



Is biological aging accelerated in drug addiction?

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Drug-addiction may trigger early onset of age-related disease, due to drug-induced multi-system toxicity and perilous lifestyle, which remains mostly undetected and untreated. We present the literature on pathophysiological processes that may hasten aging and its relevance to addiction, including: oxidative stress and cellular aging, inflammation in periphery and brain, decline in brain volume and function, and early onset of cardiac, cerebrovascular, kidney, and liver disease. Timely detection of accelerated aging in addiction is crucial for the prevention of premature morbidity and mortality.

Addresses

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What is biological aging?

Aging is a progressive process spanning from optimal performance at maturity to gradual and advanced diminishing function involving the entire organism [1[•]], impacting physiologic systems, functional characteristics and clinical features. Chronological age conveys a rough approximation of a status, whereas biological aging results from the interaction of genetic, environmental and behavioral factors, as well as disease. Accelerated aging occurs when biological age outpaces chronological age and the emergence of typical aging phenotypes at an earlier age than commonly observed [1[•],2]. While operational definitions of aging phenotypes are inconclusive [1[•],3^{••}] and various age-related biomarkers are used in the literature [3^{••},4[•]], determining whether and to what extent a disease or risk factors contribute to premature aging is crucial in a chronic disease as addiction. Our review centers on the major pathways and interacting pathophysiological processes that may contribute to

accelerated aging in drug addiction (see [Figure 1](#) and [Table 1](#)).

Why study aging in addiction?

Drug-addiction involves premature mortality and early onset of age-related disease. For example, due to arterial, cardiac and cerebrovascular toxicity, cocaine is involved in 40.3% of emergency admissions related to illicit drug use with the highest rates occurring in men aged 35–44 [5]. Similarly the median life of smokers is reduced by at least 10 years not just from cancer, which is a hallmark disorder of aging [6], but also from damage to vascular and pulmonary systems and the brain. Vast efforts are geared toward psychosocial and occupational rehabilitation of individuals with substance use disorders. Yet, the early-onset of diseases triggered (e.g., cirrhosis of the liver by alcohol) or exacerbated by drugs of abuse (e.g., pulmonary hypertension by methamphetamine [7]) remains mostly undetected, resulting in silent disease progression, amounting to a vast personal, social and economic burden [8]. We propose that substance use promotes accelerated aging, and that its early detection is crucial for the prevention of premature morbidity and mortality.

