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Multiple effects of arginine vasopressin on prostaglandin E_2 synthesis in fibroblasts

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Abstract

Recent evidence supports the viewpoint that vasopressin, a neurohypophyseal peptide, should be also considered as a neuroendocrine modulator of immune and inflammatory responses. In this work we investigated the role of vasopressin in the regulation of prostaglandin E_2 synthesis by human dermal fibroblasts. Recombinant human interleukin-1β increased prostaglandin E_2 synthesis in fibroblasts about sixfold. The prostaglandin E_2 response to interleukin-1β was attenuated by lower concentrations of vasopressin (10^{-10}–10^{-9} M). By contrast, higher concentrations (10^{-8}–10^{-7} M) of vasopressin effected significant enhancement of the interleukin-1β-induced prostaglandin E_2 synthesis. In a similar way, vasopressin (10^{-8}–10^{-7} M), in the absence of interleukin-1, significantly increased prostaglandin E_2 production. An inhibitory effect of lower concentrations of vasopressin was also observed on basal production of prostaglandin E_2. The effects of vasopressin on basal and interleukin-1β-induced prostaglandin E_2 synthesis were antagonized by selective vasopressin receptor antagonists. The findings presented here disclose a novel modulatory role of vasopressin on prostaglandin E_2 synthesis in human dermal fibroblasts and suggest a possible role of vasopressin in the regulation of inflammation.

Keywords: Interleukin-1; Vasopressin; Prostaglandin; Inflammation

1. Introduction

Arginine vasopressin is a 9-amino-acid peptide hormone synthesized in the posterior pituitary gland together with oxytocin. Vasopressin plays a major role in the regulation of plasma osmolality and body fluid volume as well as in the maintenance of blood pressure. Vasopressin also exerts a wide array of additional physiological effects, notably corticotrophin release. Although vasopressin alone has little corticotrophin secretagogue activity by itself, it potentiates the secretagogue effect of corticotrophin-releasing hormone (CRH) and stimulates the release of the proopiomelanocortin (POMC) peptides adrenocorticotropic hormone (ACTH) and β-endorphin from the anterior pituitary in response to stressful stimuli (Antoni, 1986). By subsequently activating glucocorticoids secretion, central vasopressin participates in the suppressive effects of stress on immune or inflammatory mechanisms.

Recent evidence supports the viewpoint that vasopressin by itself is also a modulator of immune and inflammatory responses. In different experiments, vasopressin exerted either pro- or anti-inflammatory effects on immune cells. For example, it was shown to replace the interlukin-2 requirement for interferon gamma production in vitro (Johnson et al., 1982). Potentiation of immunoglobulin M antibody production by vasopressin was observed in vivo (Croiset et al., 1990). On the other hand, the i.c.v. administration of vasopressin suppressed the proliferative response of splenic T cells and natural killer cytotoxicity in an adrenal-independent manner (Yirmiya et al., 1989). Vasopressin also attenuated endotoxin-induced fever in rats (Jansky, 1992). Chrousos' group described increased vasopressin secretion in the inflammatory disease-susceptible Lewis rats and concluded that vasopressin and corticotrophin-releasing hormone participate in the excessive inflammatory response of Lewis rats as locally acting proinflammatory agents (Patchev et al., 1992). In addition, the parvocellular vasopressin system was shown to play an important role in the adaptation

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of the hypothalamo–pituitary–adrenal axis to experimentally induced chronic stress of arthritis (Patchev et al., 1992, 1993). Moreover, a number of studies have reported the presence of vasopressin as well as CRH, ACTH and β-endorphin in immune tissues. Thus, vasopressin was identified in the epithelial cells of the thymus (Geenen et al., 1987; Markwick et al., 1986) and plasma cells of the spleen (Jessop et al., 1995).

