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Stress, genetics and epigenetic effects on the neurobiology of suicidal behavior and depression

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Abstract

Alterations in a number of neurobiological systems have been associated with suicidal behavior including the serotonergic and noradrenergic systems and the hypothalamic-pituitary-adrenal axis. Altered functioning of these systems may stem from both genetic and developmental causes. Adversity in early-life has developmental consequences on these systems that persist into adulthood. Genetic differences may also contribute to alterations in functioning of neurobiological systems. Moreover, the interaction of early-life experiences of adversity and genetic vulnerability is increasing thought to play a role, including via epigenetic mechanisms.

STRESS RESPONSE AND SUICIDE IN MAJOR DEPRESSION

Decades of research have documented abnormalities in the hypothalamic adrenal (HPA) axis, and the noradrenergic and serotonergic systems in suicidal behavior and major depression. These three systems are also responsive to stress and raise the question as to how genes and childhood experience mold stress responses in the brain and thereby affect the risk of suicide in major depression.

In suicide and more lethal but nonfatal suicide attempts, serotonin system abnormalities include low levels of the serotonin metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid (CSF 5HIAA) and of serotonin and/or 5-HIAA in the brainstem serotonin nuclei, and altered serotonin receptor and transporter binding in postmortem brain of suicides [19]. These findings appear to be independent of psychiatric diagnosis and share a common feature of being related to suicide or nonfatal attempts. Metaanalysis of prospective studies, found that major depression characterized by below median levels of CSF 5-HIAA has 4.5 times higher odds ratio for suicide compared with major depression with CSF 5-HIAA in the above median group [16]. In non-fatal suicide attempt lower CSF 5-HIAA is associated with violent and/or higher lethality attempts [19]. CSF 5-HIAA is under genetic control such that about half the variance is heritable. It is lower after maternal deprivation in non-human primates with the low expressing promotor alleles of the serotonin transporter gene (5HTTLPR), and this effect persists into adulthood. It may contribute to more aggressive traits in man as they are related to low CSF 5-HIAA, and to recurrent major depression which is known to be characterized by a trait deficit in serotonin system function. Both aggressive traits and recurrent major depression are important psychopathologic risk factors for suicide and nonfatal suicide attempts.

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Postmortem studies of suicide indicate a localized reduction in serotonin transporter binding in the ventromedial prefrontal cortex and anterior cingulate [19]. This brain region is associated with willed action, decision-making, and mood. Abnormalities can increase the risk of impulsive, disinhibited behavior, favoring a higher risk for suicide. Impaired serotonin input to this brain region may underlie the impaired decision-making, that increases the risk for suicidal behavior. Impaired serotonin input to other brain regions like the dorsal lateral prefrontal cortex, subgenual prefrontal cortex and the amygdala may contribute to impaired mood regulation and major depression that can also increase the risk for suicidal behavior.

The causes of altered serotonin system function may be genetic, epigenetic, and/or related to childhood adversity. Some of these effects may be directly reflected in aspects of the observed abnormalities, but these abnormalities may also be due to the stress of acute psychiatric illness and contemplating suicide. For example, reports from animal studies suggest that the findings in suicide of more serotonin neurons may be due, in part, to maternal deprivation. Greater TPH2 gene expression and more TPH protein and mRNA per neuron may be a stress response, as has also been reported in animal stress models. These hypotheses remain to be tested. Less serotonin transporter mRNA and fewer binding sites in the serotonin raphe nuclei, and more 5-HT_{1A} inhibitory autoreceptors, are part of the serotonin system dysfunction but it is not clear if these changes are causal, responses to stress, or homeostatic responses to less serotonin release at nerve terminals [19]. *In vivo* imaging studies further identify serotonergic alteration in non-fatal attempts of high lethality for example, a correlation between lethality of suicide attempt and rCMRGlu in the anterior cingulate, right superior frontal, and right medial frontal gyri in response to fenfluramine (a serotonin agonist) challenge is indicative of prefrontal cortex hypofunction [21].

