UNIVERSITI TEKNOLOGI MARA

EFFECT OF LEPTIN ON N-METHYL-N'-NITRO-N-NITROSOGUANIDINE INDUCED HISTOLOGICAL AND GENETIC CHANGES IN STOMACH OF MALE SPRAGUE-DAWLEY RATS

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Obese individuals are at a higher risk of developing gastric cancer. Whether this is related to the higher serum leptin levels in obese individuals is uncertain but leptin has been shown to promote the proliferation of gastric cancer cell *in vitro*. Its impact on tumour formation *in vivo* has not been examined. This study therefore examined the effect of leptin in a rat model of N-Methyl-N′-Nitro-N-Nitrosoguanidine (MNNG)-induced gastric adenocarcinoma. Six-week old male Sprague-Dawley rats were divided into 4 groups (n=8). Group 1 served as controls. Group 2 was given 24 mg/kg/day of MNNG in drinking water. Group 3 was given intraperitoneal injection of 60 µg/kg/day of leptin. Group 4 was treated with both MNNG and leptin. Body weight and water intake were measured weekly. Rats were euthanized after 40 weeks and stomachs were collected for histopathological examination, microarray, and RT-qPCR. Data were analysed using one-way ANOVA and Fisher's exact test. Gastric hyperplasia was observed in 50 % of MNNG-treated stomachs ($p<0.05$), with no significant changes in gene expression. Compared to control, 25% of LEPT-treated stomachs showed hyperplasia and dysplasia, and upregulated genes include *Furin* (protein maturation), *Eef1a1* and *Eif4g2* (translation factors), *Tmed2* (vesicular trafficking), *Rab7a* (plasma membrane trafficking), *Rfwd2* (protein degradation), *Fth1* and *Ftl1* (oxygen transport), *Tspan8*, *Tspan1*, *Fxyd3*, and *Rack1* (cell migration), *Pde4d* (signal transduction), *Nupr1* and *Ybx1* (transcription factors), *Ptma* and *Tmem134* (oncogenes), *Srsf2* (mRNA maturation), and *Reep5* (cell proliferation). MNNG + LEPT-treated rats showed gastric changes including hyperplasia, dysplasia, hypertrophy, and adenocarcinoma ($p<0.01$) in 75% of the rats. Genes upregulated include microRNAs, olfactory receptors, transcription factor (*Hey2*), vesicular trafficking (*Tmed2*), and cell proliferation (*Lcn11*). Lungs of LEPT-treated rats (25%) and MNNG + LEPT-treated rats (50%) showed presence of lung adenocarcinoma. No tumours were found in the lungs of control and MNNG-treated rats. There was no evidence of tumours in the livers of all rats. No significant differences were evident in body weight and water intake between the groups. It appears that leptin administration induced significant changes in carcinogenic genes and microscopic changes in stomach of rats, and its combined treatment with MNNG further enhances gastric carcinogenesis. These findings suggest leptin's role as an inducing and contributing factor towards the increased prevalence of gastric cancer amongst obese people.

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I sincerely hope and dream that this thesis will be a good reference to all future postgraduate students. Insya-Allah.

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