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Effects of Histamine on the Intensity-Response Function of the Electroretinographic b- and d-Waves in Dark Adapted Frog Eyes

Elka Popova*, Petia Kupenova

Department of Physiology, Medical University of Sofia, Sofia, Bulgaria

Email adresses:
epopova@abv.bg (E. Popova), pkupenova@abv.bg (P. Kupenova)
*Corresponding author

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Abstract: It is known that histamine is neurotransmitter of the retinopetal axons that originate from the tuberomamillary nucleus of the posterior hypothalamus, but its role in visual information processing in the retina is not well understood. The aim of this study was to give insight into the significance that histamine has for the distal retina function revealed by electroretinogram (ERG). The effect of 5 μM histamine on the intensity – response function of the b-wave (ON response) and d-wave (OFF response) of ERG was investigated in dark adapted perfused frog eyecup preparations. Perfusion with histamine caused a significant enhancement of the amplitude of both the ON and OFF responses over the entire intensity range studied in comparison with corresponding values obtained in the control experiments. The enhancing effect of histamine was more pronounced upon the OFF than ON response in the lower intensity range, where the responses were mediated by rods. The reverse was true for the higher intensity range, where the responses were cone-dominated. The b-wave V – log I function had a steeper slope and narrower dynamic range during histamine treatment. Histamine did not alter significantly the relative sensitivity of the ON response, while it significantly increased the relative sensitivity of the OFF response. The present results clearly demonstrate that histamine has a significant effect on the intensity-response function of frog ERG b- and d-waves. This effect shows some ON/OFF asymmetries in dependence of the photoreceptor input.

Keywords: Electroretinogram, Iintensity-Response Function, Histamine, Retina

1. Introduction

Some data indicate that histamine is a neurotransmitter of the retinopetal axons that originate from the tuberomamillary nucleus of the posterior hypothalamus in guinea pig [1], mouse [2], monkey and rat [3, 4]. These axons terminate in the inner plexiform layer (IPL), where synaptic contacts between bipolar, amacrine and ganglion cells are made. It is still unknown, however, how these retinopetal projections contribute to visual information processing in the retina. It has been shown that histamine hyperpolarizes ON, but not OFF bipolar cells in macaque retina and increases the delayed rectifier component of their voltage-gated potassium current [5]. The selective H_3 receptor agonist (R)-α-methylhistamine (RAMH) has the same effect, suggesting that the effect of histamine is mediated by H_3 receptors expressed on the ON bipolar cell dendrites. The authors proposed that "a larger $I_{K(V)}$ might be expected to decrease the amplitude and shorten the duration of the depolarizing responses to increments in light intensity". In accordance with this suggestion are the results of Akimov et al. [6], who reported that histamine reduced the light sensitivity of all types of ON cells in dark adapted monkey retina, while having no effect on the OFF ganglion cells. Under conditions of light adaptation, however, no ON-OFF asymmetry of histamine effects was seen. The light responses of both ON and OFF ganglion cells were either decreased in amplitude or unaffected by histamine [7].

Histamine action in amphibian retina may differ in some aspects from that described in primate retina. It has been shown that histamine reduces the cone-mediated light responses of broadly stratified amacrine cells, with the ON responses being more affected than the OFF responses [8].

Because the function of these cells is to mediate inhibitory interactions between strata of the IPL, it could be expected that a decreased inhibition would lead to enhanced ganglion cell light responses under the influence of histamine. The effects of histamine on the narrowly stratified amacrine cells are more variable with no difference between the ON and OFF responses [8]. The authors suggest that the direct histamine effects on broadly stratified amacrine cells are mediated by H_1 as well as other types (H_2, H_3) of histamine receptors on amacrine cells, while the indirect effects of histamine on narrowly stratified amacrine cells are due to its action on H_1 receptors localized on horizontal cells [8]. Similar localization of H_1 receptors on both horizontal and amacrine cells has also been found in monkey retina [9].

