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Relationship Between Cortical Electrical and Cardiac Autonomic Activities in the Awake Lizard, *Gallotia galloti*

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ABSTRACT ECG and EEG signals were simultaneously recorded in lizards, *Gallotia galloti*, both in control conditions and under autonomic nervous system (ANS) blockade, in order to evaluate possible relationships between the ANS control of heart rate and the integrated central nervous system activity in reptiles. The ANS blockers used were prazosin, propranolol, and atropine. Time-domain summary statistics were derived from the series of consecutive R-R intervals (RRI) of the ECG to measure beat-to-beat heart rate variability (HRV), and spectral analysis techniques were applied to the EEG activity to assess its frequency content. Both prazosin and atropine did not alter the power spectral density (PSD) of the EEG low frequency (LF: 0.5–7.5 Hz) and high frequency (HF: 7.6–30 Hz) bands, whereas propranolol decreased the PSD in these bands. These findings suggest that central β-adrenergic receptor mechanisms could mediate the reptilian waking EEG activity without taking part any α_1-adrenergic and/or cholinergic receptor systems. In 55% of the lizards in control conditions, and in ~43% of the lizards under prazosin and atropine, a negative correlation between the coefficient of variation of the series of RRI value (CV_{RRI}) and the mean power frequency (MPF) of the EEG spectra was found, but not under propranolol. Consequently, the lizards' HRV-EEG–activity relationship appears to be independent of α_1-adrenergic and cholinergic receptor systems and mediated by β-adrenergic receptor mechanisms. *J. Exp. Zool. 287:21–28, 2000.*

It is generally assumed that the electrical activity of the mammals' neocortex may be both endogenous and exogenous. The endogenous electrical activity comprises the large-amplitude irregular slow activity, whereas the exogenous activity comprises both the low-voltage fast activity, as a result of cholinergic and serotonergic inputs, and the rhythmical spindle activity, which appears to depend on an input from the thalamus (Vanderwolf, '90). The principal systems involved in short-term cardiovascular control on the time scale of seconds to minutes are the sympathetic and parasympathetic nervous systems (Akselrod et al., '81). A close connection between the subcortical sources of some EEG rhythms and the autonomic control of beat-to-beat heart rate variability (HRV) have been suggested in mammals (Johnson and Davidoff, '64; Heikkilä et al., '87; Yli-Hankala et al., '90; Troncoso et al., '95).

The EEG of reptiles, which has been extensively studied (Parsons and Huggins, '65; González and Rial, '77; Belekhova, '79; Gaztelu et al., '91; De Vera et al., '94), has the same wide spectrum of frequencies as in mammals, which varies depending on the brain part and state studied (Bullock and Başar, '88).

With regard to heart activity, lizards in waking state exhibit, like mammals, spontaneous short-term oscillations in their heart rate and systolic blood pressure, which are mediated by the autonomic nervous system (ANS; De Vera and González, '97, '99). This raises the distinct possibility that central nervous system and cardiac autonomic activities are related in awake lizards. One way to examine this correlation is to study the effects of different ANS blockers on simultaneous HRV and EEG signals in reptiles.

At present there is a large amount of experimental data supporting the idea that the cerebral adrenoreceptors of mammals are related to the basic mechanisms of the EEG (Monti, '82),

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since physiological effects of noradrenaline are mediated via the interaction of this catecholamine with α- and β-adrenoceptors and their subtypes (Palacios et al., '87; Sebban et al., '87). Similarly, the alteration of central cholinergic transmission through pharmacologic blockade of muscarinic receptors induces pronounced changes in the cortical EEG of mammals (Loizzo and Longo, '77; Santucci et al., '81).

Substances such as prazosin and propranolol inhibit the interaction of adrenaline, noradrenaline, and other sympatomimetic drugs with adrenergic receptors (Hoffman and Lefkowitz, '91). Particularly, prazosin, which is a selective antagonist at the α_1-adrenoceptors, has been used in different EEG studies on mammals (Sebban et al., '87; Riekkinen et al., '93; Ferger and Kuschinsky, '94). With regard to the central action of the β-adrenergic blocking agents, propranolol, a nonselective β-adrenergic blocking lipophilic agent, affects not only peripheral autonomic functions but also the activity of, and the output from, a number of central nervous structures (Koella, '85). Drugs such as atropine, scopolamine and several others are competitive antagonists of the action of acetylcholine and other muscarinic agonists (Brown, '91). In short, most authors agree that atropine, a centrally acting cholinergic blocking agent, has a slow-wave inducing effect on the EEG of mammals (Meldrum et al., '70; Santucci et al., '81). It is thought that this slow activity reflects the blockade of corticopetal pathways (Santucci et al., '81) and that atropine consistently produces a kind of cortical deafferentation (Schaul et al., '78).

