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Suicide and the Polyamine System

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Abstract

Suicide is a significant worldwide public health problem. Understanding the neurobiology is important as it can help us to better elucidate underlying etiological factors and provide opportunities for intervention. In recent years, many lines of research have suggested that the polyamine system may be dysregulated in suicidal behaviors. Initial research in animals provided evidence of a dysfunctional polyamine stress response system, while later work using post-mortem human brain tissue has suggested that molecular mechanisms may be at play in the suicide brain. In this review, we will describe the research that suggests the presence of alterations in the polyamine system in mental disorders and behavioral phenotypes, with particular attention to work on suicide. In addition, we will also describe potential avenues for future work.

Keywords

Epigenetics; Major Depressive Disorder; Neurobiology; Polyamines; Polyamine Stress Response; Spermidine/Spermine-N^1-Acetyltransferase; Suicide

1 – Introduction

Suicide, most often associated with major depressive disorder (MDD) [1], is an important cause of premature death around the world [2]. According to the World Health Organization (www.who.int, 2012), approximately one million people die by suicide annually, and the rate of suicide attempts is 20 times greater than that of suicide completion (www.who.int, 2012). As such, suicidal behaviors (SB) are an important source of public health concern. The etiology of suicide is complex [3], and commonly understood as resulting from the interaction of predisposing (distal) and precipitant (proximal) factors [4]. Biological alterations resulting from a combination of genetic and environmental risk factors underlie predisposition to suicide, but the exact molecular mechanisms at play remain largely unclear. As such, it is important that we gain a better understanding of the molecular processes associated with suicide in order to identify new avenues for prevention and intervention.

Over the past several decades, molecular studies of suicide and MDD have focused on the monoamine system. Beginning in the late 1960s, research into the neurobiology of suicide

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was focused primarily on 5-hydroxyindoleacetic acid, the main metabolite of serotonin and noradrenaline [3]. Over the next decades, dopamine, serotonin, norepinephrine, and other monoamine neurotransmitters and associated receptors were investigated in the neurobiology of suicide and SB. Although important, alterations in this system account for only part of the neurobiological changes associated with MDD and suicide [3].

More recently, there has been growing evidence to support the involvement of a polyamine-mediated stress-response signaling system in the neurobiology of suicide. This evidence includes findings of altered polyamine levels and altered expression of polyamine genes in cortical brain areas of suicide completers [5,6], which are associated with sequence variation and environmental influences on polyaminergic genes [7,8]. In this review, we aim to describe the putative function of polyamines in the neurobiology of suicide and propose avenues for future research.

2 – Polyamines

2.1 – Biosynthesis

Polyamines are ubiquitous aliphatic molecules containing two, three, and four amine groups. These include agmatine, putrescine, spermine, and spermidine; each of which is incorporated into a highly regulated signaling pathway (fig. 1). The major rate-limiting enzymes of this pathway are ornithine decarboxylase (ODC), spermidine/spermine N^1-acetyl transferase (SAT1), and S-adenosylmethionine decarboxylase (AMD1), whose activities are influenced by numerous regulatory proteins as well as the polyamine levels [9]. In addition, not only are polyamines known to influence neurotransmitter systems, such as catecholamines [10,11], gamma-aminobutyric acid (GABA) [12], glutamate [13], and nitric oxide [14], but agmatine is also believed to act as a neurotransmitter [15]. Finally, polyamines are also able to influence the properties of several transmembrane channels, thereby affecting cell excitability [16].

Within the central nervous system (CNS), synthesis and storage occurs both in neuronal and non-neuronal cell types depending on the polyamine. For instance, it is believed that spermine and spermidine are stored in astrocytes and synthesized in neurons. These findings originated from the discovery that ODC, a rate-limiting enzyme responsible for the conversion of ornithine to putrescine, is absent in astrocytes [17]. Recently, however, it has been shown that putrescine may be derived through an alternative pathway that includes agmatine, a compound that is mainly synthesized in glia cells [9] but predominantly found in neurons [18]. This, and the identification of the neuronal localization of spermine synthase and spermidine synthase, provided more concrete evidence of the location of these polyamines.

