Oxygen sensing by ion channels

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Abstract

The ability to sense and react to changes in environmental oxygen levels is crucial to the survival of all aerobic life forms. In mammals, specialized tissues have evolved which can sense and rapidly respond to an acute reduction in oxygen and central to this ability in many is dynamic modulation of ion channels by hypoxia. The most widely studied oxygen-sensitive ion channels are potassium channels but oxygen sensing by members of both the calcium and sodium channel families has also been demonstrated. This chapter will focus on mechanisms of physiological oxygen sensing by ion channels, with particular emphasis on potassium channel function, and will highlight some of the consensuses and controversies within the field. Where data are available, this chapter will also make use of information gleaned from heterologous expression of recombinant proteins in an attempt to consolidate what we know currently about the molecular mechanisms of acute oxygen sensing by ion channels.

Introduction

A characteristic common to all cells is the ability to drive and maintain ionic gradients across their plasma membranes. The primary point of gradient generation is the ubiquitously expressed Na+/K+-ATPase (the ‘sodium pump’),

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which is responsible for pumping out of the cell three sodium ions in exchange for two potassium ions during a single enzymatic cycle as one molecule of ATP is hydrolysed. The continued and tightly regulated activity of this pumping system generates opposing sodium and potassium gradients across the plasma membrane of cells, the potential energy of which is harnessed by numerous integral plasma membrane transporters and ion channels in order to co-ordinate the cell-specific processes which define cellular phenotype. Of particular note, and common to all eukaryotic cells, is the rapid diffusion of potassium across the plasma membrane through potassium-selective channels, with the physiochemical consequence that a negative transmembrane potential develops at rest, termed the $E_m$ (resting membrane potential). The magnitude of the resting potassium permeability (in the absence of any marked change in the potassium gradient) is the single most important regulator of $E_m$ in most excitable and non-excitable cells. It follows therefore, that any factors which directly affect cellular potassium permeability will have a dramatic influence on the $E_m$ and excitability of cells. One factor which has emerged in recent years as an important regulator of potassium permeability is the availability of molecular oxygen.

Excitable cells, by definition, do more than maintain their $E_m$ at between $-40$ and $-80$ mV. Rather, they have the ability to generate action potentials, a process which is characterized by a rapid loss of their negative $E_m$ as the action potential upstroke is generated by the rapid diffusion of sodium into the cell down its chemical gradient through specialized, voltage-dependent sodium channels. This drives the $E_m$ briefly to potentials approaching the equilibrium potential for sodium. Such cell depolarization increases the membrane permeability of a third cation, calcium. Influx through VGCCs (voltage-gated calcium channels) has a profound effect on numerous cellular processes including vesicular neurotransmitter release and muscle contraction. Cells then repolarize as voltage-dependent sodium channels close through inactivation and voltage-dependent potassium channels open, promoting potassium flow out of the cell again. As for the $E_m$, it follows that factors affecting this orchestrated opening and closure of voltage-dependent ion channels will have a dramatic impact on the electrical characteristics of excitable cells and their biochemical sequelae. Again, one such factor is the availability of oxygen.

To date, the activity of specific members of almost all ion channel families have been shown experimentally to be regulated by acute changes in the $PO_2$ (partial pressure of oxygen). However, in many cases (such as central neuronal potassium channels, neuronal sodium channels and cardiac sodium channels) these effects are likely to reflect a pathological response to oxygen deprivation, such as is experienced in stroke or myocardial infarction, and so will not be discussed in detail here (but see [1] for further details). Instead, this chapter focuses primarily on proposed mechanisms of physiological oxygen-sensing by ion channels and outlines the consensuses and controversies which surround a number of worked examples. In so doing, this draws on data obtained from
ion channels expressed natively in tissues classically thought of as oxygen-sensing, whose function it is to regulate whole organism oxygen levels (such as the carotid body and vascular smooth muscle). In addition, data are drawn from tissues not normally associated directly with oxygen-sensing, but whose responses to hypoxia can still be considered as a physiological rather than a pathological phenomenon (such as T-lymphocytes). Where available, it also makes use of information gleaned from heterologous expression of recombinant proteins in an attempt to consolidate what we currently know about the molecular mechanisms underlying the important process of acute oxygen sensing by ion channels.

