Review

Neurotransmission in the carotid body: transmitters and modulators between glomus cells and petrosal ganglion nerve terminals

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Abstract

The carotid body (CB) is the main arterial chemoreceptor. The most accepted model of arterial chemoreception postulates that carotid body glomus (type I) cells are the primary receptors, which are synaptically connected to the nerve terminals of petrosal ganglion (PG) neurons. In response to natural stimuli, glomus cells are expected to release one (or more) transmitter(s) which, acting on the peripheral nerve terminals of processes from chemosensory petrosal neurons, increases the sensory discharge. Among several molecules present in glomus cells, acetylcholine and adenosine nucleotides and dopamine are considered as excitatory transmitter candidates. In this review, we will examine recent evidence supporting the notion that acetylcholine and adenosine 5′-triphosphate are the main excitatory transmitters in the cat and rat carotid bodies. On the other hand, dopamine may act as a modulator of the chemoreception process in the cat, but as an excitatory transmitter in the rabbit carotid body.

Theme: Sensory systems
Topic: Somatic and visceral afferents

Keywords: ACh; ATP; Carotid body; Co-transmission; Dopamine; Petrosal ganglion

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1. Introduction

The carotid body (CB) is the main arterial chemoreceptor that senses the arterial levels of PO_2, PCO_2 and pH, playing an important role in respiratory, cardiovascular and neurohumoral regulation. The CB consists of glomus (type I) cells synaptically connected to the nerve terminals of petrosal ganglion (PG) neurons and engulfed by sustentacular (type II) cells, where glomus cells are the primary transduction loci and PG neurons convey chemosensory activity to the central nervous system (Fig. 1). In response to hypoxia, hypercapnia and acidosis, chemosensory discharges in the carotid sinus nerve increase [15,16,24]. The most accepted model of chemoreception proposes that transduction of natural stimuli

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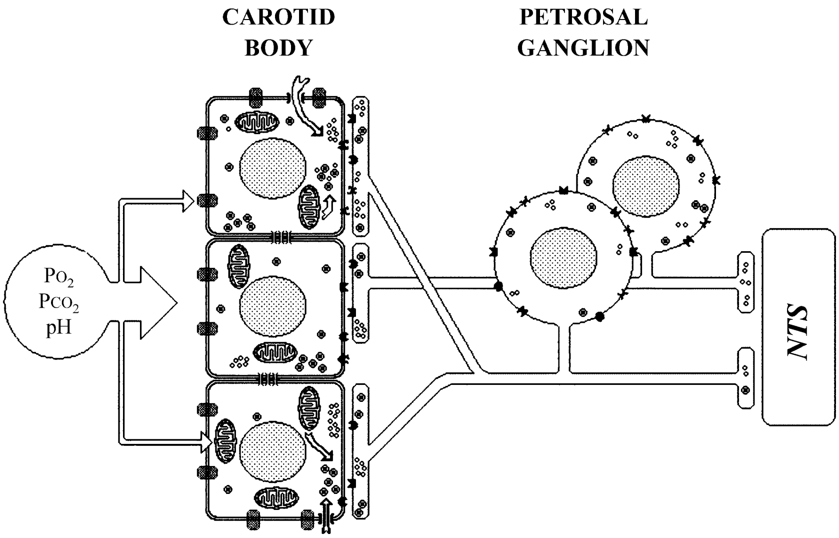

Fig. 1. Arterial chemical stimuli (PO_2, PCO_2, pH) act on carotid body glomus (type I, receptor) cells, through both membrane and mitochondrial transduction mechanisms. The transduction process(es) induces an intracellular [Ca^{2+}] increase, mediated by Ca^{2+} influx through voltage-dependent calcium channels and/or Ca^{2+} release from intracellular stores. This Ca^{2+} increase mediates the exocytotic release of one or more transmitters that bound to specific membrane receptors located on the sensory terminals of petrosal ganglion neurons. The resulting chemoafferent activity is conveyed through the carotid sinus nerve to the relay nucleus in the central nervous system: the nucleus tractus solitarius.

by glomus cells increase its intracellular [Ca^{2+}], which mediates the exocytotic release of one (or more) transmitter(s). This transmitter, acting on specific post-synaptic receptors, increases the rate of discharge in nerve fibers of PG neurons projecting to the CB [16,24]. Glomus cells contain several molecules, such as catecholamines, acetylcholine (ACh), adenosine nucleotides and peptides, that are candidates to act as excitatory transmitters in the junctions between glomus cells and nerve terminals [15,24]. A high degree of co-localization for amine-synthesizing enzymes (tyrosine hydroxylase, dopamine-β-hydroxylase and choline acetyltransferase), and substance P and met-encephalin have been found in the glomus cells of cat CB [55]. Therefore, it is likely that glomus cells store and release more than one excitatory transmitter in response to natural stimuli. In this review, we will examine this possibility, focusing on the role played by ACh, adenosine 5′-triphosphate (ATP) and dopamine (DA) in CB chemoreception, with special emphasis on the their possible interactions.

