Labour-associated changes in the regulation of production of immunomodulators in human amnion by glucocorticoids, bacterial lipopolysaccharide and pro-inflammatory cytokines

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Parturition is associated with changes in the production of inflammatory mediators by gestational tissues. An explant system was established to study the change in response of human amnion to various regulating factors during labour. Disks of tissue (6 mm) were excised from amnion membranes obtained either at term by Caesarian section before labour (n = 5–6) or after spontaneous vaginal delivery (n = 3–7). After 24 h equilibration in media, the tissues were treated with interleukin 1β (10 ng ml⁻¹), tumour necrosis factor α (100 ng ml⁻¹), lipopolysaccharide (5 μg ml⁻¹) and dexamethasone (1 μmol l⁻¹) or an appropriate vehicle control for 24 h (n = 3 wells per treatment). Media were harvested and interleukin 10, interleukin 6 and prostaglandin E₂ concentrations were determined by immunoassay. In tissues taken both before and after the onset of labour, basal interleukin 10 production by amnion explants was near to the limit of detection. Basal production rates of PGE₂ by amnion explants were significantly higher (P < 0.0012; Mann–Whitney U test) in tissues taken during labour than in tissues taken before the onset of labour, while interleukin 6 production was not significantly altered by labour. Production rates of interleukin 6 and prostaglandin E₂ were significantly increased by interleukin 1β, tumour necrosis factor α and lipopolysaccharide in explants from tissues taken during and before labour, while the responsiveness of interleukin 10 production to these treatments was inconsistent. Dexamethasone had no effect on interleukin 6 production by amnion explants, but significantly inhibited prostaglandin E₂ production, although this inhibition was approximately 30% lower in tissues obtained after the onset of labour. These results support the presence of inflammatory positive feedback cycles, coincident with a deficiency of an anti-inflammatory factor within gestational tissue, which may be involved in the progression or maintenance of labour.

Introduction

Amniotic fluid contains detectable quantities of a variety of immunomodulatory factors. These include pro-inflammatory cytokines (for example, interleukin 1β (IL-1β), tumour necrosis factor α (TNF-α), IL-6 and IL-8) and derivatives of arachidonic acid metabolism, such as prostaglandins (PGs). The concentrations of these substances in amniotic fluid increase with labour at term, and preterm in the presence of intrauterine infection (Hillier et al., 1990; Romero et al., 1991, 1992, 1994, 1996; Laham et al., 1993; Opsjon et al., 1993; Halgunset et al., 1994; Stallmach et al., 1995; Gomez et al., 1997). Indeed, the increased concentration of cytokines, particularly of IL-6, in the amniotic fluid may be of use as a diagnostic indicator for intrauterine infection-associated preterm labour and delivery (Dudley et al., 1994a; Andrews et al., 1995).

In addition to these pro-inflammatory mediators, anti-inflammatory cytokines, such as IL-10, have also been measured in human amniotic fluid during late gestation (Heyborne et al., 1994; Greig et al., 1995; Dudley et al., 1997a). Interleukin 10 is produced by T cells, B cells, macrophages and cells of human chorion, decidual and placental tissues (Howard and O’Garra, 1992; Moore et al., 1993; Mosmann, 1994; Cadet et al., 1995; Roth et al., 1996; Dudley et al., 1997b; Jones et al., 1997; Paradowska et al., 1997; Trautman et al., 1997). Interleukin 10 displays predominantly inhibitory effects on cell-mediated inflammatory reactions throughout the body (Howard and O’Garra, 1992). With respect to the tissues of pregnancy, cytokine and prostaglandin production by human chorion, decidual and placental cells in culture are inhibited by IL-10 (Dudley et al., 1994b, 1996b; Spencer et al., 1995; Fortunato et al., 1996, 1997; Keelan and Mitchell, 1996; Trautman et al., 1996; Goodwin et al., 1998).

