Possible Mechanisms of Disorders in Saccadic Eye Movements in Parkinsonian Patients

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Electrooculogram recording was used to examine the centrifugal horizontal saccades through an angle of 40° in patients with Parkinson's disease and healthy subjects. The patients demonstrated prolongation of latency and duration, as well as appearance of multiple saccades. The mean values of latency in the right and left saccades were significantly longer in patients than in normal subjects. Although the saccade duration in patients did not differ significantly from that in normal subjects, this parameter tended to increase in value and dispersion. The courses of the vision-controlled saccade disturbances in parkinsonian patients are discussed and hypothesis is forwarded on the disorder mechanisms with particular attention to GABAergic system.

Key Words: *eye movements; substance nigra; superior colliculi; oculomotor disorder mechanisms; Parkinson's disease*

Almost all levels of central nervous system participate in programming and performing of the saccadic eye movements (SEM), which accounts for SEM disturbances occurring in many psychoneurological diseases. When localization of brain disturbance is established, the mechanisms of oculomotor disorders can be determined with a high degree of accuracy. The Parkinson's disease (PD) belongs to this kind of mental disorders, and it is characterized by the triad which includes rigidity, tremor, and akinesia; it is related to structural damage of the compact portion of substance nigra. Although a great number of papers are devoted to study of the oculomotor reactions during PD [7,8,10,11], there is no consistent view on the nature of SEM disorder mechanisms. This problem is expeored in our study.

MATERIALS AND METHODS

Eight patients with PD were examined, including 4 women and 4 men (49-69 years, mean age 61 year), as well as 7 practically healthy subjects (the control group) at the age of 48-65 years (mean age 58 years).

The PD diagnosis was verified according to international standards: the Mini-Mental State Examination (MMSE) scale and Webster neural deficiency scale. The stages of PD were determined according to Hoehn and Jahr (Table 1). Ambulatory examinations of all patients included cerebral computer tomography, oculist examination, ultrasound dopplerography of great cerebral vessels, and rheoencephalography. All PD patients demonstrated the full-scale oculogyration, and they had no focal transformation in the retina. Some patients were examined with proper correction of vision to 1.

Electrooculogram was used to determine the unidirectional vision-controlled centrifugal horizontal SEM through 40° (light adaptation at 50 lx) during fixation of the head that was controlled according to our method [1]. To minimize the component of latency related to attention, which is particular large in PD patients, the visual stimulus was forestalled with a command "Attention!", and the sound costimulus (a click) was given together with optical

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stimulation. Electrical signals from the eyes were fed into a UBF4-03 bioamplifier (time constant 2.2 sec, upper frequency 150 Hz) and then to a computer via ADC with the range of ±5 V. Data acquisition program was started simultaneously with switching the targets over and it used two channels with sampling period 4 msec and analysis epoch 1-2 sec. Monitoring of the eye movements made it possible to apply stimulus only at the moment of gaze holding in the absence of artifacts.

Data were kept in a computer and were used to calculate latent period (LP), duration of the first and following (tuning) saccades. The results were statistically analyzed using Student's *t* test.

RESULTS

Three basic factors described in literature [10] were encountered by examination of SEM in PD patients: an increase of LP, a marked prolongation of SEM, and reaching the peripheral target by one, two, and more saccades (Table 2).

Figure 1 shows typical normal and pathological cases characterized by a pronounced prolongation of LP and saccade duration and by a decrease in its velocity.

Although the mean LP value of the right (215±10 msec) and left (224±11 msec) saccades in patients significantly differed ($p<0.01$) from the corresponding values of healthy subjects (172±8 and 181±5), paired comparison of LP did not reveal any significant difference in some cases.

Some patients (No. 1 and No. 2) demonstrated significant difference between LP of the right and left saccades ($p<0.01$). It is shown in Fig. 2, *c, I,* and *II,* where the lower histograms are shifted to the right relative to the upper histograms. We failed to correlate these differences with the initial side of disease lateralization. Other patients did not demonstrate any significant difference between LP of the right and left saccades (Table 2), although sometimes there was a tendency of asymmetry in histograms of LP for right and left eyes (Fig. 2, *b, I, II*).

