

DETERMINANTS OF LONG-TERM FACILITATION IN HUMANS DURING WAKEFULNESS AND AFTER REPEATED EPISODIC HYPOXIA

In order to conduct studies for models of sleep apnea during wakefulness, willing and qualified participants were recruited through newspaper advertisement. Inclusion criteria were: BMI < 30 kg/m², not taking any medications, and not having sleep apnea. Qualifying participants were administered several tests, including the Grass polygraph and the Mac Power Lab monitor brain (electroencephalograph [EEG]), eye (electroculograph [EOG]), skeletal muscle (electromyography [EMG]) electrical activity, heart rhythm (electrocardiography [ECG]), and breathing functions such as tidal volume, flow, supraglottal pressure, PET CO₂ and SaO₂. The tests determine long-term facilitation (LTF) in humans during wakeful bed rest. Long-term facilitation is an increase in motor outflow after repetitive episodes of hypoxia by substituting oxygen for nitrogen. The brain detects low oxygen levels after it is sensed at the carotid bodies and reacts to this sudden change by gasping for more oxygen to compensate. The respiratory rate increases and the genioglossus (tongue muscle) contracts as a result of the hypoxia. After these episodes of hypoxia, breathing patterns do not return to normal for a long time. Data for genioglossus activity, as determined by analysis through a computer macro, was collected after inserting two electrodes on the right and left sections of the tongue. These electrodes record the contractions/relaxations as a response to the ventilatory driving force of higher CO₂/lower O₂ and lower CO₂/higher O₂. We concluded that exposure to episodic hypoxia is necessary to generate peak genioglossus activity and LTF. There was no evidence of LTF during wakefulness. We hypothesized that sleep is required to exhibit LTF and need further study to test this hypothesis.

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INTRODUCTION

Intermittent hypoxia during sleep can evoke long-term facilitation (LTF) of ventilatory motor output in humans. Furthermore, LTF of the genioglossus (GG) muscle is seen in elevated levels of carbon dioxide in humans during wakefulness. Manifestations of LTF include decreased upper airway resistance, increased minute ventilation (V_i) and activation of GG activity. We wished to determine whether sleep is required to manifest LTF, or whether brief isocapnic hypoxia during wakefulness elicits LTF. We hypothesized that LTF will occur in wakefulness following repetitive episodic, isocapnic hypoxia of less than one minute duration. LTF has not been demonstrated in wake humans exposed to 2 minute or longer isocapnic hypoxia periods.

MATERIALS AND METHODS

We studied nine healthy non-snorers during wakefulness as shown through EEG recordings. There were 3 females, 6 males, aged 19 to 41 years, BMI < 30 kg/m². We calculated the flow and volume with a pneumotachometer and determined the phasic genioglossus EMG activity with electrodes on the bilateral tongue, which was peak-integrated from the moving-time average and expressed in arbitrary units from mV. We also determined the SaO₂ with a pulse oximeter, the change in post end-tidal CO₂ with

a CO₂ analyzer, and supraglottal airway pressure with a pressure-tipped transducer catheter. These parameters were collected by polygraph and Power Lab analog-to-digital converter acquisition systems used for analyzing the data, which all will ultimately help determine LTF of the genioglossus during wakefulness.

The participants were placed in the supine position and given five minutes of relaxed room air breathing. Then, we used 100% N₂ to lower O₂ saturation to 89% for 15 episodes of hypoxia (<1 minute each). After 2–3 breaths, a hypoxic trial was terminated and two breaths of 100% oxygen were given, followed by room air. At the end of the 15 trials, a 20-minute recovery period followed with the subject on room air. Isocapnia was maintained at control levels by monitoring end-tidal CO₂ and bleeding in 7% CO₂ as needed throughout the experiment. Sham studies were performed on each of the participants only on constant room air for the duration of the study with time markers as parallel to preliminary five minutes of relaxed room air breathing, 4 × 10 breaths of control and 20 minutes of recovery.

RESULTS

After the recovery period, there was no significant difference between peak and phasic genioglossus EMG activity, as compared to control for either hypoxia or either recovery point. Dur-

ing the hypoxia trials, SaO₂, was decreased while the volume increased. Lastly, no significant difference between the sham and the corresponding recovery period during the studies for GG EMG was evident.

DISCUSSION

The aim of this experiment was to determine whether LTF was present after repetitive hypoxic exposure in wake patients, which had only been shown in patients during NREM (non-rapid eye movement) sleep. During the hypoxic trials, we wanted to understand how patients with sleep apnea would breathe during wakefulness. In doing so, we will be able to develop models for sleep apnea and diagnosis of sleep disorders.

In this study, there was no evidence of LTF during wakefulness. The effect of brief isocapnic hypoxia is similar to the effect of longer episodes of hypoxia. Our findings support the hypothesis that sleep is required to manifest LTF. We conclude that exposure to episodic hypoxia is necessary to induce LTF and peak genioglossus muscle activity.

The next step in this project will be to treat sleep apnea patients with nitrogen to see if LTF can be seen in subjects during wakefulness.

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RESOURCES

For more information, please contact authors of the following studies:

1. Determinants of long-term facilitation in humans during NREM sleep. Babcock M, Shkoukani M, Aboubakr SE and Badr MS. Sleep Research Laboratory, Medical Service, John D. Dingell Veterans Affairs Medical Center, and Division of Pulmonary/Critical Care and Sleep Medicine, Department of Medicine, Wayne State University School of Medicine, Detroit, Michigan, 48201.
2. Long-term facilitation of ventilation and genioglossus muscle activity is evident in the presence of elevated levels of carbon dioxide in awake humans. Harris DP, Balasubramanian A, Badr MS, Mateika JH. Physiology, Wayne State University, Detroit, Michigan; Research and Development, John D. Dingell VA Medical Center, Detroit, Michigan.
3. Long term facilitation in wakefulness after repeated episodic hypoxia. Washington J, Peyyeti, P; Kimler, VA; Sarikonda K, Dogra S and Badr MS. Research Service, John D. Dingell VA Medical Center and Division of Pulmonary, Critical Care and Sleep Medicine, Wayne State University, Detroit, MI 48201.