In contrast to the above cited results, recently Greferath et al. [10] have reported that retinal structure and function are unchanged in mice that lack expression of the rate limiting enzyme in the formation of histamine, histidine decarboxylase ($Hdc^{-/-}$ mouse) compared to wild type controls. Retinal function has been evaluated by recording electroretinogram (ERG) that provides information about the function of cohorts of retinal neurons. No differences between the two strains have been seen in respect to rod photoreceptor function (estimated by modeled a-wave amplitude and sensitivity), rod and cone mediated b-wave responses and isolated oscillatory potential responses. The authors concluded that in the mammalian retina, histamine only plays a minor role in modulating synaptic signalling. In our previous work [11] we demonstrated that histamine enhances the amplitude and shortens the implicit time of both the ON (b-wave) and OFF (d-wave) responses of dark adapted frog ERG. In the study cited a light stimulus with constant intensity was applied, which evoked ERG responses mediated by both rods and cones. Thus, no information about the dependence of the histamine effects on the photoreceptor input in amphibian retina was obtained. Our previous study did not answer also the question how the histamine action influences the sensitivity (absolute and relative) and the dynamic range of the ERG responses. The air of the present study was to investigate the effects of 5 μM histamine on the V – log I function of the ERG b- and d-waves in frog retina. It was found that histamine enhanced the amplitude of both waves compared to control experiments over the entire intensity range studied. The effect was more pronounced upon the OFF than ON response in the lower intensity range, where the responses were rod-dominated, while the reverse was true for the higher intensity range, where the responses were cone-dominated. The absolute sensitivity of the both responses was increased, while the relative sensitivity only of the OFF response was elevated. Thus, a clear ON/OFF asymmetry of histamine effects on frog ERG was demonstrated.

2. Material and Method

Twenty seven eyecup preparations of frog (*Rana ridibunda)* were used in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The procedure has been approved by protocol № 8/15.04.2015 from the Committee for ethics in scientific research of Medical University of Sofia, Bulgaria. The eyecups were continuously superfused with Ringer solution and supplied with moistened oxygen. Histamine dihydrochloride (Sigma-Aldrich) was dissolved in Ringer solution to a concentration of 5 μM. Similar concentrations have been used by other authors working on retinal preparations [5, 6, 8, 9, 12].

2.1. Light Stimulation

Diffuse light from tungsten halogen lamp was used for test light stimulation. Stimulus intensity (I_t) was varied in a range of 12 log units by means of neutral density filters with maximal intensity (denoted by 0) of 6×10^8 quanta s^{-1} μm^{-2} at the plane of the retina. Intermittent light stimulation with ON and OFF periods of 5 sec and 25 sec, respectively, was applied in the dark. As it has been pointed in our previous works [13, 14] this wide range of the test stimulus intensities allowed us to obtain rod-dominated responses by using lower I_t ($I_t < -8$), mixed rod-cone responses at middle I_t ($-8 < I_t < -6$) and cone-dominated responses by using higher I_t ($I_t > -6$).

2.2. Experimental Procedure

The frogs were kept in dark for 24 hours before the experiments. The eyecups were prepared under dim red light and then placed in the perfusion chamber. The eyecups were dark adapted for another 30 minutes during perfusion with Ringer solution. The experimental protocol was the same as that described in our previous works [13, 14]. Briefly, the V - log I function of the ERG waves was obtained using stimuli with increasing intensity (intensity series). Two stimulus intensity series were presented in one and same eyecup. The eyecups were perfused with Ringer solution only during the both intensity series in the *control experiments*. In the *test experiments,* the eyecups were perfused with Ringer solution during the first intensity series and they were perfused with 5 μM histamine during the second intensity series. The perfusion was switched from Ringer to histamine solution 3 minutes before the beginning of the second intensity series.

2.3. ERG Recording and Data Analysis

The electroretinograms were recorded in a standard manner by Ag/AgCl electrodes at bandpass of 0.1 - 1000 Hz. The amplitude of the b-wave was measured from the peak of the a-wave to the peak of the b-wave. The amplitude of the d-wave was measured from the baseline to the peak of the wave. The V - log I function was constructed by using the amplitudes of the responses to stimuli of different I_t. For evaluation of parameters of the intensity-response functions, the same approximations were made as those described in our previous works [13, 14, 15]. Briefly, the b-wave V - log I function was fitted to Naka-Rushton equation [16]: $V = V_{max}$

