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Learning tasks as a possible treatment for DNA lesions induced by oxidative stress in hippocampal neurons

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Research Highlights

(1) This review presents the current status of therapeutic methods used in treating neurodegenerative diseases induced by reactive oxygen species and proposes a new approach based on existing data.
(2) Some forms of cognitive stimulation seem to have a beneficial effect on various forms of dementia. But the underlying mechanism remains unclear.
(3) The cognitive stimulation task is documented to activate p300 protein which plays a central role in base excision repair pathway and thereby repair hippocampal neuronal DNA injuries.

Abstract

Reactive oxygen species have been implicated in conditions ranging from cardiovascular dysfunction, arthritis, cancer, to aging and age-related disorders. The organism developed several pathways to counteract these effects, with base excision repair being responsible for repairing one of the major base lesions (8-oxoG) in all organisms. Epidemiological evidence suggests that cognitive stimulation makes the brain more resilient to damage or degeneration. Recent studies have linked enriched environment to reduction of oxidative stressin neurons of mice with Alzheimer's disease-like disease, but given its complexity it is not clear what specific aspect of enriched environment has therapeutic effects. Studies from molecular biology have shown that the protein p300, which is a transcription co-activator required for consolidation of memories during specific learning tasks, is at the same time involved in DNA replication and repair, playing a central role in the long-patch pathway of base excision repair. Based on the evidence, we propose that learning tasks such as novel object recognition could be tested as possible methods of base excision repair facilitation, hence inducing DNA repair in the hippocampal neurons. If this method proves to be effective, it could be the start for designing similar tasks for humans, as a behavioral therapeutic complement to the classical drug-based therapy in treating neurodegenerative disorders. This review presents the current status of therapeutic methods used in treating neurodegenerative diseases induced by reactive oxygen species and proposes a new approach based on existing data.

Key Words

neural regeneration; reviews; neurodegenerative disorder; reactive oxygen species; base excision repair; cognitive stimulation; p300; grants-supported paper; neural regeneration

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INTRODUCTION

The genome is inherently subjected to spontaneous errors *via* a range of chemical reactions. These reactions include some significant replication errors, as well as degradation processes involving endogenous reactive oxygen species or some environmental agents such as ultraviolet light. Reactive oxygen species have been implicated in conditions ranging from cardiovascular dysfunction, arthritis, cancer, to aging and age-related disorders, including Alzheimer's disease[1].

Various medications have been developed to treat such disorders and although these drugs appear to be effective in treating the early forms of neurodegenerative disorders, one issue is their side effects. A parallel approach is to develop treatment methods based on physical and mental exercise. The objective of this review is to present the current status of therapeutic methods used in treating neurodegenerative disorders and to propose a new approach based on existing experimental data. If this method proves to be effective, it could be the start for designing similar tasks for humans, as a behavioral therapeutic complement to the classical drug-based therapy in treating neurodegenerative disorders.

THE ORGANISM'S NATURAL PATHWAY FOR REPAIRING DNA LESIONS INDUCED BY REACTIVE OXYGEN SPECIES

Genomic lesions induced by reactive oxygen species include oxidative damage of nucleobases, AP (abasic) sites, and DNA strand breaks. Among these damages, 7,8-dihydro-8-oxoguanine (8-oxoG) and ring-opened fapyguanine (FapyG) are the major base lesions. 8-OxoG preferentially mispairs with adenine during DNA replication, generating G-C to T-A transversion mutations, hence making it particularly mutagenic[2]. The pathways whereby cells counteract reactive oxygen species-induced damage (or so called "oxidative stress") include enzymatic systems targeting reactive oxygen species directly (superoxide dismutases, catalases, peroxidases) and systems directed at correcting the damage inflicted by reactive oxygen species upon various cellular components – including DNA. Base excision repair represents a pathway for protection of DNA in situations where damaged or inappropriate bases are present (generated endogenously or induced by genotoxicants like reactive oxygen species) and is primarily responsible for repairing 8-oxoG in all organisms[1]. Base excision repair is evolutionarily conserved in all animals. This pathway is initiated with a base excision made by a DNA glycosylase, the resulted apurinic/ apyrimidinic site being then processed *via* two distinct pathways: the short-patch pathway and the long-patch pathway[3]. The short-patch pathway involves a single base replacement catalyzed by a DNA polymerase, an AP endonuclease, DNA ligase III and XRCC1, while in the long-patch pathway, a replicative DNA polymerase performs more extensive DNA synthesis, displacing a flap of parental DNA which is subsequently removed by the Fen1p endonuclease. In the next step, the DNA is ligated by DNA ligase I and XRCC1[3]. In mammalian cells, the first step of base excision repair is catalyzed by the enzyme 8-oxoguanine glycosylase (OGG1), which excises 8-oxoG and other damaged base substrates from DNA. The bound enzyme, after removal of the base, further carries out a lyase reaction to cleave the DNA strand at the damaged site[4]. OGG1 is thus a "bifunctional lyase", with lyase as well as AP endonuclease activity.