2. Acetylcholine

ACh meets most of the criteria to be considered an excitatory transmitter between the glomus cells and the nerve terminals [19]. ACh is present in the CB and its content remains unchanged after the section of the carotid sinus nerve [17] or the removal of the superior cervical ganglion [25]. Choline acetyltransferase, the enzyme responsible for ACh synthesis, is localized in rat [42], cat and rabbits glomus cells [54], and a high affinity, sodium-dependent choline uptake mechanism has been reported in the cat CB [54]. Moreover, the cat CB in vitro releases ACh in response to electrical stimulation [14], and in response to hypoxia and hypercapnia [19,20,22,47]. Exogenous application of ACh to the CB increases chemosensory discharge in a dose-dependent manner in most species, with the exception of the rabbit where ACh depresses the chemosensory activity in vivo [12] and in vitro [15]. In the cat, the excitatory effect of ACh is mimicked by nicotinic agonists and is blocked by nicotinic antagonists, such as hexamethonium and mecamylamine [14], while the depression appears to be mediated by muscarinic receptors [21]. Immunocytochemical studies have shown the presence of both α4 and α7 subunits of the nicotinic ACh receptor in cat glomus cells and PG neuron terminals and perikarya [27,48].

Sensory neurons perikarya share several properties with its peripheral endings [23,35,38]. Thus, we studied the responses elicited in the carotid sinus nerve and glossopharyngeal branch by local application of CB putative transmitters to the cat and rabbit PG ganglion in an in vitro preparation [1,4,7]. Using this preparation, we assessed the effects of ACh and nicotine applied to the PG on the evoked antidromic nerve activity in both carotid sinus nerve and glossopharyngeal branch. The application of ACh to the cat PG selectively increases the antidromic neural discharge in the carotid sinus nerve in a dose dependent-manner (Fig. 2A), but ACh has little or no effect on the neurons projecting through the glossopharyngeal branch. The response presents a high degree of temporal desensitization, is reversibly blocked by mecamylamine (Fig. 2A) and hexamethonium [1,4], and is mimicked by nicotine [1] but not by bethanecol. The sensitivity of the response increases in the presence of neostigmine, an inhibitor of the ACh metabolizing enzyme acetyl-cholinesterase [57]. ACh induces sim-

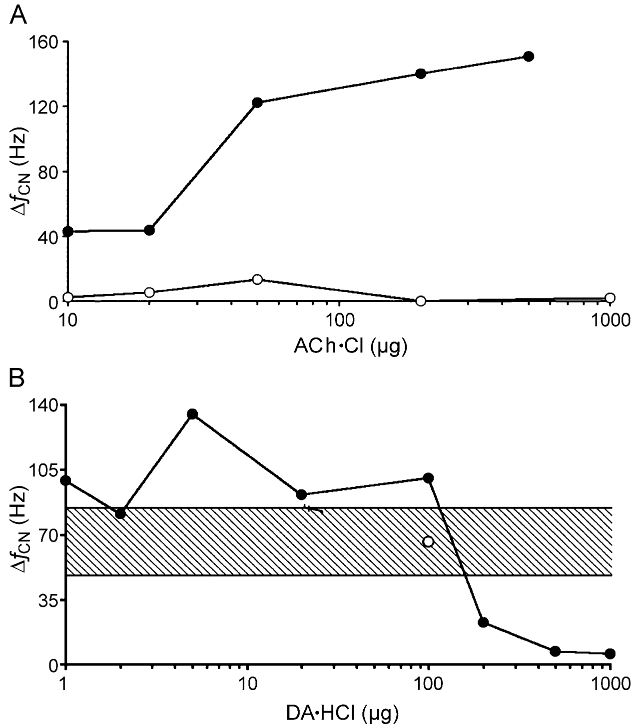

Fig. 2. Increases in carotid nerve frequency discharge (Δf_{CN}) induced by ACh applied to the petrosal ganglion. (A) Dose–response relationship in control conditions (filled circles) and during superfusion with the cholinergic receptor antagonist mecamylamine (100 μM; empty circles). (B) Responses induced by ACh (100 μg) preceded by increasing dopamine doses (filled circles). Mean (empty circle) and 99% confidence interval (lined area) of the Δf_{CNS} ($n=7$) induced by 100 μg of ACh in control conditions.

ilar responses in the rabbit PG, although little or no desensitization is observed [7]. Despite the fact that the cholinergic muscarinic agonist bethanecol has no effect on the basal activity, it temporarily reduces the responses induced by further applications of ACh in the rabbit [7]. Moreover, the responses induced by ACh are blocked by hexamethonium but enhanced during cholinergic muscarinic block with atropine [7]. Intracellular recordings of cat PG neurons in tissue culture show that application of ACh induces depolarization and spike generation [52] in a large number of neurons. Similarly, whole-cell recordings of rat PG neurons in tissue culture show that ACh induces depolarization (current clamp) and inward currents (voltage clamp), effect mimicked by nicotine and blocked by hexamethonium [59]. In cat PG neurons in culture ACh induces inward, outward or biphasic currents, accompanied by membrane potential changes [49]. Inward currents are partially blocked by specific α4 or α7 ACh receptor subunit antagonists, while outward currents are blocked by 4-aminopyridine and sometimes by atropine [49]. It is noteworthy that about 70% of the cat and rat cultured neurons respond to ACh [52,59], a number that far exceeds the expected population of PG neurons projecting through carotid sinus nerve [15,39]. In the rat, about 50% of PG neurons projecting to the tongue respond to ACh with depolarization [34] indicating that—at least in the rat—this neuronal population is also endowed with ACh receptors. Thus, ACh-induced responses appear confined not only to PG neurons projecting through the carotid sinus nerve. However, species differences can account for the responses evoked by ACh on isolated rat PG neurons projecting to the tongue through the glossophayngeal branch. Similarly, the high incidence of ACh-induced responses recorded in cultured PG neurons suggest that culture conditions could select special subsets of neurons, or culture conditions change the expression of receptors in the soma of the neurons. The above data suggest that PG neurons projecting through the carotid sinus nerve are endowed with nicotinic ACh receptors, and that ACh released from the glomus cells may increase the chemosensory afferent discharge in the carotid sinus nerve. In co-cultures of neonatal rat CB cells and neurons from the petrosal–jugular ganglion complex, neurons juxtaposed to the glomus cells exhibited spontaneous synaptic-like potentials [43,44,58,60]. Hypoxia causes a depolarization of the neurons and an increase in frequency of the synaptic-like potentials and spikes, responses partially and reversibly blocked by hexamethonium [58,60] and mecamylamine [43,58]. Recently, we have characterized the responses of cat PG neurons in an in vitro preparation, where the PG and the CB are excised together and differentially superfused in a two compartment chamber, but remained anatomically and functionally connected through the carotid sinus nerve (PG–CB preparation). In this preparation, identified PG neurons projecting to the carotid body (chemosensory neurons) respond to acidification and flow interruption of the CB medium with increased action potential firing rate, response that is partially blocked by hexamethonium and suramin but completely abolished by joint application of both blockers [53]. Almost 95% of the identified chemosensory neurons were depolarized and fired action potentials when ACh was applied to the ganglion, while none of the PG neurons projecting to the carotid sinus (barosensory neurons) responded to this stimulus. Moreover, about 90% of these ACh-sensitive chemosensory neurons also responded to ATP when it was applied to the ganglion [53].

