant murine IL-1α, latex beads or lipopolysaccharide (LPS)

On day five after plating Sertoli cells from 19-day-old rats were incubated further in the presence or absence of residual bodies (5×10^6/ml), recombinant murine IL-1α (5 ng/ml; Genzyme, MA), latex beads (7×10^8/ml; Sigma) or LPS (9 μg/ml; Sigma) for various periods of time without change of medium. In a study by Gérard et al. (1992), these concentrations of residual bodies, latex beads and LPS were shown to give nearly maximal IL-1α secretion by primary cultures of Sertoli cells. All cell experiments were carried out $2\times$ or more.

2.3. Isolation of total RNA and Northern analysis

Sertoli cells were lysed in guanidium isothiocyanate (4 M). Total RNA was pelleted by centrifugation through cecium chloride cushions and purified by phenol/chlorophorm extractions (Chirgwin et al., 1979). Total RNA was denatured in 50% formamide and 6% formaldehyde and subjected to elecrophoresis in a 1.5% agarose gel containing 6.7% formaldehyde. The RNA was visualized by staining with ethidium bromide and then transferred to BioTrans nylon filters (ICN, Schwarz/Mann Biotech, Cleveland, OH) by capillary blotting technique (Sambrook et al., 1989). The hybridization was carried out according to the protocol supplied by the manufacturer (ICN) with ^{32}P-labeled cDNA probes. Autoradiography was carried out using Amersham HMP films and intensification screens (Hyperscreen RPN, Amersham, UK).

2.4. Probes

The plasmids pmIL1AcDNA and pGEMBL IL-1R containing murine IL-1α cDNA and IL-1R type I cDNA, respectively, were obtained from American Type Culture Collection (IL-1α; ATCC no. 63106, IL-1R; ATCC no. 7563). The cDNA probes (IL-1α; 1152 bp, IL-1R; 2300 bp) were labeled by using [α-^{32}P]dCTP (Amersham) and a standard random priming kit (Amersham).

3. Results

Fig. 1 shows the distribution of IL-1α and IL-1 receptor type I mRNA in somatic cells and immature germ cells from rat seminiferous tubules. Whereas IL-1α mRNA was primarily detected in the germ cells and not in the Sertoli cells (SC) (Fig. 1(A)), IL-1 RI mRNA was present in Sertoli cells and peritubular cells (PTC), but not in pachytene spermatocytes (PS) or in round spermatids (RST) (Fig. 1(B)).

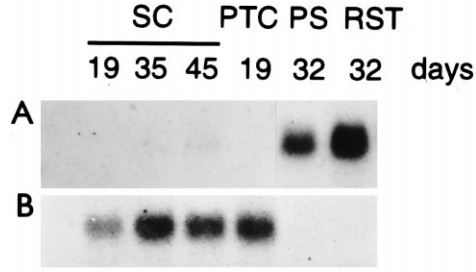

Fig. 1. Expression of mRNA for IL-1α A) and IL-1 RI B) in different cell types from rat seminiferous tubules. Total RNA was isolated from Sertoli cells SC) from 19-, 35- and 45-day-old rats, peritubular cells PTC) from 19-day-old rats, pachytene spermatocytes PS) and round spermatids RST) from 32-day-old rats. Total RNA 20 μg) was loaded in each lane and subjected to Northern blot analysis. The resulting filter was probed with ^{32}P-labeled IL-α cDNA A) and IL-1 RI cDNA B).

In Fig. 2 the effects of recombinant murine IL-1α (rmIL-1α) on the levels of mRNA for IL-1α and IL-1 RI in primary cultures of Sertoli cells are depicted. As seen in Fig. 2(A), high levels of IL-1α mRNA were observed after treatment for 1 h with rmIL-1α, whereas basal levels were undetectable. After 7 h of stimulation, IL-1α mRNA levels had almost returned to basal. In contrast, the increased IL-1 RI mRNA levels seen after 2 h of stimulation with rmIL-1α were maintained throughout the experimented period (Fig. 2(B)).

Treatment of Sertoli cells with residual bodies resulted in a biphasic stimulation of mRNA for both IL-1α and IL-1 RI. As seen in Fig. 3(A), the IL-1α transcript (2.2 kb) was detected already 1 h after incubation with residual bodies. The signal intensity showed a maximum after 4 h followed by a decrease to very low levels at 12 h. Surprisingly, 24 h after addition of residual bodies the IL-1α mRNA expression again increased and reached very high levels at 40 h which persisted throughout the period of investigation. Northern blot analysis of residual bodies revealed no IL-1α mRNA (data not shown).

