The antiaging role of oxytocin

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The human life expectancy is continuously rising. In the past two decades, a large number of studies have been extensively exploring the molecular mechanisms which play critical roles in determining longevity.

Aging is a physiological and dynamic process resulting from biological, physiological, environmental, psychological, behavioral, and social changes.

Different biological processes that lead to acceleration of molecular damage, responsible for structural and functional abnormalities in cells, tissues, and systems are caused by aging. The environment could also contribute to accelerating or breaking this process acting on body's ability to overcome stress and correctly respond to external insults or stressors, constituting the primary determinant of longevity.

On the biological level, nine hallmarks of aging are recognized: genomic instability and telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion and altered intercellular communication. Indeed, telomere attrition is considered the primary hallmark of aging process.

Oxidative stress is one of the accepted theories correlated with aging. In cells, during aerobic metabolism, reactive oxygen species, including hydroxyl radicals, superoxide anions, and hydrogen peroxide, can be produced, when reactive oxygen species are elevated they could not be eliminated by the antioxidant capacity of cells, so they react with lipids, proteins, and nucleic acids in cells, leading to oxidation or peroxide formation. These processes lead to the destruction of the cell membrane structure, changes in permeability, and cytotoxic reactions.

Oxidative stress could cause another potential contributor to the aging process: telomere shortening (Boonekamp et al., 2017).

The aging process is regulated by a powerful "biological clock," represented by the telomere/telomerase system. Telomeres are repeated sequences of non-coding DNA located at the terminal ends of chromosomes and they play a major role in maintaining chromosome stability at the end of each chromosome in mammals, including the protection of genetic material from degradation during cell division.

Beyond preserving the information in the human genome, telomeres have been shown to shield the natural chromosome end from inappropriate repair and to distinguish them from intrachromosomal double stranded breaks (O'Sullivan and Karlseder, 2010). Telomeres have been involved in the replicative aging process shown in the instability of genome in cancer development and other aging-related diseases (Callaway, 2010).

The inability of the enzyme DNA polymerase to preserve the length of telomeres cause loss of a part of nucleotides at each cell division or replication event, so telomeres became shorter. When the length of telomeres is too short they loss their function, cells stop to divide and become senescent.

The ability to restore or lengthen telomeres depends mainly on the action of a ribonucleoprotein enzyme called "telomerase," which provides a powerful telomere maintenance mechanism (Boccardi and Boccardi, 2019).

The telomere length (TL), a sensitive indicator of tissue-specific cellular aging (Callaway, 2010), is also tightly linked to psychological stress. It has been well described that a relationship exists between stress, telomere shortening, and mental disorders, even if the nature of this link remains mostly unknown.

Free radicals induced oxidative stress, known also as potential contributor to the aging process which arise as damaging byproducts of energy metabolism in the mitochondria (Boonekamp et al., 2017), can also lead to telomere shortening. However, no definitive unique mechanism that accounts for telomeres shortening across these various conditions is identified. Telomere length is mainly measured in white blood cells, indicated as leukocyte telomere length (LTL). Recently, a "telomeric brink" hypothesis has been postulated, which states a causal role for telomere shortening in longevity modulation: very critically short telomeres increase the risk of death (Boccardi and Boccardi, 2019).

A considerable number of researches have suggested that telomere length, indexing cellular aging, serves as an early predictor of aging-associated diseases and earlier mortality (Callaway, 2010).

It is recognized that poor social support has an important role in disease and accelerated aging. In particular, it is associated with reduced TL. Social support is also fundamental for healthy aging, associated with increased immunity, better overall health, and a longer lifespan. Even if the exact mechanisms that lead social support to promote healthy aging are unknown, we could hypothesize that the hypothalamic neuropeptide oxytocin (OXT) may play an important role in this process (Stevenson et al., 2019).

One important study of hypothalamic control in aging was carried by Zhang et al. (2017) that investigated the contribution of adult neural stem progenitor cells in aging.

The study of Zhang et al. (2017) was innovative because besides the classical function of the hypothalamus in secreting neuropeptides, found that hypothalamic neural stem progenitor cells bear a new type of endocrine function by secreting exosomal miRNAs that are responsible of hypothalamic anti-aging effects.