I^n / (I_σ^n + I^n), where V, b-wave amplitude; V_{max}, b-wave maximal amplitude; I, stimulus intensity; I_σ, stimulus intensity required to produce half-maximal amplitude; *n*, an exponent, related to the steepness of the V - log I function. As the d-wave intensity-response function deviates from Naka-Rushton equation, a method for smooth approximation of data was used instead of χ^2 fit to this equation [17]. The absolute sensitivity of the ERG responses was assessed by 10 μV threshold values and their relative sensitivity - by I_σ values. The b-wave dynamic range was estimated as the intensity span of the responses with 5 - 95% V_{max} amplitude. The d-wave dynamic range could not be determined because of the complex character of its V – log I function.

The Student's t-test and Two-Way ANOVA (Origin Pro 8 software, Origin Lab Corporation, Northhampton, MA) were used for statistical evaluation of the data.

3. Results

3.1. Control Experiments

Some differences of the V- log I function were obtained between the first and second intensity series in one and the same eyecup in the control experiments. The b-wave amplitude diminished significantly during the second intensity series at the lower intensities (It < -8; Two-Way ANOVA, $p < 0.027$) and in the higher intensity range ($I_t > -6$; Two-Way ANOVA, $p < 0.0005$) (Fig. 1 a). The b-wave absolute sensitivity (determined with threshold value) was also decreased during the second intensity series (Table 1). The relative sensitivity of the ON response (determined with I_δ value) as well as its dynamic range were not changed significantly during the second intensity series in comparison with the first one (Table 1).

