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EXPERIMENTAL ARTICLES

The Behavior and Neurotransmitter Contents in Brain Structures of Rats with Alzheimer's Disease Modeled by Administration of $A\beta_{25-35}$

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Abstract—We studied behavioral and neurochemical alterations that were induced by modeling of Alzheimer's disease (AD) using bilateral intracerebroventricular administration of $A\beta_{25-35}$ at a dose of 7.5 nmol in each ventricle. After 5.5 weeks, cognitive and psychoemotional alterations in the Morris spatial learning and Porsolt's forced-swim tests were observed in rats with strong symptoms that are typical of AD. Measurement of the contents of monoamines and their metabolites in rat-brain structures was performed using the HPLC with the ECD method 1 day after the end of the tests. In the dorsal striatum, we found a decrease in the contents of metabolites of dopamine (DA), including homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), and 3-methyltyramine (3-MT), and a decrease in the indices of DA utilization, including DOPAC/DA and HVA/DA, whereas the DA content was stable in this structure. In the nucleus accumbens (NA, ventral striatum), we found a decreased level of the HVA/DA ratio, which reflects the lower turnover of extracellular DA. We also found a lower turnover of serotonin (5-HT), which was seen as a decrease in the 5-hydroxyindolacetic acid (5-HIAA)/5-HT ratio, whereas the 5-HT content was elevated. In the hypothalamus, we revealed a significant decrease in the DA level and the levels of its metabolites, including 3-MT and HVA, and 5-HT turnover. We found that $A\beta_{25-35}$ influenced the indices of amino-acidergic neurotransmission, which was reflected by the higher glutamate content in the striatum. Our data show that cerebral neurotransmitter systems, such as the tuberoinfundibular, mesolimbic, and nigrostrial dopaminergic and the striatal serotonergic and glutamatergic systems, are involved in pathophysiological mechanisms of the development of cognitive and psychoemotional impairments that occur in AD, as modeled by administration of $A\beta_{25-35}$.

Keywords: Alzheimer's disease, $A\beta_{25-35}$, monoamine metabolism, brain structures, liquid chromatography, depression, cognitive impairments, Morris maze

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INTRODUCTION

It has been recently shown that the dopaminergic system is one of the primary targets of damage during the development of neurodegenerative diseases. In Parkinson's disease, death of dopaminergic nigrostriatal neurons is a leading mechanism of pathogenesis, while even in the premotor stage of disease a nearly 60% loss of dopamine-containing neurons is observed [1, 2]. A loss of dopaminergic neurons followed by a 40–70% decrease in the dopamine content in the striatum was found in 35% of the patients with Alzheimer's disease (AD) [3–5]. Due to this fact, AD patients, in addition to cognitive impairments, also exhibit extrapyramidal and psychoemotional disturbances that are similar to those found in Parkinson's disease [6, 7]. The occurrence of these clinical signs in AD is related not only to the changes in the functional state of the dopaminergic system but also of the serotonergic neurotransmitter system [8–10]. Thus, in AD patients with mild cognitive impairments and depression, the decreased levels of dopamine (DA) and serotonin (5-HT) metabolites, such as homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA), respectively, were observed, which is probably related to the lower contents of DA and 5-HT in the brain tissue or their declined metabolism [11]. An accumulation of amyloid-β plaques is a key step in AD pathogenesis, which causes neuronal death [12]. Intracerebral administration of $A\beta_{1-40}$ into the retrosplenial cortex of animals decreased the number of dopaminergic and norepinephrinergic neurons in the locus coeruleus by 57 and 35%, respectively, serotonergic neurons in the dorsal and medial raphe nuclei by 32 and 54%, respectively, and cholinergic neurons in the laterodorsal tegmental nucleus by 24% [13].

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In the present study, we examined cognitive functions and depressive-like behavior, as well as the functioning of the monoaminergic, specifically dopaminergic, serotonergic, and norepinephrinergic systems, and amino acid-ergic neurotransmitter systems in the rat brain after administration of $A\beta_{25-35}$ into the cerebral ventricles.

