Epigenetics and Suicidal Behavior Research Pathways

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Suicide and suicidal behaviors are complex, heterogeneous phenomena that are thought to result from the interactions among distal factors increasing predisposition and proximal factors acting as precipitants. Epigenetic factors are likely to act both distally and proximally.

Aspirational Goal 1 aims to find clear targets for suicide and suicidal behavior intervention through greater understanding of the interplay among the biological, psychological, and social risk and protective factors associated with suicide. This paper discusses Aspirational Goal 1, focusing on the research pathway related to epigenetics, suicide, and suicidal behaviors. Current knowledge on epigenetic factors associated with suicide and suicidal behaviors is reviewed and avenues for future research are discussed. Epigenetic factors are a promising area of further investigation in the understanding of suicide and suicidal behaviors and may hold clues to identifying targets or avenues for intervention.

(Am J Prev Med 2014;47(3S2):S144–S151)

Introduction

Suicide and suicidal behaviors (SSBs) are complex, heterogeneous phenomena that, as contemporarily defined, are commonly manifested in the presence of mental illnesses.[1] SSBs are complex because they are multifactorial and not all individuals manifesting SSBs share the same underlying etiologic factors. In other words, risk factors for SSBs are not universal.[2]

Numerous models have been proposed over the years while attempting to understand SSBs. Despite the complexity and etiologic heterogeneity of these phenomena, most contemporary models of SSBs are remarkably similar and basically assume two levels of risk factors: those acting more distally and those acting more proximally.[3] On one end, risk factors acting more distally are thought to increase predisposition; on the other end, risk factors acting more proximally are thought to be precipitants.[3] These relationships are described in Figure 1. Examples of distal factors include genetic makeup and early-life adversity (ELA), whereas typical proximal factors are recent life events and last 6-month psychopathology including current substance (alcohol/drug) abuse.[3]

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0749-3797/$36.00

http://dx.doi.org/10.1016/j.amepre.2014.06.011

Aspirational Goal 1 aims to find clear targets for intervention through greater understanding of the interplay among the biological, psychological, and social risk and protective factors associated with suicide. This paper discusses this Aspirational Goal and focuses specifically on the research pathway related to epigenetics and SSBs.

Epigenetics

Epigenetics refers to the study of the epigenome, the chemical and physical modifications of the deoxyribonucleic acid (DNA) molecule that functionally regulate the collection of genes of an organism by altering the capacity of a gene to be activated and produce the messenger ribonucleic acid (mRNA) it encodes.[4] Epigenetic regulation of gene function allows for genomic plasticity, that is, the adaptation of the genome to the needs of the organism.

It has long been clear that epigenetic processes occur as a result of physical and chemical environmental signals. However, only recently has it been revealed that the social environment also triggers epigenetic responses.[4–6] As such, it is possible to conceptualize the epigenome as an interface through which the environment can influence genetic processes and, as a result, regulate behavior at least partially in response to environmental needs.[3]

Epigenetic Factors and Suicidal Behavior

Stable epigenetic factors are likely to act distally, increasing predisposition, whereas dynamic epigenetic factors and proteomic changes are likely to underlie

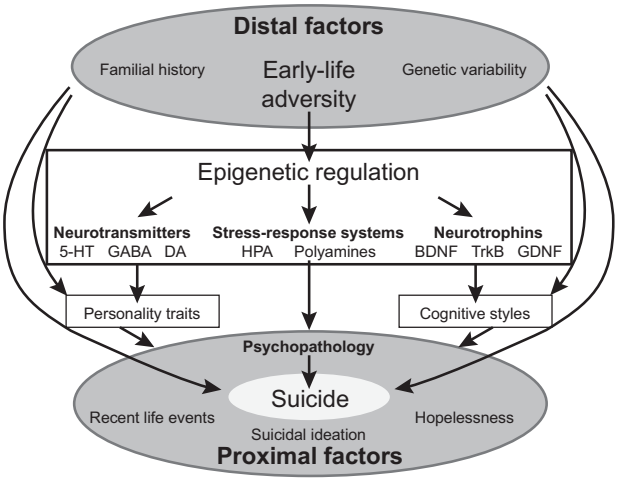

Figure 1. Proposed model for epigenetic factors acting distally on risk of suicide and suicidal behaviors
BDNF, brain-derived neurotrophic factor; DA, dopamine; GABA, γ-aminobutyric acid; GDNF, glial cell–derived neurotrophic factor; HPA, hypothalamus–pituitary–adrenal axis; HT, hydroxytryptamine; TrkB, tyrosine kinase B

