PERSPECTIVES

# Respiratory plasticity in sleep apnoea: should it be harnessed or restrained?

**George B. Richerson**[1,2]
[1] *Departments of Neurology and Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, CT 06510, USA*
[2] *Veterans Affairs Medical Center, West Haven, CT 06516, USA*

Email: george.richerson@yale.edu

Sleep apnoea is a common disorder that leads to a variety of sequelae, including hypertension, heart failure, stroke and hypersomnolence. Unfortunately, the therapies are not ideal. Standard treatment is continuous positive airway pressure (CPAP) given to patients while they are sleeping. However, the mask is often not well tolerated, so many patients are not compliant with treatment.

There is considerable interest among the scientific community in the neural mechanisms of respiratory control during sleep, in part because it is justifiably believed that defining these mechanisms may help to identify new treatments for sleep apnoea. The most obvious intervention would be to selectively increase respiratory output during sleep, and especially to increase upper airway dilatation. Long term facilitation (LTF) of breathing offers a window into a potential way to accomplish this goal. LTF is an increase in ventilation or of respiratory motor output (e.g. phrenic nerve activity) that is induced by a short episode of intermittent hypoxia, but that continues for a long period of time (>90 min) after return to normoxia. It is due in some cases to plasticity of the carotid body, and in other cases to plasticity of neurons involved in respiratory control. A lot of attention has been focused on LTF in part because it may be possible to selectively target the pathways involved in this respiratory plasticity for treatment.

LTF has been widely studied, but remains poorly understood. Rather than being a single entity, this term encompasses phenomena that share some features, but differ in other respects. As referred to above, one form of LTF occurs within the carotid body, and is due to changes intrinsic to glomus cells that alter their response to hypoxia (Peng *et al.* 2003). A different form of LTF occurs as a result of strengthening of the synapse from respiratory pre-motor neurons onto phrenic motor neurons. It involves a serotonin-dependent increase in BDNF generation (Mahamed & Mitchell, 2007), and shares mechanisms with synaptic plasticity seen in hippocampal long-term potentiation (Richerson & Bekkers, 2004). This form of LTF is typically studied in anaesthetized rats (Mahamed & Mitchell, 2007), and is manifest as an increase in phrenic nerve output that does not begin until after a long delay (often >30 min). In contrast, the LTF that has been described in awake humans is manifest as an increase in ventilation that occurs immediately after termination of hypoxia, and may actually be a continuation of 'progressive augmentation', which begins during the hypoxia. These differences in time course suggest that the mechanisms of these forms of LTF may be very different. Thus, different forms of LTF require different patterns of intermittent hypoxia to elicit them, occur in different loci, and utilize different mechanisms.

A number of important questions remain about LTF. What is the physiological significance of LTF? What are the optimal ways to elicit each of the forms of LTF? Which mechanisms are shared and which differ? And of particular significance to treatment of patients, is LTF adaptive or maladaptive?

In a recent issue of *The Journal of Physiology*, Lee *et al.* (2009) present new data that intersect with many of these questions about LTF. They studied human patients with sleep apnoea, who presumably subject themselves to chronic intermittent hypoxia (CIH) at night, and compared them to healthy subjects. Both study groups had LTF in response to acute intermittent hypoxia while they were awake, but it was more robust in the sleep apnoea patients. Interestingly, pre-treatment with antioxidants reduced LTF in the sleep apnoea patients to the level seen in the controls, suggesting that CIH enhanced LTF due to generation of reactive oxygen species (ROS) by chronic hypoxia that occurred at night.

Generation of ROS is usually considered bad for you, so a natural conclusion is that treatment of sleep apnoea patients with antioxidants should be good for you. But shouldn't the increase in respiratory output seen with LTF be helpful in preventing hypoxia during sleep? As the authors point out, it may not be that simple. In some ways LTF may be helpful (Mahamed & Mitchell, 2007), but in other ways it may be maladaptive (Mateika & Narwani, 2009). These data point to some exciting possibilities for new treatments, but first require a better understanding of the mechanisms involved.

There are several issues about LTF in awake humans that still need to be addressed. For example, the authors note that mild hypoxia may have had different effects on ROS than severe hypoxia. Those with severe hypoxia may induce a different form of LTF from those with mild hypoxia. Is the role of ROS different in the two cases? In this study the authors used supplemental $CO_2$ under baseline conditions, because LTF is not elicited when patients are normocapnic. Why is there a dependence on $CO_2$? Is this related to the fact that serotonin has a permissive effect on LTF, and hypercapnia is needed in order to increase serotonin release (Richerson, 2004)? How do studies in human patients given supplemental $CO_2$ relate to the situation when patients are sleeping normally while breathing room air? What will be needed is data that examine whether it is better to treat patients with drugs that prevent LTF or enhance it, and whether it is better to increase or decrease ROS. Answering these questions may allow us to bypass hypoxia and directly target the pathways involved – ideally downstream of ROS generation – to specifically prevent apnoeas and augment motor output to the upper airway muscles. Accomplishing this goal could free many patients from the hassle of wearing a mask every night, and prevent sequelae in the many other patients who are non-compliant with CPAP.

## References

Lee DS, Badr MS & Mateika JH (2009). *J Physiol* **587**, 5451–5467.
Mahamed S & Mitchell GS (2007). *Exp Physiol* **92**, 27–37.
Mateika JH & Narwani G (2009). *Exp Physiol* **94**, 279–296.


DOI: 10.1113/jphysiol.2009.184440

Peng YJ, Overholt JL, Kline D, Kumar GK & Prabhakar NR (2003). *Proc Natl Acad Sci U S A* **100**, 10073–10078.

Richerson GB (2004). *Nat Rev Neurosci* **5**, 449–461.

Richerson GB & Bekkers JM (2004). *Nat Med* **10**, 25–26.

**Acknowledgements**

This work was supported by the NICHD, Bumpus Foundation and VAMC.