The role of oxygen-sensing ion channels in physiology

The first definitive demonstration of acute oxygen-sensing by any ion channel came from the groundbreaking work of Lopez-Barneo et al. [2]. This seminal work demonstrated the reversible inhibition of a specific potassium conductance in rabbit carotid body glomus cells. Such potassium channel inhibition was proposed to account for glomus cell depolarization, voltage-dependent calcium influx and consequent neurotransmitter release during hypoxia. Thus hypoxic inhibition of potassium channels is central to the carotid body chemoreflex that initiates the increased ventilatory response in the face of reduced arterial $P_{O_2}$. In addition to the carotid body-derived response to systemic hypoxaemia, airway hypoxia evokes vasoconstriction in the pulmonary vascular bed, thus shunting blood away from poorly ventilated alveoli. Although controversial, there is a large body of evidence to suggest that oxygen-sensing, particularly by potassium channels, is central to this vasoconstrictor response (see Chapter 5). Even more contentious is a role for pulmonary neuroepithelial bodies of the lung in the oxygen-sensing. Neuroepithelial bodies (and cellular models thereof) certainly express oxygen-sensing potassium channels and release serotonin during hypoxia. Furthermore, they exhibit an innervation pattern characteristic of other pulmonary receptors even though their physiological function remains somewhat elusive. Oxygen-sensing potassium channels have also been implicated in processes as diverse as control of catecholamine release from the fetal adrenal medulla and T-lymphocyte activation. As hypoxia is evoking ventilatory compensation and pulmonary vasoconstriction, several other vascular beds begin to dilate in order to optimize oxygen delivery to important vascular beds such as the cerebral and coronary circulations; such vasodilatation is dependent upon hypoxic inhibition of a specific member of the VGCC family.

Oxygen-sensing by potassium channels

Potassium channels represent the largest and most diverse of the ion channel families, but can be subdivided according to the structure of their pore-forming $\alpha$-subunits. The most commonly described are represented in Figure 1, alongside a list of oxygen-sensitive examples which are dealt with in more detail below.
Shaker channel family

Oxygen-sensing by members of the *shaker* family of potassium channels (termed KCNAx) has been implicated in the physiological responses to hypoxia in the carotid body, pulmonary arterioles, T-lymphocytes and chromaffin cells. KCNA1 (Kv1.1) null mice show a greater hypoxic ventilatory response and larger carotid sinus nerve discharge during hypoxia than do the wild-type controls. KCNA1 is expressed in the carotid body, petrosal ganglion cells and the nucleus of the tractus solitarius, all constituent parts of the afferent limb of peripheral chemosensory reflexes. The molecular nature of this hypersensitivity is not clear but since there has been no demonstration of ‘innate’ oxygen sensitivity of KCNA1, the simplest explanation is that its absence may simply evoke an increase in excitability by bringing chemosensory cells closer to threshold [3]. KCNA2 (Kv1.2) has been shown to be oxygen-sensitive in PC12 cells [4] and, when expressed in combination with KCNA5 (Kv1.5), is inhibited by hypoxia in pulmonary arteriolar smooth muscle [5]. KCNA3 (Kv1.3) is involved in T-lymphocyte activation. When co-expressed with the Src tyrosine kinase, KCNA1 is inhibited by hypoxia [2], which may explain its role in oxygen-sensing.

**Figure 1. Known oxygen-sensitive potassium channels**

The cartoon depictions at the left of the figure represent generic and predicted topologies of the three known families of potassium channel proteins known to be inhibited by acute hypoxia. On the right of the figure the molecular identity of each individual potassium channel is shown along with the three methods of classification. These are, from left to right, the HGNC (Human Genome Name Classification), the IUPHAR (International Union of Pharmacology) classification and the initial drosophila classification (Other).
kinase, Lck, KCNA3 becomes oxygen-sensitive and is inhibited by hypoxia, in part explaining why lymphocyte proliferation/activation is impaired in low oxygen environments, such as tumours [6]. KCNA5 is oxygen-sensitive when overexpressed in pulmonary arterial myocytes [although not in mesenteric arterial myocytes or HEK (human embryonic kidney) cells] suggesting that a pulmonary-specific interaction with this channel is required to confer oxygen sensitivity [7]. KCNA6–10 have not been shown to be sensitive to acute hypoxia although there is a suggestion that a splice variant of KCNA7 may have the potential for such sensing in the heart [8].

