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Review Article

Beneficial Effects of Telomerase Activator (TA-65) Against Chronic Disease

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Abstract

The telomere activator-65 (TA-65), extracted from the Chinese herb *Radis astragali*, has been shown to have protective effects against a number of chronic conditions including insulin resistance, neural depression, cardiovascular disease and age-related macular degeneration among others. Telomeres are protective nucleotide repeats (TTAGGG) located at the end of chromosomes. These telomeres are shortened after cell division and trigger cell senescence and tissue degeneration. Once they become quite short the effects of TA-65 on chronic disease are related to its function of activating telomerase and leading to increases in telomere length. Telomere shortening is associated with aging and age-related diseases. Cell and animal studies have shown a protective effect against age-related macular degeneration, oxidative stress and cardio metabolic risk factors. In this review, some of the more important findings related to the action of TA-65 are highlighted. There is a need for more clinical trials to determine specific effects in populations at risk for chronic disease.

Keywords: *Cycloastragenol, TA-65, Astraglosides, Telomere Elongation, Oxidative Stress, Chronic Disease*

Abbreviations

ADM: Age Related Macular Degeneration; AST IV: Astragalosides IV; CAG: Cycloastragenol; CD: Cluster of Differentiation; DMSO: Dimethyl Sulfoxide: HEK: Human Epidermal Keratinocytes: MEF: Mouse Embryonic Fibroblasts; mTRT: Mouse Telomerase Reverse Transcriptase; TA-65: Telomerase Activator 65; TXNIP: Thioredoxin-Interacting Protein

Introduction

Telomere activator-65 (TA-65), is a component extracted from *Radix astragali*a Chinese herb, which has been used traditionally for increasing life-span [1]. In 2014, RevGenetics, the world's leading source of specialized small molecule supplements, demonstrated that Cycloastragenol (CAG) is the active ingredient in TA-65 supplements [1]. The potential of TA-65 to increase telomerase activity has been demonstrated as well as that of other compounds in an established cell model of telomere shortening [2].

Radix astragali is one of the most popular Chinese herbs, which has been used for thousands of years. It can be used alone or in combination with other medications. If used as traditional treatment, it is mostly prepared in concoctions or in soups from the shredded root [3] and it has been shown to have effects in enhancing the immune system, increasing stamina as well as improving cardiac output [4,5]. The first isolated metabolite is astragaloside IV (AST-IV), which has been demonstrated to have cardio protective effects mainly against hypertension [6-9]. CAG is the second metabolite isolated from *Radix Asragali* that together with AST IV, has been identified as a telomerase activator, whose function is to increase the length of telomeres, a protective sequence at the end of the chromosome [10-15].

Telomeres are protective nucleotide repeats (TTAGGG) located at the end of chromosomes. However, due to the lagging strand of the chromosome, there is an end replication problem [16], which results in a truncated replication [17] therefore the telomere is shortened after each cell division, and will ultimately trigger cell senescence and tissue degeneration when telomeres become extremely short [16,17].

In addition to cell division, oxidative stress can also cause telomere shortening. There is some evidence that oxidative stress-mediated DNA shortening is an important determinant of telomere shortening [18]. This could explain the difference between the estimated loss per division (~20 base pairs) due to the end-replication problem and the actual telomere shortening rates (50 - 100 base pairs). Compared to the end-replication problem, the oxidative stress appears to determine a more significant role on shortening of telomeres.

Telomere shortening is associated with aging, mortality and age-related diseases. In regards to aging, Cawthon., *et al*. [19] discovered that longer telomerases are correlated with longer lifespan. Some current results suggested that telomere length is associated with advanced age-related macular degeneration [20] and telomere attrition plays an important role in a variety of disease including AMD [21,22]. TA-65 could enhance the replicative capacity of the retinal pigment epithelium and thus provide a treatment effect on AMD patients [23].

In addition, and according to recent research from Beijing University [24], it was demonstrated that CAG was a potential therapeutic candidate for alleviating obesity and hyperlipidemia. In another study investigating the regulation of endothelial homeostasis in the setting of endoplasmic reticulum stress, it was found that AST IV and CAG ameliorated endothelial dysfunction by inhibiting inflammation and reducing cell apoptosis. Further, another investigation showed that AST IV and CAG were equally effective in the regulation of endothelial homeostasis [25]. In terms of the sub-chronic toxicity and genotoxic potential of CAG, daily ingestion of CAG at up to 150 mg/kg body weight/day via oral gavage was well tolerated by rats [3]. *In vivo* assays also provided strong evidences that CAG lacks mutagenic and/or clastogenic potential [3].

