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Forum Editorial

Control of Neuronal Plasticity by Reactive Oxygen Species

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BIOLOGICAL ORGANISMS have long been wielding the double-edged sword that is Oxygen. This molecule, which serves as a readily available oxidant, is maintained in living cells under strict control, enabling it to promote life and not destroy its building blocks. Over the past decade, we are increasingly appreciative of how fine the blade of that sword becomes and how it affects not only life and death decisions made by cells but also the fine tuning of signaling within. Finely tuned signal cascades are particularly important in neurons. The ability to discriminate between ionic fluctuations arising from dendritic branches that are micrometers apart and the ability to maintain that discrimination over decades of activity underlies our ability to learn and remember. The fine tuning of these networks by ambient levels of oxygen is the focus of the present series of review articles.

Our understanding of the involvement of reactive oxygen species (ROS) in the life of neurons is undergoing a revolution in recent years. In 1992, Barry Halliwell presented a seminal review of the current knowledge explaining how ROS affect neurons (7). This article had a profound impact on the approach of researchers to studying the effects of ROS on neurons. These views affected the type of experiments that were designed, the kinds of assays that were deemed relevant, and the array of concentrations of ROS employed in these studies. The hypothesis underlying these studies may be termed as one of "Generalized damage," which, according to a recent review by Halliwell (6) "(ROS) conspire to kill neurons" that are "inadequately equipped with antioxidant defense systems." This hypothesis was further extended to assume that there is, in fact, an evolutionary rationale behind neurodegeneration driven by oxidative stress, since older individuals no longer mate (6, 13). Interestingly, human males retain their ability to mate in senescence, allowing for a skeptical acceptance of this hypothesis.

Over the course of the last decade, another approach has emerged that we term the "Generator-Sensor" model (Fig. 1). Research conducted under this hypothesis (reviewed in Refs. 4 and 5) has found many biological systems in which ROS act as second messengers being generated in one part of a cell or a neighboring cell as a specific response to well-defined stimuli and altering the activity of an enzyme or an organelle containing a ROS activated switch or "sensor" elsewhere in the cell. This regulatory system has been found in many cases to modulate the activity of protein kinases and phosphatases. This system of signaling through ROS provides cells with the ability to regulate phosphorylation rates in a way that is not dependent solely on the kinetics and concentration of free phosphate ions in endless phosphorylation/dephosphorylation loops. It is no surprise then that evidence for ROS as signaling molecules was indeed found in neurons.

The current issue of ARS is focused on the effects of ROS on neuronal plasticity. Neuronal plasticity can be defined at different spatio-temporal scales that correlate with different activities of neurons. Neurons are born from progenitors in the embryonic neural crest and find their way to the peripheral and central nervous system (CNS), where they remain under highly selective control involving the concerted effects of various signaling cascades arising from within and out of the neuron. Many of these neurons maintain their position and function over decades of life, responding with ionic currents to a barrage of signals that is integrated by them. Some of these neurons undergo apoptosis as the appropriate response to relevant signals, and some are born later in life in germinal zones in the CNS. Neurons need to adjust their size and shape to fit the role for which they are selected, and they need to survive long enough for the organism to utilize what they have acquired. These functions are carried out using mechanisms of synaptic plasticity akin to those underlying long term potentiation (LTP) (3) of synaptic efficacy in response to a conditioning stimulation. The expression of LTP requires synapse specific transient increase in intracellular calcium concentrations ($[Ca^{2+}]_i$), which are then transduced to a persistent synapse-specific change in the expression of voltage/ligand gated ion channels.

