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New approaches to hormonal acceleration of fetal lung maturation

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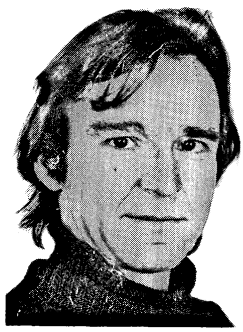
1 Introduction

Administration of glucocorticoids to women at risk of preterm delivery for the prevention of neonatal respiratory distress syndrome (RDS) has become a routine treatment in many obstetrical centers. In the quest for more efficient methods to accelerate lung maturation in the fetus a number of compounds have been investigated in experimental animals [2]. Thyroid hormones [1, 12, 33, 44], bromhexine metabolite VIII (ambroxol) [41, 48], carnitine [40] and thyrotropin stimulating hormone (TRH, LIGGINS unpublished) have recently also been used in humans.

In this paper we will review the effects on lung maturation of glucocorticoids and report recent relevant findings from our laboratory.

Curriculum vitae



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2 Glucocorticoids

2.1 Experimental data

Experiments in vitro and in vivo in several species including humans have shown that glucocorticoids stimulate the synthesis and secretion of pulmonary surfactant, promote morphological development of the lung and enhance survival of prematurely born fetuses [13, 15, 18, 22, 23, 34]. Glucocorticoid receptors have been demonstrated in lung tissue and in cultures enriched in adult or fetal alveolar type II cells [7, 16]. A number of direct and indirect mechanisms of glucocorticoid action has been proposed:

1– Increase in surfactant synthesis through enzyme induction [38],
2– Increase in surfactant secretion (through 3,?) [13, 19, 36],
3– Induction of pulmonary β-adrenergic receptors [9, 31],
4– Stimulation of production of fibroblast – pneumonocyte factor [14, 37],
5– Increase in plasma levels of triiodothyronine (in part through 6) [47],
6– Conversion of thyroxine to triiodothyronine [47],
7– Induction of conversion of noradrenaline to adrenaline [32],
8– Stimulation of glycogenolysis [17].

Lung maturation at term fails to occur in sheep hypophysectomized at 110 days gestation [26]. While infusion of ACTH at term increases distensibility and stability of the lungs in hypophysec-

tomized fetuses, infusion of cortisol is ineffective [26]. Conversely, infusion of ACTH at term to fetal sheep adrenalectomized at 100 days gestation fails to accelerate lung maturation whereas infusion of cortisol increases distensibility of the lung although stability of the lung and alveolar surfactant levels are not increased [27]. This suggests that cortisol and at least one other factor are required for lung maturation in sheep and that structural changes (rather than surfactant alone) contribute to changes in distensibility.

2.2 Clincial data

Although it is well established that antenatal glucocorticoid treatment reduces the incidence and severity of RDS in prematurely born infants it is also evident that a significant number of fetuses do not respond to the treatment [4, 8, 10, 21, 25, 35, 45, 50]. This is of particular consequence in very immature fetuses which have been found by some authors not to respond to glucocorticoids [4, 10, 50]. In the Auckland trial, the incidence of RDS was lower in treated males of less than 30 weeks gestation than in controls (21% versus 61%, $p < 0.015$) but not in females [20]. The study of BALLARD et al suggested that the incidence of RDS is significantly reduced by betamethasone treatment in infants of about 27 to 30 weeks of gestation (birth weight between 751 g and 1250 g), but that smaller and larger infants do not benefit from the treatment [4]. In a retrospective controlled study on 678 infants with a mean birthweight of 1100 g and a mean gestational age of 28.5 weeks, perinatal mortality was nearly halved and body weight and head circumference were greater at two years of age in treated infants than in controls [11].

When 24 mg of betamethasone is administered intramuscularly either in two divided doses 12 h apart or in four divided doses 12 hourly, levels of fetal glucocorticoid activity are in the range of those in newborns with RDS or with prolonged premature rupture of the membranes [5, 6]. It is therefore unlikely that these regimens produce teratogenic effects [3, 5]. Extensive physical, psycho-motor, general medical, neurological, pulmonary and immunological testing of infants treated antenatally with glucocorticoids have confirmed that child development is unlikely to be affected by antenatal glucocorticoid prophylaxis [20, 24, 29, 30, 49].

