

Implication of the polyamine system in mental disorders

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The polyamine pathway has an essential role in many cellular functions and has been implicated in several pathological conditions. Accumulating evidence suggests that the polyamine system also plays a role in the etiology and pathology of mental disorders. Alterations in the expression and activity of polyamine metabolic enzymes, as well as changes in the levels of the individual polyamines, have been observed in multiple conditions, including schizophrenia, mood disorders, anxiety and suicidal behaviour. Additionally, these components have been found to be altered by various psychiatric treatments. Further, the polyamines and their precursors have demonstrated both antidepressant and anxiolytic effects. Overall, findings to date suggest that the polyamine pathway represents an important frontier for the development of neuropharmacological treatments.

La voie des polyamines joue un rôle essentiel dans un grand nombre de fonctions cellulaires et elle a été mise en cause dans plusieurs pathologies. Des données de plus en plus nombreuses indiquent que le système des polyamines joue aussi un rôle dans l'étiologie et la pathologie des troubles mentaux. On a observé des altérations de l'expression et de l'activité des enzymes métaboliques des polyamines, ainsi que des variations de la concentration de certaines polyamines dans de multiples affections, y compris la schizophrénie, les troubles de l'humeur, l'anxiété et le comportement suicidaire. On a aussi constaté que divers traitements psychiatriques modifiaient ces composantes. De plus, les polyamines et leurs précurseurs ont montré des effets à la fois antidépresseurs et anxiolytiques. Dans l'ensemble, les constatations actuelles indiquent que la voie des polyamines représente une frontière importante pour la mise au point de traitements neuropharmacologiques.

Introduction

Mostly owing to the elucidation of the molecular targets of effective psychopharmaceutical agents, much of the neurochemical work in mental disorders to date has focused on the role of the monoaminergic system. Despite the success of monoamine-related pharmacologic treatments, they are not effective in many patients, indicating that these systems are not the sole factors involved in these conditions. The role in mental illness of an alternative pathway, the polyamine system, has been gaining support. Although they are known better for their role in modulating the cell cycle, and consequently their relevance to cancer, research in the last few decades has shown the importance of the polyamines in numerous neurodegenerative conditions, and substantial evidence is emerging that supports their role in the pathophysiology of psychiatric disorders. Accordingly, the polyamines represent an important system for understanding the causes

of mental illnesses and, in addition, provide a new pharmacologic target for their treatment.

This review focuses on evidence pertaining to altered levels of the polyamines and their metabolic enzymes in psychiatry, as well as on the possible role the polyamine system plays in the etiology of these disorders and mechanisms by which its effects may occur. First, however, we discuss the basic properties of the polyamines, as well as their metabolism, localization in the central nervous system (CNS) and relevant cellular functions.

Properties of the polyamine system

The polyamines are ubiquitous aliphatic molecules comprising putrescine, spermidine and spermine, which contain 2, 3 and 4 amino groups, respectively. In addition, the guanidino-amine agmatine, whose presence in mammalian brains was discovered much more recently than that of the

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other polyamines,¹ may also be considered among this group.² Because of their essential roles in many cellular functions, their homeostasis is highly regulated through their biosynthesis, degradation and transport, as well as by the interconversion between individual polyamines.

Metabolism and accumulation

Both the polyamine synthesis and interconversion pathways have been extensively studied, and the major reactions are depicted in Figure 1.

Because of their vital roles, the polyamine metabolic pathways are highly regulated. The major rate-limiting enzymes are ornithine decarboxylase (ODC), S-adenosylmethionine (SAME) decarboxylase (AMD1), and spermidine/spermine N¹-acetyltransferase (SAT1), whose activities are controlled at multiple levels by numerous mechanisms, including feedback control by the polyamines themselves.³ The activities of spermidine synthase (SRM) and spermine synthase (SMS) are generally constant, although there may be induction under certain conditions.⁴ Polyamine oxidase (PAO) activity appears to be regulated by substrate availability.⁵

Multiple transport systems have been identified and have been found in various cell types, including hepatocytes, synaptosomes, synaptic vesicles and glial cells.⁶⁻⁸