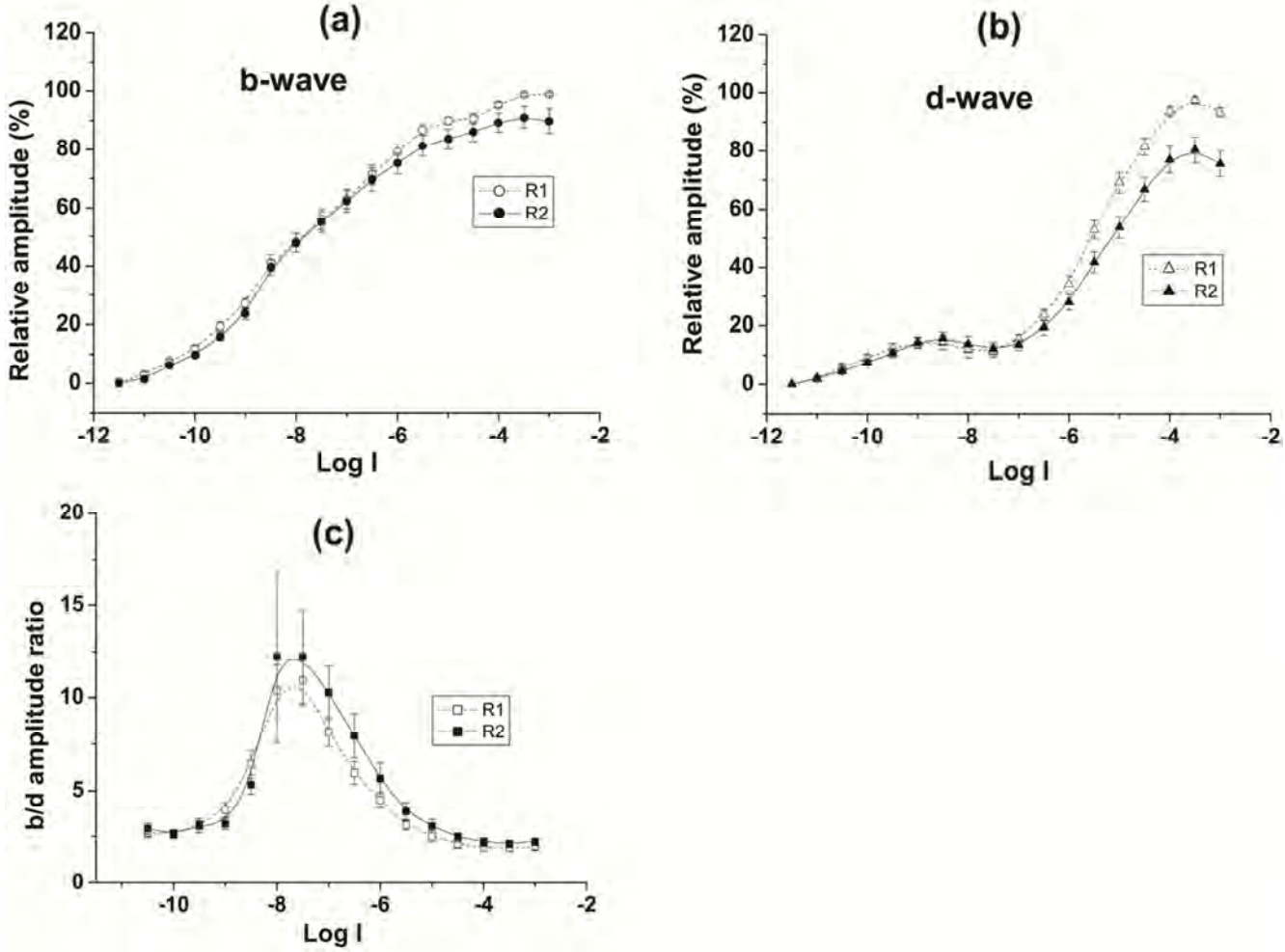

Figure 1. *(a), (b) V - log I function of the ERG b- and d-waves, obtained in control experiments. The amplitudes of the ERG waves are normalized to V_{max} of the responses obtained during the first series of the experiments. Mean values ± SEM are shown (n = 16). The symbols, representing the responses obtained during the first (R1) and second (R2) intensity series, are denoted in the legends. (c) Changes of the b/d amplitude ratio during the first (open circles) and second (filled circles) intensity series in control experiments. Mean values ± SEM are shown.*

The d-wave amplitude showed significant differences between the first and second intensity series only in the higher intensity range (It > -6) (Fig. 1 b), where it had lower values in the second series (Two-Way ANOVA, $p < 0.0001$). Because the d-wave amplitude diminished to a greater extent than that of the b-wave, the b/d amplitude ratio was significantly increased at higher intensities (Two-Way ANOVA $p < 0.0076$). This ratio was not significantly changed at lower and middle intensities (Fig. 1 c). The absolute and relative sensitivity of the OFF response showed no significant differences between the two

intensity series in the control experiments (Table 1).

Table 1. *Threshold values and parameters of V – log I function of the ERG b- and d-waves in control and histamine experiments.*

ERG wave	Threshold (lgI_t)		Iσ (lgI_t)		N		Dynamic range (log units)	
	I series	II series	I series	II series	I series	II series	I series	II series
Control								
b-wave	-10.89 ± 0.11	-10.61 ± 0.13	-7.78 ± 0.15	-7.93 ± 0.13	0.39 ± 0.02	0.41 ± 0.02	6.77 ± 0.27	6.53 ± 0.37
	p<0.0003		ns		ns		ns	
d-wave	-9.98 ± 0.24	-10.01 ± 0.22	-5.50± 0.11	-5.50 ± 0.10				
	ns		ns					
Histamine								
b-wave	-10.63 ± 0.13	-10.64 ± 0..11	-7.52 ± 0.16	-7.60 ± 0.19	0.39 ± 0.02	0.43 ± 0.03	6.73 ± 0.32	6.23 ± 0.38
	ns		ns		p<0.029		p<0.019	
d-wave	-9.82 ± 0.14	-10.11 ± 0.11	-5.39 ± 0.09	-5.46 ± 0.09				
	p<0.043		p<0.01					

The statistic significance of the differences between the values obtained in the first and second intensity series of control and test experiments is evaluated using paired t-test. ns – no significant difference.

