ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Levels of Polyamines in Autopsy Materials of Some Structures of Brain Lymbic System and Reticular Formation of Patients with Schizophrenia.

SP Syatkin, IP Smirnova, OM Kuznetsova, TA Lobaeva, ML Blagonravov, EA Ryskina, RI Sokuyev, and NA Shevkun.

Russian Peoples' Friendship University, Miklukho-Maklaya str., 8, Moscow, 117198, Russia.

ABSTRACT

The polyamines levels in autopsy brain materials of 8 patients with paranoid schizophrenia with continuous progredient type of course of disease who died of pneumonia or sharp heart deficiency at the age of 44-58 have been investigated. The results of investigations of spermine, spermidine and putrescine content in 8 autopsy brain structures of patients with schizophrenia (frontal and temporal lobes, convolution of the cingulum, hypothalamus, thalamus, almond-shaped core, caudate core, black substance) have been demonstrated. The highest concentrations of spermidine, calculated per 1g of raw materials or per 1 mg of protein, were discovered in grey substance of frontal lobe, in grey and white substance of temporal lobe. The highest level of putrescine is in the hypothalamus, frontal lobe and cingulate convolution. The lowest level of putrescine was discovered in thalamus as compared to another tested structures. The greatest concentration of spermine was discovered in black substance, in white substance of frontal lobe and convolution of the cingulum. It was established, that levels of spermine in grey substance of the frontal and temporal lobes as well as in the grey substance of cingulate convolution have been the lowest. Possible role of polyamine's interference in mechanism of psychosis development is discussed.

Keywords: polyamines, schizophrenia, limbic system and reticular formation, continuous progredient type

Corresponding author

ISSN: 0975-8585

INTRODUCTION

High concentrations of polyamines, which quantitatively exceed other brain amines, have been found in the central nervous system of animals and a human [[1]]. Polyamines in the mature brain play a role in the brain's response to injury and stress, the regulation of ion fluxes and neuronal ion channels [2], the modulation of various receptors and neurotransmitter [3], as well as the control of axon genesis and neurite elongation during synaptogenesis [2]. It should be noted that, for obvious reasons, there has been an extremely small number of studies of polyamines in the brain performed. There is only insignificant information regarding the distribution of polyamines in the normal human brain. However, these studies were limited to the one of the fetal brain, or a small number of cases (n = 2), or the study of the holistic brain specimens. The only exception is the work by Morrison et al (1995) [4], which describes the regional distribution of the polyamines in 10 areas of the brain of people of different age groups. These studies were carried out on 57 autopsy samples of neurologically and neuropsychiatrically normal human brain. It was shown that polyamines are distributed heterogeneously in the mature brain.

These results are important in studying the polyamines in the central nervous system both in normal and in various pathologies, especially when endogenous mental illnesses.

The objective of this paper was the study of the distribution and fractional composition of polyamines in certain regions of the brain of schizophrenic patients, particularly in those structures of the limbic system and the reticular formation, which are most relevant to the etiopathogenesis of schizophrenia according to modern concepts.

MATERIALS AND METHODS

Diagnosis of schizophrenia was performed using diagnostic criteria and classification of schizophrenia proposed by the Institute of Psychiatry of AMS USSR, as well as using a BPRS diagnostic scale [5]. The data obtained were recorded into a specially designed examination record.

To determine the content of polyamines in biological samples a modified Selier and Knodgen method was used (1979) [6].