Thus, the experimental data taken together strongly support the hypothesis that ACh is released in response to hypoxia from the glomus cells and increases the rate of chemoafferent discharge by acting on cholinergic nicotinic receptors in the terminals of PG neurons. The presence of cholinergic muscarinic receptors in PG neurons may be restricted to some species (i.e., rabbit) and participate in the control of the generation of the afferent activity by ACh. However, a major problem to recognize ACh as the unique excitatory transmitter in the CB is that cholinergic antagonists that block the excitatory effect of exogenous ACh, are unable to abolish the excitatory response to hypoxia. Similarly, nicotinic ACh receptor antagonists fail to completely block the neuronal basal discharges as well as the hypoxia-induced neuronal activity [58,60] in co-cultures of rat CB and neurons from the petrosal–jugular ganglion complex, or the acidic- or stop-flow-induced responses in the PG–CB preparation in vitro [53]. Indeed, a cocktail of nicotinic and muscarinic antagonists only partially block the chemosensory response of the CB to hypoxia [21].

3. Adenosine 5′-triphosphate

Large amounts of adenine nucleotides have been found by fluorescence microscopy in glomus cells, stored within specific granules in addition to catecholamines and proteins [10]. Intracarotid injections of adenosine and ATP evoke a dose-dependent increase in chemosensory discharge in the cat CB [40,41,45], but adenine, inosine, guanosine, cytidine and uridine have no appreciable effect on chemoreceptor discharge [41]. These results suggest that ATP exerts its action through its hydrolysis to adenosine 5′-monophosphate or adenosine [41,45,46]. However, in the cat CB perfused in vitro, ATP and the stable analogues α,β-methylene ATP (α,β-MeATP) and adenosine 5′-[γ-thio]-triphosphate stimulate the chemosensory discharge with similar dose-dependence, whereas adenosine has little effect [50]. Nevertheless, responses to adenosine have been recorded in the same preparation of the CB [46]. Continuous ATP infusion for 2 min evokes an initial stimulation of the discharge followed by a decline to baseline [50]. Previous evidence supports the notion that ATP may play a physiological role in the CB.

Recently, we studied the effects of the application of adenosine nucleotides to the isolated cat PG in vitro. ATP induces a brief, dose-dependent, increase in discharges in both the carotid sinus nerve and the glossopharyngeal branch (Fig. 3A). However, in the carotid sinus nerve, the increase in discharges induced by ATP is larger and has a lower threshold than the ones evoked in the glossopharyngeal branch [3]. This response shows little temporal desensitization, is marginally mimicked by adenosine 5′-monophosphate and is not modified by Reactive Blue 2, an antagonist of metabotropic nucleotide receptors (P2Y). In rat PG neurons in tissue culture, voltage-clamp recordings show that ATP induces a fast, dose-dependent, partially inactivating current, effect mimicked by α,β-MeATP and blocked by suramin, in a dose-dependent manner [58]. At resting membrane potential ($V_m = -60$ mV) ATP induces an inward current, whose amplitude is reduced when the cell is depolarized, and reverses in direction for positive membrane potential values [58]. The pharmacological and kinetic properties of ATP-induced responses in rat PG neurons suggest that these neurons express ionotropic ATP receptors (P2X), probably a $P2X_{2,3}$ heteromultimer [58]. Immnostaining with antibodies against the P2X receptor subunits show that $P2X_2$ and $P2X_3$ subunits are present in PG neurons perikarya and peripheral processes within the carotid body [44,58]. It is noteworthy that in co-cultures of rat carotid body and PG neurons, basal activity of spontaneously active neurons, as well as hypoxia- and hypercapnia-induced responses are reduced by suramin [44,58]. Moreover, similar effects are obtained with hexamethonium and mecamylamine blockage [43], while the application of both suramin and hexamethonium produce an almost complete blockage of both the basal and the hypoxia induced activity [58]. All the above data suggest that ATP, alone or in conjunction with other transmitters, may participate in the generation of chemoafferent activity.