Shab channel family
Of the two known shab potassium channel members (termed KCNBx), only KCNB1 (Kv2.1) has been shown to be oxygen sensitive in certain tissues and cell types. Although there are reports that this channel is inhibited by hypoxia in pulmonary smooth muscle [9], it seems likely that it requires co-expression of the silent KCNS3 (Kv9.3) subunit [5,10].

Shaw channel family
KCNC1 (Kv3.1b) has been suggested as the main target of hypoxic inhibition in pulmonary arteriolar smooth muscle by a number of investigators [11,12]. Recombinant KCNC3 (Kv3.3b) demonstrates oxygen sensitivity and this is maintained when natively expressed in the putative airway oxygen-sensing tissue, the neuroepithelial bodies [13], where the upstream sensing system requires free radical generation (in this case hydrogen peroxide) by the membrane-localized NADPH oxidase [14]. KCNCx family members are the primary oxygen-sensing potassium channels in the mouse carotid body [15], showing that species (or even strain) differences are important when considering the integrated effect of hypoxia on a particular tissue or reflex (see below for information regarding oxygen-sensitive potassium channel identities in the carotid bodies of other species).

Shal channel family
To date, oxygen-sensing by shal potassium channel members (termed KCNDx) has been only demonstrated in the rabbit carotid body. Inhibition by hypoxia of KCND1 (Kv4.1) and KCND3 (Kv4.3), either as homomers or heteromers, appears to account for the rabbit glomus cell chemosensitivity [16]. Although KCNC channel members have been excluded from the list of oxygen-sensitive channels in the carotid body isolated from normal rabbits, a recent report [17] suggests that congestive heart failure evokes a remodelling of the glomus cell potassium channel expression pattern. The resultant differential down-regulation of KCNC4 (Kv3.4) results in chronic glomus cell depolarization, which amplifies the effect of hypoxic inhibition of KNCD1/3 and explains the consequent augmentation of the hypoxic chemoreflex in congestive heart failure [17].
Kv β-subunits
It has long been appreciated that activity of the pore-containing Kv α-subunits (KCNA-D, above) is known to be modulated by co-expression with Kv β-subunits (Kvβx). Such modulatory activity may well include the conference of oxygen-sensitivity to Kv channels. For example, recombinant KCND2 (Kv4.2) is only able to respond to hypoxia when it is co-expressed with Kvβ1.2 [18] whilst Kvβ1.2 and Kvβ1.3 confer oxygen-sensitivity to KCNC1 in the pulmonary vasculature [11].

Tandem P domain potassium channel family
Members of the tandem P domain potassium channel family (termed KCNKx) are major determinants of $E_m$ and regulators of cellular excitability as they are characteristically open at potentials around the $E_m$. Recombinant KNCK3 (also known as TASK1) is inhibited by hypoxia in HEK-293 cells [19] and a native KCNK3-like current has been implicated in oxygen-sensing of the carotid body [20]. KCNK3, perhaps in combination with KCNK9 (also known as TASK3), underlies the oxygen-sensitive current in the immortalized cellular counterpart of the neuroepithelial body, H146 cells [21]. That KCNK3 almost certainly requires a subsidiary oxygen-sensing system to respond to hypoxia is evidenced by the cell-specificity of its hypoxic inhibition [22], a notion strongly supported in H146 cells [23], native neuroepithelial bodies [14] and recombinant systems [17], where it has been shown that the oxygen sensitivity of this channel is conferred by the activity of an NADPH oxidase enzyme which contains either NOX2 or NOX4 subunits. KCNK3 has also been suggested to play a role in hypoxic pulmonary vascular constriction [24] and hypoxic excitotoxicity of central neurones [25], although the precise mechanisms of action are currently unknown. A further candidate for control of central neuronal excitability is KCNK2 (also known as TREK-1) which is oxygen-insensitive in some circumstances [26] and oxygen-sensitive in others [27]. Where hypoxic inhibition is apparent, it appears dependent upon structural elements within the C-terminus [28]. Recombinant KCNK13 (also known as THIK-1) is inhibited by hypoxia [29] and is expressed in efferent fibres innervating the carotid body [30], suggesting a role in modulation of the chemoreflex.

