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Telomere length in alcohol dependence: A role for impulsive choice and childhood maltreatment

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ABSTRACT

Telomere shortening, a marker of cellular aging, has been considered to be linked with psychosocial stress as well as with chronic alcohol consumption, possibly mediated by oxidative stress and inflammatory response. Recent findings suggested that early life adversity on telomere dynamics may be related to impulsive choice. To further our understanding of the association of impulsive choice and childhood trauma on telomere length, we examined whether delayed discounting and childhood trauma or their interaction is related to leukocyte telomere length, while controlling for multiple potential confounding variables, in patients with alcohol dependence who are considered to have higher impulsive choice and shorter telomere length. We recruited 253 male patients with chronic alcohol dependence. All participants performed the delay discounting task, and the area under curve was used as a measure of delay discounting. Steeper delay discounting represents more impulsive choices. The modified Parent-Child Conflict Tactics Scale was used to measure childhood maltreatment. In addition, confounding factors, including socio-demographic characteristics, the Alcohol Use Disorders Identification Test, the Buss-Perry Aggression Questionnaire, the Resilience Quotient, the Beck Depression Inventory, and the Beck Anxiety Inventory, were also assessed. Hierarchical regression analyses showed a significant main effect of delay discounting ($\beta = 0.161$, $t = 2.640$, $p = 0.009$), and an interaction effect between delay discounting and childhood maltreatment on leukocyte telomere length ($\beta = 0.173$, $t = 2.138$, $p = 0.034$). In subsequent analyses stratified by childhood maltreatment, patients with alcohol dependence and high childhood trauma showed a significant relationship between delay discounting and leukocyte telomere length ($\beta = 0.279$, $t = 3.183$, $p = 0.002$), while those with low trauma showed no association between them. Our findings suggest that higher impulsive choice is associated with shorter telomere length, and childhood trauma may exert a moderating effect in the relationship between impulsive choice and telomere length.

1. Introduction

Telomeres are repetitive "TTAGGG" sequences found at the ends of chromosomes. They cap and protect chromosome ends from fusion and deterioration, and maintain chromosome stability and integrity (Lu et al., 2013). Telomere length gradually declines over time and shortens at a rate of 20–40 base pairs per year (Starkweather et al., 2014). It has been suggested that telomere length is a marker of cellular aging, and that short telomere length is associated with age-related disease and early mortality (Calado and Young, 2009). Furthermore, increasing evidence suggest that acceleration of telomere shortening is associated with psychosocial stress (Oliveira et al., 2016; Wolkowitz et al., 2011), childhood trauma (Drury et al., 2012; Price et al., 2013), and stress-related psychiatric disorders such as depression (Shalev et al., 2014). Although the precise underlying mechanisms remain unclear, several key factors, such as oxidative stress and chronic inflammation, may be linked to telomere shortening (Lindqvist et al., 2015).

Chronic alcohol consumption has been reported to be associated with age-related diseases and early mortality (Spencer and Hutchison, 1999; Stevenson, 2005). Since people with alcohol dependence tend to choose more immediate pleasurable experiences than the later benefits of increased health from abstinence (Mitchell, 2011), more risky

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behaviors in alcoholics may contribute to early mortality. In addition, although the relationship between telomere length and alcohol consumption has not yet been clearly established, a few studies on telomere biology have proposed that alcohol consumption may lead to enhancement of oxidative stress and acceleration of telomere shortening (Chen et al., 2011; Pavanello et al., 2011; Strandberg et al., 2012). Pavanello et al. reported that telomere length was nearly halved in alcohol abusers compared to healthy controls (Pavanello et al., 2011).

Moreover, human research of telomere biology has suggested the influence of psychological, socio-environmental, or behavioral factors on telomere length (Lindqvist et al., 2015; Puterman et al., 2013; Starkweather et al., 2014). Interestingly, a recent study in college students found that higher delay discounting, an impulsivity trait characterized by impatience to delays and risk-based decision-making, was associated with shorter leukocyte telomere length (LTL) (Yim et al., 2016). Delay discounting in humans is a core endophenotype of several psychiatric disorders, such as alcohol dependence and attention deficit hyperactivity disorder (ADHD) (Nautiyal et al., 2017). An animal study showed that adult birds with greater developmental telomere attrition preferred impulsive choice (smaller but more immediate food) compared to birds with less developmental attrition (Bateson et al., 2015). Such finding suggests that early life adversity on telomere dynamics is associated with impulsive choice in adulthood. Although childhood trauma is considered a risk of psychiatric problems and age-related diseases by various neurochemical pathways, including disrupted neuroendocrine system and inflammation (Danese and McEwen, 2012), conflicting findings exist over the impact of childhood trauma on telomere length (Glass et al., 2010; Price et al., 2013; Savolainen et al., 2014; Verhoeven et al., 2015). Furthermore, the relationship between impulsive choice and childhood trauma on telomere dynamics has been little explored in humans.

