

LOW DOSE RADIATION ADAPTIVE PROTECTION TO CONTROL NEURODEGENERATIVE DISEASES

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□ Concerns have been expressed recently regarding the observed increased DNA damage from activities such as thinking and exercise. Such concerns have arisen from an incomplete accounting of the full effects of the increased oxidative damage. When the effects of the induced adaptive protective responses such as increased antioxidants and DNA repair enzymes are taken into consideration, there would be less endogenous DNA damage during the subsequent period of enhanced defenses, resulting in improved health from the thinking and exercise activities. Low dose radiation (LDR), which causes oxidative stress and increased DNA damage, upregulates adaptive protection systems that may decrease diseases in an analogous manner. Though there are ongoing debates regarding LDR's carcinogenicity, with two recent advisory committee reports coming to opposite conclusions, data published since the time of the reports have overwhelmingly ruled out its carcinogenicity, paving the way for consideration of its potential use for disease reduction. LDR adaptive protection is a promising approach to control neurodegenerative diseases, for which there are no methods of prevention or cure. Preparation of a compelling ethics case would pave the way for LDR clinical studies and progress in dealing with neurodegenerative diseases.

Key terms: DNA damage, Adaptive Protection, Low dose radiation, Neurodegenerative diseases

INTRODUCTION

A recent publication (Suberbielle *et al.*, 2013) entitled “Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid- β ” and the associated News and Views article in *Nature Neuroscience Journal* (Herrup *et al.*, 2013) entitled “Breaking news: thinking may be bad for DNA” have raised concerns regarding the observed increased DNA double-strand breaks (DSBs) following learning activity in the brains of mice. Concerns have also been expressed about the observed increase in DNA damage from even five minutes of strenuous exercise in an article (Fogarty *et al.*, 2011) entitled “Exercise-induced lipid peroxidation: Implications for deoxyribonucleic acid damage and systemic free radical generation”. Another cause of DNA damage that has traditionally been a concern since the 1950s is low dose radiation (LDR) (UNSCEAR, 1958) and it continues to be a concern (NRC, 2006). This article points out that the expressed concerns regarding the increased

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DNA damage in these three instances may not be justified as they have arisen because of incomplete consideration of the full consequences of the oxidative damage from these causes. When the effects of adaptive protections on the oxidative damage are considered, there is likely to be reduced DNA damage and improved health.

INCREASED DNA DAMAGE IN THE BRAIN FROM THINKING

The brain is known to consume about 20% of the oxygen utilized by the body (Clarke and Sokoloff, 1999), and the process of oxygen metabolism subjects the brain to oxidative stress and DNA damage (Gandhi and Abramov, 2012). Mental activity has been observed to increase oxidative metabolism in the brain (Roland *et al.*, 1987) and this increases the DNA damage. The accumulation of DNA damage in the aging brain (Moller *et al.*, 2010) has been implicated in the pathogenesis of many neurodegenerative diseases including Alzheimer's and Parkinson's diseases (AD and PD) (Jeppesen *et al.*, 2011). There is also evidence for declining DNA repair capacity in the brain with aging (Imam *et al.*, 2006). Hence the concerns expressed in the articles by Herrup *et al.* (2013) and Suberbielle *et al.* (2013) regarding the increased DNA damage from thinking, especially in the elderly with increased amyloid- β , appear to be well-justified.

However, there is also evidence for increased antioxidant stimulation (Rothman and Mattson, 2013) and upregulation of DNA repair enzymes from the increased neuronal activity (Yang *et al.*, 2011) which decreases the DNA damage in the brain during the subsequent period of elevated levels of such defenses. In addition, an enriched learning environment is known to result in increased neurogenesis (Brown *et al.*, 2003) which has shown promise in reducing neurodegenerative diseases (Abdipranoto *et al.*, 2008). When such adaptive protections are taken into consideration, it may be reasonable to conclude that learning activities actually reduce DNA damage in the brain. Epidemiological studies have shown considerable evidence for the beneficial health effects from thinking activities in the elderly, e.g. a protective effect of mental activity on cognitive decline has been observed in a review of a large number of studies (Wang *et al.*, 2012). Also, delay in cognitive decline in older persons with dementia has been observed from increased mental exercises (Cheng *et al.*, 2013).

