Oxidation of potassium channels by ROS: a general mechanism of aging and neurodegeneration?

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A wealth of evidence underscores the tight link between oxidative stress, neurodegeneration and aging. When the level of excess reactive oxygen species (ROS) increases in the cell, a phenomenon characteristic of aging, DNA is damaged, proteins are oxidized, lipids are degraded and more ROS are produced, all culminating in significant cell injury. Recently we showed that in the nematode, Caenorhabditis elegans, oxidation of K+ channels by ROS is a major mechanism underlying the loss of neuronal function. The C. elegans results support an argument that K+ channels controlling neuronal excitability and survival might provide a common, functionally important substrate for ROS in aging mammals. Here we discuss the implications that oxidation of K+ channels by ROS might have for the mammalian brain during normal aging, as well as in neurodegenerative diseases such as Alzheimer’s and Parkinson’s. We argue that oxidation of K+ channels by ROS is a common theme in the aging brain and suggest directions for future experimentation.

ROS play a key role in the aging process

Oxygen metabolism leads to the synthesis of reactive oxygen species (ROS), molecules that play important roles in cell signaling. If unchecked, ROS can diffuse within the cell and begin to oxidize a variety of essential components, including lipids, ribonucleic acids and proteins. From these facts arose the idea that, as time progresses, slow leakage of diffusible ROS causes cellular wearing and eventually death [1]. Applied to the nervous system, this idea has been invoked to explain the loss of cognitive, sensory and motor function characteristic of senescence (reviewed in Ref. [2]).

Neurons exist to store and convey information in the form of electrical impulses generated by ion channels. There are several examples showing that ROS can indirectly modulate channel function by acting on the cell pathways that regulate gene transcription, trafficking, turnover and proteasomal degradation (reviewed in Ref. [3]). However, because ROS can also interact directly with and modify ion channels (Table 1), it seems obvious to point to oxidation of channels by ROS as one of the culprits for neuronal aging. And yet, despite the fact that the free-radical theory was proposed a long time ago, and while ROS have been shown to act as modulatory molecules of ion channels in several physiological processes (Table 1), until recently no supporting evidence had been presented in support of a role of channel oxidation in aging [4]. Once again an invertebrate organism has provided the key to capture the essence of the problem. KVS-1 is a Caenorhabditis elegans voltage-gated K+ channel that operates in a subset of neurons (amphid chemosensory neurons) mediating the animal’s ‘taste’ for soluble molecules (chemotaxis) [5]. As in mammals, where taste has played a key role during evolution, this sensory function is very important for the worm because C. elegans track the bacteria on which they feed by sensing the by-products of bacterial metabolism – salts, vitamins, amino acids, and other chemicals [6]. A transgenic worm harboring a KVS-1 variant resistant to oxidative modification (Cys to Ser at position 113, C113S-KVS-1) was generated and its gustatory function was monitored over time [4]. In aging C113S-worms, the decline in gustatory function was significantly lessened compared to that of controls because the lack of oxidative modifications of KVS-1 acted to preserve the normal excitability of the sensory neurons (Figure 1). Furthermore, reducing agents could ‘rejuvenate’ old neurons in wild-type animals by reversing the modifications in the KVS-1 current caused by ROS, thereby restoring normal excitability. The fact that age-related oxidation of a K+ channel underlies a specific type of neuronal aging in C. elegans provides a paradigm for understanding neuronal aging in mammals. While this concept can be applied generally to many ion channels (Table 1), we limit our discussion to cases involving oxidation of K+ channels because comprehensive treatment of the subject would go beyond the scope of this review (an extensive review of the topic can be found in Ref. [7]). The extremely high genetic and functional diversity of K+ channels, unmatched by other types of channels, places these channels (by statistical probability alone) as primary targets of ROS. Therefore, in the reminder of this article, we critically review the role of K+ channel oxidation by age-related leakage of ROS in the mammalian brain, and in both normal and disease states. We argue that ROS-mediated oxidation of K+ channels is a recurring theme in the aging nervous system and is intrinsically involved in certain neuropathies.
Oxidation of K⁺ channels in brain during normal aging

