POLYAMINES IN MENTAL DISORDER

A MSc Dissertation Report by:

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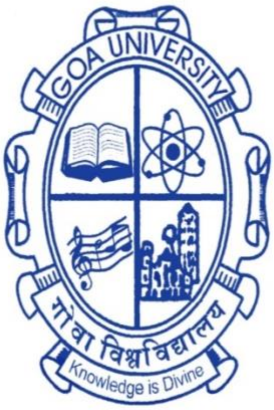

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POLYAMINES IN MENTAL DISORDER

A DISSERTATION REPORT (literature review)

Submitted in Partial Fulfilment

of

The Degree of M.Sc. (Biochemistry)

By

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To the

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Goa University

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DECLARATION

I declare that the literature review titled, '**Polyamines in Mental Disorder'** has been carried out by me as part of my M.Sc. Biochemistry program in the Chemistry department, School of Chemical Sciences, Goa University. All the information (text, figures) derived from the literature review has been duly acknowledged in the text and a list of references is provided.

Dr. Diksha Arlekar

Signature:

Date:

CERTIFICATE

This is to certify that the literature review entitled, '**Polyamines in Mental Disorder'** submitted by the student is the record of research work carried out by the candidate during the academic year 2021-22 under my supervision in partial fulfilment of the requirements for the degree of Master of Science in Biochemistry

Dr Kanchanmala Deshpande (Project Guide)

Prof. Vidhyadatta M. Shet Verenkar (Dean of SCS, Goa University)

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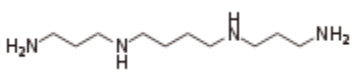
POLYAMINES IN MENTAL DISORDER

Brief history

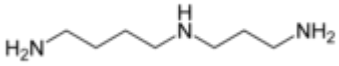
The history of polyamines began with the first microscopic observations of the human semen by van Lewenhoek who reported, in 1677, the presence of crystals in these samples after several days of standing. In 1878, Schreiner identified those crystals as phosphate derivatives of an organic base. This base was subsequently named “spermine” because of the source from which it was initially isolated. However, the precise chemical composition and structure of the base remained unclear, and its correct structure was determined only in 1924, when isolated spermine from bovine brain notwithstanding, a basic compound named “neuridine” was isolated from brain tissue in 1885,by Krieger. This compound was subsequently found to be identical to spermine. Two interesting and more detailed reviews of the history of polyamine research were published by Shaw and Bachrach[50].

Introduction

A **polyamine** is an organic compound having more than two amino groups. Natural polyamine are low-molecular-weight linear polyamines are found in all forms of life. The principal examples are the triamine and tetraamine spermidine and spermine. They are structurally and biosynthetically related to the diamines putrescine and cadaverine. Polyamine metabolism is regulated by the activity of the enzyme ornithine decarboxylase (ODC) Polyamines are found in high concentrations in the mammalian brain [82,83]



Spermine



Spermidine

Spermine is a polyamine involved in cellular metabolism that is found in all eukaryotic cells. The precursor for synthesis of spermine is the amino acid ornithine. It is an essential growth factor in some bacteria as well. It is found as a polycation at physiological pH. Spermine is associated with nucleic acids and is thought to stabilize helical structure, particularly in viruses.

Spermidine is a polyamine compound ($C_7H_{19}N_3$) found in ribosomes and living tissues and having various metabolic functions within organisms.

Spermidine is an aliphatic polyamine. Spermidine synthase (SPDS) catalyzes its formation from putrescine. It is a precursor to other polyamines, such as spermine and its structural isomer thermospermine.

Polyamine research is a very active area with numerous publications covering genetic, biochemical and physiological studies using mammals, plants, protozoan parasites and many microorganisms, including thermophiles that have a wider variety of polyamines.[75]

POLYAMINE SYNTHESIS

The only polyamines synthesized in mammalian cells are putrescine, spermidine and spermine. Agmatine (decarboxylated arginine) is not produced by mammal[76] but is synthesized by plants and by many bacteria, including the intestinal flora. It is possible therefore that it may be derived from food or intestinal microorganisms, although there is an active mammalian agmatinase that degrades it[77]. Agmatine has been shown to be active as a neurotransmitter but it is not established that it this is physiologically important and the function of agmatinase may be to limit any effect of dietary agmatine.

