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Commentary

Beta-2 Agonism: A Potential Therapeutic Target for Dyslipidemia

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Since the early 1980s, there has been clinical data demonstrating the effects of beta-adrenergic agonist on lipid levels. Terbutaline was shown to raise HDL-c levels in healthy subjects after just two weeks of treatment (Hooper et al., 1981). This data in conjunction with other trials which revealed that beta-blockers lowered HDL-c and raised LDL-c as well as triglycerides (Harvengt et al., 1987), supported the hypothesis that stimulation of the beta-2 receptor could result in favorable lipid changes. Maki et al. (1996) found that albuterol administration was associated with favorable changes in the serum lipid profile with significant lowering of LDL-c and increases in HDL-c in a small human trial without marked impairment of glucose tolerance or its physiologic determinants (Maki et al., 1996). Ye et al. (2015) of *EBioMedicine* found that another selective beta-2 agonist, R-bambuterol also significantly lowered LDL-c in a relatively small healthy volunteer population (Ye et al., 2015). Since the racemic mixture of bambuterol was not effective in modifying the lipid levels, this suggests that there may be inhibitory effects between R and S bambuterol on the beta-2 receptors that regulate lipoprotein metabolism, Therefore, there is compelling hypothesis generating human data that selective beta-2 agonist may have beneficial effects on lipid metabolism.

Beta-2 agonism stimulates intracellular cAMP, which regulates a number of pathways involved in lipid and glucose metabolism. Sterol regulatory element-binding proteins (SREBPs) are major transcription factors regulating the biosynthesis of cholesterol, fatty acids and triglycerides (Xiao and Song, 2013). SREBP is controlled by cAMP, which may explain why beta-2 agonism may affect LDL-c, HDL-c and triglyceride. In addition, cAMP stimulates ABCA1 upregulation, which results in HDL mediated cholesterol efflux from macrophages or hepatocytes (Fournier et al., 2003).

Statin therapy and more recently PCSK9 monoclonal antibodies have demonstrated robust efficacy for lowering LDL-c but there remains significant unmet medical need especially for patients that are refractory or intolerant to these treatment. A recent study, found that of 647 patients with coronary heart disease prescribed statins, about 20% failed to have a significant LDL-lowering response to treatment, and instead saw LDL-cholesterol levels increased 6.2%, compared to a drop of 44.5% among those who responded to the treatment (Kataoka et al., 2015). In addition, approximately 10% of dyslipidemic patients are statin intolerant (Jacobson, 2014). SREBP is an important target for novel drug development and this new clinical data by Ye and colleagues may provide helpful insights into role of beta-2 agonism in lipid metabolism which may provide another class of agents that address an unmet clinical need in patients with dyslipidemia (Ye et al., 2015).

Disclosure

The author disclosed no conflicts of interest.

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