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BOOK REVIEWS

Free Radicals in the Brain - Aging, Neurological and Mental Disorders
L. Packer, L. Prilipko and Y. Christen (Eds.)

As the editors state in the preface of the book, free radicals have been implicated in a wide range of disorders affecting brain e.g from Parkinson's disease to AIDS. Indeed, the recent report in the journal Nature (Vol 362, p 59) that a mutation on the gene encoding for superoxide dismutase may be the cause of familial amyotrophic lateral sclerosis, adds another disease to this list. The large number of disorders where free radicals have been implicated is not surprising since the brain is prone to free radical attack. This is mainly due to the presence of high levels of polyunsaturated fatty acid side chains in the membrane lipids, low levels of catalase, superoxide dismutase and glutathione peroxidase, and a high iron content. Although, the high iron content may be essential for normal neuronal function, the cerebrospinal fluid bathing the brain has very little spare iron binding capacity, since the levels of transferrin are low and are almost fully saturated. Hence, any tissue damage may result in the release of reactive iron that can stimulate free radical reactions. Consequently, in some neurological disorders, increased free radical attack may not be the primary cause of cell death, but the release of iron may trigger a secondary cascade of cellular damage.

Hence, a book dealing specifically with the effects of free radicals in the brain, will not only be topical but would also fill a gap in the book market. The question is whether this book will be well thumbed and quoted or will it gather dust on the book case? Looking at the title and contents page the book has a lot to offer for just a slim volume of 181 pages. However on closer examination it becomes clear that some of the chapters do not live up to their titles, whilst other do.

The book opens with a chapter on "Free radical scavengers and antioxidants in prophylaxy and treatment of brain disease" by L. Packer. Such an opening chapter should be one of the foundations for the rest of the book detailing the various free radical scavenging mechanism and how they interact to provide the brain with a defence against free radical damage. However, the author concentrates mainly on the actions of vitamin E in the first part of the chapter, ignoring the many other antioxidant systems except to discuss their role in the regeneration of vitamin E. There is also no comparison between the levels of antioxidants in the periphery and the brain, an important point since the brain is highly susceptible to free radical attack. The second half of the chapter concentrates on the beneficial effects of various antioxidants in the gerbil ischemia reperfusion model.

In contrast, the second chapter "Reactive oxygen species and the central nervous system" by B. Halliwell gives a concise account of the nature of free radicals - both general free radicals and those which can be formed particularly in the brain e.g autoxidation of dopamine to form 6-hydroxy-dopamine, a known neurotoxin. The account also deals with the toxic nature of free radicals, whether some radicals are useful e.g O_2^- in phagocytic bacterial killing, and if not what damage do they cause. Since the brain has a rich blood supply and that certain areas of the brain contain high amounts of iron, Professor Halliwell naturally deals with the role of

iron in free radical reactions and its potential sources in the brain. The author then takes a common sense look at two diseases, Parkinson's disease and Alzheimer's disease, in which free radicals have been implicated and the possible use of antioxidant therapy in these diseases. This chapter clearly demonstrates the ability of the author to take a common sense look at the involvement of free radicals in a physiological system, in this case the brain. Personally, I think this should have been the opening chapter and should have set the standard for the rest of the book.

Although the brain may be highly vulnerable to free radical attack, the brain is unique in having a primary defence against peripheral toxins in the form of the blood brain barrier. Dr Bourne details the special nature of the blood brain barrier in the chapter on "Protection against peroxidation by radicals in cerebral capillaries and microvessels during aging". Although the cerebral capillaries also contain a high level of polyunsaturated fatty acids, they have have also been shown to contain higher levels of glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase than the brain itself. In addition the levels of these protective enzymes in the cerebral capillaries do not change with age, unlike the brain.

