Potentiated Antibodies Against Morphine: Effects on Biogenic Amines and Lipid Peroxidation in Chronically Morphinized Rats

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The efficiency of potentiated antibodies against morphine was studied on the model of chronic morphine intoxication. Test antibodies stimulated catecholamine metabolism in the hypothalamus (*i.e.*, prevented initiation of catecholamine- and histaminergic peripheral reactions) and normalized lipid peroxidation.

Key Words: *potentiated antibodies against morphine; morphine; biogenic amines; lipid peroxidation*

We studied the effects of potentiated antibodies against morphine (PAB-M) on changes in the content of biogenic amines and intensity of lipid peroxidation (LPO) produced by pretreatment with morphine.

MATERIALS AND METHODS

Morphine dependence in rats was produced by intraperitoneal injection of morphine in increasing doses of 1-10 mg/kg for 8 days. After morphine withdrawal the animals perorally received 0.1 ml PAB-M (10^{-60} wt %) 2 times a day for 7 days. The rats were decapitated on the next day after the last treatment. The contents of catecholamines, serotonin, and amino acid precursors were measured in the frontal neocortex, hypothalamus, hippocampus, amygdaloid complex, and whole blood [1]. The concentrations of malonic dialdehyde (MDA) [2] and conjugated dienes [3] and acetylcholinesterase (AChE) activity [4] were estimated in blood plasma.

The results were analyzed by Student's *t* test.

RESULTS

The content of biogenic amines in brain structures changed in chronically morphinized rat, but returned to normal after morphine withdrawal. We revealed only a slight increase in the concentrations of dopamine and norepinephrine in the frontal cortex and amygdaloid complex, respectively. Besides this, the contents of tyrosine, tryptophan, and serotonin in the hippocampus increased by 153, 136, and 136%, respectively (Table 1).

PAB-M normalized the contents of these substances in the hippocampus, neocortex, and amygdaloid complex. However, in rats receiving PAB-M the concentrations of tyrosine and norepinephrine in the hypothalamus were higher than in morphinized animals. After treatment with PAB-M epinephrine level decreased in the hypothalamus and frontal cortex, but increased in the amygdaloid complex (Table 1). The concentrations of tryptophan and serotonin decreased in the frontal neocortex. These changes indicate that PAB-M activate catecholamine metabolism in the hypothalamus and reduce serotoninergic activity in cortical structures of rat brain (Table 1).

The concentrations of dopamine, tryptophan, serotonin, and histamine and AChE activity in the peripheral blood increased by 25-87% 7 days after morphine withdrawal, which reflected activation of the autonomic nervous system (Table 2). In rats receiving PAB-M the contents of dopamine, histamine, and epinephrine decreased to the control level. However, PAB-M had no effect on serotonin- and cholinergic processes. These data show that PAB-M normalized peripheral catecholamine- and histaminergic functions, but did not modulate the effects of indole compounds and acetylcholine.

MDA content decreased after morphine withdrawal. In rats receiving PAB-M the concentration of MDA did not differ from that in intact animals (Table 2).

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TABLE 1. Contents of Biogenic Amines (nmol/liter) and Amino Acid Precursors (mmol/g) in Rat Brain Structures (*M*±*m*, *n*=6-11)

Brain structure		Intact	Morphine	PAB-M
Frontal cortex	tyrosine	7.1±0.6	8.40±0.65	6.50±0.68
	dopamine	2.40±0.17	3.30±0.44**	1.90±0.33^{+}
	norepinephrine	1.90±0.18	1.80±0.29	1.40±0.32
	epinephrine	0.54±0.07	0.67±0.09	0.24±0.05*$^{+}$
	tryptophan	13.0±1.4	15.3±0.8	9.8±1.3^{+}
	serotonin	3.00±0.34	4.00±0.42	2.20±0.48^{+}
Hypothalamus	tyrosine	19.5±2.3	15.6±1.8	24.0±3.1^{+}
	dopamine	4.70±0.58	3.60±0.53	3.30±0.58
	norepinephrine	3.90±0.41	3.5±0.5	5.20±0.67^{++}
	epinephrine	1.10±0.12	1.20±0.18	0.70±0.11*$^{+}$
	tryptophan	19.8±1.9	21.0±1.2	19.8±3.8
	serotonin	8.10±0.94	6.60±0.74	9.90±1.42^{++}
Amygdaloid complex	tyrosine	10.2±0.7	10.4±1.2	9.7±1.5
	dopamine	3.90±0.28	3.80±0.47	3.70±0.37
	norepinephrine	1.40±0.18	2.00±0.27**	1.9±0.3
	epinephrine	0.49±0.05	0.46±0.06	0.66±0.04^{+}
	tryptophan	18.3±2.1	17.1±0.3	12.5±2.2
	serotonin	5.00±0.54	5.60±0.79	5.80±0.78
Hippocampus	tyrosine	9.1±1.6	13.9±1.5*	15.2±1.5*
	dopamine	1.80±0.19	2.20±0.19	1.90±0.16
	norepinephrine	1.90±0.23	1.80±0.21	2.50±0.38
	epinephrine	0.35±0.05	0.47±0.06	0.36±0.06
	tryptophan	5.70±0.31	7.70±0.66*	6.30±0.84
	serotonin	3.20±0.38	4.40±0.27*	3.60±0.56

Note. Here and in Table 2: *p<0.05 and **p<0.01 compared to intact rats; ^{+}p<0.05 and $^{++}$0.05<p<0.01 compared to morphinized animals.

TABLE 2. Contents of Biogenic Amines (nmol/liter) and Amino Acid Precursors (mmol/liter), AChE Activity (nmol/mg protein/min), and Concentration of LPO Products (mmol/liter) in the Blood and Plasma from Rats (*M*±*m*, *n*=6-11)

Material		Intact	Morphine	PAB-M
Blood	tyrosine	10.7±1.0	15.4±2.6	12.8±0.6
	dopamine	80.7±6.5	110±11*	72.9±3.9^{+}
	norepinephrine	69.3±5.7	64±10	70.1±8.5
	epinephrine	37.1±3.3	39.2±4.2	23.0±2.8^{+}
	tryptophan	16.2±0.9	24.9±2.9*	21.4±1.9*
	serotonin	807±50	1507±168*	1673±186*
	histamine	1685±91	2115±127*	1651±50^{+}
Plasma	AChE	2.50±0.22	3.70±0.25*	3.60±0.31*
	MDA	11.8±0.6	7.9±0.2*	11.2±1.6^{++}
	conjugated dienes	50.9±9.9	68.0±9.1	52.7±2.9

Our results show that administration of PAB-M after long-term treatment with morphine stimulates catecholamine metabolism in the hypothalamus and slightly attenuates the action of serotonin in cortical structures of rat brain. The preparation produces a more pronounced effect in peripheral tissues. PAB-M normalize the intensity of LPO and prevent activation of catecholamine- and histaminergic reactions, but do not affect the increased levels of tryptophan and serotonin. These properties contribute to the sedative and anxiolytic effects of PAB-M.

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