

# THE EFFECT OF ADRENALIN ON HISTAMINE METABOLISM IN NORMAL CONDITIONS AND IN DISEASES OF THE DIENCEPHALON

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In our research [4] on the study of histamine metabolism in certain forms of disease of the diencephalon, we found that absence of a histaminopeptic effect, i.e., the ability of the serum to inactivate histamine added to it in vitro, is a characteristic feature of patients with lesions of the diencephalic region. The variations in the content of histamine and diamine oxidase in these diseases do not exceed normal limits. Meanwhile, in experiments on animals [1] to study the relationship between the metabolism of histamine and adrenalin under the influence of factors causing stress, it was shown that the content of histamine and adrenalin-like substances (ALS) in the blood, the brain, and lung tissues, and the mucous membrane of the intestine, varies in different ways in these cases. Whereas the histamine content of the brain and lung tissues was reduced in response to an increase in the ALS level, the contents of ALS and histamine in the blood and the intestinal mucosa were simultaneously increased.

According to data in the literature, stimulation of the sympathetic nerve [9] or the intravenous injection of adrenalin into dogs [8] causes a transient increase in the histamine content of the blood. Similar changes are also observed in human patients suffering from various diseases (bronchial asthma, gastric ulcer, bronchitis). It has been found that, in response to the intravenous injection of adrenalin into the patients, the histamine content of the blood is increased, returning to its initial level after 10 minutes [10].

In the development of the work undertaken by our group on the study of the relationship between the clinical manifestations and the associated neurohumoral changes [2, 5, 6, 7] in the present communication, we report the results of an investigation of the histamine metabolism in the blood of healthy persons and patients under the influence of exogenous adrenalin. We used the latter as one of the functional tests to judge the limits of homeostatic reactions in the healthy and sick human subject.

## EXPERIMENTAL METHOD AND RESULTS

The subjects under observation received subcutaneous injections of adrenalin (0.3-0.5 ml of a 0.1% solution). Blood for examination was taken from the cubital vein before the injection, and 10 or 20 minutes thereafter. Estimations were made of the histamine, the diamine oxidase, and the histaminopeptic effect of the blood by means of methods previously described [4].

Observations were made on 20 patients with lesions of the diencephalic region. As a control group we used healthy subjects (33 persons) and patients with various other forms of nervous disease (11 persons).

In accordance with N. I. Grashchenkov's classification [3], nine patients with a diencephalic syndrome belonged to a group in which vegetative vascular manifestations were predominant; in 11 patients there was a well-marked neuroendocrine syndrome.

The results obtained in the healthy subjects are shown in Table 1.

In eight of the ten healthy subjects who received an injection of 0.3 ml of adrenalin, the histamine content of the blood 10 minutes after injection was lower than that before the injection. In only one case was an increase in the histamine content observed, and in this case, moreover, a considerable increase in the diamine oxidase activity was present. In all the remaining subjects the diamine oxidase activity was either very slightly increased or remained unchanged. The histaminopeptic effect was unchanged under the influence of the injection of adrenalin. If the blood for examination was taken 20 minutes after the injection of adrenalin, the changes in the histamine content were less pronounced; in four of the eight healthy subjects so tested, the histamine content was not decreased, but increased. If the volume of adrenalin injected was increased to 0.5 ml, the histamine content in the blood of the subjects in this group also fell 10 minutes after injection, but after 20 minutes there developed a slight tendency for this content to increase.

TABLE 1. Histamine Content, Diamine Oxidase Activity, and Histaminopectic Effect in the Blood of Healthy Human Subjects

