**Telomerase Reactivation by 4-OHT as a Measure to Reverse Aging**

Author: Allie Brown
Major: Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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**Aging may be defined as the progressive loss of physiological function leading to bodily deterioration. Many human diseases occur as a result of this deterioration. Primarily, aging affects the reproductive system and neurological pathways most problematically. Thus, the concept of aging in humans has garnered much attention and sparked studies of compensatory measures to delay and prevent the degenerative process. Different remedies are known to slow aging, but the ability to reverse the process has yet to be confirmed. One molecular hallmark of aging is the progressive shortening of telomere length as an organism grows older. Thus, this review outlines a study on the regenerative abilities of telomerase reactivation in mice. Results from telomere manipulation in mice suggest that certain procedures may be done to reverse many deficits of aging in humans by extending telomeres. Although this conclusion is ground breaking, more research is needed to confirm the effect of telomere reactivation in humans.**

**Introduction**

The process of aging may be characterized by substantial decline of the physiological and biochemical properties of the body. Bodily decay such as this increases an organism’s susceptibility to death and is understandably frightening to most people. In addition to this, the universal effect of aging and death on all organisms has piqued scientific interest on the subject. One specific area of study is telomere degeneration. Telomeres are regions of repetitive DNA present at the ends of every chromosome. These regions are repaired by telomerase, an enzyme responsible for maintaining the length of telomeres in DNA. However, with age, telomerase becomes less active, allowing telomeres to be shortened in each successive round of cell division. This eventually threatens the persistence of an organism’s DNA through aging. Thus, telomere deterioration is of scientific interest, as it is a natural development in the aging process and is relevant in most mammals. Specifically, telomere decay causes many deleterious effects such as organ failure, tissue deterioration, and impaired stem cell production and differentiation. With recent developments in genetic engineering and molecular biology, scientific research is able to examine measures to slow, prevent, and reverse telomere shortening and its effects on the body.

In this study, a specific allele was engineered to allow researchers the ability to reactivate telomerase. The ability of this allele was determined by its susceptibility to transcription. When it is not transcribed, telomerase is not active, but when the allele is transcribed, telomerase is reactivated. Researchers inserted this allele, referred to as TERT-ER, into the genome of diseased mice that displayed symptoms mimicking that of aged mice. Researchers did not allow this allele to be transcribed in the sample mice, which caused shortened telomeres in their DNA. By activating this allele, or effectively causing it to be transcribed, researchers were able to instigate telomere lengthening. The study first verified that mice homozygous for this allele did have dysfunctional telomeres and experienced the effects caused by damaged DNA as mentioned previously. A subset of the mice with the TERT-ER allele was then manipulated further. Researchers exposed these mice to 4-OHT, a chemical that activates the TERT-ER allele, allowing activation of telomerase. Ultimately, this created three research groups for study: TERT-ER mice, 4-OHT treated TERT-ER mice, and healthy mice serving as the control group.

 In order to determine the effectiveness of telomerase reactivation by 4-OHT treatment, the groups of mice were subjected to various tests. It was expected that TERT-ER mice have impaired functioning ability due to the effects caused by their shortened telomeres. It was also hypothesized that 4-OHT treated mice would exhibit repaired neurological and reproductive functioning because of telomerase reactivation. In order to test this hypothesis, the behavior and ability of 4-OHT treated mice were compared to that of healthy mice. Astoundingly, in every test performed, the 4-OHT mice outperformed the TERT-ER mice as well as producing similar results to the healthy controls.

**Recent Progress**

Through the experiments done on all three mice groups, this study presented probable evidence that telomerase reactivation may correct aging through telomere elongation. Initially this study provided a framework of the effects of telomerase reactivation. Cells were sampled from a subset of TERT-ER mice and grown on a plate containing 4-OHT. After four weeks of exposure, both on the plate and to the mice directly, the DNA was examined to find that telomeres were lengthened. This is notable as researchers also observed increased cell division, decreased regulation of the cell cycle, and decreased apoptosis in germ cells. This allowed these organisms to duplicate their genomes more quickly, repairing tissue damage caused by the previous degenerative telomeres. Specifically, researchers noted that these data stipulate an absence of damage signaling in the DNA of telomerase reactivated TERT-ER mice.

 After researchers had established that telomerase reactivation does lead to telomere lengthening and associated tissue repair, the study focused on the effects of reactivation on the brain and neural processing. A specific area of the brain was chosen for study, based on its ability to generate stem cells that may differentiate into neurons. This is a significant area of study as aging in humans is marked by impaired neurogenesis, the regeneration of neurons in the body. By examining stem cell proliferation in the three groups of mice, researchers found the ability to generate stem cells was severely reduced in TERT-ER mice as compared to controls. It was also found that 4-OHT treated TERT-ER mice had a significant increase in neural stem cell proliferation, ultimately comparable to the healthy controls. These results indicate that telomerase reactivation is effective in increasing stem cell proliferation, also reversing neural degeneration caused by loss of telomere integrity.

 This study then tested the effects of telomerase reactivation further on neurological function. For information about the functionality of the brain, researchers focused on the corpus callosum, the area of the brain connecting the two hemispheres. When compared to healthy controls, it was found that TERT-ER mice had less cells functioning to protect neurons in this area, while also displaying less overall brain weight. However, 4-OHT mice were found to have a restored number of these cell types as well as a mean brain weight comparable to healthy controls. Thus, researchers concluded that 4-OHT treatment and telomerase reactivation was a significant treatment to restore degenerative brain tissue, increasing overall brain weight.

 Finally, researchers aimed to understand the effect of telomere shortening and regenerative possibilities on olfaction. This study provides relevance as human aging often includes a decreased ability to sense odors. To conduct this study, researchers presented mice of all three groups with different repellent odors such as the scent of a predator or the scent of toxic chemicals. It was previously known that mice show avoidant behavior when presented with such odors, and the response from healthy controls was consistent with this finding. Interestingly, when TERT-ER mice were exposed to these odors at low concentrations, they showed indifferent behavior, and occasionally were attracted to the scents. Conversely, 4-OHT treated TERT-ER mice presented avoidance behaviors in response to scents at all concentrations. These results indicated that 4-OHT treatments and telomerase reactivation were capable of reversing the degenerative effect on olfactory function.

 Ultimately, this study demonstrated that telomerase reactivation provides significant effects on biological structure and function. When treated with 4-OHT telomerase-reactivating chemicals, organisms showed increased telomere length. These organisms further displayed improvement in multiple telomere degenerative areas. These areas included tissue rejuvenation, cell and neural stem cell proliferation, increased brain size, and improved olfaction. Overall, this study displayed that only one four-week treatment of 4-OHT is effective on telomerase activation and reversal of many detrimental aging symptoms.

**Discussion**

The results discussed in this review lead to promising possibilities in restorative medicine against aging. It is known that telomere shortening negatively affects the body in aging, but what had not been demonstrated before is the ability to reverse these detrimental symptoms. This study demonstrates, through the multiple realms of testing, the reliability and effectiveness of the 4-OHT treatment to restore functioning after symptoms of aging have appeared. Specifically, these data were supported significantly with a statistical p-value less than 0.0001. (Jaskelioff et al. 2011) When applied to humans, this study provides a possibility to change what is known of aging. This has the potential to not only change lives, but to reform the way aging is perceived universally. Further research is needed to replicate the treatment findings of 4-OHT. More attention should also be paid to how this treatment or others like it will influence human health. Verifying this treatment for human use could be monumental to preventative aging, but more information is still needed.

**References**

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