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Characteristics of Changes in Catecholamine and Serotonin Metabolism in the Brain of Rats with Cerebral Ischemia

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SUMMARY

Biogenic amines play an important role in brain metabolism and functioning, participation in synaptic transmission as neurotransmitters and neuromodulators (dopamine, serotonin, histamine and others). Catecholamines are formed from the essential amino acid phenylalanine by hydroxylating it to tyrosine with the enzyme phenylalanine-4-hydroxylase, which is subsequently converted to dioxyphenylalanine (DOPA) with tyrosine-3-hydroxylase. An intermediate metabolic link in the biosynthesis of serotonin is 5-hydroxytryptophan (5-HTP), which is formed from the amino acid tryptophan by the enzyme tryptophan hydroxylase, one of the hydroxylases Aromatic amino acids that depend on biopterin. It is subsequently decarboxylated to serotonin (5-hydroxytryptamine) by the enzyme aromatic L-amino acid decarboxylase with vitamin B6 acting as a cofactor. As a neurotransmitter, serotonin is synthesized and deposited in presynaptic neurons - serotoninergic neurons, pineal gland and catecholaminergic neurons of the brain. Serotonin is present in nine cell groups isolated from the bridge and midbrain. The limiting step of serotonin synthesis in serotoninergic neurons is the formation of 5-oxytryptophan and depends on tryptophan entering the brain through the HEB. The final metabolite of serotonin is 5-oxyindolacetate. Cerebral ischemia results in disorders of the metabolism of biogenic amines - catecholamines and serotonin, namely, disruption of catecholamine formation at the level of their conversion from the precursor amino acids phenylalanine and tyrosine and serotonin - at the level of conversion of tryptophan to 5-hydroxytryptophan.

Keywords: Catecholamine; Serotonin; Brain; Cerebral Ischemia

Abbreviations: DOPA: Dioxyphenylalanine; PCI: Partial Cerebral Ischemia; CVA: Common Carotid Arteries; TCI: Total Cerebral Ischemia; SCI: Subtotal Cerebral Ischemia; PL: Parietal Lobe

Introduction

Biogenic amines play an important role in brain metabolism and functioning, participation in synaptic transmission as neurotransmitters and neuromodulators (dopamine, serotonin, histamine and others). Catecholamines are formed from the essential amino acid phenylalanine by hydroxylating it to tyrosine with the enzyme phenylalanine-4-hydroxylase, which is subsequently converted to dioxyphenylalanine (DOPA) with tyrosine-3-hydroxylase [1-3]. Subsequently, dihydroxyphenylalanine is decarboxylated to dopamine by DOPA decarboxylase. There is an excess of DOPA-decarboxylase in the brain, with the highest activity in the hypothalamus and midbrain and the lowest in the cortex and cerebellum [4]. High DOPA-decarboxylase activity is also found in the brain capillaries, which is an obstacle to DOPA penetration into the brain due to the formation of dopamine, which passes poorly through the BBB [5-10]. Subsequently, dopamine is converted into norepinephrine and adrenaline [6]. Dopamine is involved in the regulation of many functions of the nervous system: the realization of cognitive processes, the regulation of attention and arousal, the control of emotions and motor activity. Subsequently, dopamine is hydroxylated at the β-carbon atom to noradrenaline by

the enzyme dopamine-β-hydroxylase. This enzyme is localized within vesicles that contain catecholamine and requires the presence of ATP, NAD, NADPH, and Ca to be active2+. The formation of noradrenaline mainly takes place in the perikaryons of adrenergic neurons with subsequent transport by axonal current into nerve endings and entry into vesicles [7,8].

The final step of catecholamine biosynthesis, methylation of HA to adrenaline, occurs with the participation of the enzyme phenyl ethanolamine-N-Mel transferase, whose activity in the brain is low and the adrenaline biosynthesis process is very weak. The main metabolite of catecholamines, including dopamine in the brain is dioxyphenylacetate [10]. An intermediate metabolic link in the biosynthesis of serotonin is 5-hydroxytryptophan (5-HTP), which is formed from the amino acid tryptophan by the enzyme tryptophan hydroxylase, one of the hydroxylases Aromatic amino acids that depend on biopterin. It is subsequently decarboxylated to serotonin (5-hydroxytryptamine) by the enzyme aromatic L-amino acid decarboxylase with vitamin B6 acting as a cofactor [5-8]. As a neurotransmitter, serotonin is synthesized and deposited in presynaptic neurons-serotoninergic neurons, pineal gland and catecholaminergic neurons of the brain. Serotonin is present in nine cell groups isolated from the bridge and midbrain. The limiting step of serotonin synthesis in serotoninergic neurons is the formation of 5-oxytryptophan and depends on tryptophan entering the brain through the HEB. The final metabolite of serotonin is 5-oxyindolacetate [2-9].