MATERIALS AND METHODS

Outbred male rats (from the Stolbovaya Animal Farm, Russian Academy of Medical Sciences) weighing 300–320 g were used for the experiments. The animals were housed in a laboratory vivarium; water and standard food were available ad libitum. The experiments were performed in accordance with the international guide for humane animal treatment approved by the European Communities Council (Directive of November 24,1986 (86/609/EEC) and ethical commission of the Zakusov Institute of Pharmacology, Russian Academy of Medical Sciences.

AD modeling was performed using administration of $A\beta_{25-35}$ into the rat brain [14]. $A\beta_{25-35}$ is a hydrophobic C-terminal fragment of $A\beta_{1-42}$, a principal constituent of AD senile plaques. $A\beta_{25-35}$ (Sigma, United States) was dissolved in bidistilled water at a concentration of 1.5 nmol/μL and maintained at 37°C for 4 days for peptide aggregation [15].

In accordance with the protocol developed by Stepanichev et al. [16], we performed bilateral administration of the $A\beta_{25-35}$ fragment into the cerebral ventricles using the coordinates of Buresh's stereotaxic atlas: AP, 1 mm; L, 1.5 mm; H, 3.5 mm [17]. Each experimental group consisted of nine animals. The rats were anesthetized by chloralhydrate at a dose of 350 mg/kg and aggregated $A\beta_{25-35}$ was injected into each ventricle of the brain at a dose of 7.5 nmol. The sham-operated rats were injected with equal volumes of bidistilled water into the cerebral ventricles.

Cognitive impairments were estimated 5.5 weeks after AD modeling using the method of spatial learning in a Morris water maze with some modifications [18–20]. A pool 190 cm in diameter was filled with water at room temperature, viz., 24 ± 2°C. The pool was virtually divided to four quadrants and in the "target" quadrant, a platform 12 cm in diameter was located 1.5 cm below the water surface. Platform locations were similar for all experiments. In the Morris water maze, a rat learns to escape forced swimming by finding a platform. Training was performed for 3 days; each daily session consisted of 2 trials that started from different positions: North (N) or West (W), with an interval of 1.5 h without changing the platform location. On day 5, at 48 h after the last training trial, a probe trial was performed. In the probe trial, each animal had to find the platform for 120 s. The change in the escape latency in 3-day training was recognized as an index of short-term memory and the escape latency in the probe trial was recognized as an index of long-term memory [21, 22].

Depressive-like behavior was assayed 6.5 weeks after AD modeling using the Porsolt's "forced-swim" test [23]. According to the classical procedure of the test, the rats were placed in the inescapable conditions in a glass cylinder of 46 × 20 cm, filled with water at a temperature of 27–26°C to the height of 30 cm. Two tests were performed at an interval of 24 h that continued for 10 and 6 min, respectively. The duration of the immobility (s) was recorded. Immobility was recognized as a state of complete immobility in rats, in which they performed only those movements that were necessary to maintain afloat.

The animals were decapitated 7 weeks after AD modeling, viz., $A\beta_{25-35}$ administration. Brain structures such as the frontal cortex (FC), hypothalamus (Hpt), nucleus accumbens (NA), dorsal striatum (Str), and hippocampus (Hip) were dissected on ice, frozen in liquid nitrogen, and weighed. These brain structures were homogenized in a "glass-teflon" homogenizer (0.2 mm) with a pestle that rotated at a rate of 3000 rpm. The samples were homogenized in 0.1 N $HClO_4$ with the addition of 0.5 nmol/mL 3,4-dihydroxybenzylamine (DHBA) as an internal standard. The samples were centrifuged at 15000 *g* for 10 min. The supernatant was filtered and 20 μL were directly injected into an analytic column. Noepinephrine (NE), 3,4-dihydroxyphenylacetic acid (DOPAC), dopamine (DA), homovanillic acid (HVA), 3-methyltyramine (3-MT), 5-hydroxyindolacetic acid (5-HIAA), and serotonin (5-HT) were separated on a temperature-controlled column at 35°C using a mobile phase that consisted of 0.1 M citrate-phosphate buffer containing 0.3 mM sodium octanesulfonate, 0.1 mM EDTA, and 10% acetonitrile at pH 3.2. Monoamines and their metabolites were measured using glass-carbon electrode at +0.85 V and Ag/AgCl reference electrode. The rate of the mobile phase was 1 mL/min [24].