In view of such beneficial effects from thinking activities, we would be justified in ignoring the concerns raised by the articles (Herrup *et al.*, 2013; Suberbielle *et al.*, 2013) regarding thinking. In fact, inducing stress response has been proposed recently as a treatment method for AD (Smith Sonneborn, 2012). On the other hand, excessive thinking can be unhealthy. Rumination, defined as repetitive, recurrent and uncontrollable thinking, has been implicated in cognitive impairments (Brinker *et al.*, 2013). Thus, thinking has a biphasic dose-response, with moderate amounts being beneficial and excessive amounts being harmful.

INCREASED DNA DAMAGE FROM PHYSICAL EXERCISE

A similar situation exists regarding physical exercise. Concerns have been expressed about the DNA damage observed following as little as five minutes of strenuous exercise (Fogarty *et al.*, 2011). Since DNA damage has been implicated in the pathogenesis of cancer and many other diseases, such concerns appear to be valid.

However, regular exercise is known to result in the upregulation of antioxidants (Berzosa *et al.*, 2011), DNA repair enzymes (Siu *et al.*, 2011), and immune system (Friedrich, 2008; Friedenreich *et al.*, 2010). When the effects of such adaptive protections are taken into account, it is reasonable to expect reduced DNA damage and improved health in the long term (Radak *et al.*, 2002). In a mouse study comparing an exercise group with a control group that did not exercise, reduced DNA damage markers such as micronuclei were observed in the exercise group, after both groups were subjected to subsequent oxidative stress from high dose radiation (De Lisio *et al.*, 2011). The health benefits of regular exercise in terms of reduced diseases including cancer have been well documented (Warburton *et al.*, 2006; Friedenreich *et al.*, 2010).

In view of the observed evidence for the beneficial effects of exercise, we would be justified in ignoring the concerns raised in the article by Fogarty *et al.* (2011) regarding the increased DNA damage from exercise. The beneficial health effects of exercise were nullified when antioxidant supplements were taken, indicating the key role played by the small amount of oxidative damage caused by exercise in upregulating the adaptive protection (Ristow *et al.*, 2009). Excessive exercise can however be harmful both for physical (O'Keefe *et al.*, 2012) and mental health (Kim *et al.*, 2012). Thus exercise also has a biphasic dose response.

INCREASED DNA DAMAGE FROM LOW DOSE IONIZING RADIATION

Another source of DNA damage about which there is considerable concern is LDR (NRC, 2006), for example from CT scans (Brenner and Hall, 2007). The radiation dose received from CT scans has been observed to cause DNA DSBs in lymphocytes (Beels *et al.*, 2012). Since cellular deficiencies due to DSBs have been linked to tumorigenesis (Rassool, 2003), the carcinogenic concerns regarding LDR would appear to be valid.

However, there is considerable evidence for the LDR upregulation of adaptive protections (Feinendegen *et al.*, 2011; Feinendegen *et al.*, 2013), antioxidants (Wang *et al.*, 2008), DNA repair enzymes (Bodnarchuk, 2003), and the immune system (Liu, 2007). As a consequence of such enhanced defenses, it is reasonable to conclude (analogous to the above-described examples of thinking and exercise) that LDR may reduce the accumulation of DNA damage in the long term, and result in better

health (Pollycove, 2007). For example, when mice were subjected to repeated CT scans on alternate weekdays over a period of 10 weeks, the radiated group had less DNA DSBs compared to a control group not subjected to the CT scans, when both groups were subsequently subjected to the oxidative stress from high dose radiation (Phan *et al.*, 2012). Chronic LDR has also been found to reduce DNA DSBs to below control levels in mice (Osipov *et al.*, 2013).

In comparison to the stresses of thinking and exercise for which the beneficial health effects are well known, and therefore the reports of DNA damage from these activities have not raised any major concerns, the positive health effects of low dose radiation are still being debated in the scientific community (Little *et al.*, 2009; Tubiana *et al.*, 2009). Hence, a more detailed discussion is needed to clarify the nature of its ultimate health effects, to determine whether the DNA damage from LDR should be a cause for concern.

CONTROVERSY OVER THE HEALTH EFFECTS OF LOW DOSE RADIATION

When X-rays and radioactivity were discovered at the end of the 19th century, thousands of medical practitioners began to use ionizing radiation to diagnose and treat many adverse medical conditions and diseases. They soon found out that low dose radiation had beneficial effects (on living organisms), while high exposures (acute or chronic) were harmful. After more than three decades of experience, formal radiation protection procedures and standards were developed for the practicing radiologists. The concept of this protection was the “tolerance dose” (rate). The standard issued by the ICRP in 1934 specified no more than 0.2 roentgen per day, which is about 700 mGy per year (Calabrese, 2009). A study of British radiologists suggests that radiologists who entered the profession prior to 1921 had higher cancer mortality than their peers, while those who entered after 1920 had a lower mortality (from cancer and all other causes) than their peers (Smith and Doll, 1981).