COGNITIVE STIMULATION AS A TREATMENT FOR NEURODEGENERATIVE DISORDERS

As we mentioned above, DNA damage induced by reactive oxygen species has been linked to neurodegenerative disorders such as Alzheimer's disease. Alzheimer's disease is progressive dementia typically occurring after the age of 80 that affects mainly the neocortex and hippocampus[5]. The disease is characterized by the presence of senile plaques and neurofibrillary tangles. Senile plaques are extracellular deposits of amyloid, consisting of Aβ peptide produced by the proteolysis of the amyloid precursor protein by β- then γ-secretase. Neurofibrillary tangles are intraneuronal aggregations of hyperphosphorylated forms of the microtubule-associated protein τ[6]. A previous study has shown that antibodies against β-amyloid plaques can slow cognitive decline in patients with Alzheimer's disease[7].

Various medications have been developed to treat such disorders, by targeting the cyclic adenosine monophosphate/protein-kinase A/cAMP response element binding protein (cAMP/PKA/CREB) signaling pathway. One of the most important classes of drug targets is the phosphodiesterase-4 inhibitors. PDE inhibitors are involved in many cellular signal transductions mediated by cAMP[8]. A phosphodiesterase-4 inhibitor is a class of drugs used to block the degradative action of phosphodiesterase-4 on cAMP. One of the best known drugs, part of this class, is Rolipram. Studies have shown that Rolipram restores

spine density and the cAMP/PKA/CREB signaling pathway in Alzheimer's disease models[9]. In addition to phosphodiesterase-4 inhibitors, some scholars proposed that acetylcholinesterase inhibitors could be used as a treatment for Alzheimer's disease[10]. Some scholars also proposed that inhibition of histone deacetylases might be suitable for neurodegenerative diseases associated with learning and memory impairment[11]. Although these drugs appear to be effective in treating the early forms of neurodegenerative disorders, one issue is their side effects. Nausea, emesis, and related general intestinal side effects are the most common side effects of phosphodiesterase-4 inhibitors[12]. Therefore, in addition to the effort of developing drugs without significant side effects, one option would be to find non-invasive forms of treatment, which are not based on drugs.

Various studies revealed that synapse loss is strongly correlated with cognitive decline in Alzheimer's disease[13]. The plastic properties of synapses make them subject for modulation by environmental stimulation, and this process could lead to the slowing or reversal of cognitive decline. Learning and other forms of cognitive stimulation seems to have a beneficial effect on Alzheimer's disease, and other forms of dementia, so these methods could be used as a possible treatment, or preventive strategy[6]. Progression of synaptic plasticity, such as long-term potentiation, is widely considered a cellular correlate of learning and memory[14]. Clinical evidence suggests that synaptic abnormalities in the hippocampus correlate with the severity of neuropathology and memory deficit in individuals with Alzheimer's disease[15] and the disease begins with subtle alterations of hippocampal synaptic efficacy prior to neuronal degeneration[16]. Congruent with these data, other studies revealed that mild cognitive impairment generally represents early stage of Alzheimer's disease[17]. This evidence makes it critical to identify long-term potentiation enhancers to slow down or stop the progression of Alzheimer's disease[18]. Experimental studies suggest that cognitive stimulation and physical activity can prevent or delay the onset of Alzheimer's disease. Cognitive stimulation through various forms of environmental enrichment induces various alterations in brain structure and function[18]. Among these alterations, we mentioned to increase the birth and maturation of new neurons into functional circuits, enhance the expression of molecules involved in neuronal signaling, and also promote synaptic plasticity[6, 19]. Enriched environment increases the expression of the genes responsible for synaptic transmission and signal transduction[20] such as increase in brain-derived neurotrophic factor expression *via* epigenetic mechanisms in the hippocampus[21]. So, we can conclude that this experience-dependent increase in neuronal connectivity could explain how environmental enrichment could make the brain more resilient, protecting it from damage or degeneration.

