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Role of Neurotransmitter Gases in the Control of the Carotid Body in Heart Failure

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Abstract

The peripheral arterial chemoreflex, arising primarily from the carotid body in most species, plays an important role in the control of breathing and in autonomic control of cardiovascular function. The peripheral chemoreflex is enhanced in heart failure patients and animal models of heart failure and contributes to the sympathetic hyperactivity and breathing instability that exacerbates the progression of the disease. Studies in animal models have shown that carotid body chemoreceptor activity is enhanced under both normoxic and hypoxic conditions in heart failure due to disruption of local mediators that control carotid body function. This brief review highlights evidence that the alterations in the gasotransmitters, nitric oxide, carbon monoxide, and hydrogen sulfide in the carotid body contribute to the exaggerated carotid body function observed in heart failure.

1. Introduction

Although the concept that the arterial chemoreflex contributes to autonomic imbalance and pathogenesis of certain types of cardiovascular disease such as hypertension and heart failure was introduced over 30 years ago (Przybylski, 1981; Trzebski, 1992), it has been overshadowed by a dominant interest in baroreflex and other neural influences on cardiovascular function over much of that period. This bias is understandable given the obvious functional relationship of the baroreflex to sympathetic control of arterial blood pressure, whereas chemoreflex function has been regarded to be important mainly for control of breathing. Indeed, the prevailing assumption has been that chemoreceptors, unlike baroreceptors in the normal resting state, contribute little to neuro-humoral control of cardiovascular function.

Over the past several years, however, there has been a renewed interest in chemoreflex influences on neural control of cardiovascular function, both in normal and pathophysiological states. There is now compelling evidence that input from arterial chemoreceptors, particularly that from the carotid body, exerts a regulatory influence on

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Conflicts of Interest

The authors have no conflict of interest to disclose

sympathetic outflow under normal conditions (Stickland et al., 2011; Stickland et al., 2007) and contributes to autonomic and breathing instability associated with cardiovascular conditions such as heart failure (Despas et al., 2012; Zucker et al., 2012), hypertension (Del Rio et al., 2012; Sinski et al., 2012), renal failure (Despas et al., 2009; Hering et al., 2007) and, likely, other not yet fully recognized disease conditions.

There is now overwhelming evidence that carotid body chemoreceptor sensitivity is enhanced in heart failure and contributes to the syndrome of sympathetic hyperactivity associated with the progression and mortality of the disease (Schultz and Li, 2007; Zucker et al., 2012). Our recent studies suggest that the exaggerated chemoreflex function also contributes to the breathing instability associated with heart failure. The mechanisms responsible for this enhanced chemoreceptor function have been studied extensively by our group in rabbit and rat models of heart failure (Ding et al., 2011; Schultz, 2011; Schultz and Li, 2007). This review summarizes the known influence of the gasotransmitters, nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S) on carotid body function in heart failure.

2. Role of NO in the Carotid Body in Heart Failure

Studies from our laboratory have documented that peripheral chemoreflex sensitivity is increased in conscious rabbits with pacing-induced heart failure (Schultz, 2011; Schultz and Li, 2007; Schultz et al., 2007). Inasmuch as rabbits lack functional aortic chemoreceptors, the peripheral chemoreflex is attributable mainly to the carotid bodies in this species. We have shown that, even under resting normoxic conditions, carotid body nerve discharge is elevated and that inhibition of the carotid body reduces renal sympathetic nerve activity in heart failure rabbits (Sun et al., 1999a, b). These results support the notion that enhanced basal activity from the carotid body chemoreceptors contributes to the sympathetic activation in heart failure. The relative importance of aortic chemoreceptors to this effect is likely to be synergistic but remains unknown.