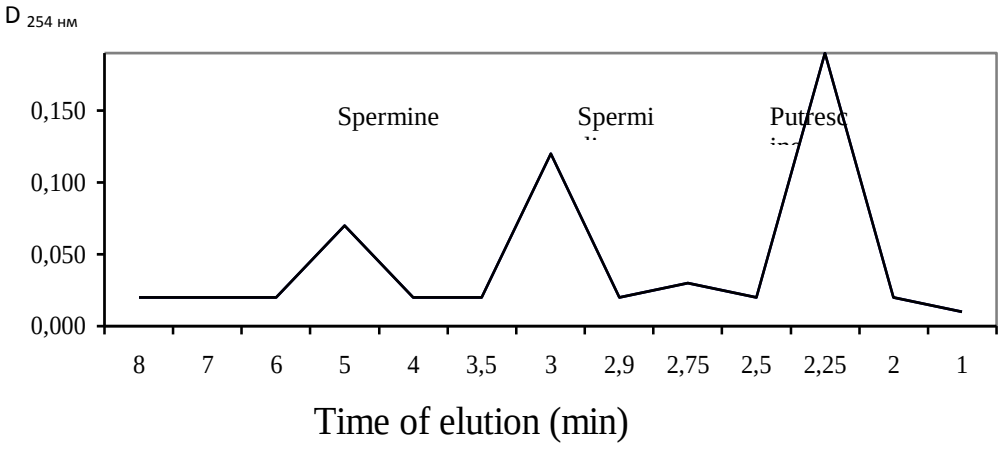

Figure 1: Separation of polyamines with the help of high-pressure high-performance liquid chromatography (chromatogram of polyamine standards: putrescine, spermine, spermidine).

Some samples were separated after thin layer chromatography using high-pressure high-performance liquid chromatography. For this purpose the "Laboratolrni apristroi, Czechoslovakia" chromatograph was used. After thin layer chromatography, dansil-polyamine spots detected in UV light were carefully scraped off with a scalpel into the tube and eluted in 50 µl of methanol or acetonitrile, and 20 µl were applied on a column (C-18, 4.6 x 300 mm). Polyamines were eluted at room temperature in methanol : water (75:25) or acetonitrile : water (80:20). Rate of elution was 1-2 min. The absorbance was measured using a UV detector at a wavelength of 254 nm. A typical chromatogram of a polyamines mixture is shown in Fig. 1.

Table 1: The concentration and distribution of polyamines in the structures of the limbic system and reticular formation of the autopsy brain of schizophrenics, nmol/g wet weight (M±m; n=8)

Brain area	Spermine	Spermidine	Putrescine	∑PA	Spermidine /Spermine
Frontal lobe*	393±89	816±130	190±17	1400±234	2.0
grey substance	240±60	890±120	185±35	1315±160	3.7
white substance	708±80	740±45	100±15	1548±210	1.04
Temporal lobe*	352±102	742±128	140±35	1234±190	2.1
grey substance	204±40	882±110	145±30	1231±210	4.3
white substance	483±60	870±110	105±40	1458±250	1.8
Cingulate convolution*	271±40	691±59	181±26	1109±121	2.54
grey substance	186±50	689±70	132±20	1007±85	3.7
white substance	664±90	686±60	105±25	1455±115	1.0
Hypothalamus	471±14	720±89	198±18	1397±107	1.54
Thalamus	304±87	754±79	115±21	1174±79	2.5
Amygdaloid body	478±126	709±126	141±14	1318±104	1.5
Caudate nucleus	396±161	765±164	154±28	1315±200	1.9
Substantia nigra	725±31	633±36	133±26	1491±88	0.87

*Note: * - is the total concentration of polyamines in the tissue.*

Statistical analysis of the results was performed by parametric and nonparametric methods. Processing, analysis and calculation of the percentage characteristics and correlation coefficients were performed using SPSS 10.0.5 for Windows 95. The reliability of the differences of the resulted mean values of the experimental groups was performed using Student t-test (Afifi, Eisen, 1982) [7].

RESULTS

The polyamines levels in autopsy brain materials of 8 patients with paranoid schizophrenia with continuous progredient type of course of disease who died of pneumonia or sharp heart deficiency at the age of 44-58 have been investigated (Table 1).

