N-acylethanolamine Acid Amidase (NAAA): A New Molecular Target for The Treatment of Alcohol Use Disorders

Yannick Fotio, Roberto Ciccocioppo, and Daniele Piomelli

Background: N-acylethanolamine acid amidase (NAAA) is an intracellular cysteine hydrolase that terminates the biological actions of oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), two endogenous lipid-derived agonists of the nuclear receptor, peroxisome proliferator-activated receptor-α. OEA and PEA are important regulators of energy balance, pain, and inflammation, but recent evidence suggests that they might also contribute to the control of reward-related behaviors.

Methods: We developed three selective and potent NAAA inhibitors (ARN077, ARN726, and ARN19702) and explored their systemic and intracerebral effects in the two-bottle choice model of voluntary alcohol drinking and operant alcohol self-administration. Procedures were carried out in genetically selected Marchigian Sardinian alcohol-preferring (msP) rats.

Results: Intraperitoneal injections of the systemically active NAAA inhibitor ARN19702 (3 and 10 mg/kg) lowered voluntary alcohol intake in a dose-dependent manner, achieving ≈ 47% reduction at the 10 mg/kg dose ($p<0.001$). Water, food, or saccharin consumption was not affected by the inhibitor. Similarly, ARN19702 dose-dependently attenuated alcohol self-administration under both fixed-ratio 1 (FR-1) and progressive ratio schedules of reinforcement. Furthermore, microinjection of ARN19702 (1, 3, and 10 μg/μl) or of two structurally distinct NAAA inhibitors, ARN077 and ARN726 (both at 3 and 10 μg/μl), into the midbrain ventral tegmental area (VTA) produced dose-dependent decreases in alcohol self-administration under FR-1 schedule. Such effect was not observed when ARN19702 was microinfused into the nucleus accumbens (NAc).

Conclusion: NAAA-regulated lipid signaling in the mesolimbic system modulates excessive alcohol intake, pointing to NAAA as a possible molecular target for the treatment of alcohol use disorders.

References: Piomelli D, Scalvini L, Fotio Y, Lodola A, Spadoni G, Tarzia G, Mor M. N-Acylethanolamine Acid Amidase (NAAA): Structure, Function, and Inhibition. J Med Chem. 2020 Jul 23;63(14):7475-7490.

This work was partially supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) grant AA017447.