Non-nutritive Sweeteners Acesulfame Potassium and Sucralose Competitively Inhibit P-glycoprotein

Laura Danner,1 and Stephanie Olivier-Van Stichelen2

1Medical Coll of Wisconsin; and 2Medical College of Wisconsin

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Non-nutritive sweeteners (NNS) are popular sugar replacements that are used in a wide range of foods, beverages, and medications. Although NNS are recognized as safe by the Food and Drug Administration, the effects of NNS on specific patient populations and human development are not completely understood. Previously, our lab showed that mouse pups exposed to NNS during early development present compromised liver detoxification. Thus, we questioned whether NNS might disrupt detoxification in the liver, including efflux transporters such as P-glycoprotein (ABCB1/ PGP). We hypothesize that two common NNS, acesulfame potassium (AceK) and sucralose (Sucr), inhibit PGP’s efflux function and alter PGP expression, suggesting reduced detoxification capacity and altered distribution of certain drugs. To investigate the effects of NNS on PGP, we first exposed the HepG2 liver carcinoma cell line to AceK and Sucr and assessed ABCB1/ PGP transcript and protein levels. Combined NNS treatment significantly increased ABCB1 expression and PGP levels, an effect also commonly observed with some PGP inhibitor drugs. We, therefore, investigated NNS effects on PGP’s efflux action. An in vitro PGP substrate retention assay performed in HepG2 and HEK293 demonstrated that combined NNS significantly increased the intracellular retention of PGP substrate Calcein-AM, confirming PGP inhibition by NNS. Individual AceK or Sucr incubation on HepG2 cells also significantly inhibited PGP efflux, validating the PGP inhibition by both compounds. In a cell-free assay measuring PGP’s ATPase activity, AceK and Sucr also significantly increased PGP ATPase activity in a dose-dependent manner, revealing them as competitive inhibitors of PGP. Molecular docking experiments provided further insight into NNS interactions with PGP substrate binding pockets. Like Verapamil, Sucr was found to dock primarily in PGP’s main high-affinity binding pocket. AceK shows a lower affinity for this pocket and docks mainly in two other sites within PGP’s inward-facing transmembrane channel. To conclude, our results provide evidence that two common NNS, AceK and Sucr, are substrates and competitive inhibitors of PGP, impacting PGP both functionally and at the level of mRNA and protein. Most importantly, altered PGP function was observed after exposure to concentrations of NNS within expected levels from common foods and beverage consumption, suggesting risks for NNS consumers when taking medications that are PGP substrates or modulators.