Effects of intracerebroventricular injection of histamine and H_1, H_2 receptor antagonists on electrocardiographic parameters in broiler chickens

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Summary

The aim of this study was to assess the effects of exogenous histamine and H_1 and H_2 central receptors on electrocardiographic (ECG) parameters, heart rate and mean electrical axis in broiler chickens. For this purpose, Ross broiler chickens (750-800 g weight) received intracerebroventricularly (ICV) histamine. Moreover, to determine the receptors involved in histamine-induced alterations in ECG changes, H_1 and H_2 blockers were administered to histamine-treated chickens. All ECGs were standardized at 1 mV = 20 mm, with paper speed of 50 mm/sec. Leads I, II, III, aVR, aVL and aVF were recorded. Injection of histamine (200 and 300 µg) decreased the duration of T wave and QRS complex and elevated the heart rate as compared to the control group ($P<0.05$). Chlorpheniramine (100 µg), an H_1 receptor antagonist, increased the duration rate of T wave and QRS complex and reduced the heart rate ($P<0.05$). Cimetidine, an H_2 receptor antagonist (100 µg) had no effect on ECG parameters. Pretreatment with chlorpheniramine (100 µg) significantly attenuated histamine effects (200 µg) on the duration of T wave, QRS complex and heart rate ($P<0.05$). Mean electrical axis, calculated from leads II and III, did not differ between groups and it was between -93° and -99° in all chickens. In conclusion, exogenous histamine intracerebroventricularly results in sinusoidal tachycardia in broiler chickens and central H_1 receptors mediate the stimulatory effects of histamine on heart rate, but H_2 receptors had no role in this manner.

Key words: Electrocardiogram, Histamine, Broiler chicken, Intracerebroventricular

Introduction

There is evidence that the central histaminergic system has anatomic connectivity with autonomic control centers to make significant contributions to cardiovascular regulation (Bealer, 1999). The cell bodies of all histamine (HA) containing neurons in the central nervous system (CNS) are localized to a region of the posterior hypothalamus known as the tuberomamillary nucleus (TMN) (Schwartz *et al*., 1991) and axons of these neurons project from the TMN to many areas of the brain, including most major loci contributing to autonomic regulation of the cardiovascular system (Inagaki *et al*., 1988). For example, there are dense histaminergic projections to the diagonal band of Broca (DBB), the paraventricular nucleus of the hypothalamus (PVN), the supraoptic nucleus (SON), and the bed nucleus of the stria terminalis (BST). These forebrain sites contribute to autonomic control of the cardiovascular activity through neural mechanisms and/or release of vasopressin (Bealer, 1999).

However, the potential role for central HA in cardiovascular regulation was suggested by the early observations that injections of HA into the cerebral ventricles could produce a profound pressor effect

(Bealer, 1999). Other experiments that manipulated endogenous HA metabolism support a role for neuronal HA in the control of blood pressure (Schwartz *et al*., 1991). For instance, experimentally induced pressor or depressor responses increase HA release in the hypothalamus, and inhibition of HA degradation in the brain causes an increase in blood pressure similar to that observed after central injections of exogenous HA. Furthermore, neither depletion of neuronal HA or pharmacological blockade of H_1 receptors in the CNS prevents the pressor response associated with peripheral hyperosmolality (Akins and Bealer, 1991).

Electrocardiography (ECG) gives significant information about the details of cardiac activity and serves as a laboratory aid in diagnosis of heart disease in many domestic species (Boulianne *et al*., 1992). While ECG changes have been described in infectious and non infectious diseases in birds (Cabanac and Guillemette, 2001; Çınar *et al*., 2006; Onder *et al*., 2006; Olkowski *et al*., 2008; Kostelanetz *et al*., 2009), it is used less frequently in avian species. This might be due to the scarcity of electro-cardiographic reference values in birds. Apparently, these values have been established only on a limited number of avian species including the chicken (Mukai *et al*., 1996; Olkowski *et al*., 1997), turkey (Boulianne *et al*., 1992), racing pigeon (Lumeij and Stokhof, 1985), African grey (Nap *et al*., 1992), quail (Onder *et al*., 2006), the pekin duck (Çınar *et al*., 1996), and parrot (Nap *et al*., 1992).