Materials and Methods of Research

Experiments were performed on 56 male white mongrel rats weighing 260±20 g in compliance with the European Parliament and Council Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes. CI was simulated under intravenous thiopental anesthesia (40-50 mg/kg). The studies used models of IGM of different severity: partial (PCI), subtotal (SCI), staged subtotal (SSCI) and total (TCI) cerebral ischemia. The table shows the experimental groups and the number of animals in them (Table 1). Partial cerebral ischemia (PCI) was simulated by ligation of one OSA on the right side. Subtotal cerebral ischemia (SCI) was modeled by a single-stage ligation of both common carotid arteries (CVA). Staged subtotal IC (SSCI) was performed by consecutive ligations of both OSA at 7-day (subgroup 1), 3-day (subgroup 2), or 1-day (subgroup 3) intervals. Total cerebral ischemia (TCI) was modeled by decapitating the animals. Material was taken 1 hour after surgery. The control group consisted of falsely operated rats of similar sex and weight. Biogenic amines were studied in prepared homogenates of the studied brain structures of experimental animals isolated 1 hour after ischemia modeling. For this purpose, a fragment of the parietal lobe (PL) and hippocampus (Hp) was taken after brain extraction with its subsequent freezing in liquid nitrogen. Sample preparation for the study included homogenization in a 10-fold volume of 0.2M perchloric acid, centrifugation for 15 min at 13000 g at 4°C, followed by supernatant sampling.

Table 1: Experimental groups.

Group name		Number of animals in the group
Control		8
PCI (partial cerebral ischemia)		8
SCI (subtotal cerebral ischemia)		8
SSCI (staged cerebral ischemia)	subgroup 1 (7 days)	8
	subgroup 2 (3 days)	8
	subgroup 3(1 day)	8
TCI (total cerebral ischemia)		8

Amino acids were analyzed by reverse-phase chromatography with pre-column derivatization with o-phthalic aldehyde and 3-mercaptopropionic acid in Na-borate buffer using an Agilent 1100 chromatograph [2-9]. To prevent systematic measurement error, brain samples from compared control and experimental groups of animals were studied under the same conditions.

Statistical Processing

Quantitative continuous data were obtained as a result of the research. Since small samples were used in the experiment, which had a non-normal distribution, the analysis was performed using nonparametric statistical methods using the licensed computer program Statistical 10.0 for Windows (StatSoft, Inc., USA). The data are presented as Me (LQ; UQ), where Me is the median, LQ is the lower quartile value; UQ is the upper quartile value. If the conditions of applicability were met (normality of samples and homogeneity of variance), parametric analysis of variance with a posteriori comparison of selected contrasts was used; if the conditions of applicability were not met, nonparametric analysis of variance followed by a test of multiple contrasts after Fisher's transformation was used.

Results

In cerebral ischemia there was mainly a tendency to a decrease in dopamine content, most pronounced in the hippocampus with the most severe degree of cerebral ischemia: in the 3rd subgroup of SSCI with a minimum interval of 1 day between OSA ligation, in the SSCI and TCI groups by 83% ($p>0.05$), 82% ($p>0.05$) and 81% ($p>0.05$) respectively (Tables 1 & 2). At the same time, the content of the dopamine precursor, tyrosine, increased in the TCI group by 40% ($p<0.05$). Correspondingly, the content of noradrenaline and dioxyphenylacetate tended to decrease ($p>0.05$), which indicates an impaired catecholamine metabolism at the level of tyrosine conversion to dopamine (Table 3). At CI there was a disorder of serotonin metabolism, which consisted in an increase in the content of the amino acid tryptophan in both studied structures of the brain. Thus, in TIGM its content was higher, compared to the control, by 24% in TD ($p<0.05$) and by 26% in Hp ($p<0.05$). In addition, the content of 5-hydroxytryptophan, a direct precursor of serotonin, was multidirectional: there was a tendency to increase its content in TD ($p>0.05$) and to decrease it - in Hp ($p>0.05$), while the content of serotonin and its final metabolite

5-oxyindolacetate did not change (p>0.05). These results indicate an impairment of serotonin formation at the level of conversion of tryptophan to 5-hydroxytryptophan. Thus, cerebral ischemia results in disorders of the metabolism of biogenic amines - catecholamines and serotonin, namely, disruption of catecholamine formation at the level of their conversion from the precursor amino acids phenylalanine and tyrosine and serotonin - at the level of conversion of tryptophan to 5-hydroxytryptophan.

Table 2.