2.2 – Role of Polyamines in CNS

Due to their limited capacity to cross the blood-brain barrier [19], concentrations of polyamines in the brain are generally in the nanomolar range [20]. In fact, only agmatine and arginine are able to cross the blood-brain barrier [21]. Systemic injection of agmatine has been shown to substantially increase cortical agmatine concentration in rats [22], even

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though other studies suggest that 99% of the injected agmatine is rapidly metabolized by peripheral tissues [23]. This is interesting as agmatine is believed to function as a CNS neurotransmitter by binding to NMDA receptors [24], as well as acetylcholine, imidazoline, and serotonin receptors [15]. Furthermore, agmatine has been shown to have antidepressant, anxiolytic, anticonvulsant, anti-inflammatory, and neuro-protective properties [25,26,27]. In light of these functions, although much of the agmatine is rapidly degraded, it is possible that systemic injections of agmatine induce endogenous release of this neurotransmitter such that it can exert all of its effects.

Similar to agmatine, putrescine has also been shown to possess antidepressant properties. Hippocampal levels of putrescine, spermidine, and spermine were shown to be significantly decreased in a rat model of depression, while only putrescine levels were reduced in the nucleus accumbens. Administration of S-adenosyl methionine (SAM) successfully restored the levels of putrescine in the nucleus accumbens, while only slightly increasing spermidine and spermine levels in the hippocampus [28]. In a more direct study, it was shown that systemic and central injections of putrescine reduced immobility times in the forced swimming and tail suspension tests, both of which are well-established paradigms for determining antidepressant-like properties. Further, the efficacy of putrescine was comparable to imipramine, a widely available tricyclic anti-depressant [29]. Finally, the antidepressant-like effects of putrescine were attenuated by arcaine, an antagonist of the NMDA receptor polyamine-binding site. Similar results were observed when putrescine was co-administered with agmatine, a more selective antagonist of the NMDA polyamine-binding site [24]. Together, these findings suggest that putrescine's antidepressant-like effects may be achieved through the inhibition of NMDA receptors.

2.3 – Function of Rate-Limiting Enzymes of Polyamine Biosynthesis

Although not known for its antidepressant or anxiolytic functions, SAT1 has recently been linked to depression and suicide. SAT1 is the rate-limiting enzyme of polyamine catabolism and is responsible for the conversion of spermine to acetyl-spermine and spermidine to acetyl-spermidine. Gene expression studies have shown that a downregulation of SAT1 across multiple brain areas of depressed suicide completers [6,30] is partly associated with genetic variation in the promoter [6,7]. Moreover, a polymorphism in the promoter region was also associated with suicide completion [31]. Not only have these findings been replicated in independent samples [32], but a downregulation of SAT1 gene expression was also observed in monkeys exposed to adult social stress paradigms [33]. This is of importance as exposure to social stress has been shown to lead to depressive-like behaviors in monkey [34]. Although SAT1 has been consistently linked to mood disorders and stress, questions remain regarding the biological mechanisms underlying these effects and the extent to which gene regulatory processes account for this dysregulation.

Unlike polyamine catabolism, the biosynthesis pathway contains two rate-limiting enzymes, both of which have short turnover times in mammalian tissues [9]. ODC is an enzyme that is highly influenced by the ODC antizyme (OAZ) and antizyme inhibitor. Binding of OAZ to ODC disrupts homodimeric ODC and targets it for degradation by the 26S proteasome [35]. Not only do high intracellular polyamine concentrations promote OAZ synthesis, but they

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also inhibit ubiquitin-mediated OAZ degradation [36]. Another important enzyme in the biosynthesis pathway is AMD1. It is responsible for synthesizing decarboxylated SAM, which is a necessary substrate for the conversion of putrescine to spermidine and spermidine to spermine. Once decarboxylated, SAM is irreversibly committed to the polyamine synthesis pathway. SAM has been recently implicated in MDD as it has been suggested for use as a monotherapy or as an adjunctive treatment for individuals with MDD that do not respond to traditional antidepressant therapies [37]. It is proposed that the antidepressant effect of SAM is mediated by monoamines, as it is a precursor molecule for dopamine, norepinephrine, and serotonin. [38]. Interestingly, however, it is also possible that SAM exerts its antidepressant function by normalizing putrescine, spermine, and spermine levels in the brain [28].

