Archival Report

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A Prospective 5-Year Re-examination of Alcohol Response in Heavy Drinkers Progressing in Alcohol Use Disorder

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ABSTRACT

BACKGROUND: The main neurobiological theories of the development of addiction, including tolerance, sensitization, incentive-sensitization, and allostasis, have not been tested in longitudinal human alcohol response research. To address this issue, we conducted the first controlled prospective investigation of subjective and neuroendocrine responses to alcohol measured over a 5-year interval in at-risk young adult heavy drinkers (HD) and light drinker control subjects.

METHODS: Participants were 156 individuals, 86 heavy drinkers and 70 light drinkers, undergoing an initial oral alcohol challenge testing (.8 g/kg alcohol vs. placebo) and an identical re-examination testing 5 to 6 years later. Alcohol use disorder (AUD) symptoms and drinking behaviors were assessed in the interim follow-up period.

RESULTS: At re-examination, HD continued to exhibit higher sensitivity on alcohol's stimulating and rewarding effects with lower sensitivity to sedative effects and cortisol reactivity, relative to light drinkers. In HD with high AUD symptom trajectories over follow-up, heightened alcohol stimulation and reward persisted at re-examination. HD with low AUD symptoms showed reduced alcohol stimulation over time and lower reward throughout compared with the HD with high and intermediate AUD symptoms.

CONCLUSIONS: Results support the early stage phase of the allostasis model, with persistently heightened reward sensitivity and stimulation in heavy drinkers exhibiting AUD progression in early mid-adulthood. While there are multiple pathways to development of a disorder as complex as AUD, maintenance of alcohol stimulatory and rewarding effects may play an important role in the continuation and progression of alcohol addiction.

Keywords: Alcohol response, Heavy drinking progressing with AUD, Reward sensitivity, Stimulation, Subjective, Tolerance

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Alcohol use disorder (AUD) is associated with numerous consequences for the individual and society, including psychological, occupational, and health consequences, as well as public safety harms and annual financial costs exceeding $223 billion in the United States (1). Thus, identifying the mechanisms underlying the development and maintenance of AUD has become increasingly important for AUD prevention and treatment. Four leading neurobiological theories of the development of addiction include tolerance, sensitization, incentive-sensitization, and allostasis. These theories purport nervous system adaptations to repeated alcohol exposure underlie the progression of compulsive drinking and development of addiction, but they lead to differential predictions about the nature of these responses over time. While these theories are crucial to our understanding of AUD, they are largely based on animal data and their predictions have not yet been directly tested in controlled longitudinal human studies. The present study provided the first comprehensive repeated evaluation of alcohol responses in at-risk drinkers to test these neurobiological theories of AUD progression.

The most longstanding theory of alcohol adaptation is chronic tolerance (2–7), i.e., the need for markedly increased amounts of alcohol to achieve a desired effect or experiencing markedly diminished effects with continued use of the same amount of alcohol. Tolerance, a diagnostic criteria for AUD from DSM-III (1980) to DSM-5 (2013) (8), implies that attenuation of subjective alcohol responses over time plays a key role in the development of addiction. In contrast, the sensitization theory asserts that greater stimulant effects over time underlie addictive processes (9), based on rodent data showing that stimulant-like and locomotor alcohol responses increase after repeated exposures (10,11). These effects are particularly strong in selectively bred mouse lines (12–14); sensitized responses may also include adrenal hormones (15). The incentive-sensitization theory of addiction (16,17) also emphasizes the sensitization process but specifies that repeated use of a drug produces neuroadaptations that sensitize motivational reward to drugs and associated drug stimuli (i.e., processes of wanting) distinct from the neurocircuitry mediating hedonic reward (liking), which may not

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sensitize over time. Finally, allostatic theory asserts heightened brain reward sensitivity and positive reinforcement characterize the early stages of addiction (18), but reward insensitivity and negative reinforcement underlie the later and more severe stages (18–20). Thus, while some researchers may not agree on the contributions of positive versus negative reinforcement factors underlying addiction (21,22), there is consensus on the critical need for longitudinal controlled human alcohol response investigation. Human studies in this area have been limited to retrospective patient reports (23), postmortem brain tissue methods (24), or cross-sectional laboratory paradigms (2,3,25–29), none of which directly measure alcohol responses in the same individuals over time. The few published test-retest studies of alcohol responses have included only brief between-session intervals with a focus on measurement reliability (30,31).

