Long-term facilitation of breathing following intermittent hypoxia Prof. Maja Valić University of Split School of Medicine Department for neuroscience



Basic research

- Performed to provide essential information on neurotransmitter serotonin involved in respiratory control.
- To investigate the role of specific area within medulla in excitatory or inhibitory respiratory responses.
- To investigate respiratory response to hypoxic stimulus.
- To research respiratory plasticity induced by intermittent hypoxic exposure.

Neurotransmitters and neuromodulators in neural control of breathing during sleep and wakefulness Glutamate, ACh, serotonin

GABA, glycin





sympathetic nerve activity.

Long term facilitation (LTF)

- Form of respiratory plasticitiy (vLTF, LTF_{hypogl}, LTF_{gg}).
- Increase in phrenic nerve activity (pLTF) due to acute intermittent hypoxia exposure (AIH).
- Increase lasts long after the hypoxic stimulus ceased (60 min after the last episode).
- Intermittent hypoxia can also initiate another form of respiratory plasticity called *progressive augumentation (PA)*.

Long term facilitation (LTF)

Phrenic LTF Central (spinal) neural mechanism

- Seen as prolonged increase of respiratory motor output following episodes of acute intermittent hypoxia (AIH)
- It lasts long after direct effects of hypoxia
- Very sensitive mechanism



Baker TL, Mitchell GS. J. Physiol., 2000

LTF – Where it can be seen?

- Present in many animal species
 - Cats, dogs, goats, birds, rats, etc.
 - Appears weaker and shorter in awake animals compared with anesthetized, mostly affecting respiratory frequency
- LTF was studied in the human
 - Evoked in sleeping humans during non-REM sleep
 - In awake humans under hypercapnia (Harris et al 2006, Lee et al 2009)
 - LTF considered to be an useful factor in maintainance of respiratory homeostasis during sleep?
 - LTF may increase the muscle tonus of upper airways,
 - Registered in the *phrenic nerve* (phrenic LTF; pLTF), as well as in the *hypoglossal nerve*, but also in genioglossus muscle activity, sin. car. nerve, or as ventilatory LTF.

Link between intermitent hypoxia induced respiratory plasticity and OSA?

- Since intermittent hypoxia is a prominent feature of sleep-disordered breathing, LTF may compensate for factors that predispose to OSA.
- Understanding od LTF and its underlying mechanisms, potential role in maintaining upper airway patency, stabilizing breathing and preventing OSA in humans may guide future therapeutic development.

Protocols and preparations in LTF

- Acute intermittent hypoxia (AIH)
 - Anesthetized, mechanically ventilated, paralyzed, vagotomized rats or cats
 - 5x2 min, 3x5 min, 10x45 s...
- Chronic intermittent hypoxia (CIH)
 - Can produce LTF enhancement
 - 5x5 min in 12 hours during 7 days, 10x5 min during 7 days etc.



Protocols and preparations in LTF



Serotonin and breathing

- Serotonin effects on breathing often different and opposite considering animal species and experimental model
- Serotonin effects largely depend on the receptor type
- Serotonin, especially 5-HT_{1A} receptors have important role in breathing recovery in demanding situations



M.Valic, R. Pecotic and Z. Dogas. Phrenic nerve activity is enhanced by 5-HT_{1A} receptor agonist 8-OH-DPAT in spontaneously breathing anesthetized rats. J. Physiol. Pharmacol. 59 (1):17-25, 2008.

M.Valic, R. Pecotic, I. Pavlinac, Z.Valic, K. Peros, Z. Dogas. Microinjection of methysergide into the raphe nucleus attenuated phrenic long-term facilitation in rats. <u>Exp Brain Res. 202/3: 583-9, 2010.</u>



M.Valic, R. Pecotic and Z. Dogas. Phrenic nerve activity is enhanced by 5-HT_{1A} receptor agonist 8-OH-DPAT in spontaneously breathing anesthetized rats. J. Physiol. Pharmacol. 59 (1):17-25, 2008.





Activation of phrenic nerve depends on serotonin.

R. Pecotic, Z. Dogas, Z.Valic and **M.Valic**. Blockade of 5-HT_{1A} receptors in the phrenic nucleus of the rat attenuated raphe induced activation of the phrenic nerve activity. J. Physiol. Pharmacol. 60 (3):167-172, 2009.