Generally, SEM duration did not significantly differ in patients and healthy subjects, with exception of SEM of the right eye to the right ($p<0.05$). However, in each case there was a marked tendency toward an increase in the value and dispersion of SEM duration (Fig. 3). In some patients there was a tendency toward an increase in duration of SEM to both sides for one eye in contrast to the other (Fig. 3, *b, I, II*). There was also an asymmetry in SEM duration histograms of the same eye turning to different directions, while the corresponding histograms of the other eye were similar in these cases (Fig. 3, *c, I, II*).

In many cases the patients' eyes did not aim at the peripheral target by a single SEM. Distribution of the corresponding multiple saccades is given in Table 2. For example (patient No. 2), the column "right eye, L" indicates that the total number of gaze shifting of the right eye to the left peripheral target is 25 (6+13+6): in 6 cases there was single, in 13 double, and in 6 triple or higher SEM. In all patients multiple saccades were observed for both eyes. They were directed to both sides and correlated neither with disease severity nor with its initial lateralization (Table 1). Table 2 shows that multiple saccades are a specific feature of PD patients.

The LP of SEM is determined by at least three processes: conductance of visual signals, saccade programming, and implementation of the oculomotor command. The corresponding latency components for normal SEM with LP of 215 msec are

TABLE 1. Patients' Medical Data

No	Sex	Age, years	Clinical form	Side of debut	Duration of disease, years	Stage according to Hoehn-Jahr (1-5)	Webster scale (1-4)	MMSE scale (1-4)	Treatment
1	F	69	Tremor rigidity	R	6	3	3	2	+
2	M	62	-"-	R	4	3	4	4	+
3	M	49	-"-	R	2	1	1	2	—
4	F	66	-"-	L	5	2	3	2	+
5	M	56	Tremor	L	2	1	1	1	—
6	F	69	Akinetic rigidity	R	2	4	4	3	+
7	F	55	-"-	R	6	3	4	3	+
8	M	61	Tremor rigidity	L	2	3	2	2	+

Note. Right (R) and left (L) lateralization. Disease degree according to Webster scale: *1* — light; *2* — moderate; *3* — pronounced; *4* — sharply pronounced. +) medicamentous treatment; —) without treatment.

TABLE 2. Patients' Data on Saccades (M±m)

Patients	Latency, msec				Duration, msec				Multiple saccades											
	right eye		left eye		right eye		left eye		right eye						left eye					
									R			L			R			L		
	R	L	R	L	R	L	R	L	1	2	3 and more	1	2	3 and more	1	2	3 and more	1	2	3 and more
1	179±13.2	256±20.0	176±13.2	268±19.8	106±6.9	140±8.3	130±7.2	131±8.4	21	2	0	11	10	1	20	3	0	14	7	1
2	214±8.8	247±9.8	215±8.4	256±10.8	86±3.8	96±3.5	98±5.0	84±6.0	9	15	1	6	13	6	10	15	0	8	10	7
3	187±9.3	169±4.1	186±9.7	175±4.6	94±3.2	108±2.6	142±1.5	99±4.1	12	8	5	18	6	1	13	10	2	16	7	2
4		212±10.7		241±16.0		114±5.9		122±3.7			19	5	1					19	6	0
5	255±19.1	249±9.4	254±18.0	257±9.6	89±6.0	104±2.4	120±5.4	102±2.7	11	10	2	19	6	0	18	4	1	10	14	1
6	238±9.1	232±5.7	235±8.7	233±5.9	100±2.1	110±4.9	126±2.7	109±5.7	23	2	0	16	8	1	23	2	0	12	13	0
7	201±4.7	174±3.4	197±4.5	189±3.6	101±3.4	97±1.5	106±4.8	96±2.4	15	9	1	16	9	0	21	2	1	11	14	0
8	233±8.6	250±9.1	244±7.8	252±8.6	117±7.9	109±4.6	121±5.3	133±4.0	9	9	4	13	7	5	13	8	1	15	9	1

Note. SEM to the right (R) and to the left (L).

