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Regular and chaotic behaviour of cardiac cells stimulated at frequencies between 2 and 20 Hz

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Abstract. We measured the non-linear dynamics of cardiac action potentials by varying the stimulation frequency from 2 to 20 Hz and obtained the following results: (*i*) When the fast Na^+ current initiated the action potentials ('fast action potentials') periodicity was maintained, i.e. the pattern of action potentials repeated after a finite number of stimuli. Chaotic sequences were absent. The transition from one sequence to the next occurred as a devil's staircase. (*ii*) When, however, the slow Ca^{2+} current initiated the action potentials ('slow action potentials'), we observed chaos, i.e. fully irregular behaviour, as well as bifurcations. (*iii*) Our results confirm the supposition that the global dynamics of cardiac cells can be well described by simple one-dimensional maps which predict these two kinds of behaviour.

Key words: Ventricular cardiocytes, nonlinear dynamics, chaos, devil's staircase

Introduction

The contraction of cardiac myocytes is closely related to temporal depolarizations of the cellular membrane potential ('electro-mechanical coupling', Fabiato and Fabiato 1979). Under normal physiological conditions these action potentials are regularly generated, thus guaranteeing an effective pumping of the heart muscle. However, under pathological conditions irregularities can occur, clinically known as arrhythmias. Besides the 'classical' models for arrhythmias based on impulse conduction in the tissue (for review see: Cranefield and Witt 1979; Spear and Moore 1982), theoretical considerations suggest that such an arrhythmic behaviour can already occur on the level of a single isolated cardiocyte. The Beeler-Reuter equations, which describe the ionic currents underlying the generation of action potentials (Beeler and Reuter 1977; Noble 1986), are included in the theory of nonlinear oscillators (Bélair 1986), which predicts, under defined conditions, irregular (chaotic) behaviour. In this respect, Jensen et al. (1984) demonstrated in a computer simulation that the Beeler-Reuter equations yielded periodic as well as chaotic action potential responses, depending on the input frequency of the sinusoidal stimulation (for general aspects see also Guevara and Glass 1982; Chay 1985; Glass et al. 1984). The occurrence of both periodicity and aperiodicity has also been confirmed in some experimental studies on cardiac preparations. For example, Glass et al. (1983) analysed different arrhythmic electrocardiograms with Wenckebach cycles and demonstrated that spontaneously beating heart cell aggregates responded with a very similar behaviour when forced into a given stimulation frequency (phase resetting, see also Guevara et al. 1981; Clay et al. 1984; Chay and Lee 1985). Irregularities of the heart beat, observed under the so-called 'sick sinus syndrome', have also been assigned to the theory of nonlinear oscillators (Goldberger et al. 1985; West et al. 1985). It should be noted that these irregular, chaotic phenomena can be derived from deterministic nonlinear equations and are distinct from membrane potential fluctuations caused by stochasticity of single channels (see DeHaan and DeFelice 1978; Clay et al. 1979). Since electrical phenomena of whole cardiac cells are generated by a large number of channels, they are effectively deterministic.

A complete description of the behaviour of a nonlinear system includes information on the transition from regular periodic to irregular chaotic dynamics when the input parameter, e.g. the stimulation frequency, is continuously altered within a certain range. So far, no such experimental studies on cardiac cells have been carried out, although a prediction on the possible transitions has been made using reduced one dimensional models; e.g. the phase transition curves introduced by Guevara et al. (1981, 1983). As outlined by MacKay and Tresser (1986), two extreme cases can be distinguished: (*i*) If the describing one dimensional

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function shows non-invertibility, the transitions occur via bifurcations and chaotic states are expected. (*ii*) If, on the other hand, the describing function is invertible, chaotic states are suppressed and a devil's staircase transition, i.e. inserted sequences of regular states of higher complexity (see also Keener 1980; Matsumoto et al. 1987; Rajasekar and Lakshmanan 1988), is expected.

