DUAL CHEMORECEPTIVE MECHANISMS FOR HYPOXIA SENSING

Mieczyslaw Pokorski[1, 2], Kotaro Takeda[2, 3], and Yasumasa Okada[2]

[1]Opole Medical School, Opole, Poland

[2]Clinical Research Center, Murayama Medical Center, Tokyo, Japan

[3]Fujita Memorial Nanakuri Institute, Fujita Health University, Mie, Japan

A tenet of basic physiology is that the ventilatory response to hypoxia is nearly solely generated by carotid body chemoreceptor cells. Nonetheless, the exact mechanism of hypoxia-sensing remains elusive. A recent study has shown that TRPA1 channels are at the core of hypoxia-sensing in the vagal sensory system (*Takahashi et al. Nat Chem Biol 7:701-11, 2011*). These channels, inhibited in normoxia by oxygen-dependent activity of prolyl hydroxylases (PHD), would be relieved from the inhibition in hypoxia when insufficient oxygen suppresses PHD activity, resulting in the excitatory response. That study puts TRPA1 in the limelight as the universal oxygen sensor. This communication presents an attempt to verify the role of TRPA1 in hypoxia-sensing. The premise was that if TRPA1 are key for hypoxia-sensing, then their inhibition would abrogate the hyperventilatory response to hypoxia. We tested this hypothesis in an experimental functional study in which HC-030031, an inhibitor of TRPA1, was used. Conscious mice were exposed to mild 13% hypoxia and severe 7% hypoxia before and after blockade of TRPA1. The inhibitor abrogated the ventilatory response to mild hypoxia, while that to severe hypoxia was diminished but still distinctly present. These findings counter the notion of TRPA1 being the ultimate sensor of hypoxia. We propose dual mechanisms for hypoxia sensing: TRPA1-mediated by vagally-innervated chemoreceptive cells responding to mild hypoxia and non-TRPA1-mediated by carotid chemoreceptor cells generating a full-fledged rescue response in life-threatening hypoxia. These mechanisms would overlap, with the carotid body progressive involvement with deepening hypoxia.