Neuroadaptations to Chronic Intermittent Hypoxia: Paradoxical Roles in Neurogenic Hypertension & Stroke Neuroprotection?

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Sleep apnea is a chronic condition often associated with multiple features of the metabolic syndrome, including arterial hypertension. Studies mimicking the repetitive bouts of arterial hypoxemia that occur with sleep apnea demonstrate that hypertension develops rapidly, within ~24-48 hours, to a level that is sustained with prolonged exposure. This experimental model of hypertension involves sympathetic nervous system hyperactivity linked to activation of the peripheral renin-angiotensin system and to sensitization of the arterial chemoreflex. Of particular relevance to this seminar is that the hypertension of intermittent hypoxia critically depends on activity of sympathetic control neurons in the hypothalamic paraventricular nucleus (PVN) that receive synaptic input both from angiotensin II sensing regions of the forebrain as well as from arterial chemoreceptors. Our ongoing work, and the primary focus of this seminar, indicates that the PVN experiences significant tissue hypoxia during intermittent exposure to hypoxic breathing to 10% FIO2. We hypothesize that in response to intermittent hypoxia, PVN neurons undergo adaptations that limit the maximum efficacy of NMDA receptor mediated glutamatergic neurotransmission. The mechanisms involve reduced expression of the guanylate kinase adaptor protein post-synaptic density 95 (PSD95), which is known to couple GluN2B-containing NMDA receptors to specific Ca2+-dependent signaling pathways. Evidence will be shown that the intermittent hypoxia-induced adapted state of PVN neurons not only contributes to arterial hypertension, but perhaps, paradoxically, confers protection from injury caused by focal ischemia (stroke).