In the present study, we measured the dynamic behaviour of isolated ventricular cardiocytes when stimulated at continuously increasing frequencies. Under physiological conditions (5.4 m*M* K^+) and using short rectangular stimulation pulses we could not find chaotic action potential sequences. The transitions between the different states occurred as a devil's staircase pattern. When, however, the fast Na^+ current system was blocked either by pharmacological (TTX) or by electrical (high K^+, Gaussian formed stimulation pulses) tools, bifurcations as well as chaos could be seen. The results suggest that cardiac systems have ranges of stability and ranges of chaos and that Na^+ action potentials are more stable than Ca^{2+} action potentials.

Methods

Single ventricular cardiocytes of adult guinea pigs were prepared as described elsewhere (Isenberg and Klöckner, 1982a; Hescheler et al. 1986). For the electrophysiological experiments, the isolated cells were transferred to a small test chamber and superfused with Tyrode's solution containing (in m*M*): NaCl 112, $NaHCO_3$ 24, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.0, glucose 10 and HEPES 5 (bubbled with 95% O_2 and 5% CO_2, pH 7.4 at 36 °C). Electrophysiological measurements were taken using the patch clamp technique in the whole cell arrangement (see Hamill et al. 1981). In short, the patch electrode, which had a resistance of about 2 MOhm, when filled with a solution containing (in m*M*): K-aspartate 100, KCl 50, $MgCl_2$ 1.0, HEPES 5, EGTA 0.1, Na_2ATP 3.0 (pH 7.4 at 36 °C), was moved to the surface of the cell. By negative pressure of about -20 cm H_2O, a small patch of the membrane was sucked into the opening of the pipette until a GOhm seal was achieved. Increased suction disrupted the patch and a low resistance junction to the intracellular space was achieved (whole cell configuration, see Hamill et al. 1981). The membrane potential was recorded under current clamp conditions (patch clamp amplifier L/M-EPC 7, List Medical Electronic, Darmstadt, FRG). In 86 cardiocytes, the mean resting potential ($\pm$ SD) amounted to -82.5 ± 7.3 mV. After stimulation, they developed action potentials (see Fig. 2A) with durations of 250 ± 65 ms. The plateau amplitude measured 10 ms after the stimulus amounted to 33.4 ± 5.1 mV (see also Isenberg and Klöckner 1982b). The passive electrical properties of the cell membrane, i.e. the capacitance and the input resistance were measured under voltage clamp conditions as already described (Hescheler et al. 1986). Values obtained from 64 cells were 17.9 ± 7.5 MOhm and 121.5 ± 46.5 pF for the input resistance and the capacitance, respectively (measured at the resting potential). Thus, the time constant of the membrane was in the order of 2 ms. The stimulation pulses were generated by a PDP 11/23 computer which was also used for on line measurement and storage.

Experimental procedure

Stimulation of action potentials

Fast action potentials (Figs. 2 and 3) were stimulated under normal Tyrode's solution using short (1 ms duration) rectangular current pulses. We adjusted the amplitude of the stimulation pulses before every experiment to a value slightly above the threshold for elicitation of an action potential (rheobase).

Slow action potentials (Figs. 4 and 5), whose upstroke is mainly carried by the slow Ca^{2+} current, were recorded under conditions where the fast Na^+ current was reduced. For that purpose, we chose three different experimental approaches:

(*i*) We blocked the Na^+ channels directly by 10 μM TTX.

(*ii*) We depolarized the resting potentials to -60 mV by increasing the external K^+ concentration from the physiological value of 5.4 m*M* to 10.8 m*M*. Because of their voltage dependency, Na^+ channels inactivate at this potential (Hille 1984).