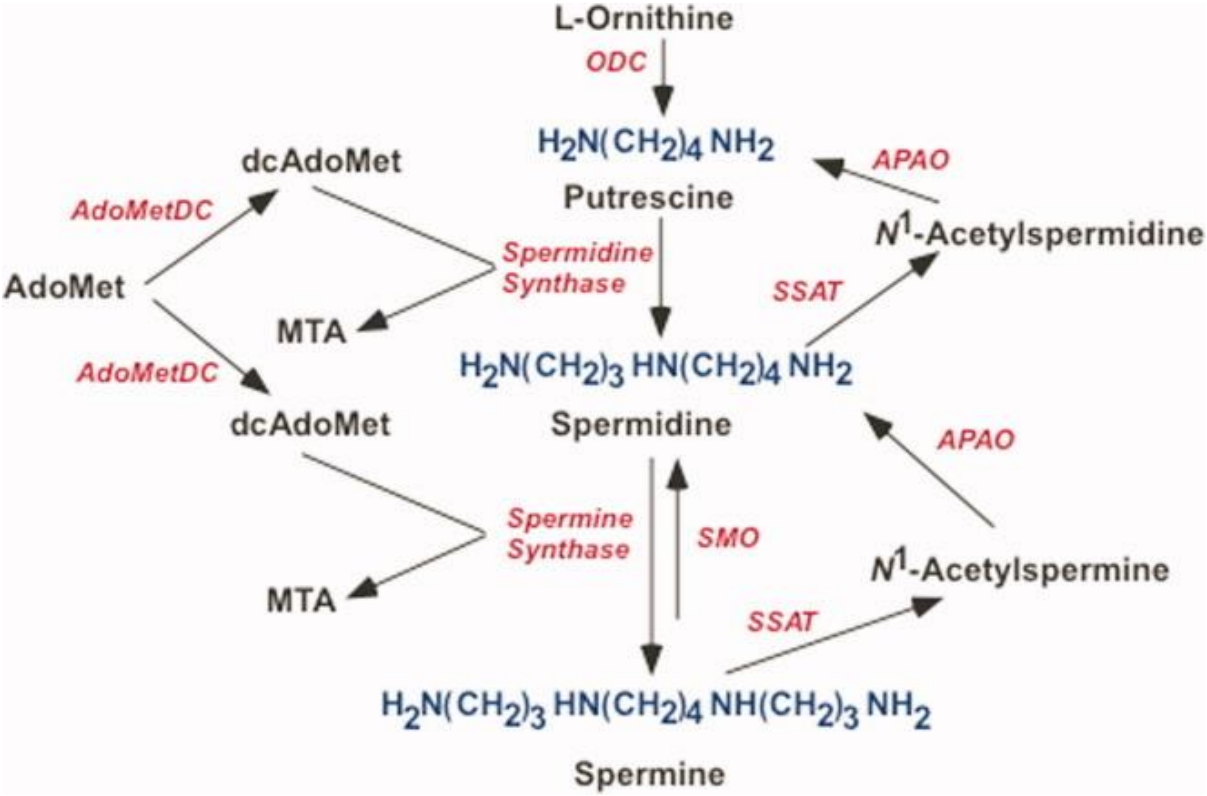


Fig 1 : Polyamine structures, biosynthesis and interconversion. Polyamine structures are shown in blue. Enzymes are shown in red italic fonts (ODC, L-ornithine decarboxylase; AdoMetDC, S-adenosylmethionine decarboxylase; SMO, spermine oxidase; SSAT, spermidine/spermine-N^1-acetyltransferase; APAO, acetylpolyamine oxidase).[84]

The polyamines synthesized by mammals are the triamine spermidine, the tetramine spermine, and their precursor putrescine.

Putrescine is formed by ornithine decarboxylase (ODC), and *S*-adenosylmethionine decarboxylase (AdoMetDC) produces dcAdoMet . The contents of ODC and AdoMetDC are very highly regulated at multiple levels in response to stimuli controlling polyamine levels. The supply of dcAdoMet limits the formation of the higher polyamines by spermidine synthase and spermine synthase. In mammals, these two aminopropyltransferases are highly specific with regard to their amine substrate [85,86]. Restrictions in the active site in spermidine synthase will not allow the binding of the larger spermidine at the putrescine substrate site [87], and the corresponding site in spermine synthase exclusively favors spermidine as substrate over putrescine.