Measurements of the contents of inhibitory (GABA, glycine, and taurine) and excitatory (aspartate and glutamate) amino acids were performed using the HPLC/FD method with some modifications [25]. Twenty-five μL of the supernatant used for measurement of catecholamines were mixed with 25 μL of 0.1 M borate buffer and 10 μL ortho-phthalaldehyde in 0.1 M borate buffer (pH 9.5) for amino-acid derivation. A mixture of aspartate, glutamate, glycine, taurine, and GABA at concentrations of 0.1 μM in 0.1 N $HClO_4$ was used for calibration. After a 20-min incubation at room temperature, 20 μL of the solution were applied to a Dr. Maish Hypersil ODS column (C18, 4 × 250 mm, 4 μm, $T = 40$°C). Separation and recording of the products of separation were performed using an Agilent 1100 chromatograph with a fluorescence detector at the wavelengths of excitation and emission of 230 and 392 nm, respectively. The mobile phase consisted of 0.05 M phosphate buffer

Table 1. Impairments of spatial learning in the Morris water maze in rats with AD induced by intracerebral administration of $A\beta_{25-35}$ (M ± S.E.M.)

Test days	Starting point	Escape latency, s			
		sham-operated animals	sham-operated animals (N + W)	animals with $A\beta_{25-35}$	Animals with $A\beta_{25-35}$ (N + W)
1st	N	109.1 ± 8.9	92.39 ± 6.92	109.2 ± 7.1	78.67 ± 8.85
	W	75.7 ± 13.4		48.1 ± 14.0	
2nd	N	55.1 ± 13.2	43.78 ± 6.57[#]	82.9 ± 11.0	68.39 ± 12.27[@]
	W	32.4 ± 9.8		53.9 ± 17.2	
3rd	N	30.7 ± 9.5	28.39 ± 5.84	48.7 ± 14.7	37.75 ± 11.8
	W	26.1 ± 6.9		28.6 ± 14.9	
5th	N	26.6 ± 8.7		61.0 ± 16.6*	

N, North; W, West. *, significant differences compared to sham-operated rats, $p \le 0.05$ according to Mann–Whitney *U*-test; [#], significant differences compared to sham-operated rats on day 1 of training, $p \le 0.05$ according to the Wilcoxon *U*-test; [@], a trend towards a difference compared to sham-operated rats, $p = 0.098$ according to the one-way analysis of variances

Table 2. The indices of a depressive-like state in the Porsolt's forced-swim test in rats with AD induced by intracerebral administration of $A\beta_{25-35}$ (M ± S.E.M.)

Groups of animals	Duration of immobility, s	Duration of swimming, s
Sham-operated animals	233.63 ± 11.48	126.11 ± 11.48
Animals with $A\beta_{25-35}$	281.10 ± 10.99*	78.99 ± 10.99

*, significant differences compared to sham-operated rats, $p \le 0.05$ according to Mann–Whitney *U*-test.

(pH 5.6), 0.025 mM EDTA, and 5% methanol. Initial data processing was performed using Agilent ChemStation software.

Statistical analysis was performed using Biostat software. We used the non-parametric Wilcoxon *U*-test for dependent samples and the parametric Student's *t*-test, non-parametric Mann–Whitney *U*-test, and a one-way analysis of variances for independent samples.