Meanwhile, geneticists discovered in the 1920s that exposure of fruit flies to high doses of radiation induced heritable gene mutations, in excess of the mutations in the controls. A typically high dose of several hundred roentgens (in tens of minutes) produced 150 times the normal number of spontaneous mutations. The number of radiation-induced mutations appeared to be proportional to the dose. A study performed in the 1940s at a low dose rate (52.5 roentgens in 21 days) showed no increase in the mutation rate in the irradiated flies over the mutation rate in the non-irradiated flies. This evidence of a threshold, which disproved the linear no threshold (LNT) model for radiation-induced mutations, was disregarded. In 1956, the LNT model for mutations was extended by the BEAR I Genetics Panel to link radiation dose to cancer mortality and

to adverse genetic effects in individuals and future generations (Calabrese, 2013).

Although there was/is no scientific evidence that supports this method of predicting adverse health effects from LDR, this LNT model has been used for the past 50 years to predict cancer risk. Data on the cancer mortality in the lifespan study of the atomic bomb survivors, that are attributed to the effect of high radiation, are extrapolated linearly to zero dose, to predict the cancer mortality due to LDR. This linkage of LDR to a risk of cancer is well established in radiation safety regulations, but the validity of the LNT model continues to be challenged in the scientific community (Tubiana, 2005).

RECENT DATA NEGATE CARCINOGENIC CONCERNS REGARDING LOW DOSE RADIATION

Recent data and analyses provide considerable evidence against the assumptions and ideas that formed the basis of the BEIR VII report. The error of linear extrapolation of high dose genetic and cancer effects to low doses becomes more obvious when one considers the widely different gene expression profiles (Ding *et al.*, 2005), proteome expression profiles (Yang *et al.*, 2006), and micro RNA responses (Chaudhry *et al.*, 2012) observed following low and high dose radiation exposures. A detailed animal study has shown no increase in cancer mortality when dogs were subjected to lifetime of chronic radiation at the rate of ~0.3 cGy per day (Fliedner *et al.*, 2012), completely contradicting the predictions of the LNT model of increased cancer risk.

According to BEIR VII report, the atomic bomb survivors provide the most important single source of data for evaluating the health risks of LDR (Page 141 of the report) (NRC, 2006). This dataset was used to justify the absence of a threshold dose for the carcinogenic effects of radiation and to rule out the possibility of beneficial effects of LDR (Page 10 of the report) (NRC, 2006). The latest update of the atomic bomb survivor data (Ozasa *et al.*, 2012; Ozasa *et al.*, 2013) is qualitatively different from the earlier data used in the BEIR VII report to justify the LNT model. The curvature in the dose response for solid cancer mortality in the 0-2 Gy region is significant with a P value of 0.02 in comparison to earlier reports where the curvature was not significant (See Table 7 on p.237 of the publication (Ozasa *et al.*, 2012)). This curvature arises due to the less than expected cancer rates for the dose range of 0.3-0.7 Gy (See text on p.238 of the publication (Ozasa *et al.*, 2012)). It results in a non-linearity of dose response that cannot be explained using the LNT model but is consistent with the radiation hormesis model (Doss, 2013).

The 15-country study of radiation workers (Cardis *et al.*, 2005), which was quoted as supportive evidence for the carcinogenic effect of LDR in Appendix V of BEIR VII Report (NRC, 2006), no longer shows increased

risk of cancer from LDR. The Canadian data, which was part of the 15-country study, has been withdrawn from use because of newly identified problems with the data (CNSC, 2011).

An analysis of the reported cancer incidence among the residents of apartments in Taiwan who were subjected to LDR from contaminated building materials (Hwang *et al.*, 2006; Hwang *et al.*, 2008) has shown a reduced overall cancer incidence in the radiated cohort in comparison to an age-matched control group (Doss, 2013).

In a study of second cancers following radiation therapy, non-cancerous tissues that were subjected to ~0.2 Gy had fewer cancers per kilogram than tissues that had zero radiation exposure from the therapies (Tubiana *et al.*, 2011).