2.4 – Putative Mechanisms of Action of Polyamines

As discussed above, there is substantial evidence suggesting that polyamines and their related enzymes may play a role in mood disorders (Table 1). Their exact mechanisms of action, however, have yet to be elucidated, although putative mechanisms have been explored. Polyamines have been shown to regulate ion fluxes by binding to NMDA, GABA, and nicotinic receptors. They also bind to ion channels, such as potassium and calcium channels, both on the cell membrane and on certain intracellular organelles [16]. Intracellularly, changes in polyamine levels have been associated with the initiation of deoxyribonucleic acid (DNA) synthesis and with the kinetics of the DNA replication fork [9]. In addition, spermine and spermidine stabilize the DNA by forming complexes that neutralize negatively-charged phosphate groups [9]. By these mechanisms, they may also be involved in regulating gene transcription, translation, and degradation.

The association between suicide, polyamines, and NMDA receptors is highly intriguing. It has been well established that NMDA receptors are involved in synaptic transmission and plasticity in the CNS [16]. The existence of a natural polyamine-binding site on these receptors [16] lends to the notion that the polyamine system may be involved in the neurobiology of SB by altering synaptic transmission. The binding of polyamines to NMDA receptors prevents the release of magnesium from the channel, which in turn inhibits glutamate transmission. Alternatively, polyamines have been shown to also block both inward-rectifying potassium channels and calcium-permeable AMPA receptors [16]. As such, a decrease in calcium transmission may inhibit proper depolarization of the cell and, consequently, prevent the removal of the magnesium blockade of the NMDA receptor. Certainly, further investigation will be necessary in determining the exact effect of polyamines on synaptic transmission. Nevertheless, it is clear that alterations of the polyamine-glutamatergic system play a role in the complex nature of the suicide brain.

2.5 – Polyamines and mood disorders

Studies using psychological autopsies have confirmed that suicide has a high comorbidity with mood and personality disorders [39,40,41]. In particular, although most people who suffer from MDD do not commit suicide, research suggests that greater than 60% of suicide completers have a history of MDD [39]. This association is of great importance as it lends to the idea that a psychiatric disorder is a necessary predisposing factor to suicide completion,

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although it may not be sufficient to commit such an act. Interestingly, SAT1 gene expression has been shown to be altered in suicide completers with a history of MDD and has also been demonstrated in stressed monkeys displaying depressive-like behaviors.

In addition to MDD, polyamines have also been implicated in schizophrenia, a disorder that is comorbid with suicide. In fact, a multitude of polyamines are increased in the blood and fibroblasts of schizophrenic patients (summarized in [38]). It appears, however, that increases in polyamine levels in these populations may be caused by neuroleptic treatment [42]. Furthermore, attempts to replicate these findings in postmortem brain tissue have been largely unsuccessful [43]. Although past research may suggest that peripheral polyamine levels are implicated in schizophrenia, significant work is required, both in blood and in brain, to determine the actual role of polyamines in this disorder.

3 – Polyamines and Suicide

3.1 – Polyamine Stress Response

The role of polyamines in MDD and suicide may best be understood in the context of their role in the polyamine stress response (PSR) system. This idea was initially proposed in the mid-1980s, but it was more broadly accepted in the early 1990s when research showed that stressful stimuli rapidly elicited changes in polyamine metabolism [44]. Following physical, emotional, or hormonal stressors, a cascade of second messenger systems activates the PSR. In the CNS, this cascade can be induced independent of the hypothalamic-pituitary axis (HPA) or by the neural circuitry itself, whereas in the periphery, PSR activation relies solely on activation of the HPA axis. Regardless of location, the traditional PSR involves prompt, transient increases in polyamine metabolism.