It is extremely important to identify the signaling events downstream to ROS formation that may lead to neurodegeneration. A wider knowledge and understanding of these events will allow us to design new treatments for prevention

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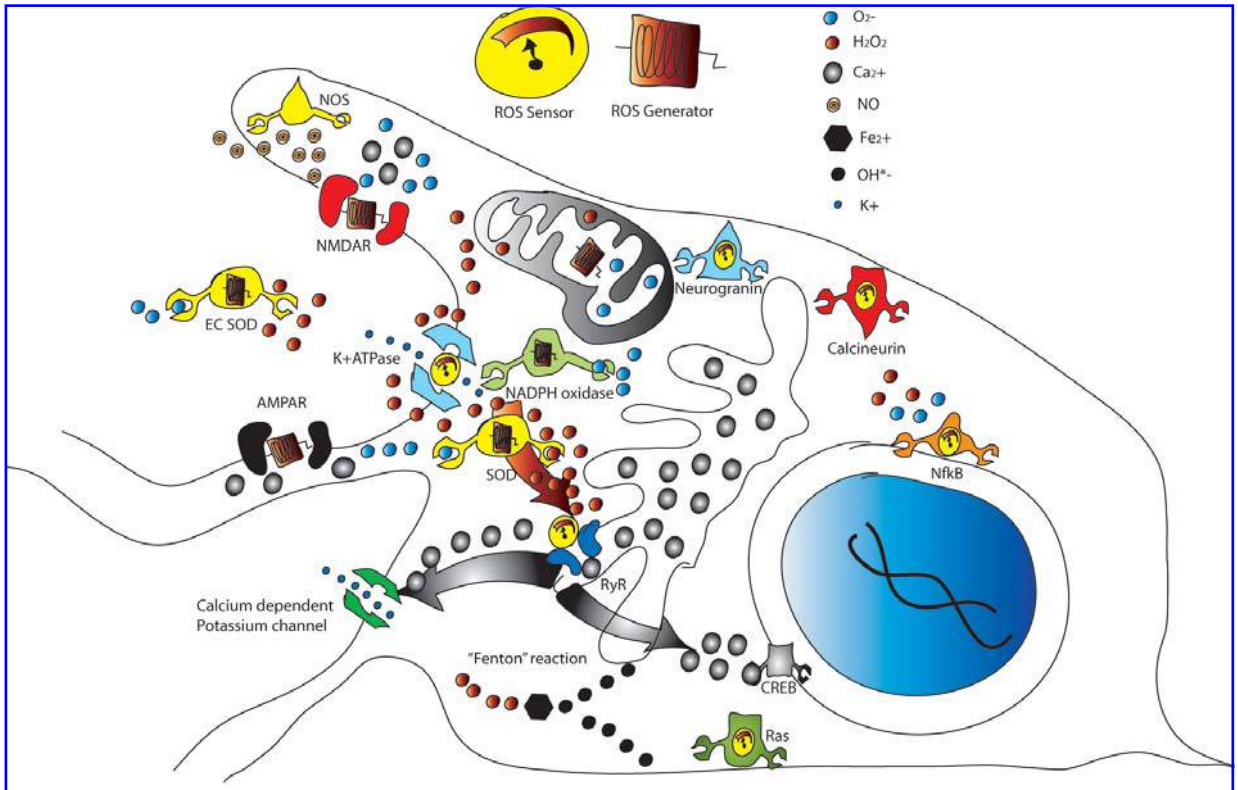

FIG. 1. "Generator-Sensor" model of ROS regulation. ROS generation is coupled to signaling event in various parts of a working neuron. The shift in ROS concentration creates a change in the redox state of specific signaling proteins that is translated to a change in activity of the cell. Some signals are further transduced by changing the permeability of calcium channels on the plasma membrane of the ER, leading to a shift in the activity of calcium-activated enzymes. CREB, cyclic AMP response element binding protein; NOS, nitric oxide synthase; ROS, reactive oxygen species; RyR, ryanodine receptor; SOD, superoxide dismutase.

of neurodegeneration and will also guide us in the optimal time and place to employ our existing arsenal of drugs. Weinreb *et al*. (17) have undertaken this task in the past few years and have studied gene expression measured by mRNA, as well as mature proteins, in an effort to solve these problems. The proteins being implicated in ROS-dependent signaling by these studies will undoubtedly provide a starting point for future efforts to understand the intracellular language of neurons.

Perhaps the largest cellular organelles engaged in buffering both ROS and calcium are the mitochondria. In fact, as Schönfeld and Reiser (15) report, mitochondria produce ROS in response to increases in cellular calcium concentrations. Whereas the generation of ROS by mitochondria from rat brains is not altered with age, the calcium storage capacity of the mitochondria is altered. With the growing body of evidence suggesting fine ROS management in every stage of neuronal life, this delicate balance between calcium and ROS, which is carried out by mitochondria and is dynamically changing during development, will surely provide us with important insights into the way neurons mature and function.

