Preventative Effects of Valproic Acid on Outcomes Associated with Caregiver Maltreatment

Catherine Zimmerman, Nicholas Collins, Tania Roth

UNIVERSITY OF DELAWARE, DEPARTMENT OF PSYCHOLOGICAL AND BRAIN SCIENCES

Introduction

- Experiences in early life play a significant role in influencing an individual's developmental trajectory[1,2]
- Early-life adversity can negatively impact the developing brain
- Caregiver maltreatment → less nurturing and more abusive care[3]
- Strong link between maltreatment and adverse behavioral outcomes[4,5]
- Epigenetics → changes genetic expression without altering the DNA sequence itself
- Examples of epigenetic mechanisms are DNA methylation, histone acetylation, and histone deacetylation
- Valproic acid (VPA) → HDAC inhibitor that prevents DNA methylation and increases gene expression

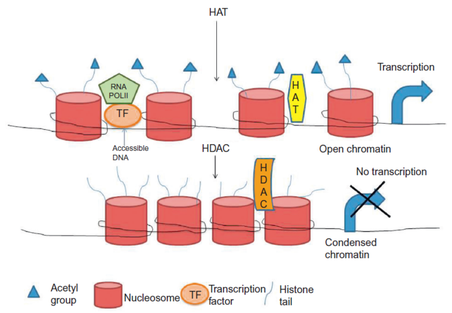

Figure 2. Histone modifications, another type of epigenetic mechanism. Histone acetylation involves a histone acetyltransferase (HAT) enzyme that adds acetyl groups to histone tails, leading to increased transcription. Histone deacetylation involves a histone deacetylase (HDAC) that removes acetyl groups from histone tails, leading to reduced transcription.[12]

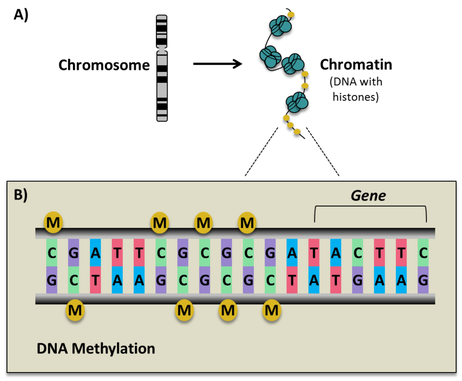

Figure 1. DNA methylation, one type of epigenetic mechanism, in which methyl groups attach to a cytosine guanine dinucleotide, typically suppressing gene transcription.[11]

- Treatment with HDAC inhibitors → positive changes in behavioral outcomes[6, 7]
- Exposure to maltreatment in infancy leads to increased DNA methylation of the *Bdnf* gene in the prefrontal cortex (PFC)[8, 9] and affects behavioral outcomes, such as future caregiving behavior[10]
- Sodium butyrate, an HDAC inhibitor, prevents maltreatment-induced changes in methylation at *Bdnf* exon IX in the PFC[8]
- Aim 1 → Investigate the preventative effects of 200, 400, and 600 mg/kg doses of VPA on maltreatment-induced DNA methylation
- Aim 2 → Examine the long-term effects of VPA administration concurrent with early-life stress

Bdnf Exon IX and Global Methylation Results

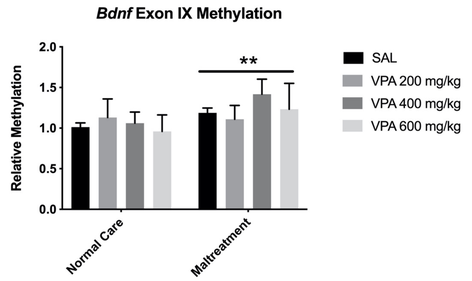

Figure 4. Relative methylation levels at *Bdnf* exon IX for assigned condition and drug dose/saline. Main effect of infant condition observed. ** denotes p<.01, n=27 litters, 8-16 per group, error bars represent SEM.