Although atropine has been frequently used in reptilian neurophysiology sleep studies (Hartse and Rechtschaffen, '82; Huitrón-Reséndiz et al., '92), there are no reports on the effects of prazosin and propranolol on the EEG of reptiles. Also, to our knowledge, the relationships between HRV and EEG in reptiles in normal conditions and/or under ANS blockade have not been examined. The present investigation was undertaken with two aims. The first was to quantify the effects of prazosin, propranolol, and atropine on the EEG of the lizard *Gallotia galloti* in order to demonstrate their possible central effects in conscious reptiles. The second aim was to study the possible relationship between HRV and the frequency content of the EEG in control and ANS-blocked animals in order to demonstrate the relationship between the cortical electrical and cardiac autonomic activities in awake lizards.

MATERIALS AND METHODS

Animals

Twenty lizards of the species *Gallotia galloti*, 9.1–12.9 cm in length (snout to vent), and 30.1–73.5 g (mean 42.3 ± 2.8 g) body mass, from the island of Tenerife (Canary Islands, Spain) were used. The animals were captured in their natural habitat and kept in terraria under a 12:12 hr light-dark cycle for at least 1 week before experiments began. A temperature of 23°C ± 1°C was maintained during the light phase, and 20°C ± 1°C during the dark. The relative humidity ranged from 54–66%. Food and water was available ad libitum. All the lizards used in this study were deprived of food for at least 24 hr before the experiments. The study protocol was approved by the Ethical Committee of the Faculty of Medicine of the University of La Laguna.

Surgery

Surgical procedures, under ether anesthesia, consisted of the implantation of electrodes to record continuous ECG and EEG. The bipolar ECG was recorded by two 6-mm-length stainless steel wire electrodes implanted subcutaneously, one near the nuchal region and the other near the sacral region. The bipolar EEG was recorded by two 3.5-mm-length stainless steel screw electrodes of 0.5 mm diameter, the tips of which were placed on the surface of the right and left medial cortex, and the whole set was glued to the skull with acrylic cement. After surgery, each lizard was housed individually in a temperature-controlled terrarium (23°C ± 1°C) and allowed to recover for 1 day before recording began. No postoperative drugs were used.

Experimental protocol

Simultaneous ECG and EEG recordings were carried out in the morning, in a room far away from any visual and acoustic disturbance, keeping the lizard in a thermostatically controlled (23°C ± 0.5°C) chamber (45 × 30 × 25 cm). The animal was kept within the chamber for a 3-hr habituation period, after which measurements were made when it was at rest. Core body temperatures were monitored by an electric thermometer (Nihon-Kohden MGA III-219) provided with a small thermistor probe that was inserted into the lizard's cloaca ~2 cm deep. The experiment consisted of a 20–30 min baseline recording session of ECG and EEG of the lizard at rest, and a 15–50 min recording session after parasympathetic or sympathetic nervous system blockade.

The ANS blockers used were prazosin (α_1-adrenergic blocker; 3 mg/kg; N = 7), propranolol (β-adrenergic blocker; 4 mg/kg; N = 6), and atropine (muscarinic blocker, 0.5 mg/kg; N = 7). All drugs (purchased from Sigma Chemical Co., St. Louis, MO) were dissolved in saline and administrated by means of a 2-ml/kg bolus injected intraperitoneally. The blocker doses used in this study were empirically determined to be twice the minimum doses necessary to remove sympathetic (prazosin and propranolol) or parasympathetic (atropine) effects from the resting heart rate (approximately 40 min after the bolus injection). Once the acute effects of these sole doses of blockers were achieved, it was observed that they always lasted at least the ~50 min duration of the longest recording session.