psychopathological states that act more proximally, precipitating suicidal behavior. To date, however, most of the research investigating epigenetic factors in SSBs has focused on presumably stable epigenetic marks that are thought to act distally.

Specifically, DNA methylation is capable of inducing stable epigenetic marks. As epigenetic marks associate with genomic responses to environmental stimuli—and because SSBs are strongly associated with histories of ELA such as childhood sexual and physical abuse as well as parental neglect—most of the initial effort to investigate epigenetic factors associated with SSBs has focused on individuals with histories of ELA.

Variations in the early social environment, as modeled by maternal care in the rat (the frequency of pup licking/grooming [LG] over the first week of life), program the expression of genes that regulate behavioral and endocrine responses to stress[7–9] such that offspring of high-LG mothers show increased hippocampal glucocorticoid receptor (GR) expression and more modest responses to stress compared to the offspring of low-LG mothers. These differences persist after cross-fostering low- and high-LG offspring to high- and low-LG mothers, respectively, revealing that the early social environment determines individual differences in stress reactivity, which is transmitted via non-genomic mechanisms.[8] Maternal LG induces an epigenetic modification of an exon 1_7 GR promoter[10] such that increased maternal care associates with decreased methylation of the exon 1_7 promoter and increased hippocampal GR expression.

Encouraged by this groundbreaking animal work suggesting that the tone of the hypothalamus–pituitary–adrenal (HPA) axis is epigenetically programmed by the early-life environment[10] and that these mechanisms are evolutionarily conserved,[11] in addition to well-established evidence suggesting that HPA axis dysregulation increases risk of suicidal behaviors, the initial work investigating epigenetic factors in SSBs has focused on the epigenetic regulation of the HPA axis by the early environment. In addition, neurotrophic factors and their receptors, as well as other signaling systems, have been investigated.[3]

Stress Response Systems

Epigenetic Regulation of the HPA Axis by the Early-Life Environment, Suicide, and Suicidal Behaviors

Early-life adversity has been proposed to induce its long-term behavioral consequences partly by altering the neural circuits involved in the regulation of stress.[12] Depressed patients with a history of ELA have been reported to exhibit higher adrenocorticotropic hormone (ACTH) and cortisol levels following stress tasks and dexamethasone challenge.[12,13] Interestingly, in these studies,[12,13] both ACTH and cortisol levels did not differ significantly between depressed subjects without history of ELA and controls. Childhood abuse has also been shown to increase corticotropin-releasing hormone (CRH) levels[12,14] and decrease cerebrospinal fluid (CSF) oxytocin levels.[15]

Hypothalamus–pituitary–adrenal axis dysregulation has also been associated with increased suicide risk. For instance, in a 15-year follow-up study, Coryell et al.[16] showed that depressed patients who were admitted to a psychiatric unit and were non-suppressors to the dexamethasone suppression test had a 26.8% risk of dying by suicide at follow-up, compared to a 2.9% risk for controls. Several other studies have produced consistent data.

A large study[17] investigating 372,696 primary care patients who received oral glucocorticoids observed a hazard ratio of 6.89 (95% CI=4.52, 10.50) for SSBs in these patients when compared to those with the same underlying medical condition who were not treated with glucocorticoids. More recently, low hippocampal GR expression levels have been reported in individuals with a history of childhood abuse who died by suicide[18,19] but not in non-abused individuals who died by suicide.

