Is $K_v$ channel inhibition a common path to hypoxic pulmonary vasoconstriction?

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See article by Hogg et al. [1] (pages 349–360) in this issue.

1. $K_v$ channels and hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV), a vasomotor mechanism that matches regional perfusion to ventilation, is initiated by depolarization of the membrane potential of pulmonary arterial smooth muscle cells (PASMC). There are still many debates as to which factor(s) is(are) responsible to induce membrane depolarization [2]. Voltage-gated potassium channel ($K_v$), calcium-activated potassium channel ($K_{Ca}$), release of intracellular calcium, change of intracellular redox potential or other factors are candidates. However, the most probable candidate for membrane depolarization so far is the inhibition of voltage-gated potassium channels ($K_v$) which leads to opening of voltage-gated calcium channels, and then to vasoconstriction [3]. The $K_v$ channels conduct an outward current which is slowly inactivating, and which is blocked by the $K_v$ inhibitor 4-aminopyridine (4-AP) but not by inhibitors of Ca$^{2+}$- or ATP-sensitive $K_v$ channels.

The $K_v$ channel family is very diverse and nine families of $K_v$ channels are recognized from cloning studies, each with subtypes. In addition, further diversification is afforded by heteromultimeric tetramerization and alternative splicing of some $K_v$ channels [4]. At least seven $K_v$ channel subfamilies mRNA were detected in pulmonary arterial smooth muscle (Kv1.1, Kv1.2, Kv1.3, Kv2.1, Kv2.2, Kv2.3, and Kv3.1b). Among them, several candidate channels have been proposed to initiate HPV, based on electrophysiological and pharmacological similarities between their characteristics in expression systems and properties of the hypoxia-sensitive $K^+$ currents in pulmonary arterial smooth muscle cells (e.g. $K_{v1.2}$, $K_{v1.5}$, $K_{v2.1}$ and $K_{v3.1b}$). Cloning and expression of homomeric $K_{v1.2}$, $K_{v1.5}$ and $K_{v2.1}$ channels revealed that they all display slowly inactivating or non-inactivating $K_v$ currents that are sensitive to block by 4-AP. Both $K_{v1.2}$ and $K_{v1.5}$ have been shown to be charybdoxin (CTX)-insensitive, whereas $K_{v2.1}$ shows some inhibition to low concentration of CTX [5]. It was recently shown that $K_{v3.1b}$ channels are present in pulmonary arterial smooth muscle cells [6]. Although the hypoxic sensitivity of $K_{v3.1b}$ has been shown in expression systems, its role in HPV is unknown. $K_{v3.1b}$ channels display greater sensitivity to TEA than does the endogenous IK of pulmonary arterial smooth muscle cells. It is generally thought that $K_{v2.1}$ and $K_{v1.5}$ are strong candidate for the initiation of hypoxic depolarization of PASMC. Hogg et al. [1] showed again that $K_{v2.1}$ channels play a pivotal role in mediating HPV. They detected $K_{v2.1}$ channel mRNA using reverse transcription-polymerase chain reaction (RT-PCR) and $K_{v2.1}$ channel proteins with immunohistochemistry in small pulmonary arteries of the rat. Anti-$K_{v2.1}$ antibody within the pipette attenuated IK by 67% at +50 mV and hypoxia in the presence of the antibody did not affect the magnitude of IKV.