Increased levels of reactive oxygen species and angiotensin II with a concomitant decreased bioavailability of NO within the carotid body seem to play a pivotal role in the development of enhanced carotid body chemosensory activity in pacing-induced heart failure rabbits (Schultz, 2011). A decrease of NO production in the carotid body contributes to an exaggerated carotid body chemoreceptor activity and carotid body function in heart failure rabbits (Li et al., 2005; Sun et al., 1999a). The two constitutive isomers of nitric oxide synthase (NOS), nNOS (or NOS-1) and eNOS (or NOS-3), are normally abundant in the carotid body as illustrated by western and immunohistochemical analysis of the carotid body. NOS inhibition enhances chemoreflex function in the normal condition (Ding et al., 2008) and both nNOS and eNOS expression in the carotid body is suppressed in heart failure (Ding et al., 2008; Li et al., 2005). Overexpression of the nNOS gene in the carotid body elevates nNOS protein expression and NO production in heart failure animals to normal levels and reverses the enhanced chemoreceptor function in heart failure (Li et al., 2005). Thus, a marked downregulation of endogenous NOS in the carotid body appears to play an important role in the enhanced peripheral chemoreflex in heart failure rabbits.

3. Role of CO in the Carotid Body in Heart Failure

CO is known to be an important signaling molecule in the carotid body (Kumar, 2007; Prabhakar, 1999). CO, similar to NO, plays a functional role in restraining hypoxic sensitivity of the carotid body in the normal condition and CO deficiency in the carotid body contributes to enhanced peripheral chemoreflex function and sympathetic activation in heart failure animals (Ding et al., 2008). The heme-oxygenase enzyme (HO) is the major pathway for CO production, and three isoforms of have been identified, the inducible HO-1, the

constitutive HO-2, and the HO-3 isoform with low enzymatic activity (Wu and Wang, 2005). HO degrades heme to CO, biliverdin (subsequently reduced to bilirubin), and ferrous iron. By degrading the prooxidant heme and generating antioxidant bilirubin, HO-1 has been shown to protect cells against oxidative stress (Wu et al., 2011a). CO increases intracellular levels of cGMP to promote vasodilation and also has antiproliferative and anti-inflammatory properties. Ferrous iron can induce ferritin expression for iron sequestration. By generating these biologically active molecules and its upregulation in response to stress conditions, HO-1 acts to protect cells and tissues from oxidative stress-induced injury.

HO-1 is upregulated in the failing heart (Wang et al., 2010). The production of CO and bilirubin via the HO system has been shown to be important protective factors in myocardial ischemia/reperfusion injury (Wu et al., 2011b). HO-1 gene delivery reduces mortality and improves left ventricular function in heart failure induced by coronary ligation in rats (Liu et al., 2006). Although HO is cardioprotective, its role in the carotid body in heart failure is less well defined. HO-2 is highly and constitutively expressed in neuronal and chemosensing tissues, including carotid body chemoreceptor (glomus) cells, but HO-1 is not (Prabhakar, 1999; Prabhakar and Semenza, 2012). We have found that HO-1 is not induced in the carotid body in heart failure animals, and surprisingly, HO-2 protein expression is markedly decreased in the carotid body (Ding et al., 2008). Furthermore, we found that the attenuated HO-2 activity in the carotid body of heart failure rabbits contributes to the enhanced chemoreflex function in heart failure (Ding et al., 2008).

Several studies have assessed the functional significance of HO-2 in the carotid body in the normal state (Prabhakar, 1999; Prabhakar et al., 1995). Zn-protoporphyrin-9, an inhibitor of HO, augments the carotid body sensory discharge in vitro, and exogenous administration of CO can reverse the augmentation of sensory discharge induced by Zn-protoporphyrin-9 (Prabhakar et al., 1995). In the anesthetized rat, HO inhibition enhances respiratory responses to hypoxia but not to CO₂, and the site of action is on the carotid body, since the effects of HO inhibition are abolished by bilateral section of the carotid sinus nerves (Prabhakar, 1999). Similarly, the respiratory response to hypoxia is greater in mutant mice lacking the HO-2 isoform than in wild-type mice (Prabhakar, 1999).

In normal rabbits the CO donor [Ru(CO)₃Cl₂]₂ does not affect renal sympathetic nerve activity during normoxia or in response to hypoxia (Ding et al., 2008). Alternatively, the HO inhibitor, CrMP increases sympathetic nerve activity during normoxia and enhances the response to hypoxia in normal animals (Figure 1). In heart failure rabbits, the same dose of [Ru(CO)₃Cl₂]₂ significantly reduces renal sympathetic nerve activity during normoxia and attenuates the response to hypoxia. CrMP does not change sympathetic nerve activity during normoxia or in response to hypoxia in heart failure rabbits. These results lead to the conclusion that HO activity and CO effects are suppressed in the carotid body in heart failure, and this deficiency contributes to the enhanced peripheral chemoreflex responses characteristic of heart failure.