The fourth chapter "Antioxidant protection of the brain against oxidative stress" by Kagan and colleagues, discusses the possibility of supplementing natural antioxidant levels with vitamin E to protect the brain from oxidative stress. Again this chapter has a central theme of vitamin E and ignores other antioxidants despite its broad title. In addition, the discussion about the benefits of vitamin E supplementation is based on research conducted on *in vitro* and *in vivo* models of oxidative stress, some of which are open to question. In particular Kagan and colleagues, reported increased levels of lipid peroxidation and reduced levels of vitamin E in the brain of rats treated for four days with a skeletal muscle depot injection of iron. The transport of iron across the blood brain barrier occurs via a transferrin receptor uptake mechanism that is strictly controlled to prevent toxicity from peripherally derived iron. Indeed, in the disease haemochromatosis where peripheral stores of iron are markedly elevated, brain iron levels are normal. Hence, it would seem unlikely that increased brain iron levels and markers of oxidative stress could result from skeletal depot iron injections.

The remainder of the book looks at the role of free radicals in various neurological conditions and the effects of antioxidant therapy. Here there is an obvious divide with some of the chapters giving an informative overview of the subject, whilst others fail to contribute to the book as a whole. Discussion in the more noteworthy chapters include:-

Chronic vitamin E deficiency syndromes in humans produces a severe neurological disorder with a clinical picture of ataxia with pigmented retinopathy. Dr Muller gives an informative overview of such syndromes in his chapter on "Antioxidant deficiency and neurological disease in humans and experimental animals" and how vitamin E supplementation can ameliorate or prevent the neurological condition. In order to research the effects of vitamin E deficiency further Dr Muller and colleagues have developed an animal mode using vitamin E deficient diets. These studies have demonstrated increased levels of free radical attack and lipid peroxidation, with the membrane bound organelles like the mitochondria being most susceptible. Such attack leads to the disruption of axonal transport and the accumulation of material in the nerve terminal, resulting in the degeneration and dying back of the axons.

One of the most common movement disorders is Parkinson's disease which is characterised by the destruction of pigmented neurones in the substantia nigra.

However, the cell loss is variable with some cells being less susceptible to the neurodegenerative process. Dr Javoy-Agid addresses this finding along with the role of free radicals in this disorder in a detailed chapter on "Dopaminergic cell death in Parkinson's disease". The dopaminergic cells that appear to be more susceptible contain high levels of neuromelanin. Mechanisms proposed as links between neuromelanin and the vulnerability of dopaminergic neurones include the generation of free radicals in the synthesis of neuromelanin, its ability to bind neurotoxins like MPP^+ and its ability to loosely bind iron in a reactive form. Indeed X-ray microanalysis has shown that neuronal iron levels are increased in the parkinsonian substantia nigra. In addition reports of increased lipid hydroperoxides, increased superoxide dismutase activity, but marked reductions in glutathione, glutathione peroxidase activity and catalase, support the involvement of free radicals.

"Role of free radicals in Alzheimer's disease and Down's syndrome" by Sinet *et al.* Down's syndrome or trisomy 21 results in mental retardation with an Alzheimer's like neuropathology. The gene for CuZn superoxide dismutase (SOD) is located on chromosome 21 which results in the high expression of SOD protein and mRNA which may result in a toxic production of H_2O_2. Similarly, in Alzheimer's disease cells with a high CuZn SOD content appear to be more susceptible to the disease process. Although this analogy between these two disorders is very revealing, the discussion on the involvement of free radicals in Alzheimer's disease could have been made complete by discussing the role of aluminium and iron which have been found in close proximity to the neurofibrillary tangles.

Out of the remaining chapters, there are three chapters with considerable overlap. This is in the area of schizophrenia and the side effects, tardive dyskinesias (TD), resulting from antischizophrenic drugs e.g neuroleptics. Although there is a consensus in these reports that vitamin E therapy can reduce the severity of the TD, a large proportion of the evidence for a free radical involvement comes from peripheral lipid peroxidation measurements in schizophrenic patients. Whether such results can be taken to indicate what is happening in the brain is debatable. In addition, these chapters do not discuss the role of iron in the development of TD, especially since increased iron levels have been found in the brains of schizophrenic patients with TD at post-mortem. Indeed, many neuroleptics are good iron chelators and have been proposed to either transport the iron across the blood brain barrier or alter brain iron metabolism.

