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Review

Mechanisms of Alcohol Addiction: Bridging Human and Animal Studies

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Abstract

Aim: The purpose of this brief narrative review is to address the complexities and benefits of extending animal alcohol addiction research to the human domain, emphasizing Allostasis and Incentive Sensitization, two models that inform many pre-clinical and clinical studies.

Methods: The work reviewed includes a range of approaches, including: a) animal and human studies that target the biology of craving and compulsive consumption; b) human investigations that utilize alcohol self-administration and alcohol challenge paradigms, in some cases across 10 years; c) questionnaires that document changes in the positive and negative reinforcing effects of alcohol with increasing severity of addiction; and d) genomic structural equation modeling based on data from animal and human studies.

Results: Several general themes emerge from specific study findings. First, positive reinforcement is characteristic of early stage addiction and sometimes diminishes with increasing severity, consistent with both Allostasis and Incentive Sensitization. Second, evidence is less consistent for the predominance of negative reinforcement in later stages of addiction, a key tenant of Allostasis. Finally, there are important individual differences in motivation to drink at a given point in time as well as person-specific change patterns across time.

Conclusions: Key constructs of addiction, like stage and reinforcement, are by necessity operationalized differently in animal and human studies. Similarly, testing the validity of addiction models requires different strategies by the two research domains. Although such differences are challenging, they are not insurmountable, and there is much to be gained in understanding and treating addiction by combining pre-clinical and clinical approaches.

INTRODUCTION

Several theories have been posited in recent years to characterize the mechanisms of alcohol addiction. Although rooted in clinical observation, these models were initially developed primarily in animals (Robinson and Berridge, 1993; Vendruscolo and Roberts, 2014; Vendruscolo and Koob, 2019). An increasing number of investigators have been examining human alcohol use disorder (AUD) in light of this animal literature on addiction neurobiology (Koob and Le Moal, 2001). Such efforts raise a number of critical translational issues. The purpose of this paper, based partly on a 2019 symposium at the Research Society on Alcoholism, is to illustrate the complexities and benefits of bridging human and animal models of addiction, using as examples two prominent theories of addiction, which are briefly summarized here. Allostasis postulates a shift from predominantly positive reinforcement (e.g. drinking for pleasure or stimulation) to negative reinforcement (e.g. drinking to minimize withdrawal), with a corresponding reduction in the stimulating and pleasurable effects of alcohol. This process, which takes place over three stages (preoccupation/anticipation, binge/intoxication, withdrawal/negative affect), involves a progressive dysregulation of neurobiological systems governing reward (decrease) and stress (increase), which can persist over long periods of time and thereby render individuals vulnerable to subsequent relapse (Koob, 2003; Vendruscolo and Koob, 2019). Incentive sensitization emphasizes a distinction between desire ('wanting') and reward ('liking'), postulating, in susceptible individuals, (a) a progressive increase in desire for a substance and sensitivity to substance-related cues, with (b) hedonic or rewarding properties either remaining the same or decreasing (Robinson and Berridge, 1993; Robinson and Berridge, 2008). The increase in wanting, when combined with compromised executive control, forms the key component of addiction. Like allostasis, incentive sensitization hypothesizes long-lasting neurobiological changes that accompany and preserve these motivational changes. Points of comparison between these models are (a) whether desire for alcohol increases over time (incentive sensitization); (b) whether rewarding properties of drinking decrease (incentive sensitization, allostasis) or remain the same (incentive sensitization); (c) whether withdrawal and negative affect (allostasis) or wanting/craving (incentive sensitization) predominate as addiction progresses; and (d) whether neurobiological changes associated with negative affect and withdrawal (allostasis) or heightened wanting (incentive sensitization) are the primary drivers of relapse. The two theories are not entirely incompatible in that both describe the initial reward and pleasure in alcohol consumption being supplanted by negative states as addiction progresses. These later stages of addiction are characterized somewhat differently by the two models; allostasis emphasizes withdrawal, stress and negative affect, whereas incentive sensitization focuses on craving or wanting. Both scenarios are negative reinforcement paradigms, spotlighting different reinforcers.

Two key addiction constructs pose challenges when extending animal work to the human domain. In animal models, stages of addiction are typically short and precisely defined by behavior and physiology, appearing in a lockstep order. In humans, however, stages are longer and less clear-cut, with individuals shifting, in varying order, between abstinence, moderate drinking and problematic use. Koob and colleagues essentially acknowledge this when they describe their three stages as interacting and repetitive, increasing in intensity over time (Koob and Le Moal, 2001). Because it is difficult to identify and track human stages precisely over long periods, researchers often consider people who are light drinkers, are heavy drinkers or have

AUD to represent, respectively, increasingly severe stages of addiction. To further complicate the issue of stages, both in humans and laboratory animals, between-subject differences (e.g. stable tendencies to be depressed or anxious) could affect their pattern.

