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Biorhythmic changes of plasma histamine levels in healthy volunteers

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Abstract

The plasma histamine levels were reported to increase in early hours of the morning in asthmatic patients. It was supposed that this phenomenon would also be observed in normal volunteers. In this study using twelve normal healthy volunteers the plasma histamine levels were examined in a pharmacokinetic manner. It could be shown that plasma histamine levels follow biorhythmic changes with 3 maxima and 3 minima. The acrophases of the maxima are 12.77 ± 0.61, 19.33 ± 0.78 and 5.42 ± 1.83 h. The most important rise in plasma histamine levels was found in the early hours of the morning representing about 55% of the total histamine available in plasma.

Introduction

Basic studies published by Reinberg [1–4], Smolensky [5], De Vries [6, 7] and Hornstein [8] established that both the tolerance of human skin against histamine or histamine liberators and the efficacy of H_1-Receptor-antagonists depend upon circadiane rhythm's. Both findings support the postulation that biorhythmic changes in plasma histamine levels can generally be assumed despite the works of Barnes [9] and Morr [10], who did not succeed in producing evidence for such biorhythmic changes of plasma histamine in healthy volunteers but showed – amongst other authors – a significant increase in nocturnal histamine levels in asthmatic patients.

Plasma histamine levels are reported to cover the range between 0.3 and ~ 2 ng/ml in normal nonallergic volunteers [11–18], but a study on the kinetics of the plasma histamine levels is not available (in literature) to the present day. In this respect the studies of Barnes [9] and Morr [10] are only of limited value due to the limited number of blood samples drawn. It therefore seemed to be necessary to carry out a study on the concentration time course of the plasma histamine level in an hourly blood sampling manner in order to decide whether plasma histamine levels follows a pattern of a certain biorhythm.

Methods

12 volunteers – 6 males and 6 females – aging from 23 to 31 years were introduced in the study. They were informed of the aims and risks of the study and signed a witnessed consent form. All volunteers were interned for a total of 2 weeks, before the study begun and for its duration in order to reach adaptation and standardized conditions respectively.

The volunteers were allowed a normal standard diet including a drink of 150 ml of mineral water every hour between 8 and 22 h. Alcoholic and xanthine-containing beverages were prohibited as

well as food intake apart from set meal times (7.30–8.00 h breakfast; 13.00–13.45 h lunch; 19.00–19.45 h dinner). Sports were ruled out for the duration of the study.

None of the volunteers reported any history of allergy. Details of the volunteers are given in Table 1.

Blood was sampled from a 45 cm long subclavian catheter which had been inserted atraumatically through the brachial vena. The catheter was left in situ for the duration of the study. Plasma was obtained by centrifugation of blood at +4 °C and stored at −20 °C.

The volunteers were divided into two groups by random for reasons of practicability and blood samples were drawn at the following times of the day:

group I 7, 9, 11, 12, 13, 15, 17, 18, 19, 21, 23, 1, 3, 5, 7. Form 1 until 7 all volunteers were asleep.

group II 7, 8, 10, 12, 13, 14, 16, 18, 19, 20, 22, 24, 2, 4, 6. Blood was sampled from sleeping volunteers between 24 and 6.

(Blood sampling times as listed above are only approximations. The maximal deviation was ± 10 minutes. Care was taken that the interval of blood sampling totalled exactly 1 or 2 hours for each volunteer.)

Plasma histamine levels were analysed fluorometrically following the procedure of Lorenz et al. [21]. Each plasma histamine level was determined twice.

Table 1
Characteristics of the volunteers.

Nr.	Group	Volunteer Initial	Sex	Age	Weight	Allergic History
01	I	E.B.	f	27	51	–
02	I	S.B.	m	28	70	–
03	II	C.M.	f	24	60	–
04	I	T.D.	m	25	72	–
05	I	J.E.	f	23	65	–
06	II	W.H.	m	25	72	–
07	I	E.F.	m	24	75	–
08	II	S.S.	f	22	56	–
09	II	M.W.	m	31	63	–
10	I	E.H.	f	25	58	–
11	II	I.K.	f	26	57	–
12	II	P.K.	m	24	75	–

Results

Measured plasma histamine levels vary from 0.01 (specifity of the analytical method) to 0.41 ng/ml dependent on the sampling time. The means of the plasma histamine levels at the various sampling times are ranging between 0.04 ± 0.04 and 0.31 ± 0.07 ng/ml (Table 2). The diurnal mean of plasma histamine levels is 0.13 ± 0.1 ng/ml. The diurnal means of the different volunteers range from 0.06 ± 0.05 to 0.21 ± 0.14 ng/ml (Table 3).

