The adrenal response of neonates to hypoxia

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THE TRANSITION OF FETAL to extrauterine life is among the most challenging and threatening situations for the organism. One of the most common causes of neonatal morbidity and mortality results from hypoxia, e.g., reduced oxygen supply to the vital organs (2, 6). Although the short- and long-term adaptational responses to hypoxia of the nervous and cardiorespiratory system have been extensively studied, little is known about the effect of prolonged neonatal hypoxia on the adrenal function in vivo. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Raff and coworkers (11) present a study, in which they investigated the role of the adrenal glands in the adaptation to hypoxic stress in neonatal rats. They report that exposure from birth to an inspiratory oxygen concentration of 12% resulted in increased basal plasma corticosterone levels despite no differences in ACTH concentrations compared with normoxic (21% O2) pups. Furthermore, hypoxia caused an augmented corticosterone, but not aldosterone, response to exogenous ACTH. This effect was greatest at 5 days of age and could not be attributed to a measurable increase of ACTH in the hypoxic pups. Finally, enhanced corticosterone formation in the hypoxic neonatal rats was associated with enhanced steroidogenic acute regulatory (StAR) protein and, to a lesser extent, peripheral-type benzodiazepine receptor (PBR) protein in the adrenal subcapsule (zona fasciculata/reticularis). These findings are remarkable for several reasons. First, they indicate that the adrenal glands are important for the adaptation to reduced tissue oxygenation in neonates. Moreover, the results suggest that steroidogenesis in response to neonatal hypoxia is differentially regulated because the aldosterone response to ACTH was not affected by low inspiratory oxygen in neonatal pups (11). The latter observation nicely fits with a study in human infants with hypoxemia due to bronchiolitis, demonstrating an augmented cortisol, but not aldosterone, response to ACTH (3). In contrast to the findings with newborn rat pups, aldosterone formation was decreased in the adult organism during hypoxia (12), indicating that fundamental differences may exist in the adrenal response to hypoxia between newborn and adults. It remains unknown at present what mechanism(s) may account for the augmented corticosterone levels in the hypoxic neonatal pups. Although the authors do not fully eliminate the possibility that a small, essentially undetectable, increase in ACTH during hypoxia may enhance steroidogenesis in the adrenals, they suggest that some factor(s) other than ACTH could also be responsible. One plausible candidate would be leptin, which has been shown to inhibit corticosterone but not aldosterone production in adult rats (7) and which was reduced in hypoxic rat pups (9, 10). Notably, StAR and PBR, two proteins, which are involved in regulating the rate-limiting step of steroidogenesis, e.g., the transport of cholesterol from the outer to the inner mitochondrial membrane (1, 8, 14), were increased in the adrenal zona fasciculata and reticularis of hypoxic rat pups. StAR and PBR were highest at 5 days of age, thus correlating with the most sensitive steroidogenic response to ACTH in normoxic and hypoxic newborn rats. These results suggest, but do not provide final proof, that StAR/PBR are critical for the adrenal response to hypoxic stress in neonatal rat pups. The question arises on the potential beneficial effects of augmented corticosterone levels in the newborn organism during hypoxia. Although increased circulating glucocorticoids may have detrimental effect on neurological development in the neonate (13), they are likely to maintain glucose delivery to the brain and heart under hypoxic conditions through decreasing insulin sensitivity (9, 10). Furthermore, the effect of corticosterone on the development of the hepatic and exocrine pancreatic function may contribute to neonatal hypoxic hyperlipidemia, which is a critical source for energy (4, 5). In conclusion, the study by Raff and collaborators provides important novel insights into adrenal function in vivo during hypoxic stress in neonates.

REFERENCES
1. Artemenko IP, Zhao D, Hales DB, Hales KH, and Jefcoate CR. Mitochondrial processing of newly synthesized steroidogenic acute regulatory protein (StAR), but not total StAR, mediates...