Prostaglandins are major inflammatory mediators biosynthesized from essential fatty acid precursors. Prostaglandin synthesis can be activated by a wide variety of stimuli including proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-α (TNF-α). Considerable amounts of prostaglandin E_2 are synthesized by fibroblasts in response to interleukin-1 (Pang et al., 1994). Prostaglandin E_2 is known to be a powerful dilator of vascular smooth muscle, partially accounting for the characteristic vasodilatation seen in acute inflammation. Prostaglandin E_2 potentiates vascular permeability and is also implicated in production of fever (Saper and Breder, 1996).

In the present study we investigated the role of vasopressin in the regulation of basal and interleukin-1-induced prostaglandin E_2 synthesis in human dermal fibroblasts. Since the latter are inflammatory cells, the present data strongly suggest a role for vasopressin in the peripheral regulation of inflammation.

2. Materials and methods

2.1. Materials

The following materials were used: arginine-8 vasopressin (Sigma, St. Louis, MO), aprotinin (Trasylol, Bayer, Leverkusen, Germany), (2*S*)1-[(2*R*,3*S*)-(5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxybenzine-sulfonyl)-3-hydroxy-2,3-dihydro-1*H*-indole-2-carbonyl]-pyrrolidine-2-carboxamide (SR49059), (1-[4-(*N*-*tert*-butylcarbamoyl)-2-methoxybenzene sulfonyl]-5-ethoxy-3-spiro-[4-(2-morpholinoethoxy)-cyclohexane] indoline-2-one, phosphate monohydrate; *cis*-isomer) (SR121463B) (generous gifts from Dr. Serradeil-Le Gal, Sanofi Recherche), recombinant human interleukin-1β (a generous gift from Dr. Newton, DuPont Merck), [β-Mercapto-β,β-cyclopentamethylenepropionyl^1, *O*-Me-Tyr^2,Arg^8]vasopressin (V2255) (Sigma).

2.2. Methods

2.2.1. Cell culture

Normal human dermal fibroblasts were initiated from foreskin explants of a child. Pieces of fresh skin were placed overnight in 0.25% trypsin–0.05% EDTA at 4 °C after trimming of subcutaneous fat and separation of the dermis from the epidermis. Pieces (1–2 mm^2) were placed in 100-mm tissue culture plates (Costar, Cambridge, MA) and allowed to attach. Other tissue fragments were aspirated, and attached fibroblasts were subcultured. Fibroblasts, used between passages 6 and 17, were laid in 24-well tissue culture plates (Greiner, Frickenhausen, Germany) and incubated at 37 °C in humidified 8% CO_2–air atmosphere. Each 16-mm well contained 1 ml Dulbecco's modified Eagle's medium (DMEM; Biological Industries, Beth Haemek, Israel) supplemented with 10% fetal calf serum (Sigma), 2 mM L-glutamine, and penicillin/streptomycin (Biological Industries) at concentrations of 100 U/ml and 100 μg/ml, respectively. Fibroblasts were used after reaching 80% confluence. Experiments were initiated by washing twice with serum-free DMEM. The test agents were added into the media containing 0.1% of fetal calf serum for the length of time indicated in each experiment.

2.2.2. Determination of prostaglandin E_2

The prostaglandin E_2 that had accumulated in the medium was measured in unextracted samples of DMEM by single antibody radioimmunoassay (RIA) with dextran-coated charcoal precipitation. DMEM did not interfere with the assay. The assay was performed in duplicate for each sample. Rabbit antibody to prostaglandin E_2 was obtained from Sigma (Sigma), and tritium-labeled prostaglandin E_2 (160 Ci/mmol) was supplied by the Radiochemical Center (Amersham, UK). Radioactivity was measured on a β-scintillation counter (1214 RackBeta, LKB Wallac, Turku, Finland). The sensitivity of the assay was 0.15 ng/ml. The prostaglandin E_2 antiserum cross reacted with other prostaglandins as follows: prostaglandin E_2, 100%; prostaglandin E_1, 165%; prostaglandin A_1, 28%; prostaglandin A_2, 7%; prostaglandin B_1, 13%; prostaglandin B_2, 6%; prostaglandin $F_{1\alpha}$, 5%; prostaglandin $F_{2\alpha}$, 1.5%; other prostaglandins, <1%. Thus, the