Human amnion synthesises and releases IL-6, IL-8 and PGE₂ both basally and in response to inflammatory stimuli and bacterial products (Casey and MacDonald, 1993; Dudley...
and Trautman, 1994; Kelly, 1994; Mitchell et al., 1995; De Jongh et al., 1996; Dudley et al., 1996a; Laham et al., 1996; Petraglia et al., 1996; Gomez et al., 1997; Keelan et al., 1997). It has been reported that amnion cells in monolayer culture express only a very weak mRNA signal for IL-10 and do not secrete detectable quantities of IL-10 protein (Trautman et al., 1997). Although the glucocorticoid agonist, dexamethasone, has been shown to inhibit IL-6 and IL-8 release from amnion epithelial cells and fibroblasts in culture (Keelan et al., 1997), PGE₂ production by amnion cells in culture can be either inhibited or stimulated by dexamethasone, an effect attributed to the outgrowth of amnion-derived fibroblasts in vitro (Mitchell et al., 1988; Potestio et al., 1988; Gibb and Breton, 1993; Economopoulos et al., 1996). The net effect of these opposing actions by glucocorticoids on amnion prostaglandin production has yet to be clarified.

The importance of inflammatory processes in labour has been postulated for some time (Opsjon et al., 1993; Halgunset et al., 1994; Kelly, 1994; Romero et al., 1994, 1996; Dudley et al., 1996a). The present study was designed to test the hypothesis that an increase in responsiveness to pro-inflammatory signals, and a decrease in anti-inflammatory responses, accompanies normal parturition. The importance of the amnion in the maintenance of pregnancy and the onset of parturition was the reason for it being selected for study. An amnion tissue explant system was used to maintain tissue integrity and to eliminate changes associated with cell dispersion for culture, thus reproducing in vivo responses more closely. Interleukin 6, IL-10 and PGE₂ production were selected for measurement since they are both representative of immunoregulators present in amniotic fluid and because of their known relevance to parturition.

Materials and Methods

Materials

Culture medium (Hams F12/DMEM) was obtained from Irvine Scientific (Santa Ana, CA). Fetal calf serum (FCS) was purchased from Life Technologies Ltd (Auckland). Bovine-gamma globulin (BGG) was purchased from Sigma Chemical Corporation (St Louis, MO). Human IL-1β was obtained from the ImmuneX Corporation, (Seattle, WA). Human TNF-α was provided by J. Fraser (University of Auckland, Auckland). Lipopolysaccharide (LPS) and dexamethasone were obtained from Sigma Chemical Corporation. Recombinant human IL-6, anti-IL-6 antisera and human recombinant IL-10 were obtained from R and D Laboratories (Minneapolis, MN), and anti-IL-10 antisera were purchased from Pharmingen (San Diego, CA). The streptavidin–alkaline phosphatase was obtained from GibCO Life Technologies (Auckland), and the phosphatase substrate (p-nitrophenol phosphate) was obtained from Sigma Chemical Corporation. Trinitiated PGE₂ for radioimmunoassay was purchased from Amersham plc, (Amersham, Bucks) and non-radio labelled PGE₂ was obtained from Cayman Chemicals (Ann Arbo, MI). Easiwash 96-well ELISA plates were obtained from Corning (New York), while all other disposable tissue culture plasticware was from Nunc (Roskilde).

Explant culture

Human term placentae were obtained with informed maternal consent, and prior approval from the Auckland Healthcare Human Ethics Committee, from the National Women’s Hospital, Auckland, New Zealand. Tissues were obtained from women at term, either by elective Caesarian section before the onset of labour (not in labour, NL) or after uncomplicated spontaneous vaginal delivery (spontaneous labour, SL). The amnion, identified as the inner, avascular membrane, was peeled from the attached choriodiudic membranes and washed in Hams F12–Dulbecco’s modified Eagle’s medium (DMEM) to remove residual red blood cells. Disks of tissue (6 mm) were excised using a sterile cork borer, transferred to six-well culture plates (six disks per well, three wells per treatment) and equilibrated for 24 h in Hams F12–DMEM supplemented with 10% FCS and antibiotics (Keelan et al. 1997) at 37°C in a humidified atmosphere of 5% CO₂–95% air. Each of the six disks in a single well was cut from random areas of the membranes to minimize the effects of any regional differences in cytokine production present in these tissues. The mean ± SD wet mass of tissue per well was 52.8 ± 22.2 mg. After equilibration, media were replaced with serum-free media containing 0.1% BGG and antibiotics and the following treatments, or appropriate vehicle controls, were added: IL-1β (10 ng ml⁻¹), TNF-α (100 ng ml⁻¹), LPS (5 μg ml⁻¹) and dexamethasone (1 μmol l⁻¹, in ethanol vehicle). After 24 h, the incubation was terminated and the media were stored at 4°C before immunoassay. Production rates were normalized to the wet mass of tissue in each well.