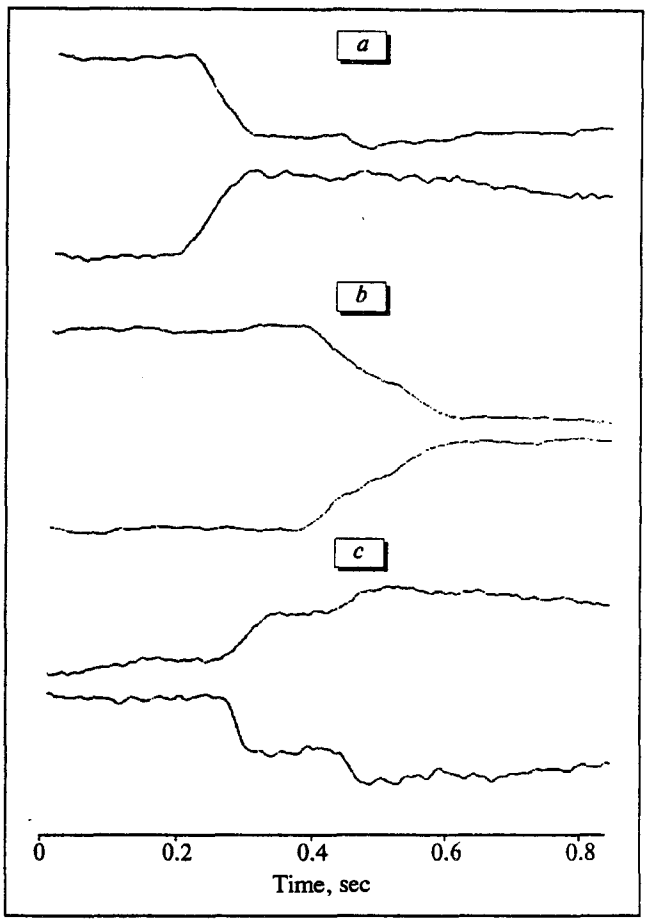

Fig. 1. Vision-controlled horizontal centrifugal saccadic eye movements (SEM) through 40°. The upper curve in each pair shows SEM of the left eye, and the lower curve does it for the right one. *a*: healthy subject, SEM to the left; *b*: parkinsonian patient No. 5, SEM to the left; *c*: parkinsonian patient No. 6, SEM to the right. SEM with increased latent periods and duration is shown in (*b*), and multiple saccades are shown in (*c*).

55, 135, and 25 msec [9]. Prolongation of LP of the visual evoked potential is disputable [3,4]. Therefore, it is not clear whether disturbances in visual conduction are the reasons for LP prolongation of SEM. Since the cortical structures (including those responsible for SEM programming, i.e., frontal visual fields, parietal and visual cortical regions, *etc.*) are not significantly changed in idiopathic parkinsonian patients, one can reasonably suppose that generation of the oculomotor command in the form of a particular pulse activity directed to inferior subdivisions should be normal.

Therefore, it can be suggested that the mechanisms of oculomotor disturbances should be searched for at the level of subcortical and truncal structures. It is considered that dopamine depletion in striatum resulting from destruction of the compact portion of substance nigra during PD leads via a number of feedback circuits to disturbance of inhibitory connec-

