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Review

Oxidative stress and redox regulation on hippocampal-dependent cognitive functions

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ABSTRACT

Hippocampal-dependent cognitive functions rely on production of new neurons and maintenance of dendritic structures to provide the synaptic plasticity needed for learning and formation of new memories. Hippocampal formation is exquisitely sensitive to patho-physiological changes, and reduced antioxidant capacity and exposure to low dose irradiation can significantly impede hippocampal-dependent functions of learning and memory by reducing the production of new neurons and alter dendritic structures in the hippocampus. Although the mechanism leading to impaired cognitive functions is complex, persistent oxidative stress likely plays an important role in the SOD-deficient and radiation-exposed hippocampal environment. Aging is associated with increased production of pro-oxidants and accumulation of oxidative end products. Similar to the hippocampal defects observed in SOD-deficient mice and mice exposed to low dose irradiation, reduced capacity in learning and memory, diminishing hippocampal neurogenesis, and altered dendritic network are universal in the aging brains. Given the similarities in cellular and structural changes in the aged, SOD-deficient, and radiation-exposed hippocampal environment and the corresponding changes in cognitive decline, understanding the shared underlying mechanism will provide more flexible and efficient use of SOD deficiency or irradiation to model age-related changes in cognitive functions and identify potential therapeutic or intervention methods.

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Hippocampal-dependent learning and memory

Hippocampus is critical for the acquisition (learning), consolidation and retrieval of declarative memories (reviewed in [1]). It is also important for the formation of spatial memory [2,3]. The hippocampus is located in the medial temporal lobe of the brain and is composed of two separate structures: the dentate gyrus (DG)[1] and the *Cornu Ammonis* areas (CA1 and CA3). The entorhinal cortex serves as a connection between hippocampus and other parts of the cerebral cortex. Information from the cerebral cortex is relayed to the granule cells of hippocampal dentate gyrus by axonal projection from the entorhinal cortex. Axons form the dentate granule cell (called mossy fibers) then relay the information to the CA3 pyramidal cells whose axons project to the CA1 pyramidal cells, which then send the information back to the deeper layers of entorhinal cortex to complete the neural circuit in the hippocampal formation [4–6]. Severe damage to the hippocampus often leads to failure in forming new memories [7,8].

In mammals, adult neurogenesis – the process of production and maturation of new borne neurons beyond the early postnatal stage – occurs primarily in two areas of the central nervous system [9]. These areas are subventricular zone (SVZ) of the lateral ventricles, which supplies new interneurons to the olfactory bulb; and the subgranular zone (SGZ) of dentate gyrus, which generates granule cells to the dentate gyrus of hippocampus. More recently, olfactory neuroepithelium has been shown to continue production of sensory neurons into old age in mice [10]. Results from experimental animals show that the production of new neurons in these areas is important for synaptic plasticity [11,12]. However, the process of neurogenesis can be impeded by various physiological changes. Hippocampal neurogenesis in particular, is exquisitely sensitive to changes in its microenvironment, often leading to reduced production of new neurons.

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[1] *Abbreviations used:* DG, dentate gyrus; SVZ, subventricular zone; SGZ, subgranular zone; SODs, superoxide dismutases; Gpxs, glutathione peroxidases; Prdxs, peroxiredoxins; Grxs, glutaredoxins; CuZnSOD, Cu and Zn-containing SOD; MnSOD, Mn-containing SOD; EC-SOD, extracellular Cu and Zn-containing SOD; Trx, thioredoxins; TrxR, thioredoxin reductase; ESC, embryonic stem cells; GDE2, glycerophosphodiester phosphodiesterase 2; HIF-1α, hypoxia-inducible factor 1 alpha; ROS, reactive oxygen species; DHE, dihydroethidium.

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In the hippocampal dentate SGZ, neural progenitor cells go through asymmetrical replication and generate neuroblasts, which then differentiate into immature neurons. In the next three to 4 weeks, newborn immature neurons put out axons and complex dendritic trees as they migrate further into the granule cell layer and finally establish synaptic integration into the existing neuronal network in hippocampal formation. It is estimated that roughly 10% immature neurons survive the maturation process and develop into fully functional mature neurons [13].

The SGZ of hippocampal dentate gyrus is an active site of neurogenesis throughout life in humans and other mammals [14,15], and recent data show that the newly born neurons are functionally integrated into the hippocampal circuitry [16–20]. In laboratory mice, the rate of adult hippocampal neurogenesis decreases exponentially from 1 month of age at the rate of 30–40% per month [21]. At the same time, the rate of apoptotic cell death in the granule cell layer peaks at 1 month and gradually decreases with age. In balance, the number of granule cells in the hippocampus stays relatively constant [21], and the majority of granule cells will probably last for the entire lifespan of the animal. Similar observation has also been made in other species.

The potential importance of neurogenesis, as it relates to the hippocampal functions of learning and memory, is highlighted in normal animals where a positive correlation has been established between dentate neurogenesis and behavioral performance [18,22–26]. Environmental enrichment (e.g. increased environmental complexity, toys, running wheels, etc.) increases the numbers of new hippocampal neurons [27,28], suggesting that the new cells may be important in learning and forming new memories. Recent studies show that these new cells become functionally integrated into the dentate gyrus and have passive membrane properties, action potentials and functional synaptic inputs similar to those found in mature dentate granule cells [29]. Most importantly, the new neurons play a significant role in synaptic plasticity, which can be considered a cellular substrate for learning. A recent study provides strong evidence that these are not just correlative observations. Cell lineage tracking and expression of learning-related immediate early genes show that adult-generated granule cells in the SGZ are preferentially incorporated into the spatial memory networks in the dentate gyrus of the hippocampus [30].