To the authors' knowledge, the role of the central hitaminergic system in cardiac activity of chickens has not yet been studied. Therefore, the present study was conducted to evaluate the effects of ICV injection of histamine, chlorpheniramine (H_1 receptor antagonist), and cimetidin (H_2 receptor antagonist) on ECG parameters of broiler chickens.

Materials and Methods

Animals

Eighty four male Ross broiler chickens (Dorbar Hatchery, Borojerd, Iran) were reared in a temperature-controlled room at 33°C with continuous lighting until 3 weeks of age. Birds were provided with a mash diet (21% protein and 2,869 kcal/kg of metabolizable energy) and water *ad libitum*. When the birds reached 2 weeks of age, the temperature of the animal room was maintained at 22 ± 1°C in addition to the continuous lighting condition.

Drugs

Histamine, Chlorpheniramine and Cimetidine were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All solutions were prepared in pyrogen-free 0.9% NaCl solution (saline) that served as control.

Surgical preparation

At 3 weeks of age, broilers were anesthetized intramuscularly with ketamine (30 mg/kg) and xylazine (1 mg/kg) (Thurmon *et al*., 1996) and a 23-gauge thin-walled stainless steel guide cannula was stereotaxically implanted into the right lateral ventricle, according to the technique described previously by Denbow *et al*. (1981). The stereotaxic coordinates were AP = 6.7, L = 0.7, H = 3.5-4 mm below the duramater with the head oriented as described by Denbow *et al*. (1981). The cannula was secured with three stainless steel screws placed in the calvaria surrounding each guide cannula, and then acrylic dental cement (Pars acryl) was applied to the screws and guide cannula. An orthodontic # 014 wire (American Orthodontics) trimmed to the exact length of the guide cannula was inserted into it while the chicks were not being used for experiments. Lincospectin (Razak) was applied to the incision to prevent infection. The birds were allowed a minimum of 5 days recovery prior to injection.

Experimental design

In this study three trials were conducted to determine the possible effects of histaminergic system on the electro-cardiographic parameters of chickens. Injections were made with a 29-gauge, thin-walled stainless steel injecting cannula which extends 1.0 mm beyond the guide cannula. This injecting cannula was

connected through 30-cm-long PE-20 tubing to 10 µl Hamilton syringe. Solutions were injected over a period of 30 sec. A further 30 sec period was allowed to permit the solution to diffuse from the tip of the cannula into the ventricle. All experimental procedures were performed during a 0200 p.m. to 0500 p.m. period. In trial 1 the birds were infused ICV with 0, 100, 200 and 300 µg of histamine in a volume of 10 µl into the right lateral ventricle (n = 7 for each group). In trial 2 and 3 each bird received two injections. The first injection consisted of either 0 or 100 µg chlorpheniramine (Table 1) or cimetidine (Table 2) in 5 µl saline. The second injection consisted of either a 0 or submaximal effective dose of histamine (200 µg) from trial 1 in 5 µl saline, 5 min after the first injection as described in Tables 1 and 2 (n = 7 for each group). In this study, the selection of chlorpheniramine and cimetidine doses was made based on previous studies (Meade and Denbow, 2001; Taati *et al*., 2009). ECGs were recorded 5 min before and 15 min after injections.

Table 1: Injections procedure in trial 2

Groups	Injections
I (n=7)	Saline + saline
II (n=7)	Saline + histamine
III (n=7)	Chlorpheniramine + saline
IV (n=7)	Chlorpheniramine + histamine

Table 2: Injections procedure in trial 3

Groups	Injections
I (n=7)	Saline + saline
II (n=7)	Saline + histamine
III (n=7)	Cimetidine + saline
IV (n=7)	Cimetidine + histamine

