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Perspectives

PERSPECTIVES

Temporal Dynamics and Therapeutic Implications of Phrenic Long-Term Facilitation in Respiratory Control

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A Perspective on "Magnitude and Mechanism of Phrenic Long-Term Facilitation Shift Between Daily Rest vs Active Phase"

Breathing is an autonomic function essential for life, yet it functions with a remarkable capacity for adaptive changes.[1,2] Notably, the respiratory control system, specifically the phrenic motor system, demonstrates this flexibility in its response to acute intermittent hypoxia (AIH). Detailed investigations into respiratory motor plasticity have shown that during AIH—characterized by cycles of 5 min of reduced oxygenation (PaO2 35-45 mmHg) alternating with 5 min intervals of normoxia—the phrenic motor system can increase the strength of phrenic nerve activity. This adaptive response is known as phrenic long-term facilitation (pLTF) and can be measured at multiple levels, including the ventral cervical spinal cord.[3] Phrenic long-term facilitation not only plays a crucial role in the regulation of breathing patterns but also offers insights into the broader scope of neural plasticity, with implications for developing therapeutic treatments.

Mechanisms driving pLTF similarly exhibit flexibility, demonstrated by distinct molecular processes depending on the severity of hypoxic exposure. During moderate acute intermittent hypoxia (mAIH, PaO_2 40-55 mmHg), pLTF primarily depends on serotonin, activating serotonin-mediated signaling at 5-HT2A receptors known as the "Q-Pathway." Conversely, under conditions of severe AIH (PaO_2 25-30 mmHg), the molecular basis of pLTF shifts from serotonin-dependence to a predominantly adenosine-driven mechanism activating A_{2A} receptors, referred to as the "S-Pathway."[4] Importantly, these two pathways are critically influenced by cross-talk inhibition, such that excess 5-HT can dampen adenosine-dependent pLTF and vice versa, adding complexity to the understanding of pLTF. Addressing this complexity in the current issue of *FUNCTION-APS*, Marciante et al. investigate how circadian fluctuations in neuromodulators can additionally influence the mechanisms driving pLTF.[5] From a clinical perspective this is critically important, given that much of the pLTF research has been conducted on nocturnal rodents, which may not directly correspond to the physiological responses of diurnal humans.

The authors initially observed that the baseline spinal adenosine levels fluctuate between the rest and active periods of the day, with higher adenosine levels during the active period, compared to the rest period. Conversely, serotonin stays consistent between the active and rest periods. These findings suggest a temporal balance between 5-HT and adenosine that could have extensive implications for spinal plasticity, as adenosine fluctuations might affect various neural processes. Upon manipulating adenosine and serotonin receptors, Marciante and colleagues further discovered that the primary mechanism driving pLTF is contingent on the time of day. A key finding was that adenosine-driven pLTF predominates during the active phase, while serotonin-driven pLTF is more relevant during the rest phase. This challenges the traditional view of pLTF,[6] introducing the notion that adenosine plays a significant role in pLTF primarily during active periods, with its influence fluctuating over

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time. Thus, understanding how timing influences the mechanisms of pLTF opens new opportunities for therapeutic interventions, especially for individuals with spinal cord injuries or neurodegenerative diseases. For diurnal humans, treatments that focus on the active phase may differ in effectiveness compared to those based on nocturnal models, where serotonin's role in pLTF during rest is emphasized.

In addition to the circadian influence on pLTF mechanisms, the authors demonstrated the modulation of adenosine levels through shorter (1 min) hypoxic episodes. This significantly intensified pLTF during the rest phase due to lower adenosine levels. In the active phase, moderate hypoxia (5 min) triggered adenosine, leading to adenosine-driven pLTF. This underscores the importance of the timing and duration of AIH induction, promoting serotonin dominance during rest and adenosine dominance during activity. The authors' findings also indicate that blocking adenosine receptors during the active phase promotes serotonin-dominant pLTF. This discovery is noteworthy, suggesting that manipulating the duration of hypoxic exposure can influence adenosine levels during both mid-active and mid-rest phases. Furthermore, blocking adenosine receptors could potentially promote serotonin-driven plasticity, irrespective of the mid-active or mid-rest phases, and yield maximal pLTF. This finding holds promise for developing effective therapeutic strategies for spinal cord-related conditions or rehabilitation programs.

Taken together, this study underscores the importance of the timing and duration of AIH in promoting pLTF. An important takeaway is the necessity of tailoring AIH protocols in clinical trials to align with the patient's active/rest cycle. For diurnal humans, treatments that focus on the active phase may differ in effectiveness compared to those based on nocturnal models, where serotonin's role in pLTF during rest is emphasized. However, the authors present a viable strategy to "shift" the mechanism of pLTF to serotonin-dependent during the active phase by modulating the duration of hypoxic exposures. This may be important as more information regarding the efficacy of therapeutic strategies involving adenosine-dependent versus serotonin-dependent pLTF begins to emerge.

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Conflict of Interest

All authors declare no conflict of interest.

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