The aminopropyltransferase reactions are effectively irreversible, but the polyamines can be interconverted by oxidative degradation directly via spermine oxidase or by acetylpolyamine oxidase after acetylation via spermidine/spermine-N^1-acetyltranferase (SSAT). The latter pathway is effectively controlled by the content of SSAT, a highly regulated cytosolic enzyme, which responds to high polyamine levels.[88]

Possible implication in mental disorders

According to the World Health Organization one in four people will be affected by mental or neurological disorders at some point in their lives. In the past years, many studies have focused on understanding the mechanisms underlying mental illness [21-24]; much of the literature has analyzed the role of the monoaminergic system, in particular, the serotonin and catecholamine involvement in the etiology of these pathologies [25-27]. The impairment of the monoaminergic system alone cannot explain all the aspects related to these diseases, since over the years it has become increasingly clear the contribution of other players such as PAs[28]. PAs can affect neuronal excitability since they interact with different transmembrane channels [29], in the light of this important role in central nervous system (CNS), over the last three decades extensive research has pointed out their implications in different psychiatric conditions. In fact, an alteration of the PA content and their metabolic enzymes have been found in different mental illness, such as schizophrenia, mood and anxiety disorders

Polyamines and the Brain

In vertebrates, the brain behaves as an autonomous and closed system with regard to the PA metabolism. There is a high variation in PA levels between the different brain regions and in general, the levels of Spd and Spm are much higher than those of Put [30]. Different studies have shown a neuroprotective role of PAs, nevertheless in pathological conditions they can cause neurotoxicity due to their oxidation and conversion into aldehydes and reactive oxygen species [30-32]. In recent years, the key role of PAs in different brain syndromes and diseases has been increasingly recognized. This role seems to be mainly due to their ability to modulate and regulate different ion channels [33].

CNS localization

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. Putrescine, spermidine and spermine possess only a limited capacity to cross the blood–brain barrier, their localization in the healthy CNS largely represents those which have been endogenously synthesized. Concentrations in brain tissues are typically in the nM range. The localization and concentrations of each of the metabolic enzymes and polyamines are not identical for brain region or cell type, indicating that synthesis and storage may not occur in identical locations.[1]

Ion channel modulation by polyamines

Endogenous PAs, in particular Spm, are able to interact and modulate different ion channels and receptors involved in the maintenance of homeostasis of calcium, sodium and potassium.

Intracellular Spm, at μM concentrations, acts as an important blocker of inwardly rectifying potassium channels, by specifically plugging the ion channel pore. In fact, an increase of its content is responsible for an increase of the channel gating and rectification, which leads to a rise in cellular excitability [35]. Polyamines can also modulate the activities of ion channels responsible for the flux of cations through the cellular membrane. Additionally, PAs, by different intra/extra cellular interaction sites, can modulate voltage activated calcium channels. A specific interaction exists between PAs and the a1 subunit of L-type calcium channel. Only Put induces an increase in the flux of current via the protein kinase C pathway, while Spd and Spd are unable to produce this effect [36]. These channels are involved in synaptic transmission and plasticity and respond to ligands such as glutamate. Ionotropic glutamate receptors are divided into three groups: N-methyl-D-aspartate receptor (NMDAR); α-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and kainite receptor (KAR). Intracellular PAs can block the pore of the AMPAR and KAR, altering sodium and calcium flux, causing channels rectification, in particular affecting AMPAR lacking a GluR2 subunit and KAR lacking a GluR6 subunit [37]. The AMPAR rectification by Spm is dependent on the voltage and can regulate the calcium flux and the excitability threshold of synapses [38]. Polyamines can regulate another glutamate receptor, the NMDAR, a channel gate calcium and sodium containing two copies of NR1 and NR2 subunits. Polyamines, Spm in particular, are able either to stimulate or inhibit the NMDAR, according to the concentrations of glutamate, glycine and magnesium. Spermine can increase the frequency of the channel opening causing a strengthening of the NMDAR current in presence of saturating concentration of glycine. Only in the absence of magnesium extracellular Spm can block NMDAR in a voltage dependent manner. The inhibitory effect may take place because the extracellular Spm interacts with the negatively charged residues of the NMDAR, creating a steric obstruction for the passage of ions leading to a reduction of current through the channel. At physiological magnesium concentrations, only Spm-driven NMDAR stimulation can occur [39].