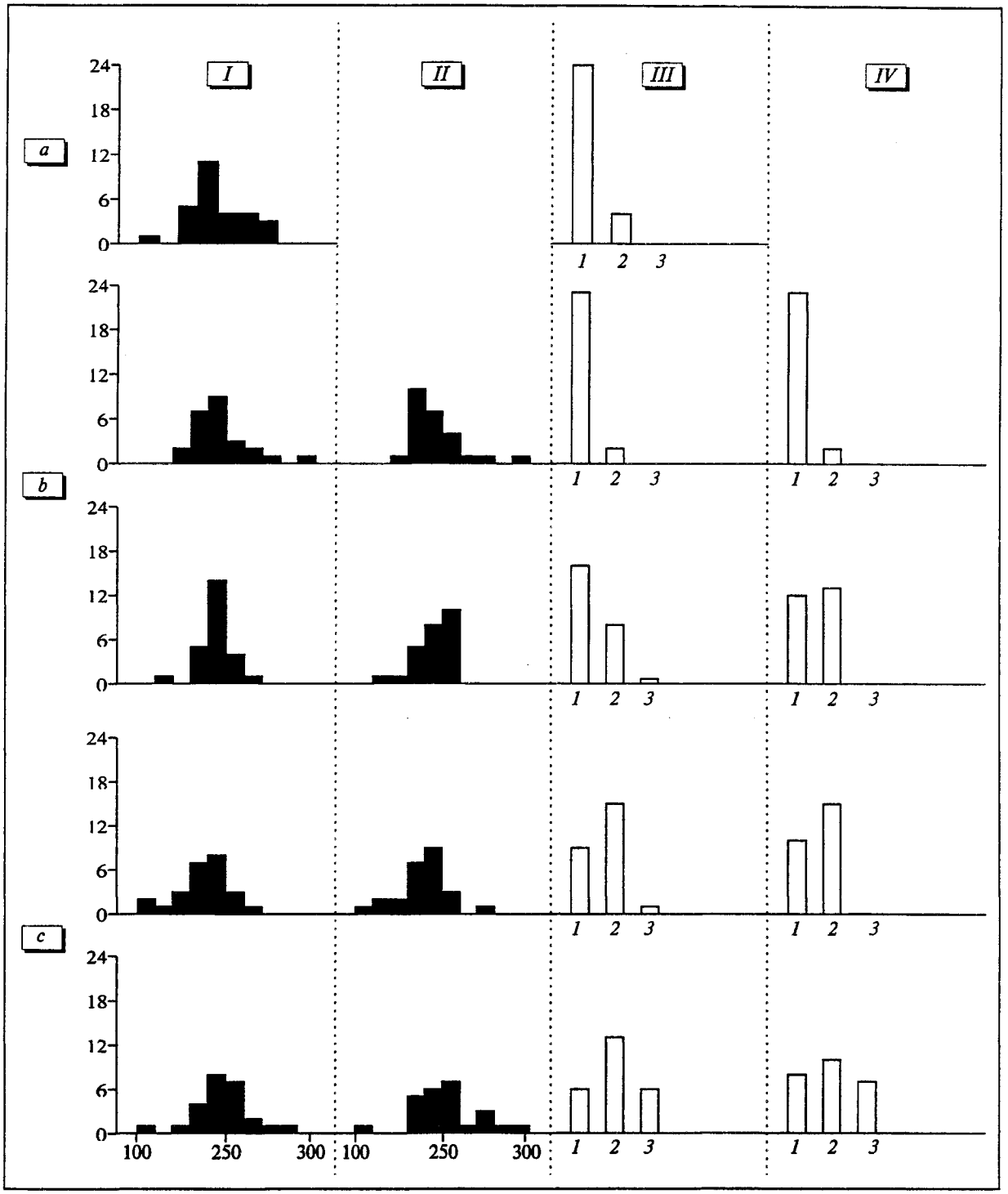

Fig. 2. Latent period histograms of the vision-controlled horizontal centrifugal saccadic eye movements (SEM) through 40° (*I*, *II*) and the diagrams of multiple SEM (*III*, *IV*) in healthy subject (*a*) and in parkinsonian patients No. 6 (*b*) and No. 2 (*c*). *a*: latent periods of SEM to the right for the right eye; *b* and *c*: the upper plot — SEM to the right, the lower plot — SEM to the left; *I*) latent periods for the right eye to the right and left; *II*) the same for the left eye. Abscissa — *I*, *II*: every bin is 30 msec; *III*, *IV*: types of SEM — (*1*) single, (*2*) double, (*3*) triple and higher order.

