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Selektive Glukokortikoid-Rezeptor-Agonisten (SEGRA): Eine neue Klasse anti-inflammatorisch wirksamer Substanzen

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Since their introduction, the extraordinary importance of glucocorticoids (GCs) in the treatment of inflammatory and autoimmune disorders is undisputed, despite their known undesired effects. In the nineties, major scientific progress was made with the discovery that the positive and negative regulation of gene expression via the glucocorticoid receptor (GR) are mediated by different mechanisms. In the last years it has been accepted that many of the anti-inflammatory activities of GCs are exerted by their suppressing activity of certain target genes via the GR (transrepression).

In contrast, several side effects of GCs seem to be mediated by transactivation of target genes. This discovery led to the assumption that it might be possible to dissociate the therapeutic effects of GCs from their side effects by using ligands which specifically or preferentially address one of the two pathways.

We characterized a first representative of a novel class of GR ligands aiming predominantly at via transrepression and to a minor extent via transactivation. The potency in transrepression of our compound is clearly better than that of prednisolone whereas transactivation efficacy is markedly lower.

The novel GR ligand reaches full inhibition of inflammatory effects in the croton oil induced ear inflammation model and its maximum anti-inflammatory efficacy is comparable to GCs of moderate potency. The compound shows clearly less topical side effects than prednisolone and almost no systemic side effects after topical high-dose treatment for a long period of time.

Thus, the dissociated GR ligand represents a useful novel therapeutic modality which may complement existing therapeutic principles for topical and systemic treatment of inflammatory diseases.