Social memory

In 2002, Mikolajczak [48,49] published two studies investigating the effect of spermidine and of acamprosate, a putative ligand at the polyamine binding site atthe NMDAr, on the social memory of rats. In this behavioral task the animals are exposed to a juvenile for a short period (5 min) and social-investigatory behavioris measured [50]. The repeated injection of spermidine (5 mg/kg) improves social memory, measured as a decrease in the time spent investigating a familiar juvenile, without altering the time spent investigating an unknown juvenile. Interestingly, ifenprodil, which decreases polyamine binding to the polyamine binding site at the NMDAr, has no effect on social memory [48]. In accordance with the view that polyamines improve memory, multiple acamprosate and a single spermidine administration lead to a better performance in the social memory test. Moreover, the antagonist of the polyamine binding site at the NMDAr arcaine prevents the facilitatory effect of acamprosate. However, arcaine paradoxically improves social memory per se [49]. In this regard, it is possible that adaptive changes due to chronic arcaine administration have contributed for the paradoxical effect of arcaine and lack of effect of ifenprodil in these animals .

Snyder-Robinson syndrome

Polyamines are tightly regulated polycations that are essential for life. Loss-of-function mutations in spermine synthase (SMS), a polyamine biosynthesis enzyme, cause Snyder-Robinson syndrome (SRS), an X-linked intellectual disability syndromE.loss of dSms in Drosophila recapitulates the pathological polyamine imbalance of SRS and causes survival defects and synaptic degeneration. SMS deficiency leads to excessive spermidine catabolism, which generates toxic metabolites that cause lysosomal defects and oxidative stress. Consequently, autophagy–lysosome flux and mitochondrial function are compromised in the Drosophila nervous system and SRS patient cells. Importantly, oxidative stress caused by loss of SMS is suppressed by genetically or pharmacologically enhanced antioxidant activity.[57]

The polyamine biosynthesis pathway consists of two successive steps catalyzed by two aminopropyltransferases: spermidine synthase converts putrescine to spermidine, and spermine synthase (SMS) converts spermidine to spermine[58,59]. In the past decade, mutations in human SMS (hSMS) have been found to cause the X-linked intellectual disability.

(XLID) Snyder-Robinson syndrome[60,61,62,63,64]. SRS is characterized by a collection of clinical features including mild to severe intellectual disability, hypotonia, skeletal defects, movement disorders, speech and vision impairment, seizure, and cerebellar circuitry dysfunction [61 , 64 , 65]. SRS was one of the earliest reported XLID syndromes[65]and thus far the only known genetic disorder associated with the polyamine metabolic pathway. So far, animal models for studying the pathology of SRS, as well as polyamine-associated neurological disorders, are limited. The hemizygous Gy male mice with partial deletion of both SMS and downstream gene PHEX (phosphate-regulating endopeptidase homolog, X-linked) was originally used as a model for X-linked hypophosphatemia for defects in phosphate transport[66,67]. Gy mice have decreased spermine levels and in addition to hypophosphatemic rickets show neurological phenotypes including circling behavior and inner ear abnormalities; however, the compounding effects from loss of PHEX function made it difficult to pinpoint the underlying pathophysiology of SMS deficiency[68]

