Summary and Conclusion....
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Male accessory gland infections account for almost 15% of all cases of male infertility seen in fertility clinics. The harmful effects of infection and inflammation are mainly mediated through the induction of inflammatory cytokines and the production of increased reactive oxygen species. The Leydig cells are particularly susceptible to infection and inflammation because of their close proximity to testicular interstitial macrophages. Cytokines including TNF-α produced from infections interfere with steroidogenesis at the level of the adrenals, testes and ovaries. Since cytokines mediated inhibition of testicular Leydig cell steroidogenesis occurs mostly at the expression level of different steroidogenic enzymes, it will be valuable to study the regulation of Leydig cell steroidogenesis in response to endogenous cytokines production.

On the other hand, mitochondria play highly specialized, indispensable roles in the production of steroid hormones, which are necessary for life-sustaining homeostasis and reproduction in all vertebrates. The testicular Leydig cell mitochondria are the site of the first enzymatic step in steroidogenesis and hence the disruption of mitochondrial function leads to infertility. Therefore, investigation of cytokine mediated mitochondrial dysfunction and inhibition of Leydig cell steroidogenesis will help us in the design of novel clinical interventions to prevent and treat inflammatory diseases associated subfertility or infertility.

The present study demonstrates that the effect of bacterial LPS induced inflammation on mitochondrial SIRT4 and its implications in testicular steroidogenesis and cellular apoptosis. The salient findings of this study are briefly highlighted here:

- LPS treatment in LC-540 Leydig cells showed increased pro-inflammatory cytokines and ROS generation with significant decrease in intracellular GSH content.

- LPS treatment considerably reduced the expression of ANT2 and concomitantly increased the expression of AMPK in LC-540 cells. Further, our investigations showed that LPS significantly decreases the expression of LRH-1, StAR, P450sc, 3β-HSD, and 17β-HSD. The enzymatic activities of 3β-HSD and 17β-
HSD were also dramatically decreased in LPS treated LC-540 cells. Overall, these results suggest that LPS treatment significantly impairs energy metabolism and steroidogenesis in Leydig cells.

- LPS treatment significantly reduces the mitochondrial membrane potential along with disruption in intracellular distribution of Bcl2 family members such as Bcl2 and Bax. These events eventually cause Leydig cell apoptosis by increasing cytochrome c release and caspase activation.

- The expression of SIRT4 was decreased by 5 fold approximately in LPS treatment at 48h in both in-vivo and in-vitro when compared to the respective controls.

- Studies on the pathways of intercellular transduction that regulate SIRT4 expression under LPS treatment demonstrated that LPS activates the JNK/MAPK pathway, thereby downregulates SIRT4 expression in LC-540 Leydig cells.

- Further, SIRT4 overexpression significantly increased steroidogenesis and decreased cellular apoptosis by improving mitochondrial functions in LPS added Leydig cells.

- Interestingly, we found that resveratrol and NAC pretreatment significantly increase the mitochondrial expression of SIRT4 and protects Leydig cells from LPS induced apoptosis by increasing steroidogenesis.

To conclude, LPS causes mitochondrial dysfunction via suppression of SIRT4; which in turn affects Leydig cell function by modulating steroidogenesis and cellular apoptosis.
Graphical data: overall summary....
References....
References


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