Oxidative Damage to Behavior During Aging

ROBERT A. FLOYD

WHY DO BIOLOGICAL SYSTEMS AGE? THIS QUESTION HAS puzzled experimentalists and creative thinkers for centuries. Increasing age leads to many changes in behavior and physiological function. The proposition that free radicals may be an important factor in aging (*1*) remains to be rigorously proven; but the presence of increased amounts of oxidized proteins in aging biological systems (*2*) supports the notion. The results of new experiments in Mongolian gerbils indicate that the accumulation of oxidatively damaged proteins during aging may be a cause of behavioral deficits in aging experimental animals and that this chronic oxidation may be reversible with compounds that react with and stabilize free radicals (*3*).

Normal, older gerbils differ from younger gerbils in that the brains of the older animals contain twice as much oxidized protein as those of younger animals and the amounts of two enzymes, glutamine synthetase and neutral protease, are lower in older than younger animals. Glutamine synthetase, a pivotal enzyme in brain nitrogen metabolism, synthesizes glutamine from the substrates glutamate, ammonia, and adenosine triphosphate (ATP). Neutral proteases catalyze the degradation of oxidized proteins (*4*). In addition to the protein changes, old gerbils make about twice as many errors as young gerbils in a radial-arm maze, a test that measures spatial and short-term memory (*3*). Evidence that these behavioral deficits and brain protein oxidation may be linked is provided by experiments that reverse protein oxidation in old animals (*3*).

PBN (*N-tert*-butyl-α-phenyl nitrone), a so-called spin-trapping compound (*5*), reacts with free radicals and yields a stable nitroxyl product. PBN offers protection from, and traps free radicals during, ischemia-reperfusion–mediated injury to heart (*6*) and brain (*7*) of experimental animals. Daily administration of PBN to old gerbils causes a decrease in the amount of oxidized protein and an increase in both glutamine synthetase and neutral protease activity in brain, as well as a decrease in the number of errors made in the radial-arm maze test for memory (*3*). In other words, PBN administration reversed the chemical and behavioral parameters of the older gerbils to nearly those values observed in the younger gerbils. Furthermore, after cessation of PBN administration, the amount of both oxidized protein as well as glutamine synthetase and neutral protease activities gradually returned to the values found in normal, older gerbils (Fig. 1). PBN did not have these effects in young gerbils.

It is known that oxidative damage destroys the activity of glutamine synthetase (*2*). Oxidative damage in biological systems is most likely caused by the destructive reactions that oxygen free radicals (*8*) undergo in the presence of the trace metals Fe or Cu (7). Therefore, in the older gerbils, PBN is probably trapping reactive, oxygen-derived free radicals and interfering with the cascade of free radical reactions that causes oxidative damage. PBN may be trapping a unique reaction product in brain and, as such, manifesting its action very specifically.

Oxidative damage to a biological system is a net result of the oxidative damage potential and the antioxidant capacity of the tissue (7), plus any repair processes. If PBN manifests its action by trapping a certain fraction of the free radicals, thus lowering the oxidative damage potential, then the ratio of oxidative damage potential to antioxidant capacity must increase with the age of the animal. The PBN-mediated reversal to the young state and its subsequent restoration to the old state after PBN cessation indicates that the oxidative damage is due to processes in dynamic equilibrium and that several components are responsible, all of which may change with the age of the animal.

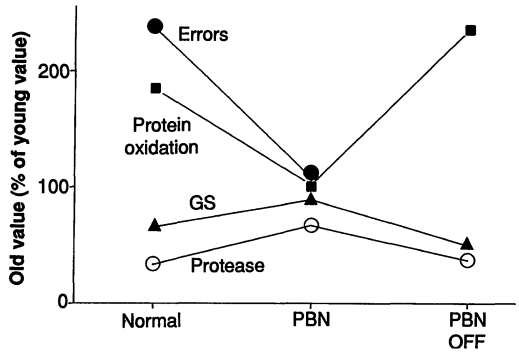

Fig. 1. The effect of PBN administration in old gerbils on the activities of glutamine synthetase (GS), neutral protease, and oxidized proteins, and the errors made in a radial-arm maze (an index of spatial and short-term memory). Data redrawn from (*3*).

The resiliency of this oxidative damage set point in old animals suggests that the system is at a regulatory optimum. This set point appears to be fairly rigidly regulated, changes with age, and is probably genetically determined (*2*). It is unknown, but will be of interest to determine, whether chronic PBN administration throughout the animal's life time permanently alters the oxidative damage set point.

PBN administration causes an increase in neutral protease activity, thereby increasing the catabolism of oxidized protein. It is possible that the neutral protease, which catalytically removes oxidatively damaged protein (*4*), is damaged by oxidative events (*2*). Thus, the mechanism for removal of oxidative damage may itself be damaged by oxidation (*2*). If so, then the age-associated expression of neutral protease activity may be a crucial control point. Glutamine synthetase removes glutamate and ammonia; both substances can be neurotoxic, so it is possible that oxidative damage to this crucial enzyme may contribute to the death of neurons. This mechanism would be most important during ischemia-reperfusion injury to the brain (7).

In summary, accumulating data clearly support the notion that free radicals influence the aging process (*9*).

Molecular Toxicology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104.

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