3 Synergistic hormonal effects

3.1 Experiments in fetal sheep

In fetal sheep, infusion of cortisol at around 125 days gestation (term is 147 days) produces only a small increase in pulmonary distensibility [43] or has no detectable effect on lung maturation [28]. Although combined infusion of cortisol + triiodothyronine or cortisol + adrenaline or cortisol + triiodothyronine + prolactin increase alveolar surfactant, only a combination of cortisol + triiodothyronine + prolactin increases distensibility of the lung above values obtained with infusion of cortisol alone [43]. This suggests that

- there is synergism on alveolar surfactant production between cortisol and triiodothyronine and between cortisol and adrenaline,
- there is synergism between cortisol, triiodothyronine and prolactin in increasing distensibility of the lung, and
- distensibility of the lung does not depend on surfactant levels alone.

Elastin and collagen concentration were higher in lungs that were distensible and stable after hormone infusion than in non-distensible and unstable lungs, suggesting that changes in connective tissue are associated with changes in the mechanical properties of the fetal lung [42].

Similar results were obtained in fetal sheep infused with TRH between Days 121 and 128 of gestation. Infusion of TRH, which increases ovine fetal plasma levels of triiodothyronine and prolactin [46], does not increase distensibility and stability of the ovine fetal lung, whereas combined infusion of TRH + cortisol produces distensible and stable lungs [28].

3.1 Possible clinical applications

In humans, TRH crosses the placenta and produces a rise in fetal plasma triiodothyronine [39]. As in sheep, there appears to be refractoriness of the human lung to glucocorticoids at an early gestational age [4, 10, 20, 50]. Given the excellent response of the sheep fetus to combined treatment with TRH and cortisol at a gestational age when the response to cortisol alone is negligible [28], administration of TRH + betamethasone to women at risk of very premature birth may be more efficient than treatment with betamethasone alone. The validity of this speculation is currently being tested in our institution by a controlled, double-blind clinical trial.

4 Conclusion

Although the efficacy of antenatal glucocorticoid therapy for the propylaxis of RDS is well established it is also true that many fetuses, particularly of low gestational age, do not respond to the treatment. Multihormonal treatment accelerates lung maturation in sheep at an early gestational age when infusion of cortisol alone is ineffective. It remains to be seen whether such therapy is effective in the human fetus.

Summary

The paper reviews the effects on lung maturation of glucocorticoids in animals and humans and presents relevant recent findings from the author's laboratory. It is now well established that antenatal glucocorticoid treatment reduces the incidence and severity of the respiratory distress syndrome (RDS) in prematurely born infants. The recommended doses of glucocorticoids produce fetal glucocorticoid activity levels similar to those of newborns with RDS or prolonged rupture of the membranes. Extensive follow-up studies have shown that adverse effects on child development are unlikely to occur. It is also evident that a significant number of fetuses do not respond to the treatment, which is of particular consequence in fetuses of less than 28 weeks gestation. These fetuses are less likely to respond to glucocorticoid therapy than fetuses between 28 and 32 weeks gestation and are at a higher risk of developing complications due to their immaturity. In fetal sheep, there is a similar decrease in the efficacy of glucocorticoids on lung maturation with decreasing gestational age. Simultaneous infusion of cortisol, triiodothyronine and prolactin but not of any of these hormones administered singly or in combination of two produced mature lungs in fetal sheep of 125 days gestation. Similar results were obtained with thyrotropin releasing hormone (TRH) and cortisol. It remains to be seen whether the combined administration of glucocorticoids and TRH accelerates lung maturation in human fetuses.

Keywords: Fetal organ maturity, follow-up studies, glucocorticoids, lung, prolactin, respiratory distress syndrome-prevention, sheep, thyrotropin releasing hormone, triiodothyronine.