The areas under the curves (0–24 h) are between 1.35 ng × h/ml and 4.785 ng × h/ml (Table 4).

Dependent on the sampling times the plasma histamine levels show minima and maxima with the following coordinates:

Minima:
1. $t_1 = 10.42 \pm 1.00$ h and $c_1 = 0.03 \pm 0.03$ ng/ml
2. $t_2 = 16.50 \pm 1.09$ h and $c_2 = 0.05 \pm 0.05$ ng/ml
3. $t_3 = 23.17 \pm 1.47$ h and $c_3 = 0.05 \pm 0.05$ ng/ml

Maxima:
1. $t_1 = 5.42 \pm 1.83$ h and $c_3 = 0.28 \pm 0.09$ ng/ml
2. $t_2 = 12.77 \pm 0.61$ h and $c_1 = 0.24 \pm 0.08$ ng/ml
3. $t_3 = 19.33 \pm 0.78$ h and $c_2 = 0.20 \pm 0.07$ ng/ml

Table 2
Mean plasma histamine level and standard deviation (ng/ml) at the different blood sampling times.

7.00	0.21±0.07
8.00	0.10±0.06
9.00	0.08±0.05
10.00	0.04±0.04
11.00	0.04±0.04
12.00	0.16±0.10
13.00	0.19±0.13
14.00	0.05±0.05
15.00	0.17±0.06
16.00	0.01±0.01
17.00	0.14±0.08
18.00	0.08±0.06
19.00	0.19±0.07
20.00	0.07±0.04
21.00	0.12±0.06
22.00	0.04±0.04
23.00	0.08±0.05
24.00	0.06±0.05
1.00	0.13±0.09
2.00	0.11±0.05
3.00	0.31±0.07
4.00	0.17±0.04
5.00	0.27±0.06
6.00	0.13±0.03
7.00	0.23±0.08

Table 3
Mean diurnal plasma histamine levels of the twelve volunteers (ng/ml).

01	0.17±0.1
02	0.14±0.1
03	0.12±0.05
04	0.18±0.09
05	0.20±0.12
06	0.07±0.06
07	0.15±0.11
08	0.09±0.08
09	0.09±0.07
10	0.21±0.14
11	0.06±0.05
12	0.07±0.05
$\frac{1}{n} \cdot \Sigma$	0.13±0.1

Table 4
Areas under the curve (AUC) between the individual minima of plasma histamine levels of each volunteer (ng · h/ml) and total AUC.

	AUC_1	AUC_2	AUC_3	AUC_{total}
01	0.835	1.34	1.89	4.065
02	0.845	0.56	2.13	3.535
03	0.635	0.72	1.57	2.925
04	1.425	1.015	1.65	4.09
05	0.995	1.11	2.68	4.785
06	0.325	0.36	0.88	1.565
07	1.195	0.395	1.805	3.595
08	0.45	0.385	1.255	2.09
09	0.445	0.43	1.415	2.29
10	0.865	1.295	2.21	4.37
11	0.11	0.165	1.075	1.35
12	0.27	0.27	1.33	1.87
$\frac{1}{n} \cdot \Sigma$	0.70 (23.1%)	0.67 (22.1%)	1.66 (54.8%)	3.03

Discussion

This study on twelve healthy volunteers aging from 23 to 31 years shows mean plasma histamine levels which are in the lower scale of that reported previously [11–18]. We determined values between 0.06±0.05 ng/ml and 0.21±0.14 ng/ml in contrast to the formerly reported range of 0.3 to ~2 ng/ml. These differences may be explained by the different analytical methods [15, 18, 19], the different age of the healthy volunteers, – because there is evidence that postexercise plasma histamine levels increase both in asthmatic patients and healthy volunteers with increasing age [20] –, as well as by different sampling techniques and protocols (e.g. rise of plasma histamine levels by physical stress situations, rise of plasma histamine levels induced by local trauma [12] etc.), and also by the different sampling times.

The plasma histamine levels of all the volunteers show biorhythmic changes dependent upon the time of blood sampling (Fig. 1). It may be concluded from the data that there are 3 minima and 3 maxima (Fig. 2).

Maximum 2 and 3 are recorded at lunch and dinner time. We are not able to resolve the question whether these two maxima are induced by the intake of food or whether they are dependent on other biorhythmic changes, but breakfast between 7.00 and 7.30 h did not prevent the decrease in the level of plasma histamine between the maximum 1 and the minimum 1.