ECG recordings

Because of the thickness of poultry chest muscle, it is impossible to obtain any recording by using chest leads. Therefore, we recorded standard bipolar (I, II, III) and augmented unipolar (aVR, aVL, aVF) leads (Çınar *et al*., 1996, 2006; Espino *et al*., 2001; Onder *et al*., 2006). Alligator clip electrodes were attached to the skin at the base of the right and left wings and gastrocnemius muscle of the right and left limbs (Rodríguez *et al*., 2004; Çınar *et al*., 2006; Onder *et al*., 2006; Talavera *et al*., 2008). Good clip-to-skin contact was established by using electrode gel (Rodríguez *et al*., 2004). The chickens were placed on a wooden table and calmed down by covering them with a cloth for 5 min before recording (Çınar and Donmez, 2001; Çınar *et al*., 2006; Onder *et al*., 2006). The ECGs were recorded by a digital electrocardiograph (Kenz 110, Japan) and all recordings were calibrated to 1 mV/10 mm, with a paper speed of 50 mm/sec (Rodríguez *et al*., 2004; Çınar *et al*., 2006; Onder *et al*., 2006; Talavera *et al*., 2008). The ECG was recorded while animals were conscious. All procedures took place in an isolated quiet room in order to minimize the stress for birds. The duration and amplitude of waves on the trace were measured in lead II (Çınar *et al*., 1996, 2006; Espino *et al*., 2001; Rodríguez *et al*., 2004; Onder *et al*., 2006) and mean electrical axis (MEA) of ventricular depolarization in the frontal plane was calculated using leads II and III (Çınar *et al*., 1996, 2006; Espino *et al*., 2001; Onder *et al*., 2006). Measurement of heart rate was also taken in lead II (Rodríguez *et al*., 2004; Çınar *et al*., 2006; Onder *et al*., 2006).

Statistical analysis

All results were analysed using SPSS/PC program. The difference among groups before or after injection was separately analysed using one-way ANOVA. Moreover, to determine the difference in each group between before and after administration, paired sample t-test was applied. All measurements are expressed as mean ± SEM.

Results

ECG findings of chickens that received intracerebroventricularly histamine and chlorpheniramine are displayed in Tables 3 and 4. Administration of cimetidine had no effect on ECG parameters (data not shown).

In lead I, traces were very low amplitude. The P wave was positive in leads I-III, aVL and aVF, and negative in lead aVR. The QRS polarity was negative in I-III and aVF leads, being positive in aVR and aVL leads. The Q wave was not seen in any

leads and QRS complex was in the form of rS in all leads. T wave was positive in leads I, II, III and aVF and negative in leads aVR and aVL. T wave was in the form of P-T, except that chickens treated only with chlorpheniramine had P waves separated from the T. Although the duration of T waves and QRS complexes was significantly decreased following the injection of histamine with doses of 200 and 300 µg (Table 3), the heart rate of these chickens (402 and 416 beats/min) increased compared to the control (309-311 beats/min) ($P<0.05$, Table 3). In trial 2, injection of chlorpheniramine increased the duration of T waves and QRS complexes at a dose of 100 µg, and decreased the heart rate (280 beats/min) compared to control group (307-309 beats/min) ($P<0.05$, Table 4). When birds were pretreated with chlorpheniramine followed by histamine, the effects of histamine on the ECG parameters were significantly attenuated ($P<0.05$, Table 4). Injection of chlorpheniramine and/or histamine did not significantly influence other ECG parameters (Tables 3 and 4).

Discussion

Due to extensive use of broiler chickens in the poultry production industry where stress causes major economic losses (Olkowski *et al*., 2008) and our previous study on the role of Histaminergic system in broiler food intake (Taati *et al*., 2009), we used Ross 308 broiler strain as an experimental model of chickens with rapid growth for evaluation of the histaminergic system on electrocardiographic parameters.

The results of this study showed that morphological patterns and values of P-QRS-T deflections in all leads obtained from control and treatments in three trials were predominantly in agreement with the previous studies on chickens and other species of birds (Nap *et al*., 1992; Burtnick and Degernes, 1993; Çınar *et al*., 1996; Casares *et al*., 2000; Çınar and Donmez,

Table 3: The durations and amplitudes of waves in lead II, mean electrical axis and heart rate in control and histamine-treated chickens (mean ± SEM)