Dose and time of second blood sampling	Patient No.	Histamine (in $\mu\text{g } \%$ )		Diamine oxidase (in $\mu\text{g/ml}$ )		Histaminopectic effect (in $\%$ )	
		before adrenalin injection	after adrenalin injection	before adrenalin injection	after adrenalin injection	before adrenalin injection	after adrenalin injection
0.3 ml 10 min	1	5.6	3.0	0	0	17	17
	2	17.2	3.6	2.0	2.0	28	28
	3	5.6	4.6	0	0	—	33
	4	8.2	5.0	0	0	25	25
	5	5.2	10.6	0	13	55	55
	6	4.0	4.0	3.0	3.5	47	52
	7	16.0	6.0	1.2	1.5	—	—
	8	13.0	11.0	0	0	30	30
	9	4.0	3.4	2.0	3.0	50	47
	10	12.4	10.4	4.0	8.0	38	—
0.3 ml 20 min	11	8.6	11.7	1.0	1.0	25	25
	12	11.6	10.2	0	0	31	22
	13	7.2	9.6	0	0	24	30
	14	11.6	10.2	2.0	2.0	30	30
	15	5.6	3.0	0	0	25	25
	16	16.0	20.0	2.0	0	25	25
	17	3.0	3.6	0	4.4	40	40
	18	6.6	5.0	3.6	0	49	48
0.5 ml 10 min	19	6.8	4.6	0	1.2	0	1
	20	4.6	3.4	5.4	6.0	41	38
	21	8.0	4.6	2.8	2.2	43	40
	22	7.6	3.8	0	0	20	24
	23	6.8	4.2	7.0	3.2	45	40
	24	10.4	15.0	0	0	30	28
	25	17.6	10.4	0	0	36	36
0.5 ml 20 min	26	15.6	16.0	2.0	2.0	30	28
	27	5.0	11.2	3.0	0.0	36	28
	28	4.6	5.2	—	—	36	20
	29	5.0	9.3	3.0	5.0	27	22
	30	7.2	7.6	0	0	10	14
	31	7.0	8.6	0	0	40	59
	32	6.6	7.6	0	3.0	41	35
	33	11.2	13.2	0	0	17	27

After the injection of histamine in these doses, in the majority of healthy subjects (30 persons) no obvious clinical reaction was observed, and the general condition remained satisfactory. A well-marked clinical reaction, manifesting itself in the form of headache, shivering, rigors, and changes in the arterial pressure, pulse, and respiration, was observed in only three persons who received adrenalin in a dose of 0.5 ml, which coincided with an increase in the blood-histamine concentration (Nos. 24, 27, and 29). In four subjects only an increase in the arterial pressure was observed. At later stages (after 30-40 minutes) a partial or clear-cut clinical reaction was observed in 19 of 30 subjects.

In Table 2 we give the results obtained from investigation of these indices in patients with different forms of nervous disease.

In contrast to the results obtained in the healthy subjects, in diencephalic diseases (in 14 of 15 cases) a clinical reaction was observed 10 minutes after the injection of 0.3 ml of adrenalin. In 11 patients the

blood-histamine concentration was increased, and in four it was lowered. The diamine oxidase activity was unchanged or lowered, but the serum histaminopectic effect showed no significant change. In most subjects a perceptible increase in the blood-histamine level coincided with the onset of a clearly marked clinical reaction.

The histamine content was very slightly lowered in four of the five patients from whom blood for the second examination was taken 20 minutes after the injection of 0.3-0.5 ml of adrenalin. In seven of eleven patients with other forms of nervous disease, a small increase in the blood-histamine content was observed after the injection of adrenalin, in the absence of changes in the diamine oxidase and the histaminopectic effect. At the time of taking blood, a clinical reaction was observed in only two of these patients (Nos. 24 and 30).

As the results described show, the changes in the blood-histamine content under the influence of small doses of adrenalin, both in healthy subjects and in pa-

TABLE 2. Histamine Content, Diamine Oxidase Activity, and Histaminopectic Effect in the Blood of Patients with Various Forms of Nervous Disease

Dose and time of second blood sampling	Patient No.	Diagnosis	Histamine (in $\mu\text{g } \%$ )		Diamine oxidase (in $\mu\text{g/ml}$ )		Histaminopectic effect (in $\%$ )	
			before injection of adrenalin	after injection of adrenalin	before injection of adrenalin	after injection of adrenalin	before injection of adrenalin	after injection of adrenalin
0.3 ml, 10 min	1	Diencephalic syndrome	7.2	20.0	2.0	0	16	16
	2	The same	8.6	12.4	8.0	4.0	13	10
	3	" "	4.2	8.0	—	—	0	0
	4	" "	7.4	16.6	4.0	4.0	0	0
	5	" "	6.6	9.0	5.8	4.4	0	0
	6	" "	8.6	5.6	0	1.8	0	0
	7	" "	6.0	7.1	1.0	1.2	0	0
	8	" "	5.6	4.0	0	0	0	0
	9	" "	5.0	3.5	0	1.4	20	20
	10	" "	6.0	7.0	0	0	0	0
	11	" "	7.6	4.0	9.0	2.0	0	0
	12	" "	15.0	18.0	0	0	8	10
	13	" "	10.2	17.6	0	0	0	0
	14	" "	9.2	13.4	4.6	4.6	0	0
	15	" "	7.4	11.2	0	0	0	0
0.3-0.5 ml, 20 min	16	" "	6.0	4.0	0	1.0	0	0
	17	" "	14.8	11.8	0	6.0	—	—
	18	" "	9.6	10.6	5.0	3.0	0	0
	19	" "	9.2	9.0	0	0	0	0
	20	" "	6.6	5.6	2.0	2.0	—	—
0.3 ml, 10 min	21	Vegetative vascular dystonia	3.2	4.6	1.4	—	0	0
	22	and neurasthenia	12.4	8.6	9.4	10.6	0	0
	23	Residual manifestations of arachnoencephalitis	10.2	9.8	1.2	1.2	0	0
	24		6.2	3.0	4.2	1.4	12	18
	25		16.6	24.4	1.6	1.8	0	0
	26		4.6	9.0	0	0	—	—
	27	Narcolepsy	10.0	11.0	9.0	3.0	0	0
	28	Lipodystrophy	4.8	8.2	1.5	4.6	20	19
	29	Allergy	13.9	8.2	10.4	8.0	—	—
	30	Disease of the muscles	14.5	15.0	0	0	—	—
	31	Adenoma of the adrenals	7.5	8.6	1.0	1.0	0	0