The most important maximum is that possessing the acrophase 5.42±1.83 h which does certainly not correlate with any food intake. This maximum in plasma histamine levels is also found in asthmatic patients with severe symptoms. Our data correspond with that of Barnes and coworkers [9] who could also show an increase of plasma histamine levels in normal healthy volunteers without statistical significance, however. This lack of significance may be understood on the basis of the blood sampling times (4 a.m. and 4 p.m.). Both times do not meet the acrophases of either the minimum or the maximum so that the level of significance seems to have diminished. The possible clinically important maximum of plasma histamine level during the early morning hours does not interfere with the findings of Morr and coworkers [10] who did not succeed in showing the biorhythmic dependence of plasma histamine levels due to the limited number of sampling times (6, 12, 14, 16, 22 h).

The twelve volunteers differ significantly in mean diurnal plasma histamine levels. Especially 3 volunteers (nos. 6, 11, 12) show very low plasma histamine levels. We do not know whether this is a casual finding or what could have influenced the plasma histamine levels. There are no special findings in the characteristics as sex, age and weight. However we are able to show that the biorhythm occurs in all volunteers, as can be noted from Figure 1 showing the individual plasma histamine levels at different sampling times.

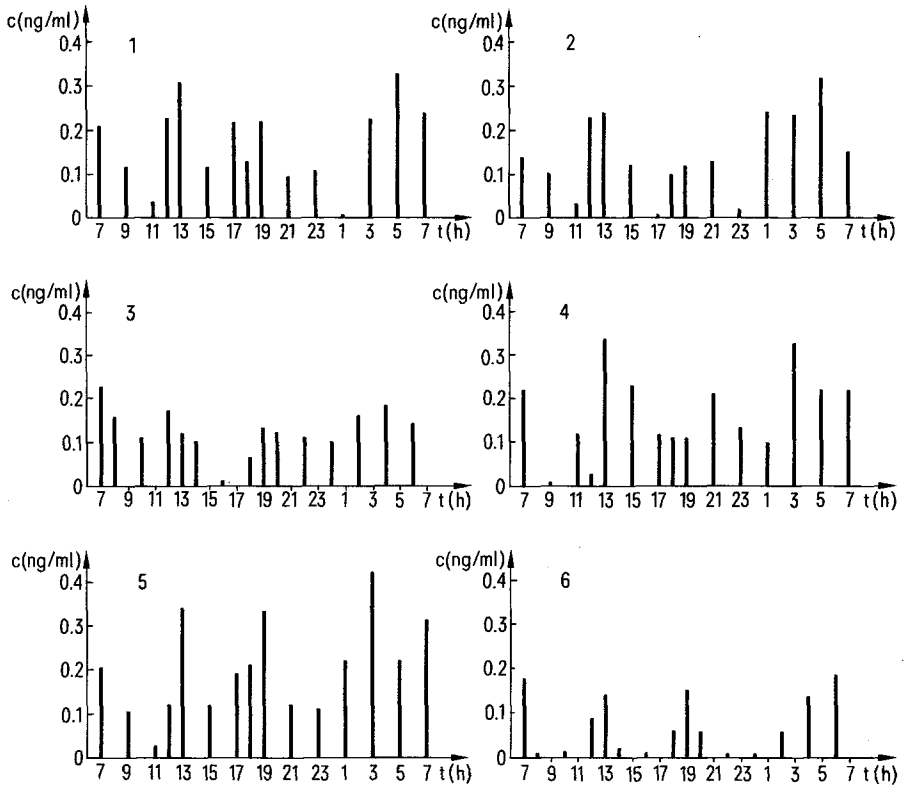

Figure 1
24 h-pattern of plasma histamine levels in young healthy male or female volunteers (1–12).

Despite the increase of the standard deviation due to the observed differences between the volunteers the differences between maxima and minima are statistically significant (Fig. 2). It is possible that the increase in plasma histamine levels in the early hours of the morning depends on the decrease of epinephrine found in normal volunteers [9].

The minimum recorded at about 16.00 h may support this assumption because epinephrine has a maximum at this time but maxima at lunch and dinner time can not be explained using this hypothesis.

The areas under the plasma histamine level versus time curve (AUC) show that the volunteers differ significantly not only in peak plasma histamine levels but also in the total amount of histamine available in plasma. The maximal total AUC_{0-24} is about 4.8 (ng×h/ml), the minimal AUC 1.35 (ng×h/ml). Despite these differences in the total amount of plasma histamine it should be noted that all volunteers follow a similar pattern of the AUC's calculated between the individual minima.