RESULTS

We studied the spatial learning of the animals in a Morris water maze at 5.5 weeks after surgery. The animals treated with $A\beta_{25-35}$ required significantly more time to find a hidden platform compared to sham-operated rats on days 2 and 3 of training (Table 1). In the group of sham-operated animals, we observed a two-times lower latency spent to find a hidden platform on day 2 compared to that on day 1 ($P \le 0.05$). On day 2 of training, in the rats with AD, the time for finding the platform was 68.39 ± 12.27 s, which was similar to that observed on day 1, viz., 78.67 ± 8.85 s, and was higher than the respective latency in the sham-operated rats by a factor of 1.5 ($P = 0.098$). These data indicate the development of impairments of short-term memory in these animals. On day 3, the animals of both groups exhibited similar indices of behavior. On day 5, the time that was spent to find the platform increased from 37.75 ± 11.8 to 61.0 ± 16.6 s ($P \le 0.05$) in the animals with AD as compared to the indices that were exhibited by the sham-operated animals, viz., 28.39 ± 5.84 and 26.6 ± 8.7 s, respectively (Table 1).

Depressive-like behavior in the rats with AD was estimated in Porsolt's forced-swim test. In the sham-operated animals, the immobility duration was 233.6 ± 11.5 s for a 6-min observation, whereas in the animals with AD this index was significantly higher, viz., 281.1 ± 10.9 s. These data demonstrate the development of a depressive-like state in these rats (Table 2).

Chromatographic study on the contents of monoamines and their metabolites in brain structures of the rats with AD revealed significantly lower levels

of DA metabolites, including HVA, DOPAC, and 3-MT in the dorsal striatum compared to the sham-operated animals. However, the DA level remained unchanged and thus, the indices of DA metabolism, such as DOPAC/DA and HVA/DA, decreased (Table 3).

In the NA of the rats with AD, extracellular metabolism of DA, i.e., the HVA/DA ratio, was substantially lower, which was expressed as a trend towards a decrease in the HVA level and an increase in the DA content in the tissue. In this structure, we also observed a significant decrease in the index of serotonin utilization (5-HIAA/5-HT), which was associated with an increase in the 5-HT content (Table 3).

In the Hpt, we found decreased contents of DA and its metabolite 3-MT. Here, we also revealed a lower level of the other DA metabolite, HVA ($P \leq 0.1$), and significant slowing of 5-HT utilization, which was expressed in the decreased 5-HIAA/5-HT index (Table 3).

We did not find any significant differences in the contents of DA and 5-HT in the Hip and FC of rats with AD compared to the sham-operated animals. We also did not reveal any changes in the activity of the norepinephrinergic system in all the brain structures we studied (Table 3).

Studies on the effects of $A\beta_{25-35}$ on the indices of the amino acid-ergic brain systems revealed an increase in the glutamate and GABA levels in the striatum ($P \leq 0.05$; Table 4).

DISCUSSION

Studies on cognitive impairments in a Morris water maze at 5.5 weeks after administration of $A\beta_{25-35}$ demonstrated that in the experimental animals, short-term memory was impaired compared to the sham-operated rats, which is supported by the data from day 2 of training. Disturbances in spatial learning in the rats with developed AD were also observed during a recall session at 48 h after training, viz., on day 5 of the experiment. They were expressed in the more than doubled time that was spent to find the hidden platform (61.0 ± 16.6 s) compared to the respective duration (26.6 ± 8.7) that was observed in the sham-operated rats. This may be recognized as impairments in long-term memory. In addition to cognitive impairments, rats with AD exhibited alterations in emotions. We revealed depressive-like behavior in rats with AD, which was expressed in the increased immobility duration (281.1 ± 10.9 s) that was observed in Porsolt's forced-swim test compared to the duration that was observed in the sham-operated animals (233.6 ± 11.5 s).