A second challenging construct found in both allostasis and incentive sensitization, is negative reinforcement, in which alcohol consumption is driven by its ability to alleviate aversive conditions. As noted above, aversive conditions emphasized differ between allostasis and incentive sensitization. More generally, negative reinforcement in human alcohol consumption encompasses phenomena that range widely in both content and intensity—for example, drinking to combat severe withdrawal or depression versus drinking to reduce mild anxiety—and their roles in the addiction process therefore might vary considerably. In animal studies, by necessity, researchers are more restricted in their ability to measure negative reinforcement and often employ withdrawal of alcohol to induce a presumed aversive state.

In this narrative review, we survey recent results from several prominent research groups that address alcohol addiction from a variety of perspectives. We focus largely, but not exclusively, on results relevant to allostasis and incentive sensitization, as examples of the translational challenges involved. The studies vary not only in their use of animal or human subjects, but in their timeframes (cross-sectional versus longitudinal) and the degree to which they focus on behavior, self-report and/or neurophysiology. The final section addresses the particular translational challenges involved in identifying genetic underpinnings of findings based on animal and human studies.

Pre-clinical and clinical evidence for new pharmacological treatment of AUD

The interplay between pre-clinical and clinical analyses is exemplified in the work of Vendruscolo, Koob and colleagues, who have conducted a series of animal and human explorations of the allostatic model, targeting the biology of both reward-based and relief-based consumptions. Ghrelin is a peptide associated with food (Al Massadi *et al.*, 2019) and alcohol (Farokhnia *et al.*, 2019) consumption and may play an especially prominent role in the escalation of drinking that characterizes early addiction. These researchers have employed a binge-like model in which rats are conditioned to sweetened alcohol and then allowed to self-administer it for restricted periods of time. Using this paradigm, rats with deletion of a ghrelin receptor drink less and are less motivated to do so, compared with control rats (Zallar *et al.*, 2019). Similarly, preliminary data suggest that pharmacological blockade of the ghrelin receptor may reduce alcohol craving in heavy drinking and alcohol drinking and preference in mice (Godlewski *et al.*, 2019; Lee *et al.*, 2020). A second set of studies has targeted glucocorticoid receptor (GR) functioning, which is associated with the stress sensitization characteristic of late-stage, negative reinforcement-driven addiction. The authors have found that GR expression and function were altered in several brain regions in alcohol-dependent rats, and they hypothesized that reducing GR signaling would reduce compulsive consumption (Tunstall *et al.*, 2017). Consistent with this prediction, the administration of the GR antagonist mifepristone significantly reduced alcohol drinking and motivation for alcohol selectively in alcohol-dependent rats (Vendruscolo *et al.*, 2012, 2015; Edwards *et al.*, 2015; Repunte-Canonigo *et al.*, 2015; Somkuwar *et al.*, 2017). Likewise, humans with AUD treated with mifepristone have exhibited reduced craving and alcohol consumption compared with placebo treatment (Vendruscolo *et al.*,

2015). Also, mineralocorticoid receptor (MR) levels in the amygdala (a brain region involved in negative affect and AUD) were found to be negatively correlated with anxiety-like behavior, alcohol intake and compulsive-like drinking in monkeys and rats (Aoun *et al.*, 2018). Similarly, in humans, the level of aldosterone, a MR agonist, was shown to be positively correlated with alcohol drinking, craving and anxiety (Aoun *et al.*, 2018). Vendruscolo *et al.*'s findings underscore the potential clinical utility of animal models, suggesting a key role for ghrelin signaling in binge (-like) drinking and craving and key roles for GR and MR in compulsive (-like) drinking. These researchers anticipate that targeting neurotransmitter systems based on an individual's prevailing motivation for alcohol drinking (e.g. positive versus negative reinforcement) may yield even more precise and efficacious treatments for AUD (Tunstall *et al.*, 2017).

Capturing allostatic processes in human samples

Focusing on humans, Ray and colleagues have used controlled experimental manipulations to ascertain the degree to which allostatic processes can be reliably assessed in clinical samples with AUD or heavy drinking (Bujarski and Ray, 2014; Bujarski *et al.*, 2018). Using an alcohol administration model, they have identified multiple dimensions of response and previously found that alcohol-induced stimulation, indexing the positive reinforcing effects of alcohol, was associated with alcohol craving to a significantly greater degree in heavy drinkers, as compared to individuals with current AUD (Bujarski and Ray, 2014). In a more recent work, this laboratory has observed that craving during an alcohol challenge strongly predicted self-administration and that sedation predicted lower self-administration (Bujarski *et al.*, 2018). Importantly, however, neither stimulation nor negative affect predicted self-administration; this lack of a connection with negative affect ran contrary to the predictions of the allostatic model (Ray *et al.*, 2009). Ray and colleagues have also addressed the relationship between drinking 'types'—self-defined, by questionnaire, as reward drinkers and relief drinkers—and experimental measures of subjective response and self-administration (Grodin *et al.*, 2019). Reward drinkers were more common (in this sample of treatment-seeking heavy drinkers) and reported consistently higher drinking for enhancement motives, while relief drinkers reported significantly higher drinking-to-cope motives. In parallel with Vendruscolo and colleagues, Ray's research seeks to phenotype allostatic processes and to establish their reliability and validity so that they can be applied toward precision medicine efforts (Ray *et al.*, 2019). Characterizing drinkers based on primary drinking motivation echoes Vendruscolo's point about the importance of identifying drinkers' stage in the addiction process and associated motives (Tunstall *et al.*, 2017).

