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RESEARCH HIGHLIGHT

A line before liquor: a novel model of cocaine and alcohol co-abuse reveals changes in glutamate homeostasis

Jonna M. Leyrer-Jackson[1] and M. Foster Olive[1]

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Approximately, 1.9% of the U.S. population age 12 and older are current users of cocaine, and approximately 0.9% of the U.S. population currently meet diganostic criteria for cocaine use disorder [1]. Individuals diagnosed with cocaine dependence show high comorbidity with alcohol dependence, and more than half of cocaine-dependent individuals report using both alcohol and cocaine simultaneously [2]. Alcohol is often used in conjunction with cocaine, in part, to counteract cocaine-induced withdrawal symptoms, and conversely, cocaine is often used to counteract the sedating and motor impairing effects of alcohol [3]. As well, cocaine and alcohol relapse are higher in individuals suffering from co-abuse [4], as are the incidences of cognitive dysfunction and various health issues [5]. While identifying the neuroadaptations underlying polysubstance abuse and the development of medications to treat such disorders rely on rodent models, the successful development of rodent models of polysubstance abuse remains a key unaddressed issue. Many studies have extensively studied the neuroadaptations of cocaine and alcohol use alone, yet have failed to address possible changes induced by polysubstance abuse and importantly the comorbidity of cocaine and alcohol co-abuse.

Thus far, rodent studies examining the neuroadaptive effects of abused substances have examined glutamatergic transmission within the mesocorticolimbic circuitry, due to its role in mediating the relapse/reinstatement of drug seeking. A breadth of current literature has concluded that altered glutamatergic efferent projections from the medial prefrontal cortex into the nucleus accumbens significantly contributes to drug seeking [6]. In addition, postsynaptic alterations in glutamate regulation mechanisms, including downregulation of the glutamate transporter, GLT-1, and downregulation of the glutamate/cysteine exchanger, xCT, have been repeatedly shown following exposure to drugs of abuse. Further, pharmacological agents which restore glutamatergic tone within the nucleus accumbens have shown promising ability to inhibit reinstatement of drug seeking [7]. However, the degree to which modifications are made to this circuit can vary based on drug type, exposure time, and withdrawal. While changes within glutamatergic circuits have provided insight into treatment options for patients suffering from both cocaine and alcohol abuse disorders, current studies fail to address possible changes induced from polysubstance abuse and the comorbidity of the two.

In their recent article, Stennett et al. [8] have used a rat model of sequential cocaine and alcohol self-administration. This model has been designed to explore neuroadaptations underlying co-use of cocaine and alcohol, which may be different than the neuroadaptations induced by either of these substances alone. In addition, Stennett et al. [8] determined whether ceftriaxone, a compound known to inhibit both cocaine or alcohol seeking, could elicit similar effects for co-use of both substances. In this study, male rats underwent intravenous cocaine self-administration (2 h/day) directly followed by 6-h access to unsweetened alcohol (20% v/v) for either 10 or 12 consecutive days. Rats then underwent daily 2-h extinction sessions for a minimum of 12 days, where active lever presses no longer resulted in cocaine infusions or associated cues. Stennett et al. [8] examined the behavioral and neurobiological underpinnings of alcohol/cocaine co-self-administration and the potential efficacy of ceftriaxone in preventing relapse/reinstatement in "polydrug" self-administering rats.

Stennett et al. [8] demonstrated that rats reliably self-administered both cocaine and unsweetened alcohol. Interestingly, rats that self-administered cocaine consumed similar amounts of alcohol as compared to yoked-saline rats, and rats with access to alcohol did not self-administer more cocaine than those with access to water only. While these findings differ from the authors' previous work showing that noncontingent administration of cocaine increased consumption of alcohol, the newer procedure reports notable methodological differences that could account for this discrepancy.

When examining brain tissue following self-administration procedures, in agreement with previous literature, Stennett et al. [8] show that cocaine self-administration alone decreases GLT-1 surface expression in the nucleus accumbens, while alcohol consumption had no effect on GLT-1 surface expression in yoked-saline infused rats. However, the authors report that rats self-administering cocaine + alcohol display significantly higher GLT-1 surface expression compared to cocaine + water and yoked-saline-alcohol rats, which the authors suggest may be due to increased GLT-1 transcription. In addition, in separate groups of rats exposed to saline or ceftriaxone after self-administration procedures and prior to reinstatement of drug seeking induced by cocaine + cue exposure, Stennett et al. [8] showed greater Fos expression within the prefrontal cortex and nucleus accumbens core for all cocaine self-administration groups compared to control groups. Fos expression in the nucleus accumbens shell, but not the core, was negatively correlated with alcohol intake, whereas expression in the basolateral amygdala was positively correlated with alcohol intake, and no correlation between alcohol intake and Fos expression in the prefrontal cortex was found.

In agreement with prior studies, Stennett et al. [8] demonstrated that ceftriaxone, administered daily for 5–7 days prior to reinstatement testing, attenuated cue- and cocaine-primed reinstatement in alcohol-naïve rats. Using in vivo microdialysis, the authors

[1]Department of Psychology, Arizona State University, Tempe, AZ 85287, USA
Correspondence: M. Foster Olive (foster.olive@asu.edu)

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show extracellular glutamate levels in the nucleus accumbens to be reduced throughout baseline and reinstatement in alcohol-naïve rats that received ceftriaxone. However, ceftriaxone was unable to attenuate cue- and cocaine-primed reinstatement in rats with a history of cocaine + alcohol consumption. Notably, these rats displayed higher baseline extracellular glutamate levels compared to ceftriaxone-treated cocaine + water rats, and no increase in glutamate efflux from baseline was observed during reinstatement resting. The authors conclude that ceftriaxone's inability to prevent reinstatement may be due to the fact that neither GLT-1 expression nor glutamate efflux display the same pattern in alcohol consuming rats compared to alcohol-naïve rats, and as such the efficacy of ceftriaxone appears to rely on restoring GLT-1 expression levels and the ability of drug and/or cue exposure to induce glutamate efflux in the nucleus accumbens.

Overall, the highlighted study reports that in a rat model of cocaine and alcohol co-abuse, the neuroadaptations induced by these two drugs are different from those produced by either drug alone. However, it remains to be addressed whether different doses of cocaine or concentrations of alcohol would yield similar results to those presented here, or if the order of drug intake (i.e., cocaine prior to alcohol or alcohol prior to cocaine) is an important factor. Further studies examining the influence of dose, a history of dependence on either drug, or temporal order of intake could potentially reveal behavioral phenotypes that more closely mimic those observed in humans [2] and monkeys [9]. In addition, it is likely that many users co-abuse cocaine and alcohol simultaneously, and thus incorporating simultaneous access to both drugs would provide a more translational component to the model developed here. Nonetheless, the experiments presented by Stennett et al. [8] address understudied questions that are important clinically, and warrant further exploration of neurochemical and neurocircuitry alterations underlying polysubstance abuse. Collectively, the model and results presented by Stennett et al. [8] will hopefully inspire future preclinical models and studies to examine the neuroadaptations induced by different aspects of polysubstance abuse.

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ADDITIONAL INFORMATION

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