In addition to production of new neurons in the hippocampus, maintenance of axons and dendrites – the structures that project from the cell body of neurons and form synapses with axons and dendrites from other neurons for transmission of electrochemical signals – is equally important for learning and memory. Consequently, reductions in hippocampal neurogenesis are not always consistent with defects in hippocampal functions of learning and memory [31–33], and loss of dendritic spines – the post synaptic element of excitatory synapses – is an early event in mouse models of Alzheimer disease, and it correlates with synaptic loss and deficits in learning and memory [34,35].

Redox potential and cell fate decision

Changes in intracellular redox potential and the extracellular microenvironment can impact cell fate decisions, including entering or exiting cell cycle, proliferation or differentiation, and survival or cell death. Redox couples, such as GSH/GSSG and $NADPH/NADP^+$ are presence in high abundance in cells and the status of these redox couples can serve as important indicators for the reduction potential of intracellular environment, which then influence the activity of redox-sensitive proteins involved in cell fate decisions [36]. Within the normal cellular environment, a more reduced redox environment usually favors proliferation, whereas a more oxidized environment favors differentiation. In a pathogenic environment, moderately increased oxidative stress usually leads to a more controlled apoptotic cell death, whereas very high level of oxidative stress would lead to a more sweeping necrotic cell death [36]. The redox potential also changes as cells progress through the cell cycle with the level of superoxide radicals increasing as cells progress from G1 to M phase [37,38], and the balance between hydrogen peroxide and superoxide concentration influences the decision to enter or exit the cell cycle [39].

At the center of redox control is the superoxide-metabolizing enzymes, superoxide dismutases (SODs) [40,41], and the H_2O_2/peroxide-metabolizing enzymes, catalase, glutathione peroxidases (Gpxs), peroxiredoxins (Prdxs), and glutaredoxins (Grxs). In the mammalian system, there are three SODs that are encoded by different genes and the proteins are located in different subcellular compartments. The cytoplasmic Cu and Zn-containing SOD (CuZnSOD) is a dimeric enzyme and is present in high abundance in most tissues. In addition to the cytosol, CuZnSOD is also present in the intermembrane space of mitochondria and in the nucleus [42]. Mutant mice deficient in CuZnSOD (*Sod1*−/− mice) are viable, but have increased incidence of liver cancer as they age and have a reduced life span compared to wild type controls [43]. *Sod1*−/− mice also have defects in the neuromuscular junctions, resulting in skeletal muscle atrophies [44]. Although *Sod1*−/− mice are viable, primary cells derived from *Sod1*−/− mice are not able to survive in the conventional tissue culture system due to toxicity from the ambient oxygen [45].

The mitochondrial Mn-containing SOD (MnSOD) is a tetrameric enzyme and is present in the matrix of mitochondria. The protein is present at low levels in most tissues, but the production MnSOD is highly inducible under conditions of oxidative stress. Tissues that rely heavily on oxidative phosphorylation for energy production maintain a higher level of MnSOD. Mutant mice deficient in MnSOD (*Sod2*−/− mice) suffer from severe mitochondrial defects and, depending on the genetic background, die prenatally or peri-natally with dilated cardiomyopathy, metabolic acidosis, and vacuolar degeneration in the brain [46–48]. MnSOD has been shown to be important for cell cycle progression by controlling the balance between hydrogen peroxide and superoxide as cells progress from G1 to M phase [39,49]. Marked reduction in MnSOD levels is commonly observed in transformed cells, and reconstitution of MnSOD expression in transformed cells can increase cell doubling time and reduce tumorigenicity [50]. Consistent with the in vitro observation, mutant mice with 50% reduction in MnSOD (*Sod2*−/+) develop significantly higher incidence of lymphoma as they age [51], whereas increased MnSOD in normal tissues is shown to delay entry into the S phase in a partial hepatectomy experimental model with transgenic mice expressing elevated levels of MnSOD in the liver [52]. Reduction of MnSOD in transformed cells is usually due to deletion or epigenetic modification of *Sod2* [53–56]. The role of MnSOD in cancer initiation, progression, and metastasis is more complex than cell cycle control. Multiple studies have shown elevated levels of MnSOD in the invading front of metastatic tumors, and molecular and biochemical studies suggest a role of MnSOD in enhancing the invasive and migratory activity of tumor cells by controlling the signaling events that drive tumor metastasis [57–59].

The extracellular Cu and Zn-containing SOD (EC-SOD) is a tetrameric enzyme and is mainly present on cell surfaces by attachment to the extracellular matrix via its heparin binding domain at the C-terminus [60]. The heparin binding domain is cleaved in a small percentage of EC-SOD, allowing the enzyme to diffuse further away from the cell surface and, in the case of endothelial cell-derived EC-SOD, enter the circulation [61]. Compared to CuZnSOD and MnSOD, EC-SOD is produced at very low level in most tissues. Mutant mice deficient in EC-SOD (*Sod3*−/− mice) are viable and with no overt