(*iii*) Instead of short rectangular stimuli we used pulses with a slow rate of rise. From previous studies it is known that Na^+ channels can only be activated if the upstroke velocity of the depolarizing stimulation pulse is faster than the activation time constant (about 1 ms, Hille 1984). If a cell is stimulated by slow pulses, the Na^+ current is depressed and Ca^{2+} current initiates slow action potentials. In the present experiments we used Gaussian shaped pulses (effective duration 30 ms, amplitude adjusted to rheobase); similar effects could be also obtained with sinusoidal or triangular stimuli. The computer simulation (using the Beeler-Reuter formalism) of Fig. 1 elucidates the dependency of the membrane potential as well as of the ionic currents from the shape of the stimulation pulse. Gaussian shaped pulses of various duration were used. While the Ca^{2+} current (lane c) was almost unchanged, both the upstroke velocity

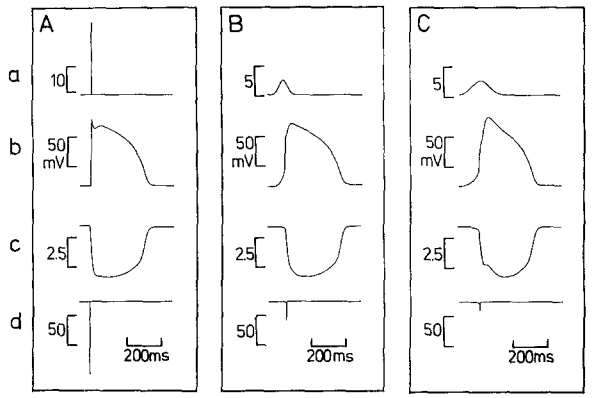

Fig. 1 A–C. Electrical inactivation of the fast Na^+ current system by Gaussian formed stimulation pulses. The shape of the action potentials (*b*) as well as of the Ca^{2+} (*c*) and Na^+ (*d*) current was computer-simulated using the Beeler-Reuter formalism. Three different kinds of stimulation pulses (*a*) were assumed: **A** fast rectangular shaped pulse (amplitude: 25 $\mu A/cm^2$, duration: 1 ms); **B** and **C** Gaussian shaped pulses with amplitudes of 2.5 $\mu A/cm^2$; durations: 30 ms (**B**) and 60 ms (**C**). Smoothing of the stimulation pulses caused an appreciably slower upstroke velocity of the action potential, which was related to a decrease of the Na^+ current. The amplitude of the Ca^{2+} current remained unaffected. The numbers on the calibration bars in (*a*), (*c*) and (*d*) indicate $\mu A/cm^2$

of the action potentials (lane b) and the amplitude of the Na^+ current (lane d) decreased with prolonged stimuli.

Measurement of the 'Feigenbaum' diagrams

In contrast to previous experimental studies where action potential sequences were measured only at fixed stimulation frequencies (see e.g. Guevara et al. 1981), we continuously varied this parameter in order to determine the transitions between the different states. A train of 6,000 stimuli was computer-generated with the longest interval between two pulses being 500 ms (2 Hz) and the shortest 50 ms (20 Hz). The stimulation frequency was linearly varied by 3 mHz/pulse resulting in a duration of the whole experiment of 15 min. In some experiments (see parts B of Figs. 3 and 5), a smaller range of frequencies (between 2 and 8 Hz) was used. For the 'Feigenbaum' representations (Feigenbaum 1978; Ott 1981; Eckmann 1981) of Figs. 3 and 5 we plotted the membrane potential amplitude, which was measured with a delay of 10 ms after the maximum of the stimulation pulse, versus the actual frequency.

Regularities in the electrical response were seen in the Feigenbaum diagrams as a finite number of distinct levels of amplitude, i.e. if i levels occurred, the action potential pattern repeated after i stimuli. Consequently, a cycle of action potentials will be called an i-cycle if i is the smallest number of stimuli after which the membrane behaviour repeats. For a better description of the transitions, we used the term 'rotation number' which is derived from the theory of one dimensional models (see e.g. Arnold 1983; MacKay and Tresser 1986). Here, the rotation number will be defined as the fraction of the number of fully activated action potentials within a cycle divided by the length of the cycle. If, for example, an i-cycle contains k fully activated action potentials and $(i - k)$ small responses, the rotation number will be $r = k{:}i$ (see also Matsumoto et al. 1986). The frequency range with cycles of $r = k{:}i$ is called a $k{:}i$-window. In contrast to these regular windows, irregular or chaotic domains showed infinite high values of i, i.e. no number of stimuli could be given after which the action potential pattern repeats.