The observations from studies in rats suggesting that maternal behavior regulate the tone of the HPA axis via methylation were recently translated to humans through studies investigating hippocampal tissue from individuals who died by suicide with and without a history of childhood adversity, as well as normal controls.[18,19] Notably, methylation levels in the exon 1F promoter of

the GR in abused individuals who died by suicide were significantly higher than among non-abused individuals who died by suicide and healthy controls.

In addition, similar to what was found in rats, a significant hypermethylation in a nerve growth factor inducible A (NGFI-A)–binding site was found in abused individuals who died by suicide but not in the other groups. This epigenetic mark was shown to repress the binding of NGFI-A to its cognate DNA sequence and decrease GR transcription.[19] A growing number of independent studies have been published with consistent results. Higher levels of methylation in the promoter of GR 1F have been reported in the infants of mothers reporting intimate partner violence during their pregnancy compared to those born from mothers who did not report intimate partner violence during pregnancy.[20]

Another study[21] reported significant correlations between GR 1F promoter methylation levels and parental loss, child maltreatment, and suboptimal parental care. Furthermore, DNA methylation levels in the GR 1F promoter were shown to be positively correlated with childhood sexual abuse, its severity, and the number of maltreatment events in individuals with major depressive disorder, and with repetition of severe types of abuse in patients with bipolar disorder.[22]

Together, this suggests that ELA may induce specific long-lasting epigenetic alterations affecting gene expression. In a different study[23] assessing the expression of several GR exon 1 variants expressed in the limbic system of depressed individuals who died by suicide, GR 1F and GR 1C hippocampal expression were significantly decreased in depressed individuals who died by suicide. NGFI-A protein levels in the hippocampus were significantly decreased in depressed individuals who died by suicide, suggesting that the decrease in GR expression found in these individuals may be mediated by different molecular pathways depending on the presence or absence of ELA.

More recently, a study[18] investigating other brain-expressed GR variants in the hippocampus of individuals who died by suicide according to histories of ELA indicated that the expression of the non-coding exons 1B, 1C, and 1H was significantly different in individuals who died by suicide with a history of ELA compared to non-ELA individuals who died by suicide and controls. The assessment of methylation levels in the promoter of GR 1C revealed methylation differences that were inversely correlated with GR 1C expression, in accordance with the previous findings reported by the same group on the 1F variant.

On the other hand, the GR 1H promoter showed site-specific hypomethylation, and methylation was positively correlated with human GR 1H expression. In other words, less methylation significantly correlated with lower expression, suggesting that active demethylation is also a functional mechanism that may be regulated by the early-life environment. Although this is a mechanism that has received less attention, more work is required to elucidate its potential implication in the context of ELA.

Other Stress Response Systems

Alterations in stress response systems other than the HPA axis have also been reported in suicide, particularly involving polyamines, which are highly regulated small molecules containing two or more amine (NH_2) groups.[24] Polyamines have a multitude of functions including regulation of gene transcription and posttranscriptional modifications, as well as modulation of several protein activities.[25] They are released following stressful stimuli, and in the mammalian brain, polyamines present a unique pattern of response known as the polyamine stress response (PSR).[26] The PSR can be induced by direct neuronal stimuli or in response to hormonal signals, such as glucocorticoids.

Both human and animal studies suggest that polyamine dysfunction is involved in psychopathology.[27] Studies investigating the effects of antidepressants indicate a role of the polyamine system in the antidepressant response, particularly the interaction of the polyamine agmatine or putrescine on *N*-methyl-D-aspartate (NMDA) receptors.[28–31] Several studies have indicated alterations in the mRNA and protein levels of several components of the polyamine system in cortical and subcortical brain regions of individuals who died by suicide,[32–35] as well as in peripheral samples from suicide attempters[36] and psychiatric patients.[37]

Interestingly, significant epigenetic regulation of some key polyamine genes in the brain have been reported.[38–40] Although preliminary evidence suggests differential epigenetic regulation of some of these genes in suicide,[38] further studies are necessary to understand if polyamine genes are regulated by the early environment in a similar fashion like that observed for HPA axis genes.