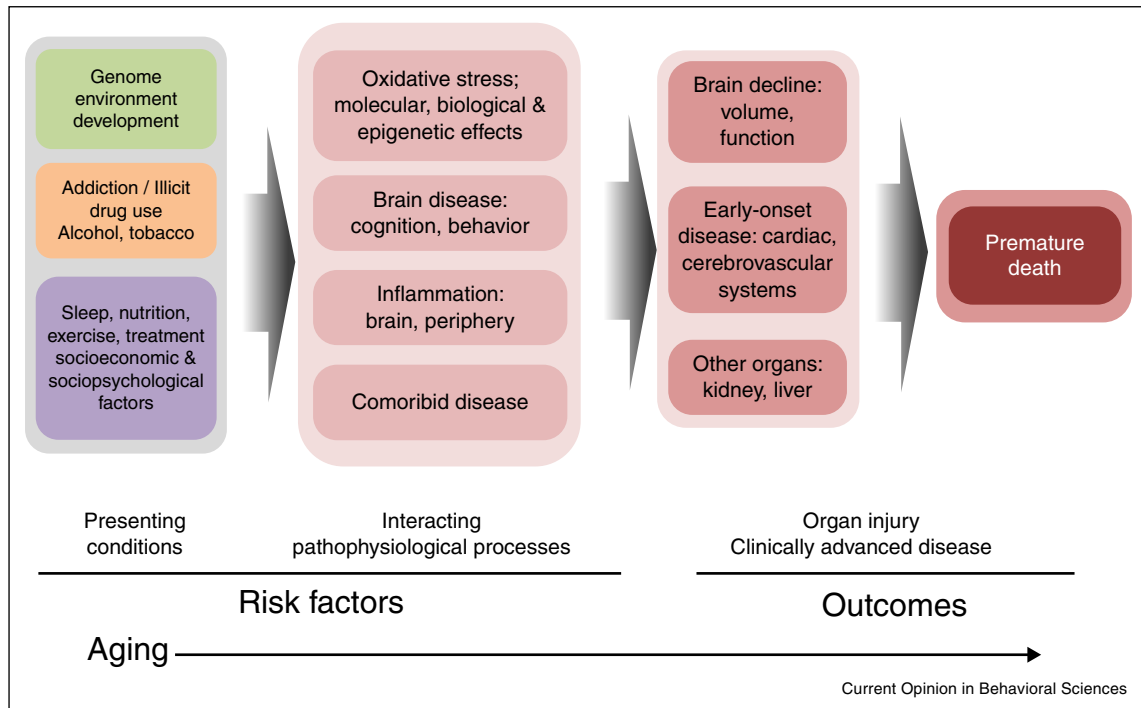
Presenting conditions

Contribution of addiction-related phenomenology to premature aging

Addiction is considered a chronically relapsing brain disorder associated with abnormal brain morphology [9^{••}] and function [10]. It has been conceptualized as a syndrome of impaired response inhibition and salience attribution ('IRISA') encompassing deficits in higher-order cognitive control and motivational functions, functions of the prefrontal cortex including the orbitofrontal cortex and anterior cingulate cortex, and neuroanatomically connected subcortical and limbic reward structures. Frontal cortical areas are activated in addicted individuals during intoxication, craving, and bingeing, and they are deactivated during withdrawal, and their functioning vis-à-vis the subcortical reward pathways are suggested to contribute to long-term self-control and motivational deficits [11], leading to perilous lifestyle.

Genetic factors that contribute to variability in response to psychoactive agents can enhance hemodynamic reactivity, incidence of coronary vasoconstriction, vascular damage and cardiac and pulmonary pathology. Additionally, synergistic effects between multiple environmental, psychosocial and behavioral factors comprising the addiction

Figure 1



Conceptual model for aging in addiction. This figure illustrates the progression of disease among drug addicted individuals, from presenting phenotypic conditions constituting risk factors, through interacting with pathophysiological processes to cumulative organ system injury, and outcome of advanced clinical disease and eventually death.

phenomenology could enhance potential age-related disease.

The life-course and complexity of addiction is comprised of years (often decades) of chronic stress and comorbid

use of drugs (including illicit drugs with alcohol and/or tobacco) that potentiate cellular harm and systemic toxicity [12]. Drug addiction is associated with risky health behaviors including unprotected sex or intravenous drug use that increase exposure to infections, which in turn activate the immune and inflammatory systems and potentially hasten vasculature-aging and neuronal toxicity. The prevailing low socio-economic status, limited use of health and follow-up care, lack of sleep, insufficient exercise, and poor nutrition, could further promote age-related disease [13]. Such lifestyle factors may mediate aging-related mechanisms rather than being directly causally inducing accelerated aging. For example, cocaine and alcohol addiction are associated with robust alterations in sleep architecture, including disturbances in slow-wave sleep and rapid eye movement (REM), which has implications for several age-related diseases, since sleep contributes to the homeostatic regulation of the neuroendocrine and immune systems [14*] (e.g., the amount of REM sleep correlates with the production of the proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)- α [15]).

Pathophysiological processes

Oxidative stress and cellular aging

Oxidative stress occurs when levels of reactive oxygen/nitrogen species overwhelm the cellular antioxidant

Table 1

Factors by which substance use disorders contribute to accelerated aging in drug addicted individuals including alcoholics and cigarette smokers.

Toxic effects of drugs in brain

- Acceleration of aging in dopamine systems
- Cerebrovascular pathology
- Neuroinflammation
- Enhanced sensitivity to stressors

