Thyroid hormone and Na\textsuperscript{+}-K\textsuperscript{+}-ATPase: more than simple transcription

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FLUID SECRETION INTO THE DEVELOPING lungs’ air spaces is essential for normal lung development, but this fluid must be cleared at birth so that effective gas exchange can occur. Impaired clearance of this fetal lung liquid, which arises from immaturity of the distal lung epithelium’s active Na\textsuperscript{+} transport system (for review, see Ref. 17), causes transient tachypnea of the newborn (2, 12, 13), and, if combined with immaturity of the surfactant system, neonatal respiratory distress syndrome (nRDS) (4, 17). Clearance of air space fluid is driven by active transepithelial Na\textsuperscript{+} transport resulting from synchronized activity of apical Na\textsuperscript{+} permeant ion channels (e.g., epithelial Na channel, ENaC) and basolateral Na\textsuperscript{+}-K\textsuperscript{+}-ATPase. The chemical and electrical gradients for Na\textsuperscript{+} absorption are, respectively, maintained by Na\textsuperscript{+}-K\textsuperscript{+}-ATPase and K\textsuperscript{+} channels. Perinatal changes in Po\textsubscript{2}, glucocorticoids, \beta\textsubscript{-}-agonists, and thyroid hormones interact to increase transepithelial Na\textsuperscript{+} absorption, to bring about the switch from net fluid secretion to net absorption as lung liquid is cleared at birth. However, despite considerable data from molecular, transgenic, cell culture, and in vivo studies, the fundamental mechanisms of this crucial developmental shift are incompletely understood (5, 19). Barker and coworkers (6) demonstrated that thyroid hormone [triiodothyronine (T3)] played an important role in maturation of the fetal lungs’ ability to respond to an infusion of epinephrine by switching to fluid absorption, and others showed that thyroid hormone in concert with glucocorticoids increased the expression of ENaC (18, 22). Although T3 classically acts as a direct transcriptional activator of target genes and has been shown to potentiate dexamethasone-stimulated transcription of the ENaC promoter (20), T3-induced upregulation of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in adult rat alveolar epithelial cells was recently shown to be insensitive to actinomycin D (15). This has functional significance. For example, it has been demonstrated that overexpression of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase via adenoviral-mediated gene transfer is sufficient to increase alveolar fluid clearace (21).

It is known that thyroid hormones have profound effects on the maturation of the fetal lung and that premature infants with nRDS have lower thyroid hormone levels than well preterm infants (9, 10). However, when clinical trials have been conducted wherein augmentation of the thyroid hormonal axis has taken place, there has been no demonstrable benefit. The THORN trial of T3 and hydrocortisone supplementation in preterm infants of less than 30 wk gestation found that low thyroid hormone levels were associated with higher mortality and ventilator dependence (7, 8). However, this trial (8) was unable to demonstrate beneficial effects of T3 and hydrocortisone infusion. Similarly, the provision of thyroid-releasing hormone to infants who had received antenatal glucocorticoid and postnatal exogenous surfactant therapy did not result in a change in nRDS, bronchopulmonary dysplasia, or death (1, 3). Together, these findings suggest that either much of our information regarding thyroid hormone’s effects on the lung is incorrect or that we have too little knowledge as to how the fetal lung responds to developmental signals in general and specifically to stimulation of the thyroid axis. The report from Lei et al., one of the current articles in focus (Ref. 16, see p. L6 in this issue), suggests that the latter is indeed the case.

The work by Lei et al. (16) represents an important advance in the understanding of perinatal regulation of lung ion transport as the authors investigated the timing of acquisition of the T3 stimulatory effect on Na\textsuperscript{+}-K\textsuperscript{+}-ATPase in rat fetal distal lung epithelial (FDLE) cells. The investigators used both primary culture FDLE isolated from fetuses at 17-, 18-, 19-, and 20 days of gestation and cell lines derived from primary FDLE isolated at 18 and 19 days of gestation. In both primary cells and the immortalized cell lines, T3 sensitivity of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity was gained at gestational day 19. Subsequent experiments suggested that this T3 sensitivity in late gestation FDLE was via nongenomic pathways including phosphatidylinositol 3-kinase (PI3K). As the authors had previously shown in adult alveolar epithelial cells (15), in late-gestation fetal cells, the T3-induced increase in Na\textsuperscript{+}-K\textsuperscript{+}-ATPase was paralleled by an increase in phosphorylation of Akt and was sensitive to the PI3K inhibitor wortmannin. Transient transfection of a constitutively active PI3K mutant in the cell line derived from 18-day gestation FDLE significantly increased Na\textsuperscript{-}-K\textsuperscript{-}-ATPase activity and cell surface expression of the \alpha\textsubscript{1}-subunit, leading the authors to suggest that the developmental switch is located at or upstream of PI3K in the T3 response pathway (Fig. 1). One caveat to this interpretation is to consider whether overexpression of a constitutively active PI3K may yield higher kinase activity than T3 exposure, perhaps overcoming a block at phosphorylation and tensin homolog deleted on chromosome 10 in these earlier gestation cells.

The study by Lei et al. (16) in FDLE indicated that 6-h exposure of the cells to T3 did not significantly increase total cell amounts of \alpha\textsubscript{1} or \beta\textsubscript{1} Na\textsuperscript{-}-K\textsuperscript{-}-ATPase proteins, as assessed by Western blot analysis, suggesting an increased distribution to the plasma membrane. The mechanistic details of nongenomic pathways by which T3 exerts physiological regulatory functions are not well understood (11), and Akt affects many cellular pathways (Fig. 1). However, a very recent publication by Kenessey and Ojamaa (14) provides convincing evidence for a direct interaction between the T3 receptor and the p85\textsubscript{\alpha} subunit of PI3K, resulting in rapid downstream phosphorylation of Akt and mammalian target of rapamycin, and increased rates of protein synthesis in T3-treated cardiomyocytes. In light of these findings, further work is needed to fully elucidate the mechanism of T3-stimulated Na\textsuperscript{-}-K\textsuperscript{-}-ATPase in late gestation FDLE and adult alveolar type II cells. It would be interesting to examine the effects of T3 stimulation on rate of protein...
Fig. 1. Phosphatidylinositol 3-kinase (PI3K)/Akt pathways influence many intracellular signaling pathways related to cell growth, cycling, and survival. Akt (protein kinase B) activation downstream of PI3K can be blocked by PTEN (phosphatase and tensin homolog deleted on chromosome 10). Akt promotes cell survival by blocking apoptosis and increases protein synthesis by increasing both translation initiation and ribosome biogenesis via the mTOR (mammalian target of rapamycin) pathways. BAD, Bcl2 antagonist of cell death; Casp9, caspase-9; FKHR, forkhead; GSK3α, glycogen synthase kinase 3; MDM2, ubiquitin-protein ligase E3 Mdm2; PDK1, phosphoinositide-dependent protein kinase 1; Rheb, Ras homolog enriched in brain; TSC2, tuberous sclerosis complex 2; T3, triiodothyronine.