3.2. Test Experiments

Perfusion wit 5 μM histamine caused significant enhancement of the b-wave amplitude at the middle (-8 < It < -6; Two-Way ANOVA, $p < 0.0018$) and higher (It > - 6; Two-Way ANOVA $p < 0.0001$) intensities compared to the corresponding values obtained in the first intensity series (Fig. 2 a). Histamine did not change the b-wave amplitude in the lower intensity range (It < -8) and thus it did not alter significantly the b-wave absolute sensitivity (Table 1). Because the b-wave threshold value was elevated during the second intensity series in the control experiments, we compare its changes with that obtained in the test experiments. The change of the b-wave threshold value was significantly smaller in test (-0.004 ± 0.05) than control experiments (0.28 ± 0.06; t-test, $p < 0.01$). Thus, it is evident that the pure effect of histamine is an enhancement of the b-wave absolute sensitivity. The enhancing effect was well seen over the whole range of stimulus intensities. This statement can be demonstrated by comparing the relative amplitude change of the b-wave amplitude in control and test experiments (Fig. 2 c). The relative amplitude change at each I_t was estimated by normalization of the values obtained in the second intensity series to the values obtained in the first series (%). There was statistically significant difference between the test and control groups over the entire intensity range (Two-Way ANOVA, $p < 0.001$ for middle I_t; $p < 0.0001$ for lower and higher I_t). The enhancing effect of histamine on the b-wave amplitude was nearly equally expressed at all stimulus intensities. Two-Way ANOVA revealed no significant interaction between stimulus intensity and difference in the relative amplitude change between histamine and control experiments. As a consequence, the relative sensitivity of the ON response was not significantly altered (Table 1). On the other hand, the slope of the b-wave V – log I function was increased and its dynamic range was significantly narrowed under the influence of histamine (Table 1).

Perfusion wit 5 μM histamine caused significant enhancement of the d-wave amplitude at lower intensities (It < -8) in comparison with the values obtained in the first intensity series (Two-Way ANOVA $p < 0.0002$) (Fig. 2 b). Histamine enhanced the absolute sensitivity of the OFF response, which is evident from the significantly lower value of the d-wave threshold (Table 1). Its enhancing effect was evident over the entire intensity range where the responses were mediated by rods. Perfusion with histamine did not change significantly the d-wave amplitude at middle intensities ($-8 < I_t < -6$) and diminished it at higher intensities ($I_t > - 6$; Two-Way ANOVA $p<0.0001$) compared to the values obtained in the first intensity series (Fig. 2 b). Because the d-wave amplitude diminished also during the second series in the control experiments, the pure effect of histamine was evaluated by comparing the d-wave relative amplitude change in the test and control experiments. The comparison demonstrated that, over the entire intensity range, the d-wave amplitudes obtained during the second series of the experiments and normalized to those obtained during the first series, were higher in histamine comparative to control experiments (Fig. 2 d). An enhancing effect of histamine was thus revealed also in the middle (Two-Way ANOVA $p < 0.0006$) and higher (Two-Way ANOVA $p < 0.002$) intensity range. The effect showed clear intensity dependence. The Two-Way ANOVA revealed significant interaction between stimulus intensity and d-wave relative amplitude change ($p < 0.0003$). The effect was greatest at lower intensities ($I_t < -8$) and much smaller at higher intensities ($I_t > -6$). As a consequence, the relative sensitivity of the OFF response was significantly increased (Table 1). Thus, both the absolute and relative sensitivity of the OFF response were enhanced during histamine treatment.