The impairments of cognitive activity and the development of a depressive-like state in the animals with AD were accompanied by alterations in the functioning of the monoaminergic and amino acid-ergic systems. We found a decrease in the levels of DA metabolites, viz., HVA, DOPAC, and 3-MT, in the striatum, which were associated with a stable content of DA per se; this may indicate the attenuated release of DA into the synaptic cleft. This may be related to destruction of the synaptic membrane. We believe that this compensation of the DA content was probably due to activation of tyrosine hydroxylase induced by a decrease in the DA level in the synaptic cleft via a negative-feedback mechanism. Similar data were observed in the premotor stage of a model of Parkinson's disease, which was not associated with a massive loss of dopaminergic neurons [1]. There are literature data on a decrease in the density of dopaminergic neurons by 56% after a single administration of Aβ [13]. Perez Sylvia et al. reported similar data from transgenic APPswe/PS1ΔE9 mice with depressive-like behavior. Accumulation of amyloid plaques in these mice was associated with the destruction of neurons of the nigro-striatal pathway, which was followed by a decrease in the DA content and its metabolism in the striatum and substantia nigra [26]. In its turn, slower DA metabolism and a decrease in the DA content may induce accumulation of insoluble Aβ forms, which are toxic for neurons. DA, L-DOPA, and other catecholamines may dissolve fibrils of alpha-synuclein and Aβ peptide [27]. In AD patients, slowing of DA metabolism in the striatum is associated with a loss of D2 receptors in this structure [4]. On the other hand, alteration of the functioning of the dopaminergic system in the striatum may be a consequence of the impaired cholinergic innervation of dopaminergic neurons that is observed during AD progress. In experiments that were performed in vitro and in vivo, endogenous cholinergic activity modulated voltage-dependent DA release in the dorsal and ventral striatum [28, 29], whereas Aβ disrupted cholinergic control of DA release from the synaptic boutons of rat brain neurons due to a massive loss of cholinergic neurons [10, 11].

In addition to changes in functioning of the dopaminergic system that were found 7 weeks after administration of $A\beta_{25-35}$, we observed an increased content of glutamate in the striatum. This is a negative prognostic index of neurodegenerative processes in the brain [30]. For example, glia atrophy in the brains of transgenic animals with genetically predetermined accumulation of amyloid plaques resulted in a high glutamate content due to dysfunction of astrocytes [31, 32]. There are data on the negative effect of A β on glutamate uptake by astrocytes in various brain structures [33, 34]. It has been recently shown that impaired glutamate uptake by astrocytes resulted in a substantial increase in the glutamate contents in plasma and cerebrospinal fluid in AD patients [35]. Our data on the elevated glutamate level in the striatum also indicate alterations in communication between astrocytes and neurons in this structure. The dorsal striatum is directly involved in memory consolidation in the late phase; therefore, altered functioning of this structure disturbs the transition from short-term memory to long-term memory and recall of

Table 3. The effects of Aβ25–35 on the contents of monoamines and their metabolites in brain structures of mongrel male rats ($M \pm m$)

