EPIGENETIC PROGRAMMING BY MATERNAL BEHAVIORS

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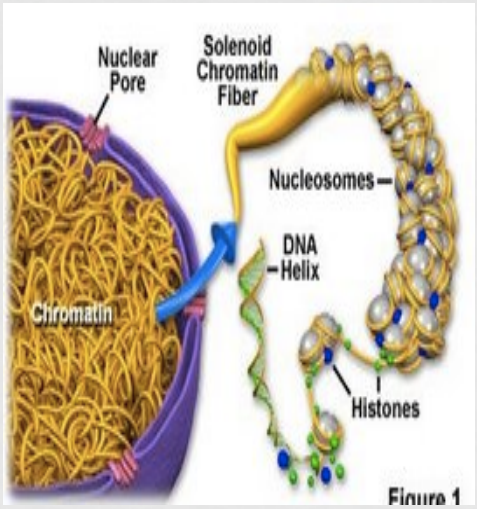
http://www.news.wisc.edu/newsphotos/images/Gammie_lab_mice_pups04_5909.jpg

EPIGENETICS

- What is it?
  - Environmentally mediated changes in gene expression
  - Caused by chemical alterations of chromatin and histone structure



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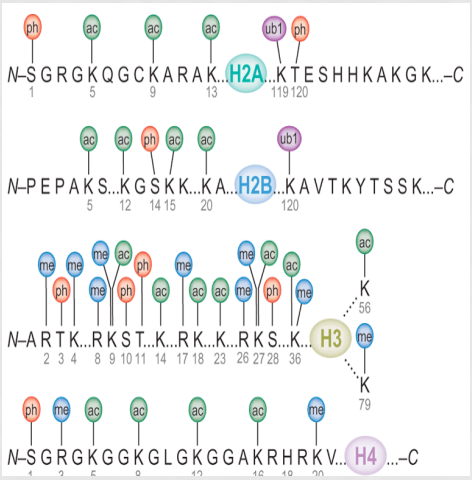
EPIGENETICS

- How do these mechanisms work?
  - Methylation – tightens, inhibits txn
  - Acetylation – loosens, facilitates txn

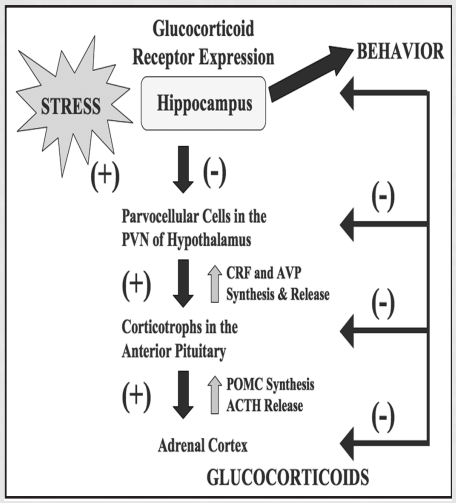


INTRODUCTION

- Maternal behavior in the rat alters hypothalamic-pituitary-adrenal (HPA) responses to stress
  - High Licking Grooming-Arched Back Nursing (LG-ABN) pups show more modest stress response than Low LG-ABN pups
    - Fear response
  - Cross fostering studies show pups exhibit behaviors of foster parents

INTRODUCTION

- Maternal behavior in the rat alters HPA responses to stress
  - Measured by release of corticotropin-releasing factor (CRF)
  - Magnitude of response mediated by effects on gene expression
    - High: increased glucocorticoid receptor (GR) expression and more mild CRF expression



Weaver IC. 2007. Epigenetic programming by maternal behavior and pharmacological intervention. Nature versus nurture: let's call the whole thing off. Epigenetics. Jan-Mar;2(1):22-8. Epub 2007 Jan 15. Review.

INTRODUCTION

- Glucocorticoid receptor
  - Increased expression correlated with expression of nerve growth factor-inducible protein A (NGFI-A)
  - Promoter 1_7 of non-coding exon 1 contains binding site for NGFI-A
    - Higher expression in high LG-ABN groups

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

Hypothesis: Maternal care alters DNA methylation of the GR exon 1_7 promoter, and that these changes are stably maintained into adulthood and associated with differences in GR expression and HPA responses to stress