Initial research suggested that the PSR's adaptive neuronal mechanisms differ based on the intensity and duration of the stressor [45]. Following acute stress, a seemingly incomplete PSR led to transient increases in ODC and putrescine, while spermidine and spermine levels remained unchanged. This likely occurred as a result of the tightly regulated homeostatic mechanisms that balanced polyamine metabolism with its SAT1-induced catabolic activity. On the contrary, persistent changes in polyamine levels caused by extreme or chronic stressors induced longer-lasting increases in ODC and putrescine. Levels of spermidine and spermine remain unchanged following a single stressful event but gradually increase after repetitive stimuli. Based on these initial findings, it is suggested that not only is putrescine playing a protective role in the CNS, but also the dynamic nature of the PSR is essential in effectively coping with both acute and chronic stressors. Follow-up research into the PSR system primarily used dexamethasone, a synthetic glucocorticosteroid, to induce stressful stimuli in rats. In the brain, stress-induced increases in ODC were inhibited if lithium was given at least 7 days prior to dexamethasone challenge. Similarly, the increases in AMD1 and SAT1 following dexamethasone injection were also prevented by the chronic lithium treatments [46]. Of the polyamines, only the levels of putrescine were attenuated with chronic lithium treatments following dexamethasone challenge, while levels of spermidine and spermine were not significantly altered [47]. Lithium treatment alone, given for 2 weeks, caused major increases in putrescine and minor increases in spermidine and spermine. Interestingly, without a stressor, chronic lithium treatment had no effect on levels

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of ODC. These studies suggest that lithium treatment may exert its effect by increasing SAT1 expression, thereby increasing polyamine turnover through the SAT1-mediated catabolic pathway rather than an ODC-mediated metabolic pathway.

Repeated stressful events are associated with an increase in the risk of negative mental health outcomes, including depression and suicide. The PSR appears to be an important component in the appropriate response mechanisms. In the brain, the same stress-induced changes in putrescine and ODC are seen after each stressful stimulus, whereas the response to chronic stress of AMD1, spermidine, and spermine are adaptive. Research has shown that long-term lithium treatment could block the PSR when given either prior to or after the application of stressful stimuli. Thus, by imposing an effect on SAT1-mediated polyamine catabolism, lithium may exert its role by taming a hypersensitive PSR.

As has been shown above, a significant interaction exists between stress, polyamines, and glucocorticoids. As such, it is no surprise that polyamines also regulate glucocorticoid receptor (GR) activity. Along with NF-E2-related factor 2, polyamine-modulated factor 1 (PMF-1) has been shown to regulate not only SAT1 expression [48], but also GR activity. It is suggested that PMF-1 binds directly to GR and negatively influences its activity [49]. As such, one can hypothesized that, in addition to its role in reducing the PSR, stress-induced increases in SAT1 may also lead the repressive effects PMF-1 on GR. This link is interesting as decreases in GR gene expression have been associated with suicide completers who suffered childhood abuse [50]. Although, levels of DNA methylation in the promoter of GR have been correlated to these gene expression results [50,51], we should not discount the potential influence of polyamines. Certainly further investigation will be necessary to elucidate the role of PMF-1 on GR expression in suicide completers.

3.3 – Polyamine Gene Expression

The link between polyamine metabolism and suicidal behaviors has gained significant support in recent years, largely sparked by results of a gene expression study identifying downregulated expression of SAT1 across brain regions of suicide completers [6]. As this gene represents one of the main rate-limiting enzymes in polyamine metabolism, these changes in gene expression were theorized to lead to disruptions in polyamine homeostasis. Follow-up studies have indicated that functional genetic variants in the SAT1 promoter region are partially responsible for the observed variation in gene expression [6,7]. Moreover, certain polymorphisms in the promoter region were also associated with suicide in individuals with MDD [31], and DNA methylation had a significant negative effect on SAT1 expression in the brain [8]. Most recently, the SAT1 promoter single nucleotide polymorphism (SNP) rs6526342 originally reported in suicide completers [6,7] was also linked to suicide attempters [52]. In addition to SAT1, other genes active during polyamine catabolism were also investigated. Gene expression levels of SAT2, an acetyltransferase that shares identity and homology with SAT1 [53], and ornithine aminotransferase-like 1, involved in the production of ornithine, were both found to be increased in the hippocampus of suicide completers [54]. In addition, the expression levels of spermine oxidase (SMOX) and spermine synthase (SMS), enzymes responsible, respectively, for the breakdown and