Twenty years ago, it was generally thought that the brain had little regenerative capacity, being unable to produce new neurons after development. But, in the early 1990s, Elizabeth Gould during her work on investigating the effects of adrenal hormones on the hippocampus, observed numerous cells with neuronal morphologies being born in the rat hippocampus[22]. Hence, a remarkable discovery was made by accidents, conveying that neural cells from the adult brain could be stimulated to proliferate *in vitro* and differentiate into neurons and glia[23]. In the late 1990s, Fred Gage and colleagues using brain samples from cancer patients that had received BrdU to label tumor proliferation have demonstrated that neurogenesis occurs also in the human hippocampus[24]. This was a major discovery in the field of adult neurogenesis, leading not only to the acceptance of this phenomenon, but also to significant interest as to what it could mean for brain function and repair[25]. Environmental responsiveness suggests that adult neurogenesis is functionally important and leads to inquiry into the functional relevance of newborn adult neurons[26-27].

Various studies revealed that enriched environment, exercise, learning and memory, influence the rate of neurogenesis and the survival of new neurons. This implies that mental and physical activity induced regulation of neurogenesis should be combined with some other therapeutic methods in order to direct the function of new neurons[28]. Given the known role of the hippocampus in spatial learning[29], the focus of research was directed to test the possible connection between spatial learning and adult neurogenesis. Experimental studies have shown that during learning, neuronal networks are modified by some specific selection and suppression of different populations of newly born neurons[30]. Also, Deng and colleagues[31] found that adult-born dentate granule cells that undergo maturation make important contributions to spatial memory and contextual fear extinction. Furthermore, Trouche *et al* [32] discovered that these new neurons from the hippocampal dentate gyrus are recruited into neuronal networks that might support retrieval of spatial memory. Moreover, their activation is context-specific, so the authors hypothesized that the new neurons that are activated during this critical period, become tagged, and after they mature, are preferentially recruited into hippocampal networks underlying spatial

memory representation when encountering a similar context or experience. Although learning increases the number of immature neurons that survive and mature in the adult hippocampus, it is not enough for their survival. It seems that re-exposure of these new neurons to the initial information that leads to their birth, is necessary to save these cells. The timing of re-exposure is also critical. Anderson *et al* [33] found that cells which were 1–2 weeks of age at the time of training, are more likely to survive in response to successful learning than cells in animals that are exposed to training but do not manage to learn the task.

