SELECTIVE MODULATION OF NUCLEAR RECEPTORS TO ATTACK METABOLIC SYNDROME AND CANCER

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Nuclear Hormone Receptors (NRs) play widespread important roles in disease. While it activities of these conditional transcription factors can be modulated with native ligands or derivatives, improved understanding of NR structure and function suggests that it will be possible to develop selective nuclear receptor modulators (SNRMs) that either elicit beneficial effects of native hormone in the absence of deleterious effects or specifically antagonize deleterious effects. We focused on thyroid hormone (TH) receptors (TRs), which play roles in regulation of metabolism. Evidence from human patients and mouse knockout models indicates that the TRβ isoform mediates beneficial effects on circulating cholesterol and body fat whereas TRα mediates deleterious effects on heart. We created TRβ selective agonists that reduce serum cholesterol and body fat without noticeable harmful effects. However, the compounds also display preferential uptake into liver and gene-specific effects, and we suggest that these actions may underlie unexpected effects, including reduced atherogenic triglycerides and improved insulin sensitivity. We designed new TR antagonists. These compounds have potential applications in treatment of cardiac arrhythmias and initial analysis confirms that they antagonize TH action in cells and animals, but also display gene-selective agonist effects. We propose that it will be conceptually hard to design pure antagonists for TRs and similar classes of receptors. Existing NR modulators bind to the buried hormone binding that acts as an allosteric site and we examined whether it is feasible to develop compounds that bind protein interaction sites on the surface of the receptor (active sites). We used functional and X-ray chemical screens to identify TR and androgen receptor (AR) surface interacting compounds and found that these compounds work in cell culture. It may be possible to create new surface interacting drugs to treat hormone resistant breast and prostate cancers.