2. $K_{v1.5}$ vs. $K_{v2.1}$

Different genes can produce $K_v$ channels with similar electrophysiological properties. Hypoxic inhibition of $K_{v2.1}$ channel is established [1,7,8]. Hypoxia reversibly inhibited $K_{v2.1}$ current. However, the inhibition occurs usually at the depolarized region, not in the voltage range of physiological membrane potentials. The problem is worse in case of $K_{v1.5}$. The results depended upon the laboratories. Human and rat $K_{v1.5}$ were not inhibited by hypoxia [7]. On the
other hand, HPV was impaired in mice lacking the voltage-gated potassium channel K\textsubscript{v1.5} [9]. Pulmonary arterial smooth muscle cells in mice lacking K\textsubscript{v1.5} had less hypoxia-sensitive IK than wild-type cells and depolarized less to hypoxia. However, there was still hypoxia-sensitive K current and membrane depolarization. This was associated with some residual HPV in isolated lungs from mice lacking the voltage-gated potassium channel K\textsubscript{v1.5} [9]. This residual HPV might come from K\textsubscript{v2.1} [1]. Further studies are needed using mice lacking both K\textsubscript{v1.5} and K\textsubscript{v2.1}. In fact there were reports about heterotetramerization of K\textsubscript{v} channel subfamilies. The K\textsubscript{v1.2}/K\textsubscript{v1.5} and K\textsubscript{v2.1}/K\textsubscript{v9.3} heterotetramers were inhibited by hypoxia [7,8]. The heteromeric channels are inhibited by hypoxia in the voltage range of the resting membrane potentials. Other heterotetramers of K\textsubscript{v} channel subfamilies are expected to be shown as a candidate for HPV in the near future.

3. Do K\textsubscript{v} channels need O\textsubscript{2} sensor?

Hypoxic inhibition of K channels has been shown to be a membrane-delimited process [10], which occurs in the pulmonary arterial smooth muscle itself [6]. While the K\textsubscript{v} channels in pulmonary arterial smooth muscle cells are the effectors of HPV, it is uncertain whether they are intrinsically O\textsubscript{2}-sensitive or are under the control of an O\textsubscript{2} sensor. Certain K channels are rich in cysteine, and respond to the local redox environment, tending to open when oxidized and close when reduced [11,12]. O\textsubscript{2}-responsive tissues may have unique oxygen sensors that provide the proximal signal linking pO\textsubscript{2} to K\textsuperscript{+} channel gating. While HPV was shown to be impaired in mice lacking the voltage-gated potassium channel K\textsubscript{v1.5} [9], homeric K\textsubscript{v1.5} channels are not sensitive to hypoxia when expressed in mouse L-cells [7]. COS cells or MEL cells [6]. Currents recorded from cloned K\textsubscript{v2.1} channels were reversibly inhibited by hypoxia, but the hypoxic response was detected in 99 and 56% of cells examined when expressed in mouse L-cells [7] and COS-7 cells [8], respectively.

NADPH oxidase is present in phagocytes, pulmonary arterial smooth muscle cells, carotid body type 1 cells, neuroepithelial bodies, and endothelial cells. It includes a membrane-bound flavocytochrome containing two subunits, gp91 phox and p22 phox, and the cytosolic proteins p47 phox and p67 phox, which bind to the flavocytochrome to form the active enzyme complex. NADPH oxidase was suggested as the O\textsubscript{2} sensor in pulmonary airway chemoreceptor [13]. Hypoxia (pO\textsubscript{2} = 15–20 mmHg) reversibly inhibited K currents (46%) in wild type cells whereas hypoxia had no effect on K current in oxidase-deficient cells. However, O\textsubscript{2} sensor in pulmonary arterial smooth muscle cells was preserved in mice lacking the gp91 phox subunit of NADPH oxidase [14]. Considering that there are other types of NADPH oxidase, further studies are needed for the roles of the other NADPH oxidases.

4. Other channels or factors?

There are also non-K\textsubscript{v} channels that respond to hypoxia in other O\textsubscript{2}-responsive tissues. (1) L-type Ca channel was modulated by redox agents and hypoxia when stably expressed in HEK cells [15]. (2) TASK-like background potassium channel was considered as a candidate for O\textsubscript{2} sensor in rat arterial chemoreceptor cells [16]. (3) Large conductance Ca\textsuperscript{2+}-dependent K channel was modulated by O\textsubscript{2} in a membrane-restricted manner [17]. It might be fair not to rule out the other channels considering the roles of ion channels in mediating HPV. And also there are still many important questions (O\textsubscript{2} sensor molecule, role of intracellular calcium release, and involvement of endothelium etc.) to be answered.

References

coexpression in HEK293 cells confers O₂ sensitivity to Kv4.2 but not to Shaker channels. J Gen Physiol 1999;113:897–970.