TA-65 and Telomere length

There are only four original research papers addressing CAG telomerase activator's function in the last ten years. To demonstrate the effect of GAG on telomerase activity and telomere length, a study was conducted in mice [10]. In this study, three different experiments were carried out to investigate whether *ex vivo* mouse embryonic fibroblasts (MEF) incubated with TA-65 could lead to an increase in telomerase activity as well as an increase in the length of critically short telomeres in a telomerase-dependent manner. At the same time, it was determined whether, TA-65 as a component of the diet in mice could improve certain health-lifespan indicators [10]. However, authors concluded that TA-65 administration for 4 months did not change the mean or maximum lifespan of female mice. Notably in this study, TA-65 intake did not increase the incidence of cancer as well as other detectable negative secondary effects.

It has been demonstrated that TA-65 is an effective telomerase activator in human immune cells, neonatal keratinocytes and fibroblasts [11,12]. To demonstrate whether TA-65 could have an impact on telomerase-dependent telomere extension, an ex vivo experiment was conducted in a telomerase-haploinsufficient model [10]. Investigators crossed $Terc^{+/-}$ (Terc gene mutation/deficient could result in decreased telomerase activity and accelerated telomere shortening) female mice with G2 $Terc^{-/-}$ male mice to generate littermate populations of MEF which is either G3 $Terc^{+/-}$ or G3 $Terc^{-/-}$. Using a telomere repeat amplification protocol assay (TRAP), it was found that TA-65 was capable of activating telomerase by approximately 2-fold in telomerase-haploinsufficient MEFs. In addition, it was observed that mice treated with 0.1% Dimethyl sulfoxide (DMSO), the control telomerase reconstituted G3 $Terc^{+/-}$ showed a significant decrease in "signal-free" ends as well as critically short telomeres compared to G3 $Terc^{-/-}$. In contrasts, TA-65 telomerase-proficient cells at concentrations of 1 or 10μm led to an extra decrease of the "signal-free ends" to 1.6% and 2.9%, and short telomeres to 1.9% and 3.3%, respectively, compared to the control set treated with 0.1% DMSO. Importantly, G3 telomerase-deficient $Terc^{-/-}$ treated with TA-65 presented similar number of short telomeres or "signal-free ends" compared to baseline, which demonstrated that the action mechanism of TA-65 is telom-

erase-dependent. Furthermore, when treated with 10 μm of TA-65, there was an increase of average telomere length in G3 Terc$^{+/-}$ [10].

A higher cellular level of gamma-H2AX is the result of the presence of short or uncapped telomeres, which is an indicator of activation of DNA damage response. Control G3 Terc-/- MEFs presented a higher level of nuclear gamma-H2AX compared to G3 Terc$^{-/-}$ group. Again, 10-μm dose of TA-65 treatment decreased the nuclear gamma-H2AX level only in telomerase-proficient G3 Terc$^{+/-}$ cells but not in telomerase-deficient G3 Terc$^{-/-}$ cells, which demonstrated the previous conclusion that the effect of TA-65 on preventing DNA damage is telomerase-dependent [10].

To explore whether a dietary supplement with TA-65 would influence telomere changes in vivo, two cohorts of mature or old female mice (1 or 2 years old, respectively) were fed for 4 months, either with control vehicle which was fruit mash or vehicle plus TA-65, while the final concentration is 25 mg/kg/bw/day [10]. The mouse telomerase reverse transcriptase (mTRT) mRNA levels were measured at 3 months' post-treatment in different tissues for the 2-year-old TA-65-treated and control cohorts. As a result, there was a significant 10-fold increase in mTERT mRNA and protein levels in the liver at the time point of 3 months' post-treatment. For other tissues, there was also a modest increase of mTERT mRNA levels including kidney, lung and brain, although these changes did not meet statistical significance.

To delineate the effect of TA-65 on telomerase-dependent telomere elongation, the telomere length was measured from blood samples of the 1- and 2-year-old TA-65 treatment and control groups at 3 months' post-treatment [10]. The finding was that there was no significant increase of telomere length in the treatment group compared to the control group. However, there was a significant decrease in very short telomeres in the treatment group at 3 months' post-treatment, which demonstrated that TA-65 has a significant and consistent capacity to promote rescue of short-telomeres both in *ex vivo* (MEFs) and *in vivo* (mice) [10].