Measurements

ECG and EEG signals were continuously and simultaneously measured by a recording system (Nihon Kohden RM-85). The EEG signal was recorded using a 0.3-sec time constant and a 30-Hz high filter. The analog signals from the recording system were led to a 14-bit A/D converter card, controlled by a 486-DX PC for on-line processing by means of a BASIC program and an ASSEMBLER subroutine. This program, which was developed in our laboratory, sampled the ECG signal at a frequency of 1 kHz, and calculated the series of R-R consecutive intervals (RRI) from this signal by means of an ECG peak R detection and an R-R interval measurement algorithm. Basically, this algorithm detects the QRS complex of the ECG through the selection of an adequate signal threshold, and computes the differences between the values of successive samples until a slope change is detected. This slope change indicates when a peak R occurs. The time between neighboring R spikes in the ECG signal gives a well-defined measure of the time between the corresponding cardiac beats (i.e., the cardiac period).

Whenever a set of 100 RRIs was computed, an EEG signal segment of 20.48 sec duration was obtained at a sampling frequency of 100 Hz. Therefore, a normal recording session of approximately 1,200 RRIs included 11 distinct EEG signal segments of 20.48 sec duration each. Also, whenever a set of 100 RRIs was computed, a 20.48-sec duration RRI variability time series was formed from the RR consecutive intervals of the ECG. This data processing procedure was carried out in order to get a cardiac electrical activity sample simultaneous with the corresponding EEG signal segment recorded. Due to the intrinsic variability of the cardiac period, as well as to the different mean heart rates corresponding to a particular experiment, the number of RRIs computed in each 20.48 sec duration RRI variability time series was not constant, but fluctuated from ~9 under propranolol to ~26 under atropine, going through ~15 in control conditions. To sum up, in a typical recording session, 11 RRI variability time series of 20.48 sec duration each, simultaneous with 11 EEG signal segments of 20.48 sec duration each, were obtained from each lizard in every experimental condition (control-blockades).

Time-domain analysis of RRI

The short-term variability of the RRI series was quantitatively estimated by means of statistical indexes such as the standard deviation of the values (SD_{RRI}) and their coefficient of variation ($CV_{RRI} = SD_{RRI} \times 100/\text{mean value}$).

Spectral analysis of the EEG segments

The 20.48-sec duration EEG signal segments (sets of 2,048 data points sampled at 100 Hz), were spectrally analyzed using a fast Fourier transform (FFT) algorithm to obtain their power spectral density function (PSD). In order to perform this analysis according to time-series analysis standards, all signal segments were first linear-trend removed by means of the least squares method and, in order to reduce leakage in the spectrum, were cosine tapered over the first and last 10% of the samples (Bendat and Piersol, '71). A total of 1,023 spectral coefficients with a frequency resolution of 0.0488 Hz were obtained from each EEG spectrum. After processing all signal segments of a recording session from a particular lizard, an average power spectrum was obtained. Two average spectra for each experimental animal were obtained, one in control conditions and the other under a particular autonomic nervous system blockade (ANSB). The average spectra from the EEG signals were analyzed calculating the cumulative PSD in two spectral bands: low frequency band (LF: 0.5–7.5 Hz) and high frequency band (HF: 7.6–30 Hz). Moreover, the mean power frequency (MPF) of the global EEG band (0.5–49.9 Hz) of each spectrum (Chang et al., '95) was also calculated. The MPF parameter gives an indication of the spectrum's "center of gravity."

Statistical analysis

Data are expressed as mean ± SD. The statistical analysis of differences in RRI values, RRI variability parameters, and EEG parameters between the control condition and after a particular ANSB

was performed using a nonparametric Wilcoxon's Signed Rank test for paired data. The interdependence between RRI variability parameters and EEG parameters was estimated through the Pearson's Product Moment correlation coefficient. The statistical analysis of the differences between these correlation coefficients, in control conditions and after a particular ANSB, was performed using a nonparametric Mann-Whitney U test for independent samples. Comparisons were considered to be statistically significant at $P < 0.05$.

