Inhibition of EtOH-induced $GABA_AR$ potentiation as a novel mechanism for the treatment of alcohol use disorder

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Abstract

Current pharmacotherapies for the treatment of alcohol use disorder are largely ineffective and/or associated with major side effects. There are currently no treatment options that target the direct neurological effects of ethanol, despite this mechanism of pharmacotherapy demonstrating efficacy in the treatment of opiate use disorder. Dihydromyricetin (DHM) is a natural flavonoid that could provide a link to the development of medications targeting ethanol-induced intoxication, through interaction with $GABA_A$ receptors. Dihydromyricetin demonstrated remarkable potential in preclinical studies in rats. For instance, dihydromyricetin (IP administration) demonstrated efficacy at counteracting EtOH intoxication, reducing voluntary EtOH intake, preventing EtOH-induced plasticity of $GABA_AR$s and withdrawal symptoms, and preventing physiological effects of fetal alcohol syndrome. Evidence indicates that the mechanism is linked to inhibition of ethanol-induced $GABA_AR$ potentiation and $GABA_AR$ positive allosteric modulation through mutually exclusive binding with imidazobenzodiazepines. Despite this promising bioactivity, inadequate pharmacokinetic properties, prevent the effective clinical use of DHM for AUD. Thus, the aim of this study is to determine the pharmacophore of this promising bioactivity to enable lead optimization. Our work has included the design of synthesis of dihydromyricetin analogs that explored structure activity relationships utilizing patch-clamp recordings in Xenopus oocytes expressing α5ß3γ2 $GABA_AR$s, and molecular modelling studies in the benzodiazepine binding site of α1β2γ2 $GABA_AR$s. The results of our studies have provided insight into necessary functional groups of dihydromyricetin for $GABA_AR$ activity. This study has also led to the identification of a novel and chemically stable derivative of dihydromyricetin that is a $GABA_AR$ positive allosteric modulator. Our findings highlight the potential for optimization of dihydromyricetin $GABA_AR$ activity, forging a path towards the development of a $GABA_AR$ positive modulator and inhibitor of ethanol-induced $GABA_AR$ potentiation, as a novel and effective mechanism for the treatment of AUD.

Biography:

Eileen Carry is a doctoral candidate in the Medicinal Chemistry Department at Rutgers University. Her research focuses on early drug discovery targeting novel medications for the treatment of alcohol use disorder. She has taken a lead role in the design and synthesis of flavonoid derivatives targeting $GABA_A$ R positive allosteric modulation and inhibition of ethanol-induced $GABA_AR$ potentiation, flavonoid pharmacokinetic studies, and in silico modelling of the $GABA_AR$ benzodiazepine binding site. Eileen is committed to a career dedicated to AUD drug discovery, providing a Medicinal Chemistry perspective to the field.

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Figures

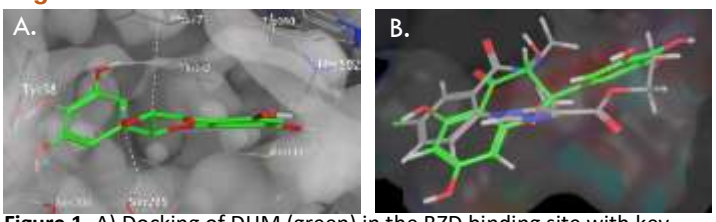


Figure 1. A) Docking of DHM (green) in the BZD binding site with key interactions. H-bonds are represented with dashed lines B) Overlay of DHM and Cryo-EM structure of bound flumazenil (grey).

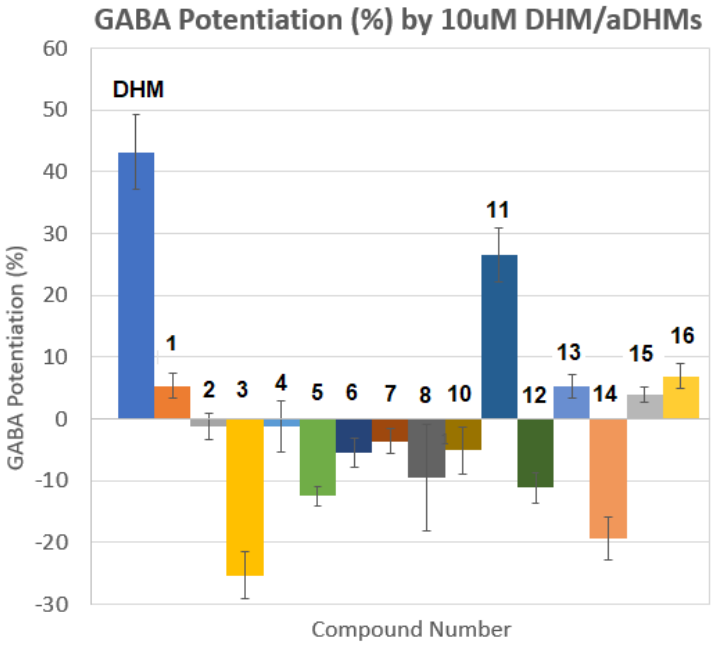


Figure 2. $GABA_AR$ potentiation by 10 µM select compounds. Please note novel structures are not included to protect intellectual property. Publication of this data is pending patent filing.

Recent Publications

Zhao, D., Yuan, B., **Carry, E.**, Pasinetti, G.M., Ho, L., Faith, J., Mogno, I., Simon, J. and Wu, Q. Development and validation of an ultra-high performance liquid chromatography/triple quadrupole mass spectrometry method for analyzing microbial-derived grape polyphenol metabolites. *Journal of Chromatography B* 1099 (2018): 34-45

Carry, E., Zhao, D., Mogno, I., Faith, J., Ho, L., Villani, T., Patel, H., Pasinetti, G.M., Simon, J.E. and Wu, Q. Targeted analysis of microbial-generated phenolic acid metabolites derived from grape flavanols by gas chromatography-triple quadrupole mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis* 159 (2018): 374-383

Ho, L., Cheng, H., Wang, J., Simon, J.E., Wu, Q., Zhao, D., **Carry, E.**, Ferruzzi, M.G., Faith, J., Valcarcel, B. and Hao, K. A comprehensive database and analysis framework to incorporate multiscale data types and enable integrated analysis of bioactive polyphenols. *Molecular pharmaceutics*, 15.3 (2017):840-850

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