Cytokine immunoassays

Interleukin 10 and IL-6 were measured by enzyme-linked immunosorbent assays (ELISA). The ELISA for IL-6 was performed as described by Keelan et al. (1997). The assay was performed with a sensitivity of approximately 20 pg ml⁻¹ and an intra-assay precision of 5.5%. Interassay precision was 16.1%. The IL-10 ELISA used a monoclonal anti-human IL-10 capture antibody combined with a biotinylated rat anti-human IL-10 detection antibody. The signal was quantitated using streptavidin–alkaline phosphatase with p-nitrophenol phosphate. The standard curve for the IL-10 assay ranged from 0 to 2500 pg ml⁻¹. The assay performed with a sensitivity of about 15 pg ml⁻¹ and an intra-assay precision of 2.6%. Interassay precision was 11.2%.

Prostaglandin E₂ immunoassay

Media were assayed for PGE₂ by a direct radioimmunoassay similar to that described by Lundin-Schiller and Mitchell et al. (1991), with the exception that the antisem was used in house in rabbits against PGE₂-BSA and BSA-thyroglobulin conjugates. Media samples or standards prepared in media (100 μl) were incubated overnight with [³H]PGE, tracer (about 5000 c.p.m. per tube) and antisera (sufficient to give approximately 25% B₀) at 4°C. Unbound tracer was removed with cold dextran-coated charcoal, and the radioactivity in the
supernatant (bound fraction) was determined in a scintillation counter. Curve fitting and data extrapolation were performed using Ultratrace II software (Wallac Oy, Finland). No significant crossreaction (<0.02%) of the antiserum was detected with the following eicosanoids: PGF$_{6o}$, 6-keto-PGF$_{1o}$, PGA$_{9r}$, thromboxane B$_{2}$, 5-hydroxyeicosatetraenoic acid (HETE), 12-HETE, 15-HETE, leukotriene B$_{4}$ (LTB$_{4}$), LTC$_{4}$, and arachidonic acid. None of the cytokines used in this study crossreacted in the assay. The assay sensitivity was approximately 5 pg ml$^{-1}$, intra- and interassay precision were 5.6 and 17.8%, respectively.

Statistical analysis

Prostaglandin and cytokine production rates are expressed as either pg mg$^{-1}$ wet mass of tissue per 24 h (median) or as percentage of control values (mean ± SEM). Values were derived from pooled data from experiments performed on triplicate samples from 3-7 separate placentae. Differences between basal production rates from tissues taken before and after labour onset, and the effects of the various treatments, were tested for statistical difference using the Mann–Whitney U test for non-parametric data. $P < 0.05$ was considered significant.

Results

Basal production of IL-6, IL-10 and PGE$_{2}$ by amnion explants before and after labour

Basal production rates of PGE$_{2}$ by amnion explants were significantly higher ($P < 0.0012$) in tissue taken after labour than in tissue taken before labour (median = 2810 versus 809 pg mg$^{-1}$ tissue per 24 h; Fig. 1). However, there was only a slight and not statistically significant increase in median IL-6 production with labour (median = 137 versus 106 pg mg$^{-1}$ tissue per 24 h).