Groups		Parameters					
		QRS (mV)	QRS (sec)	T (T+P) (mV)	T (T+P) (sec)	HR	MEA
Control	Before injection	0.09±0.03	0.075^{a}±0.003	0.1±0.03	0.125^{a}±0.067	309^{a}±23	-95^{0}±10
	After injection	0.1±0.06	0.069^{a}±0.003	0.09±0.05	0.097^{a}±0.001	311^{a}±35	-94^{0}±9
Histamine (100 µg)	Before injection	0.1±0.04	0.08^{a}±0.004	0.095±0.032	0.1^{a}±0.003	305^{a}±12	-93^{0}±12
	After injection	0.11±0.05	0.079^{a}±0.001	0.11±0.01	0.09^{a}±0.001	317^{a}±34	-95^{0}±8
Histamine (200 µg)	Before injection	0.11±0.06	0.078^{a}±0.002	0.12±0.073	0.11^{a}±0.023	318^{a}±25	-99^{0}±14
	After injection	0.125±0.07	0.05^{b}±0.002	0.12±0.042	0.072^{b}±0.005	402^{b}±26	-98^{0}±11
Histamine (300 µg)	Before injection	0.1±0.07	0.072^{a}±0.007	0.09±0.081	0.094^{a}±0.004	312^{a}±38	-97^{0}±15
	After injection	0.13±0.09	0.041^{b}±0.001	0.12±0.077	0.079^{b}±0.003	416^{b}±48	-98^{0}±14

Means with different superscripts (^{a}, ^{b}) within each column are significantly different ($P<0.05$). Mean electrical axis (MEA), and Heart rate (HR)

Table 4: The durations and amplitudes of waves in lead II, mean electrical axis and heart rate in control and chlorpheniramine + histamine-treated chickens (mean ± SEM)

Groups		Parameters					
		QRS (mV)	QRS (sec)	T (T+P) (mV)	T (T+P) (sec)	HR	MEA
Control (saline + saline)	Before injection	0.1±0.05	0.081^{a}±0.002	0.095±0.03	0.11^{a}±0.056	307^{a}±25	-94^{0}±10
	After injection	0.135±0.03	0.072^{a}±0.004	0.11±0.02	0.125^{a}±0.003	309^{a}±20	-96^{0}±8
Saline + Histamine	Before injection	0.09±0.07	0.079^{a}±0.003	0.11±0.06	0.09^{a}±0.008	315^{a}±31	-95^{0}±11
	After injection	0.11±0.05	0.048^{b}±0.003	0.12±0.05	0.069^{b}±0.005	395^{b}±23	-99^{0}±12
Chlorpheniramine + Saline	Before injection	0.12±0.02	0.069^{a}±0.009	0.098±0.062	0.098^{a}±0.005	320^{a}±17	98^{0}±7
	After injection	0.1±0.06	0.1^{c}±0.006	0.13±0.02	0.145^{c}±0.003	280^{c}±22	-95^{0}±9
Chlorpheniramine + Histamine	Before injection	0.09±0.08	0.071^{a}±0.002	0.11±0.07	0.121^{a}±0.002	325^{a}±18	-94^{0}±13
	After injection	0.13±0.03	0.068^{a}±0.005	0.09±0.08	0.089^{a}±0.006	301^{a}±30	-97^{0}±12

Means with different superscripts (^{a}, ^{b}, ^{c}) within each column are significantly different ($P<0.05$). Mean electrical axis (MEA), and Heart rate (HR)

2001; Espino *et al*., 2001; Rodríguez *et al*., 2004; Çınar *et al*., 2006; Onder *et al*., 2006; Talavera *et al*., 2008). The HR, duration of QRS complex and T (P+T) wave altered after ICV injection of chlorpheniramine and histamine in trials 1 and 2. In trial 3, ICV administration of cimetidine alone or together with histamine had no effect on ECG parameters.

The T wave was seen in the form of P-T in all groups except chickens that received intracerebroventricularly chlorpheniramine. With a rapid HR, P wave and preceding T wave as well as T wave and preceding QRS complex may intermix (Tilley, 1992; Machida and Aohagi, 2001). Previous studies have suggested that when P-on-T phenomenon is not associated with high HR, it may indicate alterations in ventricular repolarization or may be related to ascites (Olkowski *et al*., 1997). In the current study, P-on-T phenomenon is related to the high HR.