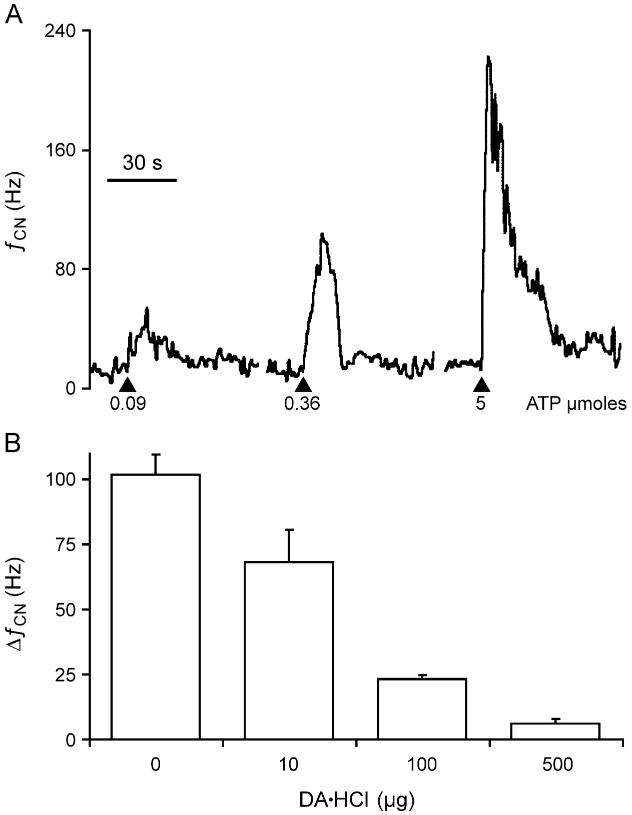

Fig. 3. Increases in carotid nerve frequency discharge (f_{CN}) induced by ATP applied to the petrosal ganglion. (A) Increases in f_{CN} induced by increasing ATP doses. (B) Responses induced in a single preparation by ATP (900 nmoles) when preceded by increasing dopamine (DA) doses.

Using the whole-cell technique we recorded the action potentials (current-clamp) or ionic currents (voltage-clamp) evoked by electrical stimulation, and the responses evoked by ACh and ATP on isolated cat PG neurons in tissue culture. Under voltage-clamp, ATP induces a dose-dependent inward current that presents partial desensitization, while ACh induces a fast inactivating inward current. About half of the neurons responded to both ACh and ATP, and a vast majority responded to ATP or ACh (60–80%). In current-clamp recordings, ATP and ACh depolarized the neurons and may induce action potentials when threshold level is attained [5]. Our results show that ACh or ATP can activate most PG neurons, with half of the population being depolarized by both putative transmitters.

In the PG–CB preparation, chemosensory neurons respond to acidification and flow interruption of the CB medium with increased action potential firing rate, response that is partially blocked by suramin but completely abolished by joint application of suramin and hexamethonium [53]. Almost 93% of the identified chemosensory neurons were depolarized and fired action potentials when ATP was applied to the ganglion. Moreover, about 96% of these chemosensory neurons also responded to ACh when applied to the ganglion [53].

All preceding evidence indicates that ATP, present in glomus cells, depolarizes and induces firing in PG neurons by acting on ionotropic P2X receptors. Moreover, the activity induced in cat carotid chemosensory PG neurons by acidification and flow interruption, as well as that evoked by hypoxia and hypercapnia in rat reconstituted chemosensory system in tissue culture are partially blocked by nucleotide receptor blockers. Thus, ATP and its receptors appear to be partly involved in the generation of the chemoafferent activity, although other transmitter molecules participate in the generation and/or maintenance of the chemoafferent activity.

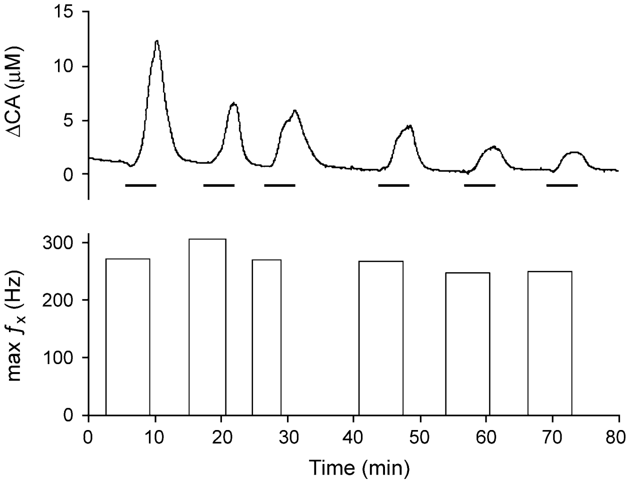

Fig. 4. Effects of repeated hypoxic perfusion (bars, $PO_2 \approx 30$ Torr) on CA effluxes above background and chemosensory discharges in one CB perfused with Tyrode equilibrated with room air plus 5% CO_2. ΔCA, catecholamine efflux. maxf_x, maximal frequency of carotid chemosensory discharges attained during hypoxia.