To address this issue, we conducted the Chicago Social Drinking Project (CSDP), a prospective alcohol response re-examination study. The CSDP examined 190 nonalcohol dependent young adult heavy (HD) and light drinkers (LD) who were primarily in their 20s (mean age 25.6 ± 3.2 SD years) at enrollment. Our previously published results showed that compared with light drinkers, heavy drinkers exhibited higher alcohol sensitivity, in terms of subjective stimulation and reward (liking and wanting) (29), as well as lower sensitivity, in terms of subjective sedation (29) and salivary cortisol reactivity (29,32). These findings were replicated in a second independent heavy drinker cohort using identical procedures (33). Further, in heavy drinkers, greater alcohol stimulation and reward and lower sedation predicted binge drinking escalations at 2-year follow-up (29), with greater stimulation and reward predicting more AUD symptoms experienced through 6 years (34).

In the current phase of CSDP, participants were invited back between their fifth and sixth year of the study to participate in two re-examination laboratory sessions. The goal was to conduct empirical tests of the neurobiological theories of alcohol adaptations underlying the propensity to develop addiction. We examined whether the alcohol response differences observed at initial testing persisted or changed in heavy versus light drinkers and whether the degree of change related to trajectories of AUD progression among the heavy drinkers. Tolerance theory would be supported if the heaviest drinkers over time showed an overall reduced alcohol response at re-examination compared with initial testing, whereas sensitization would be supported if the heaviest drinkers showed higher stimulant responses. The allostasis model's early phase of addiction, which may most closely match a 5-year interval in young adults, would be supported if alcohol reward sensitivity was maintained, and the later stage would be supported if reward sensitivity was diminished. Finally, increases over time in alcohol wanting would support the incentive-sensitization theory.

METHODS AND MATERIALS

Design

The CSDP is a within-subject, double-blind, randomized-order study of responses to alcohol and placebo beverages in 190 young adult nonalcohol dependent drinkers. The study was approved by the University of Chicago Institutional Review Board. Initial laboratory testing was conducted March 2004 to July 2006, and re-examination testing was conducted March 2009 to October 2011. Participants returned for re-examination, on average, 63 months (±1.5 SD) after their initial assessment. Both testing phases included two 4½-hour individual sessions separated by at least 24 hours and were conducted at the Clinical Addictions Research Laboratory at the University of Chicago. Participants completed measures before and after ingesting a blinded beverage that contained either .8 g/kg alcohol or placebo administered in random order at each phase.

Initial Testing Phase

Participants were recruited via local media and internet advertisements and word-of-mouth referrals. Initial inclusion criteria were age 21 to 35 years; weight 110 to 210 pounds; good general health; not pregnant or lactating; no current or past major medical or Axis I psychiatric disorders, including alcohol and substance dependence (other than nicotine); and no current use of any centrally acting medications. The medical screening by the study nurse included a brief physical assessment, health history, vital signs, a blood draw to confirm normal liver enzyme levels (≤ 2 SD of normal range), a urine toxicology screen (cocaine, opiates, benzodiazepines, amphetamines, barbiturates, and phencyclidine), and pregnancy test for women. A trained research assistant conducted the alcohol Quantity-Frequency Interview (35) and the alcohol disorders module from the Structured Clinical Interview for DSM-IV, nonpatient version (36). The participant also completed demographic measures, a two-generational biological family history (FH) tree for alcohol use disorders and the FH Research Diagnostic Criteria for drinking consequences (37), an Alcohol Timeline Followback for past month drinking (38), the Alcohol Use Disorders Identification Test (39), and the Drinker Inventory of Consequences (40). Heavy drinkers were defined as weekly binge drinkers (consuming ≥5 drinks for men and ≥4 drinks for women, per occasion, one to four times weekly) with at least 10 but no more than 40 drinks consumed per week for at least the past 2 years. Light drinkers averaged consuming one to five drinks per week with no/rare binge episodes (≤ 5 times per year). These criteria were based upon established guidelines (41–43) and were consistent with prior studies (44–50). Positive FH was defined as having at least one biological first-degree relative or two or more second-degree relatives with alcohol use disorders.

Laboratory Procedures

The testing sessions for both phases were conducted in the afternoon and commenced between 12:00 PM and 5:00 PM. To reduce alcohol expectancy, the Alternative Substance Paradigm (51) was used. Participants were informed that their allocated beverage might contain a stimulant, sedative, alcohol, or a placebo or a combination of these substances. Upon arrival, the participant completed self-report measures and engaged in objective breath tests to confirm compliance with recent alcohol abstinence. Urine samples were collected before one session, chosen randomly, for toxicology in all

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