National Institute on Aging

US Government Four Year Study on Protandim Regarding Lifespan

Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α-glucosidase inhibitor or a Nrf2-inducer Protandim.

Summary

The National Institute on Aging Interventions Testing Program (ITP) evaluates agents hypothesized to increase healthy lifespan in genetically heterogeneous mice. Each compound is tested in parallel at three sites, and all results are published. We report the effects of lifelong treatment of mice with four agents not previously tested: Protandim, fish oil, ursodeoxycholic acid (UDCA) and metformin – the latter with and without rapamycin, and two drugs previously examined: 17-α-estradiol and nordihydroguaiaretic acid (NDGA), at doses greater and less than used previously. 17-α-estradiol at a threefold higher dose robustly extended both median and maximal lifespan, but still only in males. The male-specific extension of median lifespan by NDGA was replicated at the original dose, and using doses threefold lower and higher. The effects of NDGA were dose dependent and male specific but without an effect on maximal lifespan. Protandim, a mixture of botanical extracts that activate Nrf2, extended median lifespan in males only. Metformin alone, at a dose of 0.1% in the diet, did not significantly extend lifespan. Metformin (0.1%) combined with rapamycin (14 ppm) robustly extended lifespan, suggestive of an added benefit, based on historical comparison with earlier studies of rapamycin given alone. The α-glucosidase inhibitor, acarbose, at a concentration previously tested (1000 ppm), significantly increased median longevity in males and 90th percentile lifespan in both sexes, even when treatment was started at 16 months. Neither fish oil nor UDCA extended lifespan. These results underscore the reproducibility of ITP longevity studies and illustrate the importance of identifying optimal doses in lifespan studies.

Key words: acarbose; fish oil; metformin; NDGA; Protandim; rapamycin; UDCA; 17-α-estradiol.

Protandim (Prot)

Beginning at 10 months of age, one group of mice was fed chow containing Prot at 600 ppm, to approximate the intake of humans who consume this commercially available nutritional supplement. The dose of Prot was increased from 600 to 1200 ppm when the mice reached 17 months of age, because testing of mice not included in the longevity cohort had indicated that 600 ppm, contrary to expectation, did not modulate levels of liver mRNA for genes involved in xenobiotic responses. As shown in Figure 1 and Table 1, there was a significant effect ($P < 0.012$) of Prot on survival of male mice in the pooled population, with a 7% increase in median survival. There was no significant difference in the proportion of control and Prot mice alive at the age at 90% mortality ($P = 0.1$ by the 'Wang–Allison test'). A secondary analysis of the survival data from individual sites revealed a significant increase in median survival ($P = 0.03$) at the UT site but no significant effects at the TJL and UM sites (Fig. S3 and Table S1, Supporting information). There were no significant effects of Prot on median or maximal survival of females in the pooled data (Table 1, Fig. 2) or in the data from any individual site (Table S1, Fig. S3, Supporting information).

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Table 1 C2011 mice, pooled across sites

Group	Number	Median days	Median % increase	Log-rank *P*-value	90th percentile days	90th percentile increase	Wang–Allison *P*-value
Males: pooled across sites							
Control	294	780			1064		
17aE2	144	925	19	0.000	1193	12	0.000
Prot	155	834	7	0.012	1130	6	0.103
Met	148	835	7	0.348	1046	−2	0.405
Met/Rapa	158	959	23	0.000	1175	10	0.000
UDCA	149	832	7	0.448	1063	0	0.868
Females: pooled across sites							
Control	281	874			1092		
17aE2	135	883	1	0.981	1091	0	0.864
Prot	134	896	3	0.291	1154	6	0.163
Met	140	872	0	0.791	1094	0	0.617
Met/Rapa	142	1078	23	0.000	1278	17	0.000
UDCA	133	865	−1	0.762	1105	1	0.491