*Proceedings of the Nutrition Society* (2012), **71 (OCE2)**, E56 doi:10.1017/S0029665112001139

*Summer Meeting hosted by the Irish Section, 16–19 July 2012, Translational nutrition: integrating research, practice and policy*

# The effect of ageing and short-term dietary restriction on the epigenetic, transcriptomic and phenotypic profile of base excision repair in mouse brain and liver

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Accumulation of unrepaired DNA damage has profound effects on cell function which may cause the characteristic features of ageing. Base excision repair (BER) is the primary mechanism used by cells to repair oxidative DNA damage. However it is thought that BER mechanisms become less effective with age. Evidence suggests that epigenetic events contribute to the ageing process and may be functionally important through regulation of gene expression. Dietary restriction (DR) increases longevity in several animal species and is an important model for studies of nutritional modulation of ageing.

In this study brain and liver from male C57BL6 mice were analysed for methylation and expression of *Ogg1* and *Apex* (enzymes involved in the first 2 steps of the BER pathway) using pyrosequencing and RT-qPCR respectively. BER DNA incision activity was assessed using the *in vitro* comet-based assay[1]. Tissues were obtained from animals aged 6, 17 and 30 months fed *ad libitum* (AL) diet and 17 month old mice exposed to 26% DR for 3 months.

**Table 1.** Methylation and expression of BER genes and repair in ageing brain and liver.

| Tissue | Promoter Methylation | | Gene Expression | | BER incision activity |
|---|---|---|---|---|---|
| | *Ogg1* | *Apex* | *Ogg1* | *Apex* | |
| **Brain** | young 1.37%<br>old 1.42% | young 3.07%<br>old 3.79% | ↓ 43.54% with age | ↓ 75.79% with age | ↓20% |
| **Liver** | young 1.81%<br>old 2.05% | young 3.32%<br>old 1.93% | ↓ 17.15% with age | ↓ 52.25% with age | ↑2 fold |

Methylation in the brain was higher in older animals ($P>0.05$) while in the liver it decreased with age for *Apex* ($P = 0.03$) and increased for *Ogg1* ($P>0.05$). Expression of *Ogg1* and *Apex* genes decreased with age in the brain ($P = 0.001$) and liver ($P>0.05$). BER DNA incision activity decreased with age in the brain ($P>0.05$) and increased in the liver ($P = 0.02$).

**Table 2.** Effect of DR on methylation and expression of BER genes and repair in brain and liver

| Tissue | Promoter Methylation | | Gene Expression | | BER incision activity |
|---|---|---|---|---|---|
| | *Ogg1* | *Apex* | *Ogg1* | *Apex* | |
| **Brain** | AL 11.54%<br>DR 1.64% | AL 10.32%<br>DR 3.40% | ↑33.71% in DR | ↑37.98% in DR | No change |
| **Liver** | AL 1.15%<br>DR 1.40% | AL 1.69%<br>DR 2.97% | DR had little effect | | ↑ 60% |

DR decreased methylation in the brain for *Apex* ($P = 0.02$) and *Ogg1* ($P>0.05$) and increased methylation in livers for *Apex* ($P = 0.02$) and *Ogg1* ($P>0.05$) gene promoters. Expression of both genes was up-regulated ($P = 0.01$) in DR compared to AL animals in the brain but had little effect in the liver. DR had no effect on incision activity in the brain but increased activity in the liver ($P = 0.01$).

Responses of brain and liver to ageing and to DR differed for the 2 genes under study. These differences may result from contrasts in the proliferative nature of the 2 tissues (brain is essentially post-mitotic) as well as different roles of the enzymes in the BER pathway and other cellular mechanisms. Short-term DR affected the methylation and expression status of the target genes to some degree but these did not translate into detectable changes in BER. Further work will determine effects of long-term dietary restriction on the DNA repair mechanisms during the ageing process.

This work was funded by BBSRC as part of the Lifelong Health and Wellbeing Initiative.

1. Langie SAS, Cameron KM, Waldron KJ *et al.* (2011) *Mutagenesis* **26**, 461–471.