Results

Behaviour of fast action potentials

Cardiocytes were bathed in the standard Tyrode's solution and stimulated by 1 ms long rectangular current pulses whose amplitude was adjusted to the rheobase. When, under these conditions, the stimulation frequency was varied, the cells responded with action potential sequences which showed remarkable regularities (see Fig. 2). At low frequencies (below 4 Hz), every stimulus excited one full action potential, i.e. the membrane depolarized from − 80 to 30 mV (Fig. 2 A). At frequencies around 7 Hz, one full action potential was followed by one small response, the cycle resembling Wenckebach arrhythmia with a rotation number 1:2 (Fig. 2 B). It should be noted that the partial potential responses cannot be considered as simple capacitive stimulation artifacts since their durations (about 30 ms) were much longer than it might be expected from the relaxation time constant of the membrane (about 2 ms, see Methods). Cycles with a rotation number of 1:3 were observed around 8.5 Hz (Fig. 2 C), 1:4 around 11 Hz, 1:5 around 13 Hz (Fig. 2 D) and so on. Maximal rotation numbers were about 1:11 which occurred at frequencies around 20 Hz (Fig. 2 F). At higher frequencies, the cells remained in a depolarized state of about 20 mV (not shown).

In some experiments we measured action potentials before and after application of high frequency stimulation trains. Since there was no obvious difference, it can be assumed that the electrical properties of the cardiocytes were not altered during excitation at different frequencies. In multicellular preparations it was noted, that the resting potential depolarizes at high stimulation frequencies; and this was attributed

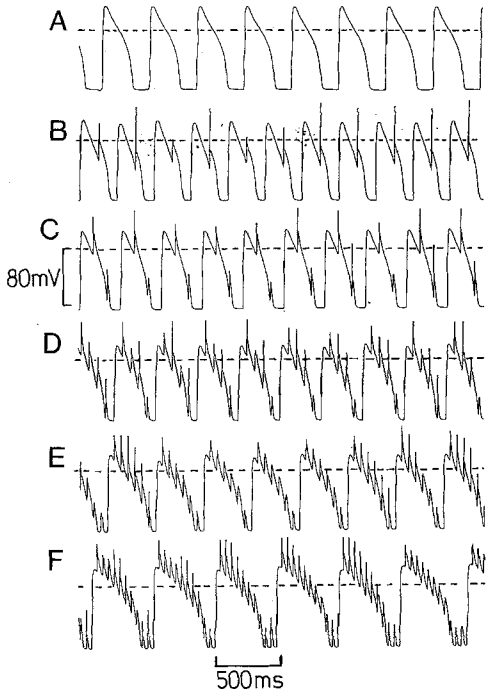

Fig. 2 A–F. Fast action potential sequences measured at different stimulation frequencies. The cardiocytes was excited by rectangular current pulses of 1 ms duration and an amplitude adjusted to the rheobase. The stimulation frequency in traces **A–F** amounted to 2.5, 7, 8.5, 13, 18 and 20 Hz, respectively. Cycles with rotation numbers 1:1, 1:2, 1:3, 1:5, 1:7 and 1:11 can be seen

