CHANGES IN BALANCE OF BIOGENIC MONOAMINES AND THEIR METABOLITES IN RATS WITH HYPERBARIC EPILEPSY

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A protective role of monoamine oxidase inhibitors in hyperbaric epilepsy has been reported [2], confirming involvement of the brain monoaminergic systems in the development of seizure activity. However, changes in the balance of monoamines and their metabolites in different phases of the epileptiform seizure have not yet been studied. Moreover, there are virtually no data on the role of monoaminergic systems of the heart in the genesis of oxygen poisoning.

The aim of this investigation was to study changes in concentrations of biogenic amines and their metabolites in certain parts of the brain and heart of rats exposed to a session of toxic hyperbaric oxygenation of varied duration.

EXPERIMENTAL METHOD

Biogenic amines and their metabolites were determined by high-performance liquid chromatography (HPLC) with electrochemical detection [4]. The convulsive form of oxygen poisoning was induced by exposing noninbred male albino rats in a pressure chamber to oxygen in a pressure of 6 atm for 5-60 min. Periods of compression and decompression each lasted 20 min. At the end of decompression the rats were decapitated and brain and heart structures were removed in the cold and kept in liquid nitrogen until use.

EXPERIMENTAL RESULTS

Three stages of hyperbaric epileptic fit were investigated: compensatory (exposure for 5 min), convulsive (exposure 27 min), and terminal (exposure 60 min). The results are given in Tables 1 and 2. It will be clear from Tables 1 and 2 that under normal circumstances the concentration of catecholamine (CA) metabolites in the rat heart was much lower than in the brain: in the left and right ventricles homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DHPAA) were absent; no 3-methoxy-4-hydroxyphenylglycol (MHPEG) could be found and the 5-hydroxyindoleacetic acid (5-HIAA) level was very low. Compared with the left ventricle, the right contained more 3,4-dihydroxyphenylglycol (DHPEG), noradrenalin (NA), and adrenalin (A), but less dihydroxyphenylalanine (DOPA). No metabolites of dopamine (DA) were present in the ventricles of the heart, but its precursor (DOPA) was present. No 3,4-dihydroxymandelic acid (DHMA) was found in the atria (total preparation), but concentrations of serotonin (5-HT) and 5-HIAA were significantly higher than in the ventricles; metabolites of DA, and also MHPEG, were absent but the DOPA concentration was lower than in the left ventricle but higher than in the right. In the septum of the heart concentrations of NA and A were much lower than in the ventricles and atria; neither DHMA nor HVA was found, but DHPAA was present in higher concentrations that in other parts of the heart, but the 5-HIAA concentration was very low. The results showing the distribution of monoamines and their metabolites in the normal rat brain and heart justify the conclusion that the principal monoaminergic substances in the rat heart are NA and A, and that virtually all the monoamines and their metabolites studied are well represented in the brain.

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TABLE 1. Concentrations of Biogenic Amines in Rat Brain during Hyperbaric Epilepsy

Experimental conditions \ Part of brain	Substance, ng/g tissue									
	A	NA	DHMA	DHPEG	MHPEG	DOPA	DHPAA	HVA	5-HT	5-HIAA
Striatum										
Normal	109±70	247±115	—	118±30	390±100	200±100	15±6	500±150	84±50	2490±800
5 min of HBO	—	115±20	—	120±30	—	—	42±21	25±10	188±13	280±10
27 min of HBO	10±10	300±70	—	400±150	—	48±9	44±9	—	90±20	170±20
60 min of HBO	12±7	139±67	—	111±23	—	19±10	95±50	105±20	104±40	175±65
Cerebral cortex, normal	50±25	68±30	200±50	80±8	—	12±2	98±50	—	100±30	83±60
5 min of HBO	—	60±5	—	77±10	—	50±5	117±32	50±10	181±22	172±12
27 min of HBO	50±20	20±15	—	300±125	—	330±80	631±220	—	165±80	185±80
60 min of HBO	2±2	41±20	—	109±22	—	20±5	137±80	149±90	93±30	170±60
Hypothalamus										
Normal	114±30	903±200	250±100	151±20	—	443±200	166±45	100±40	387±120	3900±2000
5 min of HBO	—	452±36	—	104±14	—	—	154±42	—	554±155	660±78
27 min of HBO	—	35±35	—	256±125	—	—	204±80	—	289±10	349±85
60 min of HBO	—	341±89	—	135±8	—	—	227±80	—	130±5	276±50

Legend. Here and in Table 2: mean results of 2-7 determinations and their standard deviations are shown. HBO) Hyperbaric oxygenation.

TABLE 2. Concentrations of Biogenic Amines in Rat Heart during Hyperbaric Epilepsy