Abnormal stress response has been documented in both the HPA axis and noradrenergic system in suicidal behavior in the context of depression. Depressed suicides have fewer norepinephrine (NE) neurons in the locus ceruleus and, greater β -2 adrenergic cortical receptor binding, and lower α -adrenergic cortical binding have been reported [19]. Lower cerebrospinal fluid 3-methoxy-4-hydroxyphenylglycol (CSF MHPG), a metabolite of noradrenalin, predicted future suicide attempt in one year follow-up in individuals with major depression as well as the lethality of those attempts [10], although others don't observe any association [14]. Animal studies indicate that maternal deprivation can lead to an excessive stress response in adulthood as manifested by noradrenergic release. If there are fewer neurons then there is more likelihood that the norepinephrine will become depleted and in animal studies that is associated with giving up behavior. In clinical studies hopelessness predicts the risk for suicide and in our studies low CSF MHPG predicts the risk of suicide attempts and the greater the deficiency the more lethal the suicide attempts. What remains to be demonstrated is whether the stress leading up to the suicide attempt or suicide results in excessive norepinephrine release and depletion. That type of study would also seek a link between the development of excessive hopelessness and degree of norepinephrine depletion.

With respect to the HPA axis, postmortem studies of suicides have reported fewer corticotrophin releasing hormone (CRH) receptor binding sites in the prefrontal cortex and higher CSF CRH concentrations in major depression [19]. Hyperactivity of the HPA axis has been associated with suicidal behavior, evidenced by a failure to suppress cortisol secretion following the administration of dexamethasone (DST). Metaanalysis found a four-fold higher risk of suicide death in MDD characterized by non-suppression on the DST [17], however there is less consistency in DST findings with respect to non-fatal suicide attempt [18]. Consistent with dexamethasone resistance, some older studies reported that higher rates of corticosteroid excretion in urine predicted suicide. Other, not well replicated, isolated indices of HPA axis function in non-fatal suicide attempters provide additional evidence of abnormal function,

including lower CSF CRH but no difference in plasma CRH or plasma cortisol, higher urinary cortisol in violent attempters, and higher serum cortisol after 5-hydroxytryptophan administration [19].

Stress response systems and serotonergic system interaction

The HPA axis has bidirectional relationships with the serotonergic and noradrenergic systems further complicating the biological picture. With respect to the HPA axis, CRH neurons of the central amygdala project to the raphe nuclei [22], the principal serotonin source to the forebrain, and projections from the raphe nuclei extend to various brain regions that contain CRH and participate in the stress response [22]. HPA hyperactivity observed in suicidal patients may mediate or moderate some of the serotonin abnormalities observed in these patients, and corticosteroid modulation of serotonin receptors as a response to stress may have important implications for the pathophysiology of suicide [15].

The HPA axis also has a bidirectional relationship with the NE system. Stress activates not only the HPA axis but also the locus ceruleus the major source of NE neurons in the brain. This activation leads to increased NE release during stress. LC neurons influence the neuroendocrine stress response system through their broad innervation of the paraventricular nucleus projection pathways. Reciprocal interactions connecting cerebral NE and CRH systems may generate a “feed-forward” loop [9]. The NE overactivity and hyperactivity of the HPA axis observed in suicide and suicide attempt, may be a correlate of severe anxiety in response to stress. These interactions suggest multiple pathways through which stress may contribute to the biological anomalies observed in suicidal behavior, both directly through dysfunction of the HPA axis and the noradrenergic system and interactions between these two systems, as well as indirectly through downstream effects on serotonergic system function.

HERITABILITY AND FAMILIAL TRANSMISSION OF SUICIDAL BEHAVIOR

Family, twin, and adoption studies provide evidence of the heritability of suicide and attempted suicide, in part independent of the familial transmission of major psychiatric disorders, with estimates of heritability for suicide range between 21–50%, and 30–55% for a broader phenotype of suicidal behavior and ideation [30]. Transmission of suicidal behavior is likely to occur via the transmission of elements of the diathesis, and both its psychopathologic and biologic intermediate phenotypes that include altered stress responses and have their origins in genes and early-life experience.

Candidate Genes

Heritability of CSF 5-HIAA is estimated to be 25–50%, and a range of serotonergic system candidate genes have been investigated for association with suicidal behavior, and for functional effects on serotonergic system activity. Most studied is the serotonin transporter 5' functional promotor variant., serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} receptors, monoamine oxidase A (an enzyme responsible for the degradation of serotonin), and tryptophan hydroxylase 1 and 2 (TPH1, TPH2), the rate-limiting biosynthetic enzyme for serotonin, have been investigated in respect to suicidal behavior with suggestive but inconclusive results [25]. The most promising candidate to date is the serotonin transporter 5' promoter variant (5-HTTLPR), for which metaanalysis found an association between the low-expressing S allele and suicide [1] although its association with stress responsive depression has not been supported by another meta-analysis lately.