CNS localization

The polyamines and their biosynthetic enzymes are found throughout the body, including the CNS, where they display specific regional distributions. Many methods have been used to assess these distributions in the CNS (for a review, see Bernstein and Müller⁹). Both agmatine and its precursor arginine have been shown to cross the blood–brain barrier, allowing both the concentration and localization of agmatine in the brain to be determined by peripheral agmatine and arginine levels as well as through endogenous synthesis by the inducible enzyme arginine decarboxylase.^{11,10} Putrescine, spermidine and spermine possess only a limited capacity to cross the blood–brain barrier,¹¹ and as such, their localization in the healthy CNS largely represents those which have been endogenously synthesized. Concentrations in brain tissues are typically in the nM range.¹² The localization and concentrations of each of the metabolic enzymes and polyamines are not identical for brain region or cell type,^{9,13-20} indicating that synthesis and storage may not occur in identical locations.

Cellular effects

The polyamines have numerous roles and are involved in many aspects of cellular function. Owing to their cationic

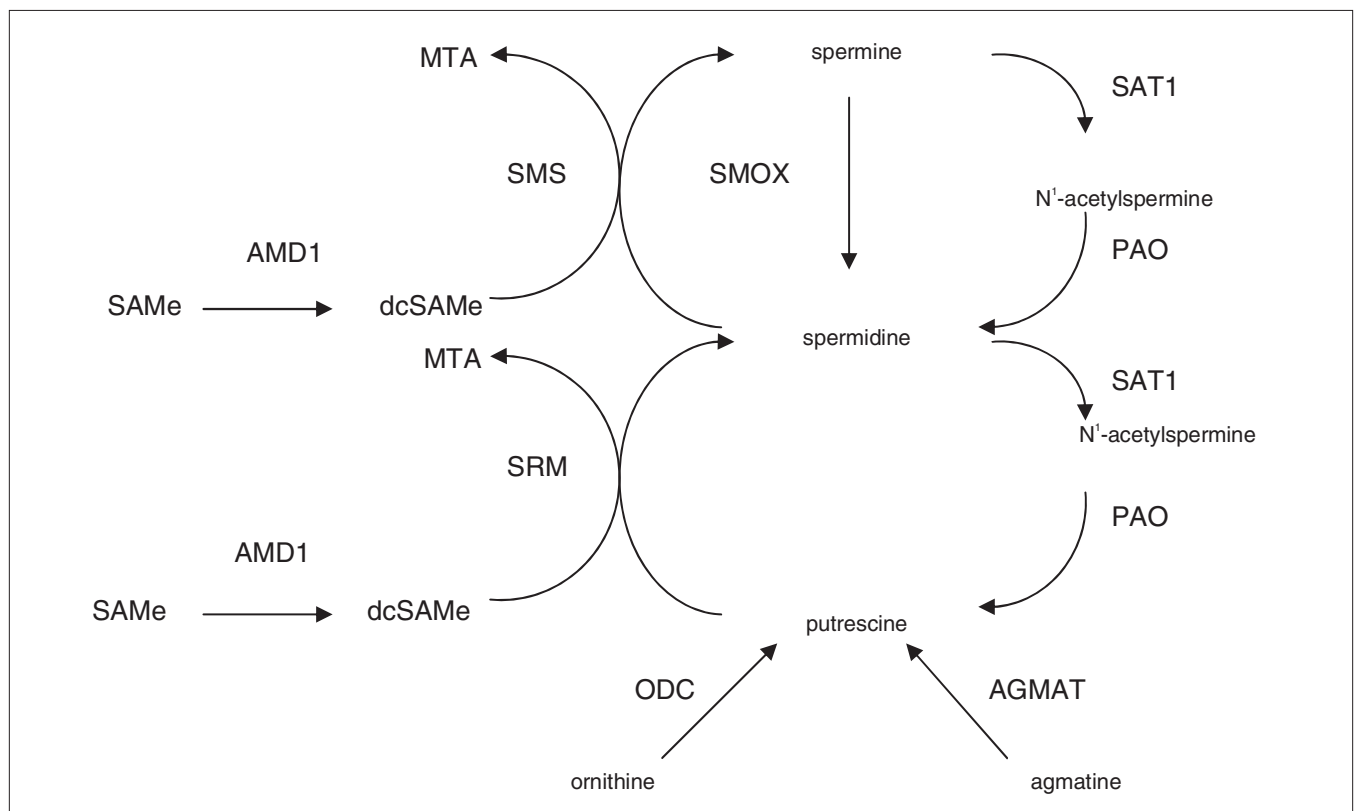


Fig. 1: Polyamine synthesis and interconversion pathways. MTA = 5' methylthioadenosine; SAT1 = spermidine/spermine N¹-acetyltransferase; SMS = spermine synthase; SMOX = spermine oxidase; AMD1 = S-adenosylmethionine decarboxylase; PAO = polyamine oxidase; SAME = S-adenosylmethionine; dcSAME = decarboxylated SAME; SRM = spermidine synthase; ODC = ornithine decarboxylase; AGMAT = agmatinase.

nature, they interact well with nucleic acids and, not surprisingly, are involved in many aspects of gene expression.³ In addition, polyamines influence the properties of proteins and membranes^{3,21} and function as antioxidants and scavengers of reactive oxygen species.^{22,23}

The polyamines have an important role in cell proliferation and demonstrate both pro- and antiapoptotic effects.²⁴ Additionally, the polyamines are involved in many signalling pathways through their effects on G proteins, protein kinases, nucleotide cyclases and receptors, as well as by their regulation of the expression of proteins involved in these processes.^{3,24,25} Owing to their interactions with several transmembrane channels, they also influence the electrical properties of excitable cells.