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SERMs: how do they work?

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Selective Oestrogen Receptor Modulators (SERMs) are molecules characterised by high-affinity binding to the oestrogen receptor (ER), but no specific affinity for any other steroid hormone receptor. Each of these compounds has a characteristic set of molecular and pharmacological actions. These unique actions are, according to our present understanding, mediated primarily by the specific conformation of the ER–ligand complex resulting from this interaction. Our understanding of the potential for SERM action is just beginning to emerge [1].

ERs belong to Class I of the classical nuclear receptors, and some aspects of their structure and function have been extensively investigated. Many compounds fitting the SERM definition have been identified. These include compounds already in the clinical realm, such as oestrogen metabolites, clomiphene, tamoxifen and raloxifene. High-affinity, specific binding to the ER has been demonstrated for these compounds, as well as for many other entities in the research arena. Important evidence links many actions of these compounds to their ER binding properties [2].

Structural exploration of the ERs has raised many potential mechanisms for specific and selective, ER-mediated activity. These mechanisms can be grouped into three potential layers of complexity. First, and probably best understood, are those mechanisms which involve the direct interaction of ligand and the ER. The diversity of ligands demonstrated to bind specifically and with high affinity to the ER is great, and the available evidence suggests that a wide range of potential activity profiles is associated with these SERMs. Clinical data, however, are currently available for only a small number of these compounds [1].

It is apparent that a unique conformation of the ligand-ER complex is induced by each SERM. Although few data currently link a specific conformation with a specific biological action, the links are being established at a remarkable rate. In recent years, the picture has become more complex, however, with the characterisation of distinct ER subtypes. Most notable is the identification of the ER-alpha and ER-beta subtypes, but additional ER species, as well as receptor mechanisms via non-classical pathways, have been suggested by recent work. Dimerisation of the ER, an essential element of the 'classical' ER action pathway, has recently been shown to occur not only with ER-alpha and ER-beta homodimers, but also with heterodimers involving both receptor subtypes. The distribution through various body tissues of ER subtypes adds an additional layer of complexity to the situation.

A level of complexity that is just beginning to emerge involves ER regulatory proteins. Classical ER action involves a number of cellular regulatory proteins, many of which bind to ER complexes. Alterations of ER conformation lead to alterations of such interactions. This pathway clearly contributes to alterations in ER mechanistic pathways, in ways that have thus far been characterised in only a few instances.

Finally, recent investigation has identified numerous genomic response elements, in addition to the classic oestrogen response element (ERE), which can be activated by ER-mediated actions. This final layer of complexity adds additional challenges to current efforts to elucidate SERM mechanisms of action [1].

As SERM mechanisms are better understood, the potential for prospectively designing molecules to achieve desired sets of pharmacological actions becomes more and more realistic. The coming years should bring many exciting developments in this field.

References

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