Mini Review

Thyromimetics: What does the future hold?

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ABSTRACT

Thyromimetic agents that can treat dyslipidemia without adverse effects like cardiac arrhythmias and osteoporosis are attractive options. Initial experience with desssicated thyroid hormone extract and DT4 were disappointing. Thyroid hormone has nuclear action with four receptor isoforms- TR α1, TRα2, TRβ1, TRβ2. TR α1 has predominant effects on CVS, TRβ2 acts mainly on the pituitary and TRβ1 has hepatoselective action and decrease cholesterol levels. Eprotirome and Sobetirome are 2 thyromimetics that have selective TRβ1 activity. They act in dyslipidemia by multiple mechanisms. They are presumably safe on the pituitary- thyroid axis.

Key words: Thyromimetics, dyslipidemia

Introduction

It is well-known that hypothyroidism is associated with dyslipidemia and that this can be reversed by thyroxine therapy.[1] However, can this knowledge be used to further the treatment of dyslipidemia, even in persons without thyroid disease? Obviously, thyroxine therapy in such euthyroid subjects with dyslipidemia would be expected to result in osteoporosis and cardiac arrhythmias- unless, of course, designer thyroid hormones were to be used i.e. thyromimetic agents that could treat dyslipidemia without any adverse consequences of hyperthyroidism. This article will focus on the exciting role of thyromimetic agents in the management of dyslipidemia, for that is, arguably, a most foreseeable use of these agents in future.

Initial disappointments with thyromimetics

Taking the afore-mentioned hypothesis further, some researchers attempted to give desiccated thyroid in high doses to treat hypercholesterolemia.[2] These high doses reduced cholesterol levels, but there were trade-offs: Tachycardia, diarrhea, insomnia, weight loss, and even hyperthyroidism- moreover, there was an escape after 20-30 weeks. Understandably, desiccated thyroid was abandoned. The next molecule tried was D-thyroxine. A large clinical trial in the 1960s assessed the role of D-thyroxine (DT4) for dyslipidemia. The consequence was undesirable-at the end of 36 months, there was a higher proportion of fatalities in the DT4 group. There were two problems with this study, however.[2] One was that the samples of DT4 were contaminated with levothyroxine, or LT4. The second problem was that this trial recruited subjects who were already at a very high risk of heart disease, already having suffered from problems like angina and heart failure. However, DT4 therapy too was abandoned. However, eventually, newer thyromimetics were developed.[2]

Thyromimetics make a beginning, again

Thyroid hormones have a nuclear action, eventually changing the functioning of the transcription machinery.[2,3] The understanding of these nuclear thyroid hormone receptors (TR) was furthered by reports that these TRs have 4 isoforms- TRα1, TRα2, TRβ1, and TRβ2, and their transgenic and knockout models have helped understand receptor function. For example, knocking out the TRα1 resulted in bradycardia and other changes in the cardiovascular system- that could not be reversed by giving T3. On the other hand, TRβ1 is the major mediator of T3 actions on cholesterol and lipoprotein

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metabolism, and probably acts via the liver. This fuelled researchers to attempt to develop thyromimetic agents that could selectively target dyslipidemia. By selectively targeting the TRβ1 receptor alone, could dyslipidemia be corrected? While developing the thyromimetic, a special consideration would be to target only the TRβ1, and that the TRα and TRβ2 receptors should *not* be stimulated. Stimulation of the TRα1 receptor isoform would lead to undesirable cardiovascular toxicity. It is to be noted that TRα2 stimulation is probably not clinically very relevant, as it is a non-hormone binding receptor that acts as a negative regulator. Stimulation of the TRβ2 receptor isoform may result in suppression of the TSH- this is because the TRβ2 receptor isoform action resides mainly in the pituitary, and the conversion of T4 to T3 in the pituitary, and the subsequent signaling caused by T3 is the most important regulator of TSH production. Hence, the challenge was to develop a thyromimetic that could have a hepatoselctive effect, precisely targeting the TRβ1- this might help in aggressively tackling hepatic cholesterol metabolism and correcting dyslipidemia. Research focusing on this area led the way to the development of selective thyromimetics. Eprotirome and Sobetirome are, among others, two examples of thyromimetics that are currently in development.[3-7]

How do thyromimetics target dyslipidemia?

