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Invited review

Studies using macaque monkeys to address excessive alcohol drinking and stress interactions

Vanessa A. Jimenez [a], Kathleen A. Grant [a, b, *]

[a] Oregon Health & Science University, Department of Behavioral Neuroscience, Portland, OR, USA
[b] Oregon National Primate Research Center, Division of Neuroscience, Beaverton, OR, USA

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ABSTRACT

The use of non-human primates (NHPs) in studies of volitional, oral self-administration of alcohol can help address the complex interplay between stress and excessive alcohol consumption. There are aspects to brain, endocrine and behavior of NHPs, particularly macaques, that provide a critical translational link towards understanding the risks and consequences of alcohol use disorders (AUDs) in humans. These include wide individual differences in escalating daily alcohol intake, accurate measures of hypothalamic-pituitary-adrenal (HPA) axis hormonal interactions, neuroanatomical specificity of synaptic adaptations to chronic alcohol, genetic similarities to humans, and the ability to conduct in vivo brain imaging. When placed in a framework that alcohol addiction is a sequence of dysregulations in motivational circuitry associated with severity of AUD, the NHP can provide within-subject information on both risks for and consequences of repeatedly drinking to intoxication. Notably, long-term adaptations in neurocircuitry that mediate behavioral reinforcement, stress responses and executive functions are possible with NHPs. We review here the substantial progress made using NHPs to address the complex relationship between alcohol and stress as risk factors and consequences of daily drinking to intoxication. This review also highlights areas where future studies of brain and HPA axis adaptations are needed to better understand the mechanisms involved in stress leading to excessive alcohol consumption.

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1. Introduction

As this special issue on the neuropharmacology of alcoholism highlights, a useful approach to conceptualizing alcohol use disorders (AUDs) is based in understanding the cascading effects of repeatedly drinking to intoxication on neurocircuitry that mediate behavioral reinforcement, stress responses and executive functions (Koob and Volkow, 2016). Notably, this framework provides specific, testable hypotheses regarding the temporal sequence and specific mediators of dysregulation in motivational circuitry associated with severity of AUD. In this review, we highlight the non-human primate (NHP) studies of volitional, oral intake of alcohol and focus on the changes in the stress system as well as the proportion of monkeys that escalate and maintain drinking excessive

* Corresponding author. 505 NW 185th Ave, Beaverton, OR 97006, USA.
E-mail address: grantka@ohsu.edu (K.A. Grant).

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Abbreviations

ACTH	adrenocorticotropin hormone
AVP	arginine-vasopressin
AUD	alcohol use disorder
BEC	blood ethanol concentration
BNST	bed nucleus of the stria terminalis
CRF-BP	corticotropin-releasing factor binding protein
CRF	corticotropin-releasing factor
DHEA	dehydroepiandrosterone
DMR	differentially methylated region
DOC	deoxycorticosterone
FSCV	fast-scan cyclic voltammetry
GABA	gamma-aminobutyric acid
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenal
ISM	immune-signaling molecule
KOR	kappa opioid receptor
LGN	lateral geniculate nucleus
MAO-A	monoamine oxidase A
MAOA-LPR	monoamine oxidase promoter
MRI	magnetic resonance imaging
MSN	medium spiny neuron
NAcc	nucleus accumbens core
NHP	nonhuman primate
o-CRF	ovine-corticotropin-releasing factor
OXY	oxytocin
PVN	hypothalamic paraventricular nucleus
THDOC	(3α,5α)-3,21-dihydroxypregnan-20-one

levels. We emphasize the importance of NHPs as a translational link to human AUD both in terms of neuroendocrine physiology and the capacity to longitudinally assess neurocircuitry changes amenable to addressing the paradigm put forward by Koob and colleagues.

There is now strong evidence that the mammalian response to stress is an orchestration of endocrine, neural and behavioral processes that, in the face of chronic alcohol, can become maladaptive and propagate further escalations in alcohol intake (Becker, 2012; Blaine et al., 2015; Sinha et al., 2011). This underscores the phenomenon that the relationship between stress and alcohol is bidirectional. On one hand, stress is an etiological factor in the development of alcohol use disorders (Keyes et al., 2012) while on the other hand, pathological (i.e., allostatic) adaptations in the stress response occur due to continued alcohol consumption (Richardson et al., 2008; Sinha, 2012). Hypothalamic-pituitary-adrenal (HPA) axis activation is integral to the definition of stress, which is defined as any physical or psychological stimulus that challenges homeostasis and activates the HPA axis (Smith and Vale, 2006). However, regulation of the HPA axis is complex, flexible and reactive to changes in both the internal and external environments. Under chronic stress, the hypothalamic and extra-hypothalamic response loses flexibility and undergoes a compromised response to additional stressors resulting in a shift from homeostasis to allostasis (McEwen et al., 1993; McEwen, 1998).