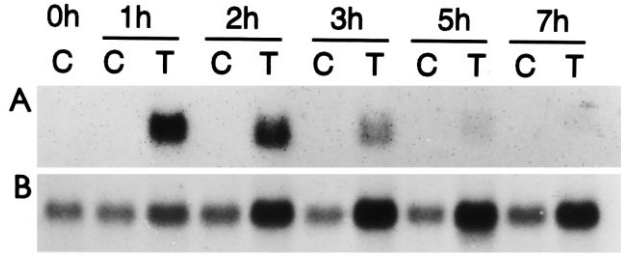

Fig. 2. Effects of recombinant murine IL-1α rmIL-1α) on the expression of mRNA for IL-1α A) and IL-1 RI B) in primary cultures of Sertoli cells from 19-day-old rats. The Sertoli cells were cultured in the presence T) or absence C) of recombinant murine IL-1α 5 ng/ml) for various periods of time 0–7 h). Total RNA 20 μg) was loaded in each lane and subjected to Northern blot analysis. The resulting filter was probed with ^{32}P-labeled cDNA for IL-1α A) and IL-1 RI B).

Fig. 3(B) shows that the mRNA levels of IL-1 RI mRNA were stimulated in a similar, cyclic manner to that of its ligand. The maximum signal intensity during the first wave of response was observed 4 h after addition of residual bodies. During the second wave of response the maximum levels were observed after 36 h.

In addition to the 5.1 kb transcript normally seen in other cell types (Aksamit et al., 1993; Lacey et al., 1993; Simon et al., 1993), two smaller-sized transcripts of ≈1.7 and 3.5 kb appeared after 32 h (Fig. 3(B)).

Stimulation of Sertoli cells with latex beads resulted in a large and transient increase in IL-1α mRNA levels with maximum after 20 h (Fig. 4(A)), whereas only very weak signals were seen after treatment with lipopolysaccharide (LPS) (Fig. 4(A)). Slightly elevated levels of IL-1R mRNA were seen after treatment with both latex beads and LPS.

4. Discussion

In the present study, IL-1α mRNA was not detected in unstimulated, primary cultures of Sertoli cells from rat, as also shown in our previous study (Haugen et al., 1994). However, stimulation by IL-1α resulted in a rapid and transient production of IL-1α mRNA. This is the first time IL-1α mRNA is demonstrated in rat Sertoli cells. In contrast to our findings with IL-1α mRNA, IL-1 RI mRNA is constitutively expressed in cultured Sertoli cells. In a recent study using RT-PCR, Gomez et al. (1997) detected IL-1 RI mRNA in all the somatic testicular cell fraction studied (Leydig cells, Sertoli cells, testicular macrophages, peritubular cells), as well as low levels in immature germ cells (pachytene spermatocytes and round spermatids). The latter finding is in contrast to our results where IL-1 RI mRNA was undetectable in pachytene spermatocytes and round spermatids by Northern analysis. Low production of IL-1 RI mRNA by rat germ cells may require an ultrasensitive method like RT-PCR for detection. In line of this notion, Gomez and coworkers also detected IL-1 RI mRNA in a variety of mouse testicular cells, including germ cells, using light and electron microscopic in situ hybridization.

Our finding that IL-1 RI mRNA is constitutively expressed by Sertoli cells is in line with Gomez et al. (1997) and indicates that Sertoli cells are targets for IL-1α. The fact that mRNA for both IL-1α and IL-1 RI are upregulated upon stimulation by IL-1α suggests, at least in part, an autocrine role for IL-1α in Sertoli cells. Autoregulation of IL-1 has also been observed in other cell types (Dinarello et al., 1987; Warner et al., 1987). However, IL-1α originating from germ cells (Haugen et al., 1994) may also have a paracrine action on Sertoli cells.