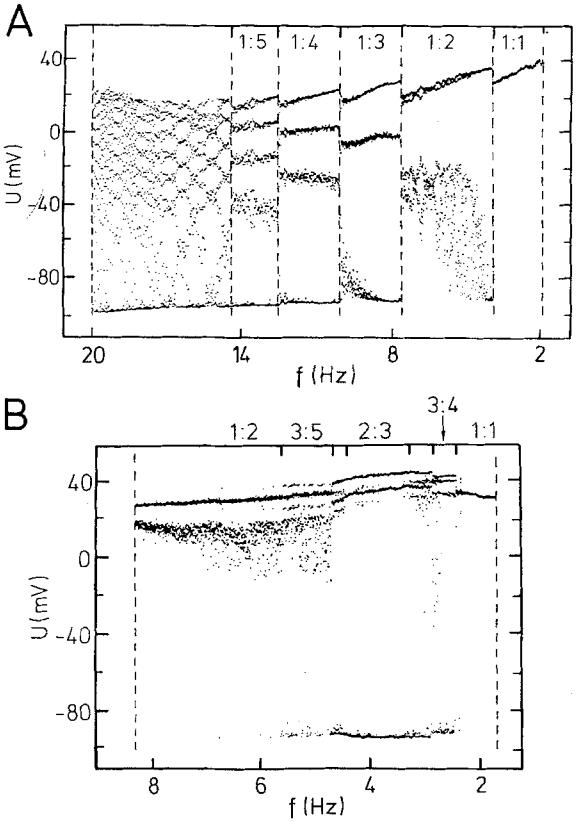

Fig. 3 A and B. Feigenbaum plots of fast action potentials (measured under same conditions as described for Fig. 2). The amplitude (U) was determined 10 ms after each stimulus (y-axis) and plotted versus the stimulation frequency (f) (x-axis). **A** The frequency was linearly decreased from 20 to 2 H. The whole train consisted of 6,000 stimulation pulses. Windows with rotation numbers 1:1 to 1:5 could be discriminated; at frequencies above 14 H the resolution got worse. The transitions between the windows appeared to be fast. **B** In another experiment, the frequency was varied from 8 to 2 Hz, resulting in an increased resolution of the x-axis. The fast action potentials showed a devil's staircase

to the accumulation of K^+ in the extracellular space (Attwell et al. 1981). However, we did not observe such an effect in the present experiments (see Fig. 2), indicating that accumulation plays no role in the isolated cells. A possible depolarization of the resting potential by accumulation of K^+ which may occur in tissue results in a behaviour described for slow action potentials (see below).

For determination of the transitions from one action potential sequence to another, the stimulation frequency was continuously varied between 2 and 20 Hz. As shown in the measured Feigenbaum diagram (Fig. 3 A), defined windows with increasing rotation numbers were obtained; 1:1-cycles were seen in the frequency range between 2 and 3.7 Hz, 1:2-cycles between 3.7 and 8.5 Hz, 1:3-cycles between 8.5 and 9.9 Hz, 1:4-cycles between 9.9 and 12.5 Hz and 1:5-cycles between 12.5 and 14 Hz. At higher stimulation frequencies, the resolution was no longer good enough to recognize cycles with higher rotation numbers. The transitions from one window to the next appeared to be very fast, i.e. the action potential sequence with the rotation number $1:i$ seemed to switch directly to the $1:(i+1)$-cycle without interpolated action potential patterns and no obvious chaotic sequences. However, in some experiments where the cells were stimulated in a smaller frequency range (varying from 2 to 8 Hz), a better resolution of the transition between cycles with the rotation numbers 1:1 and 1:2 was obtained (see Fig. 3 B). Between these two windows we observed new windows of small width, but no chaos. These new i-cycles had a more complex structure than the previous ones. Again i stimuli were needed to repeat the pattern, but more than one of these i stimuli evoked a full action potential response. In general, there were $k (1 \leq k \leq i)$ fully activated action potentials and $(i-k)$ small responses, i.e. the rotation number of this i-cycle was $r = k:i$. The interlocking of the intervals in Fig. 3 B can now be described as a devil's staircase: between an i-cycle ($r = k:i$) and a j-cycle ($r = m:j$), a $(i+j)$-cycle ($r = (k+m):(i+j)$) is interpolated. For example, between the 1-cycle ($r = 1:1$) and the 2-cycle ($r = 1:2$), there is a 3-cycle ($r = 2:3$). Between the new 3-cycle ($r = 2:3$) and the 2-cycle ($r = 1:2$), there is a 5-cycle ($r = 3:5$) and so on.