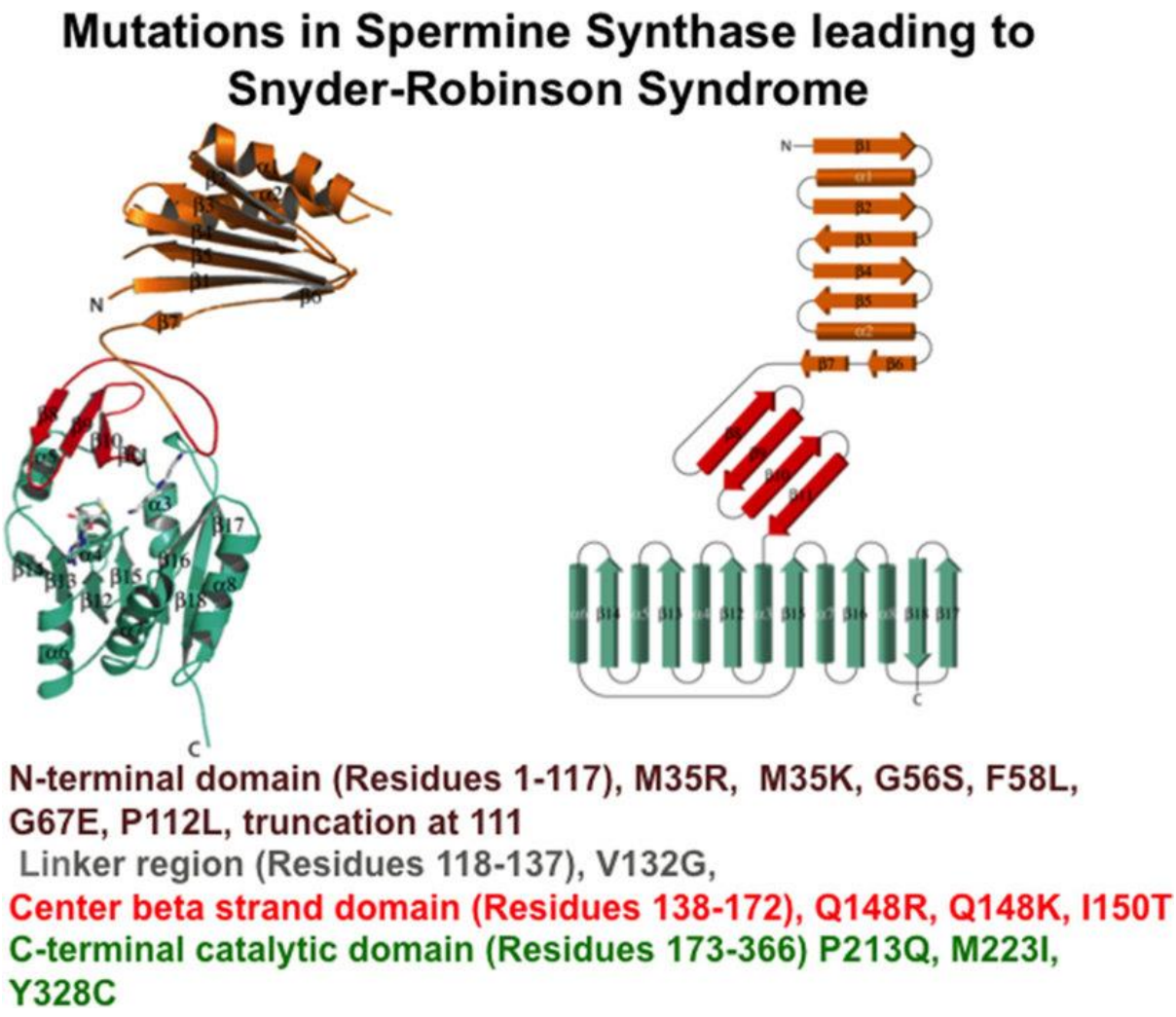


Figure 2: Mutations causing Snyder Robinson Syndrome. A monomer of human spermine synthase is shown as a ribbon (left) and topology diagram (right) (PDB IDs 3C6K and 3C6M). The N-terminal, central, and C-terminal domains are shown in brown, red, and green, respectively. The loop connecting the N-terminal and central domains is in gray. [89]

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. [2,3] 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.

Increased blood levels of all polyamines have been observed in schizophrenia patients[.4,5–6,7] Levels appear to be related to neuroleptic treatment because increased concentrations were observed in treated patients in comparison with untreated patients and control subjects[8]

Studies examining serum from schizophrenia patients have shown increased levels of polyamine oxidative enzymes which were normalized in patients who showed improvement in clinical symptoms after electroconvulsive therapy (ECT).[9,10]

Potential mechanisms: 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 clinicaloutcome of anti-dopaminergic treatments.[1]

Polyamines alter the functioning of N-methyl-D-aspartate receptors (NMDAR),[11] 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.[8]

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,[12] 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.