Nearly a quarter of the total AUC is represented by plasma histamine level rises observed at lunch and dinner time respectively, the most important rise in plasma histamine levels however is found during the early hours of the morning. This fraction is equivalent to approximately 55% of the total histamine available in plasma. There were no statistically significant differences between male and female volunteers regarding the histamine available in plasma expressed as the total AUC.

AUC_1 and AUC_2 are statistically not significantly different. Both AUC_1 and AUC_2 differ from AUC_3 statistically significant ($p < 0.001$).

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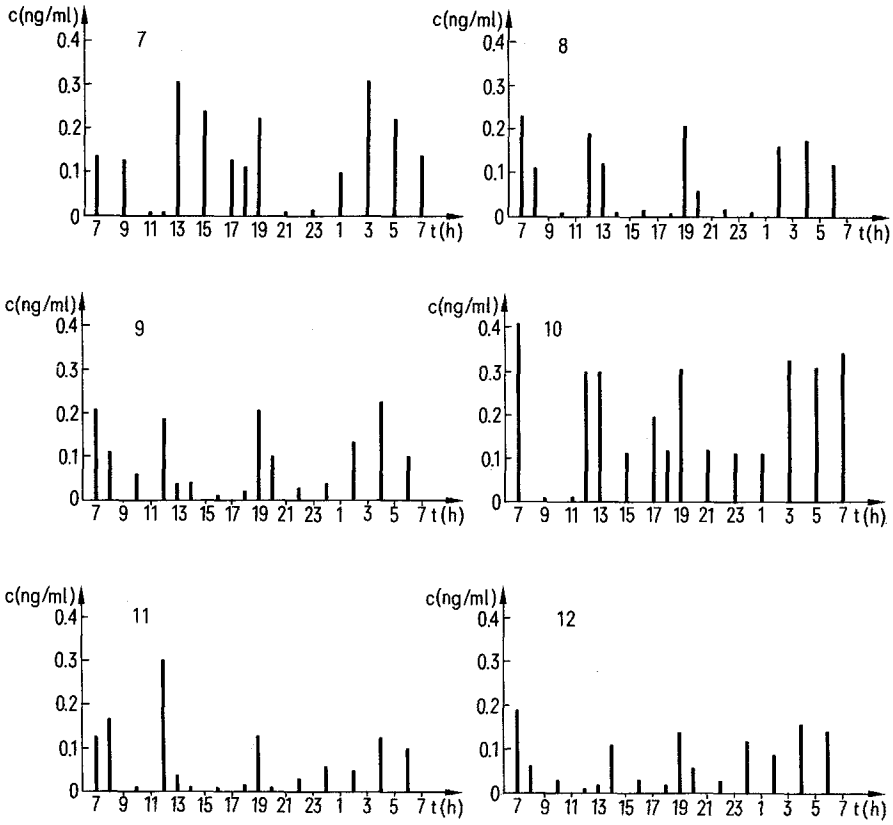

Figure 1 (Fortsetzung)

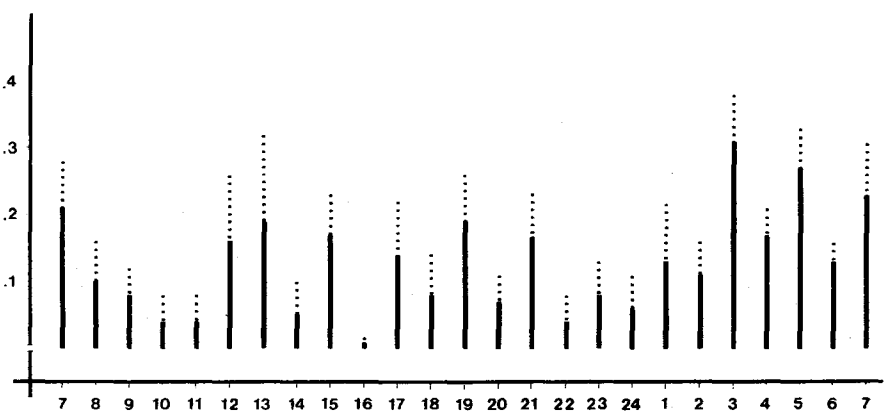

Figure 2
Mean plasma histamine versus time curves showing significant biorhythmic changes during the 24-h-period (histamine in ng/ml).

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