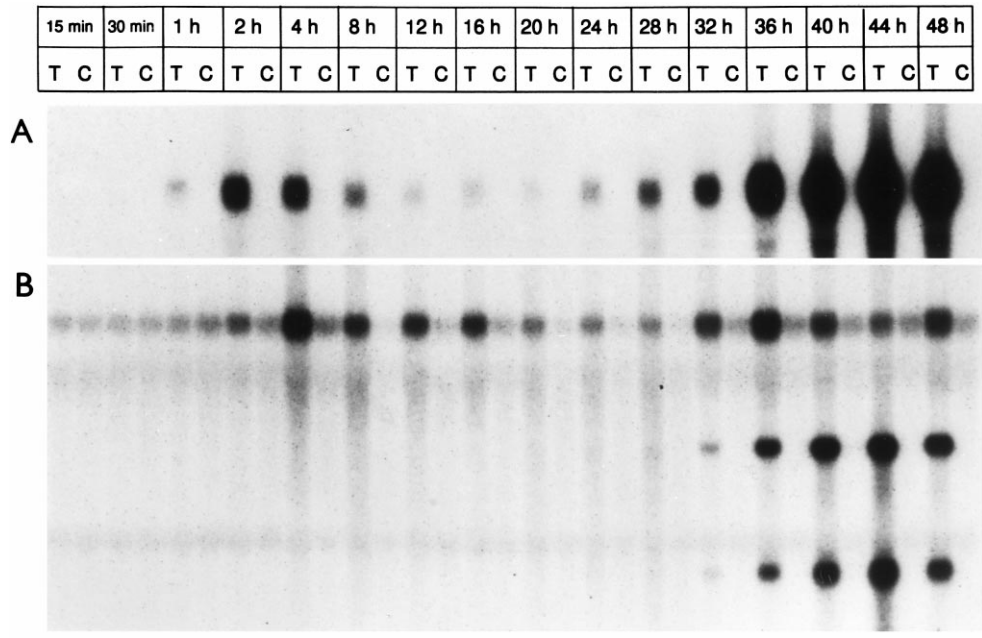

Fig. 3. Effects of residual bodies on the expression of mRNA for IL-1α A) and IL-1 RI B) in primary cultures of Sertoli cells from 19-day-old rats. The Sertoli cells were cultured in the presence T) or absence C) of residual bodies 5×10^5/ml) for various periods of time 15 min–48 h). Total RNA 15 μg) was loaded in each lane and subjected to Northern blot analysis. The resulting filter was probed with ^{32}P-labeled cDNA for IL-1α A) and IL-1 RI B). $\ll 15' \gg$ and $\ll 30' \gg$ denote 15 and 30 min, respectively.

The present study further shows that residual bodies increase IL-1α mRNA levels in cultured rat Sertoli cells. These findings support the hypothesis put forward by others that residual bodies are important modulators in the local regulation of the spermatogenesis (Roosen-Runge, 1952; Gérard et al., 1992). Whether

