

The Sugars in Alcohol Cocktails Matter

Ken T. Wakabayashi,* Esther A. Greeman, Scott T. Barrett, and Rick A. Bevins

 Cite This: *ACS Chem. Neurosci.* 2021, 12, 3284–3287

Read Online

ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: While sugar consumption and alcohol drinking have traditionally been studied by different basic science fields, most commercially available flavored alcoholic beverages are sweetened with some kind of sugar. The prevailing view is that these sugars potentiate drinking by making the alcohol taste better, particularly for adolescents, overlooking that some central nervous system circuits implicated in alcohol drinking are also sensitive to brain penetrant sugars like glucose. In this Viewpoint, we highlight the need for basic researchers to carefully consider how the sugars mixed with alcoholic beverages may impact the neurochemical and biological mechanisms influencing alcohol drinking and the development of alcohol use disorder.

KEYWORDS: *Sugar consumption, flavored alcoholic beverages, alcohol drinking, brain penetrant sugars, alcohol use disorder, central nervous system*

■ WHAT'S IN THAT DRINK?

In the United States alone, about 15 million people aged 12 and older, or 5.3% of the population, have alcohol use disorder (AUD), including 414 000 adolescents aged between 12 and 17. Alcohol use leading to AUD is often initiated in early adolescence. Importantly, adolescent drinking is strongly linked with flavored alcoholic beverages (FAB), a broad category of commercially available alcoholic beverages that differ widely in their alcohol and sugar content. Approximately half of young drinkers aged 13–20 years report drinking a FAB in the past 30 days.¹ Strikingly, approximately 70–77% of underage drinkers exclusively consuming either supersized “alcopops” or ready-to-drink FABs report episodic heavy drinking compared to only ~45% of drinkers consuming non-FABs.¹ While the factors influencing underage drinking of FABs are complex and may include the alcohol concentration, cost, convenience, and marketing, a predominant view is that sweeteners added to alcohol potentiate adolescent drinking.¹ Indeed, preclinical animal models also regularly use a well-established “sweetened fade” procedure to facilitate the acquisition of alcohol self-administration. Importantly, the role of sweeteners like sugars in FABs and their use in preclinical models is often explained solely in terms of taste and palatability. However, this perspective overlooks the fact that different types of sugars have divergent direct effects on the brain. In Table 1, we provide a list of resources highlighting why these central effects may be a critical factor to consider with alcoholic beverages.

■ NOT ALL SUGARS ARE CREATED EQUAL

Commercially available FABs often contain glucose and fructose monosaccharides in varying proportions. These can range from 42% to 70% fructose versus glucose, with the 55% fructose, 45% glucose mixture highly prevalent in beverages. In animal studies, sucrose is often used in sweetened-fade procedures. In this context, sucrose is widely considered

equivalent to 50% glucose and fructose, perhaps because they are calorically identical. However, in a sucrose solution, the glucose and fructose monomers remain bound together and are only broken apart by gastric activity or enzymes found in the small intestine. Thus, the sugars consumed by humans in FABs and the sugars often employed in preclinical research represent distinct chemical compounds. This point is particularly important when considering that glucose, the main metabolic fuel of the brain, can rapidly cross the blood–brain barrier (BBB) by facilitated, gradient dependent diffusion via the glucose transporter-1 (GLUT-1). More recently, investigators have discovered that fructose can directly enter the brain through GLUT-5 transporters in the BBB. GLUT-5 is expressed much less than GLUT-1, making the transport of fructose into the brain compared to glucose much slower and lower. Thus, while glucose, fructose, and sucrose share many common characteristics, because of the different metabolic and transport pathways, each sugar differs in its pharmacokinetics.

■ CONSEQUENCES OF DIFFERENT PHARMACOKINETICS

The pharmacokinetic differences between glucose and fructose, namely, when the sugar arrives in the brain from when it is tasted and consumed, as well as how much of the sugar crosses into the brain, may have repercussions in learning to drink alcohol and the development of AUD. In this regard, glucose is a unique reward itself and a sweetener in FABs. It has a strong peripheral sensory effect as a tastant and can easily cross the

Received: August 6, 2021

Accepted: August 11, 2021

Published: August 24, 2021

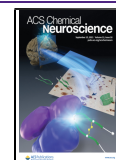


Table 1. Other Resources Linking Sugars Mixed with Alcoholic Beverages and Alcohol Drinking

