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Angiotensin and Carotid Body Chemoreception in Heart Failure

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Abstract

The carotid body (CB) plays an important role in the control of breathing and in autonomic control of cardiovascular function. CB chemoreceptor activity is enhanced in chronic heart failure (CHF) and contributes to the sympathetic hyperactivity that exacerbates the progression of the disease. Studies in the past few years have revealed that a local angiotensin (Ang) system exists in the CB and plays an important role in altering CB function in CHF as well as other conditions, such as chronic hypoxia. This brief review highlights recent revelations that Ang I metabolites exert effects within the CB, and focuses on the influence of Ang II and Ang-(1–7) on CB function in CHF.

Keywords

Carotid Body; Angiotensin; Heart Failure

Introduction

Carotid body (CB) chemoreceptors serve an important regulatory role in the control of alveolar ventilation, but they also exert a powerful influence on cardiovascular function. Activation of CB chemoreceptors by hypoxemia or hypercapnia increases sympathetic outflow to systemic vascular beds to compensate for the direct vasodilating effects of the blood gas disturbance on these vessels and to redistribute blood flow to essential organs. CB chemoreceptor activity and reflex function are enhanced in chronic heart failure (CHF) [1–3]. Their heightened level of activity acts at central autonomic nuclei to exacerbate the tonic sympathetic hyperactivity associated with the disease [3–5]. Recent studies have established that the local angiotensin (Ang) system in the CB contributes to sensitization of chemoreceptor function in CHF [6,7].

Ang I is converted by various peptidases to several active intermediate metabolites, namely Ang II, Ang III, Ang IV, and Ang-(1–7), which are known to exert a variety of physiological effects. While the importance of most of these metabolites on CB function has yet to be elucidated, a relationship of Ang II to altered CB function in CHF has been established [6,7]. More recent evidence suggests that Ang-(1–7) in the CB may play an opposing role to Ang II in the control of CB function (JX Yin, et al., abstract in *FASEB J* 2009,

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23:1009.1012). This review brings together these concepts to suggest that Ang metabolites may act to fine tune CB sensitivity through a balance of functionally-opposing effects. The role of impaired blood flow as a potential mechanism to disrupt this balance in CHF is discussed.

Role of Angiotensin II in the CB in Heart Failure

It has been known for several years that a locally generated angiotensin system exists in the CB and that Ang II activates CB chemoreceptor afferent activity [8,9]. The chemical sensor of the CB resides at the level of the type I glomus cell and its afferent nerve terminal. Type I cells express both angiotensinogen and the Ang II receptors, AT₁R and AT₂R [8–10]. The stimulatory effect of Ang II on CB afferent activity is mediated, at least in large part, by the AT₁R [7,8]. Although the functional effects of the AT₂R are generally opposite that of AT₁R in vascular and neural tissue, its effect on the CB has not been studied.

The functional significance of Ang II in the CB under normal conditions is not clear as blockade of AT₁R does not markedly affect resting ventilation or reflex responses to acute hypoxia in healthy young men [11], rats [12*] or rabbits [7], or CB chemoreceptor nerve activity in rats [8] and rabbits [7]. However, in conditions in which CB Ang II levels are elevated, such as chronic [13] and intermittent [12*] hypoxia and CHF [7], CB chemoreflex or afferent responsiveness to acute hypoxia are enhanced. These effects are reversed, at least in part, by AT₁R blockade [7]. The signaling pathways by which AT₁R activation enhances CB chemo-responsiveness in these conditions has not been extensively studied; however, recent studies in CHF animals have revealed some insight into this condition.

Production of Ang II in CB tissue and the expression of the AT₁R [7,14**] and Ang converting enzyme (ACE) are elevated in CHF rabbits (Fig.1). Blockade of AT₁R in conscious CHF rabbits attenuates (i.e. normalizes) the exaggerated hypoxia-induced chemoreflex activation of sympathetic outflow observed in this condition [7]. Conversely, systemic administration of Ang II in normal rabbits (to levels equivalent to the endogenous plasma Ang II level in CHF rabbits) enhances hypoxia-induced chemoreflex responses [7]. Afferent nerve recordings from the isolated CB confirm that the elevation of Ang II and AT₁R in the CB enhances chemoreceptor sensitivity in CHF rabbits [7,14**].

