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## Reaction-Diffusion Models of Compartmentalization of Steroid Synthesis

Steroidogenic enzymes can be compartmentalized at different levels, some by virtue of being membrane bound in specific intra-cellular compartments. Although both 3β-hydroxysteroid dehydrogenase/$\Delta^5$-$\Delta^4$ isomerase (3β-HSD) and 17α-hydroxylase/17,20-lyase cytochrome P450 (P450c17) are expressed in the endoplasmic reticulum (ER) membrane, these proteins may still be spatially separated within this membrane system. Side chain cleavage cytochrome P450 (P450scc) is anchored to the inner mitochondrial membrane and this organelle is the major source of pregnenolone feeding steroidogenesis. Furthermore, steroidogenic enzymes can also be partitioned in different cells. Although well recognized, the effect of enzyme compartmentalization on the rate of steroid synthesis and the balance of different steroids is unclear. This study uses mathematical modelling to investigate the effect of enzyme compartmentalization on steroid synthesis in a human-ovine-bovine model of steroid synthesis. Three levels of enzyme compartmentalization examined are: 1) the spatial separation of the enzymes within the ER; 2) the enzyme compartmentalization into different organelles of a cell, and 3) the enzyme partitioning into different cells.

Steroids are small molecules that have a high intracellular diffusion coefficient, hence it is expected that the spatial separation in the ER and the compartmentalization in a cell of steroidogenic enzymes has minimal effect on steroid synthesis (1). To test this, a reaction-diffusion model of the network of reactions catalyzed by P450c17 and 3β-HSD is developed. Simulations are run with a proposed enzyme distribution within the ER and the cell. The results of the model with these spatial configurations are compared to that of the non-compartmentalized model which did not consider any spatial distribution of enzymes (1).

To study the effect of partitioning into different cells of the enzymes required for oestrogen synthesis, an extended reaction-diffusion model is developed that also includes the aromatisation of androstenedione to oestrone catalyzed by P450arom. Two models of organisation of the cells containing different enzymes are examined: two-cell and two-layer-of-cell models. The results of simulations with three different scenarios of enzyme partitioning in each model are compared. This is to test the hypothesis that tissue-specific partitioning of steroidogenic enzymes could be an important regulator of steroid synthesis.

Model simulations show that the spatial separation of steroidogenic enzymes within the ER has a minimal effect on steroid synthesis. The compartmentalization of the enzymes into different organelles of a cell creates small cellular steroid gradients. The partitioning of steroidogenic enzymes in different cells reduces the rate of steroid synthesis. The greater is the distance between the cells that contain different enzymes the more the rate of steroid synthesis is reduced. Additionally, when 3β-HSD is not in the same cell with P450scc and P450c17, the enzyme become less competitive than P450c17 for their common substrates, hence the balance of $\Delta^5$-pathway product (oestrone) to $\Delta^4$-pathway product (17α-hydroxy-progesterone) is favoured. It is also proved that neither the enzyme compartmentalization within a cell nor the enzyme partitioning into different cells alter the qualitative behaviours of steroid synthesis in response to variation in enzyme activity or the rate of P5 supply, as shown in the non-compartmentalized model (1).

Reference:

1. **Nguyen PTT, Lee RSF, Conley AJ, Sneyd J, and Soboleva TK.** Variation in 3β-hydroxysteroid dehydrogenase activity and in pregnenolone supply rate can paradoxically alter androstenedione synthesis. *J Steroid Biochem Mol Biol* 128: 12-20, 2012.