In addition to spatial learning, enriched environment also leads to adult neurogenesis. Environmental enrichment refers to different housing conditions relative to standard housing conditions, like home cages or exploratory chambers that facilitate enhanced sensory, but also to the cognitive and motor stimulation. Environmental enrichment could also include increased social stimulation through larger numbers of animals per cage. Adar, Nottebohm and Barnea[34] found that the 1-month-old neurons were more likely to survive if the animals were exposed to a complex social setting than if they were exposed to a simple one. Their explanation for these results is that new neurons which are not yet committed to a specific job are more readily selected for a new job. These new neurons may be more able to process and store new information, so increased use of replaceable neurons may promote their survival. The authors hypothesize that the greater the amount of new information, the greater the proportion of young new neurons that will find employment and subsequent survival. They also launched the hypothesis that parts of the brain that are more sensitive to novelty of information are likely to serve as storage places for more recent events, whereas those more resistant to new information, are likely to store older memories. In parts of the brain populated by what they call “replaceable neurons”, previous events may determine how recently new neurons were incorporated there and, according to their theory, how ready they will be to assimilate new information and hence to survive. This is relevant for us because the dentate gyrus – where adult neurogenesis takes place - is known to be involved in processing and encoding new stimuli[35-36]. In addition, recent studies linked enriched environment with reduction of cerebral oxidative stress. Herring *et al* [37] kept female TgCRND8 mice (with Alzheimer’s disease-like disease) under standard and enriched housing from day 30 until 5 months of age. They found that environmental enrichment attenuated pro-oxidative processes and triggered some anti-oxidative defense mechanisms. These defense mechanisms were diminished biomarkers for reactive oxygen and nitrogen species, decreased expression of pro-apoptotic caspases, downregulation of pro-inflammatory and pro-oxidative mediators, and upregulation of SOD1 and SOD2. Interesting and closely related to the hypothesis we present in the last part of this material, are the recent results obtained by Suberbielle and her colleagues, showing that exploration of a novel environment causes DNA double-strand breaks in hippocampal dentate gyrus neurons. This region is involved in learning and memory, and the double-strand breaks that occur here as a result of normal physiological activity are repaired within 24 hours, at least in adult wild-type mice. They also discovered that in mice transgenic for human amyloid precursor (which simulate key aspects of Alzheimer’s disease) amyloid-β exacerbates DNA damage by eliciting synaptic dysfunction[38].

Although there is sufficient evidence about the positive impact of enriched environment on the brain in general and for prevention of neurodegenerative disease in particular, it is not clear what aspect of enriched environment is critical. Traditionally, enriched environments consist of a combination of new environment, physical exercise, toys and social interactions. In order to identify the effect of each component, this topic needs clarifications. Further we will try to focus on a more specific behavioral task, with an already identified mechanism that made the connection between learning and DNA repair.

MOLECULAR MECHANISMS LINKING LEARNING AND DNA REPAIR

In the previous chapter, we mentioned that exploration of a novel environment causes DNA double-strand breaks in dentate gyrus neurons. These findings can be put in relation with one study from Muotri *et al* [39] which found that exposure to a new environment stimulates experience-dependent LINE-L1 retrotransposition in the dentate gyrus. LINE elements are parts of the retrotransposon family, which are mobile elements of the genome located inside introns and other noncoding regions of DNA[40]. This is relevant to our discussion because it is known that endonuclease activity of endogenously expressed LINE-L1 elements could contribute to double-strand breaks formation in somatic tissues[41]. Morrish *et al* [42] has already shown that endonuclease-independent L1 insertions lack the hallmarks of TPRT. These data suggests that LINE-L1 elements can inte-

grate into and repair double-strand breaks. Other authors suggest that endonuclease-independent retrotransposition might be an ancestral mechanism of RNA-mediated DNA repair that was used before LINEs, acquired an endonuclease domain[43]. Hence, there is evidence suggesting that non-LTR retrotransposons in general might provide an additional mechanism for maintaining human genome integrity. Also studies made on nonhomologous end-joining (NHEJ) – a repair mechanism for double-strand breaks – suggest that mechanisms of DNA recombination and/or repair are involved in learning and memory processes[44]. Although it sounds counterintuitive, it seems that normal activity related with exploration and learning trigger both DNA damage and DNA repair processes inside the brain cells. Mattick and Mehler[45] tried to explain these findings suggesting that the potential recoding of DNA in nerve cells might be a mechanism by which learned changes induced by RNA editing are sent back to the DNA *via* RNA-directed DNA repair pathways. This mechanism has the role to fix the altered genotype once a particular neural circuitry and epigenetic state has been established. Further we will propose a possible mechanism responsible for DNA repair within the context of a hippocampus dependent learning task.