The hippocampus is the part of the limbic system responsible for long-term memory and spatial orientation. In rodents, lower primates and presumably humans, particular hippocampal neurons become more excitable when the animal passes through a specific place in their environment. The presence of these ‘place cells’ in the hippocampus suggests that this part of the brain might act as a cognitive map in which its neurons ‘switch on’ every time the animal recognizes a specific location in the map – ‘a neural representation of the layout of the environment’ [8]. Hippocampal neurons fire bursts of action potentials separated by periods of quiescence (reviewed in Ref. [9]). The periods of activity are associated with a progressive rise in intracellular calcium that leads to cellular after-hyperpolarization (AHP). Three characteristic AHPs are observed: a fast AHP (fAHP, lasting ~5 ms) between consecutive action potentials, and medium (mAHP, lasting ~50 ms) and slow AHP (sAHP, lasting several seconds) between bursts of action potentials [10]. All three AHPs play crucial roles in learning tasks because an increase in the duration of each reduces excitability. For example, rabbits can be trained to blink conditionally in response to a sound by initially pairing the sound to a puff of air in the eye (eye-blink conditioning), and learning this task is associated with a decrease in the sAHP [11]. Interestingly, the amplitude of the sAHP is increased in old rabbits compared with young animals but, when the old animal learns eye-blink conditioning, a decrease in the mAHP follows [12]. Pharmacological and animal models (i.e. knockout mice) studies have shown that the mAHP is mainly produced by potassium currents conducted by small conductance KCa (SK) channels [13,14]. It was shown that upregulation of a SK isoform (isoform 3) that is expressed in hippocampus CA1 pyramidal neurons causes age-related memory loss in mice [15], and this loss can be compensated by cannulating old mice with oligonucleotide antisense against SK3. In this case, age-dependent changes in the activity of a K⁺ channel are responsible for a physiological process underlying a loss of cognitive function associated with senescence.

By contrast, ROS levels increase in the aging brain [16], suggesting that oxidative stress could be a significant damaging factor. In support of this idea, hippocampus-mediated learning is improved in aging rodents overexpressing superoxide dismutase, a strong anti-oxidant [17]. These findings, in addition to the fact that ROS, in C. elegans, can act directly to modify a voltage-gated K⁺ channel and, as a consequence, neuronal excitability, argue that K⁺ channels might generally provide physiologically important substrates for ROS in the aging mammalian brain.

Another example of K⁺ channels that could be affected by ROS are found in CA1 hippocampal neurons: large-conductance Ca²⁺-activated K⁺ (BK) channels control the fAHP, and also contribute to the repolarization of the action potential [10,18–22]. The shorter the fAHP, the higher the frequency at which the neuron fires; therefore possible that oxidation of these channels by ROS is a damaging factor. In support of this idea, hippocampus-mediated learning is improved in aging rodents overexpressing superoxide dismutase, a strong anti-oxidant [17]. These findings, in addition to the fact that ROS, in C. elegans, can act directly to modify a voltage-gated K⁺ channel and, as a consequence, neuronal excitability, argue that K⁺ channels might generally provide physiologically important substrates for ROS in the aging mammalian brain.