Experimental conditions \ Part of heart	Substance, ng/g tissue									
	A	NA	DHMA	DHPEG	MHPEG	DOPA	DHPAA	HVA	5-HT	5-HIAA
Left ventricle										
Normal	695±300	369±100	200±100	148±65		300±100	—	—	38±20	10±5
5 min of HBO	10±1	135±20	—	111±42	—	20±1	2±2	—	55±30	11±3
27 min of HBO	10±10	74±40	—	61±15	—	10±10	—	—	44±15	5±5
60 min of HBO	30±10	—	—	—	—	—	—	—	89±30	50±25
Right ventricle										
Normal	4000±2000	535±200	120±40	426±300	—	10±2	20±5	—	46±15	45±30
5 min of HBO	10±2	210±35	—	45±15	—	10±5	5±2	—	60±40	43±15
27 min of HBO	—	58±12	—	25±25	—	—	=	—	55±30	11±11
60 min of HBO	—	—	—	—	—	—	—	—	160±80	150±15
Atria										
Normal	4000±1500	983±256	—	112±40	—	80±35	—	—	174±50	112±50
5 min of HBO	10±2	339±63	—	139±85	—	—	—	—	152±64	48±13
27 min of HBO	39±15	30±10	—	125±25	—	—	—	—	63±25	20±5
60 min of HBO	150±100	40±20	—	—	—	—	—	—	95±5	257±59
Septum										
Normal	177±80	263±90	—	69±30	—	20±5	200±70	—	74±20	20±10
5 min of HBO	10±2	134±10	—	84±12	—	30±10	2±2	—	65±34	11±6
27 min of HBO	15±15	137±20		49±20	—	—	2±2	—	36±15	11±5
60 min of HBO	194±30	346±20	300±100	—	—	—	—	—	125±30	150±40

It will be clear from Tables 1 and 2 that during the oxygen-induced epileptiform seizure the balance of monoamines and their metabolites in the rat brain and heart was considerably shifted. For instance, after an exposure of only 5 min (the compensatory phase of the seizure) both A and DOPA and also the NA metabolites DHMA and MHPEG had disappeared from the brain, and the NA, DHPEG, HVA, and 5-HIAA levels were reduced. However, despite the fall in the A level in the brain, no convulsions occurred during this period, possibly because of elevation of the 5-HT level (Table 1), which, according to data in the literature, can delay the onset of oxygen convlusions [1]. According to our data, at the beginning of exposure the velocity of hydroxylation reactions in the course of CA synthesis was sharply reduced, and reactions of methylation and deamination of CA also were slowed. At the same period, the fall in the levels of all CA and of DHMA showed the greatest fall, whereas concentrations of 5-HT and 5-HIAA and of NA and DA metabolites were unchanged; only in the septum of the heart was the 5-HIAA level raised. Thus the compensatory phase of the oxygen epileptiform seizure is characterized by a parallel course of change in the balance of monoamines and their metabolites between the CNS and the cardiovascular system.

The convulsive period begins with the 27th minute of exposure. Table 1 shows that during this period unequal changes take place in the balance of biogenic amines in different parts of the brain. In the hypothalamus, for instance, the NA level continues to fall, in

the cerebral cortex it remains unchanged, and in the striatum it rises. On the whole, except HVA, NA, 5-HT, and 5-HIAA in the hypothalamus and striatum, all the remaining substances either remain unchanged in the brain or they are at a higher level than after exposure for 5 min. Conversely in the heart at this time there is virtually no DHPAA or DOPA (except in the left ventricle), no A in the right ventricle, and the concentrations of DHPEG, NA, and A in the left ventricle, and 5-HT and 5-HIAA in the atria and septum continue to fall. By contrast with the atria, the 5-HT level in the ventricles is unchanged compared with exposure for 5 min, or it rises. Thus by the beginning of seizure activity, a mosaic pattern of distribution of biogenic amines and of their metabolites was observed in the brain heart.

The terminal stage of the oxygen-induced epileptiform seizure (exposure for 60 min), as is clear from Table 1, was characterized by an increase in concentrations of NA, 5-HT, and 5-HIAA in the striatum and of HVA in the cerebral cortex and striatum, but not to normal, by normalization of the DHPEG level, and lowering of the DHPAA level in the cerebral cortex and also of the 5-HT level in the hypothalamus and cortex. No DHPEG or NA was found in the ventricles of the heart at this time, and the NA level in the atria and septum remained almost unchanged compared with the beginning of the convulsive period. Unlike NA, A was absent only in the right ventricle, and in the other parts of the heart its level was very slightly raised. The 5-HIAA concentration was increased in the heart, but the 5-HT concentration only in the right ventricle and septum. Thus whereas in the rat brain after exposure for 60 min partial restoration of the NA and 5-HT levels was observed, almost complete absence of NA and A was found in all parts of the heart.

It can be concluded from analysis of the results that throughout the period of hyperbaric oxygen epilepsy disturbances of the balance of the biogenic amines and their metabolites were observed both in the CNS and in the cardiovascular system. For instance, starting with the 5th minute of exposure, the concentrations of CA and their metabolites in the brain and heart were considerably reduced, and the compensated state of the CNS was evidently maintained by elevation of the 5-HT level in the hypothalamus. During the period of development of seizure activity the NA and 5-HT levels in the hypothalamus fell, the CA concentration in the heart continued to decline, and in the terminal phase of the seizure the concentrations of monoamines in the brain were partially restored to normal, whereas in the heart an acute deficiency remained, mainly of A and NA. The physiological action of hyperbaric oxygen on the body can be compared with the effect of cortisone [3], in agreement with our data on exhaustion of the monoamine reserves of the brain and heart throughout the period of oxygen poisoning. The subsiding of seizure activity in the terminal stage of the convulsive oxygen-induced seizure evidently correlates with the partial normalization of the brain monoamine balance, which we found, during this period (Table 1), where the extremely low level of A and NA in the heart may be evidence that not only the respiratory system, but also the cardiovascular system plays an important role in the pathogenesis of death following exposure to hyperbaric oxygen. It can be concluded from our results that the compensatory, convulsive, and terminal phases of the oxygen-induced epileptic seizure differ not only electrophysiologically [3], but also at the level of biogenic amine metabolism in the CNS and cardiovascular system, and they also emphasize the important role of the latter in the formation of relations between the vital systems of the body, that are incompatible with life, in the experimental pathology which we have been studying.

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