Specific Features of Biogenic Amine Content in the Cerebral Cortex during Experimental Intracerebral Hemorrhage in Rats with Various Behavioral Characteristics

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Experiments on Wistar rats showed that modeling of hemorrhage in the left caudate nucleus of the brain in behaviorally passive specimens is mainly accompanied by an increase in biogenic amine content in the sensorimotor cortex of the right cerebral hemisphere (particularly on day 3 after the surgery). Norepinephrine content in the sensorimotor cortex of the right cerebral hemisphere in behaviorally active rats was reduced over 7 days after the development of intracerebral hemorrhage. The contents of dopamine and serotonin in brain tissue of behaviorally active animals most significantly increased on day 7 after experimental stroke. Our results indicate that experimental hemorrhage in the left caudate nucleus of rats with various behavioral characteristics is accompanied by specific changes in biogenic amine content in the sensorimotor cortex of the right cerebral hemisphere. We conclude that neurochemical processes in brain structures distant from the site of hemorrhage play an important role in the pathogenesis of hemorrhagic stroke.

Key Words: *rats; behavioral activity; intracerebral hemorrhage; biogenic amines*

Intracerebral hemorrhage (ICH) is the most serious form of acute disturbances in cerebral circulation (20% of acute strokes). The mortality rate of patients reaches 35-50% over 1 month after the development of this disease. The majority of survived patients are characterized by persistent neurological disorders [2,3,11].

Arterial hypertension is one of the major reasons of ICH [1,6,11]. The elevation of BP is mainly caused by emotional stress.

Our previous studies revealed the existence of animals that are resistant and predisposed to emotional stress (according to the survival rate in the same conflict situations) [10,13]. Behavioral testing of rats in a novel situation allowed us to evaluate the prognostic criteria for their resistance to emotional stress [5]. During emotional stress under conditions of cerebral ischemia, the survival rate of rats with high score of open field activity is greater than that of passive animals [8,10].

Previous experiments showed that rats with various emotional resistance differ in catecholamine content in the adrenal glands and brain structures [7,13], concentration of neuropeptides (*e.g.*, delta sleep-inducing peptide, β-endorphin, substance P, and angiotensin P) in CNS and blood [8-10], and expression of the *c-fos* gene in the brain [12].

This work was designed to compare the dynamics of changes in biogenic amine content in the sensorimotor cortex of the brain in rats with various behavioral characteristics under control conditions and during experimental ICH.

MATERIALS AND METHODS

Experiments were performed on behaviorally active (n=11) and passive (n=11) male Wistar rats weigh-

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ing 250-300 g. The experiment was conducted in accordance with the Order of the Russian Ministry of Health (No. 267, 19.06.2003) and "Rules of Studies on Experimental Animals" (P. K. Anokhin Institute of Normal Physiology; protocol No. 1, 3.09.2005). The animals were housed in cages at 20-22°C and artificial light/dark cycle (8.00-20.00, lightness; 20.00-8.00, darkness). They had free access to water and food. The animals were adapted to novel conditions for 5 days after delivery to the laboratory. Individual-and-typological characteristics of rats were evaluated from their behavior in a modified open-field test with special computer software [5]. Depending on the results of testing, the animals were divided into 2 groups of behaviorally active and passive specimens.

The animals were intraperitoneally anesthetized with 400 mg/kg hexochloral. The autoblood (60 μl) was stereotactically administered into the left caudate nucleus using a round-end needle No. 22 [14]. To form hematoma, the blood was taken from the femoral vein immediately before infusion to the brain. Heparin was not added to the blood. This approach allowed us to form hematoma of the same size in all experimental animals. The localization of experimental hemorrhagic stroke in rats was similar to that of ICH in patients with ruptured lenticulostriate arteries.

Sham-operated rats were subjected to all stages of hemorrhagic stroke modeling except for blood infusion to the brain.

Concentric microdialysis probes were implanted into the right sensorimotor cortex of rats simultaneously with the modeling of ICH. The size of membrane pores in these probes was 20 kDa. The dialysate was collected for 20 min. Before sampling of dialysates, the probes were perfused for 2 h to achieve equilibrium of substances on both sides of the membrane. Dialysates were obtained on days 1, 3, and 7 after ICH modeling or sham operation.

The content of biogenic amines in dialysates was measured by HPLC and electrochemical detection with a GOLD TURBO ODS column (4-1.5 μ, 33×4.6 mm; MAISCH). The significance of differences was estimated by ANOVA and Student's *t* test.

RESULTS

Under basal conditions, the mean content of norepinephrine in the right sensorimotor cortex of active and passive rats was 160.03-179.05 and 100.05-110.15 pg/ml, respectively (Table 1). Only trace amounts of dopamine and serotonin were found in dialysates from these animals.