Polyamines and depression

Alteration in PA systems have also been found in animal models of depression. In rats affected by depression a hippocampal decrease of Put, Spd and Spm has been observed, while only a decrease of Put levels was observed in the nucleus accumbens [40]. Putrescine was shown to possess antidepressant properties, since its administration by injection can reduce immobility time in forced swimming and tail suspension tests. Analysis of plasma from humans suffering from depression showed a high level of Agm that is restored to normal levels after antidepressant treatments, highlighting the critical role of this molecule in depression [41]. Previously, the role of neurotransmitter has been proposed for Agm in the CNS. This was confirmed by its accumulation in synaptic vesicles and by the ability of Agm to be secreted following depolarization [42]. Moreover, it has been proved that Agm is a selective antagonist of the NMDA polyamine-binding site [43]. All these data confirm the involvement of the PA system in depression. In a similar way to what was observed in schizophrenic patients, high levels of PAs were also found in the plasma of patients suffering from depression [44]. Evidence showed that the transcript and protein levels of different elements of the PA system are altered in several brain regions of suicide completers; in particular post-mortem studies have highlighted changes in the SSAT enzyme which shows a lower level of expression compared with healthy people [45,46]. It has been proposed that in the brains of depressed people, the lowering of the expression of SSAT could be a compensatory mechanism to cope with the excessive presence of PA [46]

ALZHEIMER AND PARKINSON DISEASES

Alzheimer (AD) and Parkinson (PD) diseases are generally associated with aging and cause progressive decline of cognitive function. These severe neurological impairments are associated with accumulation of phosphorylated tau protein that forms neurofibrillary tangles and neurotoxic amyloid beta-peptide (Aβ), which is responsible for theformation of the senile plaques The AD patients exhibit increase in the activity of ODC and PA levels in the brain, which had been implicated in the PAs role in both cognitive deficit andsynaptic loss.

Exposure of neuronal cell cultures to Aβ increased PA levels, NMDAr activation, and synaptic loss. The intracerebral injection of Aβ induced cognitive impairment in experimental animals,which was reversed by NMDA antagonists, suggested a role in memory loss.Also, blocking the PA binding site in NDMAr either by arcaine or inhibiting PA synthesis by DFMO reversed the Aβ25-35-induced memory impairment in mice . Collectively, these studies provide evidencethat PAs are deleterious to Aβ-accumulation and higher PA levels under these conditions cause cognitive decline , a stipulationopposite to the effects of high

PAs in improving learning and memory innaive animals. Parkinson's disease reduces expression of SAT1, a catabolicPA enzyme, and consequently higher PAs levels increased in patients. This increase in PAs levels has been implicated in cognitive reduction in Parkinson patients via NMDAr pathway [51].

Metabolic profiling of serum samples of PD patients suggested thatalteration of PA metabolism can be used to predict cases of rapidprogression [52]. In another study, PD patients were found to have higher concentrations of Put, Cad, acetylated derivatives of Cad and Spd (N1 -acetyl-Cad and N1 -acetyl-Spd) and lower levels of Spd in the cerebrospinalfluid. In red blood cells of PD patients, Put levels are decreased and Spd and Spm levels are increased [53]. Similar to these results from PD, metabolic profiling of brains of AD patients revealed elevated levels of Put, Spd, Spm and acetylated Spd and Spm [54]

Polyamine and Epilepsy

Epilepsy is classified into different categories: childhood absence epilepsy, benign focal epilepsy, juvenile myoclonic epilepsy and temporal lobe epilepsy (TLE). The latter is the most common epilepsy occurring in adults [71,72]. Over the years, different research groups have focused their studies on the role that PAs could have in the molecular mechanisms underlying epilepsy. Since the knowledge, derived from clinical human studies, was not sufficient to improve understanding of the epileptic pathways, it was necessary to use the correct genetic models. In fact, extensive studies have been carried out using animal models in order to characterize the different form of epilepsy and better define the physiological importance of PAs in order to develop treatment therapies to be applied in epilepsy [73,74]

Mood disorders and suicide

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 , 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-Nicolescu [70] 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 specific 6 .

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.