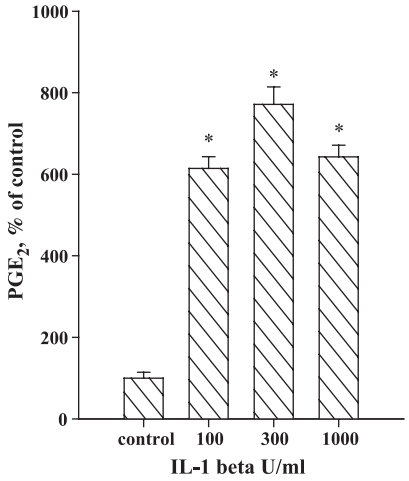

Fig. 1. Induction of prostaglandin E_2 production by interleukin-1β. Human dermal fibroblasts were incubated with various concentrations of interleukin-1β for 24 h. The media were collected and assayed for prostaglandin E_2. Results represent the means ± S.E.M. of $n=12$. *$P<0.05$ vs. control.

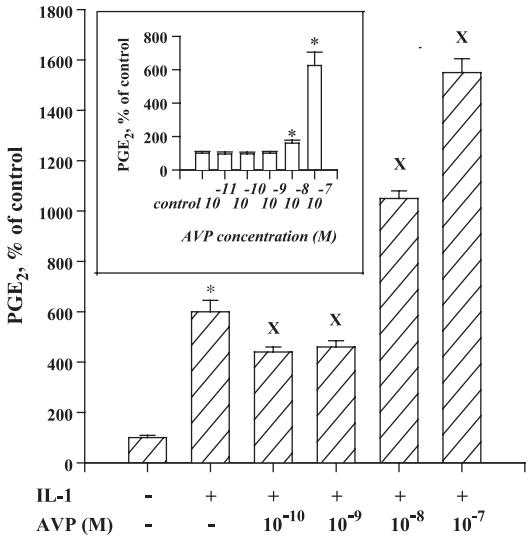

Fig. 2. Effect of vasopressin on basal and interleukin-1β-induced prostaglandin E_2 production by human dermal fibroblasts. Cells were incubated with vasopressin (at increasing concentrations) alone (inset) or together with interleukin-1β (100 U/ml) for 24 h. Thereafter, the media were collected and assayed for prostaglandin E_2. Results are means ± S.E.M. of $n=12$. *$P<0.05$ compared with control, $^{x}P<0.05$ vs. interleukin-1β.

assay could identify prostaglandins of the E series and their dehydration products (prostaglandins A and B). Because human tissues produce dienoic prostaglandins, the radioimmunoassay results were interpreted as measuring prostaglandin E_2.

2.2.3. Determination of protein content

After removal of the medium, the attached cells in each well were dissolved in 1 ml of 10 mM NaOH and transferred into test tubes. Protein concentrations were determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Richmond, CA) comprising an acidic solution of Coomassie blue that shifts from 465 to 595 nm when bound to protein. Bovine serum albumin (Sigma) was used as standard.

2.2.4. Determination of cell count

After removing the medium, cells were harvested by trypsinization, collected, dissolved in 5 ml isoton solution (NaCl 7.9 g/l, KCl 0.4 g/l, NaF 0.3 g/l, EDTA, disodium salt, 0.4 g/l, Na_2HPO_4 1.9 g/l NaH_2PO_4 0.2 g/l) and counted in a Model Z1 Counter (Coulter Electronics, Luton, Beds. England).

