Are cardiorespiratory complications a question of epigenetics?

Hugo Lagercrantz[1]
Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

The character Joe from Charles Dickens' *The Posthumous Papers of the Pickwick Club* (1837) was markedly obese and often fell asleep in an uncontrollable way during the day (1). This is probably one of the first cases of sleep apnea syndrome described in the literature. Sleep apnea is most often due to upper airway obstructions during sleep (2) and is regarded as a national disease affecting approximately 4% of the adult population. It results in intermittent hypoxia, leading to cardiovascular complications such as hypertension, coronary artery disease, heart failure, and stroke (3). The incidence of intermittent hypoxia is also common among infants, particularly if they are born prematurely (4). It increases the risk for developing cerebral palsy and sudden infant death syndrome (SIDS) (5).

In PNAS, Nanduri et al. (6) report epigenetic regulation of hypoxic sensing. Neonatal rats from day 1 to day 10 were exposed to intermittent hypoxia in alternating cycles for 15 s of 5% oxygen with air for 5 min, which corresponds fairly well with clinical apnea. When their respiration and other autonomic functions were monitored as adults they showed exaggerated responses to hypoxia by the carotid bodies. Furthermore, the authors found that the adrenal chromaffin cells responded to the hypoxia with enhanced catecholamine secretion. It seems likely that the sympathetic nervous system was also activated, possibly leading to hypertension.

Adaptation to Hypoxia

The fetus is well adapted to a low oxygen pressure, which was discovered by the British physiologist Sir Josef Barcroft, who also coined the expression, "Mount Everest in utero." The peripheral chemoreceptors are set at a lower sensitivity, which is increased a few days after birth (7). Tibetans and Himalayan Sherpas are well adapted to live in an environment with low oxygen levels at a high altitude. They seem to be better adapted than the people in the Andes, who moved to high altitude later (8). This form of hypoxia has quite different physiological effects from the intermittent hypoxia caused by apnea in infants and adults. The former blunts, whereas the latter facilitates the sensitivity of the carotid bodies, the frontline warning system against hypoxia.

Dopamine seems to play an important role in the setting of this sensitivity. Dopamine turnover is relatively high at birth in carotid bodies of rat pups, which is related to a low chemoreceptor reflex (9). After a couple of days this reflex, corresponding to the hypoxic ventilatory drive, increased substantially, which was related to decreased dopamine turnover. However, if the rat pups are exposed to hypoxia around birth, high dopamine turnover is sustained, which is associated with a weaker carotid reflex. Thus, it seems likely that dopamine may also be involved in the setting of peripheral chemoreceptor sensitivity in the adult. However, several other neurotransmitters and neuromodulators are involved, such as acetylcholine, substance P, ATP, GABA, nitric oxide, and excitatory amino acids (6, 10). These neurotransmitters are tightly coupled to transmembrane ion channels K^+, Na^+, and Ca^{2+}, setting the redox state of the membrane. This is also regulated by prooxidant and antioxidant enzymes.

Nanduri et al. report epigenetic regulation of hypoxic sensing.

The different effects of chronic vs. intermittent hypoxia may be due to the activation of different genes encoding for transcription factors and synthesizing enzymes. Sustained hypoxia activates hypoxia-inducible factor-1, resulting in an increased expression of genes encoding erythropoietin, vascular endothelial growth factor, and inducible nitric oxide synthase. This helps adapt to overcome the initial effects of hypoxia by increasing tissue perfusion and oxygenation. Chronic intermittent hypoxia, which is most common at sea level, has different effects. It causes an increase in normoxic ventilation, which persists into adulthood. The ventilatory response to hypoxia is exaggerated, leading to destabilization of the breathing rhythm (11). The signaling events activated by intermittent hypoxia are much less well understood.

Developmental Programming

A possible mechanism is now presented in PNAS (6): a decreased expression of genes encoding antioxidant enzymes. The decreased expression of the Sod2 gene was associated with hypermethylation of a single CpG dinucleotide. When Nanduri et al. treated the neonatal rats with an inhibitor of DNA methylation (decitabine), they prevented the enhanced hypoxic sensitivity and autonomic dysfunction.

This finding has several clinical implications. Ex-preterm infants who have sustained intermittent hypoxia seem to be more prone to die of SIDS (5). Infants who have been exposed to passive smoking during fetal life have also been found to have more apnea and abnormal cardiovascular responses to tilting (12, 13). These abnormalities seem to persist up to adult age. Ex-preterm infants, when tested as young adults, suffered more often from sleep apnea (14) and hypertension (15).

