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Long-Term Facilitation (LTF) and Obstructive Sleep Apnea

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In this issue of the Journal, McGuire et al. (2007) once again demonstrated that LTF of phrenic nerve activity can be easily induced with a minimal regime of intermittent hypoxia (IH). However, they now demonstrate that once established, LTF seems to be remarkably resistant to 5 min episodes of hypercapnia or hypocapnia with or without PEEP with ventilation quickly returning to the augmented level (LTF-induced) observed prior to the CO₂ manipulation.

Why are these observations potentially important in our understanding of the only condition in man (or animals) known to cause intermittent hypoxia, that being sleep apnea (particularly obstructive sleep apnea (OSA))? Patients with OSA, over the course of an apnea, clearly develop hypercapnia in addition to hypoxia. These patients also often become frankly hypocapnic during the hyperventilation which occurs during the recovery from the apnea which is often associated with arousal from sleep. Thus the authors of this paper would have us believe that, once established, the effects of LTF on the ventilatory control system can persist despite the fluctuations in P_{CO2} which repetitively occur in the apnea patient. Positive end-expiratory pressure (PEEP) which is similar to the continuous positive airway pressure (CPAP) used to treat sleep apnea also seems to have little effect on established LTF. However, the real life situation, particularly in humans, may be more complicated than a well-controlled animal study would suggest.

One must first ask whether LTF can be induced in man and, if so, under what conditions. Early studies suggested that, at least during wakefulness, LTF could not be induced in man with both ventilation and genioglossal (an upper airway dilator muscle) activity being carefully examined (McEvoy et al., 1996; Jordan et al., 2002). However, subsequent human studies by Badr and his colleagues conducted during NREM sleep suggested that intermittent hypoxia could lead to LTF (Babcock and Bader, 1998; Babcock et al., 2003). However, most of the accumulated evidence from these studies suggested that the increased ventilation observed following intermittent hypoxia was a product of reduced pharyngeal airflow resistance during sleep rather than an actual stimulation of ventilation. This fall in resistance during sleep would almost certainly be the product of an increase in the activity in

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the upper airway muscles resulting from IH although actual muscle activity during sleep under these conditions has never been measured. If LTF can only be induced during sleep in humans and only affects the upper airway dilator muscles, it would seem to be a very different physiologic event than what has been observed in both awake and anesthetized animals.

However, Harris et al. (2006) recently demonstrated in awake humans that LTF could be induced in both ventilation and genioglossal activity if hypercapnia (5 mm Hg above basal levels) was maintained throughout the period of IH and the subsequent interval during which LTF was assessed. Allowing the P_{CO_2} to return to normal levels at the end of these protocols was associated with a rapid return of ventilation and genioglossal EMG to basal unstimulated levels. Thus it would seem that sustained hypercapnia can bring out LTF in man while intermittent hypoxia alone cannot. However the increased P_{CO_2} must be maintained for this to occur. Similar studies during sleep have not been reported to date. The obvious question that emerges from these studies is how do the paradigms used to induce and maintain LTF in man (or animals) relate to what actually occurs in patients with OSA?

As is obvious to most readers, and is stated above, patients with OSA have cycling hypoxia (as is used in all paradigms to induce LTF), but also have cycling intermittent hypercapnia which alternates with either normal P_{CO_2} levels or actual hypocapnia. The data from McGuire et al. (2007) in this issue of the Journal would suggest that such swings in P_{CO_2} will have little effect on LTF if it is well established. However, the only paradigm that clearly induced LTF in man (Harris et al., 2006) required sustained hypercapnia with a rapid return of ventilation and genioglossal activity to basal levels when P_{CO_2} fell. Thus, it is unclear at this time whether LTF can be induced in humans with the swings in P_{O_2} and P_{CO_2} that characterize obstructive sleep apnea. Until this actual combination of blood gas changes is tested, particularly during sleep (although waking studies would be welcome information), we don't know if LTF can be induced in man under real life conditions.

We also don't know what LTF in man would do to the pharyngeal airway during sleep. If the increased respiratory activity resulting from LTF is primarily directed at upper airway dilator muscles, then airflow resistance would likely improve and apnea severity lessen. The work of Aboubakr et al. (2001) suggests this may be the case as 10 episodes of intermittent hypoxia in OSA patients during NREM sleep reduced upper airway resistance, but had little effect on ventilation. However, if LTF induced an increased drive to respiratory pump muscles with little or no increase in the activity of pharyngeal dilator muscles, airway patency would not likely improve and could actually deteriorate. In addition, it is unclear exactly how LTF would work in OSA. Would the LTF induced by one night of intermittent hypoxia in these patients carry over to the next night often 16 hours later? Animal data have not demonstrated that LTF persists for this length of time (Olson et al., 2001). The alternative would be that LTF is reinduced each night following the first series of apnea-induced hypoxia episodes. If this is the case and LTF has a positive effect on pharyngeal airway patency, then one might expect for apnea severity to fall over the course of the night. However, most data suggests the opposite with apnea frequency increasing as the night progresses (Oksenberg et al., 2001). Although, there are certainly other possible explanations for this worsening of apnea severity over time each night, it does not suggest

that LTF has a major positive effect on apnea severity. However, the possibility remains that the patient's apnea would be worse if LTF were not active. Thus, there remains much to learn about LTF in man and the role it plays in the pathophysiology or progression of obstructive sleep apnea.

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