Group	Structure	DA	DOPAC	HVA	3-MT	DOPAC/DA	HVA/DA	NE	5-HT	5-HIAA	5-HIAA/5-HT
Sham-operated animals	FC	0.522 ± 0.163	0.069 ± 0.046	–	–	0.127 ± 0.08	–	1.047 ± 0.242	3.376 ± 0.587	1.017 ± 0.84	0.354 ± 0.42
	Hpt	1.957 ± 0.221	0.003 ± 0.004	0.141 ± 0.051	0.051 ± 0.031	0.002 ± 0.001	0.072 ± 0.026	5.257 ± 0.611	5.566 ± 0.569	1.768 ± 0.231	0.318 ± 0.028
	NA	63.923 ± 17.94	8.137 ± 1.95	6.826 ± 1.85	0.731 ± 0.209	0.129 ± 0.015	0.11 ± 0.027	8.361 ± 5.727	9.14 ± 1.301	3.193 ± 1.128	0.35 ± 0.116
	Str	57.720 ± 3.56	4.370 ± 0.25	4.92 ± 0.67	0.666 ± 0.11	0.076 ± 0.007	0.085 ± 0.011	0.86 ± 0.18	3.12 ± 0.7	1.89 ± 0.652	0.617 ± 0.054
	Hip	0.089 ± 0.083	0.061 ± 0.005	–	–	0.815 ± 0.623	–	1.491 ± 0.274	1.972 ± 0.235	1.191 ± 0.264	0.602 ± 0.093
Animals with $A\beta_{25-35}$	FC	0.477 ± 0.192	0.097 ± 0.046	–	–	0.203 ± 0.092	–	1.072 ± 0.264	3.59 ± 0.642	0.77 ± 0.204	0.22 ± 0.068
	Hpt	**1.636 ± 0.223***	0.003 ± 0.003	**0.077 ± 0.04$^{\$}$ $P = 0.061$**	**0.016 ± 0.06***	0.002 ± 0.002	0.047 ± 0.02	5.208 ± 0.649	5.932 ± 0.643	1.678 ± 0.357	**0.282 ± 0.045$^{\$}$ $P = 0.071$**
	NA	73.51 ± 14.83	8.649 ± 1.643	**5.048 ± 1.467$^{\$}$ $P = 0.085$**	0.592 ± 0.225	0.119 ± 0.017	**0.068 ± 0.009***	7.084 ± 3.365	**11.433 ± 1.93***	2.827 ± 0.761	**0.246 ± 0.042$^{\$}$ $P = 0.062$**
	Str	53.891 ± 6.53	**4.113 ± 0.536***	**3.837 ± 0.577***	**0.511 ± 0.085***	**0.077 ± 0.009***	**0.072 ± 0.013***	0.716 ± 0.258	3.693 ± 0.654	1.908 ± 0.556	0.511 ± 0.086
	Hpt	0.207 ± 0.251	0.149 ± 0.226	–	–	1.032 ± 0.74	–	1.301 ± 0.179	1.739 ± 0.285	1.163 ± 0.191	0.68 ± 0.149

FC, frontal cortex; Hpt, hypothalamus; NA, nucleus accumbens; Str, striatum; Hip, hippocampus. *, significant differences compared to sham-operated rats, $p \leq 0.05$ according to the Student's t test; $^{\$}$, a trend towards a difference compared to sham-operated rats, $p < 0.1$ according to the Student's t test.

Table 4. The effects of $A\beta_{25-35}$ on the contents of amino acids in the brain structures of mongrel male rats ($M \pm m$)

Group	Structure	Aspartate	Glutamate	Glycine	Taurine	GABA
Sham-operated animals	FC	1.867 ± 0.144	9.118 ± 0.613	1.219 ± 0.294	19.12 ± 1.663	1.254 ± 0.114
	Hpt	1.711 ± 0.135	6.281 ± 0.443	1.241 ± 0.079	17.077 ± 1.05	2.799 ± 0.194
	NA	3.862 ± 0.143	15.331 ± 0.429	2.137 ± 0.085	48.915 ± 1.455	7.214 ± 0.481
	Str	0.91 ± 0.135	4.337 ± 0.45	0.643 ± 0.083	19.485 ± 2.525	1.295 ± 0.118
	Hip	1.024 ± 0.102	6.323 ± 0.57	0.854 ± 0.085	16.433 ± 2.032	1.249 ± 0.113
Animals with $A\beta_{25-35}$	FC	1.875 ± 0.237	8.861 ± 0.913	0.898 ± 0.095	19.35 ± 2.577	1.107 ± 0.127
	Hpt	1.828 ± 0.139	6.545 ± 0.429	1.3 ± 0.095	18.7 ± 1.493	2.87 ± 0.261
	NA	3.12 ± 0.307	13.14 ± 1.325	1.889 ± 0.266	39.59 ± 4.126	7.169 ± 1.309
	Str	1.071 ± 0.083	**5.743 ± 0.368***	0.731 ± 0.049	22.633 ± 1.835	**1.787 ± 0.171***
	Hip	1.122 ± 0.122	7.03 ± 0.683	0.892 ± 0.082	19.171 ± 1.844	1.276 ± 0.123

FC, frontal cortex; Hpt, hypothalamus; NA, nucleus accumbens; Str, striatum; Hip, hippocampus. *, significant differences compared to sham-operated rats, $p < 0.05$ according to Student's t-test.