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

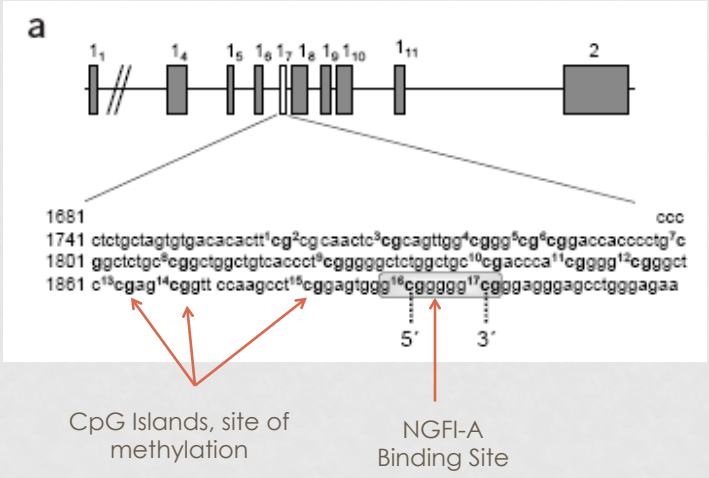
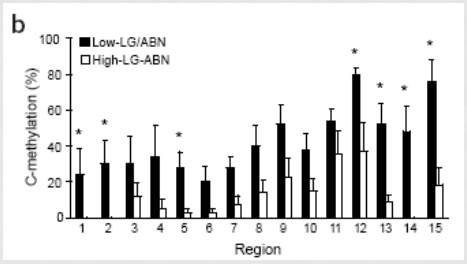
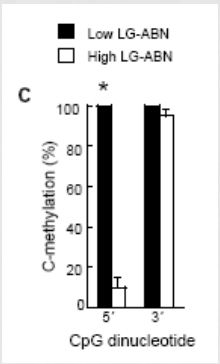


Figure 1

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

How does CpG methylation in the 1_7 promoter differ in high and low LG-ABN groups?



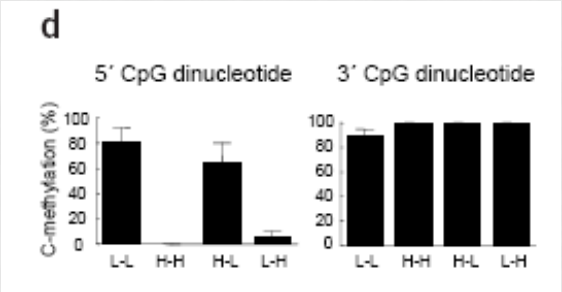


Exon 1_7 of low LG-ABN offspring is more methylated than of high LG-ABN offspring.

Figure 1

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

Is there a causal relationship between maternal behavior and DNA methylation of offspring?

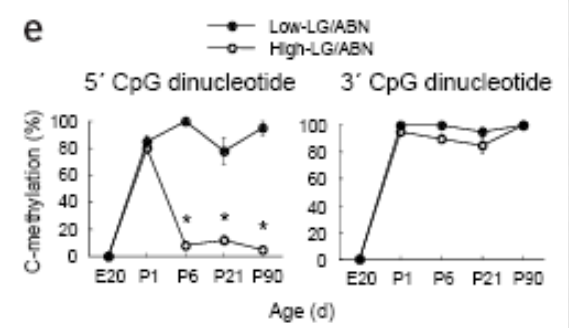


Cross fostering shows that the maternal behavior determines methylation levels of exon 1_7 of the GR gene

Figure 1

How is 'environmental programming' established and sustained in the offspring?

Knowing that maternal care only differs in the first week between high and low LG-ABN offspring, does this week correspond to the appearance of differing levels of DNA methylation?

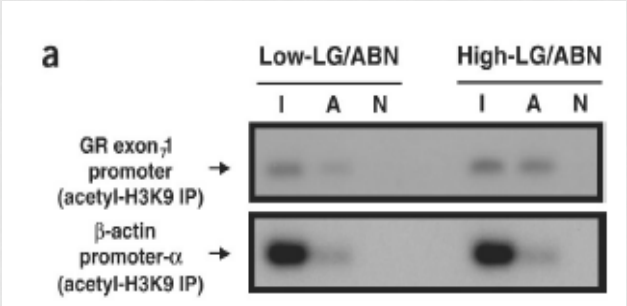


Differences in methylation correspond to timing of differential maternal care

Figure 1

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

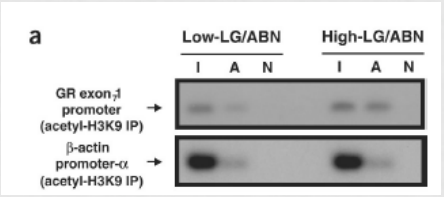
What is the functional importance of these differences in methylation?

