ROLE OF HYDROGEN SULFIDE IN STATIN-INDUCED INHIBITION OF INSULIN SECRETION

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Statins inhibit cholesterol synthesis and are used in the prevention and treatment of cardiovascular diseases. However, recent studies indicate that statins may increase the incidence of type 2 diabetes. Hydrogen sulfide (H_2S) is the important endogenous. It has been demonstrated that H_2S inhibits insulin secretion by pancreatic beta cells by activating ATP-sensitive K^+ channels. In addition, by inhibiting coenzyme Q (CoQ) synthesis, statins increase H_2S level in some tissues by impairing its mitochondrial oxidation by sulfide:quinone oxidoreductase (SQR) We examined the effect of statins on insulin secretion and the possible involvement of H_2S. Wistar rats were treated with atorvastatin (20 mg/kg/day) or rosuvastatin (5 mg/kg/day) for 1 week. Neither atorva- or rosuvastatin had any effect on insulin sensitivity measured by hyperinsulinemic euglycemic clamp. However, both statins reduced glucose-induced insulin secretion both in vivo and ex vivo by isolated islets. Statins increased net H_2S production by isolated islets, however, had no effect on the expression or activity of H_2S synthesizing enzymes. In contrast, statins reduced mitochondrial H_2S oxidation. Statins had no effect on mitochondria density, inner membrane potential or SQR activity but decreased CoQ concentration in both plasma and pancreatic islets. The effect of statins on insulin secretion was mimicked by H_2S donor, Na_2S, and was attenuated by the inhibitor of H_2S synthesis, propargylglycine, ATP-sensitive K^+ channel blocker, glibenclamide, or CoQ supplementation. In conclusion, although statin-induced up-regulation of H_2S signaling may be beneficial for the cardiovascular system, H_2S may contribute to diabetogenic effect of these medications.

Keywords: statins, hydrogen sulfide, diabetes mellitus, insulin