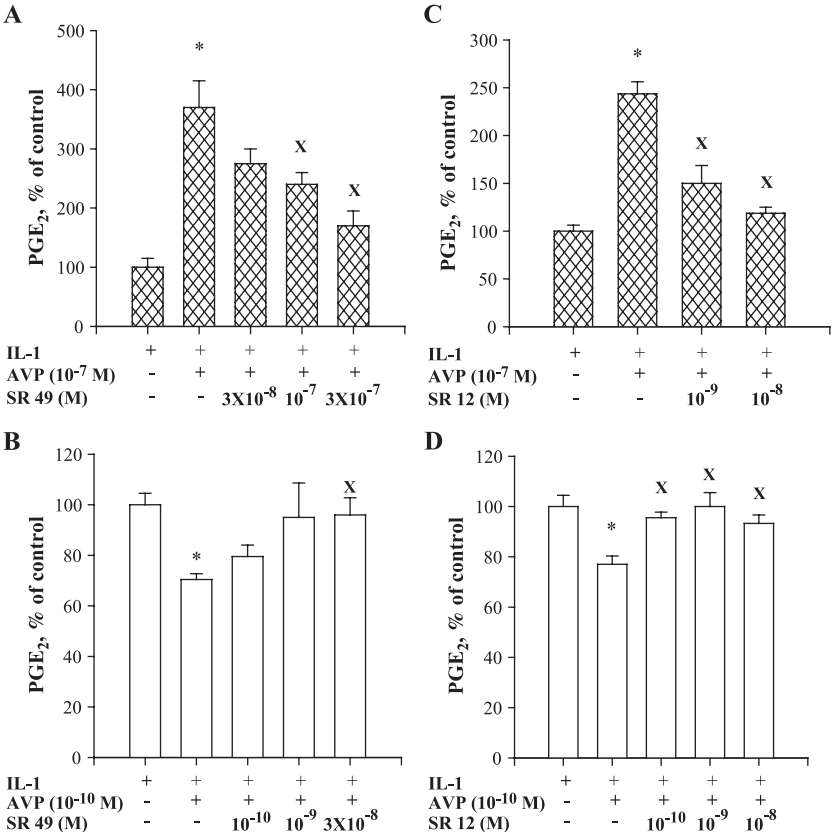

Fig. 3. Effect of vasopressin receptor antagonists on vasopressin- and interleukin-1β-induced prostaglandin E_2 production. Human dermal fibroblasts were incubated with: interleukin-1β (100 U/ml) and 10^{-7} M (A, C) or 10^{-10} M vasopressin (B, D) in the absence or presence of the V_1 receptor antagonist SR49059 (SR49) (A, B), or the V_2 receptor antagonist SR121463B (SR12) (C, D) at increasing concentrations. The media were collected and assayed for prostaglandin E_2. Results are means ± S.E.M. of $n=12$. *$P<0.05$ vs. interleukin-1β; $^{x}P<0.05$ vs. vasopressin.

2.3. Data analysis

Results are expressed as the mean ± S.E.M. for each experiment. Statistical analysis of the results was performed using two-tailed Student's *t*-test. $P < 0.05$ was considered significant.

3. Results

Recombinant human interleukin-1β enhanced prostaglandin E_2 synthesis in fibroblasts about sixfold after 24-h treatment (Fig. 1). Fig. 2 shows the effect of vasopressin at different concentrations on basal (inset) and interleukin-1β-induced prostaglandin E_2 synthesis. Exposure to interleukin-1β (100 U/ml, equivalent to 5.55×10^{-14} M) for 24 h increased prostaglandin E_2 synthesis about sixfold, and the lower concentrations of vasopressin (10^{-9}–10^{-10} M) significantly diminished the interleukin-1β-induced prostaglandin E_2 production. By contrast, the higher concentrations (10^{-8}–10^{-7} M) of vasopressin effected significant enhancement of the interleukin-1β-induced prostaglandin E_2 synthesis. In a similar way, in the absence of interleukin-1, vasopressin (10^{-8}–10^{-7} M) significantly increased prostaglandin E_2 production (Fig. 2, inset).

