Inhibitions by Aspirin and Salicylate of Ethanol Metabolism with Human Alcohol and Aldehyde Dehydrogenases

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Aspirin, i.e. acetylsalicylic acid, is one of the most widely used nonprescribed medications in the world. It has been documented that aspirin may increase the bioavailability of ingested ethanol in humans. However, knowledge with regard to the kinetic interactions between aspirin and human alcohol dehydrogenase (ADH) isozymes and aldehyde dehydrogenase (ALDH) isozymes has been lacking. Functional polymorphisms of the ADH1B, ADH1C, and ALDH2 isozyme genes have been described influencing ethanol metabolism and susceptibility to the development of alcoholism. In this study we investigated the inhibitions by aspirin and its hydrolytic product salicylic acid, of ethanol oxidation with recombinant human ADH1A, ADH1B1, ADH1B2, ADH1B3, ADH1C1, ADH1C2, ADH2, and ADH4, and of acetaldehyde oxidation with recombinant human ALDH1A1 and ALDH2 at near physiological pH 7.5 and a cellular coenzyme concentration, 0.5 mM NAD. Aspirin acted as a competitive inhibitor (I) for ADH1A, ADH1C1, ADH1C2, ADH2, and ADH4 with the slope inhibition constants (K_{is}) ranging from 0.59 to 107 mM; and as a noncompetitive inhibitor for ADH1B2 and ADH1B3 with K_{is} of 34 and 28 mM and the intercept inhibition constants (K_{ii}) of 42 and 33 mM, respectively. Salicylate exhibited similar inhibition patterns as did aspirin but with much lower corresponding inhibition constants, ranging from 0.17 to 6.8 mM for K_{is} for ADH1A, ADH1C1, ADH1C2, ADH2 and ADH4, and 2.6 and 1.4 mM for K_{is} and 3.5 and 2.4 mM for K_{ii} for ADH1B2 and ADH1B3, respectively. It is noted that although salicylate was competitive inhibitor for ADH1B1 with K_{is} of 1.4 mM, aspirin appeared not to be an inhibitor for this allozyme. Acetaldehyde oxidation of ALDH1A1 was competitively inhibited by aspirin and salicylate with K_{is} of 12 and 0.53 mM, respectively. Aspirin was uncompetitive inhibitor for ALDH2 with K_{ii} of 3.9 mM, whereas salicylate was a noncompetitive inhibitor for this isozyme with K_{is}, 0.37 mM, and K_{ii}, 0.55 mM. The kinetic explanations for the observed drug inhibition patterns of ADHs and ALDHs in this study can be attributed to the formation of the abortive ternary-complex intermediates in catalysis, i.e., E-NAD-I for the slope inhibition effects and E-NADH-I for the intercept inhibition effects. Kinetic simulations using the experimentally determined numerical steady-state rate equations of human ADH and ALDH families show that the ethanol-oxidizing activities of ADH1A can be inhibited up to 47 and 75% by 1 mM aspirin and 1 mM salicylate, respectively, and those of the inhibitions of ADH1B2, ADH1B3 and ADH2, up to 24 to 75% by 1 mM salicylate; and that the acetaldehyde-oxidizing activities of ALDH1A1 and ALDH2 can be inhibited by 60 to 65% with 1 mM salicylate. It is concluded that hepatic, rather than gastric, metabolism of ethanol can be significantly reduced at therapeutic levels of salicylate in social drinking settings.