RESULTS

An example of simultaneous RRI variability and EEG signals recorded in control conditions in a 39.8-g lizard is shown in Figure 1. The EEG re-

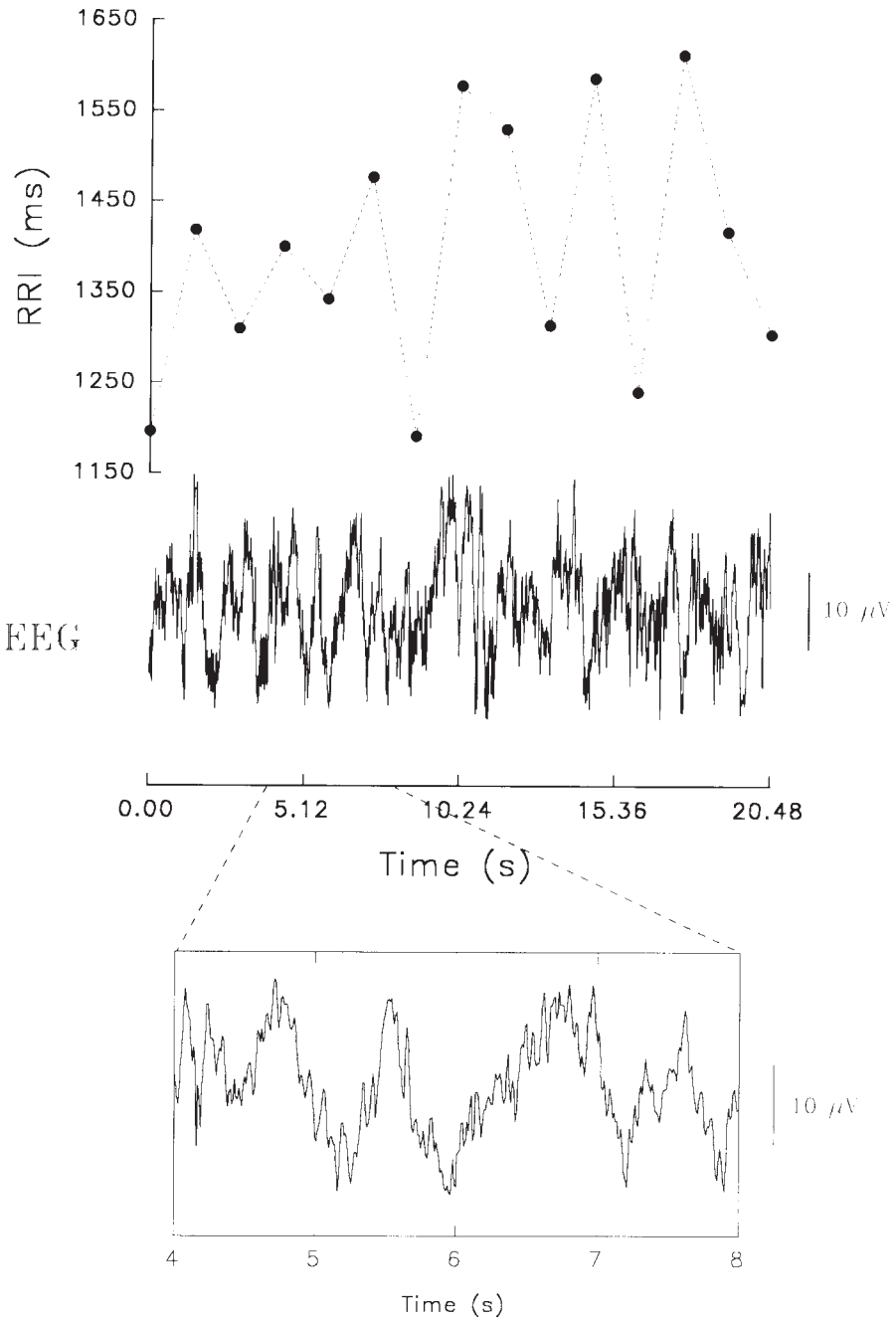

Fig. 1. Example of simultaneous digitized recordings of RRI variability (top trace) and EEG (middle trace) signals from a 39.8-g female lizard in control conditions at 23°C. In the bottom trace, which corresponds to a zoomed segment from the middle trace, the typical slow waves of the lizards' EEG can be distinguished.

