**Guggulsterone: an old approach to a new problem**

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The hepatic conversion of cholesterol to bile acids is an important mechanism for the elimination of excess dietary cholesterol. Bile acid biosynthesis and transport are regulated by the farnesoid X receptor (FXR), a member of the nuclear hormone receptor gene superfamily. Thus, therapeutic strategies that target FXR represent a promising new approach for the treatment of hypercholesterolemia. Recent studies have provided new evidence in support of the potential for FXR ligands as antihypercholesterolemic agents.

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Maintenance of normal cholesterol homeostasis is achieved through various means involving both transcriptional and post-transcriptional mechanisms. Among these, hepatic bile acid biosynthesis and subsequent secretion into the bile represents a quantitatively important route for the elimination of excess cholesterol from the liver and the body. Cholesterol is also directly transported from the liver into the bile duct, but bile acid secretion represents the major driving force for bile flow and into the gut. Enterohpetic bile flow is important not only for the elimination of cholesterol but also serves to eliminate high molecular weight drugs and xenobiotics from the body, and to facilitate the intestinal uptake of vitamins and cholesterol from the diet.

Bile acids are ligand activators of the farnesoid X receptor (FXR), a nuclear hormone receptor essential for the normal control of bile acid biosynthesis and transport. This control is achieved largely through both direct and indirect feedback regulation of genes involved in these processes. Negative regulation of genes encoding enzymes of bile acid biosynthesis (cytochrome P450 7A1 and cytochrome P450 8B1), and both positive (bile-salt export protein and ileal bile-acid-binding protein) and negative (Na+/taurocholate co-transport protein) regulation of genes encoding proteins involved in bile acid transport are important components of this system (Fig. 1). The FXR-null mouse model has confirmed a crucial role for FXR in regulating the conversion of cholesterol to bile acids and the transport of bile acids both into and out of the liver, and into the gut epithelium [1]. These mice exhibit not only profound defects in bile acid metabolism and transport, but also marked hypercholesterolemia and hepatic lipid accumulation. These results raise the possibility that pharmacological manipulation of FXR affords an opportunity for the treatment of hypercholesterolemia by a mechanism that is distinct from the 3-hydroxy-3-methylglutaryl-CoA synthase-inhibiting statin class of drugs.

The gum resin of Commiphora mukul, commonly referred to as the Guggul tree, has been used in traditional Hindu Ayurvedic medicine for nearly 3000 years. It was reported to be effective in the treatment of several conditions, including obesity and disorders of lipid metabolism. An organic extract of this gum resin, referred to as guggulipid, has been approved for use in India since 1987 as a treatment for hyperlipidemia. Studies of patients receiving this therapy and experiments with rodent models have demonstrated that guggulipid effectively lowers serum low-density lipoprotein and triglyceride levels [2]. Recent findings provide significant and novel insight into the molecular targets for guggulipid and the mechanism of the lipid lowering effect.

Urizar et al. [3] studied guggulsterone [4,17(20)-pregnadiene-3,16-dione], the active component of guggulipid largely responsible for the anti-hyperlipidemic effects of this extract. Using transient transfections with a synthetic FXR-responsive reporter plasmid, the authors demonstrated that guggulsterone is an effective antagonist of FXR. Importantly, this study also showed that administration of guggulsterone blocked hepatic cholesterol accumulation in cholesterol-fed wild-type, but not in FXR-null mice. The significance of this work is derived in large part from the empirical demonstration that direct pharmacological manipulation of FXR impacts hepatic cholesterol levels, thus providing a basis for further study of the use of FXR ligands as anti-hyperlipidemics.

A particularly intriguing aspect of the study by Urizar et al. [3] is that, contrary to the hyperlipidemic phenotype of FXR-null mice, antagonism of FXR appears to have an anti-hyperlipidemic effect. Several possibilities could account for this apparent discrepancy. For example, as correctly pointed out by the authors of the study, the developmental
and lifelong absence of FXR as occurs in the FXR-null model, can result in abnormal metabolic effects that are quite different from those caused by acute, transient antagonism of this receptor. Because the FXR-null mouse was produced using Cre-loxP technology, conditional disruption of this allele after normal development has occurred can now be used to help resolve this issue. An alternative explanation is that the site(s) of pharmacological action of guggulsterone do not include all of the tissues in which FXR is functional, such as the liver and gut (i.e. although FXR synthesis is uniformly absent from all tissues of the FXR-null mouse model, guggulsterone might antagonize FXR only within a subset of these sites). In the absence of in vivo data regarding the modulation of FXR target gene expression by guggulsterone, this is difficult to judge. Thus, it remains a possibility that the effects of orally-administered guggulsterone occur primarily at the level of the gut (i.e. versus gut and liver), for instance, by affecting cholesterol absorption and bile-acid reuptake processes regulated by FXR, rather than the hepatic biosynthesis and transport of bile acids. Again, the conditional nature of the strategy used to create the FXR-null mouse model allows for tissue-specific deletion of the FXR gene and might help resolve this issue.

As reinforced by the recent work of Urizar et al. [3], as well as by the present therapeutic use of bile-acid binding resins for hypercholesterolemia, there exists an intimate linkage between bile acid and cholesterol metabolism. Recent demonstrations that FXR is also involved in the regulation of genes (e.g. encoding apolipoprotein A-I, apolipoprotein C-II and phospholipid transfer protein) [4–6] more closely linked with lipid rather than bile-acid homeostasis, presents additional avenues by which FXR ligands could be beneficial for the treatment of disorders of lipid metabolism. As suggested by the work of Urizar et al. [3] and others (e.g. [7]), careful and comprehensive study of the effects of natural products, such as guggulsterone, on the function of nuclear hormone receptors, is likely to yield additional agents with desirable therapeutic effects.

References

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Time to consider new brain clock signals
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The suprachiasmatic nucleus is well recognized as a central nervous system controller of circadian rhythms. The mechanisms underlying the ability of neurons in this region to generate such rhythms are, at best, poorly understood. Two recently published reports suggest that circadian change in the expression of L-type Ca2+ channels, and a novel protein prokineticin, might play essential roles in molding crucial circadian output from this nucleus.

Circadian rhythms provide mechanisms that regulate crucial physiological functions, presumably to meet varying functional needs throughout the day. This preset programming can influence all aspects of human physiology, including corticosteroid release, cardiovascular function, feeding behavior, locomotor activity and wakefulness. Disruption of the circadian cycle by lack of sleep, abnormal meal schedules, sudden changes in the light-dark cycle, or continuous exposure to light or dark can result in significant disruption of many physiological systems, which can detrimentally affect activities of daily living.

For many years, our understanding of the central control of circadian rhythms has focused on the suprachiasmatic nucleus (SCN) – a unique area of the brain in which neurons display rhythmic and synchronous firing patterns attuned to a 24-h diurnal cycle, with activity highest during relative daytime. The SCN is known to receive visual inputs that allow intrinsic resetting of the circadian cycle in response to changes in the external light-dark cycle, and sends efferent connections to numerous other central nervous system (CNS) regions, regulating arousal, cardiovascular function, feeding behavior and hormone secretion. Current dogma accepts the unique intrinsic ability of the SCN to function as a master circadian clock in addition to its ability to synchronize activity both of the neurons contained within this region and in other crucial CNS regulatory centers. Although the molecular mechanisms that regulate the intrinsic master circadian clock have been fairly well characterized, the mechanisms underlying rhythmicity and synchronization of cell excitability in the SCN are less clear. Two recent reports have provided intriguing new evidence regarding both potential cellular correlates of intrinsic rhythmicity, and the chemical messengers that communicate such