Baseline IL-10 production by amnion explants was near to the limit of detection in all tissues (Fig. 1). Two of the six NL placentae produced a small amount of IL-10 (<1.4 pg mg$^{-1}$ tissue per 24 h), while production rates from all of the SL placentae were below detection limits. There was no significant difference between IL-10 production rates before and after labour (median = 0.25 and 0.19 pg mg$^{-1}$ tissue per 24 h, respectively).

Regulation of IL-6, IL-10 and PGE$_{2}$ production by inflammatory mediators before and after labour

Interleukin 6 production from tissues taken both before and after labour showed a 3-7-fold increase relative to controls in response to IL-1β (10 ng ml$^{-1}$) and an approximate twofold increase in response to TNF-α (100 ng ml$^{-1}$) (Fig. 2). There were no significant changes in IL-6 production in response to LPS from tissues taken before labour whereas, in tissues taken after labour, LPS did induce a significant increase in IL-6 production to approximately 3.5-fold of control production. In absolute terms, IL-6 production rates in response to IL-1β and TNF-α were similar in tissues taken before and after labour, while median IL-6 production in response to LPS was significantly greater in tissues taken after labour (Table 1).

The responsiveness of IL-10 production by amnion explants was inconsistent. In general, IL-10 production remained below detection limits but, occasionally, a small response was evident. In the two NL placentae that had detectable basal IL-10 production rates, production of IL-10 was stimulated by IL-1β (2-25-fold), TNF-α (3-16-fold) and LPS (approximately fivefold). Interleukin 10 production rates from the other four placentae remained below detection levels.

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**Fig. 1.** Basal production of interleukin 10 (IL-10), prostaglandin E$_{2}$ (PGE$_{2}$) and IL-6 by explants of amnion tissues taken before (NL; $n = 6$) and after (SL; $n = 7$) labour. All points below the dashed line were below the limit of detection for the IL-10 assay. Horizontal bars represent the medians (median IL-10 production was below the limit of detection). There was a significant increase in PGE$_{2}$ production after labour ($P < 0.001$); however, there were no significant differences between IL-10 and IL-6 production rates by tissues taken before or after labour. Results were analysed by Mann–Whitney U test for non-parametric data.
Table 1. Effects of inflammatory mediators on production of interleukin 6 (IL-6) and prostaglandin E₂ (PGE₂) by amnion explants

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>IL-1β (10 ng ml⁻¹)</th>
<th>TNF-α (100 ng ml⁻¹)</th>
<th>LPS (5 μg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>NL</td>
<td>106 (13–715)</td>
<td>371 (35–2330)</td>
<td>217 (23–2535)</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td>138 (108–333)</td>
<td>470 (242–2294)</td>
<td>251 (194–357)</td>
</tr>
<tr>
<td>PGE₂</td>
<td>NL</td>
<td>809 (241–7991)</td>
<td>4222 (355–14173)</td>
<td>2382 (330–9547)</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td>2810 (1346–10931)*</td>
<td>6802 (2663–14285)*</td>
<td>7619 (4794–9208)*</td>
</tr>
</tbody>
</table>

Data represented as median (range). *P < 0.05 versus NL by Mann–Whitney U test.
NL: term not in labour; SL: term spontaneous labour; IL-1β, interleukin-1β; LPS, lipopolysaccharide; TNF-α, tumour necrosis factor α.

Fig. 2. Interleukin 6 (IL-6) production by amnion explants in response to treatment with IL-1β, tumour necrosis factor α (TNF-α), lipopolysaccharide (LPS) and dexamethasone (Dex) over 24 h. ○, Tissues taken before labour (NL; n = 5–6); ■, tissues taken after labour (SL; n = 3–7). Production is expressed as a percentage of the control (mean ± SEM). *P < 0.05 from control; †P < 0.05 from NL. (Mann–Whitney U test).