²⁶ Agmatine is believed to act as a neurotransmitter by its actions through several receptors, and this theory is supported by its storage in synaptic vesicles and its capacity to be released on depolarization.²⁷ Spermine has also been shown to be released from synaptic vesicles on depolarization, indicating that the polyamines may function as neuromodulators.⁷ Additionally, polyamines influence the properties of several neurotransmitter pathways known to be involved in mental disorders, including the catecholamines,²⁸⁻³² γ -amino-butyric acid,³³⁻³⁶ nitric oxide³⁷ and glutamate.³⁸⁻⁴²

Possible implication in mental disorders

Schizophrenia

The role of the polyamine system in the pathology of schizophrenia and other psychotic disorders was first proposed by Richardson-Andrews, who noted that the structures of certain neuroleptics and antimalarials both contain a spermidine

moiety and are associated with extrapyramidal symptoms and psychosis.^{43,44} Since this time, alterations of many aspects of the polyamine system have been observed in both human schizophrenia patients and animal models. Further, certain treatments for schizophrenia have been shown to alter both polyamine levels and the activities of polyamine-related enzymes, supporting the role of the polyamine system in the pathophysiology of this disorder. A summary of relevant studies performed in human subjects is found in Table 1.

Polyamine levels

Increased blood levels of all polyamines have been observed in schizophrenia patients.^{50,52-54,60} Levels appear to be related to neuroleptic treatment because increased concentrations were observed in treated patients in comparison with untreated patients and control subjects.⁵⁷ This effect may be related to treatment response because no changes in polyamine levels were found after clozapine treatment of neuroleptic-resistant schizophrenia patients.⁵³

Unlike the periphery, a study of human brains found no differences in polyamine levels in the frontal cortex or hippocampus of schizophrenia patients in comparison with control subjects.⁵⁵ However, because levels of the polyamines and some of their metabolic enzymes are known to vary with postmortem interval^{13,14,16,55} which could not be fully controlled for in this experiment, further studies are warranted to confirm these findings.

Enzyme activities

Studies examining serum from schizophrenia patients have

Table 1: Summary of findings from studies analyzing the polyamine system in schizophrenia