The CREB (or CREB/ATF) family of transcription factors includes three homologous genes: creb, cAMP response element modulator (crem), and activating transcription factor-1 (atf-1); the respective families of proteins are known as CREB, CREM, and ATF-1[46]. CREB and ATF-1 are expressed in all cells, whereas CREM are mainly present in the neuroendocrine system[47]. The transactivation domain of CREB is bipartite, including a constitutive (Q2) and a kinase-inducible domain. The Q2 domain mediates interaction with a component of the TFIID complex, whereas the kinase-inducible domain promotes isomerization by recruiting the co-activator factors CREB binding protein (CBP) and p300 to the promoters. The kinase-inducible domain region is active only when it is phosphorylated at Ser-133 by protein-kinase A in response to cAMP and is critical for the activation of CREB[48-49]. Protein kinase A consists of four subunits – two regulatory and two catalytic. Binding of cAMP to the regulatory subunits of protein-kinase A causes release of the catalytic subunits. In the next step, these subunits can enter the nucleus and interact with transcriptional factors, and this process determines gene transcription[49]. In its phosphorilated form, CREB binds to a DNA sequence called cAMP response element and its interaction with the CBP or p300, enhances transcription of CREB target genes. Hence, CBP and p300 are transcription co-activators which have intrinsic histone acetyltransferase activity[50], and this histone acetyltransferase activity is necessary for mediating transcription enhancement[47]. These proteins were found to acetylate Lys residues in histones but also in many transcription factors, and were later named factor acetyltransferases. p300/CBP were thus proposed to be components of chromatin-remodeling complexes[51].

p300 is at the same time implicated in DNA replication and repair. p300 functions as histone H3 and H4 acetyltransferases at double-strand break sites in NHJE[52]. Also, studies revealed that p300 acetylates 5' flap endonuclease 1 (FEN1), responsible for removing the RNA primer of nascent Okazaki fragments and also for processing the 5' termini at DNA strand breaks during base excision repair[53]. p300 protein interacts with proliferating cell nuclear antigen, which in turn stimulates FEN1[54]. It was found that OGG1 is acetylated by p300 and Lys338 and Lys341 are the major acetyl acceptor sites[55]. Thus, together with other proteins, we can conclude that p300 plays a central role in the long-patch pathway of base excision repair.

CREB factors were shown to be involved in many important functions of the nervous system including neurogenesis and neuronal survival[56], brain development[57], synaptic plasticity, and memory formation[58-59] but also in neuroprotection and regeneration[60]. Specifically, p300 is required for certain forms of memory and the histone acetyltransferase and carboxy-terminal domains play a critical role[47]. p300 seems to be involved in consolidation of memories, linking the memory of some objects with the memory of the context in which they appear[61]. One study found that p300 transgenic mice show deficits in hippocampus dependent long-term (24 hours after training) recognition memory measured with novel object recognition task[62]. In novel object recognition task, mice are put in the cage in the presence of two identical objects and allowed to explore for 15 minutes. After a retention interval of 24 hours, mice are placed again in the same cage where this time, one of the objects was replaced by a novel one. Mice are again allowed to explore for 15 minutes. It is considered exploration of the objects when mice are facing the objects and/or touching them. Preference for the novel object is measured as the percentage of time spent exploring the novel object relative to the total time spent exploring both objects.

One may thus note that p300 is involved in base excision repair, as well as in learning. Based on the evidence, we

propose that hippocampus dependent learning tasks like novel object recognition could be used as a method of facilitating base excision repair, and hence repairing the DNA in the hippocampal neurons involved in this type of learning (Figure 1). If this method proves to be effective, it could be the start for designing similar tasks for humans, as a behavioral therapeutic complement to the classical drug-based therapy in treating neurodegenerative disorders.