A thyromimetic that could have a hepatoselctive effect, precisely targeting the TRβ1 isoform would be useful, as it could target dyslipidemia in several ways.[3-7] The main mechanism would be by the up-regulation of the LDL receptor. This would reduce the LDL particles. Eventually, this would significantly reduce the serum cholesterol and triglyceride levels. A second mechanism to reduce the cholesterol and triglyceride level is the inhibition of the hepatic transcription factor sterol regulatory element-binding protein 1 (SREBP1), as this would prevent VLDL assembly. A third (and arguably the most exciting and interesting) mechanism is the promotion of reverse cholesterol transport (Rev-CT). The Rev-CT describes a pathway that carries cholesterol to the liver for fecal excretion. Cholesterol is carried from several sources like atheromatous plaques and macrophages by the Rev-CT, and this is facilitated by HDL. Selective thyromimetics activate Rev-CT by increasing hepatic expression of the HDL receptor scavenger receptor B-I (SR-BI). The SR-B1 increases the clearance of HDL cholesterol but does not alter the number of the HDL particles. In simple terms, this means that the macrophages and plaques are cleansed of their cholesterol. While these mechanisms were widely studied in animal model, humans have another unique pathway of HDL transport. In this pathway, the HDL cholesterol is transferred to LDL particles, and this is carried out by the intermediary called cholesteryl ester transfer protein (CETP). The cholesterol thus transferred is then cleared through hepatic LDL receptors. As thyromimetics can cause up-regulation of the LDL receptor, this is an additional mechanism by which they improve Rev-CT. In addition to all these mechanisms by which thyromimetics could benefit dyslipidemia, there is a final mechanism via which they reduce cholesterol. Thyromimetics may reduce intestinal absorption of dietary sterols, and this could happen due to competition with steroids of biliary origin. Linked to all these mechanisms is the fact that thyromimetics might be able to stimulate the activity of cholesterol 7α-hydroxylase (CYP7A1). This CYP7A1 is the rate-limiting enzyme for bile acid synthesis and induces hepatic ABCG5 and ABCG8 (ABCG5/G8) - taken together, this pathway induces biliary cholesterol secretion.[3-7]

Clinical trial evidence

Eprotirome is a recent thyroid hormone analog and has two bromides. The molecule is reasonably liver-specific. The benefits of Eprotirome were studied in a larger, 12-week, randomized, placebo-controlled trial. This study was done in subjects with statin-treated dyslipidemia.[8] The primary outcome of this study was a lowering of the LDL cholesterol. The results of the study were remarkably positive. There was a dose-dependent reduction in LDL cholesterol, accompanied by improvement in the levels of lipoprotein (a), Apo-E, and triglycerides. Eprotirome presumably was safe as far as the pituitary-thyroid axis was concerned (it did not change the TSH and the T3 levels). However, Eprotirome resulted in a slight decrease in the T4 levels. In addition, a slight, transient increase in serum alanine transaminase (ALT) was also documented. The reductions in T4 levels due to Eprotirome are interesting, and there could be two explanations.[8,9] Firstly, the reduction in the thyroxine-binding globulin levels by Eprotirome may have, to some extent, been responsible for the low total T4 levels. However, it is unlikely that this factor alone provides a complete answer. Hence, it is possible that there is a second explanation, and this probably relates to the way that that thyroid hormones act on the hepatic tissues and cause an augmentation of the type 1 iodothyronine monodeiodinase activity (this enzyme is a deiodinase that converts T4 to T3). It is possible that this factor might explain the low T4 and a normal T3 level. Eventually, if Eprotirome and related thyromimetics do live up to their promise and potential, there could be a breakthrough in the management of dyslipidemia.[9,10]

References

1. Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence

and correction of hypothyroidism in a large cohort of patients referred for dyslipidemia. Arch Intern Med 1995;155:1490-5.
2. Tanceviski I, Eller P, Patsch JR, Ritsch A. The resurgence of thyromimetics as lipid-modifying agents. Curr Opin Investig Drugs 2009;10:912-8.
3. Joharapurkar AA, Dhote VV, Jain MR. Selective thyromimetics using receptor and tissue selectivity approaches: prospects for dyslipidemia. J Med Chem 2012;55:5649-75.
4. Johansson L, Rudling M, Scanlan TS, Lundasen T, Webb P, Baxter J, *et al*. Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice. PNAS 2005;102:10297-302.
5. Baxter JD, Dillmann WH, West BL, Huber R, Furlow JD, Fletterick RJ, *et al*. Selective modulation of thyroid hormone receptor action. J Steroid Biochem Mol Biol 2001;76:31-42.
6. Berry MJ, Kates AL, Larsen PR. Thyroid hormone regulates type i deiodinase messenger RNA in rat liver. Mol Endocrinol 1990;4:743-8.
7. Angelin B, Rudling M. Lipid lowering with thyroid hormone and thyromimetics. Curr Opin Lipidol 2010;21:499-506.
8. Ladenson PW, Kristensen JD, Ridgway EC, Olsson AG, Carlsson B, Klein I, *et al.* Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. New Engl J Med 2010;362:906-16.
9. Unnikrishnan AG, Kumar H, Jayakumar RV, Jeyapathy P, Pillai BP. The promise of Eprotirome. Thyroid Res Pract 2011;8:3-4.
10. Pedrelli M, Pramfalk C, Parini P. Thyroid hormones and thyroid hormone receptors: Effects of thyromimetics on reverse cholesterol transport. World J Gastroenterol 2010;16:5958-64.

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