Study	Findings	System
Meltzer et al ⁴⁵	Plasma amine oxidase activity lower in schizophrenia patients, only significant for acute cases.	Plasma
Baron et al ⁴⁶	Plasma amine oxidase activity unaltered after 3 mo neuroleptic treatment.	Plasma
Baron et al ⁴⁷	Reduced plasma amine oxidase activity associated with schizophrenia spectrum disorders within families.	Plasma
Baron et al ⁴⁸	Small, nonsignificant reduction in plasma amine oxidase activity.	Plasma
	Familial transmission may occur in families where probands have extremely low activity.	
Gruen et al ⁴⁹	Plasma amine oxidase activity unrelated to subtype, diagnostic criteria, prognosis or age at onset.	Plasma
Svinarev ⁵⁰	Increased spermidine.	Serum
Flayeh ⁵¹	Increased spermidine oxidase activity, unrelated to sex, age or treatment.	Serum
Das et al ⁵²	Increased polyamines, no correlation with sex or treatment.	Whole blood, plasma
	Increased PAO activity.	
Das et al ⁵³	Increased polyamines in neuroleptic-resistant patients compared with healthy control subjects, unchanged after 6 mo clozapine treatment.	Blood
Ramchand et al ⁵⁴	Increased polyamines in fibroblasts.	Skin fibroblasts
	Increased spermine in culture medium.	
Gilad et al ⁵⁵	No alterations in polyamines, ODC, AMD1 or SAT1.	Frontal cortex, hippocampus
Bernstein et al ⁵⁶	No alterations in ODC immunoreactivity.	Entorhinal cortex
Das et al ⁵⁷	Increased total polyamines in neuroleptic-treated schizophrenia patients compared with control subjects and untreated patients.	Skin fibroblasts
Dahel et al ⁵⁸	Increased PAO activity, normalized in patients improved after ECT.	Serum
Middleton et al ⁵⁹	Decreased activities of OAT, AZIN1 and OCD, no relation to treatment.	Prefrontal cortex

PAO = polyamine oxidase; ODC = ornithine decarboxylase; AMD1 = S-adenosylmethionine decarboxylase; SAT1 = spermidine/spermine N¹-acetyltransferase; ECT = electroconvulsive therapy; OAT = ornithine aminotransferase; AZIN1 = antizyme inhibitor; OCD = ornithine cyclodeaminase.

shown increased levels of polyamine oxidative enzymes,^{51,58} which were normalized in patients who showed improvement in clinical symptoms after electroconvulsive therapy (ECT).^{51,58} Early studies of the relation between plasma amine oxidase and schizophrenia demonstrated a trend toward decreased activity that may have been associated with familial transmission of the disorder.^{45,47,48} Although plasma amine oxidase is not specific for the polyamines, decreases in activity combined with increases in polyamine concentrations might be expected to alter its substrate profile.

The role of ODC is less clear. Studies in schizophrenia patients found no differences in ODC levels or activity in the frontal cortex, hippocampus, or entorhinal cortex.^{55,56} However, increased activity was observed in cortical neurons from a rat model of schizophrenia.⁶¹ Although these results may indicate that the animal model does not properly represent the neurobiology of schizophrenia, it may be that differences in ODC activity are found only in specific CNS regions that have not yet been clearly identified in humans. Interestingly, ECT has been shown to increase ODC activity in multiple regions of rat brains.^{62,63}

Regardless of the findings with ODC, there is support for the hypothesis of alterations in ornithine metabolism in schizophrenia because the activities of ornithine aminotransferase (OAT), antizyme inhibitor (AZIN1) and ornithine cyclodeaminase (OCD) were shown to be decreased in the prefrontal cortex of both treated and untreated patients.⁵⁹

Information on the activities of other enzymes is lacking, although, in addition to no evidence of altered polyamines or ODC activity, Gilad and colleagues⁵⁵ were unable to demonstrate changes in AMD1 or SAT1 activities.

Potential mechanisms

The complexity of this system makes it unlikely that a single mechanism is responsible, and hence, a simple explanation is impossible. One possibility is that the increased peripheral polyamine concentrations are a result of decreased plasma amine oxidase activity and that the increased PAO activity is a compensatory mechanism to decrease these levels. It would be of interest to determine whether the normalization of PAO activity in clinically improved patients is also associated with normalization of polyamine levels. Additionally, oxidative deamination by both plasma amine oxidase and PAO yields compounds capable of causing cell damage,²⁴ and as such, alterations in their activities could reflect either a causative role or compensatory mechanisms to reduce this damage.

The mechanism in the brain is even less clear, and further studies are necessary to provide a consensus on the actual levels of the polyamines in each brain region as well as on the activities and relations between each enzyme. The decreased expression of OAT and OCD in the prefrontal cortex should theoretically provide increased ornithine for polyamine production, but decreased expression of AZIN1 would allow for increased inhibition of ODC. It has been proposed that these results may reflect either a mechanism to compensate for increased polyamine levels or, possibly, an attempt to down-regulate the entire pathway.⁵⁹

As mentioned above, the polyamines act on the dopamine pathway. Because this system is strongly associated with the pathology of schizophrenia, its modulation by the polyamines could be of great relevance to both the etiology of this illness and in influencing the clinical outcome of anti-dopaminergic treatments.