Neurotrophins, Suicide, and Suicidal Behaviors

Neurotrophins, also referred to as neurotrophic factors, are important candidate molecules for understanding the development of psychopathology because of their role in neuronal survival and plasticity, as well as their expression in brain regions from the limbic system, where emotions and related behaviors are processed. For instance, it is hypothesized that their alteration could partly underlie changes in plasticity observed in the brains of individuals who died by suicide as well as the mood symptoms observed in depressive patients.

Brain-derived neurotrophic factor (BDNF) has received most of the attention in neurobiological research of psychiatric conditions such as depressive disorders and suicide. For instance, patients who are depressed present low serum and brain BDNF expression levels,[41–43] and serum BDNF levels are normalized by antidepressant treatment.[44–46]

BDNF epigenetic regulation has been investigated in mice and rat models of stress-induced depressive symptoms,[47,48] as well as in a rat model of exposure to traumatic events.[49] Chronic social stress in mice decreases the expression of two specific BDNF transcripts (III and IV) in the hippocampus,[47] and maternal maltreatment decreases prefrontal cortex (PFC) BDNF mRNA expression in rats.[48] The BDNF expression alterations observed in chronic social stress in mice are mediated through increased histone H3K27 demethylation levels in transcripts III and IV promoters,[47] and site-specific DNA hypermethylation is found in transcripts IV and IX promoters of maltreated rats.[48]

In the latter study, site-specific hypermethylation seems to follow a developmental pattern such that exon IX promoter hypermethylation occurs immediately after the maltreatment regimen, whereas promoter IV methylation increases gradually to reach significantly altered levels only in adulthood. These findings illustrate that ELA or chronic stressors may alter different epigenetic mechanisms with common transcriptional consequences. On the other hand, these results may also highlight the heterogeneity of stress-induced epigenetic alterations between species.

Pharmacologic treatment with the tricyclic antidepressant imipramine reverses the effect of chronic stress on BDNF transcription in mice.[47] However, this reversal does not seem to be due to the normalization of histone H3K27 methylation levels but rather through an increase in both histone H3K4 methylation and histone H3K9 acetylation levels.

Consequently, these results suggest the existence of a compensatory mechanism in the reinstatement of basal BDNF levels by chronic imipramine treatment following chronic stress and emphasize the importance of chromatin hyperacetylation induced by antidepressant treatment. There is evidence in humans suggesting that antidepressants act by promoting an open chromatin structure (i.e., lower H3K27 methylation levels) in the promoter of BDNF in the prefrontal cortex,[50] and consistent results were found when investigating peripheral samples from depressed patients treated with the typical selective serotonin reuptake inhibitor citalopram.[51]

Recently, the methylation state of BDNF was also assessed in post-mortem brains from individuals who died by suicide. Keller and colleagues[52] used three different methods to quantify DNA methylation levels in a region encompassing part of non-coding exon IV and its promoter in the Wernicke area; their results showed that DNA methylation was significantly increased in individuals who died by suicide (n=44) compared to controls (n=33). In addition, BDNF expression in subjects with high DNA methylation levels was significantly lower than in those with low and medium DNA methylation levels, supporting the repressive effects of methylation within the promoter on transcription.

Transmembrane receptor tyrosine kinase B (TrkB) is the receptor for BDNF and has long been investigated in the neurobiology of mood and related disorders.[41,53–55] Lower TrkB expression has been reported in the prefrontal cortex of depressed subjects[56,57] and antidepressant treatment has been shown to increase its expression in cultured rat astrocytes.[58]

In investigating the astrocyte-expressed splice variant T1 of the TrkB gene, TrkB-T1, it has been recently reported that a subset of individuals who died by suicide with low levels of TrkB-T1 expression revealed two sites where methylation levels were higher compared to controls.[59] The methylation pattern at those two sites was negatively correlated with the expression of TrkB-T1 in individuals who died by suicide, and this effect was specific to the prefrontal cortex because no significant difference was found in the cerebellum.

