results from usage of a different exon 9 to that used in the `classic' (GR alpha) form (1). The GR beta variant, which cannot bind ligand, may exert a dominant-negative effect on glucocorticoid signalling and a number of reports suggest that aberrant expression is linked to disease. Controversy continues to surround the likely significance of this variant, however, particularly with regard to its apparently low level of expression. Other splice variants include GR-P (alternatively known as GR delta), which lacks exons eight and nine (2), and a group of exon 2 splice variants (3). We are currently studying an evolutionarily conserved splice variant, GR gamma, that utilises the first three bases of the intron separating exons three and four to code for an additional arginine that is located in the DNA binding domain of the receptor (4).

An additional level of complexity in GR variants is introduced by the reported use of alternative initiating codons (5) which leads to isoforms with different amino-termini, each of which may regulate both a common and a unique set of genes.

Although a unique function has not yet been definitively assigned to any of these variants, the important possibility arises that some or all of them could fulfill distinct functions, perhaps providing a route to pharmacological modulation of signalling through different pathways.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

SA4

Glucocorticoid receptor and chromatin remodelling

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In the eukaryotic nucleus, genetic information is stored within the intimate association of DNA and histone proteins, resulting in a dynamic polymer called chromatin. The fundamental structural unit of chromatin is the nucleosome which consists of ~146 bp of DNA wrapped around an octamer of histones containing two copies each of four core histones, H2A, H2B, H3 and H4. We have developed model systems to study the mechanisms by which steroid receptors control many physiological activities by regulating gene expression within this chromatin organization. Our studies have focused on the glucocorticoid receptor (GR) and its ability to remodel chromatin which is mediated by BRG1 ATPase as part of the human SWI/SNF complex. We demonstrate that transactivation from a chromatin template requires an intact BRG1 remodelling activity, and this activity cannot be substituted by other ATP-dependent remodelling proteins. Further, we have designed, characterized and utilized BRG1 truncation and deletion mutants in a series of assays which allow independent evaluation of transcriptional activation and chromatin remodelling by the GR. Our results suggest BRG1 may contain previously uncharacterized functional motifs important for transcriptional activity. Finally, they reveal that protein-protein interactions both within the complex as well as between the remodelling complex and nuclear receptors necessary and sufficient for glucocorticoid receptor functions *in vivo*.

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SA5

Transcription factor mobility and promoter progression

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The classical view of nuclear receptor action postulates the static binding of liganded receptors to the promoter. We have discovered, however, that nuclear receptors interact dynamically with regulatory elements in living cells, and have proposed the hit-and-run hypothesis for receptor function. Two separate, ATP-dependent mechanisms have been implicated in rapid exchange, the first related to chromatin remodelling, and a second involving molecular chaperone action.

We have also observed that steroid receptor responsive promoters move through a complex series of activity states, a phenomenon we term promoter progression. Genome-wide profiling of glucocorticoid receptor (GR) regulated loci reveals several classes of response, including genes that are transiently activated and genes that are transiently repressed.

Thus receptor action either leads to a series of events programmed into each promoter, or the receptor and/or associated factors are subject to a time-dependent modification of their activity states. These findings illustrate the complexity of the GR response and indicate the dynamic nature of hormone action throughout the eucaryotic genome.