The final chapter I wish to discuss is that by Dormandy and colleagues "Free radical activity in chronic ethanol intoxication in humans". Despite the title of the book this chapter concentrates on the peripheral measurement of indices of oxidative stress in patients with ethanol intoxication and makes very little reference to the brain. There is a wealth of literature concerning the effects of ethanol on the brain and the possible involvement of free radicals. Since this is one of the widely abused chemicals, this chapter would have been an important inclusion in the book. In its present form it should have been deleted since it does not contribute to the final discussion.

CONCLUSIONS

Overall the structure and design of the book could have been better. With a more strict remit to the individual authors this collection of papers could have been turned into the book the title promised it to be. Certain chapters were obviously out of

sequence e.g details of free radical scavengers were given before the formation of free radicals was described, also the book could have been subdivided, linking similar topics.

In the preliminary chapters a greater emphasis could have given to the function of free radicals in the brain. Although Professor Halliwell mentioned that nitric oxide (NO) is formed in the brain, since this free radical has been reported to act as a secondary neurotransmitter, whilst some reports indicate that NO interaction with O_2^- might be damaging to cells, perhaps more attention should have been given to this molecule.

One of the main faults with the book is that some of the chapters do not live up to their titles, with the chapter content only covering part of what should have been discussed. Also three of the chapter had large overlaps in content, whilst some contained poor scientific methods or little relevant information about the brain. Perhaps some of these chapters should have been amalgamated or removed to include other topics where free radicals have been implicated e.g the involvement of copper in Wilson's disease, motor neurone disease, manganese induced Parkinson's disease.

However, a large proportion of the chapters were well written and gave good overall coverage of the topics in question. Hence, overall the book "Free Radicals in the Brain" does contain some well written chapters on specific topics that will be useful as reference material and will be read on numerous occasions. However, the value of the book as a whole is reduced by some poorly written work that will be rarely cited.

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Ginkgo biloba Extract (EGb 761) as a Free Radical Scavenger, Advances in Ginkgo biloba extract research, volume 2
Edited by C. Ferradini, M.T. Droy-Lefaix and Y. Christen,
Elsevier, Paris, 1993, 186 pages

This slim attractive paperback volume reports the proceedings of a meeting held in Budapest June 1992. Since evidence has accumulated in recent years that oxygen-derived species are involved (although not necessarily important in) most, if not all, human diseases, interest has grown in the use of synthetic and natural antioxidants as therapeutic and preventive agents. Thus plant-derived antioxidants, such as flavonoids, are attracting increasing attention. *Ginkgo biloba* extract has long been claimed to have antioxidant and therapeutic properties, and the present volume was proposed to demonstrate its "protective action against free radical pathogenicity." Its ability to react with $OH^{\cdot}$ and $O_2^{\cdot -}$ is described using pulse radiolysis, although almost every organic compound reacts fast with $OH^{\cdot}$ and so these results are not surprising. More interestingly, EGb 761 was observed to inhibit haemoglobin-dependent lipid peroxidation, suggesting that one or more of its components can react with ferryl and/or amino acid peroxyl radicals. Several authors confirmed the ability of this extract to inhibit lipid peroxidation in cells or membrane preparations (such as synaptosomes), but possible effects of EGb 761 on the assay procedures themselves were not ruled out.

Several papers described interesting studies of the effects of *Ginkgo biloba* extract on ocular structures – protection against retinal damage caused by laser light, by toxic drugs, and by exposure to excess O_2 or light. An interesting paper by Cazals *et al.* examined its effect on salicylate-induced cochlear damage. EGb 761 was also reported to diminish reperfusion-induced arrhythmias in isolated rat hearts.

Given the rising interest in "natural" antioxidants, this book is timely. It is a useful compendium of data, and I am pleased to have it on my bookshelf. However, I have a feeling in the back of my mind that the authors set out to find good things about EGb 761 and did not look for bad things.

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