To further assess the nature of receptors involved in vasopressin's effects on interleukin-1-induced prostaglandin synthesis, we used vasopressin receptor antagonists. SR49059 has high affinity for both human and rat vasopressin V_{1a} receptor ($K_i = 1.1$–6.3 nM), and SR121463B is specific for V_2 receptor ($K_i = 0.26$–0.4 nM). Fig. 3 shows the effects of SR49059 (A, B) and SR121463B (C, D), respectively, on interleukin-1β and vasopressin-modulated prostaglandin E_2 output. The effects of the receptor antagonists were studied in relation to the stimulatory effect produced by the higher concentration (10^{-7} M) (A, C) and the inhibitory effect of a lower concentration (10^{-10} M) of vasopressin (B, D). Both V_1 and V_2 receptor antagonists effectively block the interleukin-1β enhancement of vasopressin (10^{-7} M)-induced prostaglandin E_2 synthesis in human dermal fibroblasts in a concentration-dependent manner (Fig. 3A,C). Similarly, both receptor antagonists abrogated the suppressive effect of vasopressin (10^{-10} M) on interleukin-1β-induced prostaglandin E_2 production (Fig. 3B,D).

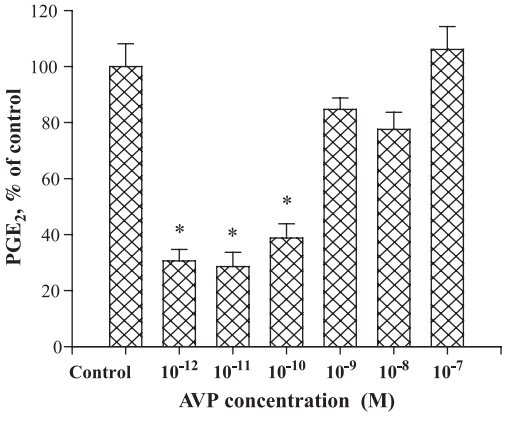

Fig. 4. Effect of 1 h exposure to vasopressin on prostaglandin E_2 synthesis in human dermal fibroblasts. Cells were incubated with increasing concentrations of vasopressin (10^{-12}–10^{-7} M) for 1 h. Then the media were collected and assayed for prostaglandin E_2. Results are means ± S.E.M. of $n = 8$. $^*P < 0.05$ vs. control.

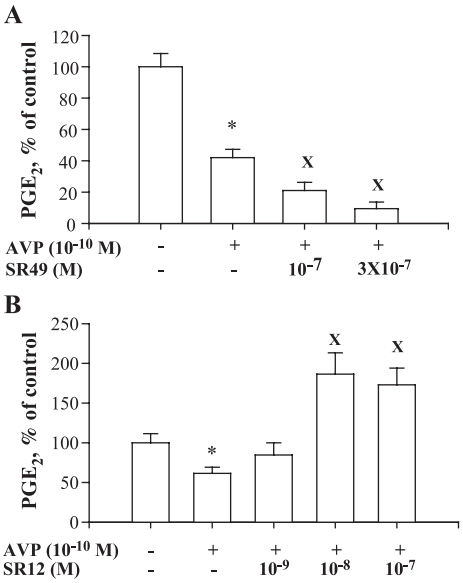

Fig. 5. Effect of vasopressin receptor antagonists on vasopressin-induced attenuation of prostaglandin E_2 production. Human dermal fibroblasts were incubated with vasopressin (10^{-10} M) alone or together with the V_1 receptor antagonist SR49059 (SR49) (A) or the V_2 receptor antagonist SR121463B (SR12) (B) for 1 h. Thereafter, the media were collected and assayed for prostaglandin E_2. Results are means ± S.E.M. of $n = 8$. $^*P < 0.05$ vs. control; $^xP < 0.05$ vs. vasopressin.