Large conductance, calcium-activated potassium channels
These channels are variously known as KCNMAx, slo, BKCa and Maxi-K channels. The first demonstration of oxygen-sensing by this channel family came from patch-clamp studies in the rat carotid body glomus cells where hypoxia inhibits the channels [31]. Subsequently, it was demonstrated that both native (carotid body-derived [32]) and recombinant (KCNMA1 [33]) forms of this channel were inhibited by hypoxia in isolated membrane patches but perhaps require another protein to confer full hypoxic inhibition.
Other potassium channels
Several members of the KCNNx (termed SK) channel family have been implicated in hypoxic signal transduction. Hypoxic inhibition of KCN2 (SK2) in prenatal adrenal medulla may contribute to fetal catecholamine release during labour [34]; the postnatal tissue is oxygen-insensitive, presumably due to tonic inhibitory influences of adrenal innervation after birth. Oxygen-sensing by members of the KCNJx (inward rectifiers or Kir) appears to be restricted to the coronary arterial smooth muscle where hypoxia results in current activation via increased production of cAMP and vessel dilatation [35]. This is the only potassium channel known to be activated by hypoxia and such activation has only been seen in a non-pulmonary setting, again suggesting that sensitivity of potassium channels to hypoxia is a tissue-specific phenomenon and serves to reinforce the idea that the nature of the cell-specific protein partners (close or distant from the channel itself) are key to understanding responses to reduced $PO_2$.

Mechanisms of hypoxic channel inhibition
Although a picture has slowly been emerging concerning the increasingly widespread physiological roles of oxygen-sensitive potassium channels in various tissues, the identification of mechanisms to account for such observations has proved more elusive, and certainly more contentious (see [36] for a recent review). Several mechanisms have been proposed, as shown schematically in Figure 2, originating with the idea that redox modulation was key to potas-

Figure 2. Principal proposed mechanisms of oxygen-sensing by potassium channels
Each channel family is depicted by its proposed topology. Haemoxigenase-2 (HO-2) produces biliverdin (BV), iron (Fe) and carbon monoxide (CO) in the presence of molecular oxygen and NADPH. Carbon monoxide is a tonic activator of BK$_{\text{Ca}}$ (KCNMx) and its reduction during hypoxia results in channel closure. The multi-component enzyme complex NADPH oxidase (NOX) produces ROS in normoxia. During hypoxia, ROS production is reduced which evokes either direct channel closure (of KCNKx and KCNA/B/C/D) or produces an indirect effect via augmented GSH:GSSG ratio. Alternatively, ROS from mitochondria may rise and cause channel closure. Reduced mitochondrial electron transport (mito ETC) activity augments the AMP:ATP ratio, activates AMPK and closes channels via AMPK-dependent phosphorylation.
sium channel inhibition by hypoxia. Put simply, this idea suggests that levels of ROS (reactive oxygen species) vary according to oxygen levels, and thereby alter channel activity either directly, or via changes in redox-sensitive molecules such as glutathione. However, there are fundamental issues concerning this idea that currently remain unresolved.

First, what happens to ROS when cells are exposed to hypoxia? This seems a straightforward question, but is highly contested, particularly in the study of hypoxic pulmonary vasoconstriction, where there are compelling arguments that ROS decrease in hypoxia [37], yet substantial alternative data suggest ROS increase in hypoxia [38]. Secondly, what is, or are, the intracellular sources of ROS? Even those authors who disagree about the effects of hypoxia on ROS come together in the belief that oxygen-dependent ROS production originates from mitochondria. However, other sources have been proposed. In particular, hypoxic reduction of ROS by NADPH oxidase has been proposed as a mechanism by which hypoxia inhibits potassium channels in airway neuroepithelial bodies [13,23], a finding which is strongly supported by lack of potassium current inhibition in NADPH oxidase-deficient transgenic mice [14]. However, carotid body chemoreception and hypoxic pulmonary vasoconstriction continues unabated in these mice. To add to the confusion, there is good evidence that hypoxic pulmonary vasoconstriction does not rely on potassium channel inhibition (or, at least, on the voltage-gated calcium entry arising from channel inhibition), but instead depends on release of calcium from intracellular stores. This concept (see Chapter 5) again puts mitochondria in the spotlight as the key to oxygen-sensing, but not via altered ROS production. Instead, subtle changes in the cytoplasmic AMP:ATP ratio have been proposed to activate AMPK (AMP-activated protein kinase), thereby initiating hypoxic pulmonary vasoconstriction. Indeed, AMPK activation may also be important in carotid body chemotransduction since its pharmacological activation mimicked the effects of hypoxia to cause voltage-gated calcium entry [39].