The mechanism by which Ang II enhances the hypoxic sensitivity of the CB chemoreceptors involves, at least in part, an interaction with oxygen sensitive potassium channels to suppress their voltage-gated currents (I_{Kv}) in CB glomus cells [15]. Hypoxia inhibits I_{Kv} and this effect is enhanced in isolated CB glomus cells from CHF rabbits [15]. Blockade of AT₁R alone is capable of reversing this enhanced hypoxic sensitivity of glomus cell I_{Kv} [15]. In addition, exposing normal rabbit CB glomus cells to Ang II mimics this effect of CHF on I_{Kv} [15]. The specific types of K⁺ channels involved in glomus cell function varies by species, but in the rabbit, the suppression of I_{Kv} observed in CHF appears to involve the Ca⁺⁺-sensitive K⁺ channel (BK) [16], Kv3.4 and Kv4.3 [3,15]. Other K⁺ channels also may play a role but have not been examined.

In vascular and neural tissue, AT₁R promotes activation of NADPH oxidase (NOX) to enhance superoxide ($O_2^{\bullet-}$) production. In the CB, expression of NOX2 subunits and $O_2^{\bullet-}$ production are enhanced in CHF rabbits [6]. The elevated $O_2^{\bullet-}$ can be normalized by AT₁R antagonists, NOX inhibitors, and the $O_2^{\bullet-}$ scavenger tempol [6]. Similarly in CHF rabbits, NOX inhibitors and tempol normalize the enhanced CB chemoreceptor discharge to hypoxia, and normalize the enhanced sensitivity of I_{Kv} to hypoxia in CB glomus cells [6]. These results suggest that the NOX- $O_2^{\bullet-}$ pathway mediates the effects of Ang II in the CB to enhance chemoreceptor sensitivity in the CHF state.

Recent studies have demonstrated that both copper/zinc superoxide dismutase (CuZnSOD) and manganese SOD (MnSOD), endogenous scavengers of $O_2^{\bullet-}$, are suppressed in glomus cells of the CB in CHF [17*,18*]. These changes serve to enhance the Ang II- $O_2^{\bullet-}$ activation of CB chemoreceptor activity. Gene transfer to restore expression of either of the SOD isoforms in the CB reverses the enhanced CB chemoreceptor and chemoreflex activation, and suppression of glomus cell I_{Kv} observed in CHF [17*,18*], implicating a dual role of both cytosolic and mitochondrial $O_2^{\bullet-}$ in the Ang II-NOX signaling cascade within CB glomus cells.

While these results suggest that Ang II- $O_2^{\bullet-}$ mediated inactivation of I_{Kv} contributes to enhanced glomus cell excitability in CHF, the effects of Ang II on other ion channels may also be important. For example, voltage-gated Ca^{++} currents (I_{Ca}) are enhanced in CB glomus cells in CHF [19]. Ang II-AT₁R activates I_{Ca} via a PKC pathway in neurons [20], but the signaling pathway in CB glomus cells is not defined. Ultimately, there are many ion channels and channel modulators known to influence glomus cell excitability [2,21,22] that may participate in $O_2^{\bullet-}$ induced sensitization of the CB.

The molecular mechanism by which $O_2^{\bullet-}$ inhibits I_{Kv} in glomus cells is an important question that has not yet been addressed. Ang II is known to activate PKC and CaMKII pathways that lead to suppression of I_{Kv} [20]. A recent study, however, suggests that oxidation of channel protein thiols could play a key role in modulation of I_{Kv} in glomus cells [23].

Role of Other Angiotensin Peptides on CB Function

Apart from Ang II, various protease enzymes can generate several other bioactive angiotensin peptides. These include Ang III, Ang IV, and Ang (1–7). Ang II is degraded to the heptapeptide Ang III by aminopeptidase A. Ang III can activate AT₁R and AT₂R and a novel non-AT₁, non-AT₂ receptor [24]; however, the role of Ang III in the CB remains unknown.

Ang III is degraded by aminopeptidases to Ang IV, which binds to a specific receptor AT₄R, but also may interact with the AT₁R [25]. A recent study has shown that AT₄R is localized to CB glomus cell clusters in rat and that its expression is increased with exposure to chronic hypoxia (CH) [26**]. In addition, Ang IV was shown to activate CB glomus cells, and this effect was enhanced in rats exposed to CH [26**]. Thus, Ang IV and Ang II share a similar effect to enhance CB chemoreceptor activity, and both signaling pathways are upregulated by CH. It is not known if Ang IV contributes to enhanced CB function in CHF, but the speculation seems plausible given the similarities in Ang II and Ang IV signaling in the CB. Nonetheless, further studies are needed to better define the role of Ang IV on CB function.

