

Pharmacodynamics and Pharmacogenomics of Corticosteroids: Towards Systems Analysis

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The clinical use of corticosteroids remains extensive and frequently chronic. These agents are important drugs for treatment of various immunological disorders, organ transplantation, bronchial asthma, and inflammatory conditions. The multiple and potent metabolic effects of steroids become prominent upon chronic dosing, leading to adverse effects and limiting their clinical usefulness.

Figure 1. Cell diagram depicting the major steps controlling both rapid and delayed effects of corticosteroids.

Steroid responses can be classified either as rapid effects (cell trafficking, cortisol suppression) which can be usually captured with indirect response models or as delayed effects (receptor/gene-mediated protein induction or repression). Proteins that are induced or repressed via genomic processes include both metabolic and immunosuppressive genes. Pharmacodynamic models have been proposed to explain the time-course of receptor and mRNA dynamics and enzyme induction upon single or serial doses of methylprednisolone (MPL) in rats as reflected by our 5th-generation model. We examined induction of tyrosine aminotransferase (TAT), the rate-limiting and regulatory anabolic enzyme controlling tyrosine metabolism in the liver in great detail as the basis for modeling diverse genomic effects.

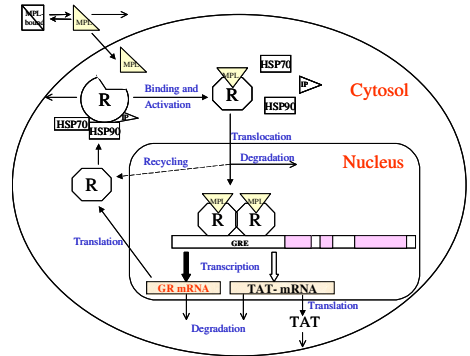
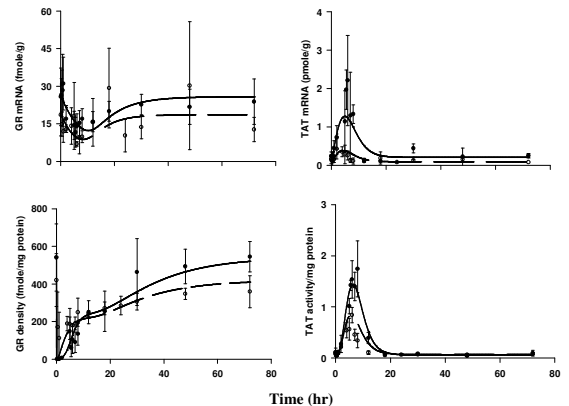
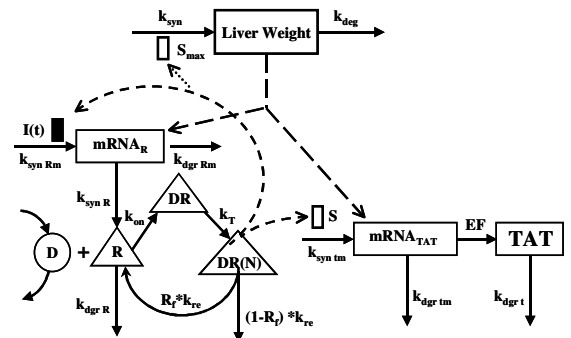


Figure 2. Time-course of receptor occupancy, mRNA profiles for TAT and glucocorticoid receptors (GR), and TAT in rats after IV dosing with 10 and 50 mg/kg MPL.



The 5th-generation model for receptor/gene-mediated effects of steroids with one set of PK/PD parameters was based on results from several types of studies in adrenalectomized (ADX) rats. More recent modeling efforts examined and quantitatively described MPL effects on gene regulation in rat liver, muscle, and fat using microarrays augmented by QRT-PCR measurements.

Figure 3. Fifth-generation PK/PD/PG model for steroid receptor/gene mediated effects which includes MPL kinetics, receptor binding and recycling, synthesis and degradation of mRNA and TAT, and increased liver weight.

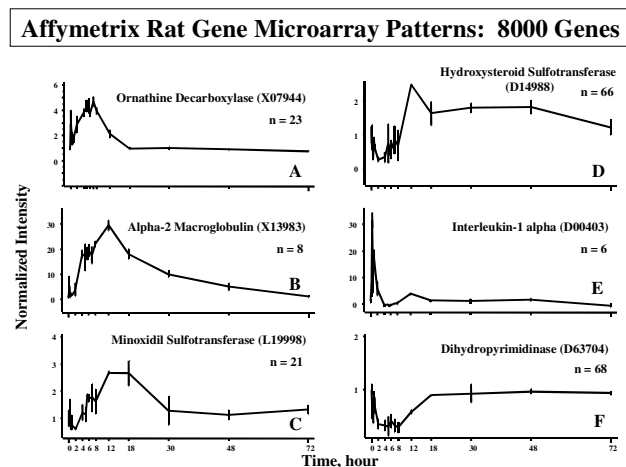


MPL was dosed IV to ADX and normal rats at 50 mg/kg and by 7-day pump infusions. Tissues were excised at various time points over 3 to 7 days. RNAs from individual tissues were used to query Affymetrix GeneChips (Santa Clara, CA). Data are available at: (<http://microarray.cnm.research.org/>). Cluster analysis was performed initially on 8000 mRNA profiles using GeneSpring (Silicon Genetics). Our 5th-generation model of CS PK/PD/PG (Figure 3) and relevant literature was used to evolve mechanistic models to describe the time patterns for diverse CS-responsive genes for baselines and MPL exposures.

Our initial cluster analysis revealed 6 major temporal patterns containing 197 CS-responsive probe sets representing 143 genes (Figure 4). Two clusters (A, B) showed increased expression with differences in onset rate and duration of induction. A PD model assuming CS stimulation of mRNA synthesis captured all genes in these two clusters. Two other clusters (C, D) showed an initial decline followed by delayed enhanced expression, but with differences in effect duration, suggesting that two mechanisms might be involved. An additional cluster (E) showed an abrupt increase in message followed by a rapid decrease. These genes were of lymphoid origin and were modeled combining the fast gene induction effects of CS on lymphoid cells and its direct lymphocyte trafficking effect. Another cluster (F) showed rapid reduction persisting for 18 hr, and was described by CS inhibition of mRNA synthesis.

Figure 4. Typical genes in each of 6 major mRNA expression patterns showing normalized response profiles over 72 hr after 50 mg/kg IV MPL.

Subsequent analysis of these gene arrays by alternative methods including filtering and ‘hashing’ revealed numerous additional clusters with quantitative differences. Comparison of acute versus chronic dosing of MPL showed that response patterns seen after acute dosing are only sometimes predictive of chronic exposure responses. Normal rats exhibited various baseline circadian rhythms and the joint effects of corticosterone and MPL were modeled.



Our results reveal the marked diversity of genes regulated by CS through an array of patterns in liver, muscle and kidney after single and chronic exposure to MPL. Changes in gene expression were related to immunosuppression, blood clotting, dyslipidemia, carbohydrate metabolism, amino acid metabolism, and xenobiotic metabolism and ongoing bioinformatic efforts are seeking relevance to the extensive literature on steroid effects. Our PD models provide means of quantification of CS pharmacogenomics, present insights into understanding of diverse mechanisms of CS effects, allow formulation of hypotheses for future experiments, and reflect ‘small systems analysis’ opportunities for further experimental and modeling efforts.

References

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