cordings were polymorphic and mixed in frequency, their main feature being the presence of slow, high-voltage waves upon which high-frequency spindles were often found. The mean baseline RRI value obtained in resting conditions (N = 20) was 1388.1 ± 476.7 ms. Table 1 shows RRI mean values and RRI variability time-domain parameters mean values obtained in control conditions and after ANSB with prazosin, propranolol, and atropine. α_1-Adrenergic blockade with prazosin decreased the RRI (–26.9 ± 10.9%, P = 0.018) and the SD_{RRI} (–56.7 ± 22.8%, P = 0.018), but did not change the CV_{RRI}. β-Adrenergic blockade with propranolol increased the RRI (75.3 ± 39.6%, P = 0.027), the SD_{RRI} (179.3 ± 114.3%, P = 0.027), and the CV_{RRI} (102.1 ± 82.0%, P = 0.027). Parasympathetic blockade with atropine decreased the RRI (–40.1 ± 13.8%, P = 0.018), SD_{RRI} (–84.6 ± 10.3%, P = 0.018), and the CV_{RRI} (–76.0 ± 11.7%, P = 0.018).

Examples of PSDs corresponding to 20.48-sec-duration EEG segments, recorded in control conditions and after ANSB with prazosin, propranolol, and atropine, are shown in Figure 2 (a), (b), (c), and (d), respectively. Prazosin and atropine did not alter the power of the different EEG spectral bands considered. With regard to the effects of propranolol, a decrease in the LF (–56.8 ± 27.3%, P = 0.027) and HF (–45.5 ± 38.6%, P = 0.027) spectral bands was observed. The MPF spectral parameter did not change under any ANSB experimental situation (Table 2).

In 55% of the lizards in control conditions and in ~43% of the lizards under prazosin and under atropine, a negative correlation between CV_{RRI} and MPF parameters was found. Nevertheless, in all animals under propranolol, any correlation between CV_{RRI} and MPF parameters was not found.

TABLE 1. RRI and time domain RRI variability parameters evaluated in control and ANSB lizards[1]

	RRI	SD_{RRI}	CV_{RRI}
Control	1413.0 ± 466.1	71.0 ± 37.4	5.3 ± 2.0
Prazosin N = 7	983.4 ± 193.5[a]	33.7 ± 20.1[a]	3.3 ± 1.7
Control	1253.9 ± 309.8	74.7 ± 28.9	4.0 ± 1.3
Propranolol N = 6	2257.3 ± 392.7[b]	210.6 ± 116.6[b]	8.4 ± 4.3[b]
Control	1297.3 ± 392.4	59.5 ± 18.5	2.9 ± 0.9
Atropine N = 7	793.0 ± 123.7[a]	8.4 ± 4.3[a]	0.6 ± 0.2[a]

[1]RRI, RR interval (in ms); SD_{RRI}, standard deviation of the series of consecutive RRI (in ms); CV_{RRI}, coefficient of variation of the series of consecutive RRI (in percent); N, number of lizards. Statistical significance: [a]P = 0.018; [b]P = 0.027. Values are means ± SD.

The correlation coefficients between CV_{RRI} and MPF obtained in control conditions were not statistically different from those obtained between the same parameters after prazosin and under atropine. These results are summarized in Table 3. Similar results were found when analyzing the correlation between SD_{RRI} and MPF, although the number of lizards that exhibited any correlation in control conditions, as well as in all the other experimental situations, was appreciably lower than the number of lizards that exhibited a correlation between CV_{RRI} and MPF.

DISCUSSION

The control-resting RRI value reported for *Gallotia galloti* in the present investigation, and the RRI values under α_1- and β-adrenergic and parasympathetic blockades, are in accordance with values obtained by the authors in previous studies (De Vera and González, '97, '99). The changes experienced in the lizard's RRI variability time-domain parameters values, after α_1- and β-adrenergic and parasympathetic blockades in the present investigation, are also in agreement with those obtained in the frequency domain in the above-cited previous reports.

Prazosin did not affect the power of the different EEG spectral bands in lizards. This result is different from most findings reported in rats, where prazosin affected the EEG power spectra (Sebban et al., '87; Riekkinen et al., '93; Ferger and Kuschinsky, '94). Our findings suggest that, contrary to what has been observed in mammals, central α_1-adrenergic systems are probably not involved in the synaptic chemical transmission related to the EEG activity in lizards.