Polyamines alter the functioning of *N*-methyl-D-aspartate receptors (NMDAR),²⁶ and it has therefore been proposed that the increased polyamine levels in schizophrenia patients are related to the implication of hypofunctional NMDAR signalling in schizophrenia.⁵⁷ In this case, increased polyamines should be associated with increased glutamate signalling, with increases representing a compensatory mechanism. Alternatively, because excessive glutamate signalling can produce excitotoxicity,⁶⁴ polyamines may instead be destructive rather than beneficial. However, if polyamine levels are confirmed to be unchanged in the brain, these mechanisms may not be applicable.

It seems clear that the neuroleptics are capable of influencing polyamine metabolism; however, the mechanisms involved are not yet apparent. Although polyamines were higher in treated patients,⁵⁷ their lack of change in neuroleptic-resistant patients⁵³ suggests that the effects of neuroleptics on the polyamine system occur further downstream and may mediate responses rather than determining whether a response to treatment will occur.

Obviously, significant work remains to determine the precise role of the polyamine system in schizophrenia, and although it seems clear that dysregulation of the system is associated with this illness, it is not yet certain whether these alterations are etiologically related or represent compensatory mechanisms.

Mood disorders and suicide

As with schizophrenia, the ability of antimalarials to produce depressive symptoms has been proposed as an indication that the polyamines have a role in depression.⁴⁴ Although there have been fewer studies examining the polyamine system in mood disorders in humans, evidence also exists to implicate this system in their pathology. In addition, emerging evidence points to a role of the polyamine system in suicidal behaviour. A summary of studies examining the polyamine system in mood disorders in human subjects is found in Table 2, and relevant animal studies are shown in Table 3, Table 4 and Table 5.

Polyamine levels

Although Gilad and colleagues⁵⁵ found no differences in polyamine levels in the hippocampus and frontal cortex of patients with depression, a rat model displayed decreased hippocampal putrescine, spermidine and spermine, as well as decreased putrescine in the nucleus accumbens septi.⁶⁸ In addition, plasma agmatine was significantly elevated in patients with depression and was normalized by antidepressant treatment.⁶⁵ Agmatine produces both antidepressant and anxiolytic effects in animals through mechanisms involving multiple receptor systems.^{40,70-72,81,84} The antidepressant effects of

putrescine also appear to involve NMDAR,⁴² and the possibility that at least some of the role of polyamines in depression is due to modulation of NMDAR is supported by the mechanism of the antidepressant eliprodil, which acts as an antagonist at polyamine-binding sites.⁸⁸ SAME also produces antidepressant effects in humans.⁸⁹ The exact mechanism remains uncertain, but animal studies have indicated that antidepressant dosages of SAME could normalize putrescine and partially restore spermine and spermidine levels.⁶⁸ However, because SAME is also required for synthesis of dopamine, norepinephrine and serotonin and is essential for folate and vitamin B12 metabolism, each of which are implicated in mood disorders,⁹⁰ its antidepressant effects may not necessarily be mediated through the polyamine system.

Enzyme activities

As with schizophrenia patients, high levels of plasma PAO activity were observed in depression patients, and these were normalized by ECT.⁵⁸ Also similar, no differences were observed in ODC levels in the entorhinal cortex of depression patients,⁵⁶ nor were they observed in the activities of ODC, AMD1 or SAT1 in the hippocampus or frontal cortex of patients who suffered from depression or committed suicide.⁵⁵ However, studies performed by our group, using suicide

completers both with and without depression, demonstrated a downregulation of SAT1 in several brain regions.^{66,67} SAT1 expression was more profoundly decreased in suicide completers who suffered from depression⁶⁶ and was lower in the posterior cingulate gyrus of depressed, compared with non-depressed, suicide completers,⁶⁷ suggesting an important role in depression. Additional studies performed by our group have identified other polyamine-related genes that are dysregulated in the limbic system of suicide completers,⁶⁷ providing further support for an involvement of the polyamine pathway in depression and suicide.