### Table 1. Oxidative modifications of ion channels and physiological relevance*

<table>
<thead>
<tr>
<th>Channel</th>
<th>Oxidative modification</th>
<th>Physiological role</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERG</td>
<td>Accelerate activation</td>
<td>Heart remodeling?</td>
<td>[72,73]</td>
</tr>
<tr>
<td>Kv1.5</td>
<td>Accelerate activation, right shift in voltage activation, current increase</td>
<td>May be involved in initiation or perpetuation of atrial fibrillation.</td>
<td>[74]</td>
</tr>
<tr>
<td>ShakerB/C</td>
<td>Slow down inactivation</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Kv7.2, Kv7.4, Kv7.5</td>
<td>Enhance current</td>
<td>Cytoprotection and neuronal silencing during hypoxia</td>
<td>[76]</td>
</tr>
<tr>
<td>Kv1.4</td>
<td>Slow down inactivation</td>
<td>?</td>
<td>[41]</td>
</tr>
<tr>
<td>Kv1.4-Kv1β</td>
<td>Slow down inactivation</td>
<td>?</td>
<td>[38]</td>
</tr>
<tr>
<td>A-type K⁺ channel in rat DRG neurons</td>
<td>Slow down inactivation</td>
<td>Adjustment of pain sensitivity?</td>
<td>[77]</td>
</tr>
<tr>
<td>Kv1.7</td>
<td>Accelerate inactivation</td>
<td>?</td>
<td>[78]</td>
</tr>
<tr>
<td>BK</td>
<td>H₂O₂ eliminates physiological activation</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>Upregulates channel activity</td>
<td>Modulates mitochondrial ROS production in neutrophils, thereby favoring the function of these cells as anti-inflammatory</td>
<td>[80]</td>
</tr>
<tr>
<td>KATP</td>
<td>H₂O₂ activates K⁺, activity</td>
<td>Insulin, dopamine release</td>
<td>[59,81]</td>
</tr>
<tr>
<td>Naᵥ</td>
<td>Thiol oxidizers inhibit sodium currents. Methionine oxidation slows down inactivation</td>
<td>?</td>
<td>[82,83]</td>
</tr>
<tr>
<td>L-type calcium channel</td>
<td>Oxidation of -SH groups alters gating</td>
<td>?</td>
<td>[85]</td>
</tr>
<tr>
<td>CLC-0</td>
<td>Alters inactivation gating</td>
<td>?</td>
<td>[86]</td>
</tr>
<tr>
<td>CLC-1</td>
<td>Promotes the formation of a functional dimer</td>
<td>?</td>
<td>[84]</td>
</tr>
</tbody>
</table>

*Ion channels known to be modified by ROS in vitro and the presumed physiological relevance of the oxidative regulation.
opposite functional effects. Oxidation of three intracellular methionines results in increased channel activity [25], whereas oxidation of cysteines is inhibitory [26,27]. There is however evidence that, in native CA1 pyramidal neurons as well as in heterologous expression systems, generic oxidants act to enhance the activity of BK channels [28](presumably by oxidizing both types of residues). It follows that oxidation of BK channels by ROS during aging would render BK channels more active, lower the firing frequency of hippocampal neurons, and therefore might affect certain cognitive functions.

As mentioned above, the AHP is crucially dependent upon the net surplus of Ca²⁺ ions that enter the cell and that are cleared out during periods of intense neuronal activity. Another type of redox-dependent current, the rapidly activating–inactivating K⁺ (A-type, Iₐ) current, indirectly contributes to the AHP by enhancing Ca²⁺ influx through a process known as spike-frequency broadening [29]. During periods of intense activity, Iₐ channels in CA1 pyramidal neurons become progressively unavailable because the interval between two spikes becomes shorter than the time it takes for these channels to recover from inactivation. This cumulative inactivation of Iₐ channels delays the repolarization of the action potential, increasing the net influx of Ca²⁺. Generally, A-type currents are conducted by complexes formed by a voltage-gated pore-forming subunit (members of the Kv1, Kv2, Kv3 and Kv4 subfamilies are expressed in the hippocampus; Refs. [30–35]) and accessory subunits belonging to various families, including Kvβ, KCNE, DPPX and KChIPs, that endow many properties of their respective pore-forming subunits, including inactivation, voltage-dependence and trafficking to the plasma membrane (reviewed in Ref. [36]). When the gene encoding the Kvβ1.1 subunit – that is expressed in the hippocampus [37,38] – was deleted (knockout of the pore-forming subunit in mice is associated with seizures), the spike-frequency broadening was reduced and the sAHP was not augmented [29] because channels lacking the Kvβ1.1 subunit inactivate slowly [39]. The AHP-dependent spatial abilities of the knockout animal were not impaired, even though the mice were unable to retain certain long-term memories, and were conserved during aging, presumably because the increase in the sAHP was modest [40]. Evidence shows that IA channels, such as those expressed in the hippocampus, can be modified by ROS [41–43]. Oxidation of these channels results in slowed inactivation and increased open channel current, and both modifications would dampen neuronal excitability. Thus, a reasonable scenario would predict that the impact on behavior of oxidation of Iₐ by ROS during aging would resemble that of knocking out Kvβ1.1 – an amelioration of functions such as spatial orientation and impairment with respect to memory storage. It is also interesting to note that regulation of IA channels by ROS appears to be evolutionarily conserved: as with mammalian channels, oxidizing agents slow down inactivation of KVS-1, thereby converting KVS-1 from an A-type to a delayed-rectifier-type of current [4]. Most notably, Cys113 is conserved in Kv2.1 (Cys77), the mammalian K⁺ channel gene most closely related to KVS-1 and, furthermore, when the amounts of Kv2.1 current are reduced (as in the C. elegans case) cortical neurons are protected from oxidant-induced apoptosis in vitro [44].