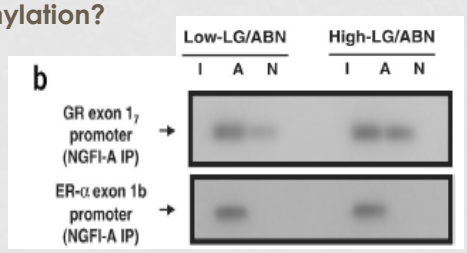


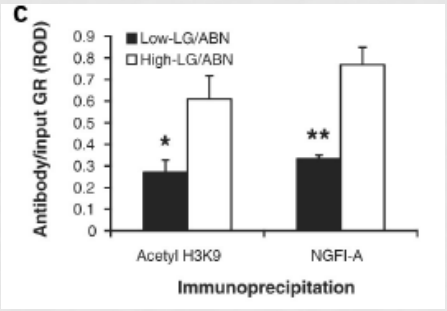
What is ChIP?

Figure 2

What is the functional importance of these differences in methylation?







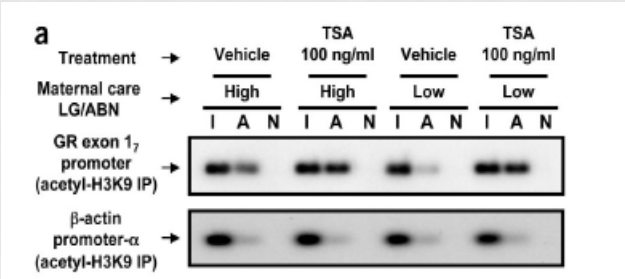
Lower levels of methylation corresponds to increased acetylation of H3K9 and NGFI-A binding.

Figure 2

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

Is the impact of early experience reversible and is epigenetic programming modifiable in adult tissues?

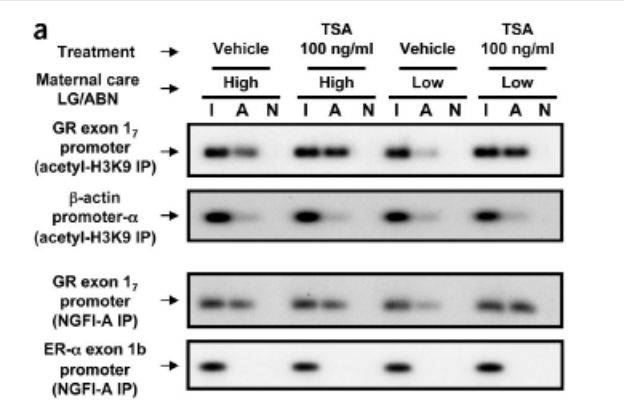
Trichostatin A (TSA) is a histone deacetylase inhibitor



Treating low LG-ABN offspring with TSA increases acetylation of H3K9

Figure 3

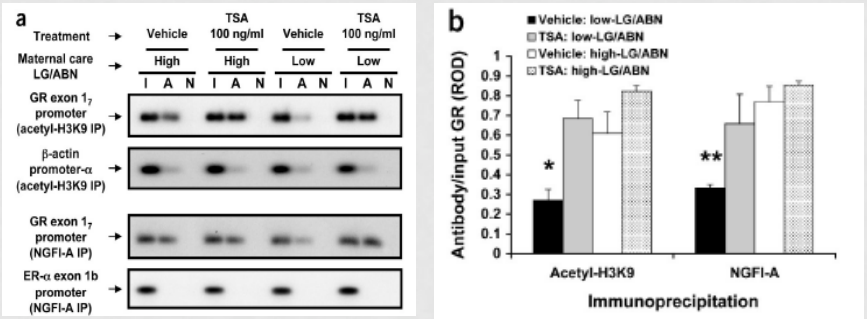
Is the impact of early experience reversible and is epigenetic programming modifiable in adult tissues?



Treating low LG-ABN offspring with TSA increases NGFI-A binding

Figure 3

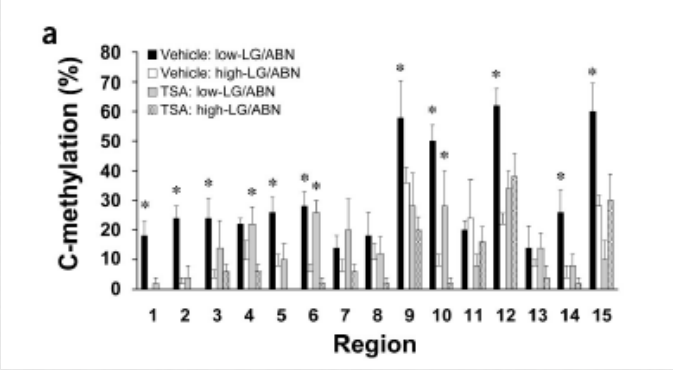
Is the impact of early experience reversible and is epigenetic programming modifiable in adult tissues?