In our study the mean amplitude of QRS complexes (0.12 mV) was lower than the previous study performed by Çınar *et al*. (2006). This discrepancy may be related to the different species and weight of chickens in these two experiments. ICV injection of chlorpheniramine or histamine could not significantly change the amplitude of QRS complexes. An increased voltage in the QRS complexes may be indicative of heart muscle hypertrophy (Olkowski *et al*., 1997). Additionally, it has been noticed that the QRS complex amplitude increases in birds that develop ascites (Odom *et al*., 1991; Owen *et al*., 1995). In trial 1, ICV infusion of histamine with doses of 200 and 300 µg significantly decreased the duration of QRS complex as compared to the control group. This effect was apparently due to the presence of sinusoidal tachycardia (402 and 416 bpm). An increase in HR should be detectable as a reduction in the duration of specific ECG wave segments, but in this study, the heart rate had no significant effect on the duration of QRS complex. In trial 2, ICV injection of chlorpheniramine alone significantly increased the duration of QRS which is related to the bradycardia (280 bpm) and pretreatment with chlorpheniramine attenuated the effects of histamine on the duration of QRS complex and increased it to the normal value. The amplitude of T (T+P) wave changed between 0.09 and 0.13 mV in the current study. Neither histamine nor chlorpheniramine significantly affected the amplitude of T (T+P) wave in trials 1 and 2. Elevated and peaked T waves were identified as a sign of hyperkalemia in ducks (Çınar *et al*., 2006). The same T pattern can be recorded in shocked raptors and after electrocution as a result of hyperkalemia (Blanco, 1993). ICV application of histamine (with doses 200 and 300 µg) and chlorpheniramine significantly decreased and increased the duration of the T wave, respectively (Tables 2 and 3). In trial 2, pretreatment with chlorpheniramine, attenuated the decrease of T wave duration induced by histamine. Indeed these alterations in the duration of the T wave were due to tachycardia (395-416 bpm) and bradycardia (280 bpm) caused by histamine and chlorpheniramine, respectively. The mean MEA in the present study was -96°, which is characteristic of the avian ECG and implies the negative polarity of QRS complex in II, III and aVF leads (Burtnick and Degernes, 1993; Lumeij and Ritchie, 1999). We first speculated that ICV injection of histamine may promote deviations in MEA by inducing arrhythmias in chickens, but the difference between mean MEA in the groups was not statistically significant.

In accordance with previous studies in chickens (Çınar *et al*., 2006), the heart rate in this study ranged from 307 to 311 in the control groups. In trial 1, histamine with only 200 and 300 µg significantly elevated the HR. Inhibition of H_1 receptors by ICV injection of chlorpheniramine significantly decreased the HR as compared to the control group and pretreatment with chlorpheniramine blocked the histamine induced tachycardia. In this study, for the first time it was shown that histamine given intracerebroventricularly modulates the heart rate through H_1 receptors and can induce tachycardia in broiler chickens.

Experiments with specific H_2-receptor antagonists in mammals have demonstrated that HA effects on heart rate are mediated directly by H_2-receptor stimulation (Poulakos and Gertner, 1989). Our findings clearly show that in contrast to mammals, H_1 receptors mediate the stimulatory effects of

central HA on heart rate in conscious chickens and H_2 receptors had no role in this manner.

It has been revealed that changes in HR after ICV injection of HA are mediated mainly by cardiac sympathetic activation (Bealer, 1999). On the other hand, HA participate in the central regulation of ACTH and β-END secretion (Knigge and Warberg, 1991) and is a mediator of the stress-induced release of these hormones (Knigge and Warberg, 1991; Miyazaki *et al*., 1997). Recently, Çınar *et al*. (2006) reported that ACTH intramuscularly induces tachycardia in chickens. Thus it is possible to postulate that when an animal encounters a noxious stimulus, a stressor, the central histaminergic system simultaneously mediates the activation of the sympathetic nerve system and ACTH release, two major physiological responses to stress. Taken together, the relationship between the histaminergic activity and cardiac abnormalities in chickens is possible.

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