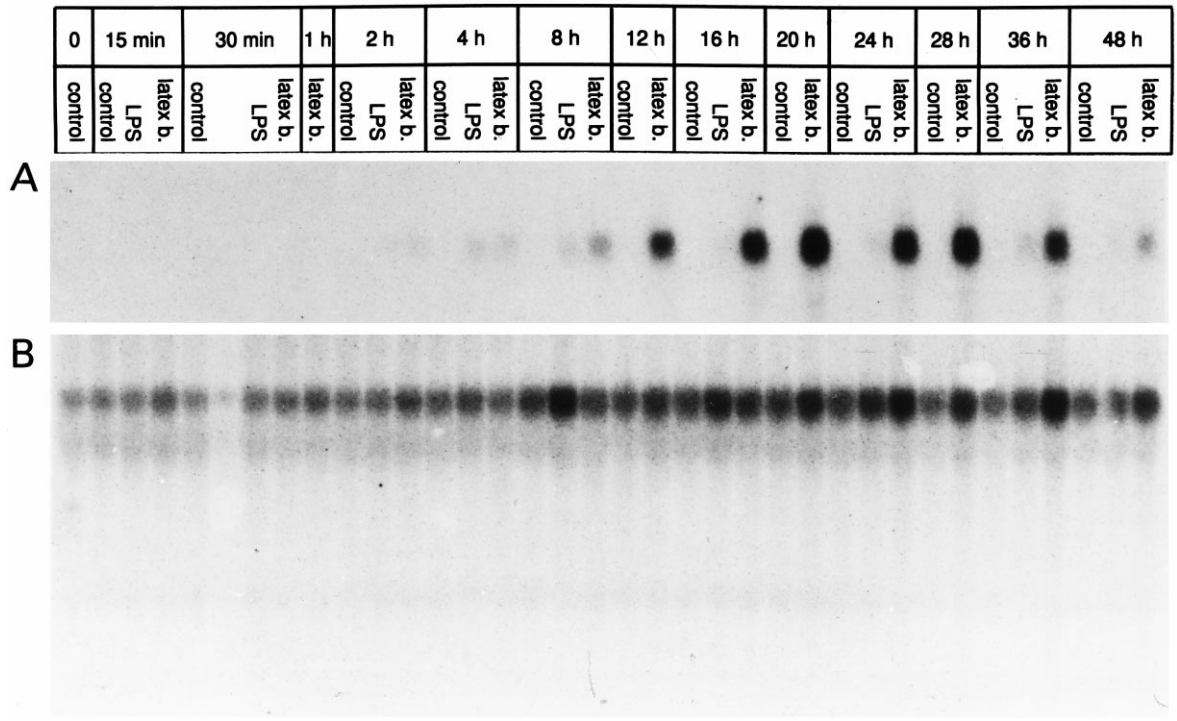

Fig. 4. Effects of latex beads and lipopolysaccharide LPS) on the expression of mRNAfor IL-1α A) and IL1RI B) in primary cultures of Sertoli cells from 19-day-old rats. The Sertoli cells were cultured in the presence or absence control) of latex beads 7×10^8 /ml) or LPS 9 μg/ml) for various periods of time 0–48 h). Total RNA 20 μg) was loaded in each lane and subjected to Northern blot analysis. The resulting filter was probed with ^{32}P-labeled cDNA for IL-1α A) and IL-1 RI B).

the effects of residual bodies on Sertoli cells are mediated by transfer of specific RNAs or is due to contact activation is still being discussed (Jégou, 1991, 1992). The rapid stimulation of IL-1α mRNA (after 1 h) suggests that binding of residual bodies to Sertoli cells, probably mediated by specific adhesion molecules (Byers et al., 1993), is sufficient for activation.

Phagocytosis of residual bodies by the Sertoli cells may be involved in a feed-back mechanism in the spermatogenesis and important for regulating Sertoli cell function. Furthermore, in light of the findings by others that IL-1α stimulates spermatogonial DNA synthesis (Söder et al., 1991), this cytokine is probably involved in maintaining the spermatogenesis. The profound second wave of IL-1 gene expression in these cells when cocultured with residual bodies, may be due to newly synthesized factors, including IL-1α. This view is supported by a study by Pineau et al. (1991) which showed that residual bodies are totally digested by Sertoli cell within 24 h of coculture. Our results may indicate that autocrine acting IL-1α is involved in this secondary stimulation. Syed et al. (1995) found that Sertoli cell IL-1α release triggers IL-6 production by an autocrine mechanism. Moreover, the secondary stimulation of IL-1α mRNA production in our results occurs at a time when Syed and coworkers found IL-6 levels to be elevated. This suggests that also IL-6 may play a role in the secondary stimulation of IL-1α production by Sertoli cells cocultured with residual bodies. The biphasic pattern seen when Sertoli cells were stimulated with residual bodies was not observed after treatment with latex beads or LPS.

The two IL-1 RI transcripts of $\approx$1.7 and 3.5 kb expressed in Sertoli cells cocultured with residual bodies, have not, to our knowledge, been previously reported. These transcripts were not observed after stimulation of the Sertoli cells with latex beads or LPS. Although three different initiation sites for IL-1 RI transcription are possible (Ye et al., 1993), this can not account for the size variation between the different transcripts. However, in other cell types, the choice of promoter has been shown to dictate different polyadenylation sites (Bergers et al., 1994; Sims et al., 1995). Accordingly, the multiple transcripts of IL-1 RI mRNA observed in Fig. 3(B) may originate from differential polyadenylation. Another possibility is that alternative splicing of the IL-1 RI pre-mRNA account for generation of the smaller transcripts. During the last five years several new proteins have been added to the IL-1 receptor family (McMahan et al., 1991; Greenfeder et al., 1995; Parnet et al., 1996; Mitcham et al., 1996). Whether the shorter transcripts observed in our study represent differentially initiated or alternatively spliced mRNAs remains to be shown.

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