Duration of the disease is 10 to 20 years. The following structures have been investigated: the cortex and white substance of the frontal and temporal lobes, grey and white substance of the cingulate convolution, hypothalamus, thalamus, amygdala and caudate nucleus and substantia nigra. Data in Table 1 show that the highest concentrations of spermidine, calculated per 1g of raw materials or per 1 mg of protein, were discovered in grey substance of frontal lobe, in grey and white substance of temporal lobe.

The highest level of putrescine is in the hypothalamus, frontal lobe and cingulate convolution ($P<0.05$). The lowest level of putrescine was discovered in thalamus as compared to an other tested structures ($P>0.05$). Differences in the putrescine levels in other areas are negligible. The greatest concentration of spermine was discovered in black substance, in white substance of frontal lobe and convolution of the cingulum. It was established, that levels of spermine in grey substance of the frontal and temporal lobes as well as in the grey substance of cingulate convolution have been the lowest.

Since the objectives of the study excluded the investigation of the content of polyamines in these normal brain structures, the results of own research were compared with literature data available. During such comparative analysis it was revealed that the levels of polyamines found in the brains of schizophrenics were significantly higher than the same in the normal brain. Thus, according to Williams - Ashman and Lochwood [8], the amount of polyamines in the grey and white substances of the frontal lobe was as follows: spermine - 240 and 200 nmol/g, spermidine - 240 and 640 nmol/g, putrescine - 30 and 40 nmol/g, respectively. As can be seen, the levels of all three polyamines in the frontal lobe detected in schizophrenic patients in our study are significantly higher.

According to Morrison et al [4], who investigated the normal brain, a similar situation was revealed. We have also presented our data in nmol/mg of protein for the convenience of the comparison since the authors expressed the levels of polyamines in nmol/mg of protein in the above paper (Table 2).

Data presented in Table 2 indicate that the levels of spermine in the investigated structures (frontal and temporal lobes, thalamus, hypothalamus) in patients with schizophrenia are by several times (3.2 - 6.2 times) higher than standard. The content of spermidine in the hypothalamus, temporal and frontal lobes of patients was increased by 1.7 - 4.4 times in comparison with healthy patients. As for the concentration of spermidine in the thalamus, no statistical difference in terms of norm and pathology was revealed. In addition, according to Morrison et al [4], the level of spermidine in the white substance of the brain is 20 nmol/mg of protein, whereas our studies have shown this figure varying within (14.1 ± 0.9) and (14.2 ± 1.2) nmol/mg of protein. It should also be noted that the levels of spermine in the white substance of the mature normal human brain is much lower than in gray substance according to the results of all studies available in the literature. Patients with schizophrenia otherwise have a higher concentration of spermine in white substance than in grey substance. This is especially expressed in the frontal lobe, where levels of spermine in the white substance are 3 times higher than in grey one, and its amount is close to the concentration of spermidine in this structure (see Table 1).

The molar ratio of the concentration of spermidine/spermine, according to the literature, is always higher in the white substance of the normal brain tissue. The study has shown that this indicator, otherwise, is much lower in white substance than in grey in patients with schizophrenia.

Table 2: The content of polyamines in some brain structures in of patients with schizophrenia and normal patients nmole/g of protein (M ± m)

Brain structure	Spermine	Spermidine
In patients with schizophrenia (own data)		
Frontal lobe		
grey substance	5.9±1.3	16.3±0.7
white substance	11.6±1.2	14.1±0.9
Temporal lobe		
grey substance	6.15±1.3	14.7±0.5
white substance	7.9±0.5	14.2±1.2
Thalamus	7.1±1.0	10.4±1.2
Hypothalamus	6.8±0.5	8.8±0.9
Normal* (Morrison et al, 1995)		
Frontal lobe	1.2	3.7
Temporal lobe	1.9	5.0
Thalamus	1.3	9.3
Hypothalamus	1.1	5.0
White substance	1.5	20.0

*Note. * - Data are presented as average value, since the paper by Morrison et al. presents a small-scale pattern. This makes it difficult to accurately calculate the standard deviation.*