Translational resources	Alcohol Facts and Statistics National Institute on Alcohol Abuse and Alcoholism (NIAAA) [WWW Document], n.d. URL https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics . (Recent statistics highlighting the number and age of people in the United States with AUD) Spear, L. P., 2016. Alcohol Consumption in Adolescence: A Translational Perspective. <i>Curr. Addict. Rep.</i> 3, 50–61, https://doi.org/10.1007/s40429-016-0088-9 . (A review summarizing preclinical and clinical research into how adolescent alcohol drinking may differ from drinking in adulthood)
Preclinical resources	Jones, S. C., Reis, S., 2011. Not just the taste: why adolescents drink alcopops. <i>Health Educ.</i> 112, 61–74, https://doi.org/10.1108/09654281211190263 . (A human study detailing the factors influencing FAB selection and preference in adolescents in Australia) Sanson, H. H., Pfeiffer, A. O., Tolliver, G. A., 1988. Oral Ethanol Self-administration in Rats: Models of Alcohol-Seeking Behavior. <i>Alcohol. Clin. Exp. Res.</i> 12, 591–598, https://doi.org/10.1111/j.1530-0277.1988.tb00248.x . (Seminal work describing the sucrose fade procedure in operant alcohol self-administration in rats) Duelli, R., Kuschinsky, W., 2001. Brain glucose transporters: relationship to local energy demand. <i>News Physiol. Sci.</i> 16, 71–76, https://doi.org/10.1152/physiologyonline.2001.16.2.71 (Review summarizing how glucose is transported into the brain) Haessel, B., Elsas, A., Froland, A.-S., Tauboll, E., Gjerstad, L., Quan, Y., Dingledine, R., Rise, F., 2015. Uptake and metabolism of fructose by rat neocortical cells <i>in vivo</i> and by isolated nerve terminals <i>in vitro</i> . <i>J. Neurochem.</i> 133, 572–581, https://doi.org/10.1111/jnc.13079 . (A preclinical study detailing mechanisms of fructose transport into the brain) Navarro, M., Olney, J. J., Burnham, N. W., Mazono, C. M., Lowery-Gionta, E. G., Pleil, K. E., Kash, T. L., Thiele, T. E., 2016. Lateral Hypothalamus GABAergic Neurons Modulate Consummatory Behaviors Regardless of the Caloric Content or Biological Relevance of the Consumed Stimuli. <i>Neuropsychopharmacology</i> 41, 1505–1512, https://doi.org/10.1038/npp.2015.304 . (A preclinical study using chemogenetics to determine the role of LH GABA neurons in alcohol drinking in mice)

BBB in comparison to fructose and sucrose. Thus, when mixed with alcohol, glucose could impact learning about alcohol drinking by several unique mechanisms. First, glucose could more rapidly activate central circuits that regulate reinforcement and shorten the delay between a predictive peripheral sensory stimulus (i.e., the taste) and the reinforcer (i.e., the central action of glucose and alcohol). After all, it is well-known that shortening the delay between a stimulus and reinforcer often facilitates learning and conditioning. Alternatively, due to more efficient transport, a higher concentration of glucose compared to another sugar may be able to cross into the brain and have a greater direct impact on central circuits involved in reinforcement, synergizing with the neurochemical effect of alcohol in the brain. Regardless of the exact mechanism, the pharmacokinetic characteristic of glucose needs to be carefully considered because several central neural systems that are glucose sensitive are also heavily implicated in alcohol drinking and AUD.

■ GLUCOSE SENSING NEURONS ARE ALSO IMPLICATED WITH ALCOHOL

Glucose-sensitive neurons are classified as such because they change their electrophysiological activity based on alterations of the extracellular glucose concentration. Notably, γ -aminobutyric acid (GABA), orexin/hypocretin, and neuropeptide Y neurons found in the hypothalamus are all inhibited when brain glucose concentrations are high.² Conversely, melanin concentrating hormone (MCH) neurons, also found in the hypothalamus, are excited when glucose levels are high.² Intriguingly, a subset of these glucose sensitive neurons has been strongly implicated in preclinical investigations of alcohol drinking. That is, activation or inhibition of the lateral hypothalamic (LH) GABA neurons can potentiate or reduce binge-like alcohol consumption in mice; this effect appears to generalize broadly to other consummatory behaviors. Moreover, direct microinjections of orexin into the paraventricular nucleus (PVN) and LH hypothalamic subregions, which activate orexin receptors, can induce alcohol drinking in rats.³ Similarly, injections of MCH directly into the PVN can also promote alcohol drinking, while injections of NPY into the PVN can induce alcohol drinking as well but only in rats with an extended history of alcohol experience.³ These studies establish that a diverse number of neurotransmitter systems are involved in both glucose-sensing and alcohol consummatory behaviors. Moreover, while the cellular mechanisms for hypothalamic glucose sensitivity in GABA, orexin, NPY, and MCH neurons are largely characterized as via changes in ion channel conductivity,⁵ the cellular mechanism for alcohol's effects on these neurons remains unclear.