One of the issues concerning many of us in the field is the question of how much ROS are really present *in vivo.* An answer to this question is crucial for the design of experiments that have a bearing on real-life physiology. This point is considered from the evidence we have regarding O_2 pressure by Barzilai (2), who considers the special characteristics neurons have that make them susceptible to ROS. This susceptibility is most evident in the vulnerability of neuronal DNA to damage, since neurons do not have corrective mechanisms associated with cellular replication, yet their DNA is engaged in transcription of a large number of messages at any given time. The importance of these issues is manifested by the fact that much of the evidence we have regarding processes of DNA protection in neurons comes from mutations that cause diseases of the nervous system.

As mentioned above, there is a growing understanding of the contribution of ROS not only to events in the lifetime of neurons that occur over years but also to millisecond long signals that are an integral part of the role of neurons in transducing and storing information. Finding where these signals originate and how they are translated into meaningful activity is the subject of the article by Kishida and Klann (14). They draw our attention to the increasing body of evidence showing that NADPH oxidase possesses the right activity in the right place and at the right time to make it an important generator of ROS that are necessary for LTP. They also take us on a guided tour of the neuron, pointing out available generators and sensors of ROS and the evidence that ties them to synaptic plasticity.

We, as well as others, have learned much about the fine tuning of synaptic plasticity by ROS from studying transgenic mice overexpressing superoxide dismutases (SODs) (12, 16). These studies have often converged in their findings but have also yielded some diverging results. Hu *et al*. (9) discuss these studies and the new insight gained by sorting the findings by the isozyme being overexpressed and the age of the mice studied. This discussion is interesting in light of recent work by Hu *et al*. (10) showing that aged mice overexpressing extracellular SOD perform better in a watermaze memory task than aged controls. This study provides a behavioral correlate for our finding that hippocampal slices from aged mice overexpressing Cu/Zn SOD exhibit enhanced LTP as compared to that of aged wild-type mice. Hu *et al*. (9) hypothesize that aged mice overexpressing Cu/Zn SOD will not be equally better at watermaze retention as are mice overexpressing extracellular SOD. Serendipitously, we report in this issue (11) that aged mice overexpressing Cu/Zn SOD do in fact perform better at watermaze retention than wild-type controls. In our study we further utilize these aged mice that perform better as a group in a memory task to investigate the relationship between adult neurogenesis and memory.

Another organelle important for integration of signals from both ROS and calcium is the endoplasmic reticulum (ER). The ER stores high concentrations of calcium that can be quickly released to provide meaningful signals in neurons. One of the gatekeepers of these signals are the ryanodine receptors (RyR) discussed by Hidalgo *et al.* (8). RyR contain sensor domains that can be modified by ROS that determine the dynamics of calcium release from the ER. Thus, an "oxidative tone" must be maintained intracellularly for neurons to work. This tone is achieved in part by iron, which is also a ROS generator in neurons.

The regulation of synaptic activity by ROS is not confined to hippocampal synapses. A series of enlightening studies by Margaret Rice (summarized in Ref. 1), have found that hydrogen peroxide modulates dopamine release in dorsal striatum through a ROS sensor on potassium channels that control the excitability of the dopamine releasing neurons. The hydrogen peroxide molecules produced in response to glutamatergic signals diffuse to neighboring dopaminergic terminals, providing a functional coupling. The question of estimating *in vivo* amounts of ROS is also raised in this article, and a summary of available fluorescent imaging reagents is discussed and utilized. Taken together, the work reported on in this issue demonstrates our growing understanding of the ways ROS are involved in regulating activity of neurons, far beyond their assumed role in neurotoxicity. As we appreciate better the complexity of this involvement, we realize that disruptions of this delicate balance cannot be solved with comprehensive "antioxidant treatment." Further discovery of ROS generators and sensors within neuronal networks will allow us to fine tune our ability to use ROS and antioxidants in the right time and place to manipulate neurons in a healthy way.

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