Figure 1. Oxidation of voltage-gated K⁺ channel KVS-1 by ROS is a cause of sensory function loss in C. elegans. Young C. elegans worms can easily localize a spot (yellow) containing a chemical attractant such as biotin. Chemotaxis is primarily mediated by the amphid ASE neurons (in the figure the right ASE neuron is depicted in color). In young worms, ROS levels are low (denoted by blue coloration) and ASE excitability is normal (typical voltage responses to input currents are shown in the inset). As the animal ages, the net surplus of ROS increases (denoted by red coloration), also leading to altered ASE excitability through oxidative modification of KVS-1 channels. As a result, chemosensory function is progressively impaired in aging worms. Exposure to oxidizing agents (e.g. hydrogen peroxide; chloramine-T) also affects chemotaxis through oxidation of KVS-1 channels, thereby recapitulating the effects of aging.
Oxidation of K⁺ channels and neurodegenerative disease

We have so far discussed the impact that oxidation of K⁺ channels by ROS could have on cognitive function during aging. We now examine the pathological consequences of this process. According to our hypothesis, oxidation of K⁺ channels by ROS might be a leading cause of neurodegenerative disease, including Alzheimer’s and Parkinson’s (Figure 2). The first neuropathology that we consider, Alzheimer’s disease (AD), is characterized by progressive loss of cognitive function leading to confusion, mood swings, language breakdown, long-term memory loss, withdrawal and eventual death (reviewed in Ref. [2]). At the cellular level, this neuropathology is characterized by the formation of β-amyloid plaques, and of neurofibrillary tangles of hyperphosphorylated tau, that begins in the hippocampus and spreads to other areas of the brain (reviewed in Ref. [2]). BK channels are responsible for the depressed postsynaptic activity observed in the CA1 region of the hippocampus of mouse models of AD such as the TgCRND8 mouse [45]. The fact that this depression can be relieved either by specific blockers of BK channels (charybdotoxin, paxilline) or by calcium chelators (BAPTA-AM) further indicates that BK channels are more active in the neurons of TgCRND8 mice. This is further corroborated by single-channel analysis showing that the BK unitary conductance is significantly upregulated (from 44% to 78%) compared to controls, an effect that is partially compensated by a decrease in a medium (~113 pS) conductance in a similar proportion (from 30% to 3%) [46]. Electrophysiological recordings from human hippocampal neurons are not available. However, medium conductance is decreased in fibroblasts of human patients with AD, but there were no significant changes in the BK conductance [47,48]. Another study came to opposite conclusions: using Rb⁺ flux measurements it was found that BK currents were downregulated in platelets of AD donors [49] (K⁺ channels are permeable to Rb⁺ and a radioactive isotope, ⁸⁶Rb⁺, was therefore used to measure K⁺ flux). Thus, while increased BK channel activity in hippocampal neurons is a phenotypic hallmark of AD mouse models, it is not clearly defined whether this is the case in human patients. This naturally raises the key question as to the mechanism underlying the modification of BK channel function and, once again, the evidence points to oxidative stress as the likely culprit. In fact, oxidative stress is a well-established cause of AD preceding and later stimulating the formation of β-amyloid plaque (reviewed in Ref. [2]). This in turn increases the net surplus of ROS [50,51] in a type of autocatalytic process (β-amyloid clogs the mitochondrial protein import machinery, causing mitochondrial dysfunction and impaired energy metabolism, inhibiting cytochrome oxidase activity, and thus increasing free-radical generation). The increased availability of ROS in mouse models of AD could therefore explain why the BK channels are more active – they are more extensively oxidized than in normal mice. Furthermore, β-amyloid has been shown to upregulate multiple types of K⁺ channels both directly and indirectly. The β-amyloid precursor protein (APP) activates BK channels through a pathway mediated by cGMP and protein dephosphorylation [52], whereas mature β-amyloid increases Kv1, Kv4 and Kv3 currents [53–56] (the latter is also subject to the effects of oxidation; Ref. [57]) through direct interactions. Hence, multiple K⁺ currents, essential to normal neuronal excitability, are upregulated directly or indirectly by interaction with amyloid peptide and, possibly, by ROS overproduced during the etiology of the disease. This concerted action results in reduced excit-
ability and therefore learning and memory impairment, but might have a more profound neurotoxic effect, including death, a possibility discussed below.