DISCUSSION

It is known that almost all biochemical hypotheses about causal factors of psychosis were based on the study of mechanisms of action of psychotropic drugs and psychotomimetics, as well as the structural similarity of neurotransmitters (e.g., noradrenaline, dopamine) with mescaline, LSD, and others. It follows from these studies that neuroleptics, in addition to similarity with dopamine, have a much greater resemblance to spermidine. This applies to both phenothiazine type neuroleptic and the butyrophenones and clozapine. Some hallucinogens - substances incompatible to antipsychotics - also have similarities with polyamines. This particularly applies to chloroquine, mepacrine, amodiaquine, clamoxyquine.

The situation when substances structurally similar to polyamines or containing spermidine chain produce opposite effects, can probably be explained by a dual effect of polyamines themselves. Thus, depending on the concentration, the latter have either stimulatory or inhibitory effects on various biochemical and physiological processes.

Intracerebral administration of polyamines has revealed that both spermine and spermidine (at a dose of 5-20 mg) introduced bilaterally into nucleos accumbens, have inhibited the hyperactivity induced by

amphetamine introduced into the same nucleus. However, if the injection is made in the corpus striatum, then none of the polyamines initiated asymmetries or whirling either spontaneously or after intraperitoneal injection of apomorphine. These results indicate a selective effect of polyamines on behavior due to the mesolimbic function of dopamine [9].

It is quite probable that the increase in the content of polyamines (putrescine) in the brains of patients may, in addition to other possible effects, be one of the causal factors neuronal wrinkling, degenerative changes, presence of pathological granularity and foci of neuron loss morphologically identified in patients with schizophrenia. These symptoms may result from the development of apoptosis.

Thus, the result of our research was the discovery of a significant increase in the concentration of polyamines in some structures of the limbic system and the reticular formation of the brain in patients with schizophrenia. These results support the opinion by Richardson-Andrews about basic violations of metabolism of polyamines in patients with schizophrenia [10].

REFERENCES

[1] Shaw G.G. Polyamine metabolism and function in brain.//Neurochem. Int. – 1981. - V.3.№2. – P. 111-112.
[2] Chu. P.-J., Saito H., Abe K. Polyamines promote neurite elongation of cultured rat hippocampal neurons.//Neurosci. Res. – 1994. – V.19 №1. – P. 155-160.
[3] Williams K., Romano C., Dichter M.A. et al. Modulation of the NMDA receptor by polyamines.//Life Sci.. – 1991. - V48 №3. – P. 469-479.
[4] Morrison L.D., Becker L., Ang L.C., et al. Polyamines in human brain: regional distribution and influence of aging.//J. of Neurochemistry. – 1995. – V.65 №2. – P. 635-642.
[5] Overall J.E., Gorham D.R. The brief psychiatric rating scale.//Psychol. Rep. – 1962. – V.10. – P. 799-812.
[6] Seiler N., Knodgen B. Determination of the naturally occuring monoacetylderivatives of di- and polyamines.//J. Chromatograph. (Biomed. Appl.) - 1979. – V.164 №1. – P. 155-168.
[7] Afifi A., Eisen S. Statistical Analysis. A computer-based approach. - M.: Mir. 1982. - 488 p.
[8] Williams-Ashman H.G., Lochwood D.H. Role of polyamines in reproductive physiology and sex hormone action.//Ann. N.Y. Acad. Sci. – 1970. – V.171. – P. 882-894.
[9] Richardson-Andrews R.C. The side effects of antimalaries drugs indicate a polyamine involvement in both schizophrenia and depression.//Med. Hypotheses. – 1985. – V.18. – P. 11-18.
[10] Hirsch S. R., Richardson-Andrews R., Costall B., et al. The effects of some polyamines on putative behavioural indices of mesolimbic versus striatal dopaminergic function.//Psychopharmacology. – 1987. – V.93 №1. – P. 101-104.