Another study by Tomas-Loba., *et al*. [26] postulated that TRT could lead to a significant increase in both mean and maximum lifespan in cancer-resistant mice. However, this study did not present any statistically significance after 4 months' treatment of TA-65. More studies need to be conducted to provide additional evidence on the role of TA-65 and life span.

A study showed the first evidence that dietary supplement TA-65 could lengthen telomeres and potentially improve health outcomes in humans with no observed safety concerns [27]. To investigate whether TA-65 can alleviate telomere attrition in CMV^{+} (cytomegalovirus) subjects, which has decreased T-cell immunity, 117 subjects were enrolled and 97 completed the study. All of the subjects were divided into 3 groups: placebo, low-dose TA-65 (250IU) and high-dose TA-65 (1000IU), after a 1 year recycle in the unit of 104 days including 90 days taking supplement and 14-day abstinence, they measured Median TL (telomere length), length of each telomere and 20th percentile of TL using Q-fish.

For the median TL, the placebo group showed a decrease at 9 and 12 months, while the low-dose TA-65 group showed a significant increase at 3 months and followed by relative stability. However, the high-dose TA-65 group showed a trend of improvement in median TL compared to placebo group, although values were not significant. The 20th percentile TL presented a similar result with median T [27].

The cause of no significant change in the high-dose group is still unknown, while some studies showed a trend that high-dose partially reserve some positive effects of TA-65, which raised a possibility that TA-65 may have a bell-shaped dose response curve. In future studies, it is necessary to increase the dose and subjects as well as monitor the compliance more tightly over time.

TA-65, Glucose tolerance and insulin resistance

To address whether TA-65 would have benefits on health span and/or life span in mice, glucose tolerance and insulin resistance were established as two indicators. The finding was that TA-65 administration for 4 months significantly improved the capacity for glucose uptake in the 1-year-old treated mice while no significant changes showed in the control group at 6 and 12 months' post treatment [10].

Additionally, 1-year-old treated mice showed a tendency of lowering insulin levels and HOMR-IR scores at 6 months' post treatment; however, it did not reach statistical significance. After 12 months post treatment, the tendency was attenuated, indicating that a discontinued TA-65 supplementation could not handle long-time health benefits. As for 2-year-old treated mice, no significance showed in the glucose tolerance, insulin levels and HOMA-IR scores [10]. There is therefore the need for more studies to test the effects of TA-65 in glucose intolerance and insulin resistance.

TA-65, Cancer and Immunity

To explore whether TA-65 supplemented diet had long-term side effects in mice with cancer tumors, a pathological analysis was performed in all female in both treatment and control groups at the time of their death [10]. The results showed that TA-65 treated mice had a similar incidence of malignant cancers at the time of death, although there was a tendency of decreased sarcomas and slightly decreased lymphomas, as well as a decreased incidence of cancer in the liver in the TA-65 treated group, which did not reach the statistical significance [10].

Another study conducted in cells used TA-65 and HTA (also called HTA98 which is 98% CAG), two extracts from *Astragalus membranaceus*, for their effects on both telomerase activity and proliferative activity of human cluster of differentiation (CD)4 and CD8 T cells [28].

Six healthy donors provided purified CD4 and CD 8 T cells. Those cells were divided into 3 groups, and treated with TA-65, HTA, or DMSO (dilute control), respectively. Telomerase activities were measured 72 hours after primary stimulation and the process repeated after 18 - 21 days for a secondary stimulation. The results showed that the HTA-mediated effect failed to reach statistical significance of all six cultures on increasing telomerase activity whereas the TA-65 group showed a significant increase in telomerase activity of all six cultures [28]. In addition, both CD4 T cells and CD8 T cells presented an increase in proliferation which was not observed in the HTA group even after a second stimulation.

Another study from the same group reported on the TAT2 telomerase activator on CD8 T cells from individuals infected with HIV, and they found that there were 1.5 - 2.5 fold increase of telomerase enhancement in the treatment group compared with the control group, which demonstrated an increase in the ability of T cells to reduce HIV production when co-cultured with infected cells [12]. These results and those from the previous paragraph suggest that TA-65 may be useful in treating both HIV disease and other clinical situations that required enhanced T cell telomerase activity. Although this study showed positive result of TA-65 on increasing telomerase and proliferative activity, the sample size was small so that future studies need to include large scale of sample size.