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synthesis of spermine, were altered in suicide completers. Neither SNPs nor epigenetic modifications were responsible for these changes [55].

Further investigation of the polyamine system showed upregulation of additional polyamine-related genes, including OAZ1, OAZ2, ARG2, and AMD1, in suicide completers with a history of mood disorders [5]. Our group reported an increase in histone H3 trimethylation at lysine 4 (H3K4me3), a marker of open chromatin, in the promoter of OAZ1, and this increase was significantly correlated with the expression of the OAZ1 gene [56]. In addition, we assessed the levels of DNA methylation in the promoter of these four genes and found significant site-specific decreases in ARG2 and AMD1 in suicide completers, which also negatively correlated with their expression levels (unpublished data).

3.4 – Protein Levels of Polyamines

To gain a more complete profile of the relationship between polyamines and suicide, it was essential to investigate not only the gene expression levels of enzymes in the synthesis and degradation pathways, but also the levels of their common substrates and products. While differences in gene expression provide consistent evidence suggesting polyamine system dysregulation in suicide, research has also identified downstream effects of these differences. The analysis of diverse polyamines in postmortem brain tissue was achieved through a series of high-resolution gas chromatography-mass spectrometry (GC-MS) based analytic methods. This technique was specifically developed for the extraction and quantification of spermine, spermidine, putrescine, and agmatine from postmortem brain [57,58,59]. Using GC-MS, it was shown that putrescine and spermidine levels were significantly elevated in the brains of depressed suicide completers [60], thus lending further support to the idea that decreases in SAT1 expression in depressed suicide completers are likely the result of a feedback regulation.

Overall, the findings discussed above (summarized in Table 2) provide complementary evidence linking polyamines to MDD and suicide. Dysregulation of SAT1 gene expression has been the most widespread and consistent result. In addition, other rate-limiting enzymes also show dysregulated gene expression patterns, and differences in protein levels of the polyamines themselves exist as well. It is therefore conceivable that changes to this biosynthetic pathway may be linked to a hypersensitive PSR in individuals with MDD and suicidal behaviors. More specifically, decreases in SAT1 gene expression may act as a compensatory mechanism to counter the increases in putrescine caused by an improper PSR. As such, the changes observed in other higher order polyamines and polyamine-related precursor molecules would therefore occur as a direct result of this compensatory decrease in SAT1 gene expression.

It is important to also note that the polyamine biosynthetic pathway is linked not only to GABA/glutamate neurotransmission, but also to the tricarboxylic acid cycle and to nitric oxide metabolism, each of which have been associated to MDD and suicide. It is therefore possible that alterations in these systems may represent the upstream activators of a hypersensitive PSR, which, in turn, lead to dysregulated polyamine metabolism. Indeed, it remains crucial that we continue to investigate each of these links in order to elucidate and better understand the neurobiology of suicide and MDD.

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4 – Future methods to study the effect of polyamines in suicide

4.1 – Next-Generation Sequencing and Epigenetics

Much of the work linking polyamines to suicidal behavior and major depressive disorder has used recent, but relatively low-throughput technologies. For the most part, the research has relied on real-time polymerase chain reaction, gene expression microarrays, and Sanger sequencing to achieve this success. With the advent of next generation sequencing technologies, the ability to accurately sequence samples of interest will soon become standard protocol. In recent years, a significant effort has been placed on reducing costs, increasing accuracy, and achieving higher throughput. Currently, these sequencing technologies are being employed in conjunction with earlier methods, such as DNA and chromatin immunoprecipitation, bisulfite treatment, RNA analyses, etc., which has greatly increased our genetic understanding of diseases and disorders.