An inhibitory effect of lower concentrations of vasopressin was also shown on basal production of prostaglandin E_2. One-hour exposure of human dermal fibroblasts to the peptide, at concentrations of 10^{-12}–10^{-10} M, significantly reduced basal production of prostaglandin E_2, whereas no effect was observed at concentrations of 10^{-9} M or higher (Fig. 4). Fig. 5 shows the effects of receptor antagonists on this modulatory action of vasopressin. The V_1 receptor antagonist SR49059 and V_2 receptor antagonist SR121463B were added simultaneously with 10^{-10} M vasopressin. In contrast to the effects of receptor antagonists on the activity of vasopressin in the presence of interleukin-1 (24 h), the short-term effects of vasopressin were altered differentially by the two receptor antagonists. Whereas SR49059 enhanced the suppressive effect of vasopressin (Fig. 5A), SR121463B reversed the effect of vasopressin and actually augmented the release of prostaglandin E_2 in comparison with 10^{-10} M vasopressin alone (Fig. 5B).

4. Discussion

The results presented in this article show that vasopressin regulates prostaglandin E_2 production by human dermal fibroblasts in more than one way. In cells stimulated with the proinflammatory cytokine interleukin-1β, higher concentrations of vasopressin (10^{-8}–10^{-7} M) increased prostaglandin E_2 production, and in contrast, lower vasopressin concentrations (10^{-12}–10^{-10} M) attenuated prostaglandin E_2 synthesis within 24 h. Moreover, low concentrations of vasopressin also reduced basal prostaglandin E_2 production in non-interleukin-1β-stimulated cells within 1 h, whereas basal levels of prostaglandin E_2 were induced after exposure of cells to higher concentrations of the peptide. This data indicates that modulation of prostaglandin E_2 production by vasopressin in fibroblasts is a biphasic process that depends on the concentration of the peptide.

Classically, the two target organs for vasopressin have been the kidney and the vascular smooth muscle. In both, vasopressin has been shown to regulate the synthesis of prostaglandins, which in turn partially mediate the effects of vasopressin. Two major types of vasopressin receptors, V_1 and V_2, which have different ligand specificities and distinct cellular mechanisms of actions, mediate vasopressin's action in the periphery (Michell et al., 1979). Activation of V_1 receptors increases phosphatidylinositol breakdown, thus causing cellular calcium mobilization (Thibonnier, 1992). On the other hand, the V_2 receptors, which mostly mediate the renal actions of vasopressin, activate G proteins and stimulate the generation of cAMP.

Antagonists of V_1 and V_2 receptors effectively reversed the effects of vasopressin in interleukin-1-treated cells, suggesting involvement of both receptors in regulation of prostaglandin synthesis. These results may also indicate a possible crosstalk between the two types of receptors. Interestingly, Okamura et al. (1997) also described involvement of both V_1 and V_2 receptors in mediation of a biphasic effect of vasopressin on ciliary arterial strips with endothelium. Vasopressin produced relaxations of canine ciliary arterial strips with endothelium at low concentrations (10^{-11}–10^{-10} M) and contractions at higher concentrations. Both the relaxant response and the contractions were inhibited dose-dependently by SR49059 (V_1 receptor antagonist) and OPC1260 (V_2 receptor antagonist).