Ang-(1–7) is produced from Ang II by the enzyme ACE2 or from Ang I by either neutral endopeptidases or prolylendopeptidases. Ang-(1–7) is of particular interest because its cardiovascular and central neural actions counteract those of Ang II. The vasodilatory, anti-proliferative and sympatho-inhibitory effects of Ang-(1–7) are mediated by the Mas receptor (MasR). Recent studies have demonstrated that Ang-(1–7) activation of MasR increases nitric oxide (NO) via neuronal NOS (nNOS) in cultured catecholaminergic neuronal cells (CATH.a) [27**] and within autonomic regions of the brain stem [28]. Ang-(1–7) activation of NO leads to increased I_{Kv} in CATH.a neurons [27**]. This action may explain its sympatho-inhibitory effect.

Preliminary studies (JX Yin, et al., abstract in *FASEB J* 2009, 23:1009.1012) indicate that Ang-(1–7) similarly enhances I_{Kv} in CB glomus cells via MasR activation of nNOS and NO production (Fig. 2): an effect that opposes the inhibitory effect of Ang II- $O_2^{\bullet-}$ on these

channels [15]. It is well known that NO plays an important role in the tonic control of CB chemosensitivity [22]. Both nNOS and endothelial NOS (eNOS) are present in the CB, and NO is inhibitory to CB activity [29]. Because O₂ is essential for biosynthesis of NO, normal basal production of NO acts as an amplifier of O₂ to suppress CB chemoreceptor discharge in normoxic conditions [29]. However, basal NO production and nNOS/eNOS expression within the CB are depressed in CHF [3,19,30]. Thus, the tonic inhibitory effect of NO on the activity of CB chemoreceptors and its enhancement of I_{KV} in glomus cells, demonstrated in the CB of normal rabbits, is virtually absent in CHF rabbits [16].

The marked down regulation of endogenous nNOS in the CB plays a major role in the enhanced CB chemoreceptor activity in CHF rabbits [16,31]. Adenoviral gene transfer of nNOS to the CB in CHF rabbits reverses the enhanced CB chemoreceptor activity seen in the CHF state [31]. Furthermore, gene transfer of nNOS to the CB in CHF rabbits reduces resting RSNA [31]. These results provide important evidence of a measurable contribution of enhanced CB chemoreceptor input to elevated sympathetic outflow in CHF, and the contribution of nNOS down regulation in the CB to this effect.

The opposing effects of Ang II and Ang-(1-7) on CB chemo-sensitivity may provide a mechanism by which CB function can be finely tuned by the balance of factors influencing Ang production and metabolism in the CB. Under normal conditions, Ang-(1-7) may act to maintain NOS expression and NO restraint of CB chemoreceptor activity. When CB Ang II level is elevated, such as in CHF, its excitatory influence on CB chemoreceptor activity overrides Ang-(1-7) and may even participate in the downregulation of MasR-NO effects seen in the CHF state. This balance is likely to be controlled by the relative expression of ACE and ACE2 activities in the CB. Consistent with this notion, ACE2 and MasR are suppressed, whereas ACE and AT₁R are upregulated in the CB in CHF rabbits (Fig.1).

Role of CB Blood Flow on Angiotensin Function in the CB

The factors responsible for upregulation of local ACE and Ang II-AT₁R-O₂^{•-} signaling and downregulation of ACE2 and Ang-(1-7)-MasR-NO in CB glomus cells during CHF are not clear. However, the changes in Ang functionality seen in the CB in CHF are similar in most respects to those described in the CB from animals exposed to chronic hypoxia [32]. This raises the question whether impaired blood flow induced by the failing heart may impair O₂ delivery to the CB sufficiently to mimic effects of chronic hypoxia. Although acute changes in systemic hemodynamics have been shown to have little effect on chemoreceptor activity, a modeling study predicts that moderate changes in carotid body blood flow can influence CB sensitivity [33]. Indeed, recent evidence indicates that a chronic reduction in CB blood flow mimics the changes in CB afferent function seen in CHF [14**].