Another group investigating heavy and alcohol-dependent drinkers has reported more clear-cut support for a positive relationship between severity of addiction and degree of negative reinforcement, as postulated by the allostatic model. Cho *et al.* (2019) used longitudinal interview and questionnaire data from the Collaborative Study on the Genetics of Alcoholism (COGA) to test how individuals' motivations for use differed across time with the onset of alcohol-related problems. Analyzing repeated administrations of the Semi-Structured Assessment for the Genetics of Alcoholism interview (SSAGA; Bucholz *et al.*, 1994) and the Alcohol Expectancy Questionnaire (AEQ; Brown *et al.*, 1987) among drinkers from both affected and comparison families, they found that only positive reinforcement was associated with alcohol consumption among individuals without an AUD. In contrast, the association between negative reinforcement and alcohol consumption became

stronger with the presence of AUD, whereas the association between positive reinforcement and alcohol consumption did not differ as a function of diagnosis. Finally, both positive and negative reinforcement were associated with the diagnosis of AUD, with the latter exhibiting a stronger correlation. Although these analyses are based on a self-report with its attendant limitations, they offer the benefit of relatively long follow-up periods and within-subject longitudinal analyses, which may partly explain why evidence for negative reinforcement was found in more severe stages of alcohol problems and consumption.

Integration of longitudinal and laboratory frameworks to study subjective responses to alcohol

Ongoing work by King, Vena and colleagues addresses both incentive sensitization and allostasis. The Chicago Social Drinking Project (CSDP) is a 15-year study that uniquely integrates repeated placebo-controlled laboratory alcohol challenges with longitudinal assessment of drinking behaviors and consequences. The CSDP has demonstrated that young adult heavy drinkers, compared with lighter drinkers, exhibit a pronounced heightened sensitivity to alcohol's stimulating and rewarding (liking, wanting) effects and a lower sensitivity to the sedating and cortisol responses to alcohol (King *et al.*, 2011). This response phenotype was reproduced in an independent second cohort of heavy drinkers and persisted through a 5-year re-examination (King *et al.*, 2016) (as well as a 10-year re-examination). Moreover, positive alcohol reinforcement and reward sensitivity were most pronounced in those persons with the heaviest binge drinking and steepest progression of AUD over time. Alcohol stimulation was inversely correlated with sedation (King *et al.*, 2019). A more recent work from the CSDP has included age-matched AUD drinkers and showed that they also exhibit heightened sensitivity to alcohol's positive effects, with stimulation, liking and wanting at levels comparable to or even higher than that observed in heavy drinkers. Thus, this uniquely designed longitudinal investigation of alcohol response in humans provides initial support for the first phase of allostasis, with a stable and persistent pattern of alcohol stimulation and reward in those developing AUD. However, both motivational (wanting) and hedonic (liking) rewards remained elevated and, in some cases, increased with severity of consumption, contrary to the incentive sensitization theory, and there was no evidence of reward deficit drinking as described in allostasis. As with the previous two sections, King's work suggests the importance of individual differences or subjective alcohol response phenotypes, in this case based on longitudinal patterns, in determining risk for AUD development and heavy drinking (Tunstall *et al.*, 2017; Grodin *et al.*, 2019). Although neither King nor Ray has found strong support for a relationship between negative reinforcement and addiction severity, it is possible that additional observations of individuals at later stages of addiction may generate findings more supportive of allostasis.