Potential mechanisms

The antidepressant effects of agmatine, putrescine and SAME support the possibility that the polyamine system has a role in depression and perhaps in other mood disorders. As with schizophrenia, however, the relation between polyamine concentrations and activities of the associated enzymes cannot be formulated into a simple explanation. To gain a better understanding of the roles of the polyamines in depression and suicidal behaviour, it is essential to determine the actual levels of each of the polyamines in the CNS. As with schizophrenia, further studies are required to assess whether dysregulation of the polyamine system should be considered a

Table 2: Summary of polyamine-related findings in human mood disorder studies

Study	Findings	System
Gilad et al ⁵⁵	No alterations in levels of polyamines, ODC, AMD1 or SAT1 in depression patients or suicide completers.	Frontal cortex, hippocampus
Bernstein et al ⁵⁶	No alterations in ODC immunoreactivity in depression patients.	Entorhinal cortex
Halaris et al ⁶⁵	Increased agmatine in depression patients, normalized after 8 wk of bupropion treatment.	Plasma
Dahel et al ⁶⁸	Increased PAO activity in patients with severe depression, normalized in patients showing improvement after ECT.	Serum
Sequeira et al ⁶⁶	Decreased SAT1 expression in suicide completers both with and without depression, results more profound in suicide completers with depression.	Orbital cortex, motor cortex, dorsolateral prefrontal cortex
Sequeira et al ⁶⁷	Increased hippocampal expression of SAT2 and OATL1 in suicide completers without depression, increased SMS in suicide completers both with and without depression. Decreased SAT1 expression in the posterior cingulate gyrus in suicide completers with depression, compared with those not suffering from depression.	Amygdala, hippocampus, anterior cingulate gyrus, posterior cingulate gyrus

ODC = ornithine decarboxylase; AMD1 = S-adenosylmethionine decarboxylase; SAT1 = spermidine/spermine N¹-acetyltransferase; PAO = polyamine oxidase; ECT = electroconvulsive therapy; OAT = ornithine aminotransferase; SMS = spermine synthase.

Table 3: Summary of findings from rodent studies examining the relation between depression and the polyamine system

Study	Findings
Genedani et al ⁶⁸	Depression model displayed decreased putrescine, spermidine and spermine in hippocampus, decreased putrescine in nucleus accumbens septi, no changes in frontal cortex. SAME normalized putrescine in nucleus accumbens, partially restored hippocampal spermine and spermidine.
Zomkowski et al ⁴⁰	Agmatine antidepressant effects involve NMDAR, L-arginine-NO pathway and α_2 -adrenoceptors.
Li et al ⁴¹	Agmatine antidepressant effects involve NMDAR.
Aricioglu and Altunbas ⁶⁹	Agmatine demonstrated antidepressant effects.
Zomkowski et al ⁷⁰	Agmatine antidepressant effects involve 5-HT _{1A/1B} and 5-HT ₂ receptors.
Zomkowski et al ⁷¹	Agmatine antidepressant effects involve δ - and μ -opioid receptors.
Zomkowski et al ⁴²	Putrescine antidepressant effects involve NMDAR.
Zeidan et al ⁷²	Agmatine antidepressant effects involve imidazoline I-1 and I-2 receptors.

SAME = S-adenosylmethionine; NMDAR = N-methyl-D-aspartate receptors; NO = nitric oxide; 5-HT = 5-hydroxytryptamine.

cause or a consequence of these disorders. However, as discussed below, evidence suggests that dysregulation of the system may precede development of mood disorders.

Polyamine stress response

Of considerable interest in regard to the role of the polyamine

Table 4: Summary of findings from rodent studies examining the relation between stress, anxiety and the polyamine system