As we delve deeper into characterizing the polyamine system and its association with suicide completion, it is evident that we must use sequencing technologies to study the epigenome. To date, epigenetic modifications, such as DNA methylation and post-transalational histone modifications have been suggested in some psychiatric phenotypes, including schizophrenia, bipolar disorder, and suicide [61,62,63]. Of particular interest is DNA methylation, a process in which cystosine nucleotides are methylated with the aid of DNA methyltransferases (DNMTs). DNA methylation does not affect base-pairing, therefore this mark can regulate gene expression without changes to the underlying DNA sequence [64]. The primary function of this mark is the silencing of gene promoters by preventing the binding of transcription factors [65]. Recent literature also suggests an activating role for DNA methylation in gene bodies [66]. Since DNA methylation is maintained through cell division [64], it has become the most well-studied epigentic mark, as it has the potential to be a diagnostic tool or a therapeutic target.

Since its discovery, DNA methylation has often been referred to as the *5th DNA base* [67]. Recently, it was discovered that methylated cytosines are converted to 5-hydroxymethylated cytosines (hmC) by the enzyme ten-eleven translocation 1 (TET1) [68]. This finding, along with that of Kriaucionis and Heintz who described the presence of hmC in purkinje neurons [69], stimulated growing interest of research describing the genomic location, the abundance in different tissues, and the putative functions of hydroxymethylation. Even though the vast majority of this research has described hmC in embryonic stem cells, there are a handful of studies on this mark in the brain. Quantifying hmC levels in multiple human tissues, Li and Liu showed that these levels are highest in the brain [70]. Furthermore, Jin and colleagues showed that hmC levels in gene bodies correlate positively with gene expression, whereas there was no correlation when comparing hmC levels at promoters with high CpG content [71]. hmC may indeed act as an epigenetic mark since the conversion of methylcytosine to hmC relies on oxoglutarate and oxygen. As such, it is conceivable that this enzymatic process is highly sensitive to the environment [72], and therefore it is an excellent target for future studies that aim to uncover underlying neurobiological alterations in suicide and MDD.

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4.2 – Polyamines of Interest

As we aim to characterize the epigenetic landscapes of the polyamine system through next-generation sequencing technologies, it will be important to expand our search to include genes both related to polyamine biosynthesis and to those associated with arginine and proline metabolism. Given the intricacy and direct links from one system to another, the inclusion of molecules that are fed into the polyamine biosynthetic pathway may provide answers as to how a tightly regulated system can be altered in SB.

The most consistent findings implicating polyamines and suicide have been those related to the downregulation of SAT1 gene expression. Although the preliminary epigenetic research performed to understand the underlying regulatory mechanisms explaining SAT1 and polyamine dysregulation has yet to produce robust results, it is likely that the progressive adoption of high-throughput and high-resolution sequencing technologies will provide more conclusive information.

In addition to SAT1, it will be interesting to investigate the link between SB and arginine, agmatine, and putrescine. These three molecules should be a particular focus as they represent potential biomarkers. Agmatine and putrescine possess anti-depressant properties, and both arginine and agmatine can cross the blood brain barrier. Altering the peripheral circulation levels of arginine and agmatine may lead to changes in the CNS, either directly or by eliciting endogenous release. As such, these polyamines may prove to be potential targets for pharmacological therapies. We must acknowledge, however, that polyamines are ubiquitous molecules involved in a large variety of cellular functions. Therefore, being able to target a specific biomarker will be a daunting task. Nevertheless, this should not stop us from investigating possible solutions, as the potential for therapeutic targets is invaluable.

