Nonsteroidal Receptors

The receptors for several classes of non-steroidal compounds, including retinoids, thyroid hormones and vitamin D, also act as ligand-dependent transcription factors. In addition, a large number of receptors without known ligands have been discovered based on sequence homology, particularly in the DNA binding domain, with known intracellular receptors. Ligands for some of these receptors have been identified, although many remain “orphan” receptors. Ligand-bound receptor complexes, which generally heterodimerize with a retinoid X receptor (RXR), act as transcription factors by binding to specific hormone response elements.

Three isoforms of retinoic acid receptors (RARs) and three isoforms of RXRs have been identified. All-trans retinoic acid was found to be a potent enhancer of RAR-dependent gene expression. Although it does not bind to RXRs, it is able to weakly activate RXR-dependent gene expression. A metabolite of all-trans-retinoic acid, the geometric isomer 9-cis retinoic acid, was subsequently found to bind to and activate the RXRs as well as the RARs. Based upon this work, isoform-specific agonists and antagonists have been identified. These studies have helped determine that RARs and RXRs have unique roles and different pharmacological effects.

The peroxisome proliferator-activated receptors (PPARs) heterodimerize with RXR isoforms to regulate gene expression by binding to peroxisome proliferator response elements. Ligands of PPARs, such as gemfibrozil and clofibrate, are clinically effective at lowering triglycerides and low density lipoproteins (LDLs) and raising high density lipoproteins (HDLs). Recent studies have shown that PPARy activation with thiazolidinediones, such as rosiglitazone or pioglitazone, is clinically useful to sensitize patients to insulin and is extremely useful in the treatment Type II diabetes. Interestingly, treatment of the RXR-PPAR heterodimer with RXR-selective ligands also yields insulin sensitization in animal models.

Triiodothyronine is the principle biologically active endogenous thyroid hormone. These hormones act upon all thyroid hormone receptor isoforms. Thyroid hormones are involved in early growth and development and have a well recognized calorigenic effect. The calorigenic response causes increased oxygen consumption in many tissues including heart, skeletal muscle, kidney and liver. Thyroid hormones have many other effects upon the cardiovascular system and also stimulate cholesterol metabolism. Lack of thyroid hormone decreases energy levels, activity and temperature control. Recent work has demonstrated that despite the great similarity of the binding sites of TRα and TRβ, selective compounds can be synthesized. This could be valuable since TRα appears to mediate some of the negative effects of thyroid hormone.

Vitamin D is rapidly converted to an active metabolite 1,25-dihydroxyvitamin D which binds directly to vitamin D receptor. This hormone plays a central role in the maintenance of plasma calcium and phosphate homeostasis. Vitamin D facilitates calcium and phosphate absorption from the small intestine and enhances calcium and phosphate mobilization from bone as well as decreasing calcium and phosphate excretion from the kidneys. Vitamin D also has immune system functions. Recently, the ligands for several orphan intracellular receptors found in the liver have been discovered. Two of these, the liver X-receptor (LXR) and farnesoid X-receptor (FXR), are involved in lipid metabolism.
and cholesterol homeostasis. LXR activation by oxysterols induces transcription of the rate limiting enzyme in bile acid synthesis, CYP7A1, while FXR activation by bile acids leads to down-regulation of CYP7A1 as well as several proteins involved in bile acid metabolism. These discoveries may prove very useful in future efforts in clinical control of lipids.

The ability to regulate the expression of enzymes of the cytochrome P450 class is exhibited by additional orphan receptors that appear to play a key role in the detoxification of xenobiotics. Thus, a total of five intracellular receptors, including PXR, CAR, LXR, FXR, and PPAR, may primarily serve to regulate cytochrome P450 enzymes in response to both endogenous hormones and xenobiotics.

The Table below contains accepted modulators and additional information. For more information and a complete list of the related products, please click: Aladdin
<table>
<thead>
<tr>
<th>Transduction Mechanisms</th>
<th>Radioligands of Choice</th>
<th>Tissue Expression</th>
<th>Physiological Function</th>
<th>Disease Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[(^{125})I]-Triiodothyronine</td>
<td>Ubiquitous (TRα2 primarily in pituitary and CNS)</td>
<td>Growth, development and regulation of homeostasis</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>[(^{125})I]-Thyroxine</td>
<td>Ubiquitous</td>
<td>Calcium absorption</td>
<td>Bone disease</td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-Dihydroxyvitamin D(_{3})</td>
<td></td>
<td>Skeletal metabolism</td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-Hydroxyvitamin D(_{3})</td>
<td></td>
<td>Lipid and glucose metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-8(S)HETE (PPAR(\alpha))</td>
<td></td>
<td></td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-Rosiglitazone (PPAR(\gamma))</td>
<td></td>
<td></td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-783,483 (PPAR(\delta))</td>
<td></td>
<td></td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>[(^{3})H]-8(S)HETE (PPAR(\alpha))</td>
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<td>Diabetes</td>
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Footnotes

a) Three isoforms (\(\alpha\), \(\beta\), \(\gamma\)) that differ in DNA sequence, but no clear evidence for pharmacological differences
b) Three isoforms (\(\alpha\), \(\beta\), \(\gamma\)) that differ in DNA sequence, but no clear evidence for pharmacological differences.
c) Two isoforms (\(\alpha\), \(\beta\)) that differ in DNA sequence, with increasing evidence for pharmacological differences.
d) Three isoforms (\(\alpha\), \(\gamma\), \(\delta\), \(\beta\)) that differ in both sequence and pharmacological activity.

Abbreviations

L-765,041: [4-(3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy)phenoxy]acetic acid
L-783,483: [4-(3-(7-Propyl-3-trifluoromethylbenzi-xazol-6-ylxylo)-propylthio)-3-chlorophenyl]acetic acid
LG 100754: (2E,4E,6Z)-7-[3-(n-Propoxy)-5,6,7,8-tetrahydro-5,8,8-tetramethyl-2-naphthyl]-3-methylocta-2,4,6-trienoic acid
LGD 1069: 4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)propenyl]benzoic acid
Ro 41-5253: RAR\(\alpha\)226-414
SR 11335: [4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-1-methoxyethyl)-2-anthracenyl]benzoic acid
TTNPB: (E)-4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propenyl]benzoic acid
Wy 14,643: [4-Chloro-6-(2,3-xylidino)-2-pyrimidino]hioacetic acid

References

Lehman, J.M., et al., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma)., J. Biol.

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