These are examples of data and analyses published since the time of the above reports (Tubiana, 2005; NRC, 2006) which have supported the views expressed by the French Academy of Sciences regarding LDR while negating the arguments presented in the BEIR VII report supporting the LNT model. Hence, for LDR also, we would be justified in ignoring the concerns raised regarding increased DNA damage. High dose radiation, on the other hand, is well known to be harmful. Hence, radiation also has a biphasic dose response.

LOW DOSE RADIATION ADAPTIVE RESPONSE TO CONTROL NEURODEGENERATIVE DISEASES

In view of the above, and in spite of the observed increased DNA damage from thinking (Suberbielle *et al.*, 2013), or indeed possibly because of the increased oxidative damage from thinking, there may be long-term health benefits as a direct result of the adaptive protection. Considering these beneficial effects from the initial DNA damage, it is tempting to suggest that periodic application of a small amount of oxidative damage to the brain would be beneficial to brain health. This method of using low level stressors to upregulate protection systems has recently been proposed as a method of reducing the impact of neurodegenerative diseases (Smith Sonneborn, 2012; Stranahan and Mattson, 2012).

A convenient method of introducing low level oxidative stress into the brain is the application of LDR, as it can penetrate the skull and cause oxidative stress in the brain. This has been studied in a mouse model. LDR has been shown to stimulate neural stem cell proliferation, which resulted in neurogenesis in the hippocampus and led to improved animal learning (Wei *et al.*, 2012). LDR also resulted in improved retinal thickness in a mouse model of retinal neurodegeneration (Otani *et al.*, 2012). One advantage of LDR in comparison with brain exercises in upregulating the adaptive protection is that LDR can induce the stimulation in the whole volume of the brain, whereas brain exercises may activate the defenses only in the parts of the brain where there is increased neuronal

activity from the brain exercises. LDR has resulted in reduced oxidative stress, mitochondrial dysfunction, and apoptosis in a rat model of PD, indicating it could play a role in reducing the impact of PD (El-Ghazaly *et al.*, 2013).

Though no human studies using LDR have been performed to study its effect on neurodegenerative diseases, there are intriguing data in some epidemiological studies that indicate possible decrease of such diseases following exposure to LDR. One such study involved fluorspar miners exposed to radon gas. The miners had higher lung cancer mortality as expected, but for mental and nervous system diseases, there was a significantly lower standardized mortality ratio of 0.59 (95% CI 0.26-0.82) based on 16 observed and 24 expected deaths (Villeneuve *et al.*, 2007, Table 3).

Thus, there is justification for conducting clinical studies to determine the effectiveness of LDR in reducing neurodegenerative diseases. The carcinogenic concern regarding LDR is the major barrier to performing such studies. The incidence of neurodegenerative diseases such as AD is set to increase considerably with the aging population (Thies and Bleiler, 2013), and there are no treatment regimens for delaying or reversing these diseases (Korczyn, 2012). Investigating approaches such as LDR should be a very urgent priority. The cancer concerns regarding LDR are not justified based on the discussions above.

SUMMARY AND CONCLUSIONS

Concerns have been expressed in publications about the increased DNA damage from the stresses of thinking, exercise, and LDR with no consideration for the beneficial effects of the upregulation of adaptive protections. The effects of thinking exercises (in reducing cognitive impairment in the elderly) and physical exercise (in improving health) are well known, and so the reports of DNA damage from such activities have not resulted in any barriers to these exercises. The signaling from the oxidative damage appears to be essential for triggering the adaptive protections, as seen for exercise. Hence, it is appropriate to suggest the application of LDR which causes oxidative damage to the brain. It may be effective in inducing adaptive protections and reducing neurodegenerative diseases, for which there are no methods of prevention or reversal. Animal studies have shown the reduction of neurodegenerative diseases using LDR. Though there are carcinogenic concerns regarding LDR, as codified in radiation safety regulations, data and analyses published recently overwhelmingly negate these concerns.

Medical practitioners are urged to prepare the benefit-risk assessments needed to authorize clinical studies. The studies would demonstrate that low dose radiation prevents the onset or delays the progression of Alzheimer's and Parkinson's diseases.

ACKNOWLEDGMENTS

This work was supported in part by the Office of Science (BER), U.S. Department of Energy, under Award No. DE-SC0001196. The views and opinions expressed herein are those of the author and do not necessarily reflect those of his employer or the funding agency. The author thanks Drs R.K.Alpaugh and J.Q.Yu for comments on the manuscript. The author thanks Jerry Cuttler for detailed suggestions for improving the manuscript and for the section in the paper “Controversy Over The Health Effects Of Low Dose Radiation”.

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