Physiological drug effects

- Cardio vascular
- Pulmonary
- Metabolic
- Immune
- Circadian

Behavioral/social drug effects

- Unhealthy life styles (poor nutrition, poor sleep patterns, lack of physical activity)
- Social isolation (stigmatization, impaired access to healthcare and family and community support, poverty)
- Infectious diseases (HIV, hepatitis, other sexually transmitted diseases)
- Involvement with Criminal Justice System

capacities [16]. While lower and moderate levels of mitochondrial reactive oxygen species (mROS) have positive function-promoting functions, elevated mROS directly damage cells [16]. When severe, extensive modifications or damage to macromolecules including nucleic acids (DNA, RNA), lipids and proteins [17] can eventually induce cell death and tissue injury [18,19]. Such damage has been linked to multiple age-dependent pathologies, including diabetes, cancer and neurodegenerative diseases [18] (e.g., neurodegeneration is associated with overproduction of mROS that induces cellular damage and subsequent neuronal deficits [19]). Addictive drugs slow cell growth and potentiate apoptosis [20]. Their use (cannabis [21], alcohol, amphetamine or its derivatives [22]; cocaine [23]; opiates [24]; inhalants, synthetic drugs [25]), or withdrawal from their acute effects, induce oxidative stress contributing to their cytotoxicity in brain, heart, liver, and kidney [26]. Cannabis increases the uncoupling of oxidative phosphorylation increasing the free radical flux from mitochondria [21]. Beyond oxidative metabolism of drugs, monoamine oxidation (by monoamine oxidases or by auto-oxidation), mitochondrial dysfunction, excitotoxicity, microglial activation, inflammation, are present [26]. The interaction of multiple drugs can lead to further oxidative damage [26]. For example, the combination of cocaine and opioids ('speedball') accentuates mitochondrial dysfunction [27], and co-abuse of cocaine and ethanol (produces an active metabolite, cocaethylene) resulted in increased ROS generation [28].

Exposure to oxidation, inflammation and stress hormones may lead to telomere (nucleotides at the ends of chromosomes) attrition thereby expediting aging [2] (e.g., leukocyte telomere length (LTL) generally decreases progressively over the lifespan, with estimates of average attrition rates ranging between 32.2 and 45.5 base pairs per year [29]). The effect of inflammation on LTL is potentially caused by LTL's association with increased immune cell replication, as well as by pathways leading from inflammation to oxidation. Oxidative stress is associated with memory and learning impairments [26], that are common in drug addiction [30]. The combination of ethanol and methylenedioxymethamphetamine increases hyperthermic and hepatotoxic effects [31]. Also, drug use (especially of opioids) reduced LTLs, as associated with relapse and route of administration (sniffing related to longer LTLs compared to other methods) [32]. In addition, stem cells (pluripotential progenitor cells from which a whole class of cells differentiate) and their health are a special focus of aging medicine and associated deficits [33]. The decline in stem cells circulating in the peripheral blood appears to be three to four times faster in addicted individuals than in the general population.

Inflammation in periphery and brain

Immune parameters in periphery and brain change with age (suppression or hyperstimulation) and are considered

biological markers of aging [34]. As a result of telomere shortening in lymphocytes that hypersecrete peripheral pro-inflammatory cytokines, senescent immune cells can lead to a vicious cycle of added inflammation, oxidative stress and subsequent telomere shortening [35]. Furthermore, inflammation coupled with increased oxidation may be especially damaging and likely to foster accelerated cell aging [36]. In the brain, whether activated microglia, involved in both addiction-related [37] and other age-related disorders [38] have a role in neuroinflammation is inconclusive [39]. Yet, it has been proposed that a collection of inflammatory changes in the hypothalamus, a critical nucleus for aging development and lifespan control, underlies advanced aging [40].

Peripheral pro-inflammatory cytokine concentrations are inversely correlated with LTL in major depressive disorder and in individuals with history of early life stress [41], comorbidities highly associated with drug abuse. Inflammation and atherosclerosis (deposition of plaques of fatty material on inner walls of arteries) are potential lethal effects of drug use that have acute and chronic systemic impact [42]. Opiate addiction is characterized by a chronic immune stimulatory profile with elevated lymphocytes and monocytes, cytokines and globulins immune activity as well as suppression. Similarly, cocaine creates an hyperactive immune-mediated inflammatory state with increased pro-inflammatory cytokines (e.g., TNF α , IL-1 β) [42,43] and decreased basal anti-inflammatory markers (e.g., IL-10) [42,43], all contributing to vascular disease (e.g., endocarditis). Also, high-sensitivity C-reactive protein (a protein produced by the liver following injury, infection, or inflammation) values were higher in addiction [44]. In the brain, most stimulants dysregulate the blood-brain barrier through alterations in tight junction complexes or through inflammation and oxidative stress. Neuroinflammation plays a particularly important role as it contributes to a feed-forward process leading to vulnerability to infiltration of inflammation markers from the periphery [45].