The identification of functional genetic variants is particularly compelling in terms of elucidating the causal pathways between genes and behavioral phenotypes via observed neurobiological alterations. Functional MR imaging studies in healthy adults, multiple studies

report that individuals with the lower expressing SS genotype show increased amygdala activity when exposed to angry or fearful faces, negative words, or aversive pictures [7]. The amygdala has a central role in encoding of emotional memories, emotional regulation and responses to stress, and is densely innervated by serotonergic neurons. It may encode the effects of childhood abuse experiences as more salient emotional memory in carriers of the lower expressing 5-HTTLPR alleles. This testable hypothesis remains an open question.

Another potential functional serotonergic system candidate gene is TPH2, where we have identified a novel TPH2 mRNA with truncated catalytic domain expressed in human brainstem [11]. This would result in the production of less serotonin, and initial findings show TPH2 SNPs related to this truncated transcript associated with major depression but not directly with suicide [11].

Stress response systems have been less studied with respect to candidate genes, with no consistent results in the noradrenergic system [8]. In the HPA axis, a promising candidate is the CRH receptor 1 gene, reported in a recent study to be associated with cortisol response to dexamethasone challenge [27], and which we have found associated with CSF CRH levels.

Early-life environmental stress

Adverse events in early-life, including reported sexual or physical abuse, neglect, parental loss, or severe family discord, have been associated with suicidal behavior [6]. One pathway via which early-life adversity increases risk for suicidal behavior later in life is through developmental alteration in neurobiological systems that have functional consequences in adulthood. These alterations in turn can increase vulnerability for the development of psychiatric disorders, increased stress sensitivity, and behavioral and personality traits such as impulsivity and aggression [6] later in life, all of which are associated with increased risk for suicidal acts.

Animal and human studies show that early-life adversity has lasting effects on serotonergic function in adulthood. Adult rats exposed to maternal separation in early life show evidence of autoreceptor super-sensitivity indicative of enduring alteration in the serotonin transporter and 5-HT_{1A} autoreceptors [2]. In humans, a history of childhood abuse has been associated with blunted prolactin response to serotonergic agonists and adult borderline personality women [23] and childhood adversity was associated with lower serotonin transporter binding in MDD and in maternally deprived monkeys in adulthood in PET studies [20].

There is also ample evidence that early-life adversity affects the stress response systems with lasting effects in adulthood. Evidence from both animal and human studies demonstrates lasting alterations in HPA axis associated with early life adversity animal [12]. Childhood abuse in humans or maternal deprivation in rodents results in excessive cortisol and ACTH release after a laboratory stressor, indicative of a pattern of stress systems including the noradrenergic system being sensitized by childhood adversity [12].

GENE*ENVIRONMENT INTERACTIONS

Animal studies show that early-life adversity interacts with genotype and that the resultant biological and behavioral alterations endure into adulthood [3,4]. In the serotonergic system, in monkeys for example, maternal separation early in childhood results in lower serotonin function in adulthood in animals with the low-expressing 5-HTTLPR S allele. In humans the 5-HTTLPR gene*early environment interaction has an effect on the vulnerability of individuals for the onset of depression in the face of stressful life events in adulthood [28], as well as risk for suicidal behavior in adulthood [24]. It is likely that such effects also occur with genes related to the other neurobiological systems involved in suicidal behavior, for example, a recent study

found an interaction effect between CRH Receptor 1 haplotype gene and early-life stress on the severity of depression [5].

EPIGENETICS

Epigenetic events alter expression for different copies of the same gene in a given cell nucleus. One such epigenetic mechanism is methylation, where transcriptional factors are blocked from gaining access to the gene, effectively silencing expression of the gene. This is a stable epigenetic modification that is maintained after cell division and is the means by which cellular differentiation occurs during development. Thus, discordance in disease in MZ twins may be in part due to differential methylation. DNA methylation is also a pathway whereby early-life adversity might produce enduring neurobiological alteration. Early-life environment has been shown to affect methylation, for example in rodents differences in maternal behavior (licking and grooming) result in differential methylation of the glucocorticoid region 1₇ in hippocampal tissues in adult offspring [29], and effect that mirrors the kinds of gene*early life environment developmental models observed in gene association studies.

SUMMARY

To understand the neurobiological etiology of suicidal behavior and major depression it is necessary to consider both genetic and non-genetic effects. There is considerable evidence that there are complex interactions between genes, environment, that increase risk or protect against the neurobiological alterations that are observed in major depression and in the diathesis for suicidal behavior. Technologies and methods for studying genetics and epigenetics are evolving quickly and an integrated approach that includes whole-genome, candidate gene, epigenetic, approaches along with an examination of early-life environment will yield new insights.

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