In addition, individuals who died by suicide with low TrkB-T1 expression showed enrichment of histone H3K27 methylation in the TrkB promoter,[60] suggesting that this variant of TrkB may be under the control of epigenetic mechanisms involving histone modifications and DNA methylation. Taken together, these data suggest that epigenetic changes in BDNF and its TrkB-T1 receptor variant might participate in the vulnerability to chronic social stress and possibly to ELA and SSBs.

The γ-Aminobutyric Acid System

The γ-aminobutyric acid (GABA)ergic system has been the focus of many research studies in post-mortem brain samples of psychiatric patients, including those who died by suicide.[61–63] For example, reductions in reelin and glutamate decarboxylase 1 (GAD1, a GABA synthesis enzyme) mRNA[61] and an increase in DNA methyltransferase (DNMT) 1 expression[64,65] were previously reported in post-mortem brains of schizophrenic and bipolar subjects who died by suicide. Consistently, promoter hypermethylation was reported for both genes in accordance with the methylating role of DNMT1.[66,67]

More recently, the hippocampal expression of GAD1 has been shown to be regulated by the early environment through maternal care in rats.[68] These findings are in

accordance with the study by Poulter et al.[69] that examined the expression of DNMTs as well as the $GABA_A$ receptor α1 subunit in the brain of individuals who died by suicide. Three hypermethylated CpG sites within the α1 subunit promoter were identified in the prefrontal cortex of individuals who died by suicide and negatively correlated with DNMT3b protein expression. In addition, DNMT1 and DNMT3a levels have also been reported to be altered in the limbic system and brain stem of individuals who died by suicide. However, histories of ELA were not reported in this study, thus one cannot assume that these effects would be similar in abused individuals who died by suicide.

Genome-Wide DNA Methylation Alteration

Although promising data have been generated using hypothesis-driven approaches focusing on candidate gene systems to investigate epigenetic factors associated with suicide and the early-life environment, there is a need to better understand epigenetic patterns associated with SSBs at the genome-wide level.

In particular, two related studies using an antibody to identify methylated sequences at the genomic level followed by hybridization to a custom-made gene promoter array have been reported. One of these studies focused on individuals who died by suicide and had a history of severe ELA.[70] Hundreds of sites were identified as being differentially methylated, both hyper- and hypomethylated, associated with the phenotype.

Interestingly, differential methylation in abused individuals who died by suicide was enriched in genes involved in neuroplasticity, a finding consistent with the notion that adversity during childhood leads to plastic changes in the brain as a response to these negative environmental stimuli. Similar observations were made in another genome-wide study, in which an unselected sample of individuals who died by suicide was investigated.[71] In this study, methylation enriched in genes was related to learning and memory.

How May Epigenetic Changes That Are Distally Associated with Suicide and Suicidal Behaviors Increase Risk?

Figure 1 depicts a diagram of putative mediating mechanisms whereby epigenetic changes acting distally may stably increase lifelong risk of suicidal behavior. Importantly, this model is based on consistent data from human studies, which indicate that emotional and behavioral dysregulation are frequently reported in individuals with histories of ELA,[72] and that these personality traits seem to mediate, to varying degrees, the relationship between ELA and suicidal behavior.[73–75]

Moving Forward

The investigation of epigenetic factors in behavioral phenotypes is a fairly new field. As such, there remains much to understand about epigenetic processes underlying psychopathology and SSBs. In addition, knowledge on epigenetic mechanisms is rapidly evolving, constantly opening new horizons for new epigenetic research. Challenges for future research investigating epigenetic mechanisms in suicide can be grouped into three main categories, including (1) challenges related to the underlying theoretic paradigm; (2) challenges related to the study design; and (3) technical challenges. Figure 2 provides a list of the most important challenges that future epigenetic studies of SSBs should consider according to each of these three categories.

Potential Roadblocks

Although epigenetic research of SSBs is likely to grow exponentially over the next decade and there is tremendous potential for breakthroughs, a number of possible roadblocks should be considered. Epigenetic marks are tissue and cell population specific. In order to understand pathology, it would be important to first understand normative processes. Therefore, it would be necessary to generate extensive reference maps for different epigenetic processes that are representative of normal development for the multitude of cell populations and circuits of the brain related to SSBs.