Our study showed that the β-adrenergic blocking agent propranolol significantly decreased the EEG-LF and HF bands in lizards. There is no general agreement in the literture on the effects of propranolol on the mammals' EEG. Thus, mainly reported has been no significant differences (Lader and Tyrer, '72; Straumanis and Shagass, '76; Hemmingsen et al., '80) or an increase (Czarnecka et al., '77; Itil and Itil, '83; Torbati, '86; Frcka and Lader, '88; Zamboni et al., '90; Kurova and Paniushkina, '92) in EEG frequencies or amplitudes, between recordings obtained before and after propranolol administration. Despite the lack of agreement in the literature about the effects of propranolol on the mammals' EEG, it could be said that, in most experiments carried out, an increase of EEG activity after administration of the drug has been reported. From this we can suggest that

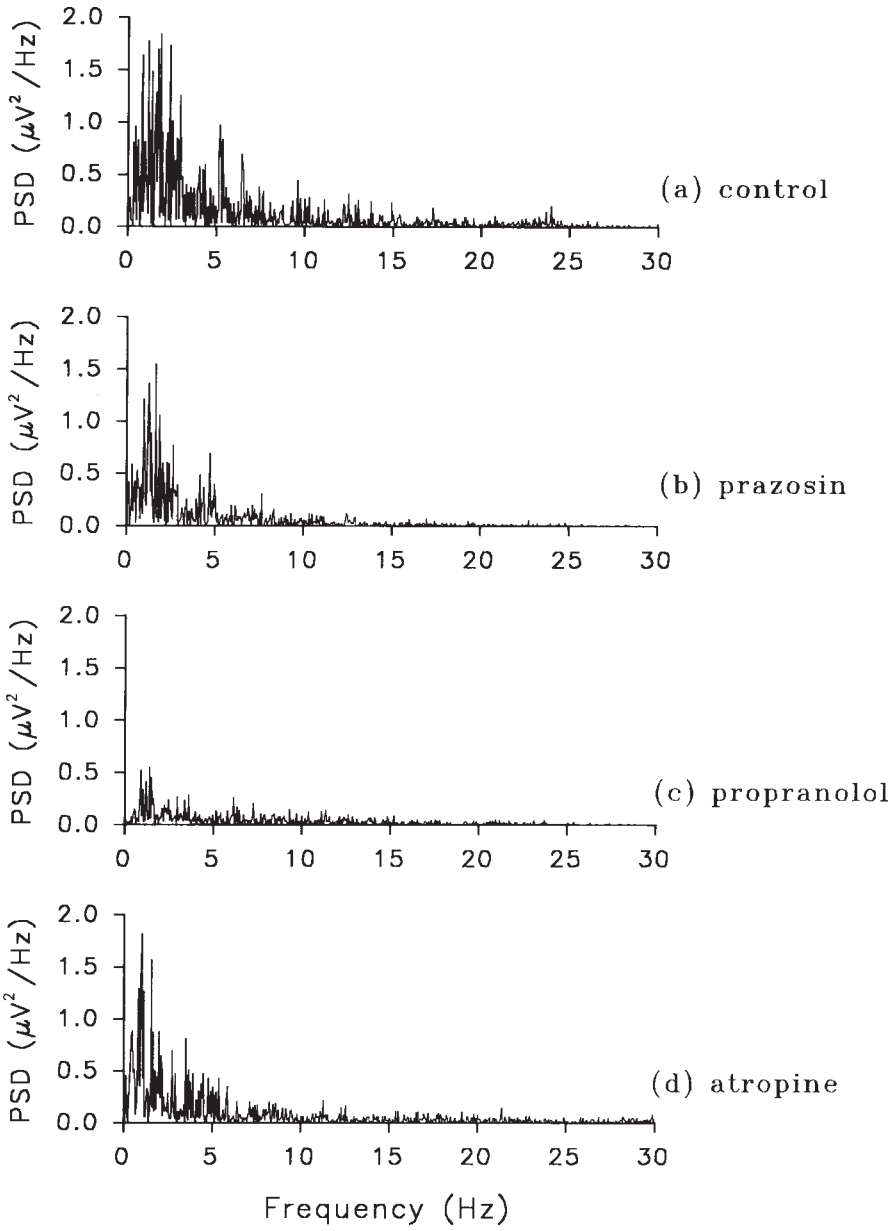

Fig. 2. Examples of power spectra obtained in three representative experimental animals in control conditions [**(a)**: lizard L2, 47.3 g body weight, female], after α_1-adrenergic blockade with prazosin [**(b)**: lizard L2], after β-adrenergic blockade with propranolol [**(c)**: lizard L12, 50.5 g body weight, male], and after parasympathetic blockade with atropine [**(d)**: lizard L17, 59.8 g body weight, male]. In order to improve visual resolution, the power spectra have been cut to the 30-Hz level.