Oxytocinergic neurons of paraventricular, supraoptic and accessory nuclei of the hypothalamus produced OXT and transported it through the axon to the posterior region of the pituitary gland, where it is accumulated in neurosecretory granules before their release into the bloodstream. Different physiological stimuli induce the release of OXT which has endocrine and paracrine activities, including the development of social recognition, sexual and maternal behaviors, neuron modulation, aggression, cognition and broad-mindedness.

Oxytocin exerts anti-inflammatory properties in the both immature and adult brains. An attenuating effect of oxytocin on the neuroinflammatory response to lipopolysaccharide has been demonstrated in isolated microglia cells pretreated with OXT and in frontal cortex tissue dissected from mice that received OXT intranasally after peritoneal injection of LPS.

Moreover, OXT exerts protective effects in experimental animal models of ischemic stroke and the OXT administration improved the behaviors of autistic mice, reducing anxiety, depression and repetitive behavior, and ameliorated social interaction.

Due to these proprieties, OXT could be a promising potential therapeutic agent to treat or prevent neurodegenerative and neurodevelopmental disorders (Panaro et al., 2020).

However, we would like to emphasize here that reducing the inflammatory and oxidation processes is just a part of anti-aging power of OXT.

Oxytocin was shown to help mediating the social bonding, attachment, and may be released during positive social interactions such us sexual intimacy. How social support prevents telomere shortening; this is one of the questions which are currently unanswered, and hence explored here the underlying mechanisms.

Whereas correlation studies have linked both oxytocin and the oxytocin receptor to telomere length (Yim et al., 2016), no studies have been conducted about the causal effects of OXT on the evaluation of functional levels of biological aging (Stevenson et al., 2019).

A great number of studies have evidenced that chronic social isolation results in an elevated level of glucocorticoids hormones that are partly mediated by OXT. This consequently affects various cellular mechanisms of aging, including an increased level of oxidative stress and shortened telomere lengths (Boonekamp et al., 2017). It has been demonstrated that along with chronic psychological stress, a variety of genetic factors and unhealthy lifestyle are potential contributors to telomere shortening. Recent studies examining how lifestyle can affect telomere length suggest that telomeres can change faster than previously thought, taking from one to six months of mental or physical training to elongate. The fascinating finding is that modulating telomeres lengthening may represent a potential target to reverse the processes of biological aging.

Puhlmann et al. (2019) have shown that TL shortening is associated with the development of several of aging-associated diseases and structural changes in various brain regions. The authors of this study were interested in studying the short-term change in LTL with cortical thickness and outcomes of mental training among healthy adults. Interestingly, they have found an association between short-term change in LTL and concomitant change in plasticity of the left precuneus extending to the posterior cingulate cortex of the brain. This supports the evidence that LTL changes dynamically and individually. Further studies are

needed to determine the potential long-term implications of these changes in relation to the process of cellular aging to better understand the development of neurodegenerative disorders.

Remarkably, recent findings on the socially monogamous prairie vole (Microtus ochrogaster) used as an alternate rodent model for the social and behavioral neuroendocrine research showed higher levels of plasma glucocorticoid hormones.

Albeit previous studies have demonstrated that oxytocin can protect against some endocrine and behavioral effects of social isolation, Stevenson et al. (2019) provided the first evidence that oxytocin can protect telomeres against the effects of social isolation. Thus, this suggests that social support and OXT can alleviate some of the negative consequences of social isolation, reducing glucocorticoid levels. Daily OXT injections in isolated voles was able to prevent the observed negative consequences of social isolation, including the telomeres shortening due to oxidative stress and the accelerated cellular aging process (Stevenson et al., 2019). Based on this evidence, OXT may completely prevent the effects of chronic isolation stress on cellular aging.

Moreover, Faraji et al. (2018) recently demonstrated that social enrichment is able to increase the plasma level of OXT in females. Consequently, it has been shown to elevate the exploratory behavior and increase TL in females. In addition, the TL examination in ear notch skin cells showed that socially raised rats had greater TL than standard animals. Indeed, social interaction may therefore provide a therapeutic window to promote oxidative stress resilience and enhance oxytocin-induced anti-aging process (Faraji et al., 2018).