TA-65 and Neural Depression

CAG may exhibit antidepressant-like properties as demonstrated by the evaluation of pharmacological effects of CAG on neuronal cells and depression-like behavior in mice [28]. The results showed that CAG promote in vitro scratch wound closure. CAG treatment (0.0110μm) improved telomerase activities significantly in human epidermal keratinocytes (HEK) while 3μm CAG induced the most significant telomerase activation, which was similar to the effect of epidermal growth factor. Treatment of CAG (3 μm) for 6 days doubled the cell growth compared to the control group, while CAG did not induce HEK cell migration at any concentration level. These results suggest CAG had the capacity for wound healing.

As for the effect of CAG in nervous system, PC12 cells, primary cortical and hippocampal neuron cultures were treated with CAG for 24h. After the RQ-TRAP assay, it was found that in PC12 cells, 1-3 μm CAG treatment induced a significant increase (about 2-fold) in telomerase activity. Cultured primary neurons (12DIV) treated with 0.01μm CAG presented a significant increase in telomerase activity. These results suggested that CAG enhances telomerase activity in a neuronal cell line and primary neurons. It was also found that both basal and CAG-induced activities are dependent on cAMP response element binding expression [28]. This study also demonstrated that CAG

could upregulate TERT mRNA expression, and because there was an up-regulation of bc12 mRNA expression, this suggests that CAG may improve pro-survival signaling in neurons.

Regarding correlations between CAG and depressions, it was found that CAG treatment for 7 days reduced the immobility time (depression-like behavior) when forcing mice to swim [29]. Notably, CAG did not lead to any psychostimulant effect, including total distance, duration in the central zone and duration in peripheral zone in the swimming test. The mechanism for the antidepressant effect could be accounted by CAG telomerase and CREB activation in PC12 cells and primary neuronal cultures.

TA-65 and Age-related macular degeneration (AMD)

Dow., *et al*. [23] conducted a study in 2016 regarding the relationship between TA-65 and age-related macular degeneration, which is the first randomized, placebo controlled study regarding the effect of TA-65 on AMD A hypothesis raised that the treatment effect was due to improved function of RPE from reducing telomere attrition via telomerase activation. 38 subjects with macular drusen aged between 52 - 83 were enrolled in this parallel, double-blinded study. All participants were divided into 2 groups, a placebo with only excipients and the other contained 8 mg purified of TA-65, followed with a micro-perimetry threshold testing at baseline, 6 months and 1 year. There were two outcomes, reduced threshold and average threshold. The TA-65 group showed a significant improvement relative to the placebo group. The border line of improvement was drawing at 6 months and maintained a relative stability at 1 year. The macular threshold sensitivity improved 0.97 dB relative to control group, while the reduced thresholds showed an 8.2% decrease compared to the placebo group.

The final conclusion in this study is that the oral TA-65 significantly improved the macular function of treatment subjects compared to control group. However, future studies are required with larger subjects and present a therapeutic chance for those with early AMD since no effective therapy for dry degeneration up to date.

TA-65 and cardiovascular disease

Wang., *et al*. [24] investigated the effect of CAG on suppressing adipogenesis in 3T3-L1 adipocytes. They found that the conversion of preadipocyte into mature adipocyte could be inhibited by the accumulation of Ca^{+}, through preventing post confluency of preadipocytes, restricting c-myc expression and regulating cAMP levels. At a 10μm dosage, CAG stimulated calcium mobilization in 3T3-L1 preadipocytes and inhibited intracellular lipid droplet accumulation. Additionally, when they conducted the toxicity test of CAG on HepG2 cells, the finding was that HepG2 cells treated with CAG were as integrated as the aspirin control group, indicating that CAG is non-toxic. Consistent with these results, Szabo., *et al*. reported [3] that no subchronic toxicity and genotoxicity were observed at 150 mg/kg/d and 2000 mg/kg in rats.

Those results demonstrated that CAG could inhibit lipid droplet accumulation in 3T3-L1 adipocytes, which may provide a potential therapeutic strategy for obesity-related disease, such as, fatty liver, metabolic syndrome, type II diabetes and coronary heart disease.

