P446 Nuclear receptors as controlling factors in chemical metabolism: Determination of regulatory signal network crucial for co-ordinating cellular response to chemicals

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The body is exposed to a wide range of external chemicals, both deliberately (e.g. medicines) and accidently (e.g. environmental contaminants). In addition, the body contains a large number of endogenous chemicals whose levels alter around a physiological mean: This may be as a result of circadian rhythms, normo- or pathophysiological processes. The body responds to changes in these chemical levels by altering flux through metabolic pathways, ensuring healthy physiology. Proteins involved in this biological response include active transport pumps, plus Phase I and Phase II metabolic enzymes, which together act to reduce the level of stimulating chemical through active efflux and metabolism respectively. The expression of many drug metabolising enzymes and drug transport proteins are under control of members of the nuclear receptor superfamily 1. These ligand-activated transcription factors include members who predominantly regulate endogenous functions, including the glucocorticoid receptor (GR), the progesterone receptor (PR) and the androgen receptor (AR), and those that act as sensors for external chemical challenge, such as the pregnane X-receptor (PXR) and the constitutive androstane receptor (CAR). However, it is becoming increasingly clear that these nuclear receptors do not function in isolation, but contribute towards a complex regulatory signal network, which allows the control of overlapping target gene sets and the refinement of biological response(s) to individual chemical challenges. Such interactions are required to meet the challenge of balancing endogenous and exogenous, producing a sensitive response to challenge by external chemicals, yet maintaining robustness within endogenous metabolic processes. We have developed a deterministic model of the nuclear receptor interaction network that regulates expression of target proteins involved in the response to both external chemical challenge and internal steroid metabolism based upon in vitro and in vivo derived data. Examining the known interactions between PXR and GR2,3, we initially developed a model that demonstrates the value within the network of feedforward and feedback loops in refining both the magnitude and duration of response to stress challenges. GR autoregulation is a requirement for the attenuation of biological response to stress signals, and to increase the rate of activation of the metabolic response, which is mediated via PXR. Finally, GR-mediated activation of PXR gene expression is important for controlling the duration of the physiological response to stress signals. In addition, we hypothesis that this response network forms part of a larger, canonical, regulatory signal network between PXR, GR, PR, PPARα, AR and FXR nuclear receptors, and present a more complex model demonstrating how such a network would function. Taken together these networks allow the rapid response to external chemical challenge whilst maintaining normophysiology.

1. Plant, N. and S. Aouabdi. Nuclear receptors: the controlling force in drug metabolism of the liver? *Xenobiotica* 2009; 39(8): 597-605
2. Pascussi, J.-M. et al. Dexamethasone induces pregnane X receptor and retinoid X receptor-a expression in human hepatocytes: Synergistic increase of CYP3A4 induction by pregnane X receptor. *Mol. Pharm*. 2000; 58: 361-372
3. Oakley, R. H. and J. A. Cidlowski. Homologous down regulation of the glucocorticoid receptor: The molecular machinery. Crit. Rev. Euk. Gene Exp.1993; **3**(2): 63-88.