Study	Findings
Butler and Schanberg ⁷³	Infant cerebellar putrescine and brain ODC activity decreased after maternal separation.
Gilad et al ⁷⁴	Only chronic lithium treatment prevented glucocorticoid-induced increases in ODC, AMD1 and SAT1 activity in hippocampus and frontal cortex.
Gilad and Gilad ⁷⁵	Hippocampal ODC activity increased after each episode of chronic intermittent stress, first episode reduced hippocampal AMD1 activity and increased liver ODC activity, but both remained constant after all subsequent treatments. Chronic lithium treatment only prevented increases in hippocampal ODC activity.
Gilad et al ⁷⁶	Decreased hippocampal ODC and AMD1 activities after acute stress at day 5, no change in striatal ODC activity. Adult PSR pattern in hippocampus and striatum apparent at day 30. Increased behavioural responses and attenuated increases in ODC activity when stressed at day 7 and then rechallenge as adults.
Gilad et al ⁷⁷	Adult behavioural responses reduced in animals subjected to mild intermittent postnatal stress and increased in animals that received acute postnatal stress. No differences in stress-induced ODC activity between adults who received either mild or acute postnatal stress. Enhanced increase in liver ODC activity when subjected to acute postnatal stressors and then rechallenge as adults. Adult polyamine concentrations unaffected by postnatal stressors.
Gilad et al ⁷⁸	ODC activity and putrescine increased in liver and decreased in thymus after acute stress at all ages, only increased in hippocampus of adults. Basal ODC activity after adrenalectomy increased in hippocampus and thymus and decreased in liver; increased basal putrescine and spermine in hippocampus and basal putrescine in thymus. Adrenalectomy enhanced stress-induced changes in ODC activity in hippocampus, liver, and thymus, and putrescine changes in liver and thymus.
Gilad et al ⁷⁹	Putrescine increased in hippocampus after each stress episode; increases in spermidine and spermine delayed and transient. α -DFMO combined with stress depleted putrescine and decreased spermidine and spermine in hippocampus, produced behavioural changes.
Sohn et al ⁸⁰	Acute stress increased putrescine in frontal cortex and hippocampus. Chronic stress did not alter putrescine, spermidine or spermine. Putrescine concentrations differ between rat strains.
Gilad and Gilad ²⁵	Greater induced changes in ODC and polyamines in rat strain more reactive to stress.
Lavinsky et al ⁸¹	Agmatine anxiolytic effects occur either through NOS, NMDAR or α_2 -adrenoceptors.
Aricioglu and Altunbas ⁶⁹	Agmatine demonstrated anxiolytic effects.
Aricioglu et al ⁸²	Increased agmatine in plasma and frontal cortex during stress, no changes in hypothalamus, medulla, cerebellum or hippocampus.
Hayashi et al ⁸³	Stress increased putrescine and decreased spermine in frontal cortex and hypothalamus, no effects in plasma. Anxiolytic pretreatment prevented putrescine increases.
Gong et al ⁸⁴	Agmatine demonstrated anxiolytic effects.
Li et al ⁸⁵	Agmatine increased hippocampal neurogenesis in chronically stressed mice.
Lee et al ⁸⁶	Stress increased brain putrescine, prevented by anxiolytic pretreatment. No alterations in spermine, spermidine or acetylated products.

ODC = ornithine decarboxylase; AMD1 = S-adenosylmethionine decarboxylase; SAT1 = spermidine/spermine N¹-acetyltransferase; PSR = polyamine stress response; α -DFMO = α -difluoromethylornithine; NOS = nitric oxide synthase; NMDAR = N-methyl-D-aspartate receptors.

Table 5: Additional animal studies examining the relation between the polyamine system and mental disorders.

Study	Findings
Hirsch et al ³⁰	Spermidine and spermine acted selectively on mesolimbic, but not striatal, dopamine system.
Bondy et al ⁶²	Transiently increased ODC activity in adrenals, hippocampus, brain stem, frontal cortex and cerebellum after ECT. Dose-response for shock intensity and ODC activity in hippocampus and brain stem.
Bo et al ²⁹	Spermine produced dose-dependent cortical synchronization and sedation. Spermidine produced cortical synchronization at low dosages and cortical desynchronization and behavioural arousal at higher dosages. Spermine and spermidine inhibited methamphetamine-induced behaviour.
Orzi et al ⁶³	Hippocampal ODC increased after repeated ECT.
Zawia and Bondy ⁸⁷	Increased cerebral ODC after single ECT, effects partially attenuated by using an NMDAR antagonist.
Bastida et al ²⁸	α -DFMO treatment with polyamine-deficient diet reduced adrenal polyamines and catecholamines and plasma corticosterone and aldosterone.