Before the V_1 and V_2 receptors were well characterized, Zipser et al. (1981) described a dual effect of vasopressin on prostaglandin production in vivo. In this study healthy subjects received vasopressin and the nonpressor vasopressin analog desamino-D-arginine vasopressin. The analog reduced urinary prostaglandin E_2, while vasopressin increased it. Infusions of another vasoconstrictor peptide, angiotensin II, also increased urinary prostaglandin E_2 excretion. Therefore, stimulation of prostaglandin E_2 secretion was thought to be due to pharmacological pressor activity (possibly V_1 receptor), while inhibition of prostaglandin E_2 synthesis was ascribed to antidiuresis (possibly V_2 receptor). As shown in Fig. 4, the antagonist results after short exposure (1 h) to vasopressin also seem to indicate that both receptor types contribute to prostaglandin synthesis in opposing directions: activation of the V_1 receptor seems to stimulate prostaglandin synthesis, while the V_2 receptor probably inhibits prostaglandin synthesis. Nevertheless, other experiments (e.g., in the presence of interleukin-1) reveal a more complex situation. Numerous reports have described stimulation of prostaglandin E_2 production by vasopressin in different organs and tissues such as mesangial cells (Scharschmidt and Dunn, 1983; Nishida et al., 1998), rat glomerular epithelial cells (Liberthal and Levine, 1984), isolated rat kidneys (Cooper and Malik, 1984), renal medullar tubular cells (Wuthrich and Valloton, 1986), aortic smooth muscle cells (Murase et al., 1992) and vascular smooth muscle cells (Valloton et al., 1989). In these models as well, the action of vasopressin to stimulate prostaglandin E_2 production is thought to be linked to the V_1 receptor.

Activation of the hypothalamo–pituitary–adrenal axis is a hallmark of the inflammatory process. Interleukin-1β stimulates this axis by a mechanism involving activation of the arachidonic acid cascade and the synthesis of prostaglandins. The primary mechanism by which cytokines stimulate the secretion of adrenocorticotropic hormone (ACTH) is increased secretion of corticotrophin-releasing factor (CRF) and vasopressin (Rivier et al., 1984). Peripheral synthesis of eicosanoids that act locally in an autocrine or paracrine manner is another pathway mediating the inflammatory process.

The present investigation highlights a novel aspect in vasopressin biology. We show that fibroblasts respond to vasopressin with either decreased (at low concentrations) or increased (at high concentrations) synthesis of prostaglandin E_2. The precise mechanisms by which vasopressin produces these effects on fibroblasts is not readily apparent. The inhibitory effect of low concentrations on prostaglandin production is immediate (1 h), and is therefore compatible with the classical signal transduction pathways known for vasopressin. On the other hand, the stimulatory effect of higher vasopressin concentrations was only apparent after long exposure (24 h) of the cells to the hormone. In this context, it may be relevant to call attention to some recent findings, namely that vasopressin and a related peptide hormone, oxytocin, affect transcription of inducible nitric oxide synthase and of cyclooxygenase-2, respectively (Umino et al., 1999; Fuchs et al., 1999). It is thus tempting to speculate that the late effect of higher concentrations of vasopressin that was observed in the present experiments might represent augmented phospholipase A_2 and/or cyclooxygenase transcription. However, confirmation of this hypothesis must await future studies.

Extrapolations from in vitro experiments to in vivo situations are always difficult. Physiological plasma levels

of vasopressin have been reported to be of the order of magnitude of 10^{-11} M (e.g., Yang et al., 2002). Increased plasma concentrations of vasopressin (10^{-10} M) were described by Chrousos' group in the inflammatory disease-susceptible Lewis rats (Patchev et al., 1992, 1993). Moreover, one may expect that local tissue concentrations of AVP during inflammatory response may be even higher. The interleukin-1β concentration used here, equivalent to 5.55×10^{-14} is within reported pathophysiological levels of interleukin 1 in vivo (e.g., Suzuki et al., 2002). Whether the magnitude of change in prostaglandin levels observed in our experiments could be relevant to in vivo inflammation can be estimated from in vivo models of inflammation, in which at least two- to threefold increases in prostaglandin levels were associated with inflammation (e.g., Nishikori et al., 2002). Inasmuch as fibroblasts play a role in inflammatory processes (Smith et al., 1997; Pang et al., 1994), our results indicate that vasopressin probably participates in the peripheral regulation of inflammation. Such regulation may be biphasic, depending on tissue concentrations of vasopressin.

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