Of the potassium channels expressed in rat carotid body glomus cells, both BK$_{Ca}$ and TASK-like channels demonstrate oxygen sensitivity. The human homologue of the BK$_{Ca}$ channel (termed KCNMA1) is closely coupled to haemoxgenase-2. This enzyme breaks down cellular haem, in the presence of NADPH and molecular oxygen, to produce carbon monoxide, biliverdin and iron. Carbon monoxide is a remarkably potent activator of recombinant [40] and native [32] BK$_{Ca}$ channels of the carotid body and systemic arteriolar myocytes [41]. It appears that the channel-associated haemoxgenase-2 (in both recombinant systems and native glomus cells) confers an increased oxygen sensitivity to the BK$_{Ca}$ channel via acute regulation of the channel activity by its downstream products. Thus, as oxygen availability decreases, carbon monoxide and biliverdin production wanes and channels close [40]. These data concur with those obtained in vitro from sinus nerve recordings in the rat (where nerve activity is augmented by blockers of haemoxgenase [42]) and in vivo from respiratory studies in haemoxgenase-2 knockout mice (where the
hypoxic ventilatory response is blunted [43]). However, recent data obtained in carotid body slices from haemoxygenase-2 knockout mice have suggested that neurotransmitter release during hypoxia is unaffected by haemoxygenase-2 gene deletion [44]. It is not clear why these studies are different from each other although it may be pertinent that the mouse carotid body primarily uses KCNCx channels (not KCNMx channels) to sense hypoxia [15], and even this species-specificity is not consistent amongst different mouse strains [45].

At present, it seems reasonable to conclude that multiple mechanisms may exist to account for modulation of potassium (and other) ion channels by hypoxia (Figure 2). Indeed, more than one mechanism may be present in the same cell. However, this field clearly requires further exploration, and some fundamental issues remain to be resolved. In addition, clarification is needed concerning the role of specific mechanisms in physiologically relevant oxygen-sensing processes. There is clearly a long way to go.

**Structural requirements for oxygen-sensing by ion channels**

Despite the widespread interest in mechanisms of oxygen-sensing by ion channels, little attention has been paid to the structural requirements of ion channels for such sensing. This is perhaps surprising, given the wealth of structure/function studies in the literature. Nevertheless, some interesting advances have been made. Whilst the research community was examining the role of hypoxic potassium channel inhibition in mediating pulmonary vasoconstriction, the intrinsic oxygen-sensing properties of systemic vascular smooth muscle (which dilates under hypoxia) were being investigated. Lopez-Barneo and co-workers [46] reported that L-type calcium channels were reversibly inhibited in isolated smooth muscle cells from various systemic vascular beds in a manner that was voltage-dependent and associated with a slowing of activation kinetics. This work was rapidly extended to account not only for systemic vasodilation, but also the dilating effects of hypoxia on pulmonary conduit (rather than resistance) vessels [47,48]. Shortly following these reports, an indistinguishable effect was reported on recombinant human L-type calcium channels expressed in HEK-293 cells [49]. Importantly, this study [49] employed the major pore-forming, voltage-sensing \( \alpha_{5C} \) subunit of the calcium channel (Cav1.2, CACNA1C), in the absence of auxiliary subunits. This immediately discounted an important role for other subunits of the calcium channel complex. Subsequent exploration of the mechanisms underlying hypoxic inhibition of calcium channels have not been forthcoming. However, insight into the structural requirements for oxygen-sensing have arisen from comparison of the three splice variants of this channel: variation occurs at a single site in the cytoplasmic C-terminal domain of the channel (Figure 3A), where an insert of 71 residues is either omitted or replaced with a shorter, structurally unrelated insert. Of these, only channels possessing the 71 amino acid insert were sensitive to hypoxia (Figure 3A).
Figure 3. Structural requirements for oxygen-sensing by two ion channels