4. Dopamine

Dopamine (DA) is the predominant catecholamine (CA) synthesized, stored in dense-cored vesicle, and taken-up by glomus cells of several species [24]. The presence of dopaminergic neurons [32,33] as well as mRNA for D2 receptors [8,11] has been shown in a population of PG neurons. The proposition that DA is the excitatory transmitter in the CB was strongly supported by the observation that hypoxia produces CA release from the CB [24] and from isolated glomus cells [51]. In fact, after incubation with [^{3}H]-tyrosine for 2–3 h, the amount of radiolabeled CA (mainly DA) released from rabbit CB superfused in vitro is roughly proportional to the intensity of the hypoxic challenge [18]. However, this method precludes the study of the temporal correlation between the chemosensory excitation and DA efflux induced by the stimuli, since the determination is based on fractions collected for 10 or more minutes. In the cat and rat superfused carotid body, the temporal correlation between CA efflux and chemoreceptor activity elicited by several excitatory stimuli has been studied using amperometric recordings with carbon-fiber microelectrodes, in conjunction with neural recordings [13,28,30,31]. If DA mediates transmission between glomus cells and nerve endings, a close temporal relationship must be expected between DA efflux and chemosensory excitation induced by stimulation, and the maintenance of such relationship upon repeated exposure to the same stimuli. Contrary to this expectation, repeated hypoxic stimulation and NaCN injections progressively reduces the amplitude of CA efflux from the cat CB, although similar increases in discharge are attained [30]. Fig. 4 shows the CA electrochemical responses (upper panel) and the concomitant chemosensory responses (lower panel) induced by repeated hypoxic stimulation of a perfused cat CB in vitro. The amplitude of the chemosensory responses remains highly preserved, but the magnitude of CA efflux is progressively reduced. In addition, mild hypercapnia and nicotine do not consistently release CA, although producing similar increases of chemosensory discharge as hypoxia and NaCN [28,31]. Similarly, repetitive anoxic stimulation results in progressive reductions in CA efflux in the rat CB, while the amplitude of the chemosensory responses remains largely unaffected [13]. Moreover, the exposure of rat CB to moderate hypoxia and repetitive anoxia produce CA releases of comparable amplitude, although the maximum chemosensory responses are significantly reduced in mild hypoxia [13]. It is noteworthy that the peak chemosensory response to hypoxia precedes the corresponding CA peak by 3 min or more. The delayed CA efflux induced by hypoxia in the cat CB in vitro preparation has similar time-course than that elicited by anoxia in the rat CB superfused in vitro [13]. After administration of DA to the CB, both the speed and the amplitude of the following hypoxia-induced CA efflux increase, but the amplitude and rate of rise of the chemosensory response remains the same [28,30]. Thus, after DA application the CA efflux peak precedes the chemosensory peak response, reversing the temporal relation between neural activity and transmitter efflux. Taken together, these observations show a clear dissociation of amplitude and in temporal relation between the chemosensory excitation and CA efflux.

Intracarotid and intravenous injections of exogenous DA produce chemosensory inhibition in most species, but excitation or dual effects have been reported in responses to large doses [15]. In the cat, intracarotid and intravenous injections of DA always produce transient inhibition of chemosensory discharges [29,37], while continuous intravenous infusion of DA decrease the CB responsiveness to

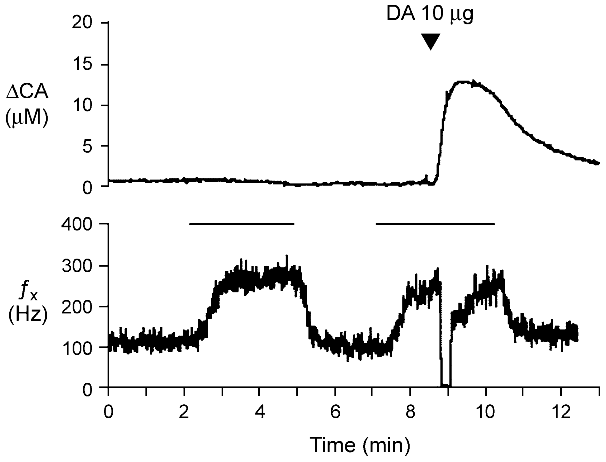

Fig. 5. Effects of a bolus injection of DA (at arrow) during hypoxic stimulation (bars, $PO_2 \approx 30$ Torr) in one CB perfused with Tyrode equilibrated with room air plus 5% CO_2. ΔCA, catecholamine efflux. f_x, frequency of carotid chemosensory discharges.

hypoxia and hypercapnia [36]. These data suggest that DA does not mediate O_2- and CO_2-induced increases in afferent chemosensory activity. Fig. 5 shows the effect of a bolus injection of DA (10 μg) to an in vitro perfused CB during hypoxia. Note that the hypoxia-induced increase in chemosensory discharge is transiently inhibited by the DA bolus. The inhibitory effect of large DA doses on chemosensory activity is blocked or reversed into excitation after block of type 2 (D_2) dopamine receptors [26,29]. Moreover, the D_2 receptor antagonist domperidone produces a sustained increase in chemosensory discharge, and enhances the responses to hyperoxia (100% O_2), hypoxia (100% N_2), and NaCN [29]. Similarly, the dopaminergic antagonist haloperidol potentiates the cat chemosensory responses to hypoxia and hypercapnia [36]. In the goat, the excitatory responses induced by DA can be selectively antagonized by serotonin receptor type 3 (5-HT_3) but not by dopamine receptor antagonists, suggesting that the excitatory action of DA may be mediated by cross activation of serotonin receptors [26]. Injections of DA applied to the superfused cat CB in vitro produce transient inhibition of chemosensory activity, but repeated injections of DA result in desensitization of the inhibitory actions, and even produced late excitatory effects in response to large doses [56]. Taken all together, these data suggest that DA is not acting as the excitatory transmitter between glomus cells and nerve terminals, but as a modulator of the transmitter(s) responsible of the afferent sensory activity. However, a presynaptic inhibitory action on glomus cells Ca^{2+} current cannot be ruled out [9].

