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MOLECULAR PHYSIOLOGY AND O_2 SENSING

FUNDAMENTAL LESSONS FROM BLUNTED CHEMOSENSORY RESPONSE OF CAROTID BODY TO HYPOXIA

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RESUMEN: Respuesta Quimiosensorial Atenuada del Cuerpo Carotídeo a la Hipoxia: Lecciones: Fundamentales

Las células del cuerpo carotideo están conectads sinápticamnete con fibras aferentes individuales, y la despolarización de la célula resulta en incrementos de la $[Ca^{2+}]_i$, de la neurosecreción y de la descarga neural. Se supone que la supresión de la corriente de K^+ por un bajo PO_2 despolariza las células del cuerpo carotideo. Por tanto, una respuesta quimiosensorial atenuada puede brindar una clave para la percepción de O_2 por las celulas insensibles al O_2. Sin embargo la literatura demostró que la depresión de los canales de K^+-O_2 por un bajo PO_2 era normal, si bien las células no se despolarizaban. Además, las fibras sensoriales con respuesta hipóxica atenuada mostraban una respuesta CO_2/H^+ normal o supranormal. Consiguientemente, deberian manifestar una depresión de corriente de K^+ normal o supranormal con estimulos CO_2/H^+ incrementados.

RÉSUMÉ: Réponse chimiosensorielle atténuée du corps carotidien à l'hypoxie : leçons fondamentales.

Les cellules du corps carotidien sont reliées synaptiquement à des fibres afférentes individuelles et la dépolarisation de la cellule entraine l'élévation de $[Ca^{2+}]_i$, de la neurosécrétion et de la décharge neurale. La suppression du courant de K^+ par un PO_2 faible est supposée dépolariser les cellules du corps carotidien. Une réponse chimiosensorielle atténuée peut donc fournir une clé à la perception d'O_2 par les cellules insensibles à l'O_2. Cependant, la littérature montre que la dépression des canaux de K^+ - O_2 par un PO_2 faible était normale, bien que les cellules ne se soient pas dépolarisées. D'autre part, les fibres sensorielles à réponse hypoxique atténuée montraient une réponse CO_2/H^+ normale ou supra-normale. En conséquence, elles devraient manifester une dépression de courant de K^+ normale ou supra-normale avec des stimuli CO_2/H^+ accrus.

Mots-clés : Réponse CO_2/H^+, Accroissement de $[Ca^{2+}]_i$, Canaux de membrane K^+-O_2, Dépolarisation de membrane, Réponse neurale, Réponse à l'O_2.

SUMMARY: Glomus cells are synaptically connected with single afferent fiber, and depolarization of the cell should result in increases of $[Ca^{2+}]_i$, neurosecretion and neural discharge. Suppression of K^+ current by low PO_2 is supposed to depolarize the glomus cells. Therefore, a blunted chemosensory response can provide a clue to O_2 sensing by the cells being insensitive to O_2 But literature showed that K^+-O_2 depression by low PO_2 was normal, although the cells did not depolarize. Also, the sensory fiber with blunted hypoxic response showed a normal or supernormal CO_2/H^+ response. Accordingly, they should manifest normal or supernormal K^+ current depression with raised CO_2/H^+ stimuli.

Key words: CO_2/H^+ response, : $[Ca_2^+]$ rise, K^+-O_2 membrane channels, membrane depolarization, neurosecretion, neural response, O_2 response

INTRODUCTION

Blunted response of carotid chemosensory discharge to hypoxia occurs in nature (1-8), a phenomenon which can provide a clue to fundamental mechanisms of O_2 sensing. Since O_2 sensing is based upon K^+ - O_2 channels of carotid body typeI glomus cells (9-11), blunting of

chemosensory discharge should be associated with the appropriate cellular responses. Also, the same fiber of carotid body responds to hypoxia and a rise in CO_2/H^+ (12) as the same K^+ channel responds to both the stimuli (13). These ideas are presented in the following postulated model, cell to chemosensory discharge (Fig. 1). Hypoxia and CO_2/H^+ cause K^+ current depression, depolarizing the glomus cell and opening the voltage gated Ca^{2+} channels. Extracellular Ca^{2+}, whose concentration is 10^6-10^7 greater than intracellular Ca^{2+}, then enters which activates neurosecretion and neural discharge. This is the main mechanism which has been postulated. There is also mechanism for mitochondrial depolarization which can release intracellular Ca^{2+} Also, a rise of $[H^+]i$ can increase $[Ca^{2+}]i$ by way of $[Na^+]$ rise first and then by exchange with $[Ca^{2+}]e$. K^+ current will be the focus of the discussion that follows revealing some gaps in our knowledge.