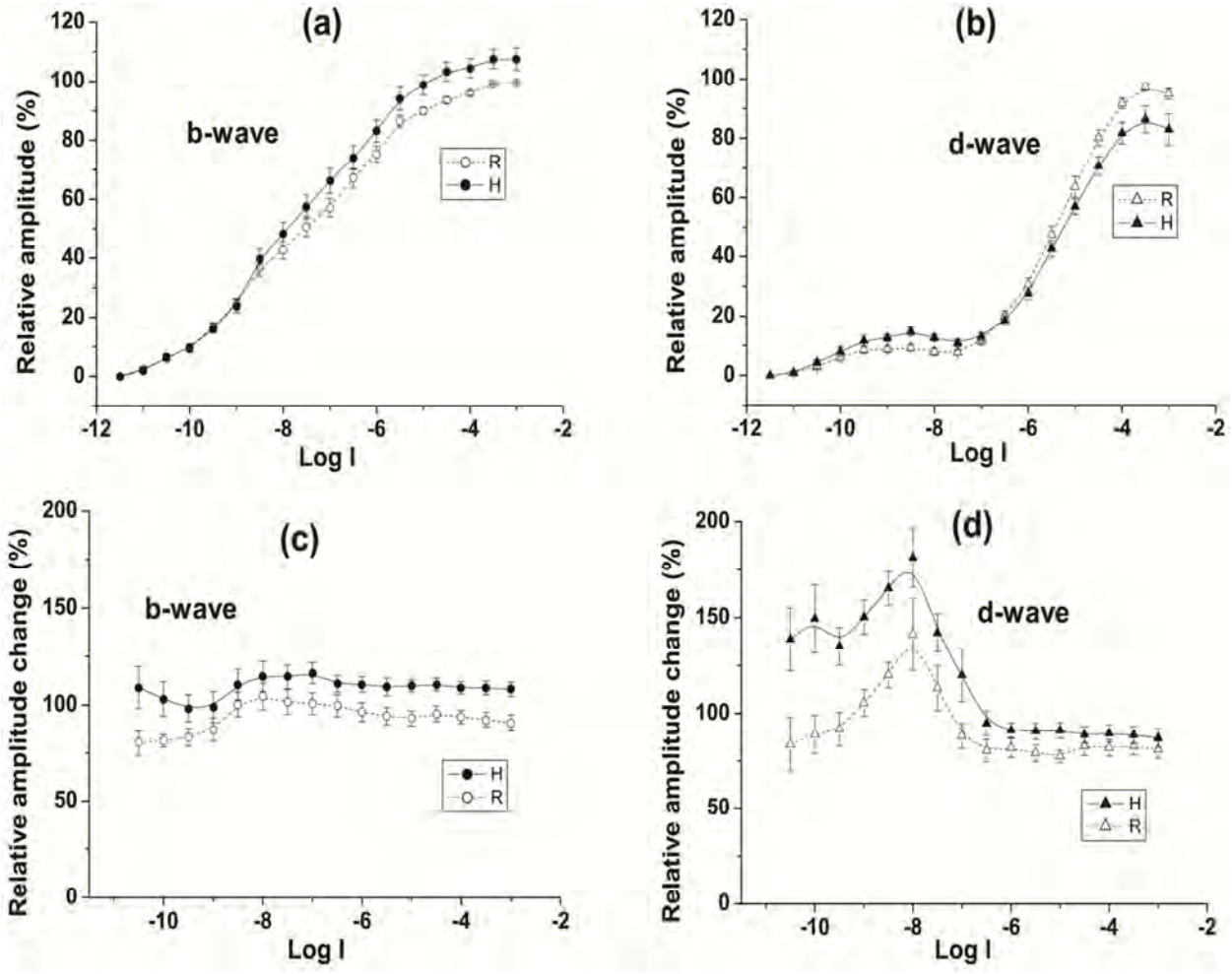

Figure 2. *(a), (b) V - log I function of the ERG b- and d-waves, obtained in histamine experiments. The amplitudes of the ERG waves are normalized to V_{max} of the responses obtained during the first series of the experiments. Mean values ± SEM are shown (n = 11). The symbols, representing the responses obtained during the first (R) and second (H) intensity series, are denoted in the legends. (c), (d) Relative change of the ERG b- and d-wave amplitude in the control experiments (open symbols) and test experiments (filled symbols). The amplitudes of the ERG waves, obtained at each I_t during the second stimulus intensity series were normalized to those, obtained during the first series. Means ± SEM are represented.*