Since DA may modulates CB chemosensory activity at the postsynaptic level, we searched for the presence of DA sensitivity at the perikarya of PG neurons in the cat superfused preparation in vitro. Applications of DA to the isolated PG in vitro have no direct effect on the activity recorded from both the carotid sinus nerve and the glossopharyngeal branch [2]. However, when DA is applied prior to ACh, it produces a dose-related modification of the responses induced by ACh (Fig. 2B). Thus, for a given ACh dose, the lowest DA doses potentiate the responses, while the largest doses produce an inhibition of the responses [2]. The inhibitory effect of DA on ACh-induced responses is partly reversed by spiperone [2], a specific blocker of D_2 receptors. In co-cultures of rat CB and PG cells, blockade of D_2 receptors has no effect on basal discharges of spontaneously active neurons or in the hypoxia-induced responses [60]. Similarly, Fig. 3B shows that in the superfused PG in vitro, ATP-induced responses present a dose-dependent reduction in amplitude when DA preceded ATP [6]. These data suggest that DA cannot—per se—initiate chemosensory activity, but if the membranes of peripheral endings and perikarya of PG neurons involved in arterial chemoreception share the same properties, DA can modulate chemosensory sensitivity. In summary, the effects of DA and D_2 receptor antagonist on cat CB chemoreception and PG neurons suggest a modulatory role for DA within the CB [56], but do not support the hypothesis of DA acting as an excitatory transmitter in the cat. However, recently we communicated that, in the rabbit PG in vitro, DA applied to the ganglion induces a dose-dependent increase in the carotid nerve discharge frequency, suggesting an excitatory action of DA on rabbit PG neurons projecting through the carotid nerve [7]. Thus, the differences reported on the actions of exogenously applied DA and its participation on the generation of afferent chemosensory activity may reflect true species differences.

5. Conclusion

Experimental evidence obtained from preparations, like the isolated PG, cultured PG neurons, and co-cultures of PG neurons and CB cells suggest that ACh and ATP could mediate excitatory transmission in the CB. In addition, DA release from the glomus cells appears to act as a modulator of the chemosensory responses in most species, but may play a more critical role in the excitatory transmission in the CB of some species (i.e., rabbit).

Acknowledgements

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References

[1] J. Alcayaga, R. Iturriaga, R. Varas, J. Arroyo, P. Zapata, Selective activation of carotid nerve fibers by acetylcholine applied to the cat petrosal ganglion in vitro, Brain Res. 786 (1998) 47–54.

[2] J. Alcayaga, R. Varas, J. Arroyo, R. Iturriaga, P. Zapata, Dopamine modulates carotid nerve responses induced by acetylcholine on cat petrosal ganglion in vitro, Brain Res. 831 (1999) 97–103.

[3] J. Alcayaga, V. Cerpa, M. Retamal, J. Arroyo, R. Iturriaga, P. Zapata, Adenosine triphosphate-induced peripheral nerve discharges generated from the cat petrosal ganglion in vitro, Neurosci. Lett. 282 (2000) 185–188.

[4] J. Alcayaga, R. Varas, J. Arroyo, R. Iturriaga, P. Zapata, Responses of petrosal ganglion neurons in vitro to hypoxic stimuli and putative transmitters, in: S. Lahiri, N.R. Prabhakar, R.E. Forster II (Eds.), Oxygen Sensing: Molecule to Man, Adv. Exp. Med. Biol., vol. 475, Plenum Press, London, 2000, pp. 389–396.

[5] J. Alcayaga, R. Iturriaga, R. Varas, Petrosal ganglion responses in vitro: from entire ganglion to single cell, in: S. Lahiri, G. Semenza, N.R. Prabhakar (Eds.), Oxygen Sensing: Responses and Adaptation to Hypoxia, Lung Biol. Health Dis., Kluwer Press, London, 2003, pp. 671–683.

[6] J. Alcayaga, M. Retamal, V. Cerpa, J. Arroyo, P. Zapata, Dopamine inhibits ATP-induced responses in the cat petrosal ganglion in vitro, Brain Res. 966 (2003) 283–287.

[7] J. Alcayaga, C.R. Soto, J. Arroyo, Responses of rabbit petrosal ganglion to carotid body putative transmitters, Program No. 826.2. 2003 Abstract Viewer/Itinerary Planner, Washington, DC: Society for Neuroscience, 2003, Online.

[8] A. Bairam, C. Dauphin, F. Rousseau, E.W. Khandjian, Dopamine D_2 receptor mRNA isoforms expression in the carotid body and petrosal ganglion of developing rabbits, in: P. Zapata, C. Eyzaguirre, R. Torrance (Eds.), Frontiers in Arterial Chemoreception, Adv. Exp. Med. Biol., vol. 410, Plenum Press, London, 1996, pp. 285–289.

[9] A.R. Benot, J. López-Barneo, Feedback inhibition of Ca^{2+} currents by dopamine in glomus cells of the carotid body, Eur. J. Neurosci. 2 (1990) 809–812.

[10] P. Bock, Adenine nucleotides in the carotid body, Cell Tissue Res. 206 (1980) 279–290.

[11] M.F. Czyzyk-Krzeska, E.E. Lawson, D.E. Millhorn, Expression of D2-dopamine receptor messenger RNA in the arterial chemoreceptor afferent pathway, J. Auton. Nerv. Syst. 41 (1992) 31–40.

[12] R.J. Docherty, D.S. McQueen, The effects of acetylcholine and dopamine on carotid chemosensory activity in the rabbit, J. Physiol. 288 (1979) 411–423.

[13] D.F. Donnelly, Chemoreceptor nerve excitation may be not proportional to catecholamine secretion, J. Appl. Physiol. 81 (1996) 2330–2337.