Zhao., *et al*. [25] investigated the CAG's regulation of endothelial homeostasis in the setting of reticulum stress Palmitate (100 μm) was used in the endothelial cells to evoke ROS-associated ER stress and then observed the effect of CAG on thioredoxin-interacting protein (TXNIP), NLRP3 inflammasome activation and mitochondrion-dependent apoptosis.

The primary result was that CAG inhibited ROS generation and attenuated ER stress inducer IRE1αphosphorylation. ER stress would lead to the increase of TXNIP expression, together with NLRP3 induction and increased IL-1βand IL-6 production. All these alternations were held back by CAG, indicating that the suppressing capability of CAG on TXNIP/NLRP3. In addition, CAG was able to restore the cell loss caused in mitochondrion caused by inflammasome activation, potentially by inhibiting caspase-3 activity, and thereby protecting cells from ER stress-induced apoptosis.

In a word, this study showed that CAG was capable of inhibiting ER stress in endothelium, which raises a possibility that the suppression of ER stress might be a potential underline mechanism for the effect of CAG on preventing cardiovascular disease.

Conclusion

CAG has been shown to have positive effect in increasing telomere length and in correcting early AMD and improving some cardiovascular factors possibly through the action of GAG in activating telomerase and thereby increasing telomere length and attenuating telomere attrition. The summary of the effects of TA-65 as shown in human, animal and cell studies is shown in Figure 1. Regarding lengthening telomere, some studies have been conducted in animal models therefore providing relatively strong evidence that CAG is effective on increasing telomere length mainly by activating telomerase. Other studies have been done in human cells models including CD4 and CD8 T cells and neuronal HEK cells with positive results. However, clinical trials for the effect of CAG on human's telomere lengthening are very few thus a strong conclusion cannot be drawn yet, indicating that more clinical trials are needed to provide stronger conclusions relative to CAG action.

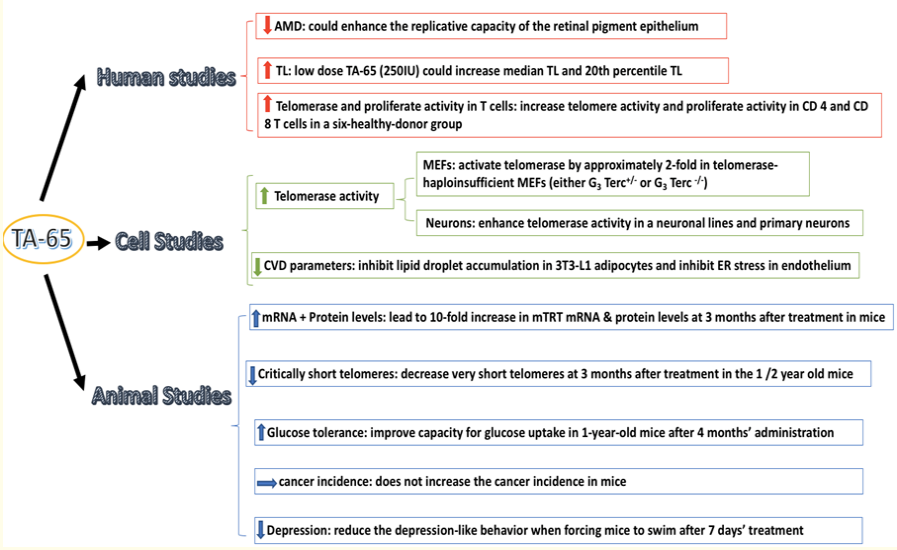

Figure 1: *Effects of TA-65 on different chronic diseases associated with its effects on Telomerase Activity.*

For AMD promotion, although one clinical trial investigated the relation of TA-65 and early AMD [23], it does not provide sufficient evidence that TA-65 could improve early AMD. More studies either with humans or animals need to be conducted to meet a therapeutic demand for those population with early AMD since there is no effective therapy for AMD yet.

Regarding the effect of CAG on cardiovascular disease, the evidence is less solid. In addition to the animal study conducted by de Jesus., *et al*. [10] demonstrating that TA-65 could improve glucose tolerance and insulin resistance in 1-year old mice, there are only another two other studies related to cardiovascular disease [24,25]. However, all those human studies are in vitro studies and only provide some potential underlining mechanism for the effect of CAG on preventing cardiovascular disease. Therefore, future studies are required, especially clinical trials, to investigate the direct effect of CAG on individuals diagnosed with cardiovascular disease.

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