Many studies[76–80] have already been conducted assuming that peripheral samples would model brain gene expression changes. Moreover, several studies[78,81,82] have assessed how representative peripheral expression studies are of central nervous system gene expression. Although conclusive evidence in this regard remains lacking, it is important to keep in mind that epigenetic marks are tissue specific and more variable between different tissues of the same individual than between the same tissue of different individuals.[83] However, there is also some evidence of within-individual epigenetic variant correlation across tissues.[83]

Another potential limitation is related to analytic capacity. Although technology advances rapidly, analytic and computational tools capable of processing and integrating multiple layers of epigenetic information move forward at a much slower pace. Overcoming such potential limitations will require significant effort coordinating different disciplines, including computational biology, mathematics, and engineering.

A further potential limitation is bench-related. Screening tools have advanced much more rapidly than the capacity to follow up on significant results and characterize their potential functional impact. Particularly, it is currently

- **Paradigm**
  - Theoretic modeling and investigation of distal epigenetic factors acting on suicide risk irrespective of early-life adversity
  - Investigation of stability/instability of distal epigenetic factors
  - Relative contribution of epigenetic changes to development of personality traits, psychopathology, and suicide risk
  - Investigation of proximal epigenetic changes and understanding their interaction with distal epigenetic factors
  - Mechanisms for potential intervention
- **Design**
  - What brain systems/circuits and cellular fractions are affected by epigenetic changes associated with increased suicide risk?—Conduct studies investigating different brain areas and cell populations
  - What sequences other than those from candidate systems are epigenetically regulated and increase suicide risk?—Conduct genome-wide studies
  - Are peripheral epigenetic marks valid markers of central epigenetic changes?—Conduct comparative studies using peripheral and central samples from the same subjects
  - Conduct prospective studies of epigenetic changes as a function of environmental stressors in longitudinal cohorts representative of the general population
  - Effect of possible covariates: better understand the role of gender, age, socioeconomic environment, substance of abuse, and other factors
- **Technical**
  - Conduct high-throughput, next-generation sequencing studies
  - Investigate different epigenetic marks and their effect on different RNA species
  - Obtain concomitant information on different epigenetic marks and RNA expression for the same samples
  - Conduct follow-up work using appropriate induced pluripotent stem cell models
  - Investigate potential for pharmacologic manipulation of epigenetic changes associated with suicide risk
  - Development of appropriate animal models

Figure 2. Most important challenges that should be considered by future epigenetic studies of suicide and suicidal behaviors

challenging to investigate interactions of molecular markers or the additive effects of several molecular processes. It is thus not surprising that most models remain relatively simple and unifactorial in spite of great technical advances. Although overcoming these potential barriers of progress will be challenging, these are all feasible undertakings.

Clinical Implications

As epigenetics allows modeling environmental influences on the individual's biology, it can aid in understanding how life events act distally and increase predisposition to SSBs, as well as how they act proximally and precipitate suicidal crises. This knowledge has tremendous clinical implications and the potential to help develop new avenues for intervention, including personalized treatment options such as monitoring of treatment efficacy.[84] Although the application of epigenetics to study behavior and psychopathology is recent, epigenetic research has already advanced the understanding of SSBs, particularly by shedding light on biological processes epigenetically regulated by ELA. These initial findings are promising; however, there remain a multitude of open questions to address and challenges to overcome in the future epigenetic investigation of SSBs.

Publication of this article was supported by the Centers for Disease Control and Prevention, the National Institutes of Health Office of Behavioral and Social Sciences, and the National Institutes of Health Office of Disease Prevention. This support was provided as part of the National Institute of Mental Health-staffed Research Prioritization Task Force of the National Action Alliance for Suicide Prevention.

The author is a Fonds de recherche du Québec - santé (FRQS) National Research Scholar and his epigenetic research is funded through the Canadian Institutes for Health Research, National Institute on Drug Abuse, FRQS, and the American Foundation for Suicide Prevention.

No financial disclosures were reported by the author of this paper.

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