(A) Cartoon of the four domains (I–IV) of the α-subunit of a voltage-gated calcium channel, each consisting of six transmembrane α-helices. The boxed area (shaded blue) in the cytoplasmic C-terminal domain represents the region of splice variation. Below the schematic of each variant is a time series plot, illustrating the calcium current amplitude evoked by successive step depolarizations from −80 mV to +10 mV (100 ms duration, 0.1 Hz). For the period indicated by shading, the cell (in each case, a HEK-293 cell transfected with the relevant splice variant) was exposed to a reduction of PO₂ from ~150 mmHg to ~20 mmHg. Reproduced from [51] Fearon, I.M., Varadi, G., Koch, S., Isaacsohn, I., Ball, S.G. and Peers, C. (2000) Splice variants reveal the region involved in oxygen sensing by recombinant human L-type Ca²⁺ channels. Circulation Research 87, 537–539, with permission from Lippincott, Williams and Wilkins. (B) Cartoon of the predicted topology of two potassium channels, KCNA2 (Kv1.2; left, blue) and KCNB1 (Kv2.1; centre, grey) along with a chimera of the two channels (right; relevant sections shaded accordingly). Below each cartoon is a time series plot, illustrating the potassium current amplitude evoked by successive step depolarizations from −80 mV to +50 mV (applied every 15 s). For the periods indicated by shading, the cell (in each case, a Xenopus oocyte, injected with the appropriate cRNA 24 h previously) was exposed to anoxia (0 mmHg oxygen). Reprinted from [51] Biochem. Biophys. Res. Commun. 306, Conforti, L., Takimoto, K., Petrovic, M., Pongs, O. and Millhorn, D., The pore region of the Kv1.2α subunit is an important component of recombinant Kv1.2 channel oxygen sensitivity, 450–456, (2003), with permission for Elsevier.
Mutagenesis studies revealed that the oxygen-sensing region resided in the proximal 39 residues of this insert [50].

At present, such information has not been applied systematically to studies of structural requirements of potassium channels for oxygen-sensing. However, one study has employed chimaeras to reveal that oxygen-sensitivity of recombinant, homomeric KCNA2 is dependent upon an interaction within the channel pore region (see Figure 3B). Thus, oxygen-sensitivity was conferred to the apparently oxygen-insensitive homomeric KCNB1 (Kv2.1) by splicing into it the S5–S6 region of KCNA2 [51]. This study also revealed that a redox-sensitive methionine residue within the oxygen-sensing region of Kv1.2 was not involved in hypoxic responses. However, it should be noted that hypoxic inhibition of the Kv1.2/2.1 chimaera was, unlike inhibition of Kv1.2 itself, irreversible. Nevertheless, this study remains the most detailed investigation of structural requirements of potassium channels for oxygen-sensing to date.

**Conclusion**

The ability of potassium and calcium channels to sense and react to acute alteration in $P_O_2$ is central to the homoeostatic function of cell-types as diverse as T-lymphocytes, vascular myocytes and neurones. The expression of oxygen-sensitive ion channels and the molecular mechanism(s) underpinning how each responds to acute hypoxia is both species and cell-specific. Moreover, it is becoming increasingly clear that the ability to sense oxygen is bestowed upon many ion channels by cell-specific protein partnerships and/or functional association with cell signalling cascades. Clearly, discovering how differential expression of these microenvironments and signalling networks is controlled within each cell type represents a significant challenge in the 21st century. That said, the ability of a particular cell-type to respond appropriately to an acute hypoxic stimulus is crucial to survival and it is, therefore, no surprise that a significant redundancy might exist in the oxygen-sensing systems. In that way, organisms will always have at least one mechanism that can be relied upon to ensure optimal performance during periods of oxygen deprivation.

**Summary**

- Oxygen levels regulate the activity of numerous ion channels, strongly influencing their physiological activity.
- Regulation of ion channels by oxygen can account for the effects of hypoxia in specific tissues, particularly chemoreceptors.
- A number of different mechanisms have been put forward to account for hypoxic regulation of ion channels, but opinions remain divided as to their relative importance.
- The structural requirements of ion channels for oxygen-sensing has not been studied in depth, and represents an important area for future research.
References


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