central β-adrenergic mechanisms in mammals could act as a buffer of EEG activity. On the contrary, our data suggest that the reptilian EEG activity could be extraordinarily dependent on the synaptic chemical transmission at the level of central β-adrenergic receptors, since all EEG spectral bands clearly decreased after blockade with propranolol.

Atropine, like prazosin, did not affect the power of the different EEG spectral bands considered. In mammals, the interaction of atropine with central cortically located cholinergic neuronal systems seems to lead to a slowing down of the EEG activity (increase of slow-range frequency amplitude relative to control experiments) (Bradley and Elkes, '53; Itil and Fink, '68; Meldrum et al., '70; Fairchild et al., '75; Florio et al., '77; Santucci et al., '81). In accordance with our results, it can be suggested that, contrary to what has been observed in mammals, central cholinergic receptor

TABLE 2. EEG parameters computed in control and ANSB lizards[1]

	MPF	LF	HF
Control	5.9 ± 2.9	33.8 ± 11.7	12.9 ± 7.5
Prazosin N = 7	6.1 ± 2.7	32.4 ± 13.0	12.6 ± 7.0
Control N = 7	5.8 ± 2.0	31.9 ± 10.9	15.3 ± 7.4

[1]MPF, mean power frequency (values in Hz); LF, low-frequency band (PSD values in μV^2); HF, high-frequency band (PSD values in μV^2); N, number of lizards. Statistical significance: [b]$P = 0.027$. Values are means ± SD.

systems are probably not involved in the synaptic chemical transmission related to the EEG activity in lizards.

From above, and with regard to the synaptic chemical transmission, it can be suggested that central β-adrenergic receptor mechanisms could mediate the reptilian waking EEG activity without taking part any α_1-adrenergic and/or cholinergic receptor systems. This is in full contrast to what happens in mammals, where biological evolution has opened the way for a morphologically and functionally more complex brain, with more diversity in the functioning and tasks of neurotransmitter receptor systems.

The negative correlation we found in control conditions between CV_{RRI} and MPF could be explained by taking into account the central and cardiac responses of lizards to an increase in body temperature and, therefore, in general activity. In fact, an increase in body temperature in reptiles produces an increase in general activity that, at the electroencephalographic level, results in a signal power shift to high frequencies (De Vera et al., '94) and, at the cardiac level, in a decrease in HRV (De Vera and González, '86). Moreover, in our lizards, this relationship not only seems to be independent of α_1-adrenergic and cholinergic receptor mechanisms (no effects of prazosin and atropine on CV_{RRI}-MPF correlation) but also mediated by β-adrenergic receptor mechanisms, as demonstrated by the lack of correlation between CV_{RRI} and MPF after blockade with propranolol. Finally, we venture to add that, from the point of view of biological evolution, the β-adrenergic receptor mechanisms we have studied, which seem to predominate over any other in our reptiles, could therefore have developed in vertebrates earlier than the α_1-adrenergic and cholinergic receptor systems also investigated.

TABLE 3. Pearson's Product Moment correlation coefficients between CV_{RRI} and MPF in control and ANSB lizards[1]

	N	CV_{RRI} vs. MPF[2]	
Control	7	–0.505 ± 0.160	(4)
Prazosin	7	–0.387 ± 0.133	(3)
Control	6	–0.497 ± 0.073	(3)
Propranolol	6	—	
Control	7	–0.567 ± 0.109	(4)
Atropine	7	–0.673 ± 0.169	(3)

[1]CV_{RRI}, coefficient of variation of the series of consecutive RRI; MPF, mean power frequency; N, number of lizards per experiment.
[2]Values are means ± SD. Numbers in parentheses indicate the number of lizards where the correlation coefficient between variables is statistically significant ($P < 0.05$).

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