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Crack cocaine addiction, early life stress and accelerated cellular aging among women

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ABSTRACT

Background: Early life stress (ELS) and addiction are related to age-related diseases and telomere shortening. However, the role of telomere length (TL) in crack cocaine addiction remains unknown. The purpose of this study was to investigate the TL in a sample of crack cocaine dependent-women who reported an ELS history and in a community-based sample of elderly women as a reference group for senescence.
Methods: This study included treatment seeking crack cocaine dependents women ($n = 127$) and elderly women without a psychiatric diagnosis (ELD, $n = 49$). The crack cocaine sample was divided in two groups according to their Childhood Trauma Questionnaire (CTQ) scores: presence of history of childhood abuse and neglect (CRACK-ELS) and absence of ELS history (CRACK). TL was assessed by T/S ratio obtained from peripheral blood DNA using quantitative *PCR* assay.
Results: CRACK and CRACK-ELS subjects exhibited shortened TL in comparison to the ELD group, despite their younger age. Among crack cocaine sample, CRACK-ELS group had significantly shorter telomeres than the CRACK group. Correlation analysis within crack cocaine group indicated that TL was negatively correlated with emotional abuse scores.
Conclusions: These results support previous findings associating telomere shortening with both ELS and drug addiction. This study suggests new evidence of a distinct biological phenotype for drug-dependent women with ELS. The results support the biological senescence hypothesis underpinning ELS experience.
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1. Introduction

The burden of cocaine addiction is estimated to be around 16 disability adjusted life years (DALYs) per 100.000 individuals (Degenhardt et al., 2014), and an increased mortality rate of up to 8 times higher than that expected in a similar population without drug abuse history (Barrio et al., 2013). Long-term cocaine use contributes to important health problems, including coronary artery disease (Degenhardt et al., 2011), major depressive disorder (Herrero et al., 2008), cognitive decline (Verdejo-Garcia et al., 2007; Viola et al., 2015), and. In addition, cocaine use has been associated with increased peripheral inflammatory mediators (Araos et al., 2015; Fox et al., 2012; Levandowski et al., 2014) and age-related atrophy in grey matter volume (Ersche et al., 2013) both of which are commonly seen in association with aging and age-related disorders (Sander et al., 2008).

Prior reports have linked cocaine abuse and other substances (i.e., alcohol and heroin) with acceleration of normal aging, suggesting a role for immunoscenecense and accelerated telomere shortening (Beach et al., 2014; Cheng et al., 2013; Pavanello et al., 2011; Reece, 2007; Yang et al., 2013). Telomeres are long nucleotide repeats located at the end of chromosomes that preserve genetic information by mitigating non-homologous recombination and nucleolytic degradation (Blackburn, 2005). Telomere shortening is a natural physiologic process that occurs in aging (Harley et al., 1990), and is also associated with several age-related diseases, such as Alzheimer Disease (Panossian et al., 2003), major depression (Ridout et al., 2016), cardiovascular (Yang et al., 2009) and autoimmune disorders (Hohensinner et al., 2011).

Recently, two studies found accelerated cellular aging in heroin addicts. One study found lower telomerase activity, a reverse transcriptase

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that limits telomere shortening, in abstinent heroin addicts compared with healthy controls without a history of substance abuse (Cheng et al., 2013). Moreover, this finding was inversely correlated with structural integrity of gray and white matter of the prefrontal cortex. The second study found reduced leukocyte telomere length (TL) in heroin users in comparison to controls (Yang et al., 2013). Considering that both heroin (Zhou et al., 2000) and crack cocaine (Zaparte et al., 2015) addiction are associated with increased oxidative stress, and this could lead to damage to telomere DNA and accelerated telomere shortening (Kawanishi and Oikawa, 2004), it is reasonable to hypothesize that crack cocaine addiction could also accelerate telomere shortening processes. However, to our knowledge, there is no previous study investigating TL in crack cocaine users.

Early life stress (ELS) is another important factor that has been associated with accelerated telomere shortening (Price et al., 2013; S. J. Ridout et al., 2015). Moreover, high rates of early life trauma have been described among women with crack cocaine dependence (Bertoni et al., 2014) and they are often more susceptible to the complications of crack cocaine compared to their male counterparts (Bastos and Bertoni, 2014). Furthermore, women with crack cocaine addiction with a severe ELS history present distinct behavioral (Francke et al., 2013), immune (Levandowski et al., 2013, 2014) and neurotrophic (Viola et al., 2014) phenotypes when compared to those without such early life exposure.

Thus, the current study was designed to investigate the TL in a sample of crack cocaine dependent women with and without a history of ELS. In order to test our hypothesis about accelerated aging, we recruited a group of elderly women as a reference group. This reference group allows us, for the first time, to test if drug addiction with and without ELS exposure could be related to cellular senescence. Therefore, our hypothesis is that crack cocaine dependent women reporting ELS will exhibit accelerated cellular senescence, as measured by TL.

