CHAPTER 8

ROLE OF LOCAL RENIN-ANGIOTENSIN SYSTEM IN THE CAROTID BODY AND IN DISEASES

MAN LUNG FUNG1 AND PO SING LEUNG2
1Department of Physiology, University of Hong Kong, Pokfulam, Hong Kong
2Department of Physiology, Chinese University of Hong Kong, Shatin, Hong Kong

1. INTRODUCTION

The carotid bodies are a pair of small organs bilaterally located at the bifurcation of the carotid artery. The organ is highly vascularized and perfused by arterial blood supply from the carotid artery. Peripheral chemoreceptors of the carotid body play a major role in the sensory chemotransduction of chemical changes in the arterial blood, which is essential to the rapid adjustment of cardiovascular and respiratory activities via the chemoreflex pathways. Under hypoxemic conditions with a fall of arterial oxygen tension below 50 mm Hg, this causes an exponential rise in the activity of the carotid sinus nerve of the carotid body. The increase in chemoreceptor afferent activities excites the neurons in the nucleus tractus solitarius, which is the primary relaying nucleus in the medulla. Activation of the chemoreflex results in the elevation of central drives and efferent nerve activities, which increases ventilation, cardiac performance and redistribution of blood flow for the physiological compensation matching metabolic needs (Marshall 1994).

Type-I glomus cells are the major cell type in the carotid body. These cells play a major role in sensory chemotransduction because these cells are closely apposed to nerve endings formed in group clusters or glomeruli (Gonzalez et al 1994). These glomeric clusters are encapsulated by glial-like (type-II) cells; however, they are not as numerous as the type-I glomus cells. In addition, it is generally believed that type-I glomus cells are the chemosensitive cells in the carotid body, because these cells respond to various physiological stimuli such as hypoxia and hypercapnic acidosis. Upon activation of the chemical stimulus, type-I glomus cells depolarize causing a rise in intracellular calcium, which is essential for signaling the vesicular secretion of catecholamines and other putative neurotransmitters such as...
acetylcholine and ATP from the chemosensitive cells (Gonzalez et al 1994; Lahiri et al 2006). This in turn elevates the excitability of the nerve endings that cause an increase in the activity of the carotid sinus nerve of the carotid body.

The carotid body is a highly vascularized organ with blood perfusion exceeding the needs of local tissue metabolism. Thus, changes in arterial oxygen tension or pH, circulating hormones and locally produced substances from the vessels and tissues acting as autocrines or paracrines can readily diffuse to the chemosensory components of the carotid body. In fact, mounting evidence suggests that vasoactive peptides can regulate the excitability of the carotid chemoreceptors. For example, studies have shown that angiotensin II modulates carotid afferent discharge of the carotid sinus nerve in the isolated carotid body superfused in vitro, thus demonstrating an effect directly on the carotid chemoreceptor, but not from the vascular and hemodynamic effect of angiotensin II (Allen 1998; Leung et al 2000). In addition, a high density of angiotensin II receptors was detected in the carotid body with in vitro autoradiography (Allen 1998). These findings provide initial evidence for a functional role of angiotensin II receptors in the carotid body and raise a number of questions on: (i) the expression and regulation of angiotensin II receptors in the carotid body under physiological or pathophysiological conditions and (ii) the physiological or pathophysiological significance of alterations of the carotid chemoreceptor activity by angiotensin II.

Research studies have shown the influence of the renin-angiotensin system (RAS) on numerous tissues and organs. The RAS is mainly a blood-borne hormone system that regulates blood pressure and fluid homeostasis (Peach 1977; Reid et al 1978). In addition, the local RAS is primarily of autocrine or paracrine origin and caters to specific organ and tissue needs through actions that are complementary to, or differ from, the circulating RAS (Campbell 1987; Leung 2004). Interestingly, our recent data have demonstrated a functional expression of RAS in the carotid body, wherein this may play a physiological role in the regulation of autonomic responses to changes in arterial chemical content. Hence, it has been reported that angiotensin II as well as other vasoactive substances can directly alter the excitability of the carotid chemoreceptor (Lahiri et al 2001; Fung 2003; Fung and Tipoe 2003; Leung et al 2003; Tipoe et al 2006). Although these findings support a physiological role for RAS in the carotid body, the significance and clinical implication have yet to be clearly defined.

Moreover, chronic exposure to moderate hypoxia (chronic hypoxia) modifies the level of gene expression in the carotid body including an upregulation of the expression of AT₁ receptors associated with increased sensitivity of the chemoreceptor to angiotensin II (Leung et al 2000; Fung et al 2002). In chronic hypoxia, alterations of the carotid body are closely linked to structural remodeling including increased vasculature, hypertrophy and hyperplasia of the glomus cells (Dhillon et al 1984; McGregor et al 1984; Bee et al 1986), as well as functional modifications such as neurochemical synthesis and release of catecholamines (Hanbauer et al 1981; Pequignot et al 1987; Czyzyk-Krzeska et al 1992; Millhorn et al 1993). Furthermore, carotid afferent activities are also known to play a role in the