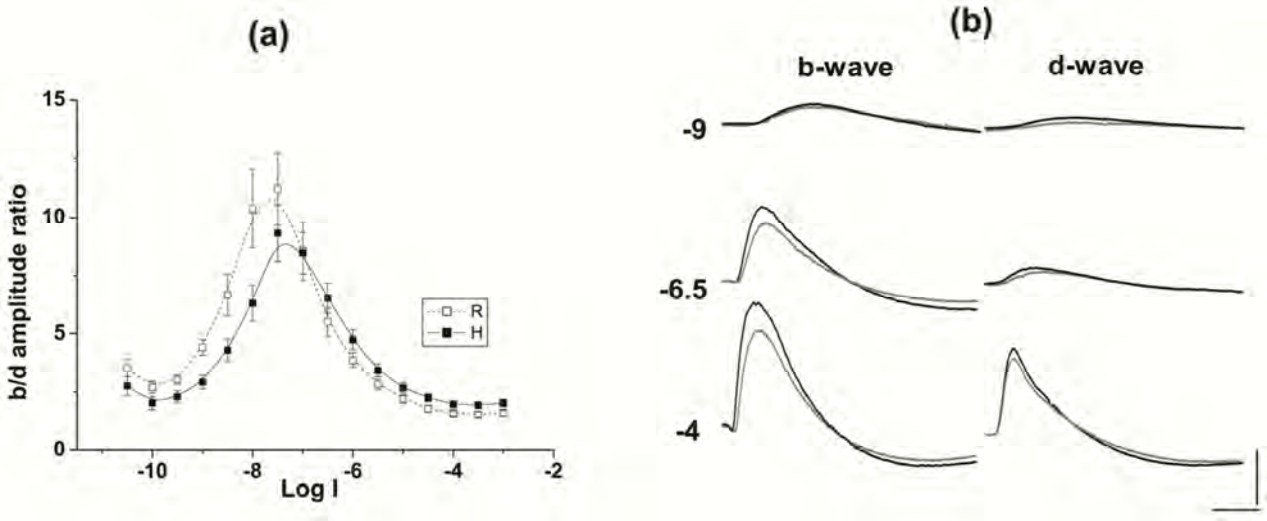

Figure 3. *(a) Changes of the b/d amplitude ratio during the first (open circles) and second (filled circles) intensity series in histamine experiments. Mean values ± SEM are shown. (b) Original ERG records, obtained with different stimulus intensities during the control period (grey lines) and during treatment with histamine (black lines). The numbers on the left side indicate stimulus intensity (log I_t). Calibration: time - 0.4 s; amplitude – 100 μV.*

The enhancing effect of histamine upon the amplitude of the rod-mediated d-wave was greater than that on the rod-mediated b-wave. This is evident from the significantly lowed b/d amplitude ratio at the lower intensities (Two-Way ANOVA $p < 0.0001$) (Fig. 3 a). The same is seen in the individual ERG recording in Fig. 3 b (upper trance). Histamine did not alter significantly the b/d amplitude ratio at middle intensities, but it increased its values in the higher intensity range (Two-Way ANOVA $p < 0.0001$) (Fig. 3 a, b). Because the b/d amplitude ratio was also increased in the control experiments (at higher I_t), the pure effect of histamine could be revealed by comparing the relative change of this ratio in the control and test experiments. We obtained that the relative change of the b/d amplitude ratio was significantly higher in the test than control experiments (Two-Way ANOVA $p < 0.043$). Thus, it appears that the enhancing effect of histamine is greater upon the cone-dominated ON than OFF response, which is opposite to that obtained for the rod-mediated responses.

4. Discussion

The present results clearly show that histamine has an enhancing effect on the ERG b- and d- wave amplitude (ON and OFF response) over a wide range of stimulus intensities. This effect starts at very low stimulus intensities and thus histamine enhances the absolute sensitivity of the ERG responses. The effect does not depend qualitatively on the type of the photoreceptor input, because an enhancement of the b- and d-wave amplitude is seen in the responses mediated by rods, cones or both rods and cones. However, the extent to which histamine affects the amplitude of the ERG responses depends on the photoreceptor input and this dependence shows clear ON/OFF asymmetry. Histamine enhancing effect is more pronounced upon the amplitude of the rod-mediated OFF than ON response, but the reverse is true for the cone-dominated responses. The relative sensitivity of the OFF, but not the ON response is increased under the influence of histamine. Similar ON-OFF asymmetry is not evident in histamine effects on the absolute sensitivity of the ERG responses. Another important effect of histamine is the narrowing of the intensity range, where the b-wave amplitude depends linearly on the log I_t.