Fig. 3. Prostaglandin E₂ (PGE₂) production by amnion explants in response to treatment with interleukin 1β (IL-1β), tumour necrosis factor α (TNF-α), lipopolysaccharide (LPS) and dexamethasone (Dex) over 24 h. ○, Tissues taken before labour (NL; n = 5–6); ■, tissues taken after labour (SL; n = 3–7). Production is expressed as a percentage of the control (mean ± SEM). *P < 0.05 from control; †P < 0.05 from NL. (Mann–Whitney U test).

limits (data not shown). Only one of the SL placenta responded to IL-1β by producing detectable amounts of IL-10 (4.6 ± 0.65 pg mg⁻¹ tissue per 24 h). In contrast, four produced detectable amounts of IL-10 in response to LPS (3.2 ± 2.0 pg mg⁻¹ tissue 24 h) (data not shown).

IL-1β (10 ng ml⁻¹), TNF-α (100 ng ml⁻¹) and LPS (5 μg ml⁻¹) induced significant increases (P < 0.05) in PGE₂ production from tissues taken both before and after labour. The responsiveness of PGE₂ production to TNF-α (a 2–2.5-fold increase relative to control) and to LPS (an approximate 1.5-fold increase relative to controls) was similar in tissues taken before and after labour. However, the responsiveness to IL-1β was significantly reduced from an approximate 4.5-fold to an approximate twofold increase relative to controls after labour. The mean absolute production of PGE₂ from tissues obtained after labour in response to all treatments was significantly higher than production from tissues taken before labour (Table 1).

Regulation of IL-10, IL-6 and PGE₂ production by dexamethasone

None of the tissues treated with dexamethasone produced detectable quantities of IL-10. Interleukin 6 production by
amnion explants was not significantly affected by dexamethasone in tissues taken either before or after labour. Conversely, dexamethasone significantly inhibited PGE\(_2\) production in both cases. However, this inhibition was significantly attenuated in tissues obtained after labour compared with tissues taken before labour (approximately 45% versus approximately 75% inhibition).

**Discussion**

There is abundant evidence that normal term labour and delivery are associated with the activation of inflammatory processes in the fetal membranes, decidua and cervix. The aim of the present study was to establish whether amnion tissue undergoes altered sensitivity to pro- and anti-inflammatory regulators during labour, with respect to the secretion of immunomodulators. It was hypothesized that not only would production of inflammatory substances increase after labour, but also production would be more responsive to inflammatory signals and, perhaps, less responsive to anti-inflammatory mediators. The results confirm that PGE\(_2\) production by amnion tissues increases markedly with the onset of labour (Olson et al., 1983; Skinner and Challis, 1985; Lopez-Bernal et al., 1987; Mitchell et al., 1995), supporting the validity of the model used and the findings of the present study. However, the finding that there was not a significant increase in IL-6 production with labour is in contrast to the findings of Laham et al. (1996) who reported an 80-fold increase in IL-6 release from amnion explants with the onset of labour. The present experiments were performed after a 24 h wash-out period to allow recovery of the tissues from the effects of exposure to stimuli associated with delivery, whereas the experiments performed by Laham et al. (1996) were conducted only 1 h after isolation and processing of the tissue. Hence, a transient increase in cytokine production after processing may have contributed towards their findings.

Interleukin 1β, TNF-α and LPS all significantly increased amnion PGE\(_2\) production in tissues taken both before and after labour, consistent with previous observations (Romero et al., 1988, 1989; Bry and Hallman, 1991; Pollard and Mitchell, 1993; Perkins and Kniss, 1997). In each case, responsiveness (measured as a percentage increase) of PGE\(_2\) production was slightly less in tissues taken after labour. However, owing to the large labour-associated increase in PGE\(_2\) production, this decreased responsiveness may reflect an attenuated capacity for increased PGE\(_2\) production in the tissues taken after labour. Nevertheless, the results provide evidence against a heightened response to inflammatory stimuli during labour. In contrast, although amnion IL-6 production was increased to a similar extent by IL-1β and TNF-α in tissues taken both before and after labour, LPS was only effective in inducing IL-6 production in tissues taken after labour. The fact that LPS was able to induce PGE\(_2\) production with similar efficiency in both categories of tissue indicates that the LPS receptor is present in the amnion before and after labour. This finding may imply that the link between the LPS receptor and IL-6 production is not functional, or is perhaps blocked, until after labour onset. Alternatively, changes in the cell population of the membranes with labour may explain these observations.