■ FRUCTOSE AND GLUCOSE INTAKE IS BEHAVIORALLY DISTINCT

In awake glucose-drinking rats, large tonic elevations above baseline levels can be detected in the nucleus accumbens 2–5 min after the rat has stopped drinking a 10% glucose solution. This tonic rise peaks ~20–30 min after drinking and is associated with periods of no drinking. Only when brain levels of glucose fall below the predrinking baseline, ~60 min, do rats begin drinking glucose again. This observation highlights that consumed glucose rapidly enters the brain at a behaviorally relevant time scale and that the levels in the brain are highly correlated with drinking (Figure 1a).⁴ Furthermore, when rats

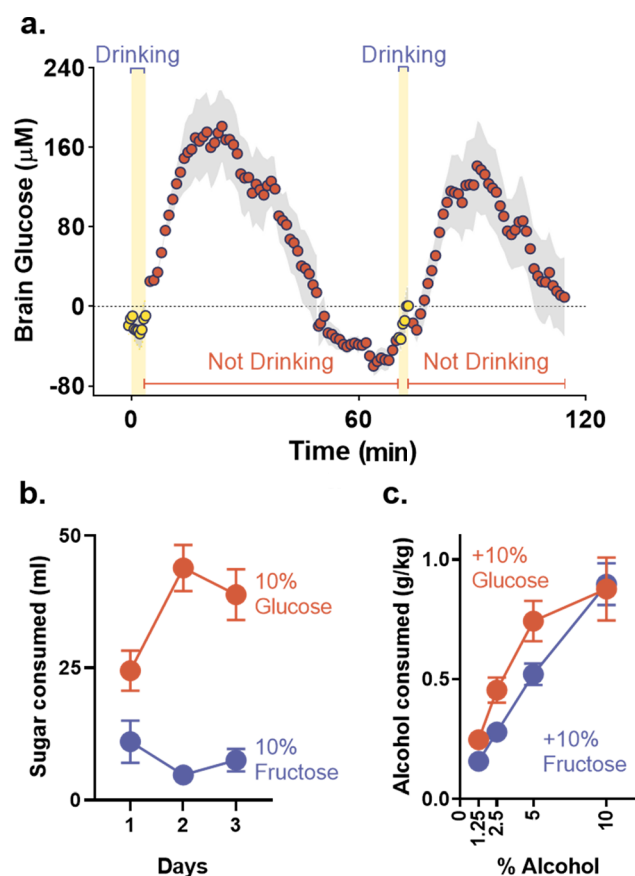


Figure 1. (a) Overall changes of extracellular glucose concentrations from baseline levels in the brain during distinct periods of glucose free drinking and no drinking, adapted from ref 4. (b) Volumes of 10% sugar solutions drunk by rats when given a choice during 4 h access over 3 days, adapted from ref 5. (c) Average amount of alcohol consumed by rats during two different single choice 4 h sessions when different concentrations of alcohol are mixed with 10% glucose or 10% fructose.

with experience drinking both sugars are given a choice between both, rats prefer to drink glucose ~5:1 over fructose (Figure 1b).⁵ When mixed with alcohol, male Sprague-Dawley rats will drink more 10% glucose-alcohol than an equally concentrated fructose-alcohol mixture during forced choice trials when the alcohol concentration is between 1.25% and 5%. However, once the alcohol concentration reaches 10%, rats drink an equivalent amount of both cocktails (Figure 1c).