These results differ from the results of Greferath et al. [10], who failed to obtain any change in the flash ERG recorded in mice lacking histidine decarboxylase ($Hdc^{-/-}$). Neither the amplitude nor the timing of the b-wave mediated by rods or cones was significantly altered in $Hdc^{-/-}$ mice. The authors suggest that the modulatory effects of histamine in the retina may be too subtle to be measured with an ERG. We may state that histamine modulatory effects can be detected with diffuse ERG recorded with long lasting stimuli in frog retina. The reason for these conflicting results is not clear, but they might be due to differences in the abundance of the histaminergic projections and histamine receptors in amphibian and mammalian retina. There are no available data where such a comparison has been made.

There is a general consensus that the neuronal generator of the b-wave is primarily the depolarizing (ON) bipolar cells, while the d-wave depends mainly on the activity of hyperpolarizing (OFF) bipolar cells with minor contribution of the photoreceptor response at stimulus offset and activity of proximal retinal neurons [reviews: 18, 19]. Thus, the effects of histamine on the ERG b- and d-wave could be related to an altered activity of the ON and OFF bipolar cells. How histamine could enhance the bipolar cell light responses is largely unknown. There are two possibilities: histamine could directly enhance bipolar cell activity or it might diminish the inhibition exerted upon them by horizontal cells and/or amacrine cells. The only known direct actions of histamine upon the ON bipolar cells are hyperpolarization and enhancement of the delayed rectifier component of their voltage-gated potassium current that are mediated by H_3 receptors in monkey retina [5]. Because the larger $I_{K(V)}$ is expected to decrease the amplitude of the depolarizing responses to light increments, this action could not account for the changes the amplitude of the ERG b-wave observed by us.

The enhancing effect of histamine on the amplitude of the b-wave might be due to an action of histamine on retinal inhibitory interneurons (horizontal and/or amacrine cells). It has been shown that histamine decreases the cone-mediated light responses of broadly stratified amacrine cells in amphibian retina [8]. If these cells directly or indirectly exert feedback inhibition upon the bipolar cells, histamine would disinhibit the latter cells and their activity would increase. Because the effect of histamine is stronger on amacrine cell ON than OFF responses, the responses of ON bipolar cells would increase to a greater degree than those of the OFF bipolar cells. This suggestion is consistent with the ON/OFF asymmetry in histamine action demonstrated by us at higher intensities, where the responses were cone-dominated. Histamine could also exert its action through dopaminergic amacrine cells, because it elevates free Ca^{2+} in these cells and thus it "would have a net inhibitory effect on dopamine release" [12]. This suggestion is supported by the results of Weber and Schlicker [20], who demonstrated a reduced dopamine release under the influence of histamine in guinea-pig retina. We have shown that dopamine receptor blockade caused a significant enhancement of the suprathreshold b-and d-wave amplitude, when the responses were mediated by rods or both rods and cones [14]. The enhancing effect was stronger on the rod-mediated OFF than ON response. If histamine reduces dopamine release in frog retina, similar effects as that described for the dopaminergic blockade, could be expected. Thus, some of histamine effects obtained in frog retina, particularly those obtained at lower and middle stimulus intensities might be due to its action on the dopaminergic amacrine cells. Such a hypothesis can be proved by investigating the effect of histamine during dopamine receptor blockade, which has not been done yet.

Histamine could affect bipolar cell responses by its action

on the horizontal cells, which express H_1 receptors in primates and amphibians [8, 9]. Activation of H_1 receptors typically stimulates phospholipase C (PLC), which releases calcium ions from internal stores [21]. Calcium could activate calcium-dependent potassium conductance [22] and thus could hyperpolarize horizontal cells. As a consequence, their inhibitory action on the bipolar cells (direct or indirect through their feedback to photoreceptors) would diminish resulting in an enhancement of bipolar cell light responses. However, this suggestion is quite speculative and further studies are needed to reveal the exact site of histamine action responsible for the frog ERG changes.

5. Conclusion

Our present results clearly indicate that histamine enhances the amplitude of the ERG b- and d-wave obtained with wide range of stimulus intensities in the dark adapted frog eyes. The histamine influence shows clear ON/OFF asymmetry which depends on the photoreceptor input. The OFF-responses (d-wave) are affected to a greater extent when the responses are mediated by rods. On the opposite, the ON-responses (b-wave) are more strongly affected when the responses are cone-dominated.

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