[14] C. Eyzaguirre, P. Zapata, The release of acetylcholine from carotid body tissue. Further study on the effects of acetylcholine and cholinergic blocking agents on the chemosensory discharge, J. Physiol. (Lond.) 195 (1968) 589–607.

[15] C. Eyzaguirre, P. Zapata, Perspectives in carotid body research, J. Appl. Physiol. 57 (1984) 931–957.

[16] C. Eyzaguirre, R.S. Fitzgerald, S. Lahiri, P. Zapata, Arterial chemoreceptors, in: J.T. Shepherd, F.M. Abboud (Eds.), Handbook of Physiology: Sect. 2 The Cardiovascular System, Peripheral Circulation and Organ Flow, American Physiological Society, vol. 3, Williams & Wilkins, Baltimore, 1983, pp. 557–621.

[17] S.J. Fidone, S. Weintraub, W.B. Stavinoha, Acetylcholine content of normal and denervated cat carotid bodies measured by pyrolysis gas chromatography/mass fragmentometry, J. Neurochem. 26 (1976) 1047–1049.

[18] S.J. Fidone, C. Gonzalez, K. Yoshizaki, Effects of low oxygen on the release of dopamine from the rabbit carotid body in vitro, J. Physiol. (Lond.) 333 (1982) 93–110.

[19] R.S. Fitzgerald, Oxygen and carotid body chemotransduction: the cholinergic hypothesis—a brief history and new evaluation, Respir. Physiol. 120 (2000) 89–104.

[20] R.S. Fitzgerald, M. Shirahata, Release of acetylcholine from the in vitro carotid body, in: P. Zapata, C. Eyzaguirre, R. Torrance (Eds.), Frontiers in Arterial Chemoreception, Adv. Exp. Med. Biol., vol. 410, Plenum Press, London, 1996, pp. 227–232.

[21] R.S. Fitzgerald, M. Shirahata, T. Ide, Further cholinergic aspects of carotid body chemotransduction of hypoxia in cats, J. Appl. Physiol. 82 (1997) 819–827.

[22] R.S. Fitzgerald, M. Shirahata, H.Y. Wang, Acetylcholine release from cat carotid bodies, Brain Res. 841 (1999) 53–61.

[23] M.S. Gold, S. Dastmalchi, J.D. Levine, Co-expression of nociceptor properties in dorsal root ganglion neurons from the adult rat in vitro, Neuroscience 71 (1996) 265–275.

[24] C. González, L. Almaraz, A. Obeso, R. Rigual, Carotid body chemoreceptors: from natural stimuli to sensory discharges, Physiol. Rev. 74 (1994) 829–898.

[25] S. Helström, Putative neurotransmitters in the carotid body. Mass fragmentographic studies, Adv. Biochem. Psychopharmacol. 16 (1977) 257–263.

[26] J.K. Herman, K.D. O'Halloran, P.L. Janssen, G.E. Bisgard, Dopaminergic excitation of the goat carotid body is mediated by the serotonin type 3 receptor subtype, Respir. Physiol. Neurobiol. 136 (2003) 1–12.

[27] Y. Ishizawa, R.S. Fitzgerald, M. Shirahata, B. Schofield, Localization of nicotinic acetylcholine receptors in cat carotid body and petrosal ganglion, in: P. Zapata, C. Eyzaguirre, R. Torrance (Eds.), Frontiers in Arterial Chemoreception, Adv. Exp. Med. Biol., vol. 410, Plenum Press, London, 1996, pp. 253–256.

[28] R. Iturriaga, J. Alcayaga, Effects of $CO_2-HCO_3^-$ on catecholamine efflux from the cat carotid body, J. Appl. Physiol. 84 (1998) 60–68.

[29] R. Iturriaga, C. Larraín, P. Zapata, Effects of dopamine blockade upon carotid chemosensory activity and its hypoxia-induced excitation, Brain Res. 663 (1994) 145–164.

[30] R. Iturriaga, J. Alcayaga, P. Zapata, Dissociation of hypoxia-induced chemosensory responses and catecholamine efflux in the cat carotid body superfused in vitro, J. Physiol. (Lond.) 497 (1996) 551–564.

[31] R. Iturriaga, J. Alcayaga, P. Zapata, Lack of correlation between cholinergic-induced changes in chemosensory activity and dopamine release from the cat carotid body in vitro, Brain Res. 868 (2000) 380–385.

[32] D.M. Katz, I.B. Black, Expression and regulation of catecholaminergic traits in primary sensory neurons: relationship to target innervation in vivo, J. Neurosci. 6 (1986) 983–989.

[33] D.M. Katz, J.E. Adler, I.B. Black, Catecholaminergic primary sensory neurons: autonomic targets and mechanisms of transmitter regulation, Fed. Proc. 46 (1987) 24–29.

[34] T. Koga, R.M. Bradley, Biophysical properties and responses to transmitters of petrosal and geniculate ganglion neurons innervating the tongue, J. Neurophysiol. 84 (2000) 1404–1413.

[35] S. Kraske, J.T. Cunningham, G. Hajduczok, M.W. Chapleau, F.M. Abboud, R.E. Wachtel, Mechanosensitive ion channels in putative aortic baroreceptor neurons, Am. J. Physiol. 275 (1998) H1497–H1501.

[36] S. Lahiri, T. Nishino, A. Mokashi, E. Mulligan, Interaction of dopamine and haloperidol with O_2 and CO_2 chemoreception in carotid body, J. Appl. Physiol. 49 (1980) 45–51.

[37] F. Llados, P. Zapata, Effects of dopamine analogues and antagonists on carotid body chemosensory in situ, J. Physiol. (Lond.) 274 (1978) 487–499.