Williams et al. (2004) suggested that HO-2 functions as an O₂ sensor by regulating K⁺ channel activity during hypoxia in carotid body cells, primarily through CO production. However, we observed that pharmacological inhibition of CO production enhances, rather than abolishes or suppresses, chemoreflex responsiveness to hypoxia. Thus it seems that, in the rabbit at least, CO, similar to NO, serves as a modulator of afferent activity, rather than as a mediator of O₂ sensing. HO-2 protein expression is markedly decreased in the carotid body glomus cell cluster (Figure 2), whereas reflex responses to hypoxia are enhanced in heart failure rabbits compared with normal rabbits. Enhanced sensitivity to hypoxia in the setting of HO-2 downregulation would be inconsistent with HO-2 serving as a primary O₂ sensor.

We have also shown that there is a functional interaction between CO and NO pathways in the carotid body. Co-administration of CO + NO donors blunts the exaggerated hypoxia-induced chemoreflex responses in heart failure rabbits to a greater extent than administration of either donor alone (Ding et al., 2008). Conversely, in normal rabbits, HO inhibition + NOS inhibition induces a greater enhancement of the sympathetic activation to hypoxia than either inhibitor alone. Thus the CO and NO pathways in the carotid body have cumulative effects to enhance peripheral chemoreflex function in pacing-induced heart failure rabbits.

The suggestion of a common downstream signaling pathway for CO and NO synthesized in the carotid body is implicated from these studies and needs to be further defined. Importantly, NO and CO share some common properties with O₂. 1) NO and CO bind to heme with greater affinity than O₂ and are coupled to activation of heme-containing proteins. 2) NO and CO are involved in regulating intracellular Ca²⁺ concentration (Prabhakar, 1999) and the Ca²⁺-sensitive K⁺ channel in glomus cells (Li et al., 2004; Williams et al., 2004). 3) Since NOS and HO-2 activities are sensitive to O₂ concentration and operate over a wide range of P_{O2}, both are capable of contributing to the O₂ sensitivity of the carotid body. 4) NO and CO responses are mediated by stimulation of cGMP production in many cells (Li et al., 2004; Prabhakar, 1999). Our studies have confirmed that the effect of NO on outward K⁺ currents (*I_K*) in rabbit carotid body glomus cells is cGMP dependent, because the guanylate cyclase inhibitor 1H-[1,2,4]oxadiazole[4,3-a]quinoxalin-1-one inhibited the effect of SNAP on *I_K* and the cGMP agonist can mimic the effect of SNAP on *I_K* in sham and heart failure rabbits (Li et al., 2004). However, further studies are needed to determine whether CO shares a similar effect.

4. Role of Hydrogen Sulfide in the Carotid Body in Heart Failure

H₂S is an important signaling molecule in the cardiovascular and nervous systems (Liu et al., 2012; Zhou and Tang, 2011). It has been shown that H₂S controls vascular relaxation and prevents apoptosis while its synthesis in the brain can regulate neuronal excitability. H₂S synthesis has been attributed to three enzymes, cystathionine γ -lyase (CSE), cystathionine β -synthase (CBS), and 3-mercaptopyruvate sulfurtransferase with CSE and CBS as the major sources for endogenous H₂S levels (Renga, 2011). While CSE is widely distributed in the periphery (e.g. heart, blood vessels, liver), CBS is predominantly located within the brain. Recent evidence indicates that H₂S can also participate as a messenger in the carotid body chemoreceptor function (Olson, 2011; Peng et al., 2010). However, conflicting results have been reported on H₂S function in carotid body oxygen sensing. Peng et al. 2010, found that CSE is constitutively expressed in the carotid body glomus cells and that hypoxic stimulation of the carotid body in vitro induced H₂S formation. Moreover, transgenic CSE^{-/-} mice display impaired carotid body chemosensory responses to acute hypoxia. Similarly, acute pharmacological inhibition of the CSE complex with DL-propargylglycine (PAG) using in vitro carotid body preparation impairs the afferent response to hypoxia (Peng et al., 2010). Furthermore, (Li et al., 2010) found that H₂S is also synthesized in the carotid body of mice by the CBS enzyme and its inhibition with amino oxyacetic acid (AOAA) or hydroxylamine reduced carotid body responsiveness to hypoxia, albeit the specificity of these antagonists for CBS is problematic. Taken together, these studies indicate that the carotid bodies constitutively express both CSE and CBS enzymes, and suggest that H₂S contributes in part to the development of the carotid body chemosensory response to hypoxia.

