Polyamines and suicide risk

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Suicidality refers to complex and diverse phenotypes that comprise presence of suicidal ideation, as well as varied self-injurious behaviors, including suicide attempts and completions. Although suicidality is a broad term that implies heterogeneous clinical presentations, which vary, among other things, in underlying psychopathology, suicide intent, as well as in content and character of suicidal ideation, presence of suicidality commonly elicits considerable concern given its potential lethal outcome. Assessment of suicide risk, however, is challenging. It is impossible to definitely predict suicide outcome and most studies suggest that both the sensitivity and specificity of suicide risk assessments, when taken at face value, are low¹. In addition, all assessments of suicide risk are conditional on the information communicated by the patient. While studies suggest that most individuals who commit suicide contact health care professionals prior to their death, most cases do not communicate their suicide intent². Therefore, as in other areas of psychiatric research, there has been growing interest in the study of biomarkers to better understand and predict suicidality, both illness-related suicidality, as well as treatment-associated suicidal events. Among different types of biomarkers, the investigation of the transcriptome offers particular advantages. Downstream effects of different predictors and correlates of suicidality – genetic and/or environmental – are mediated by changes in gene function. Granted the limitations of using peripheral tissue to infer central nervous system processes, investigating differential gene expression patterns associated with suicidality is a promising avenue to identify potential biomarkers of suicidality and obtain valuable information for new potential avenues of intervention.

In this issue of *Molecular Psychiatry*, Le-Niculescu and colleagues report on a study investigating blood mRNA biomarkers of suicidality³. To identify biomarkers, the authors used a combination of different designs and approaches. After using a prioritization process they dubbed Convergent Functional Genomics, the most significant differentially expressed gene associated with development of suicidality was spermidine/spermine N1-acetyltransferase 1 (SAT1). Investigation of SAT1 blood levels in a follow up sample suggested that high expression levels of this gene significantly predicted past and future hospitalizations associated with suicidality.

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Polyamines

SAT 1 is a rate-limiting enzyme in the catabolism of polyamines, which are ubiquitous aliphatic molecules containing two or more amine (NH₂) groups (Figure 1). Representative polyamines comprise putrescine, spermidine, spermine, as well as agmatine, whose presence in mammalian brains was discovered more recently than the other polyamines⁴. They have a multitude of functions including regulation of gene transcription and posttranscriptional modifications, as well as modulation of several protein activities. The concentrations of polyamines in the brain are in the nanomolar range, and while agmatine has been shown to cross the blood brain barrier, putrescine, spermidine and spermine must be synthesized endogenously in the brain. Polyamines influence neurotransmitter systems, including catecholamines, glutamate, GABA, nitric oxide, and agmatine itself is believed to act as a neurotransmitter⁴. Polyamines also interact with several transmembrane channels and can thus influence the properties of excitable cells⁴.

Polyamine Dysfunction in Depression and Suicide

Altered functioning of the polyamine system has been identified in animal models of depression and stress⁴, and studies from my laboratory indicated alterations in the mRNA and protein levels of several components of the polyamine system in cortical and subcortical brain regions of suicide completers, and other labs reported changes in peripheral samples from suicide attempters (reviewed in Gross⁵). Postmortem studies have consistently indicated a downregulation of SAT1 expression, and direct quantification of spermidine and putrescine by capillary gas chromatography in combination with mass spectrometry (GC-MS) indicated increased concentrations of these polyamines in cortical brain tissue. Given the antidepressive properties of polyamines (see below), these findings have been interpreted as suggesting that low SAT1 brain levels were a compensatory mechanisms whereby the brain was upregulating polyamine levels as a response to a depressive state. The findings reported by Le-Niculescu et al³ suggest an association of suicidality with increased SAT1 peripheral levels. While these findings are in the opposite direction from those observed in CNS studies, they may not necessarily be at odds. Studies with other putative biomarkers of depression and suicidal behavior, for instance brain derived neurotrophic factor (BDNF), suggest that the directionality of the association is brain region/tissue specific⁶.

Stress Response

The hypothalamic-pituitary-adrenocortical (HPA) axis system is the best characterized stress response system in humans, and has long been implicated in psychiatric disorders. There is strong evidence linking overactivity of the HPA axis to suicidal behaviors, and recent studies have shown that environmental influences also play an important role in regulating HPA axis activity through epigenetic mechanisms⁷. Like the HPA, polyamines are also a stress-response system, and their implication in depression and suicide may be best understood in this context. Accordingly, polyamines play an important role in cellular and behavioural responses to physical, emotional, and hormonal stressors⁸, whereby dysregulated function of the polyamine stress response (PSR) has been implicated in the detrimental effects of stress and anxiety⁸. Activation of the PSR results in elevated levels of putrescine and agmatine in

both the brain and peripheral tissues. The magnitude of the PSR is related to the intensity of the stressor, and is correlated with levels of behavioural and physiological responsiveness under stressful conditions⁸. The PSR can be pharmacologically manipulated, such that it can be diminished or prevented by pre-treatment with anxiolytic compounds⁹, and by chronic – but not acute – treatment with lithium¹⁰. Interestingly, a recent study investigating lymphoblastoid cell lines from bipolar patients who died by suicide (cell lines collected prior to their death) indicated that their polyamine system was less responsive to lithium treatment than those from living non-suicidal bipolar patients or controls¹¹. Finally, there is strong evidence for the beneficial effects of elevated agmatine and putrescine levels in the brain, as numerous animal studies have shown that these compounds display both anxiolytic and antidepressant effects; whereas polyamine depletion can produce altered emotional reactivity and anxiety-like behaviours (reviewed in⁴).

There is also strong evidence for a relationship between the HPA axis and the polyamine system. In rodents, the emergence of the characteristic adult PSR is correlated with the cessation of the hyporesponsive period of the HPA axis, and the relationship between these two systems is evident first in the ability of glucocorticoids to induce the PSR, and second in findings which show that polyamine depletion reduces plasma corticosteroid and aldosterone concentrations¹². Given the relationship between polyamines and HPA axis function, it is of interest to note, particularly in the context of the growing evidence suggesting epigenetic regulation of HPA activity by early-life events, that polyamine metabolism influences epigenetic modifications¹³. In addition, there is growing evidence that epigenetic processes also regulate gene coding for components of the polyamine system⁵.

In summary, there is compelling evidence suggesting a relationship between polyamines, mood regulation and suicidality. The comprehensive biomarker study reported by Le-Niculescu et al³ in this issue provides additional support to a growing literature indicating that SAT1 levels associate with depressive states and suicidality. While it is premature to consider the integration of such knowledge into clinical practice, these findings suggest that blood SAT1 levels should be considered as potential biomarkers of suicidality in psychiatric patients. Future studies should elucidate the relationship between peripheral and central polyamine measures, as well as the potential nature of this relationship. In addition, the impact of current treatment options on peripheral SAT1 levels, as well as their prediction of treatment response should be investigated.

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Figure 1. Abbreviated polyamine synthesis pathway. SAT1, spermidine/spermine N1-acetyltransferase; AGMAT, agmatinase; ODC, ornithine decarboxylase; SRM, spermidine synthase; SMS, spermine synthase; PAO, polyamine oxidase.