Parkinson’s disease (PD) is a movement disorder characterized by irreversible loss of motor skills, speech and other functions (reviewed in Ref. [2]). At the cellular level, Parkinson’s disease arises as a consequence of a chronic lack of dopamine caused by the selective loss of dopaminergic (DA) neurons in the pars compacta region of the substantia nigra (SN) and their projections in the striatum. Hydrogen peroxide ($H_2O_2$) is a component of the signaling pathway that mediates the release of dopamine in DA neurons. Levels of diffusible $H_2O_2$ increase in response to glutamatergic activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, adenosine triphosphate K+ (KATP) channels open in response, and these hyperpolarize the synapse and thus inhibit the release of dopamine [58,59]. A strong link between KATP channels and Parkinson’s disease was established when it was shown that genetic ablation of the pore-forming subunit (Kir6.2) of the KATP channel inhibits dopaminergic degeneration in two mouse models of PD: the weaver mice and normal mice subject to chronic administration of the DA neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [60]. The active metabolite of MPTP, 1-methyl-4-phenylpyridinum (MPP+), is an inhibitor of the mitochondrial complex 1, a key component of the mitochondrial electron-transport chain, suggesting a possible involvement of ROS in the chronic activation of KATP channels in PD. In fact, both MPP+ and other inhibitors of complex I increase KATP activity in SN neurons of normal mice. Most importantly, the effects of these inhibitors were suppressed by mild uncoupling of the mitochondrial respiratory chain by either pharmacological agents or by overexpression of uncoupling protein-2 (UCP-2). Mitochondrial uncoupling proteins uncouple ATP synthesis from oxygen consumption in mitochondria, thereby reducing the production of ROS [60,61]. Because in normal conditions the release of dopamine is inhibited by the production of diffusible $H_2O_2$, one could argue that Parkinson’s disease is the result of a physiological mechanism gone awry.

Nevertheless, the evidence at hand rules out this simplistic model – complex I inhibitors fail to trigger KATP activation in the presence of superoxide dismutase mimetics (an enzyme that catalyzes the reaction of superoxide into $H_2O_2$), ruling out the involvement of $H_2O_2$. This raises the intriguing possibility of a direct interaction of ROS with KATP channels in PD. In other words, under physiological conditions, $H_2O_2$ acts as a signaling molecule to modulate dopamine release via the activation of KATP channels, while in Parkinson’s disease direct interactions with other ROS are likely to be responsible for the chronic activation of the channel, and the two mechanisms are probably uncoupled. This could also explain why DA cells show a differential vulnerability to the progression of the disease: subpopulations in the SN are lost, whereas subpopulations in the neighboring ventral tegmental area (VTA), and their projections in the ventral striatum, survive [62]. In VTA, KATP channels are not chronically activated presumably as a consequence of the fact that mitochondrial respiration is uncoupled in these cells, which therefore have the natural ability to buffer ROS [60] (Figure 2).