Sham operation of animals was not accompanied by statistically significant changes in the content of biogenic amines in the contralateral brain tissue (data not shown). Hence, the data from sham-operated animals were excluded from further analysis. The content of biogenic amines in rats after ICH modeling was compared with that observed in the initial state.

Norepinephrine content in the right sensorimotor cortex of behaviorally active rats decreased by 2.1 times ($p<0.01$) on day 1 after ICH modeling in the left caudate nucleus. Serotonin content was elevated under these conditions ($p<0.05$). Similarly to intact animals, active rats with ICH were characterized by the presence of trace amount of dopamine in the sensorimotor cortex.

Norepinephrine content in the right sensorimotor cortex of active rats remained low on day 3 after ICH modeling (2.1 times lower than the baseline, $p<0.01$). By contrast, dopamine content in dialysates was higher than the baseline ($p<0.05$). Serotonin content in the sensorimotor cortex of active specimens, which was elevated on day 1 after experimental ICH, decreased significantly on day 3 of the study and did not differ from the baseline.

Norepinephrine content in the right sensorimotor cortex of active rats on day 7 after experimental ICH was slightly higher than that in the previous periods. However, norepinephrine content in brain tissue of these animals was 1.4-fold below the baseline ($p<0.05$). Active specimens were characterized by a significant increase in the contents of dopamine and serotonin in the sensorimotor cortex (compared not only to the baseline [$p<0.01$], but also to those on days 1 and 3 after the surgery).

The contents of norepinephrine and dopamine in the right sensorimotor cortex of behaviorally passive rats on day 1 after ICH modeling in the left caudate nucleus practically did not differ from the baseline. These animals were characterized by a significant increase in the content of serotonin in brain tissue ($p<0.01$ compared to the baseline). The contents of norepinephrine and serotonin in the sensorimotor cortex of passive specimens were higher than in active rats ($p<0.05$).

The contents of norepinephrine and serotonin in the sensorimotor cortex of passive rats increased significantly on day 3 after ICH modeling (compared not only to the baseline [$p<0.01$], but also to those on day 1 of the study). The amount of these biogenic amines in passive animals was much higher than in active specimens ($p<0.01$; Table 1). Similarly to day 1 of the study, no significant changes were found in the content of dopamine in brain tissue of passive rats during this period (trace amounts).

Norepinephrine content in the right sensorimotor cortex of passive rats, which was elevated on day 3 after experimental ICH, decreased significantly on day 7 of the study and practically did not differ from

TABLE 1. Biogenic Amine Content in the Right Sensorimotor Cortex of Rats with ICH (pg/ml; *M*±*m*)

Rats	Biogenic amines	Period			
		baseline	day 1	day 3	day 7
Active	Norepinephrine	160.03±15.02	78.12±13.26^{++}	75.02±24.11^{++}	113.33±10.54^{+}
	Dopamine	-	-	21.00±8.25^{+}	115.11±26.05^{++}
	Serotonin	-	66.11±47.02^{+}	-	167.12±84.25^{++}
Passive	Norepinephrine	110.11±20.47	100.02±8.74	330.8±120.66^{++}**	70.26±13.00*
	Dopamine	-	-	-	11.02±8.11**
	Serotonin	-	114.14±9.01^{++}	152.02±70.55^{++}**	84.56±10.57^{++}

Note. –, trace amounts (beyond the sensitivity limits). $^{+}p<0.05$ and $^{++}p<0.01$ compared to the baseline; $^{*}p<0.05$ and $^{**}p<0.01$ compared to active rats.

the baseline. The content of serotonin in brain tissue of passive animals during this period was lower than on day 3 after the surgery, but remained above the baseline ($p<0.01$). Similarly to the previous periods, no significant changes were found in the content of dopamine. On day 7 after experimental hemorrhage in the left caudate nucleus, the contents of norepinephrine, dopamine, and serotonin in the sensorimotor cortex of passive rats were lower than in active specimens (by 1.6 [$p<0.05$], 10.4 [$p<0.01$], and 1.9 times, respectively).

Our results indicate that ICH modeling in the left caudate nucleus of behaviorally passive rats is mainly accompanied by an increase in the content of biogenic amines in the right sensorimotor cortex. The amount of norepinephrine and serotonin in brain tissue of passive animals was highest on day 3 after the surgery.

Norepinephrine content in the right sensorimotor cortex of active rats with ICH was reduced in all periods of the study. The contents of dopamine and serotonin in brain tissue of behaviorally active animals increased most significantly on day 7 after experimental stroke. Between-group differences in biogenic amine content in the sensorimotor cortex of passive and active rats were most significant on day 3 of the study.

We conclude that experimental hemorrhage in the left caudate nucleus of rats with various behavioral characteristics is accompanied by specific changes in biogenic amine content in the sensorimotor cortex of the right cerebral hemisphere. Hence, neurochemical processes in brain structures distant from the site of hemorrhage play an important role in the pathogenesis of hemorrhagic stroke.

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