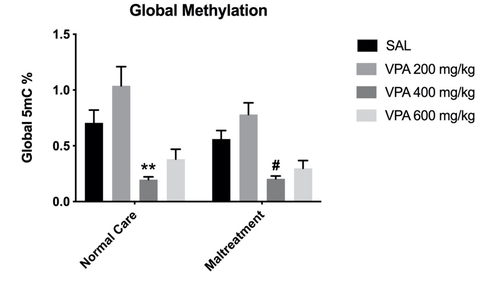

Figure 5. Global methylation levels for assigned condition and drug dose/saline. 400 mg/kg VPA significantly lowered global methylation levels in normal care condition and marginally lowered levels in maltreatment condition. ** denotes p<.01, # denotes p=.054, n=27 litters, 8-16 per group, error bars represent SEM.

Future Caregiving Behavior Results

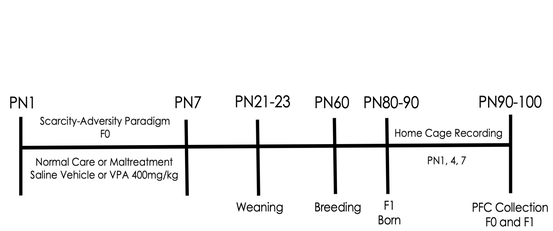

Figure 6. Experimental timeline for aim 2 of our study. F0 pups were exposed to the scarcity-adversity paradigm concurrent with either saline vehicle of 400 mg/kg VPA and were then bred at PN60 to yield the F1 generation. The caregiving behavior of the F0 generation toward the F1 pups was recorded and quantified as nurturing or aversive on PN1, 4, and 7 for F1 pups.

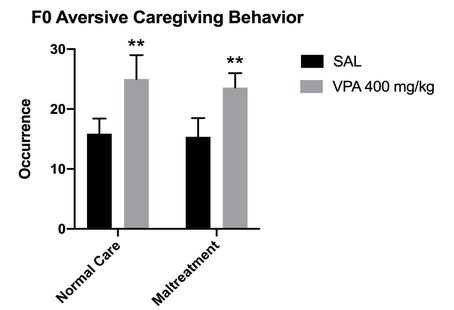

Figure 7. Occurrence of aversive behavior exhibited by F0 dams towards F1 pups. F0 dams who received 400 mg/kg VPA exhibited a greater amount of aversive behaviors than those who received saline vehicle, across both infant conditions. ** denotes p<.01, n=8-12 per group, error bars represent SEM.

Methods

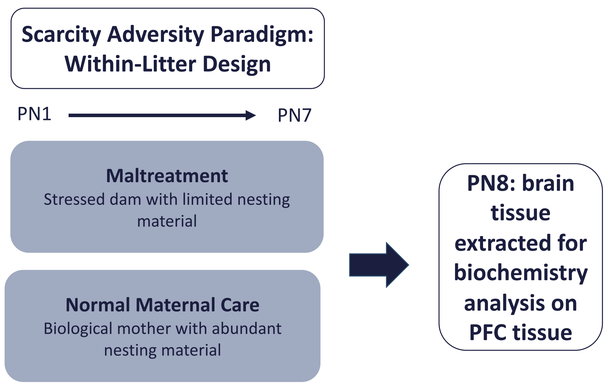

Figure 3. Pups were assigned and exposed to either the maltreatment or normal care condition for 30 min/day for 7 days.

- Daily intraperitoneal administration of 200, 400, or 600 mg/kg VPA or saline vehicle concurrent with behavioral exposure
- PN8 → brain tissue extracted and PFC isolated
- DNA extracted purified, and bisulfite treated
- Methylation-specific PCR (MSP) used to quantify methylation at *Bdnf* exon IX
- ELISA colorimetric assay used to quantify global methylation

Conclusions and Future Directions

- VPA was unsuccessful at preventing methylation at *Bdnf* exon IX across all doses
- 400 mg/kg dose of VPA was successful at lowering global methylation across the PFC
- Treatment with VPA in infancy leads to increased incidence of aversive caregiving in adulthood, independent of early-life environment
- Future work aims to analyze *Bdnf* exon IX and global methylation levels in PFC tissues collected from F0 dams and F1 pups
- Further exploration of how VPA affects behavioral outcomes. such as social interaction and fear conditioning
- Investigation into non-pharmacological interventions for early-life stress, such as environmental enrichment or exercise

References and Acknowledgements

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