Recently, Buckler (2012) reported that exogenous H₂S inhibits TASK-like K⁺ channels to depolarize isolated carotid body glomus cells, an effect consistent with an excitatory effect of H₂S on the carotid body. In contrast, Fitzgerald et al. (2011) showed that H₂S can decrease release of ACh in the cat carotid body and speculated that H₂S may have a

hyperpolarizing capacity to attenuate depolarization of glomus cells and thereby provide a negative feedback mechanism to prevent hyperactivation. This concept is supported by recent *in vivo* experiments in which intravenous injections of H₂S attenuated the ventilatory effects of moderate hypoxia in rats (Van de Louw and Haouzi, 2012). Thus, the role of H₂S in the carotid body and whether endogenous and exogenous H₂S are acting in the carotid body through similar mechanisms are embroiled in current debate (Haouzi et al., 2011; Olson, 2011).

H₂S has been reported to be cardioprotective in myocardial ischemia due to its ability to preserve mitochondrial function and prevent cardiomyocyte apoptosis (Calvert et al., 2010; Wang et al., 2011). Several treatments targeting the H₂S pathway prevent the progression of the cardiovascular dysfunction associated with heart failure. Indeed, pharmacotherapies designed to increase H₂S levels have been proposed as a novel treatment to reduce the impact of heart failure on cardiac function (Calvert et al., 2010). In these studies, mice with cardiac-selective overexpression of CSE present low levels of cardiomyocyte apoptosis following ischemia-reperfusion heart insult. Moreover, treatment with NaHS, an H₂S donor, protects the heart from oxidative stress and mitochondrial dysfunction associated with volume overload heart failure (Mishra et al., 2010). Thus, evidence indicates that H₂S is cytoprotective in the failing heart.

Myocardial infarcted rats develop heart failure and display similar autonomic and respiratory alterations compared to rabbits with pacing-induced heart failure. Indeed, potentiation of the chemoreflex responses to hypoxia is comparable in both species with heart failure. Our preliminary studies suggest that an acute injection of a CSE inhibitor (PAG, 100mg/kg i.p.) decreases chemoreflex responses to hypoxia in both normal and heart failure rats. Indeed, a 15–20% reduction of the hypoxic ventilatory response was observed following PAG treatment in heart failure animals (Figure 3). Accordingly, the carotid body chemosensory afferent response to acute hypoxia is also decreased after PAG injection (Figure 4). These results indicate that H₂S modulates carotid body chemosensory activity and chemoreflex responses to hypoxia in normal and heart failure rats. But further studies are needed to address the expression and functional contribution of the H₂S synthesizing enzymes to chemoreflex function in heart failure animals.

Recent studies by Prabhakar (2012) suggest that H₂S function in the carotid body may be linked to HO-2 due to an inhibitory influence of CO on CSE enzyme activity. Their findings suggest that CO physiologically inhibits the CSE-dependent generation of H₂S and that hypoxia, which reduces HO-2 activity and CO levels, reverses the CO-mediated CSE inhibition to augment H₂S formation and chemoreceptor stimulation. It was proposed that the interacting HO-2 and CSE proteins work in concert as a “chemosome” to mediate hypoxic sensing by the carotid body (Prabhakar, 2012). This intriguing concept may be functionally relevant to the heart failure state. Downregulation of HO-2 in the carotid body in heart failure (Figure 2) would promote CSE activity and H₂S-mediated modulation of carotid body chemoreceptor afferent activity as observed in heart failure rats (Figure 3–4). This hypothesis is consistent with the elevated level of carotid body chemoreceptor activity seen in the heart failure state under both normoxic and hypoxic conditions.