Concluding statement

Traditionally, the polyamine system has been known for its crucial role in many cellular functions such as growth, proliferation, and division. Over the last 2 decades, it has become clear that, whether it is the polyamines, their enzymes or their related compounds, this system is important in stress-response, and it is likely involved in the neurobiology of MDD and suicide. With alterations in the polyamine system observed in genomic, proteomic, and clinical studies, its role in depression and SB cannot be overlooked. Undoubtedly, significant progress has been made in this field of research. Nevertheless, it is essential that we continue to better understand and characterize previous findings and explore underlying mechanisms that may be etiologically associated with these alterations.

Abbreviations

ARG2	Arginase 2
CNS	Central nervous system
DNA	Deoxyribonucleic acid
DNMT	DNA methylytransferase

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GABA	Gamma-aminobutyric acid
GC-MS	Gas chromatography-mass spectrometry
GR	Glucocorticoid receptor
hmC	5-hydroxymethylcytosine
HPA	Hypothalamic-pituitary axis
MDD	Major depressive disorder
NMDA	N-methyl-D-aspartate
ODC	Ornithine decarboxylase
OAZ	Ornithine decarboxylase antizyme
PMF-1	Polyamine-modulated factor 1
PSR	Polyamine stress response
SAM	S-adenosylmethionine
AMD1	S-adenosylmethionine decarboxylase
SNP	Single nucleotide polymorphism
SAT1	Spermidine/spermine-N^1-acetyltransferase
SB	Suicidal behavior

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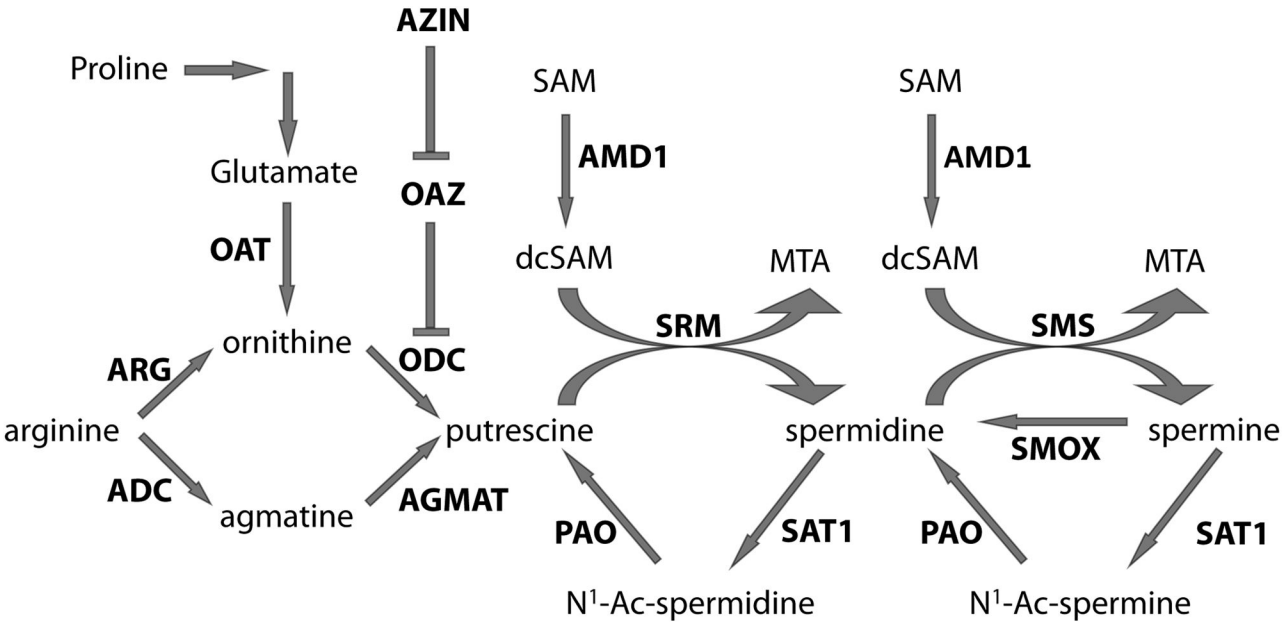

Figure 1. Polyamine biosynthesis pathway

Enzymes in bold. Abbreviations are as follows:

