Dehidrogenase lática. Gossipol, um derivado da semente do algodão, e seus derivados são inibidores da dehidrogenase lática – DHL

03/02/11

Lembrar que o gossipol foi usado como contraceptivo do homem e além de abolir a glicólise anaeróbia (benéfico no tratamento do câncer) diminui a função de várias enzimas da fosforilação oxidativa (maléfico). José de Felippe Junior

Selective active site inhibitors of human lactate dehydrogenases A4, B4, and C4.

Yu Y, Deck JA, Hunsaker LA, Deck LM, Royer RE, Goldberg E, Vander Jagt DL.

Biochem Pharmacol. 2001 Jul 1;62(1):81-9.

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Abstract

Human lactate dehydrogenases (LDH-A4, -B4, and -C4) are highly homologous with 84-89% sequence similarities and 69-75% amino acid identities. Active site residues are especially conserved. Gossypol, a natural product from cotton seed, is a non-selective competitive inhibitor of NADH binding to LDH, with K(i) values of 1.9, 1.4, and 4.2 microM for LDH-A4, -B4, and -C4, respectively. However, derivatives of gossypol and structural analogs of gossypol in the substituted 2,3-dihydroxy-1-naphthoic acid family exhibited markedly greater selectivity and, in many cases, greater potency. For gossypol derivatives, greater than 35-fold selectivity was observed. For dihydroxynaphthoic acids with substituents at the 4- and 7-positions, greater than 200-fold selectivity was observed. Inhibition was consistently competitive with the binding of NADH, with dissociation constants as low as 30 nM. By comparison, a series of N-substituted oxamic acids, which are competitive inhibitors of the binding of pyruvate to LDH, exhibited very modest selectivity. These results suggest that substituted dihydroxynaphthoic acids are good lead compounds for the development of selective LDH inhibitors. Selective inhibitors of LDH-C4 targeted to the dinucleotide fold may hold promise as male antifertility drugs. Selective inhibitors of LDH-A4 and -B4 may be useful for studies of lactic acidemia associated with ischemic events. More broadly, the results raise the question of the general utility of drug design targeted at the dinucleotide binding sites of dehydrogenases/reductases.

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Kinetic characterization of the inhibition of purified cynomolgus monkey lactate dehydrogenase isozymes by gossypol.

Stephens DT, Whaley KJ, Klimkow NM, Goh P, Hoskins DD. J Androl. 1986 Nov-Dec;7(6):367-77.

Abstract

This report describes the results of the first step in a sequence of experiments designed to test the hypothesis that the sperm-specific isozyme of lactate dehydrogenase (LDH-C4), is a site of action of the potential male contraceptive agent gossypol. Cynomolgus monkey LDH-A4, LDH-B4 and LDH-C4 were purified and kinetically characterized. LDH-A4 and LDH-B4 exhibited "linear mixed-type" inhibition by gossypol with both lactate and pyruvate as variable substrates. LDH-C4 also exhibited "linear mixed-type" inhibition with lactate as substrate. However, the C4 isozyme exhibited "parabolic mixed-type" inhibition by gossypol and substrate inhibition with pyruvate as substrate, the latter due to abortive complex formation. Of the three isozymes, LDH-C4 exhibited the lowest apparent Km for pyruvate and the highest apparent Km for lactate. The LDH-C4 form was found to be the most sensitive isozyme to gossypol inhibition, since it had the lowest apparent Ki values for gossypol inhibition. The effect of gossypol on coenzyme binding to LDH-C4 was examined and gossypol binding was found to inhibit binding and release of NADH but not NAD+, an effect possibly due to its interaction with the more hydrophobic loop region of LDH-C4.

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