tions between the reticular portion of substance nigra and superior colliculi, which causes disturbances of SEM in parkinsonian patients [8]. We suppose that this is not comprehensive and final solution to the problem of SEM disorder, because treatment of PD patients with the corresponding drugs produced no

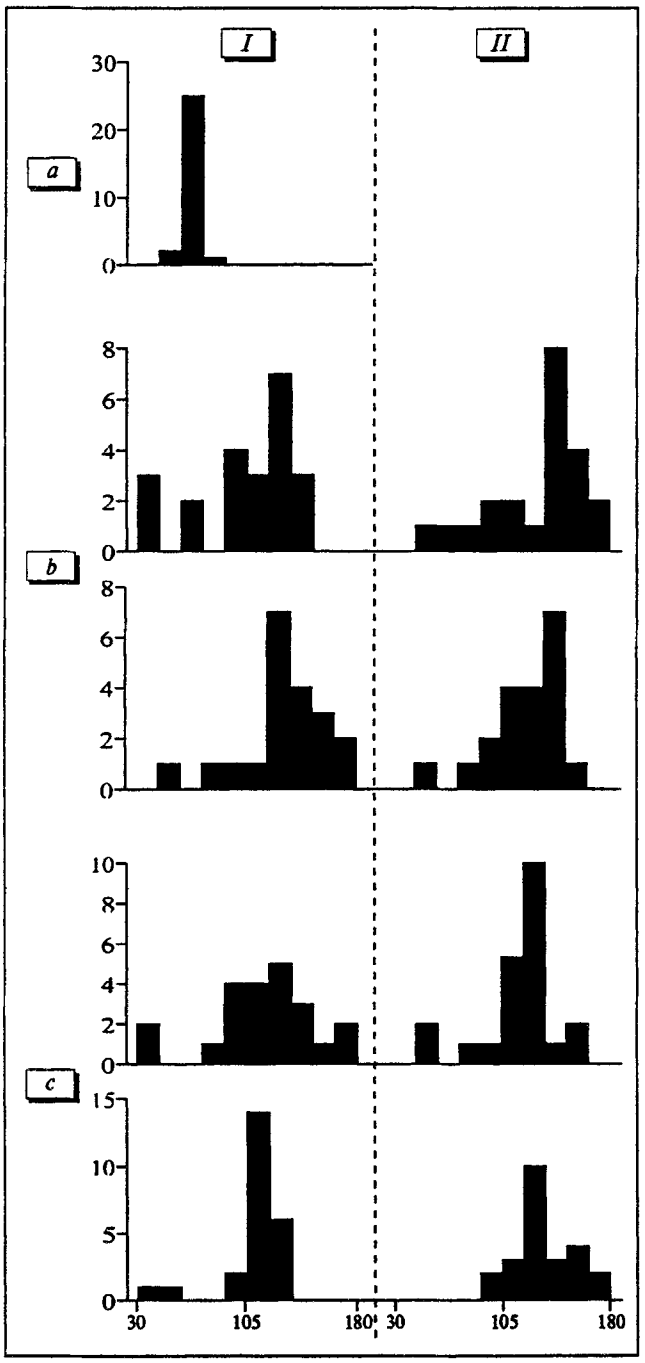

Fig. 3. Duration histograms of the vision-controlled horizontal centrifugal saccadic eye movements (SEM) through 40° in healthy subject (a) and in parkinsonian patients No. 1 (*b*) and No. 8 (*c*). *a*) duration of SEM to the right for the right eye; *b* and *c*) the upper plot — SEM to the right, the lower plot — SEM to the left; *I*) latent periods for the right eye to the right and left; *II*) the same for the left eye. Abscissa — *I*, *II*: every bin is 15 msec.

unequivocal improvement of oculomotor functions [6,7,11]. We did not observe the patients for a prolong period, and our data were obtained during a short examination. They showed that there were no marked differences in the parameters of SEM between treated and untreated patients (Tables 1 and 2). The clear improvement of the patients' condition was related to temporal restoration of the skeletal muscle motor function: elimination of tremor, rigidity, and akinesia.