ARG = Arginase; ADC = arginine decarboxylase; OAT = ornithine aminotransferase; AZIN = Ornithine decarboxylase antizyme inhibitor; OAZ = Ornithine decarboxylase antizyme; ODC = Ornithine decarboxylase; AGMAT = agmatinase; SAM = S-adenosylmethionine; AMD1 = S-adenosylmethionine decarboxylase; dcSAM = decarboxylated S-adenosylmethionine; PAO = polyamine oxidase; SRM = spermidine synthase; MTA = 5′ methylthioadenosine; SAT1 = Spermidine/spermine N1 acetyltransferase; SMS = spermine synthase; SMOX = spermine oxidase

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Table 1

Polyamine alterations in stress, anxiety, and mood disorders

Study	Major Finding
Genedani *et al.* 2001	Administration of SAM restores polyamine levels in animal model of depression
Gilad and Gilad 2003	Review on polyamine stress response (PSR) -- stress-related alterations of polyamines in rat models
Zomkowski *et al.* 2006	Systemic injections of putrescine in mice produces antidepressant-like behaviours
Gong *et al.* 2006	Agmatine displays anxiolytic effects in rats and mice
Karssen *et al.* 2007	Decreased SSAT gene expression in monkeys exposed to adult social stress
Fiori and Turecki 2008	Review on polyamines in mental disorders -- extensive list of polyamine-related findings in human and animal models of mental disorders
Taksande *et al.* 2009	Antidepressant-like effects of SSRIs may be mediated by agmatine
Papakostas *et al.* 2010	SAM used as both a monotherapy and adjunctive treatment of MDD in humans
Sokolowski *et al.* 2012	Association between suicide attempts and polyaminergic genetic variants, namely the SAT1 promoter SNP (rs6526342) and SNPs in ODC

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Table 2

Polyamine alterations in suicide completers

Study	Major Finding
Sequeira *et al.* 2006	SAT1 downregulation in BA4, 8/9, 11 of depressed suicides relative to controls (French-Canadian males) Association between a SAT1 promoter SNP (rs6526342) and suicide completion
Sequeira *et al.* 2007	SAT2 and OATL1 upregulation in hippocampus of suicide completers without MDD SMS upregulation in hippocampus of suicide completers, regardless of MDD diagnosis
Guipponi *et al.* 2008	SAT1 downregulation in ventral prefrontal cortex of suicide completers, irrespective of psychiatric pathology (independent sample)
Klempan *et al.* 2009	SAT1 downregulation in across multiple brain regions (BA4, 11, 20, 21, 44) of depressed suicides relative to controls (French-Canadian males) Additional replication of findings in BA 11 and 17 of independent sample (German origin)
Fiori *et al.* 2009	Decreased SAT1 expression associated with haplotype containing the risk allele for rs6526342
Fiori *et al.* 2010	Increased frequency of a 15 adenine deletion in suicide completers with low expression haplotype
Chen *et al.* 2010	Increased protein levels of putrescine and spermidine in post-mortem brain tissue of suicide completers
Fiori *et al.* 2010	Decreased gene expression of SMOX and increased gene expression of SMS Neither the selected SNPs nor epigenetic modifications were correlated with these changes in gene expression
Fiori *et al.* 2011	CpG methylation is negatively correlated with decreases SAT1 expression High levels of methylation at the polymorphic CpG site described in Sequeira *et al.* 2006
Fiori *et al.* 2011	Global gene expression profiling identified 14 additional polyamine genes with altered expression levels
Fiori *et al.* 2011	Increased levels of H3K4me3 in the promoter of OAZ1 in suicide completers is correlated with OAZ1 gene expression
Gross *et al.* (unpublished)	Site-specific decreases in CpG methylation in ARG2 and AMD1 are correlated with increases in their gene expression levels
Chen *et al.* (unpublished)	Decreased protein levels of agmatine in post-mortem brain tissue of suicide completers
Squassina *et al.* (unpublished)	Increased SSAT gene expression in lithium-treated cell lines from healthy controls but not in suicide completers with history of bipolar disorder

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