5. Summary

Evidence is clear that carotid body chemoreceptor sensory and reflex sensitivity is enhanced in heart failure, and alterations in gasotransmitters in the carotid body contribute to this change. Downregulation of both NO and CO production in the carotid body remove their inhibitory influence on carotid body chemoreceptor activity in both normoxic and hypoxic conditions, whereas the stimulatory effects of H₂S on chemoreceptor activity remain intact

in heart failure. These changes during heart failure shift carotid body chemoreceptor excitability toward a more active state (Figure 5). Nevertheless normalization of each of these gas transmitters individually in the carotid body does not appear to be effective in totally normalizing carotid body chemoreflex function in heart failure (Ding et al., 2008). In addition to these changes in neurotransmitter gases, oxidative stress mediated by angiotensin II and other pro-oxidant effects also play an important role (Ding et al., 2010; Schultz, 2011). Thus, it is becoming apparent that multiple factors come together in the carotid body in heart failure to alter “chemosome” control of carotid body afferent activity. The totality of these factors, their interactions, and the underlying physiological mechanisms that induce their change in heart failure remain to be more fully elucidated. These questions carry important clinical relevance given the importance of the carotid body in the genesis and maintenance of autonomic imbalance and breathing instability in heart failure.

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Figure 1.

A and C: RSNA-PaO₂ relationships before and after intravenous administration of the carbon monoxide (CO)-releasing molecule tricarbonyldichlororuthenium (II) dimer { [Ru(CO)₃Cl₂]₂ in sham and chronic heart failure (CHF) rabbits. B and D: RSNA-PaO₂ relationships before and after intravenous administration of the heme oxygenase (HO) inhibitor Cr (III) mesoporphyrin IX chloride (CrMP) in sham and CHF rabbits. Values are means ± SE; n, number of animals. *P < 0.05 vs. control. Reprinted by permission from (Ding et al., 2008).

Figure 2.

Protein expression of heme oxygenase-2 (HO-2) in carotid bodies from sham and heart failure (CHF) rabbits. *A*: representative bands have HO-2 and β -tubulin proteins. *B*: relative HO-2 protein expression in carotid body from sham and CHF rabbits. Values are means $\pm$ SE; $n = 5$ in each group. * $P < 0.05$ vs. sham. *C*: colocalization of tyrosine hydroxylase (TH) and HO-2 in carotid bodies from a sham (*a–c*) and a CHF (*d–f*) rabbit. *a* and *d*: Green Immunofluorescent image for TH; *b* and *e*: red Immunofluorescent image for HO-2; *c* and *f*: merged image (yellow) for overlap of TH and HO-2. Reprinted by permission from (Ding et al., 2008).

Figure 3.

Effect of PAG on the hypoxic ventilatory response in heart failure (CHF) rats. Ventilatory responses to 10% O_2 were obtained pre and post acute PAG (100 mg/kg i.p.) in sham and 6 week post-myocardial infarcted rats. Hypoxic ventilatory response expressed as percent change from the baseline values obtained at normoxia (F_iO_2 21%). Note that PAG reduced the response by about 15% in both groups. * $P < .05$ CHF vs. CHF+PAG; + $P < .05$ Sham vs. Sham+PAG. $n=8$ per group.

Sham

CHF

Figure 4.

H₂S contributes to carotid body chemosensory response to acute hypoxia. Representative *in situ* carotid sinus nerve recordings from one sham rat (upper panel) and one CHF rat (lower panel) before and after inhibition of H₂S synthesis. Acute PAG treatment (100 mg/kg i.p.) reduced the carotid body chemosensory response to hypoxia (F_iO₂ 10%) in both sham and CHF rats.

Figure 5.

Schematic illustration of the contribution of gas neuromodulators to carotid body chemosensory function in CHF. In normal normoxic conditions, both NO and CO exert inhibitory effects (dashed lines) on carotid body chemoreceptor (glomus) cell excitability, which in turn tempers the release of excitatory neurotransmitters at post-synaptic petrosal ganglion nerve endings to limit afferent neural discharge. By contrast, H₂S exerts an excitatory effect (solid line), which is manifested during hypoxia. In CHF, chronic downregulation of NO and CO production disinhibits excitatory influences on chemoreceptor excitability to elevate carotid body afferent discharge under both normoxic and hypoxic conditions. See Schultz (2011) for description of effects mediated by reactive oxygen species (ROS).