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THE SPIN-TRAP N-*TERT*-α-PHENYL-BUTYLNITRONE PROLONGS THE LIFE SPAN OF THE SENESCENCE ACCELERATED MOUSE

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Free radicals and oxidative damage have been proposed as underlying factors in aging, in chronic and degenerative diseases of aging and in acute clinical conditions. To test involvement of free-radicals in such processes, spin trapping agents which quench more reactive radicals to produce long-lived stable radical adducts have been used as an experimental strategy. Spin traps protect against oxidatively induced injury in numerous *in vitro* and *in vivo* model systems involving different organs. A model system for mammalian aging is afforded by the senescence accelerated mouse (SAM-P8), which exhibits many features characteristic of mammalian aging but with a much shortened lifespan. Daily intraperitoneal injection of the spin trap N-tert-α-phenyl-butylnitrone (PBN) was administered to male or female mice after they reached maturity at 3 months of age. PBN treated animals as compared with control sham injected animals revealed a remarkable extension of the mean life span in both male and female populations. Overall, a 50% mean survival rate was found of 42 weeks for control as compared to 56 weeks for the PBN administered groups. These results show that the spin trap PBN can prolong lifespan and support the free radical theory of aging.

The senescence-accelerated mouse (SAM) is a novel murine model of accelerated senescence, established by Takeda et al. (1). During aging, these mice exhibit a moderate to severe decline of activity, hair loss and lack of hair glossiness, skin coarseness, periopthalamic lesions, increased lordokyphosis of the spine, a remarkable age-dependent deterioration of memory and learning (2, 3) and a shortened life-span. Moreover, neurochemical studies have shown progressive glutamatergic, cholineragic and monoaminergic abnormalities in the SAM-P8 mouse brain (4).

N-*tert*-α-phenyl-butylnitrone (PBN) is one of the most widely used spin trapping agents (5). PBN has been successfully applied to the investigation of free radical reactions, such as in ischemia-reperfusion injury in vitro (6, 7) and in vivo (8-12) and is known to reduce the mortality of rats exposed to trauma or endotoxin, situations in which oxygen radicals were shown to be

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produced (13, 14), and fruthermore, to normalize the age-related biochemical parameters as well as physiological functions such as memory (15-16). In this study, we investigated the effect of PBN on the life-span of the SAM-P8 mouse.

MATERIALS AND METHODS

SAM-P8 mice were originally donated by Prof. Toshio Takeda (Kyoto University). They were housed under standard conditions at 25°C with a 12hr light/dark cycle (6:00-8:00) and allowed free access to water and a standard diet. At 3 months of age, they were divided to four groups: two groups (12 male and 12 female mice) for control, and the experiment groups (13 male and 12 female mice). The experimental groups were given PBN (30mg/kg i.p.) daily and their body weight was measured. The control groups were sham injected with saline.

RESULTS

Observation of all animals in the control and PBN treated groups (Fig. 1) revealed that in comparison with the control groups, PBN markedly prolonged life-span, i.e. overall the 50%

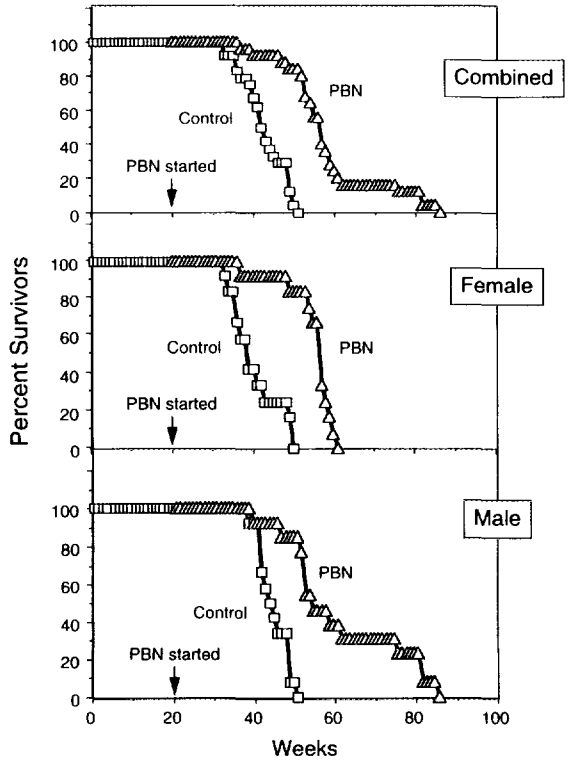

Fig. 1. Effect of chronic PBN administration of the life-span of SAM mice.

survival rate was 42 weeks in the control and 56 weeks in the PBN administrated group. The same tendency was also observed when the two sexes were compared (Fig. 1 middle and lower portion).

DISCUSSION AND CONCLUSIONS

Free radicals are thought to be an important factor in aging (17). PBN is a free radical spin trap reagent. In this study, we observed that chronic administration of PBN after 3 months of age prolonged the life-span of SAM-P8 mice, supporting the hypothesis that the free radicals may play an important role in the aging process. These experiments provide the first evidence that PBN prolongs the life-span of SAM-P8. We conclude that spin traps such as PBN could have potential prophylactic value, at least, for pathological senescence such as occurs in SAM-P8 mice.

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