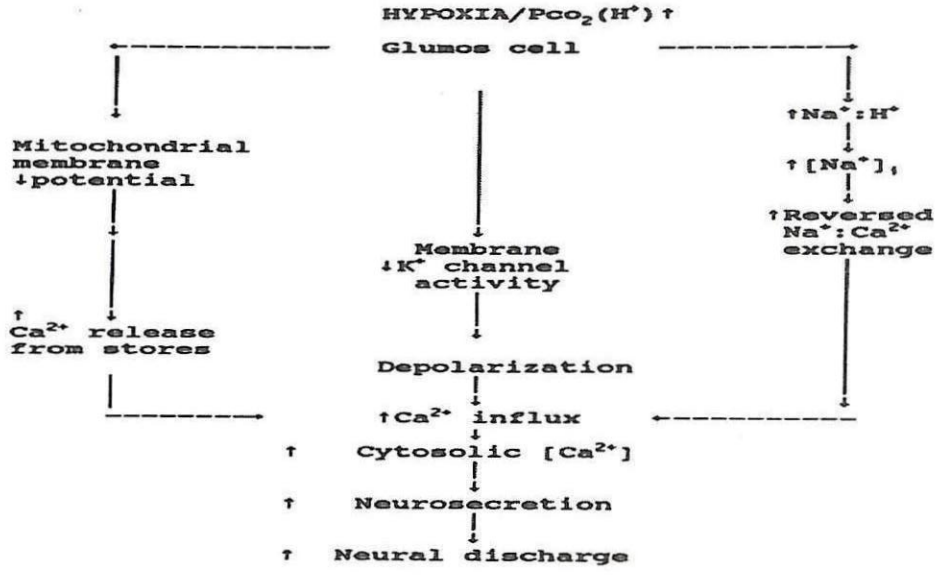

Figure 1. The postulated mechanisms for hypoxic and CO_2/H^+ stimuli in glomus cells. Note that K+ current is common to both stimuli.

HYPERTROPHY OF GOMUS CELLS AND INCREASES DOPAMINE CONTENT DURING CHRONIC HYPOXIA

Chronic exposure to hypoxia is followed by hypertrophy of glomus cells, and presumably stay that way as long chronic hypoxia persists (14,15). So is the dopamine content of the cell. However, chemosensory discharge increases first (16-18), and then becomes blunted (14). What makes the sensory response blunted is the question. We will see that K^+ channels that are sensitive to O_2 remain intact, although glomus membrane depolarize (5). many questions can be asked. What was the oxygen of the cells; what are the pathways by which the cells become hypertrophied, and like?.

EFFECT OF CHRONIC HYPOXIA: CHEMOSENSORY DISCHARGE AUGMENTS HYPOXIC RESPONSE

It is well known that chronic hypoxia causes hypertrophy of type I glomus cell of the carotid body (14,15). It is also well accepted that O_2 sensitive K+ conductance is depressed by low PO_2 (9-11). This K^+ current, however, is similarly depressed in cells which are exposed to chronic hypoxia (11). But the cells from the hypoxic rats being larger, K^+ channel density was decreased at all activating test potentials. This would tend to support the observations that chronic hypoxia initially increased hypoxic sensitivity of chemosensory discharge (16-18). This increastd discharge rate is illustrated in Fig. 2.

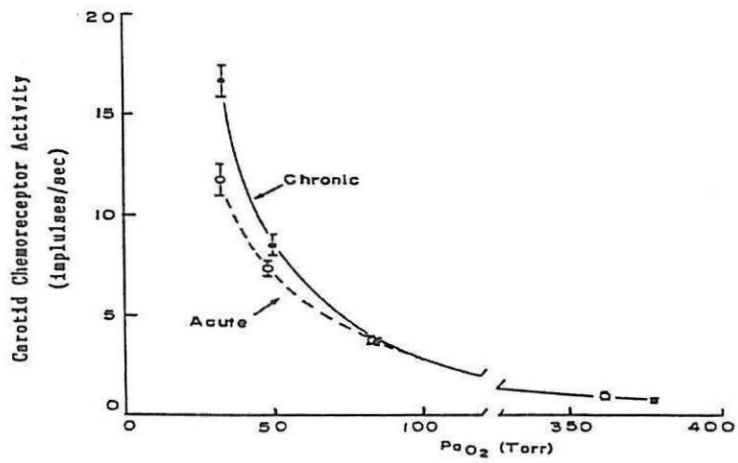

Figure 2. Cat carotid chemosensory response to hypoxia. Responses from normal (acute) and chronically hypoxic cats are compared (from Barnard et al., 1987. Ref. 16).

BLUNTED HYPOXIC RESPONSE IN CHRONIC HYPOXIA

On the other hand, prolonged hypoxia in humans (1,2) can give rise to blunted respiratory response to hypoxia. Now it is found in animals also (3,4), and glomus cell from the carotid of these animals can provide a clue as to O_2 sensing if K^+-O_2 channels is the basis of it. That is, inhibition of K^+ channels by hypoxia leads to depolarization and increased excitability of glomus cells sufficient to activate voltage-gated Ca^+ channels and neurotransmitter release and neural discharge. However, experimenting with such glomus cells from ventilatory response to hypoxia Wyatt et al. (5) found that K^+-O_2 channels were intact (see Fig. 3) but the cells failed to depolarize. That also means, that these cells would not show a rise of $[Ca^{2+}]i$ and neurotransmitter release. These experiments have not been done. However, these showed low K+ channel density, and should have shown increased sensory response to hypoxia. Instead, these cells did not depolarize and would show a chemosensory response to hypoxia.