Since an increase in basal IL-6 production by tissues taken during labour was not detected in the present study, this increased responsiveness to LPS would seem to be disassociated with a broader increase in sensitivity to inflammatory signals in this tissue. Although some effects of IL-6 on placental hormone production have been described (Neki et al., 1993; Stephanou and Handwerger, 1994), the role of IL-6 in pregnancy awaits elucidation. Interleukin 6 has been shown to be capable of stimulating prostaglandin production in gestational tissues (Mitchell et al., 1991) but only at very high concentrations. It is possible that IL-6 has currently unrecognized effects on placental or fetal tissues. There are no data on the localization of IL-6 receptors in the gestational membranes.

Dexamethasone significantly inhibited amnion PGE\(_2\) production in both tissues taken before and after onset of labour. Production of PGE\(_2\) and expression of prostaglandin-H-synthase 2 (PGHS-2) by amnion-derived fibroblasts in monolayer culture has been shown to be stimulated by dexamethasone, whereas amnion epithelial cell PGE\(_2\) production is inhibited by dexamethasone (Keelan et al., 1997; De Val et al., 1998; Economopoulous et al., 1996). The present results indicate that the net effect of glucocorticoids is a suppression of amnion prostaglandin production, supporting the possibility that the stimulatory effects observed in vitro are an artifact of culture. The inhibitory effect of dexamethasone on PGE\(_2\) production appears to decrease significantly with labour. Changes in the cell populations within the amnion may explain these findings. Alternatively, there may be a decrease in the sensitivity or responsiveness of the glucocorticoid receptor during labour. However, this seems unlikely since glucocorticoid receptor abundance in gestational membranes is unaffected by labour status (Sun et al., 1996). The lack of effect of dexamethasone on amnion IL-6 production is in contrast to findings in dispersed cell cultures (Keelan et al., 1997), which highlights the potential differences in response characteristics of tissue explants compared with dispersed cells.

Cells typically associated with IL-10 production, such as macrophages, are normally present in low numbers in the amnion mesenchyme (Bulmer and Johnson, 1984). However, IL-10 production by amnion cultures has been reported as unmeasurable, despite low concentrations of IL-10 mRNA expression in this tissue (Trautman et al., 1997). Since conditioned media from tissue explants contains higher concentrations of cytokines than media from dispersed cells in culture, it was hypothesized that amnion explants produce detectable quantities of IL-10. However, in the present study, only a few explants produced detectable amounts of IL-10, which may reflect merely a limitation in assay sensitivity. When it was measurable, IL-10 production was stimulated by IL-1β, TNF-α and LPS, which was in agreement with the results of studies on macrophages and monocytes (Mosmann, 1994; Fushimi et al., 1997) and decidual cells in culture (Dudley et al., 1997b; Jones et al., 1997; Paradowska et al., 1997; Trautman et al., 1997). Although production of IL-10 by amnion has been demonstrated, the present results neither prove nor disprove the hypothesis that this tissue is a major contributor to the IL-
10 in amniotic fluid (Heyborne et al., 1994; Greig et al., 1995; Dudley et al., 1997a). As there are no data on the passage of IL-10 across the membranes, it remains a possibility that amniotic fluid IL-10 originates in the decidua, chorion or placenta, all of which are known to produce this cytokine (Cadet et al., 1995; Bennett et al., 1996; Roth et al., 1996; Dudley et al., 1997b; Jones et al., 1997; Paradowska et al., 1997; Trautman et al., 1997). Kent et al. (1994) reported that there is only limited transfer of the cytokines IL-1α, IL-1β, TNF-α and IL-6 across intact human fetal membranes.

In conclusion, the present findings do not support the presence of an increased responsiveness to inflammatory mediators during labour in human amnion, but do indicate the existence of a labour-associated attenuation of the anti-inflammatory effects of glucocorticoids in this tissue. The mechanism behind this change remains to be defined.

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