LTF and serotonin

- Activation of spinal serotonin receptors needed for the phrenic LTF
- Millhorn in 1986, injection of metisergide (wide spectrum serotonin antagonist) blocks LTF in cats
- In anesthetized rats LTF also depends on 5-HT

Serotonin is a "trigger" for induction of LTF, but not necessary for LTF maintainance.

Fuller DD, Zabka AG, Baker TL, Mitchell GS. J Appl Physiol, 2001

Where the regulation of pLTF is going on?

- <u>Spinal level</u> The majority of prior research has focused on the postsynaptic effects of 5-HT receptor activation on spinal motorneurons (Mitchell et al. 2001).
- <u>Supraspinal level</u>? serotonergic modulation at supraspinal level, including the caudal raphe region, and its influence on phrenic LTF has not been investigated.



M.Valic, R. Pecotic, I. Pavlinac, Z.Valic, K. Peros, Z. Dogas. Microinjection of methysergide into the raphe nucleus attenuated phrenic long-term facilitation in rats. <u>Exp Brain Res. 202/3: 583-9, 2010.</u>



- I. Pavlinac, R. Pecotic, Z. Dogas, M.Valic. Role of 5-HT_{1A} receptors in induction and preservation of phrenic long term facilitation in rats. <u>Respiratory Physiology and Neurobiology 175 (2011), 146-152.</u>
- II. Ivana Pavlinac Dodig, Renata Pecotic, Maja Valic and Zoran Dogas. Acute intermittent hypoxia induces phrenic long term facilitation which is modulated by 5-HT_{IA} receptors in the caudal raphe region of the rat. J. Sleep Res. 2011.



Ivana Pavlinac Dodig, Renata Pecotic, Maja Valic and Zoran Dogas. Acute intermittent hypoxia induces phrenic long term facilitation which is modulated by 5-HT_{IA} receptors in the caudal raphe region of the rat. J. Sleep Res. 2011.

Opioids and breathing



5 sec





Propofol and pLTF



M. Carev, M.Valic, R. Pecotic, N. Karanovic, Z.Valic, I. Pavlinac, Z. Dogas. Propofol abolished the phrenic long-term facilitation in rats. <u>Respiratory Physiology and Neurobiology 170: 83-90, 2010.</u>



M. Carev, M.Valic, R. Pecotic, N. Karanovic, Z.Valic, I. Pavlinac, Z. Dogas. Propofol abolished the phrenic long-term facilitation in rats. <u>Respiratory Physiology</u> <u>and Neurobiology 170: 83-90, 2010.</u>

N. Karanovic, R. Pecotic, M. Valic, A. Jeroncic, M. Carev, S. Karanovic, A. Ujevic, Z. Dogas. The acute hypoxic ventilatory response under halothane, isoflurane and sevoflurane anaesthesia in rats. <u>Anaesthesia</u>, 65(3):227-34, Mar, 2010. Does exposure to intermittent hypoxia promote or mitigate sleep apnea?

Beneficial factors of LTF



- Persistent increase in respiratory activity
- LTF predominantly in UA dilating muscle
- Pretreatment with CIH in rats inhances AIH induced LTF
- OSA patients have greater AIH induced LTF (Lee, Badr and Mateika 2009)

Detrimental factors of LTF



- OSA symptoms worsen as the night progresses
- OSA symptoms get worse over time in many patients
- Repeated hypocapnia between OSA events inhibits LTF expression in OSA patients (Mateika and Narwani 2009)
- High HVR is thought to destabilize breathing in OSA

Figure 5. A schematic diagram showing how hypocapnia leads to the promotion of apnoea Reductions in carbon dioxide lead to disfacilitation of central and peripheral chemoreceptors and ultimately respiratory neurons, resulting in an apnoea of central origin ...



Mateika J H , Narwani G Exp Physiol 2009;94:279-296



* THANKYOU!



- Ketanserin increased acute hypoxic response, but switched off LTF
- However, 5-CT results were unexpected:
 - 5-CT not only shut off LTF, but lead to long lasting decrease of phrenic amplitude
 - Authors speculated it worked on 5-HT₁ autoreceptors which lead to long term inhibitory neuromodulation

Kinkead R and Mitchell GS.Am J Physiol, 1999