■ THE SUGAR IN YOUR DRINK MATTERS

The contributors to human alcohol drinking are complex because it involves an interaction between many elements. Moreover, adolescent drinking may involve unique characteristics distinct from those found in adulthood. In addition to sociocultural and environmental factors, the biological etiology remains a key player. Yet within the biological and neurochemical mechanisms of AUD, there is a lack of preclinical research examining how alcohol and sugars, two potent reinforcers on their own, can interact within the brain and influence behavior. This gap is even more surprising given that people of all ages often drink alcohol mixed with a wide variety of sugars. Moreover, sweetened FAB drinking is strongly associated with episodic drinking in adolescents. Additionally, there is overlap between multiple neural circuits implicated in

alcohol drinking and glucose sensitivity, suggesting a biological mechanism. Future research will need to carefully parse how different brain penetrant sugars can influence different models of alcohol intake and relapse-related behaviors. Further, studies will need to determine how adolescent exposure to these different sugar-sweetened alcohol cocktails influences alcohol drinking in adulthood. As well, the role of glucose sensitive hypothalamic neural circuits in drinking these mixtures warrants thoughtful examination. As these circuits, systems, and behaviors are also heavily influenced by sex, future studies will need to rigorously incorporate sex as a biological variable. Overlooking how vulnerable human populations consume alcoholic beverages (largely in FABs) may mean missing an important effect that could prove critical in understanding the biological mechanism of AUD.

■ AUTHOR INFORMATION

Corresponding Author

Ken T. Wakabayashi – Department of Psychology, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0308, United States; orcid.org/0000-0002-7518-572X; Phone: (402) 472-3721; Email: kwakabayashi2@unl.edu

Authors

Esther A. Greeman – Department of Chemistry, Oakwood University, Huntsville, Alabama 35896, United States
 Scott T. Barrett – Department of Psychology, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0308, United States
 Rick A. Bevins – Department of Psychology, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0308, United States; orcid.org/0000-0002-2438-2264

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acscchemneuro.1c00526>

Author Contributions

K.T.W. did the conceptualization, supervision, investigation, writing of the original draft, and visualization. E.A.G. did the investigation and the writing, review, and editing. S.T.B. and R.A.B. did the writing, review, and editing. All authors read and commented on the drafts and approved the final version of the article.

Funding

This work was supported in part by Nebraska Tobacco Settlement Biochemical Research Funds (to K.T.W.), by the Rural Drug Addiction Research (RDAR) Center (COBRE, Grant P20GM130461 to K.T.W.), and by IMARI (Increasing Minority Admissions to Research Institutions) research program (Grant 1R25GM106994-01 to E.A.G.). R.A.B. was partially supported by Grants GM130461 and DA046109 while working on the conceptual foundation and preparation of the manuscript for publication.

Notes

The opinions expressed in this Viewpoint are solely those of the authors.

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Eugene A. Kiyatkin for providing helpful comments on an early draft of this Viewpoint.

■ REFERENCES

(1) Albers, A. B.; Siegel, M.; Ramirez, R. L.; Ross, C.; DeJong, W.; Jernigan, D. H. Flavored Alcoholic Beverage Use, Risky Drinking Behaviors, and Adverse Outcomes among Underage Drinkers: Results from the ABRAND Study. *Am. J. Public Health* **2015**, *105* (4), 810–815.

(2) Routh, V. H.; Hao, L.; Santiago, A. M.; Sheng, Z.; Zhou, C. Hypothalamic Glucose Sensing: Making Ends Meet. *Front. Syst. Neurosci.* **2014**, *8*, 8.

(3) Barson, J. R.; Leibowitz, S. F. Hypothalamic Neuropeptide Signaling in Alcohol Addiction. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2016**, *65*, 321–329.

(4) Wakabayashi, K. T.; Kiyatkin, E. A. Behavior-Associated and Post-Consumption Glucose Entry into the Nucleus Accumbens Extracellular Space during Glucose Free-Drinking in Trained Rats. *Front. Behav. Neurosci.* **2015**, *9*, 173.

(5) Wakabayashi, K. T.; Spekterman, L.; Kiyatkin, E. A. Experience-Dependent Escalation of Glucose Drinking and the Development of Glucose Preference over Fructose - Association with Glucose Entry into the Brain. *Eur. J. Neurosci* **2016**, *43* (11), 1422–1430.

■ NOTE ADDED AFTER ASAP PUBLICATION

The version of this paper that was published ASAP August 24, 2021, contained an error in the unit for time in Figure 1a. This was corrected, and the paper was reposted August 26, 2021.