There is a race to discover genetic polymorphisms to explain a number of common adult diseases, like type 2 diabetes and myocardial infarction. However, genomic variations may only explain a fraction of the risk (16). Abnormal programming of homeostatic functions like control of blood sugar levels and blood pressure may be more important. David Barker, who first established the concept of developmental programming (8), has claimed that developmental programming is a more important factor than genes, diet, and exercise to predict longevity. This has been supported by a number of epidemiological studies, for example the effect of the Dutch famine on offspring born in 1945. Epigenetic mechanisms may explain the epidemiological findings. Already the mode of delivery may alter DNA methylation in infants born by cesarean section and partly explain why these children more often develop asthma and diabetes (17). Godfrey et al. (18) have demonstrated that epigenetic gene promoter methylation at birth is associated with a child's later adiposity. The present study in PNAS confirms the role of an epigenetic mechanism in developmental programming of adult disease. Of particular importance is that the authors succeeded in blocking this effect by preventing methylation. Epigenetic mechanisms are probably of great value for adapting to new environments. However, a mismatch

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[1]E-mail: hugo.lagercrantz@ki.se.

between our evolved physiological capabilities and contemporary exposures can lead to ill health.

This study highlights the potential for therapeutic targeting of signaling pathways to mitigate or reverse the maladaptive effects of repetitive hypoxia. It may be possible to manage or reverse epigenetic changes by administrating drugs that inhibit DNA methylation, histone deacetylation, and microRNA expression. An alternative way may be to target epigenetically disturbed pathways with dietary supplementation with amino acids, vitamins, or phytochemicals.

1. Bickelmann AG, Burwell CS, Robin ED, Whaley RD (1956) Extreme obesity associated with alveolar hypoventilation; a Pickwickian syndrome. *Am J Med* 21:811–818.
2. Pack AI (2006) Advances in sleep-disordered breathing. *Am J Respir Crit Care Med* 173:7–15.
3. Sullivan CE, McNamara SG (1998) Sleep apnoea and snoring: Potential links with vascular disease. *Thorax* 53(Suppl 3):S8–S11.
4. Abu-Shaweesh JM, Martin RJ (2008) Neonatal apnea: What's new? *Pediatr Pulmonol* 43:937–944.
5. Mitchell EA (2009) SIDS: Past, present and future. *Acta Paediatr* 98:1712–1719.
6. Nanduri J, et al. (2012) Epigenetic regulation of hypoxic sensing disrupts cardiorespiratory homeostasis. *Proc Natl Acad Sci USA* 109:2515–2520.
7. Hertzberg T, Lagercrantz H (1987) Postnatal sensitivity of the peripheral chemoreceptors in newborn infants. *Arch Dis Child* 62:1238–1241.
8. Barker DJP (1998) *Mothers, Babies and Disease in Later Life* (Churchill Livingstone, Edinburgh).
9. Hertzberg T, Hellström S, Holgert H, Lagercrantz H, Pequignot JM (1992) Ventilatory response to hyperoxia in newborn rats born in hypoxia—possible relationship to carotid body dopamine. *J Physiol* 456: 645–654.
10. Joseph V, Pequignot J-M (2009) Breathing at high altitude. *Cell Mol Life Sci* 66:3565–3573.
11. Bavis RW, Mitchell GS (2008) Long-term effects of the perinatal environment on respiratory control. *J Appl Physiol* 104:1220–1229.
12. Cohen G, Vella S, Jeffery H, Lagercrantz H, Katz-Salamon M (2008) Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. *Circulation* 118:1848–1853.
13. Cohen G, Jeffery H, Lagercrantz H, Katz-Salamon M (2010) Long-term reprogramming of cardiovascular function in infants of active smokers. *Hypertension* 55:722–728.
14. Paavonen EJ, et al. (2007) Very low birth weight increases risk for sleep-disordered breathing in young adulthood: The Helsinki Study of Very Low Birth Weight Adults. *Pediatrics* 120:778–784.
15. Dalziel SR, Sr., Parag V, Rodgers A, Harding JE (2007) Cardiovascular risk factors at age 30 following preterm birth. *Int J Epidemiol* 36:907–915.
16. Manolio TA, et al. (2009) Finding the missing heritability of complex diseases. *Nature* 461:747–753.
17. Schlinzig T, Johansson S, Gunnar A, Ekström TJ, Norman M (2009) Epigenetic modulation at birth—altered DNA-methylation in white blood cells after Caesarean section. *Acta Paediatr* 98:1096–1099.
18. Godfrey KM, et al. (2011) Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* 60:1528–1534.