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THE DESIGN OF NEW STEROID ANTAGONISTS

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Anti-hormones are potentially useful in three major indications : endocrine dysfunction, birth control, hormone-dependent cancers. Since inhibitors of enzymes involved in steroid biosynthesis lack specificity, attention has been turned to molecules that interact with target organ steroid hormone receptors or peptides that desensitize regulatory mechanisms. Extensive structure-affinity studies have shown that modifications of the steroid structure can alter the kinetics of interaction with the receptor giving rise to complexes dissociating much faster or slower than the natural hormones. Fast dissociating ligands are generally partial agonists/antagonists whereas slowly-dissociating ligands can be either agonists or antagonists depending upon the receptor subsites with which they interact. These interactions can be mimicked by certain non-steroids. The approach to the design of high-affinity ligands and to the delimitation of the subsites has involved the comparison of their crystallographic structures and of their receptor binding affinities (RBAs) measured in a routine screening system. Special emphasis has been given to receptor binding specificity. A possible correlation between RBAs and biological activity is more difficult to assess because of the need to consider in vivo metabolism and pharmacokinetics in different species and because of difficulties in defining unequivocal biological endpoints. Whereas the synthesis of specific proteins can often be related to receptor binding affinity, effects on cell proliferation may operate via other mechanisms. Natural hormones themselves can display both stimulatory and inhibitory actions according to dose. Thus new antihormones will be designed when the regulatory mechanisms by which steroid hormones control gene expression and cell division are known.

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Studies on the mechanisms of action of progesterone antagonists (AG)

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AG of RU-38.486-type which compete with progesterone for its receptor site in different pregnancy models reflecting either 'endometrial' (1) or 'myometrial' (2) effects were investigated.
ad 1: All tested compounds were found effective inhibitors of nidation in rats and guinea pigs (G.P.). In G.P. this inhibition was evidence for a role of embryonic progesterone by the earliest events of nidation. No comparable inhibitory effect could be obtained by ovariectomy in G.P. by day 4 p.c.
ad 2: A more complex pharmacology was found in G.P. around day 43 p.c. when the abortion was brought about by expulsion. AG with reduced antiglucocorticoid activity tended to induce abortions more effectively and with shorter induction-abortion intervals than RU-38.486. A remarkable synergism between AG and prostaglandins (PG) was found as expressed by both increased rates of aborting animals and much shorter induction-abortion intervals. Surprisingly it seemed that antiglucocorticoid properties in addition to (or rather than) antigestagenic activities bring about this synergism with PG. The employed G.P.-model for pregnancy termination thus characterized two types of AG ideal ones for monotherapy or combined use with PG, respectively. The role of myometrial and cervical effects of AG and PG in the G.P.-model and the design of effective treatments will be demonstrated.