ODC = ornithine decarboxylase; ECT = electroconvulsive therapy; NMDAR = N-methyl-D-aspartate receptors; α -DFMO = α -difluoromethylornithine.

system in the morbidity and etiology of psychiatric disorders is the polyamine stress response (PSR). This phenomenon has been reviewed by Gilad and Gilad²⁵ and is implicated in the detrimental effects of stress and anxiety and in their role in the development of other psychiatric disorders. Studies assessing the PSR, as well as animal models of anxiety, are summarized in Table 4.

Unlike the peripheral system, where acute stressors activate the PSR to increase the concentrations of all polyamines,⁹¹ acute stressors in the CNS result only in the elevation of ODC activity and putrescine and agmatine levels.^{25,82} The PSR can be induced by multiple forms of stress, and its magnitude appears to be related to the intensity of the stressor.^{74,78} Consistent with this are findings that anxiolytic pretreatment can diminish or eliminate stress-induced alterations of the polyamine system.^{83,86} Chronic stress increases ODC activity and putrescine levels after each application, whereas spermidine and spermine concentrations increase only after several treatments, which is suggestive of an adaptive response.⁷⁹

In support of a role of the PSR in behavioural responses to stress, increases in polyamine levels and ODC activity were found to be larger in strains of rats exhibiting greater behavioural and physiologic responsiveness to stress.^{25,80} Further, chronic administration of α -difluoromethylornithine (α -DFMO), an irreversible inhibitor of ODC, yielded rats which displayed distinctive behavioural changes when exposed to stressors.⁷⁹ Interestingly, memory impairments have been observed in both ODC- and SAT1-overexpressing mice, which possess substantially increased putrescine levels.^{92,93} Additionally, SAT1-overexpressing mice are hypomotoric and display decreased aggressiveness.⁹³ It has been proposed that partial blockade of NMDAR by putrescine may be involved in these effects.⁹⁴

The PSR appears to be developmentally regulated and may be associated with the development of mood disorders. Early postnatal stressors have been shown to alter putrescine concentrations and ODC activity⁷³ and yield altered behavioural reactivity and an attenuated PSR in adults.⁷⁷ Further, the emergence of the characteristic adult PSR is correlated with the cessation of the hyporesponsive period of the hypothalamic-pituitary-adrenocortical (HPA) axis system.⁷⁶ Because this developmental stage in rats is equivalent to a period in humans associated with a high incidence of affective disorders, it has been proposed that the PSR might therefore be involved in development of these conditions.⁷⁶ The HPA axis is implicated in depression, and effects are believed to be associated with dysregulation of the glucocorticoid system.⁹⁵ Consequently, the occurrence of a characteristic PSR after glucocorticoid treatment adds further weight to the theory that the PSR and the polyamines are involved in the development of affective disorders.⁷⁹ Additionally, the combination of treatment with α -DFMO and a polyamine-deficient diet reduced polyamine, catecholamine and corticosteroid concentrations.²⁸ Overall, these results suggest that the PSR, through modulation of the HPA axis, may be directly involved in the pathogenesis of depression and shed some light on the relevance of environmental influences in the etiology of this disorder.

Lithium is commonly used in the treatment of bipolar disorder, and although many cellular effects have been proposed, the precise mechanisms by which it exerts its therapeutic effects have not been fully determined. Considerable work has investigated the influence of lithium on the PSR. Specifically, chronic lithium treatment prevents stress-induced ODC activity in rat brains, thereby decreasing the intensity of the PSR.^{74,75} Decreased ODC activity is not due to a direct interaction with lithium⁹⁶ and was proposed to be a result of interference with a signal required for induction of ODC.²⁵ In vitro experiments demonstrated that these decreases may be associated with altered glial cell properties.⁹⁷

Conclusion

Several lines of evidence support a possible role for the polyamine system in the neurobiology of major psychiatric disorders and suicide. The significant number of metabolic enzymes that show altered expression in these disorders, the findings of altered levels and ratios of each polyamine and the effects of psychiatric treatments on many aspects of the polyamine system each add support for the idea that modulation of this system may represent a possible pharmacologic target in the treatment of these disorders. Because the precise mechanisms involved have not yet been fully elucidated, it seems clear that the study of this system remains a crucial frontier for understanding the pathophysiology of several mental disorders, including schizophrenia, mood disorders and suicide.

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