Treatment of low LG-ABN offspring genome with TSA causes demethylation and subsequent acetylation of genomic structures, increasing NGFI-A binding to GR gene promoter

Figure 3

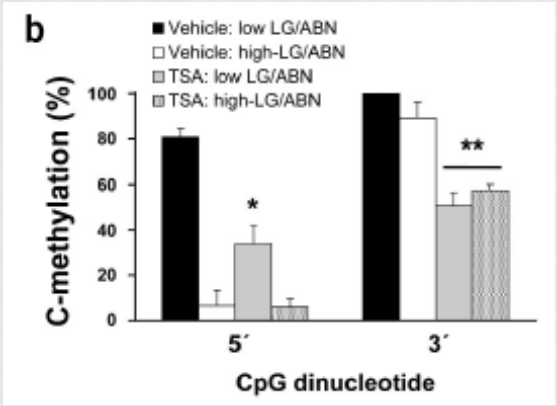
Is the impact of early experience reversible and is epigenetic programming modifiable in adult tissues?



Methylation of the first 15 CpG dinucleotides is decreased in Low LG-ABN rats treated with TSA

Figure 4

Is the impact of early experience reversible and is epigenetic programming modifiable in adult tissues?



Methylation of the 5' and 3' CpG dinucleotides of the NGFI-A binding region is also decreased in low LG-ABN rats treated with TSA.

Figure 4

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

Does TSA-mediated reversal of epigenetic modifications alter GR expression?

TSA treated low LG-ABN rats show GR expression comparable to High LG-ABN groups.

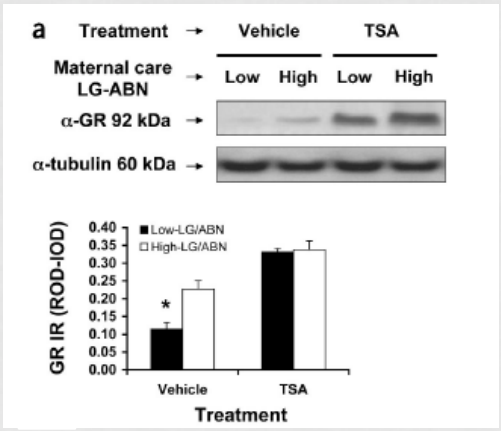


Figure 5

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

Does TSA treatment alter the adrenocortical response to stress in treated animals?

TSA treated low LG-ABN rats show markedly decreased corticosterone responses as compared to vehicle

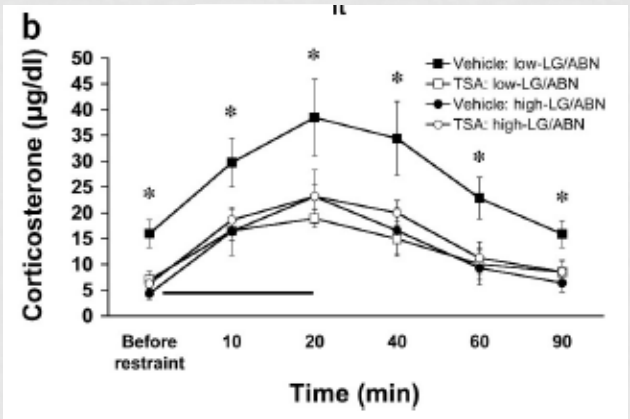


Figure 5

HOW IS 'ENVIRONMENTAL PROGRAMMING' ESTABLISHED AND SUSTAINED IN THE OFFSPRING?

- Test 1: Exon 1_7 of low LG-ABN offspring is more methylated than of high LG-ABN offspring
- Test 2: Cross fostering shows that the maternal behavior determines methylation levels of exon 1_7 of the GR gene
- Test 3: Differences in methylation correspond to timing of differential maternal care
- Test 4: Lower levels of methylation corresponds to increased acetylation of H3K9 and NGFI-A binding
- Test 5: Treatment of low LG-ABN offspring with TSA causes demethylation and subsequent acetylation of genomic structures, increasing NGFI-A binding to GR gene promoter
- Test 6: TSA treated low LG-ABN rats show GR expression comparable to High LG-ABN groups.
- Test 7: TSA treated low LG-ABN rats show markedly decreased corticosterone responses as compared to vehicle.

SIGNIFICANCE

- Relatability to humans
  - The impact of stressful environments on young people
  - Pharmacological treatment to reverse detrimental epigenetic changes
    - Children of smokers study