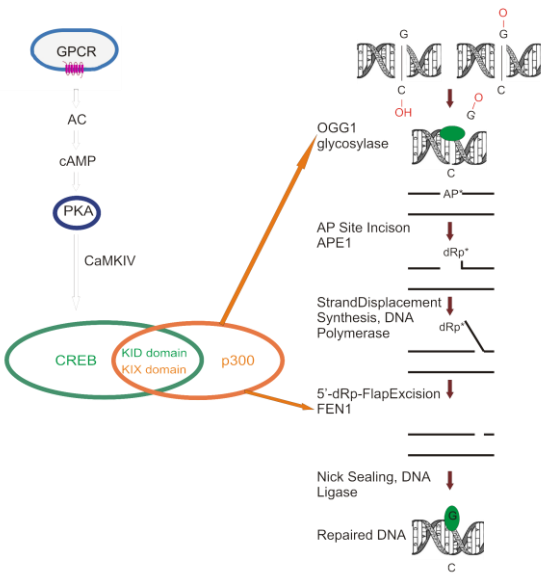

Figure 1 The connection between learning and DNA repair is made by p300.

p300 is involved in G-protein signaling. Some G proteins stimulate adenylate cyclase that results in elevation of cAMP. cAMP stimulates PKA. CREB interacts with cAMP response element and this modification is protein-kinase A mediated, promoting the interaction of the KID domain of CREB with the KIX domain of p300. p300 is a transcription co-activator with intrinsic histone acetyltransferase activity. It acetylates OGG1 at Lys338 and Lys341 and also 5' flap endonuclease 1, and in this way p300 plays a central role in the long-patch pathway of base excision repair.

AP site: Apurinic/apyrimidinic site; APE1: AP endonuclease 1; AC: adenylate cyclase; PKA: protein-kinase A; cAMP: cyclic adenosine monophosphate; CREB: cAMP response element binding protein; FEN1: 5' flap endonuclease 1; GPCR: G-protein coupled receptor; OGG1: 8-oxoguanine glycosylase; dRp: deoxyribose phosphate.

CONCLUSION

The genome is inherently subjected to spontaneous errors *via* a range of chemical reactions as well as degradation processes involving endogenous reactive oxygen species or some environmental agents such as ultraviolet light. The 8-oxoG is one of the major base lesions. Reactive oxygen species have been implicated in conditions ranging from cardiovascular dysfunction, arthritis, cancer, to aging and age-related disorders. The organism developed several pathways to counteract these effects, base excision repair being responsible for repairing 8-oxoG. Various medications have been developed to treat neurodegenerative disorders related with reactive oxygen species induced damage, by targeting the cAMP/PKA/CREB signaling pathway, one of the most important class of drug targets being the PDE-4 inhibitors. Although these drugs appear to be effective, one issue is their side effects. So, in addition to the effort of developing drugs without significant side effects, one option would be to find non-invasive forms of treatment, which are not based on drugs. Experimental studies suggest that cognitive stimulation and physical activity can prevent or delay the onset of Alzheimer's disease. Cognitive stimulation through various forms of environmental enrichment induces various alterations in brain structure and functions demonstrating that enrichment could make the brain more resilient, in the case of brain disorders, and to damage or degeneration.

Though there is sufficient evidence about the positive impact of enriched environment on the brain in general and for prevention of neurodegenerative disease in particular, it is not clear what aspect of enriched environment is critical and a clarification of the mechanisms involved in these effects is required. One direction is the CREB family proteins. The protein p300 – part of the CREB family – is a transcription co-activator with intrinsic histone acetyltransferase activity, which is necessary for mediating transcription enhancement and is proposed to be a component of chromatin-remodeling complexes. There are studies showing that p300 is required for certain forms of memory, being involved in consolidation process. It also appears to connect the memory of some objects with the memory of the context in which they appear. Recent studies linked enriched environment with reduction of cerebral oxidative stress in mice with Alzheimer's disease-like disease, while p300 was found to be implicated also in DNA replication and repair, OGG1 being found to be acetylated by p300, indicating that p300 plays a central role in the long-patch pathway of base excision repair. Based on the evidence, we propose that novel object recognition task – a hippocampus dependent task – could be used as a method of facilitating base excision repair, and hence repairing the DNA in the hippocampal neurons involved in this type of learning. If this method proves to be effective, it could be the start for designing similar tasks for humans, as a behavioral therapeutic complement to the classical drug-based therapy

in treating neurodegenerative disorders.

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