2. Material and methods

2.1. Study design

This study had a cross-sectional design and included 127 female crack cocaine dependent women and 49 elderly women without mental disorders (ELD). Crack cocaine users were split into two distinct groups in according with presence (CRACK-ELS, $n = 93$) or absence (CRACK, $n = 34$) of severe ELS history. All participants provided written informed consent before inclusion in the study, which was approved by the Ethical Committees of the participating institutions.

2.2. Participants

2.2.1. Women with crack cocaine addiction

Women with crack cocaine addiction were recruited from a public and voluntary detoxification treatment (21 days of inpatient treatment at a public hospital from southern Brazil). The inclusion criteria were as follows: (1) age between 18 and 55 years; (2) diagnosis of crack use disorder according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV); (3) absence of psychotic syndromes and other severe medical condition and (4) absence of corticosteroids, antibiotics or anti-inflammatory drug use. All participants were treated in an inpatient abstinence controlled environment, so they had no access to alcohol, cigarettes or other drugs.

All participants were receiving a symptom-driven cocaine detoxification medication protocol, composed of neuroleptics, analgesics, antidepressants or mood stabilizers. All data (clinical assessment and blood draw) were collected at the 4th day post-admission in order to avoid ongoing cocaine intoxication.

2.2.2. Elderly women

Elderly women were recruited from community-based elder support groups from the same region of Brazil. Considering our hypothesis, we chose to include elderly individuals as a reference group for cellular senescence (Sander et al., 2008). All elderly subjects were assessed for the following inclusion criteria: (1) absence of history of ELS; (2) no current symptoms suggestive of dementia or other neurological disorders; (3) no current or past cancer diagnosis and (4) no unstable or severe medical condition. We did not exclude individuals who were in regular treatment regarding chronic diseases, including diabetes ($n = 6$), hypertension ($n = 3$), osteoporosis ($n = 15$), rheumatoid arthritis ($n = 14$) and thyroid disorders ($n = 15$) due to the high prevalence of these clinical conditions in Brazilian aging samples (Schmidt et al., 2011).

2.3. Clinical assessment

The clinical characteristics of both crack cocaine and elderly group were assessed by well-trained psychologists through clinical interview. Information concerning social-demographic status, height, weight and clinical health history were also obtained. Body mass index [BMI = weight (kg)/height^2 (m^2)] was calculated and included in the protocol.

Psychiatric diagnoses were assessed using semi-structured clinical interview following the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. In addition, self-administered questionnaires were used to assess symptoms severity. The Beck Depression Inventory (BDI-II) (Gorenstein and Andrade, 1996) and the Geriatric Depression Scale – Short Form (GDS-15) were used to measure the severity of depressive symptoms in crack cocaine and elderly groups, respectively. Cocaine Selective Severity Assessment (CSSA), adapted for crack users (Kampman et al., 1998; Kluwe-Schiavon et al., 2015), was used to evaluate the severity of the withdrawal symptoms during detoxification. The Addiction Severity Index version 6 (ASI-6) (Kessler et al., 2012) was also assessed to obtain information regarding patterns of crack cocaine use, age of onset and crack cocaine abuse severity.

2.4. Early life stress

A history of ELS was assessed using the validated Portuguese version of Childhood Trauma Questionnaire (CTQ) (Grassi-Oliveira et al., 2014) which includes assessment of sexual, physical and emotional abuse and physical and emotional neglect during early life. CTQ contains a five-point Likert-type scale, including 5 subscales. ELS was classified as moderate to severe according to the cutoff point postulated by Bernstein and Fink (1998).

2.5. Telomere length (TL) assessment

Genomic DNA was isolated from peripheral blood. Prior to genotyping, DNA concentrations in samples were assessed using NanoDrop 1000 (Thermo Fisher Scientific, Wilmington, US) and set to 50 ng/ul. TL was measured as previously described by Cawthon (Cawthon, 2009). Briefly, the TL measurement via quantitative *PCR* (*qPCR*) involves determining the ratio of the telomere (T) repeat copy number to a single-copy gene (S) copy number (T/S ratio) using a standard curve. This ratio is proportional to the average TL. Telomere (T) and albumin (S) *PCRs* were performed on the same plate using a monochrome multiplex q*PCR*. One master mix was prepared containing SYBR® Select Master Mix (Life Technologies, USA) and primers for telomeres (*Tel-g*: 5′ ACA CTAAGGTTTGGGTTTGGGTTTGGGTTTGGGTTAGTGT 3′ and *Tel-c*: 5′ TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCCTAACA 3′) and for albumin (*Alb-u*: 5′ CGGCGGCGGGCGGCGCGGGC˙TGGGCGGAAATGCTG CACAGAATCCTTG 3′; *Alb-d*: 5′ GCCCGGCCCGCCGCGCCCGTCCCGCCGGA AAAGCATGGTCGCCTGTT 3′. Prior to the experiment, primer sets were tested thoroughly to determine reaction efficiency, specificity, and the

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