Other mechanisms of SEM disturbances are related to the inhibitory GABAergic system. The level of GABA markers which corresponds to neural activity decreases in the substance nigra of PD patients [2]. This results in an imbalance between excitation and inhibition in the superior colliculi. It is assumed that before starting a normal SEM, the analog of future SEM of necessary size is generated in the superior colliculi. This signal travels via a neuronal delay and pause neurons to trigger SEM generator, which feeds the value of SEM into the closed feedback circuits without providing a feedback signal for the current value of motor error [5]. Disorder in inhibitory connections between the reticular portion of substance nigra and superior colliculi may cause disturbance in triggering of the pause neurons that track this motor error. In case of single SEM one can see an increase in its duration. Prolonged SEM can be also produced by delayed (in respect to the control) performance of SEM generator. Judging from LP of the secondary and following SEM and taking into account the fact that the mean LP in all patients was no longer than 100 msec, two reasons of multiple saccade generation can be suggested. First, they can be related to "quenching" of the work of SEM generator itself. For such a closed circuit it cannot be explained entirely by dopamine deficiency, because no dopamineergic neurons were found in the regions of premotor reticular formation, oculomotor and vestibular nuclei. Second, reprogramming of the express-saccade type may occur, because exposure of the peripheral target in our experiments was rather long (1 sec and longer), so the effect of vision suppression caused by the first SEM was eliminated.

We think that disturbances of vision-controlled SEM in PD patients can result not only from depletion of the dopaminergic system, but also from the imbalance of this system in respect to other transmitter systems, the GABAergic included.

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Role of Calcium and Phosphoinositide Cell Regulatory System in Adaptation of Neurons in Olfactory Cortex Section to *In Vitro* Hypoxia

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Activities of calcium and phosphoinositide regulatory systems in sections of rat olfactory cortex are analyzed during and after anoxia of different duration. It is shown that short-term anoxia prevents the disturbances in cell regulatory systems induced by long-term anoxia via moderate but sustained rise in neuronal content of second messengers: Ca^{2+} and products of phosphoinositide hydrolysis.

Key Words: *brain; anoxia; calcium; phosphoinositides; adaptation*

The involvement of principal cell regulatory systems (CRS) (calcium, polyphosphoinositide, and cyclic nucleotides) in various physiological and pathological processes in the brain (in particular, pathologies induced by severe hypoxia) is now beyond the question [1,7,9,11]. Cellular mechanisms of adaptation to hypoxia are an important problem of modern medicine and biology. Some investigators demonstrated the role of CRS in adaptive cell mechanisms triggered by both antihypoxic drugs and non-drug antihypoxic influences, in particular, short-term hypoxia, which effectively protects neurons from long-term hypoxia [2,5,8,10]. However, the mechanisms of this protective effect of short-term hypoxia are little studied. In our previous *in vitro* studies we chose experimental conditions for realization of protective effect of preventive hypoxia. These experiments showed that adaptive process is associated with certain shifts in the content of the calcium and phosphoinositide CRS in the brain cortex, which correlate with enhanced bioelectrical neuronal activity [4,5]. The aim of the present study was to elucidate the role of calcium and phosphoinositide CRS in the reaction of anoxia of various duration and in adaptive process induced by short-term hypoxia.

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MATERIALS AND METHODS

Experiments were carried out on 300-400-μ-thick sections of the olfactory cortex from Wistar rats. The sections were placed in a flow chamber and incubated in oxygenated buffer containing (in mM): 124 NaCl, 5 KCl, 2.6 $CaCl_2$, 1.24 KH_2PO_4, 3 Na_2HCO_3, 10 glucose, and 23 Tris-HCl (37°C, pH 7.4). Activity of calcium CRS was assessed by the dynamics of cell content of bound calcium (Ca-c) in different zones of the preparation measured using a chlorotetracycline fluorescent probe [3]. Activity of phosphoinositide CRS was assessed by the content and exchange rate of di- and triphosphoinositides (DPI and TPI). To this end, the section was transferred into a

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