The development of AUDs and resultant drinking severity are associated with altered HPA axis dysregulation, with most data primarily centered on glucocorticoid regulation (Wand, 2008). Beyond the HPA axis, the glucocorticoid receptor (GR) is abundantly expressed in mesolimbic reward circuitry (Härfstrand et al., 1986; Morimoto et al., 1996) and the extended amygdala (Patel et al., 2000; Pryce, 2008). Thus, the extra-hypothalamic corticotrophin-releasing factor (CRF) system can influence responses to stress via the amygdala and other limbic regions (Schulkin et al., 1998). Counter to the suppression of hypothalamic CRF, glucocorticoids increase CRF expression in the amygdala (Schulkin et al., 1998) and up-regulation of CRF by corticosterone contributes to anxiety-like and fearful behaviors to perceived stress. Indeed, in a recent study that overexpressed CRF in the central amygdala region of young rhesus macaques, anxious temperament was increased compared to cage-mate controls (Kalin et al., 2016). In turn, anxiety and negative emotional states facilitate the initiation, maintenance and relapse to alcohol use (Sinha, 2013). Notably, in animal studies, the GR antagonist mifepristone (MIFI) blocks alcohol-induced place preference (Rotter et al., 2012), reduces alcohol intake (Koenig and Olive, 2004; Vendruscolo et al., 2012, 2015), reduces alcohol withdrawal symptoms (Jacquot et al., 2008) and protects hippocampal neurons from injury due to binge-like alcohol consumption (Cippitelli et al., 2014). The translation of the efficacy of MIFI was recently shown to reduce cue-induced alcohol craving and alcohol intake in human subjects with AUD (Vendruscolo et al., 2015). Perhaps understudied in terms of adrenal hormonal response in chronic alcohol effects is the mineralocorticoid system, which is key to fluid regulation and motivated behavior at the level of the amygdala (Sakai et al., 2000).

In order to dissect the interactions of stress and excessive drinking, animal models play a key role. Monkey models of alcohol self-administration, as with other animal models, are able to reduce the impact of several key factors (e.g., nutritional status, housing environment, age at first intoxication, exposure to stressors, etc.) and isolate critical variables related to excessive alcohol consumption (Grant and Bennett, 2003). Monkeys have a prolonged adolescence and young adulthood phase, close genetic similarities, similar expansion of the cerebral cortex, and in the case of old world monkeys, neuroendocrine similarities to humans. These similarities are especially advantageous when studying endocrine physiology, where there are notable differences between primates (human and NHP) and rodents. For example, the relative distribution of opioid receptors in the frontal cortex differs substantially between rodents and humans (Mansour et al., 1988), corticotropin releasing factor binding protein (CRF-BP) is found both centrally and peripherally in primates while only in the brain and pituitary of rodents (Bowman et al., 2001; Seasholtz et al., 2002) and important morphological differences in the pituitary gland exist between rodents and humans (Kelberman et al., 2009). At the level of the adrenal gland, the primary glucocorticoid, providing negative feedback to the brain and pituitary to restore homeostasis following HPA axis activation, is corticosterone in rodents and cortisol in primates. The zona reticularis adrenocortical layer, where the primary adrenal androgen dehydroepiandrosterone (DHEA) is synthesized, is absent in rodents (Conley et al., 2004). And finally, rats have low levels of 5β-reduced neuroactive steroids indicating species differences in neuroactive metabolites of adrenal steroids that may contribute to the subjective effects of alcohol (Helms et al., 2012c; Morrow et al., 2006; Porcu et al., 2009).

Given the translation potential of old world macaques and baboons, these NHPs have been particularly useful for addressing stress as an etiological factor in AUDs (Barr and Goldman, 2006; Cederbaum et al., 2009; Grant and Bennett, 2003; Grant et al., 2014). In comparisons to humans, macaque monkeys have similar alcohol absorption and metabolism rates and can self-administer