Another study showed that OXT receptor polymorphism rs53576 can significantly alleviate negative impact of impatience on LTL, an effect that is particularly pronounced on cellular aging in female participants (Yim et al., 2016).

High-quality relationship has been shown to be beneficial for physical and mental health. Amongst all the indices of health, stress, behavior and partner relationship quality, Cabeza de Baca et al. (2017) found that sexual intimacy showed a highly significant association with telomere length in a multivariate correlation analysis as indexed by whole and PBMC telomere length.

The association between sexual intimacy and level of OXT was also resumed in a recent study, in which it was reported that the release of OXT during sex may be closely linked to the pleasure sensation.

An increase of plasma levels of OXT has been reported during masturbation in both genders with a pick during orgasm in men. In women, baseline levels and the increase with masturbation of OXT were higher than in men and in multiorgasmic women, and the relative OXT increase was also correlated to the subjective rating of the intensity of the orgasms.

In both genders, the relative increase in plasma OXT from baseline to orgasm was found to be positively correlated to the orgasmic pelvic muscle contraction (Buemann and Uvnäs-Moberg, 2020).

Given the importance of telomeres in aging and human health, researches should focus on lifestyle factors that affect OXT system and may alter the rate of telomere shortening and increasing longevity. We suggest that providing social support and assuring a positive social relationship could not only have a positive effect on OXT system but also can be protective for the telomere length. Indirectly, OXT would increase lifespan and improve the human well-being. It is important to point out that physical contact, face-to-face interaction, such as hugging and hand shaking, remains necessary actions not only for the oxytonergic system but also for delaying aging process and preserve the human health from illnesses. The effects of oxytocin on the telomere shortening and aging process are illustrated in **Figure 1**.

Due to the importance of OXT involvement in telomerase activity, future studies would benefit from large-scale randomized controlled trials, and where possible, longitudinal design with LTL and telomerase activity measurement.

It will be crucial to correlate the OXT concentration with TL and verify if administration of OXT may be able to induce an effect on TL and consequently increase life expectancy and exert anti-aging effects.

Further investigations are warranted to address the questions on how OXT is able to mediate all these effects, which mechanism is most effective that would reverse or even stop telomere shortening and the biological aging processes and the possible improvement in lifestyle behavior and human health during healthy aging trajectory.

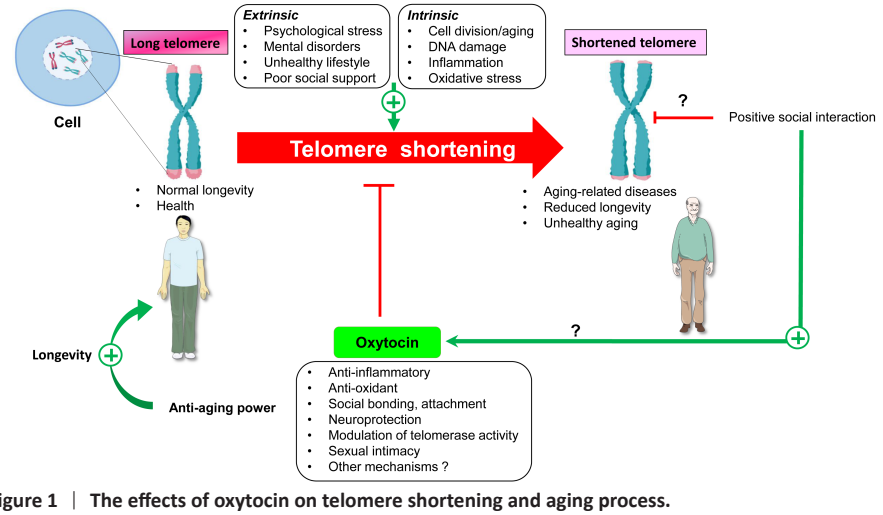

Figure 1 | **The effects of oxytocin on telomere shortening and aging process.**

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