Polyamine stress response

acute stressors in the CNS result in the elevation of ODC activity and putrescine and agmatine levels. [13,14] The PSR can be induced by multiple forms of stress, and its magnitude appears to be related to the intensity of the stressor.[15,16] Consistent with this are findings that anxiolytic pretreatment can diminish or eliminate stress-induced alterations of the polyamine system 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.[17]

PAs in Plant Origin Food

Vegetables rich in Put include green pepper, dried soybean, green peas, eggplant and green onion. High amounts of Put, in the range of 31.2–84 mgkg−1 FW with a mean value of 54.7mg kg−1 FW, were found in Japanese fresh green pepper. Spd and Spm-rich vegetables are mushrooms, broccoli,lettuce and pumpkin, along with beans. Dried soybean (Put 41, Spd 207,and Spm 69.0, mg kg−1 FW) and green peas (Put 32.4, Spd 49.5, and Spm 6.5, mg kg−1 DW) are among the top 10 vegetables rich in all the three PAs. Overall, beans seem to have higher levels of Spd and Spm while many vegetables are higher in Put and Spd. Orange, mango, and banana feature among the top ten fruits highly enriched in PAs, with Put being the main PA followed by Spd. Fruits other than these, such as lime (41.0 mg kg−1 FWPut), pear (24.0 mg kg−1 FW Put) and melon (11.7 mg kg−1 FW Spd) are also good sources of PA.

Maize (corn), brown rice and whole grain wheat are richer in Spd, with the following decreasing order: Japanese corn (43.0 mg kg−1 FW) > whole grain wheat (13.1– 21.0 mg kg−1 FW) > millet (9.1 mg kg−1 FW) > brown rice (6.4 mg/kg −1FW). Interestingly, all these grains contain more Spm than Put. In addition to vegetables, fruits and grains, nuts are also a good source of PAs. Pistachio and almonds contain high levels of all three major Pas whereas hazelnut and cashew contain higher amounts of Spd (21 mg kg−1 FW) and Spm (24mg kg−1 FW), respectively. In the context of common beverages, tea and coffee are the twomost favourite beverages consumed by humans. Black tea leaves are rich in Spm (59 mgkg−1)

followed by Spd (38.1 mg kg−1) and Put (15.3 mg kg−1) while the pattern of Pas content in green coffee was found to be in the reverse order, with Put at 10.3 mg kg−1 signiβicantly higher than Spd (6.0 mg kg−1) and Spm (4.4 mg kg−1), respectively [64].

PAs in Animal Origin Food

Many studies have indicated that Put levels in animal meat are generally lower (less than 10mg kg−1) as compared to Spm (more than 25 mg kg−1). Pheasant, duck, deer, chicken, lamb and pork contain higher levels of Spm compared to Spd and Put, with beef liver containing the highest levels, 197 mg kg−1 FW. However, fallow deer contains higher levels of Put (38 mg kg−1 FW) than Spd (14.7 mg kg−1 FW). Among the seafood—canned crab, coral scallops, raw cod, and shrimp do not follow any typical pattern, i.e., high Spm and low Put, except they are richer in Put. On the other hand, short-necked clam, muscles, octopus, salmon and sardine are rich sources of Spm and Spd while canned crab (122 mg.kg−1), scallops (43mg.kg−1), raw cod (28 mg.kg−1), and shrimp (3.7 mg.kg−1) are more enriched in Put. Spm levels in meat and meat products of warm-blooded animals are generally higher, ranging from 20 and 60 mg kg−1 whereas βish contains <10mg kg-1. It is apparent that high concentrations of Spd and Spm is typical of foods from animal origin as compared to the plant product.

CONCLUSION

Polyamines can be considered supplementary defensive shielding molecules, important to protect the brain from the development of epilepsy and mental illnesses that are caused by different types of neurons. In this contest, the modulation of polyamine metabolism may be a novel important target for the prevention and therapeutic treatment of these diseases that have a high impact on the costs of public health and considerably affect quality of life. Thus far,research has established that PAs generally boost physiological processes to reduce aging, stress-induced responses and loss of memory, but detrimentally influence pathology-related conditions such as Alzheimer and Parkinson diseases . Genetic evidence for the positive PA roles in mammals is associated with a number of growth and developmental processes, including the behavioral aspect.

food is an important source of the polyamines required to support cell renewal and growth.

Although the bioavailability and the mechanism of the uptake of polyamines in the gastrointestinal tract are not fully established, it is evident that at least some proportion of the polyamines in the diet can be absorbed and utilized by the body.A beneficial role of dietary Spd in enhancing life span of various organisms and human cell lines tightens the connection between “wellness diets” and human health.

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