Similarly to oxidative stress, inflammatory processes are further accelerated by comorbid substance abuse especially with cigarette smoking, which in addition to having negative effects on the vascular and pulmonary systems, inhibits monoamine oxidases, which are necessary for proper body detoxification [46].

Organ system injury and advanced clinical disease

Brain decline: volume, function

Aging causes changes in brain structure, neurochemistry, and function including damage to its vasculature as well as the deposition of substances that affects cognition. Brain weight declines on average by 5% per decade after age 40, where the frontal lobes undergo the greatest shrinkage in men whereas the parietal lobes show more

atrophy in women [47]. Brain volume loss encompasses the loss of neurons, synapses, neurotransmitters and receptors, especially in the neocortex, basal forebrain nuclei and brainstem monoaminergic systems. Both brain small vessels [48] and carotid arteries [49] show decrease in lumen diameter with age. Other microscopic changes with senescence include the accumulation of lipofuscin (a pigmented lipid composed of lysosomal digestion), and the proteins hyperphosphorylated tau and beta-amyloid in the form of neurofibrillary tangles and senile plaques [50]. The presence of similar changes in cognitively impaired patients may indicate that a disease state (e.g. dementia) is an exaggerated example of normal aging [47] and therefore the ‘pace of aging’ may be crucial for transition into disease.

Similarly, use of drugs accentuates age-related changes in the brain that may underlie some of the abnormalities found in addiction models. Compared to healthy controls, cocaine-dependent individuals show twice the rate of brain volume reduction a year, especially of the prefrontal and temporal regions [9**]; in methamphetamine users the rate of decline in gray matter is 6.4–8.5% a year in the frontal, temporal, insula and occipital cortices [51]. Cannabis is associated with reduced hippocampus volume [52], Cocaine [53], methamphetamine [54], and heroin [55] addicted-individuals show intra-cranial and extra-cranial artery dysfunction. Pathologies commonly observed in the brain of aged individuals (e.g., primary age-related tauopathy) indeed appear earlier in drug addicted individuals as compared to non-addicted individuals. Importantly, cognitive decline in addiction [56] may be attributed to hyperphosphorylated tau and p62-positive inclusions (neurodegeneration-related proteins) as reported with heroin use [57*] or the accumulation of amyloid as reported in cocaine [58] and methamphetamine [59] users.

Early onset of age-related illness: cardiac, cerebrovascular, kidney, and liver disease

Drug addiction causes irreversible structural and functional changes not only in the brain but also in the heart, lung and other organs such as the liver and kidney.

Cocaine-induced injury to the cardiovascular and cerebrovascular systems is well known [60]. Specifically, cocaine use is linked with hypertension, tachycardia, ventricular arrhythmias [61], myocardial infarction [62], and stroke [63]. Furthermore, cocaine is associated with muscle damage, electrolyte disturbances and elevated liver enzymes leading to renal and liver failure resulting in severe functional impairments or sudden mortality [64]. Likewise, amphetamines produce cardiac-rhythm disturbances and infarction, stroke, nephropathy (kidney damage) and generate toxic metabolites that may be the cause of hepatic injury. Similarly, heroin has been a known cause of chronic brain small vessel disease, heart disease, and as a leading cause of death among young individuals. Moreover, in

combination with alcohol, heroin triggers liver dysfunction and cirrhosis and nephropathy [65]. Endocrine pathology casts a wide net of deleterious effects. For example, the suppression of sex steroids by many addictions is far from benign, and a focus of the aging literature [66]. Also the link between opioid addiction and diabetes is often unrecognized and overlooked [67].

Conclusion

Addiction and substance abuse, prevalent conditions worldwide, contribute to accelerate aging and age-related diseases. Although the mechanisms by which these drugs accelerate the aging process remain to be established, evidence points to multiple events (e.g. oxidative stress, excitotoxicity, and mitochondrial dysfunction) which ultimately lead to degeneration and neuronal apoptosis. Drug addicted individuals exhibit unique aging-related biomarkers that are not routinely identified, and therefore, they require additional attention. Further research is needed to adapt screening tools, risk scores and prognostic models for early identification of at-risk individuals in order to reduce premature morbidity and mortality in this population.

Conflict of interest statement

Nothing declared.

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