Challenges and opportunities working across human and animal models from a genetic perspective

Knowledge gained from pre-clinical and clinical studies is further enhanced by characterizing the genetic underpinnings not only of AUD but also of particular mechanisms or stages stipulated by addiction models. These models can serve as organizing frameworks in gene searches, reducing fishing expeditions and multiple testing burden. To this end, there are some human findings that empirically or theoretically tie specific functional variants to the allostatic and incentive sensitization models (Pieters *et al.*, 2011;

Reilly *et al.*, 2017). However, gene identification remains a major challenge in bridging human and animal addiction work. Many of the fine-grained details about the mechanisms by which risk unfolds and genetic influences operate are lost in large-scale human gene identification efforts, which necessitate extremely large samples and, accordingly, often focus on broad, imprecise phenotypes available in large numbers of individuals. In contrast, animal studies necessarily involve studying the component processes associated with ethanol response. The movement toward studying polygenic signals created from genome-wide association data in humans has further separated human genetic studies and animal genetic work, which continues to focus more on individual genes. Dick and colleagues have been examining ways to bridge genetic studies conducted in humans and animals in order to advance gene identification and characterization of the mechanisms by which genetic influences impact the development of alcohol problems (Dick *et al.*, 2010; Dick and Kendler, 2012; Ksinan *et al.*, 2019). Through the Virginia Commonwealth University Alcohol Research Center and related projects, there are several approaches, including focusing on gene networks and systems rather than individual genes (Mathies *et al.*, 2017; COGA Consortium *et al.*, 2018); the integration of animal expression data to enhance polygenic signal; and the application of new multivariate genetic techniques to human datasets to help identify genes involved in various component processes related to AUD. As part of an international consortium, Dick and colleagues have gathered genome-wide association studies data representing more than 1.5 million observations for a diversity of phenotypes related to externalizing disorders and behaviors, based on the twin literature robustly demonstrating that much of the genetic predisposition to AUD is shared with other externalizing outcomes (Krueger *et al.*, 2002; Kendler *et al.*, 2003, 2007). The consortium has employed genomic structural equation modeling (Grotzinger *et al.*, 2019) to these data and identified multiple latent factors representing distinct processes through which genes influence risk for addiction. Not only do these multivariate approaches increase power to identify genes involved in alcohol use outcomes, through such novel methods, better consilience between human and animal studies can be achieved, improving our ability to map how genetic influences impact component processes of AUD.

DISCUSSION

Bridging human and animal addiction research is highly challenging but also vitally important for assessing theories of addiction etiology. The researchers' different ways of defining what alcohol addiction is (Bickel *et al.*, 2019), and what its critical underlying mechanisms are, have differential implications for its prevention and treatment.

Vendruscolo and colleagues' laboratory approach has helped to parse the somewhat blurry construct of AUD into more meaningful stages and subtypes as well as to facilitate the development and testing of new drug treatments. As a variation on within-subject changes in severity, Ray's typing of problem drinkers based on primary motivation extends a long-standing tradition of alcoholism subtypes. While acknowledging the value of this approach, caution should be exercised in order to avoid reifying the categories, because motives change over time (Littlefield *et al.*, 2010) and may be better viewed as dynamic dimensions rather than stable between-person attributes (Littlefield *et al.*, 2013).

The use of questionnaires and interviews in Ray's and Cho's research to characterize motivation or stage of addiction should be

tempered with a recognition of the limits of insight into implicit process and the more general vicissitudes of self-report. As an example, heavy smokers cannot always verbalize a reason for their addiction, because the key underlying processes are elusive and highly automatic. Related to this point, habitual behaviors, which often lack an obvious positive or negative reinforcer, can evolve into addictive, compulsive behaviors. This transition is not currently well understood and might someday be identifiable with the help of biological markers.

Work by King's group highlights the necessity of longitudinal research in evaluating addiction theories such as allostasis and incentive sensitization and understanding individual risk factors for excessive and problematic alcohol use. Although King's CSDP demonstrates that, as groups, heavy and light drinkers experience differing sensitivities to the positive stimulating and rewarding effects of alcohol, individual curves might also be examined to determine the degree of heterogeneity within each group and to indicate whether such individual differences reveal additional important information. While chronological age and time represent valuable ways to chart the course of alcohol effects, individual histories represent another complementary way to distinguish development from course of substance involvement and its correlates.

Finally, Dick's genetic work suggests the complexity and interconnectedness of AUD and one of its key drivers, externalizing behavior. For example, norm-violating behavior and impulsivity precede the onset of addiction, and it might be useful, when estimating the potential for relapse following alcohol treatment, to track not only days abstinent but also changes in these externalizing components. In addition, disinhibited behavior, which is central to externalizing, might differ considerably between individuals; some might exhibit hypersexuality, others anger, aggression or self-destructive behavior, and these differences might have differential implications for substance misuse.

This brief narrative survey—of animal and human addiction research, attendant translational issues and two models that inform these studies—is limited by not being a systematic review. Nevertheless, it is hoped that a case has been made for both the benefits and challenges of combining animal and human approaches to alcohol addiction and, by extension, to other psychiatric conditions. The continuing integration of pre-clinical and clinical work will require both creativity and rigor to ensure that this crosswalk truly improves our care for individuals afflicted by these disorders.

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CONFLICT OF INTEREST STATEMENT

The authors report no relevant conflicts.

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