

Effect of rat serum lipoproteins on mRNA levels and amiodarone metabolism by cultured primary rat hepatocytes.

Abstract

Hyperlipidemia can significantly increase amiodarone (AM) in vivo liver uptake and decrease its velocity of microsomal metabolism. Here, hepatocytes isolated from normolipidemic (NL) and hyperlipidemic rats were incubated with AM in the presence or absence of diluted NL or hyperlipidemic serum. The serum was added either as preincubation before drug, or concurrently with drug; incubations without rat serum were used as controls. The hepatocyte levels of mRNA for several proteins and enzymes were also measured. Disappearance of AM was seen up to 72 h. There was little difference between hepatocytes from NL or hyperlipidemic animals in intrinsic clearance (CL(int)) of AM. The effect of hyperlipidemic rat serum, either before or with AM, was profound, causing a significant reduction in the CL(int) . Reductions were seen in mRNA for cytochrome P450 1A1, 3A2, and 2D1, some transporters, and low-density lipoprotein receptors after exposure of hepatocytes to lipoprotein-rich sera. In conclusion, exposure of isolated hepatocytes to hyperlipidemic serum caused decreases in AM CL(int) and lower mRNA levels for some proteins involved in the uptake and metabolism of AM. When coincubated with serum, an additional effect of increased binding to lipoproteins seemed to further contribute to a reduced CL of AM.