JAK KINASE, STAT TRANSCRIPTION FACTORS, and GROWTH HORMONE (GH) REGULATION of SEX-DEPENDENT LIVER P450 GENE EXPRESSION. DJ Waxman, SHL Park, PA Baum, Boston MA, NCI, NIH, and GB Udv, SM Uvd, RP Towns, RG Snell, RJ Wilkins, HW Davev (AgResearch, Hamilton, New Zealand).

GH exerts sexually dimorphic effects on liver P450 gene transcription that are regulated by the temporal pattern of pituitary GH release, which is intermittent in male rats and nearly continuous in females. We previously identified STAT5b, a liver-expressed latent cytoplasmic transcription factor that is tyrosine-phosphorylated by JAK2 kinase and undergoes nuclear translocation to a high level in response to GH pulses in male rats. Intermittent GH pulsation also activates STAT5b's DNA-binding activity toward an upstream DNA element of the GH pulse-induced, adult male-expressed rat CYP2C11 gene. By contrast, in female rats, continuous plasma GH desensitizes the STAT5b activation pathway. STAT5b protein is thus proposed to be an important mediator of the effects of intermittent GH pulses on the specific pattern of liver P450 gene expression in male rats and near wild-type female levels in STAT5b-/- males, while female-predominant liver gene products were increased in males to near wild-type female levels.

GH also activates, stimulates STAT5b-binding, and induces nuclear translocation of SHP-1, a phosphotyrosine phosphatase that is proposed to catalyze the dephosphorylation leading to deactivation of STAT5b following a GH pulse. The importance of STAT5b for the effects of GH pulses was established using a mouse gene knockout model. Major loss of multiple sexually differentiated responses associated with the sexually dimorphic pattern of pituitary GH secretion was observed in STAT5b-/- mice thus appear to be GH pulse-insensitive, providing strong support for the hypothesis that STAT5b is the major, if not the sole STAT protein that mediates the sexually dimorphic effects of GH pulses on the liver and perhaps other target tissues. [Supported by NIH grant DK33765 and New Zealand Foundation for Research Science and Technology].

CONTROL OF STEROIDGENIC P450 GENE EXPRESSION BY A ORPHAN NUCLEAR RECEPTORS K. Morohashi
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The adrenal cortex, testis, and ovary are major steroid hormone synthetic tissues in which steroidogenic P450s catalyze reactions from cholesterol to various steroid hormones. In recent studies, it has been investigated how Ad4BP/SF-1 and DAX-1 are implicated in the regulation of the steroidogenic tissue functions. In particular, extensive studies have been performed to elucidate the transcriptional activities of the nuclear factors and the transcriptional regulation of the genes encoding these factors. These nuclear factors show similar distributions in the steroidogenic tissues with a few exceptions, and show functional correlation. With respect to the regulation of these transcription factor genes, Ad4BP/SF-1 has been found to be implicated in the regulation of both genes. Ad4BP/SF-1 seems to function as a key factor for differentiation and maintenance of the steroidogenic tissue through regulating a variety of steroidogenic tissue specific genes.

SUPRAMOLECULAR MODEL OF CYTOCHROME P-450
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A synthetic model of membrane-bound Cytochrome P-450 is described which incorporates the important features of the natural system, namely molecular oxygen as the oxidant, a metalloporphyrin as catalyst, an electron donor, and a membrane system enclosing these components. The model was created by anchoring to a synthetic vesicle membrane both a manganese(III) porphyrin and a rhodium complex, which catalyzes the sodium formate reduction of manganese(III). The rate-determining step is the formation of a rhodium(III) hydride species which reacts with manganese(III) to form manganese(II). The latter complex rapidly binds and activates molecular oxygen, and transfers it to an alkene substrate. The turnover numbers for a series of substrates lie in the same range as those observed in nature. The charge of the vesicle membrane has a considerable effect on the catalytic epoxidation activity of the mimics, which decreases in going from negatively charged to zwitterionic vesicles and then to positively charged ones. Under precisely defined conditions (L-α-dipalmitoylphosphatidyl choline vesicles, T=48 °C, [Rh][Mn]=10) the Cytochrome P-450 mimics exhibit oscillating behaviour in the reduction of the manganese(III) porphyrin.