High levels of physical activity accelerate telomere shortening in Cast/ei J mice.

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Three reports, including one from our lab (Ludlow et al 2008), have shown physical activity to be associated with telomere length in humans. We observed that moderate levels of physical activity were associated with longer telomeres compared to both very low and very high physical activity levels ($P < 0.05$). Our primary purpose was to determine the feasibility of mechanistic studies on telomeres in mice known to voluntarily run at high levels. To achieve this aim, we investigated telomere length and telomerase enzyme activity in two commonly used inbred mouse strains (Balb/c J and C57/Bl6 J) and one strain known to have short telomeres (Cast/ei J). The Balb/c J and C57/Bl6 J mouse strains had significantly longer telomere lengths when compared to both humans ($P < 0.001$) and the Cast/ei J animals ($P = 0.01$). This result was consistent across multiple tissue types in the mice, with the Cast/ei J having significantly shorter telomere lengths. No differences were observed in telomerase enzyme activity among strains, though tissue-specific differences were noted within the Cast/ei J strain (e.g., highest values in brain and liver vs. skeletal muscle). The second purpose of our research was to determine if long-term voluntary physical activity influenced telomeres in one of the above selected strains. Cast/ei J mice were subjected to a 1 yr voluntary wheel running intervention in comparison to an aged-matched sedentary group. Telomere length was measured in the exercise (wheel access, $n = 10$) and sedentary ($n = 11$) groups in red gastrocnemius skeletal muscle homogenates. The exercise group averaged 6.2 ± 2.3 km running per day over the 1 yr period. Body weight measured bi-weekly did not differ between the groups ($P = 0.42$). At the end of the 1 yr intervention, telomere length (Telomere PCR Ct to Single copy gene PCR Ct Ratio; Cawthon 2002; Callicott and Womack 2006) was significantly longer in the sedentary vs. exercise animals (sedentary = 6.55 ± 0.61 vs. exercise = 4.24 ± 0.50 AU; $P=0.007$). The exercise mice exhibited significantly higher telomerase activity in skeletal muscle tissue compared to sedentary mice (0.083 ± 0.025 vs. 0.018 ± 0.005 amoles/0.43 ug protein; $P=0.03$). We also examined mRNA levels of *Trf2, Trf1, Ku70, Ku80* and *Gapdh* in skeletal muscle of these same mice and observed an up-regulation of all telomere-related targets in the exercise vs. sedentary mice. These results provide the first evidence of change in telomere length in response to voluntary physical activity in mice. Our preliminary findings provide support for a role of physical activity in modifying telomere length, telomerase activity, and expression of telomere-related proteins. The Cast/ei J strain, a highly spontaneously active strain of mouse, likely performs a 'moderate' level of PA in a non-wheel cage and when given wheel access, exercises at an extremely high level which increases telomere attrition.

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