[38] G.C. McCarter, D.B. Reichling, J.D. Levine, Mechanical transduction by the rat dorsal root ganglion neurons in vitro, Neurosci. Lett. 273 (1999) 179–182.

[39] D. McDonald, Morphology of the carotid sinus nerve: II. Number and size of axons, J. Neurocytol. 12 (1983) 373–392.

[40] D.S. McQueen, J.A. Ribeiro, Effect of adenosine on carotid chemoreceptor activity in the cat, Br. J. Pharmacol. 74 (1981) 129–136.

[41] D.S. McQueen, J.A. Ribeiro, On the specificity and type of receptor involved in carotid body chemoreceptor activation by adenosine in the cat, Br. J. Pharmacol. 80 (1983) 347–354.

[42] C.A. Nurse, Localization of acetylcholinesterase in dissociated cell cultures of the carotid body of the rat, Cell Tissue Res. 250 (1987) 21–27.

[43] C.A. Nurse, M. Zhang, Acetylcholine contributes to hypoxic chemo-

transmission in co-cultures of rat type 1 cells and petrosal neurons, Respir. Physiol. 115 (1999) 189–199.

[44] M. Prassad, I.M. Fearon, M. Zhang, M. Laing, C. Vollmer, C.A. Nurse, Expression of P2X2 and P2X3 receptor subunits in rat carotid body afferent neurones: role in chemosensory signalling, J. Physiol. (Lond.) 537 (2001) 667–677.

[45] J.A. Ribeiro, D.S. McQueen, Effects of purines on carotid chemoreceptors, in: D.J. Pallot (Ed.), The Peripheral Arterial Chemoreceptors, Croom Helm, London, 1984, pp. 383–390.

[46] M. Runold, N.S. Cherniack, N.R. Prabhakar, Effect of adenosine on isolated and superfused cat carotid body activity, Neurosci. Lett. 113 (1990) 111–114.

[47] M. Shirahata, Y. Ishizawa, A. Igarashi, R.S. Fitzgerald, Release of acetylcholine from cultured cat and pig glomus cells, in: P. Zapata, C. Eyzaguirre, R. Torrance (Eds.), Frontiers in Arterial Chemoreception, Adv. Exp. Med. Biol., vol. 410, Plenum Press, London, 1996, pp. 233–237.

[48] M. Shirahata, Y. Ishizawa, M. Rudisill, B. Schofield, R.S. Fitzgerald, Presence of nicotinic acetylcholine receptors in cat carotid body afferent system, Brain Res. 814 (1998) 213–217.

[49] M. Shirahata, Y. Ishizawa, M. Rudisill, J.S. Sham, B. Schofield, R.S. Fitzgerald, Acetylcholine sensitivity of cat petrosal ganglion neurons, in: S. Lahiri, N.R. Prabhakar, R.E. Forster II (Eds.), Oxygen Sensing: Molecule to Man, Adv. Exp. Med. Biol., vol 475, Plenum Press, London, 2000, pp. 377–387.

[50] D. Spergel, S. Lahiri, Differential modulation by extracellular ATP of carotid chemosensory responses, J. Appl. Physiol. 74 (1993) 3052–3056.

[51] J. Ureña, R. Fernández-Chacón, A.R. Benot, G. Alvarez de Toledo, J. López-Barneo, Hypoxia induces voltage-dependent Ca^{2+} entry and quantal dopamine secretion in carotid body glomus cells, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 10208–10211.

[52] R. Varas, J. Alcayaga, P. Zapata, Acetylcholine sensitivity in sensory neurons dissociated from the cat petrosal ganglion, Brain Res. 882 (2000) 201–205.

[53] R. Varas, J. Alcayaga, R. Iturriaga, ACh and ATP mediate excitatory transmission in identified cat carotid body chemoreceptor units in vitro, Brain Res. 988 (2003) 154–163.

[54] Z.Z. Wang, L.J. Stensaas, B. Dinger, S.J. Fidone, Immunocytochemical localization of choline acetyltransferase in the carotid body of the cat and rabbit, Brain Res. 498 (1989) 131–134.

[55] Z.Z. Wang, L.J. Stensaas, B. Dinger, S.J. Fidone, The co-existence of biogenic amines and neuropeptides in the type I cells of the cat carotid body, Neuroscience 47 (1992) 473–480.

[56] P. Zapata, Modulatory role of dopamine on arterial chemoreceptors, Adv. Biochem. Psychopharmacol. 16 (1977) 291–298.

[57] P. Zapata, C. Larraín, R. Iturriaga, J. Alcayaga, C. Eyzaguirre, Interactions between acetylcholine and dopamine in chemoreception, in: S. Lahiri, N.R. Prabhakar, R.E. Forster II (Eds.), Oxygen Sensing: Molecule to Man, Adv. Exp. Med. Biol., vol. 475, Plenum Press, London, 2000, pp. 389–396.

[58] M. Zhang, H. Zhong, C. Vollmer, C.A. Nurse, Co-release of ATP and ACh mediates hypoxic signalling at rat carotid body chemoreceptors, J. Physiol. (Lond.) 525 (2000) 143–158.

[59] H. Zhong, C.A. Nurse, Nicotinic acetylcholine sensitivity of rat petrosal sensory neurons in dissociated cell culture, Brain Res. 766 (1997) 153–161.

[60] H. Zhong, M. Zhang, C.A. Nurse, Synapse formation and hypoxic signalling in co-cultures of rat petrosal neurons and carotid body type 1 cells, J. Physiol. (Lond.) 503 (1997) 599–612.