tients with lesions of the diencephalon, are consistent in character. Ten minutes after the injection of 0.3 ml of adrenalin, a fall in the blood-histamine content (from 9.1 to 6.1  $\mu\text{g } \%$  on the average) was observed in the majority of healthy subjects, with a small increase in the diamine oxidase activity (from 2.2 to 2.9  $\mu\text{g/ml}$ ) and in the absence of changes relating to the histaminopectic effect (see figure).

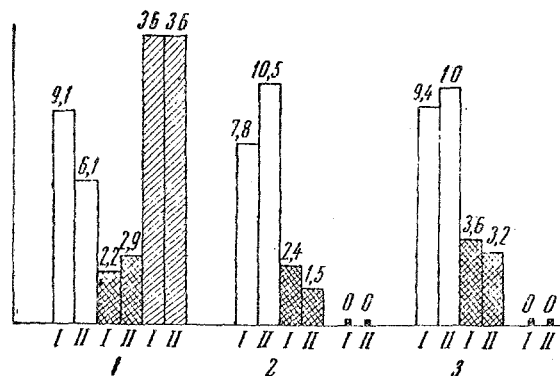
In contrast to these findings, in patients with diencephalic lesions, after injection of adrenalin, the blood-histamine content rose (from 7.8 to 10.5  $\mu\text{g } \%$  on

the average) with a slight fall in the diamine oxidase activity (from 2.4 to 1.5  $\mu\text{g/ml}$ ). In patients with other forms of nervous disease (vegetative vascular dystonia, allergy, residual manifestations of arachnoencephalitis, diseases of the muscles, and so on), in the majority of cases, the same trend was observed in the histamine metabolism as in patients with the diencephalic syndrome; these changes, however, were far less pronounced.

A characteristic finding was that in 14 of the 15 patients with the diencephalic syndrome, an obvious

clinical reaction was observed 10 minutes after the injection of adrenalin.

It has been shown [4-8] that the liberation or formation of free histamine is often connected with the sympatho-adrenal regulatory system. The brief increase in the blood-histamine content, followed by its rapid fall to a level close to its initial value, may be regarded as the reaction of the subject to the injection of adrenalin. In patients with disease of the diencephalon, this reaction is evidently disturbed, and moreover, the process of restoration of the initial level of the blood histamine is also delayed.



Histamine content, diamine oxidase activity and histaminopeptic effect in the blood of healthy subjects and patients, before the injection of 0.3 ml of a 0.1% solution of adrenalin, and 10 minutes thereafter. Unshaded columns — mean blood-histamine level (in  $\mu\text{g } \%$ ); cross-hatched columns — mean level of diamine oxidase activity ( $\mu\text{g/ml}$ ); obliquely shaded columns — mean value of histaminopeptic effect (in  $\%$ ); I) before injection; II) after injection; 1) normal; 2) disease of the diencephalon; 3) various forms of nervous disease.

#### SUMMARY

This work deals with the changes induced by adrenalin injections in the histamine content, diamine oxidase activity, and histaminopeptic effect in healthy individuals

and in patients with diencephalic afflictions.

Adrenalin administration served as a functional test to assess the limits of homeostatic reactions in healthy and sick persons. In healthy individuals, the blood-histamine content decreases, and the activity of diamine oxidase increases slightly, 10 minutes after subcutaneous injection of 0.3 ml of 0.1% adrenalin solution; as to the histaminopeptic effect — no changes are seen. As distinct from the above, in patients with a diencephalic syndrome the blood-histamine content rises and the activity of diamine oxidase decreases somewhat. These changes, accompanied by a clinical reaction, are characteristic of some forms of diencephalic pathology and may be used for diagnosis.

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