Effect of Delta-Sleep-Inducing Peptide on Activity of Enzymes of Biogenic Amine Metabolism in the Brain of Wistar and August Rats

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Activity of enzymes catalyzing synthesis and degradation of serotonin and dopamine in brain structures of Wistar and August rats was measured biochemically under normal conditions and after short-term exposure to delta-sleep-inducing peptide. The effects of the test peptide manifested in activation of the serotoninergic system and inhibition of the dopaminergic system, particularly in the caudate nucleus. These changes were most pronounced in the brain of Wistar rats.

Key Words: *Wistar and August rats; delta-sleep-inducing peptide; enzyme activities; neurotransmitter systems; brain structures*

Delta-sleep-inducing peptide (DSIP) is a well-known regulatory peptide. DSIP acts as a polyfunctional hypnagogic bioregulator in the organism [1] and possesses antistress and adaptogenic properties [11]. The effects of DSIP are realized via modulation of neurotransmitter metabolism in the brain [2,7,8]. Little is known about the influence of DSIP on individual enzyme systems of biogenic amine metabolism.

Here we studied the *in vivo* effect of DSIP on activities of enzymes catalyzing synthesis and utilization of serotonin and dopamine in cortical and subcortical brain structures in Wistar and August rats differing by behavioral characteristics and emotional reactivity [4].

MATERIALS AND METHODS

Experiments were performed on adult male Wistar and August rats weighing 180-240 g. The animals were divided into 2 groups. Control group 1 included intact rats. Group 2 rats received intraperitoneal injection of DSIP in a single dose of 60 μg/kg. They were sequestrated 30 min after treatment under light ether anesthesia. Study was conducted according to the requirements for experiments on laboratory animals. Enzyme activities were measured in the sensorimotor cortex and caudate nucleus. Subcellular fractions were consecutively isolated by differential centrifugation to estimate enzyme activities [3].

Tryptophan hydroxylase (TPH) activity was measured fluorometrically at excitation and absorption wavelengths of 290 and 540 nm, respectively [13]. L-Tryptophan was used as the substrate. Tyrosine hydroxylase (TH) activity was measured spectrophotometrically at 335 nm using L-tyrosine as the substrate [8].

Monoamine oxidase A activity was measured spectrophotometrically at 250 nm using serotonin creatinine sulfate as the substrate [14]. Monoamine oxidase B activity was measured spectrophotometrically at 450 nm using p-nitrophenyl ethylamine as the substrate [5]. The concentration of deoxyphenylethylamine was measured spectrophotomet-

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rically at 510 nm [15]. Protein content was estimated by the method of Lowry. The results were expressed in optical density units per mg protein over 60 min.

The results were analyzed by nonparametric Mann—Whitney *U* test. The differences between samples were significant at $p<0.05$.

RESULTS

DSIP had little effect on TH activity in the cerebral cortex and caudate nucleus of August and Wistar rats (Table 1). Monoamine oxidase B activity in the cerebral cortex and caudate nucleus tended to decrease in August rats (by 84.2 and 85.2%, respectively) and was significantly reduced in Wistar rats (by 29 and 18%, respectively). The concentration of deoxyphenylethylamine in the cerebral cortex and caudate nucleus decreased in August (by 13.4 and 23%, respectively) and Wistar rats (by 15.8 and 28%, respectively).

Probably, the effects of DSIP are partly related to suppression of the dopaminergic system. These changes are particularly pronounced in the brain of Wistar rats. Behaviorally, DSIP produces a relaxing effect.

Single treatment with DSIP increased monoamine oxidase A activity in the cerebral cortex of August and Wistar rats (by 47.4 and 28%, respectively). Enzyme activity in the caudate nucleus of these animals increased by 61.5 and 62.2%, respectively, compared to normal. TPH activity did not differ in Wistar and August rats. Enzyme activity in the caudate nucleus tended to increase after treatment (Table 2). The effects of DSIP were most pronounced in the caudate nucleus. Moreover, the degree of DSIP-produced changes was maximum in Wistar rats.

Previous studies showed that DSIP *in vitro* and *in vivo* activates monoamine oxidase A and increases the concentrations of serotonin and 5'-hydroxyindoleacetic acid in brain subfractions from rabbits and Wistar rats [6,10]. It was hypothesized that this peptide modulates activity of the serotoninergic system. Our experiments showed that DSIP has a similar effect on activity of the enzyme involved in serotonin synthesis. This action is of considerable importance for emotionally reactive August rats. Our findings demonstrate that these animals have low basal activity of enzymes for serotonin metabolism.

We conclude that the effects of DSIP are associated with activation of the serotoninergic system and inhibition of the dopaminergic system. It should be emphasized that the peptide most significantly modulates the system for utilization of neurotransmitters. DSIP has a systemic effect on neurotrans-

TABLE 1. Short-Term Effect of DSIP on Enzymes for Dopamine Metabolism and DOPA Concentration in Brain Structures of August and Wistar Rats (*M*±*m*)

Group		Cerebral cortex						Caudate nucleus					
		TH		DOPA		MAO B		TH		DOPA		MAO B	
		ΔE_{335}/mg protein	%	ΔE_{510}/mg protein	%	ΔE_{450}/mg protein	%	ΔE_{335}/mg protein	%	ΔE_{510}/mg protein	%	ΔE_{450}/mg protein	%
August	control	1.46±0.24	100.0	0.67±0.10	100.0	0.38±0.07	100.0	1.46±0.13	100.0	0.74±0.11	100.0	0.27±0.06	100.0
	DSIP	1.38±0.16	94.5	0.58±0.08	86.6	0.32±0.05	84.2	1.29±0.15	88.4	0.57±0.09	77.0*	0.23±0.04	85.2
Wistar	control	1.20±0.19	100.0	0.82±0.11	100.0	0.48±0.08	100.0	2.10±0.26	100.0	0.87±0.13	100.0	0.50±0.07	100.0
	DSIP	1.17±0.17	97.5	0.69±0.10	84.2	0.34±0.06	70.8*	1.72±0.23	81.9	0.62±0.11	71.3*	0.41±0.06	82.0

Note. Here and in Table 2: MAO B, monoamine oxidase B; DOPA, deoxyphenylethylamine. *$p<0.05$ compared to the control.

TABLE 2. Short-Term Effect of DSIP on Enzymes for Serotonin Metabolism in Brain Structures of August and Wistar Rats (*M*±*m*)

Group		Cerebral cortex				Caudate nucleus			
		TPH		MAO A		TPH		MAO A	
		nmol/mg protein	%	ΔE_{250}/mg protein	%	nmol/mg protein	%	ΔE_{250}/mg protein	%
August	control	0.87±0.15	100.0	0.19±0.06	100.0	2.55±0.38	100.0	0.26±0.09	100.0
	DSIP	0.91±0.16	104.6	0.28±0.06	147.4*	2.84±0.41	111.4	0.42±0.09	161.5*
Wistar	control	1.07±0.21	100.0	0.25±0.05	100.0	4.03±0.59	100.0	0.45±0.07	100.0
	DSIP	1.16±0.20	108.4	0.32±0.06	128.0	4.68±0.37	116.1	0.73±0.09	162.2*

Note. MAO A, monoamine oxidase A.

mitter metabolism in the brain of laboratory-bred rats. The effect of DSIP in August rats is more pronounced than in Wistar rats. It manifested in inhibition of locomotor behavior and decrease in orientation and exploratory activity [12]. Hence, DSIP specifically modulates neurotransmitter metabolism in the brain and functional activity of the central nervous system.

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