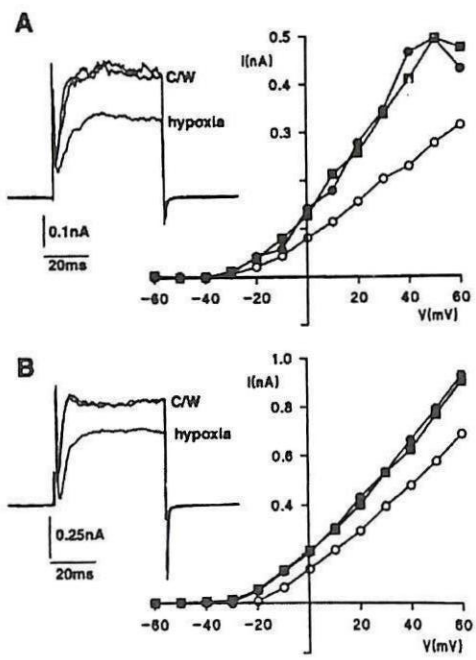

Figure 3. Effect of acute hypoxia on whole-cell K^+ currents in type I cells isolated from normoxically reared and chronically hypoxically reared neonatal rats, as measured by using the perforated-patch technique. (A) I-V relationships obtained from a type I cell isolated from a normoxically reared neonatal rat before (•), during (O), and after (•) exchange of normoxic perfusate to a hypoxic perfusate (PO_2 between 12 and 20 mmHg). (Inset) Example traces obtained from the same cell under the same three conditions (C, control; W, wash; test potential,

+20 mV). (B) Experiment identical to that in A, but in this case the K^+ currents were obtained from a hypoxically reared neonatal rat. In A and B the holding potential was - 70 mV.

Response to $C0_2/H^{\pm}$

According to the model of cellular chemoreception, (see Fig. 1) K^+channel is common to both O_2 and CO_2/H^+. Thus, when K^+-O_2 channel is insensitive, CO_2/H^+ effect should also desensitize. This experiment also has not been done.

Effects of chronic hyperoxia: blunted hypoxic but supernormal CO^2/H^+

Another testing model is the carotid body of chronically hyperoxic cats in which both ventilation and carotid chemosensory discharge are insensitive to hypoxia but it is sensitive to hypercapnia (6-8). Fig. 4 shows an illustration. Hypoxia (A) failed to elicit a response, whereas (B) initial hypercapnia manifested a huge response with an overshoot.

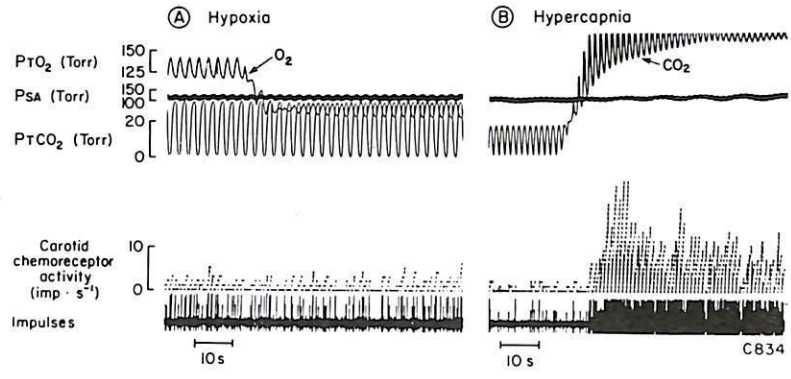

Figure 4 Blunted hypoxic chemosensory response (A) and normal Co2 response (B) of carotid body of cats which has been exposed to prolonged hyperoxia

Blunting of hypoxia but not CO_2 response of chemosensory discharge by inhibitor oxidative phosphorilation.

The blunting of chemosensory response to hypoxia but not to CO_2/H^+ occurred in oligomycin treatment of carotid body (19,20). This mimicked the foregoing responses to chronic hyperoxia.

In summary, carotid chemosensory fiber while showing a normal or super normal response to CO_2/H^+ can manifest a blunted response to hypoxia. This blunting is seen in the glomus membrane depolarization being insensitive to hypoxia whereas K^+-O_2 channel appears normal. Co_2/O_2 response of these cells is not known but K^+ channel depression and membrane depolarization are expected as the rise in sensory discharge.

In perspective, these cells with blunted hypoxic response should not show a response to $[Ca^{2+}]i$ and nourosocrotion.

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