It must be emphasized that Parkinson’s disease might not be the only condition in which reduced excitability leads to neuronal death. Enhancements of K+ currents have been described in several neuronal populations undergoing apoptosis [44,63–65] and, in particular, chronic inhibition of excitability through the ectopic expression of Kir1.1 is lethal to cultured hippocampal neurons [66]. This observation, together with the fact that addition of β-amyloid peptide to cholinergic neurons correlates with a significant increase (>50%) in K+ currents and death [63], would suggest that one of the causes of neuronal loss in AD might be related to oxidation-mediated enhancement of K+ currents. Thus, chronic neuronal silencing mediated by activation of K+ channels might represent a general mechanism of neurotoxicity in the brain. It is quite reasonable to assume that the membrane potential affects several types of proteins in addition to ion channels, and therefore indirectly impacts upon a variety of cell processes. Alternatively, the neurodegenerative effect of KATP channels in PD might stem from some non-conducting function of these channels, a notion that receives partial support from the observation that ectopic expression of inwardly rectifying K+ channel Kir1.1 is lethal to hippocampal neurons [66]. The number of cases reporting non-conducting functions of ion channels has been increasing steadily in the past few years [67–70]. For example, evidence shows that expression of EAG voltage-gated K+ channels dramatically increases the density of NIH 3T3 fibroblasts though mechanisms that are mediated by the relative movements of the voltage sensor of the protein [71], and do not involve conduction of K+ ions across the plasma membrane.

Concluding remarks

Reduced neuronal excitability through upregulation of K+ channel activities appears to be a hallmark of the aging brain in both normal and disease states, although the causes still await an explanation. In C. elegans, a major cause of reduced excitability is increased K+ channel activity due to oxidation by ROS. The fact that highly elevated levels of ROS are found in the aging brain [16], and in many neurodegenerative conditions, suggests that oxidative modification of K+ channels might be a general principle underlying aging and neurodegeneration. Standard pharmacological approaches (for instance, Ref. [28]), where possible coupled with mass spectroscopy, will enable researchers to ascertain whether K+ currents in the neurons of old animals are upregulated by oxidation and to identify the affected residues (this could be particularly important for BK channels considering the different functional consequences of oxidation of their methionine and/or cysteine residues). Knock-In (KI) mouse models, analogous to the C113S-KVS-1 transgenic worm, could further be employed to investigate K+ channel oxidation in the aging brain. One caveat intrinsic to the latter approach is that, in a KI animal, any physiological modulation of the mutated channel protein by ROS would be suppressed. The same line of thinking argues against the efficacy of therapies based on generic anti-oxidants for the treatment of
neuropathies (as well as for other types of pathologies). Modes of intervention aimed at targeting not only the specific channel protein but also the responsible ROS species (not always a simple task) appear more likely to succeed. Moreover, recent advances in drug design may open up approaches based on decreasing ROS generation (for example, by upregulating the expression of mitochondrial uncoupling proteins) and/or strengthening the mitochondrial and intracellular antioxidant machinery (and this might require a better understanding of ROS biology). In conclusion, the discovery that K+ channels can be targets of ROS during aging has opened up new challenges that, when addressed, might significantly advance our understanding and treatment of these devastating pathologies.

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References

21 Gu, N. et al. (2007) BK potassium channels facilitate high-frequency firing and cause early spike frequency adaptation in rat CA1 hippocampal pyramidal cells. J. Physiol. 580, 859–882
24 Santarelli, L.C. et al. (2006) Three methionine residues located within the regulator of conductance for K+ (RCK) domains confer oxidative sensitivity to large-conductance Ca2+-activated K+ channels. J. Physiol. 571, 329–348


Nadeau, H. et al. (2000) ROM1 (Kiri.1) causes apoptosis and chronic silencing of hippocampal neurons. *J. Neurophysiol.* 84, 1062–1075

Cai, S.Q. et al. (2005) MPP-1 is a K*+* channel beta-subunit and a serine/threonine kinase. *Nat. Neurosci.* 8, 1503–1509


Cavode, D. et al. (2003) Hydrogen peroxide modulates the Kv1.5 channel expressed in a mammalian cell line. *Naunyn Schmiedebergs Arch. Pharmacol.* 368, 479–486


Gamper, N. et al. (2006) Oxidative modification of M-type K*+* channels as a mechanism of cytoprotective neuronal silencing. *EMBO J.* 25, 4996–5004


Li, Y. et al. (2005) Oxidation and reduction control of the inactivation gating of Torpedo CIC-0 chloride channels. *Biophys. J.* 88, 3936–3945