Parietal lobe	Control	PCI 1 hour	SCI 1 hour	1 SSCI subgroup 7c	2 SSCI subgroup 3c	3 subgroups of the SSIGM 1s	TIGM
Dopamine metabolism							
Phenylalanine	29.4 (24.6/33.7)	24.4 (22.9/27.5)	30.3 (28.5/34)	31.4 (30.2/32.3)	26.9 (26.6/28.4)	27.1 (26.7/30.2)	36.2 (34.4/38.2)
Tyrosine	46.2 (40.1/50.1)	50.1 (41.7/52.3)	47.9 (43.8/50.7)	54.4 (52.5/57.3)	46.2 (42.5/62.3)	56.4 (54/61.7)*	81.2 (71.6/87)*
Dopamine	2.76 (0.723/5.84)	2.08 (1.01/4.57)	1.8 (0.888/10.2)	3.41 (0.685/14.3)	0.982 (0.64/4.32)	4.46 (1.82/16.7)	1.62 (0.759/2.88)
Norepinephrine	6.67 (6.13/7.73)	5.47 (0.967/10.8)	8.41 (6.08/9.85)	6.26 (5.9/7.47)	6.41 (5.73/7.09)	2.06 (0.988/6.15)	6.76 (6.08/7.24)
Dioxyphenylacetate	2.13 (1.59/3.22)	1.88 (1.51/3.36)	1.78 (1.59/2.55)	3.16 (2.93/3.47)	2.88 (1.58/3.43)	3.48 (2.47/4.25)	3.87 (1.69/4.69)
Serotonin exchange							
Tryptophan	27.7 (24.6/32)	22.6 (20.6/25.2)	19.8 (17.3/24.5)	37.6 (34.9/46.1)*	25 (23.4/27.7)	21.2 (20.3/25.3)	37.6 (32/40.4)*
5-hydroxytryptophan	0.11 (0.0941/0.158)	0.178 (0.144/0.223)	0.127 (0.0895/0.177)	0.212 (0.17/0.302)	0.144 (0.0952/0.187)	0.119 (0.101/0.138)	0.172 (0.15/0.279)
Serotonin	3.65 (2.78/4.48)	4.24 (3.31/5.43)	4.52 (1.62/4.78)	5.36 (4.34/6.83)	2.07 (1.68/3.81)	4.33 (3.4/5.42)	2.53 (2.17/3.24)
5-oxyindolacetate	1.82 (1.29/2.86)	1.99 (1.67/2.6)	2.3 (1.14/3.18)	2.78 (2.45/4.43)	1.61 (1.1/1.89)	2.39 (1.49/2.96)	1.82 (1.72/2)

Note: numerical values are presented as Me (LQ; UQ), * - p<0.05 versus control.

Table 3.

Hippocampus	Control	PCI 1 hour	SCI 1 hour	1 SSCI subgroup 7c	2 SSCI subgroup 3c	3 subgroups of the SSCI 1s	TCI
Dopamine metabolism							
Phenylalanine	31,6 (26/39,2)	26,8 (25/30,3)	31,3 (30,5/32,4)	32,6 (31,5/34,7)	30,6 (28,7/32,4)	34 (31,8/36,1)	37,1 (36,2/42,4)
Tyrosine	49,3 (44,6/50,2)	48,9 (42,2/56,6)	50,3 (46,1/54)	56,1 (51,2/58,2)	54,8 (45,4/65,5)	65,4 (59,3/66,9)*	82 (78/90,6)*
Dopamine	10,3 (4,37/18,8)	5,74 (0,622/21,1)	1,85 (0,933/3,92)	7,78 (1,94/10,8)	4,32 (0,892/13,3)	1,79 (0,948/8,87)	1,99 (0,636/14)
Norepinephrine	7,28 (6,76/8,44)	6,74 (3,27/7,7)	6,34 (5,89/7,39)	6,51 (5,63/7,55)	6,53 (5,82/7,66)	5,48 (1,69/7,42)	8,01 (5,4/10,9)
Dioxyphenylacetate	2,82 (2,36/3,25)	2,41 (1,9/3,51)	1,55 (1,43/1,78)	2,34 (1,51/3,36)	1,9 (1,68/2,11)	2,22 (1,61/3,33)	2,93 (2,44/4,21)
Serotonin exchange							
Tryptophan	29,8 (25,1/31,8)	24,7 (22,9/26,3)	22,7 (21,5/27,8)	42 (37,3/47,8)*	27 (26,2/28,8)	25,2 (23,3/29,2)	39 (36,4/40,9)*
5-hydroxytryptophan	0,187 (0,164/0,195)	0,156 (0,126/0,178)	0,103 (0,0798/0,128)	0,149 (0,136/0,326)	0,132 (0,0715/0,221)	0,0834 (0,0599/0,149)	0,136 (0,102/0,202)
Serotonin	5,41 (4,35/5,97)	5,47 (5,07/6,27)	3,72 (2,53/6,05)	6,14 (3,87/8,24)	5,39 (4,51/6,98)	4,88 (3,69/5,71)	5,14 (4,01/5,89)
5-oxyindolacetate	2,63 (1,9/3,08)	2,36 (1,8/2,93)	2,68 (2/4,51)	3,42 (2,59/7,52)	3,4 (2,66/4,58)	2,47 (1,87/3,4)	3,75 (2,3/5,02)

Note: numerical values are presented as Me (LQ; UQ), * - p<0.05 versus control.

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