memory about previous experience [36–38]. We believe that the impairments of long-term memory that were found during memory recall in the Morris water maze test on day 5 in the rats with AD were related to impairments in the dopaminergic system and accumulation of glutamate in the striatum. However, we did not observe any changes in the neurotransmitter profile in the hippocampus and cortex; these are brain structures that are responsible for short-term memory and memory consolidation in the early phase, although short-term memory was impaired on day 2 of the training. A large number of data support modified functioning of the cortex and hippocampus due to damage to acetylcholinergic neurons after a single administration of Aβ [16, 39]. It is possible that alteration of the neurotransmitter balances of the dopaminergic and serotonergic systems in the cortex and hippocampus are compensated and therefore could not be found.

In addition to cholinergic and dopaminergic neurons, Aβ has been reported to damage serotonergic neurons of the dorsal raphe nuclei, whose axons control the function of the DA-ergic system of the NA [10]. Under normal conditions, activation of 5-$HT1_A$-, 5-$HT2_A$-, or 5-HT3-receptors results in DA release from the synaptic boutons in the NA, whereas activation of 5-$HT2_C$-receptors inhibits the release of the neurotransmitter. According to one of the current hypotheses, the development of depression is based on the alteration of the contents and metabolites of monoamines in the NA, which is followed by disturbances in serotonin–dopamine interactions [40]. The slowing of extracellular DA and 5-HT turnover that was found in the present study and expressed in the lower HVA/DA and 5-HIAA/5-HT values and accumulation of 5-HT may be considered as a consequence of destructive processes in cholinergic, dopaminergic, and serotonergic neurons after a single $A\beta_{25-35}$ administration. We believe that the changes in the activity of the dopaminergic and serotonergic systems promoted the development of depressive-like behavior in rats with AD; the data from Porsolt's forced-swim test support this conclusion. A similar slowing of monoamine metabolism in the NA was revealed in transgenic FSL (Flinders sensitive line) rats with genetically determined depression [41]. In these rats, the DA content in the NA was lower compared to control rats by 40%. However, the level of DA in the NA of FSL rats did not increase in response to 5-HT injection. These data suggest that an imbalance between the activity of the serotonergic and dopaminergic neurotransmitter systems is one of the factors that promote the development of depression.

In the Hpt of rats with AD, we revealed decreased contents of the DA metabolites HVA and 3-MT, slower DA utilization, and a lower DA level, which indicated the negative effect of $A\beta_{25-35}$ on DA metabolism in this structure. Modification of the DA content in the Hpt, which is a structure of the tuberoinfundibular system, was observed during the development of several diseases, such as hyperprolactinemia, attention-deficit hyperactivity disorder, anorexia,

anhedonia, and others [42, 43]. Impairments of the functions of neurons of the tuberoinfundibular system in the Hpt indicate deregulation of the hypothalamus–pituitary axis and its involvement in the pathogenesis of AD.

Thus, our data demonstrate that AD modeling by a single administration of $A\beta_{25-35}$ into the cerebral ventricles of rats resulted in cognitive impairments and development of a depressive-like state, which were associated with alterations in DA synthesis in the Hpt, interaction between the seroton- and dopaminergic systems in the ventral striatum (NA), and slowing of DA metabolism and accumulation of glutamate in the dorsal striatum. These alterations were very pronounced and strong in the dopaminergic system of the Hpt, whereas in the dorsal and ventral striatum they may be considered as a compensatory response. In the FC and Hip of the animals with AD modeled by $A\beta_{25-35}$ administration, we did not find any changes in the contents of monoamines or amino acids.

Based on these data, we hypothesized that the tuberoinfundibular, mesolimbic, and nigrostriatal dopaminergic and striatal seroton- and glutamatergic neurotransmitter systems of the brain are involved in the pathogenesis of a cognitive deficit and a depressive-like state in animals with AD that was induced by $A\beta_{25-35}$ administration into the cerebral ventricles.

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