To further our understanding of the association of impulsive choice and childhood trauma on telomere length, we examined whether childhood trauma and impulsive choice is related to LTL, and whether high exposure to childhood trauma interact with impulsive choice to accelerate telomere shortening, in patients with chronic alcohol dependence who are considered to have higher impulsive choice and shorter telomere length. In addition, we also assessed other potentially associated factors, including socio-demographic factors (age, economic status, and body mass index), clinical symptoms (severity of alcohol dependence, depressive and anxiety symptoms), and individual psychological factors (hostility and resilience), all of which have been previously reported to be associated with LTL (Lindqvist et al., 2015; Puterman et al., 2013; Starkweather et al., 2014; Watkins et al., 2016); these factors were controlled in the analyses to ascertain unbiased associations of impulsive choice and childhood trauma on LTL. In our study, we hypothesized that impulsive choice and childhood trauma or their interaction would be related to telomere shortening after accounting for a number of potential variables.

2. Material and methods

2.1. Participants

A total of 253 male Korean patients with alcohol dependence were recruited from 16 mental hospitals with specialized clinics for alcohol dependence. All of the subjects were inpatients who have been hospitalized for management of alcohol withdrawal syndrome and rehabilitation, in addition to being abstinent for at least one week. All subjects were diagnosed by psychiatrists as having a primary diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (American Psychiatric Association, 2000). All subjects scored above the cut-off of eight on the alcohol use disorders identification test (AUDIT), which is indicative of hazardous drinking (Babor et al., 2001). The exclusion criteria were as follows: (1) physical or mental illness that would interfere with task performance; (2) history of other substance dependence in the past six months; (3) a score on the Mini Mental State examination – Korea version of less than 26. Participants were paid for their participation (about $15), and provided written informed consent prior to the start of this study. The study protocol was approved by the Institutional Review Board of Severance Hospital.

2.2. Measures

2.2.1. Socio-demographic characteristics

The socio-demographic variables were age, marital status (married/living with partner or not), education level, and gross income. The education level was classified into two categories (< high-school or ≥high-school). Income was collapsed into two categories (≤$10,000 or > $10,000).

2.2.2. Delay discounting task (DDT)

Delay discounting task was used for assessing impulsive choice, which refers to the tendency of preference for smaller and more immediate rewards over larger and more delayed outcomes, even where delayed rewards are more advantageous (Choi and Chung, 2011; Dixon et al., 2003). Delay discounting task consists of a series of hypothetical monetary choices between a smaller sooner option and a larger delayed option (for example, between “$10 now” and “$1000 after 1 year”). Participants were repeatedly asked to choose their preferred option on a computerized task. Participants were also informed that the rewards were hypothetical and that they would not receive the chosen rewards.

The delayed reward was always fixed at 1,000,000 Korean Won (approximately $1000) but the immediate reward changed for every trial. In the first session, the amount of delay was held constant for one week, and the 26 immediate rewards (approximately $1000, $990, $960, $920, $850, $800, $750, $700, $650, $600, $550, $500, $450, $400, $350, $300, $250, $200, $150, $100, $80, $60, $40, $20, $10, and $5) were presented consecutively on the screen in descending order, one per trial. For instance, the initial choice presented to the participant was between “$1000 now” and “$1000 after 1 week”; after selection, the next choice between “$990 now” and “$1000 after 1 week” was presented; and then, the amount in immediate rewards was decreased consecutively to $5. In the following session, the immediate monetary rewards were progressively increased in ascending order until the largest reward was presented, with a set temporal delay. The next sessions were repeated with incrementally larger temporal delays of one week, two weeks, one month, six months, one year, three years, and ten years. Within each session, the subjective value, where the preference for immediate and delayed rewards was equal, was defined as the indifference point (Ohmura et al., 2006) which refers to the smallest amount of money chosen to be received immediately, instead of waiting the specified delay, in order to receive the standard 1,000,000 Korean Won (approximately $1000). The indifference points were used to produce a delay discounting curve, and to compute the area under the curve (AUC) (Myerson et al., 2001) for each subject, which represented the degree of discounting. The AUC values ranged from zero (maximum discounting) to one (little or no discounting). Higher AUC values indicated less delay discounting (less impulsivity), while lower AUC values indicated more discounting (more impulsivity).

2.2.3. Modified parent-child conflict tactics scale (mPCCTS)

To evaluate childhood maltreatment, we used the modified Korean version of the Parent-Child Conflict Tactics Scale (Kim and Lee, 2011), which is based on the Parent-Child Conflict Tactics Scale developed by Straus et al. (Straus et al., 1998). This is a 24-item scale representing psychological maltreatment (five items), physical maltreatment (nine items), and the neglect of children (ten items). The response categories gauge the frequency with which acts were used during conflict with a parent when the subject was less than 12 years old on a six-point Likert scale (0 = never, 1 = it happened once, 2 = 2 times, 4 = 3–5 times,