Zusammenfassung

Neue Möglichkeiten zur hormonellen Induktion der fetalen Lungenreifung

Die vorliegende Arbeit liefert eine Übersicht zum Thema der Beeinflussung der Lungenreifung durch Glukokortikoide bei Menschen und Tieren. Darüber hinaus werden neuere Ergebnisse aus Versuchsreihen, die von den Autoren durchgeführt werden, mitgeteilt. Es gilt als gesichert, daß eine antenatale Glukokortikoidbehandlung die Inzidenz und den Schweregrad eines Atemnotsyndroms (RDS) bei Frühgeborenen reduziert. Die empfohlene Glukokortikoiddosis erzeugt eine Kortikoidaktivität beim Feten, wie sie auch bei Neugeborenen mit RDS oder nach vorzeitigem Blasensprung gefunden wird. Ausgedehnte Nachuntersuchungen haben gezeigt, daß unerwünschte Effekte bei der kindlichen Entwicklung sehr unwahrscheinlich sind. Offensichtlich spricht aber eine beträchtliche Anzahl von Feten nicht auf die Behandlung an. Dies ist besonders bedeutungsvoll für Feten unterhalb der 28. Schwangerschaftswoche, da diese in geringerem Maße auf die Kortikoidtherapie ansprechen als Feten zwischen der 28. und 32. Woche und eher in Schwierigkeiten geraten infolge ihrer Unreife. Beim Schaffeten sind die Glukokortikoide ebenfalls mit abnehmendem Gestationsalter weniger wirksam. Die gleichzeitige Infusion von Kortisol, Trijodthyronin und Prolaktin führte zu reifen Lungen bei Schaffeten mit 125 Tagen Gestationsdauer. Dies gilt nicht, wenn die Substanzen einzeln oder als Zweierkombination verabreicht wurden. Bei Verwendung von Thyrotropin-Releasing-Hormon (TRH) und Kortisol wurden vergleichbare Ergebnisse erzielt. Es bleibt nachzuweisen, ob auch bei menschlichen Feten die kombinierte Gabe von TRH und Glukokortikoiden die Lungenreifung beschleunigt.

Schlüsselwörter: Fetale Organreifung, Nachuntersuchungen, Glukokortikoide, Lunge, Prävention eines RDS, Prolaktin, Schaf, Thyrotropin-Releasing-Hormon, Trijodthyronin.

Résumé

Nouvelles approches concernant l'accéleration hormonale de la maturation pulonaire fœtale

Cet article passe en revue les effets sur la maturation pulmonaire des glucocorticoïdes chez l'animal et chez l'homme et présente des données récentes sur le sujet provenant du laboratoire des auteurs. Il est bien établi que le traitement par glucocorticoïdes anténatal diminue l'incidence et la sévérité du syndrome de détresse respiratoire (SDR) chez les enfants nés prématurément. Les doses recommandées de glucocorticoïdes produisent des

taux plasmatiques d'activité glucocorticoïde semblables aux taux mesurés chez les nouveaux-nés atteints de SDR et d'enfants nés après rupture prolongée des membranes. Des études de contrôle ont demontré qu'il est peu probable que le traitement ait des effets secondaires sur le développement de l'enfant. Il est aussi vrai que cette thérapie est inefficace dans un bon nombre de cas. Ceci est d'une importance capitale chez le fœtus de moins de 28 semaines de gestation. Celui-ci est particulièrement disposé à des complications dues à l'immaturité et répond moins bien aux glucocorticoïdes que le foetus entre 28 and 32 semaines. Chez le fœtus du mouton l'effet des glucocorticoïdes sur la maturation pulmonaire diminue de façon semblable avec un âge de gestation décroissant. Des perfusions de cortisol, de triiodothyronine et de prolactine administrées simultanément produisent des poumons matures dans le fœtus de mouton de 125 jours de gestation; cela ne se produit pas si une seule de ces hormones est administrée ou si deux d'entre elles seulement sont combinées. Des résultats similaires ont été obtenus avec de la thyrotropin releasing hormone (TRH) et du cortisol. Il reste à voir si l'administration combinée de glucocorticoïdes et de TRH accélère la maturation pulmonaire chez les fœtus humains.

Mots-clés: Etudes de surveillance, glucocorticoïdes, maturité des organes fœtaux, mouton, poumon, prolactine, syndrome de détresse respiratoire-prévention, thyrotropin releasing hormone, triiodothyronine.

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