A new approach to acceleration of fetal lung maturation by pioglitazone

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Induction of lung maturity via the use of antenatal glucocorticoids has been shown to improve the respiratory outcomes of preterm infants. A large body of evidence over the 20-year period from 1972 to 1995 in over 3300 infants with RDS reported favourable outcomes following treatment with corticosteroids.[1] The number needed to treat to induce lung maturation before 31 weeks of gestation was calculated to be 4.[2] Around the year 2000 there were increased concerns regarding corticosteroid treatment in pregnant women. Animal studies have shown that normal and repeat doses of corticosteroids:

- inhibit fetal growth
- increase fetal blood pressure
- may decrease birthweight[3].

Corticosteroids may also have harmful effects on neuronal myelination, the development of lung morphology and endocrinological development.[3] Given these concerns the focus has turned towards an alternative to glucorticoid treatment and the potential for alternative agents that may be administered instead of, or in combination with, glucocorticoids.

PPAR agonists: an alternative to glucocorticoids?

PPARs are group of nuclear receptor isoforms (alpha, gamma and delta) that regulate several biological functions. In particular, the activation of PPAR gamma by an agonist, such as those commonly used in the treatment of type 2 diabetes, results in:

- reduced insulin resistance
- modified adipocyte differentiation
- inhibited VEGF-induced angiogenesis
- reduced leptin levels leading to an increased appetite
- anti-inflammatory effects – evidenced by a fall in certain IL (i.e. IL-6).

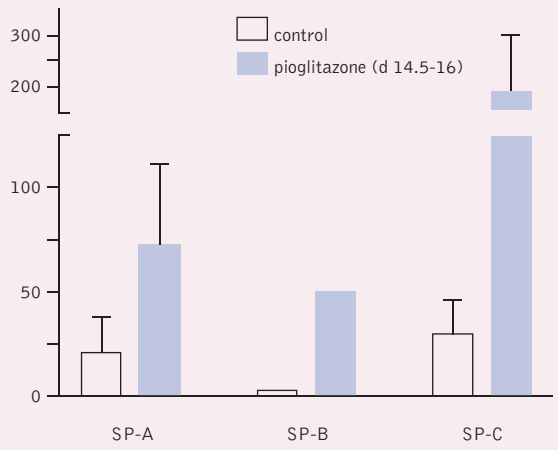
It has been hypothesised that LCFA are bound to fatty acids by two types of FABP: hard (H) and epidermal (E). E- and H-FABP transport LCFA within the cytosol and modulate phospholipid synthesis.[4] Double knockout mice have been used to study the expression of caveolin-1 and of PPAR-gamma and its cofactor. Caveolin-1 expression was significantly increased in this model, and caveolin ions may disassociate from the membrane and transport LCFA to the intracellular membrane or the nucleus.

The pharmacological effect of the PPAR-gamma agonist pioglitazone has been demonstrated in H- and E-FABP double knockout mice. In these knockout mice decreased FA uptake, reduced beta-oxidation and reduced incorporation of palmitic acid into diacylglycerol, triglycerides and DPPC were observed; administration of pioglitazone restored the uptake of FA, increased beta-oxidation and the *de novo* synthesis of phosphorylated choline. Apart from these activities, PPAR gamma agonists may exert their potential therapeutic role in the management of BPD in preterm babies interfering with the expression of the ABCA3, a causative gene for fatal surfactant deficiency. This gene has been shown to be up-regulated by glucocorticoids in lung alveolar type II cells.[5] Therefore, the beneficial effect that glucocorticoids exhibit in lung maturation and prevention of BPD might be mediated via this pathway.

In a similar study, Guthmann et al. administered pioglitazone to pregnant rats starting on fetal day 14.5 and animals were sacrificed on day 19.5 (unpublished data). In the fetal lung of non-treated rats there was very little ABCA3 expression; however, following pioglitazone administration there was greater ABCA3 expression. At day 19.5 there was also a significant increase in the expression of surfactant proteins A, B, and C in the fetal lung of rats receiving antenatal pioglitazone *(Figure 1)*.

Antenatal administration of pioglitazone resulted in a 5-fold increase in the incorporation of diacylgycerol and phosphatidyl choline in the rat fetal lung. The incorporation of choline into phosphatidyl choline was also slightly increased in A549 human cell line following 24-hour administration of ciglitazone.
A positive control performed with dexamethasone produced similar results.
After administration of pioglitazone, there was increased expression of caveolin-1, FA translocase, PPAR-gamma and ABCA3 in rat lung tissues. There was also an increase in surfactant-associated proteins A, B, and C. Interestingly, there was no PPAR response element in surfactant-associated protein genes. It has been postulated that surfactant proteins may be induced by PPAR independently as evidenced in other pathways or there may be an indirect effect via ABCA3 which increases transport into the lamellar body and a feedback mechanism increases the expression of surfactant proteins. Ciglitazone has been shown to increase the incorporation of choline into phosphatidyl choline in A549 cell lines.
The beneficial effects of the PPAR-gamma agonists observed in animal studies and in human cell lines indicate that this class of agents may potentially offer an alternative to glucocorticoids in the treatment of preterm infants with BPD.

Figure 1. Expression of surfactant protein in fetal rat lung following 5 days of administration of pioglitazone.



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