A sustained reduction in CB blood flow over 3 weeks, imposed with adjustable cuff occluders on the carotid arteries in rabbits, enhanced CB chemoreceptor discharge and the chemoreflex: the reduction in blood flow and functional CB effects were similar to changes observed in CHF rabbits over a similar time course [14**]. It is unlikely that these responses are driven simply by an acute reduction in blood flow to the CB, since chemoreflex and afferent responses were unaffected by only one day of carotid occlusion. Immunohistochemical examination of the CB after chronic carotid occlusion revealed an increase in AT₁R and decrease in nNOS expression [14**].

These results support the concept that a chronic reduction in oxygen delivery to the carotid body precipitates altered CB function in CHF. However, the signaling link between reduced CB flow and altered AT₁R and NOS function in the CB has not yet been explored. Relevant evidence indicates that ACE in the CB is markedly increased in the CB of rats within 1 week of exposure to chronic hypoxia [34]. A similar phenomenon may occur in response to

chronically reduced blood flow to the CB. Ultimately, such changes in protein expression must be related to effects on gene transcription. The transcriptional regulation of ACE expression (and possibly ACE2 expression) in vascular endothelial cells by changes in shear stress [35,36] raises the question whether an endothelial response to changes in blood flow in the CB plays an important role in regulating Ang effects on CB chemoreceptor function in CHF (Fig.3).

These results have important clinical implications. Therapeutic strategies that improve blood flow in CHF may help to maintain normal CB function and limit sympathetic activation and its contribution to the progression of cardiac dysfunction. The beneficial effects of exercise to reverse exaggerated CB and sympathetic activation in CHF [37*] may be attributable, at least to some extent, by the associated increase in blood flow.

Conclusions

The current state of knowledge of the function of the Ang system in the CB indicates that its multiple metabolites and receptors can influence glomus cell function and afferent chemoreceptor activity (Fig. 3). While little is known of the functional role of Ang III and IV and their respective receptors in the CB, it is clear that Ang II and Ang-(1–7) exert opposing influences on CB chemoreceptor activity. Ang II activation of AT₁R and subsequent NOX activation of O₂^{•−} enhances CB chemoreceptor discharge to hypoxia. Ang-(1–7) acting upon MasR activates nNOS and NO-mediated suppression of chemoreceptor activity. These opposing influences are tilted in CHF such that the Ang II chemo-excitatory pathway predominates. It is postulated that this change in balance may be governed by altered expression of ACE and ACE2 in CB endothelial cells in response to changes in blood flow. Additional studies are needed to elucidate the factors that control Ang metabolism and signaling in the CB and how they are influenced in CHF.

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*Exercise conditioning reverses exaggerated carotid body afferent and reflex function mediated by angiotensin-NO mechanisms in heart failure rabbits.

Figure 1.

Immunoblots illustrating changes in protein expression of angiotensin converting enzymes (ACE) and angiotensin receptors (ATR) in the carotid body of normal and chronic heart failure (CHF) rabbits. ACE and AT₁R are increased in CHF; whereas ACE2 and the Ang-(1–7) receptor (MasR) are decreased.

Figure 2.

Whole-cell outward K⁺ currents (I_K) evoked from carotid body glomus cells in response to Ang-(1-7). A: Representative I_K evoked by 400-ms depolarizing pulses from a holding potential of -80 mV in 20 mV increments, illustrating enhancement by Ang-(1-7) (50 nM). B: Exposure to Ang-(1-7) (50 nM) augmented I_K in glomus cells from sham rabbits to a greater extent than that from CHF rabbits. The augmented I_K evoked by Ang-(1-7) was blocked by the MasR antagonist A779 (1 μM), or by the NOS antagonist L-NNA (10 μM). # P < 0.05 compared to sham. * P < 0.05 compared to Ang-(1-7) alone.

Figure 3.

Schematic model of the angiotensin (Ang) system in the carotid body (CB) showing effects of Ang II and Ang-(1-7) on Ca^{++} and K^+ channel function in CB glomus cells, and how they may be influenced by chronic reductions in CB blood flow in CHF. Ang II exerts an excitatory influence on CB glomus cells via activation of NADPH oxidase (NOX) and mitochondrial (mito) mediated $O_2^{\bullet-}$ production to inhibit K^+ and activate Ca^{++} voltage-gated channels. Ang-(1-7) exerts an inhibitory influence on glomus cells via activation of nNOS and NO-mediated activation of K^+ channels. The Ang II pathway (solid lines) is upregulated, whereas the Ang-(1-7) pathway (dashed lines) is downregulated in CHF. These changes may occur as a result of altered transcriptional expression of ACE and ACE2 in CB endothelial cells as a result of the reduced blood flow and shear stress.