THE ROLE OF TUMOUR NECROSIS FACTOR ALPHA (TNFα) IN OBESITY

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ABSTRACT

Tumour necrosis factor-alpha (TNFα) is an inflammatory mediator and has also been described as a possible factor in obesity related insulin resistance and type II diabetes, although a clear mechanism is still to be elucidated.

This thesis describes six randomised controlled dietary intervention trials that were performed in free living subjects, with the primary aim of inducing weight loss through moderate energy restrictive (~6000 KJ/day) diets of varying nutrient composition. Each study was 12 weeks in duration and all subjects involved were either overweight or obese. In all studies plasma lipids, glucose, insulin and blood pressure were measured before and after weight loss.

The first study, described in Chapter 3, involved measuring the production of TNFα by stimulated peripheral blood mononuclear cells (PBMCs), before and after weight loss, in obese type II diabetics and non-diabetic controls. There was a fall in production of TNFα with weight loss and this was more pronounced in males compared with females. There was no correlation between TNFα production and any measure of adiposity but there was a positive association between TNFα production and blood pressure.

In the second study (Chapter 4), TNFα mRNA expression in subcutaneous adipose tissue was measured using quantitative real time RT-PCR, both before and immediately after a 12 week period of caloric restriction, in obese non-diabetic women. As found with monocyte production of TNFα, there was no association between baseline TNFα mRNA expression and obesity but a positive association was observed with blood pressure. TNFα mRNA

abundance was not altered with weight loss. There was great variation in the effect of weight loss on TNFα mRNA expression, but overall there was a tendency for TNFα mRNA to be elevated ($p = 0.06$) following weight loss.

The presence of a functional polymorphism (*G→A*) in the TNFα promoter at position –308 was determined in all of the subjects recruited for the six weight loss studies and an additional small number of obese subjects who did not undergo weight loss (Chapter 5). The TNF*A* allele in this Australian population was present at a frequency (0.21), which is comparable to other populations, but there was no difference between genotypes in initial BMI, the amount of weight lost (*GG*, 8.1 ± 0.65kg; *AG*, 6.9 ± 0.77kg; *AA*, 7.6 ± 0.12kg) or any metabolic variable.

In summary these studies show that the production of TNFα by PBMCs and expression by adipose tissue is not associated with obesity. Expression of TNFα in adipose tissue and monocyte production of TNFα respond differently to moderate weight loss. The association between TNFα expression and production and blood pressure is one that should be explored further. The disparate results between animal and human studies suggest that factors other than TNFα must also be involved in the metabolic changes associated with obesity.