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Nicotine Decreases Serum Testosterone via Autophagy in Leydig Cells

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Letter to the Editor

Many previous reports have shown that nicotine exposure have hazardous effects on testosterone [1,2], which is produced within the testis by Leydig cells [3]. Recently, a research claimed that apoptosis has been detected in Leydig cells after nicotine exposure [4]. However, our past and present data has shown that apoptosis was not detected in Leydig cells [5,6].

After construction of the nicotine-treated animal model, we detected that the concentration of testosterone in the sera of nicotine-treated mice has statistically decreased. Likewise, increase in autophagy of testis following nicotine treatment has also been detected by monodansylcadaverine (MDC) staining and immunofluorescence. Additionally, the analysis of next-generation sequencing data indicated that autophagy-related genes were increased after nicotine treatment. Our research also found that methylation of the promoter region of *TCL1* (*T-cell leukemia/lymphoma protein1*) [7] was increased in the nicotine-treated group compared to the control group. Eventually, we found that nicotine can decrease the activity of CHRNA7 [8] and reduce the expression of *TCL1* by hypermethylation of the *TCL1* promoter. Next, the Akt-mTOR pathway [9] was suppressed, and autophagy was activated, altering the structure of Leydig cells, including its mitochondria. As a result, the expression of StAR (steroidogenic acute regulatory protein), a key enzyme in testosterone synthesis, was downregulated (Figure 1). This resulted in the decrease of the concentration of serum testosterone [10].

Conclusion

In conclusion, our present study provides a novel molecular mechanism, illustrated by the TCL1-mTOR-autophagy pathway, by which nicotine can decrease serum testosterone through autophagy of Leydig cells.

Nicotine interacts with the CHRNA7 transmembrane transporter protein and methylates the *TCL1* promoter region in the cell following a phosphorylation cascade. This methylation reduces *TCL1* gene expression, thus decreasing the concentration of Akt and consequently mTOR. Decrease in concentration of mTOR encourages the accumulation of Beclin1 and LC3, promoting autophagy and downregulating StAR, which reduces testosterone production.

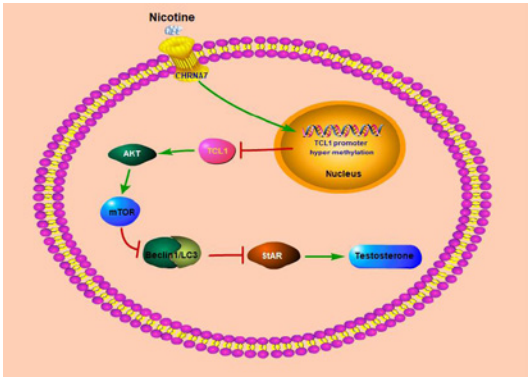

Figure 1: Mechanism for nicotine–regulated autophagy.

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