Qualitatively similar behaviour, i.e. suppression of chaotic action potential sequences and occurrence of devil's staircase transitions, was observed in all cells ($n = 37$) measured under conditions where fast action potentials were triggered. However, the length and location of the windows differed from cell to cell. Obviously, this is connected with the fact that some parameters of the cell (e.g. membrane capacity, input resistance) varied from one experiment to the other (for variability of action potentials see Methods).

Behaviour of slow action potentials

In another series of experiments the methodical procedure was identical, except that conditions were used where the Na^+ current component was reduced (see Experimental Procedure). The absence of the Na^+ current yielded action potentials with slow upstroke velocity of 5.8 ± 2.3 V/s, ($n = 59$) compared to that of fast action potentials (206 ± 47 *V/s*, $n = 32$) (see also Isenberg and Klöckner 1982b). Under these conditions, we again found at certain frequencies regular action potential sequences which could be described as *i*-cycles ($r = 1:i$), i.e. after *i* stimuli the action potential pattern repeated (not shown). However, as a new feature, we found frequency ranges where the membrane potential was fully irregular. Examples of such chaotic sequences are given in Fig. 4, where slow action potentials were obtained either by K^+ depolarization of the resting potential (part A), or by stimulation with Gaussian shaped stimuli (part B; the stimuli had a duration of 30 ms and an amplitude adjusted to the rheobase). Similar results were also obtained when the Na^+ current system was blocked by 10 μM TTX. The chaotic responses are characterized by the fact that no *i* exists after which the pattern repeats. As reported by Jensen et al. (1984) for their computer simulation, we also found a broad band noise in the power spectrum (not shown) indicating the chaotic, irregular origin of the experimentally observed action potential sequences. Whether the irregular behaviour results from a nonlinear dynamics or from a stochastic process can be decided by the Kolmogorov entropy (K), which is a measure for the loss of information per time. A stochastic process implies an infinite value of K, whereas K is finite in the case of deterministic chaos (Grassberger and Procaccia 1983; Wolf et al. 1985). From the measured action potential sequence of Fig. 4B ($n =$ 500 stimuli) we obtained $K = 2 \pm 0.5$ bits/s, indicating the deterministic origin.

The behaviour of the slow action potentials can be seen more accurately from the Feigenbaum plot. In Fig. 5A, the frequency of the Gaussian shaped stimuli was varied from 2 Hz to 20 Hz, i.e. in the same range, where the fast action potentials only responded with

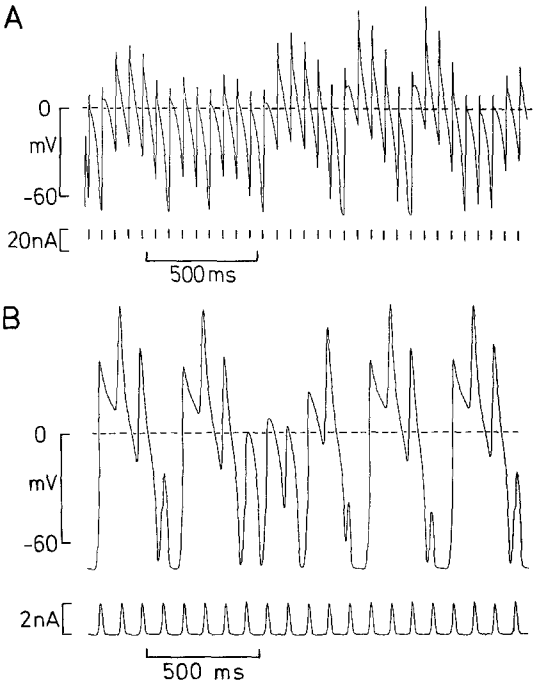

Fig. 4A and B. Chaotic behaviour of the membrane potential. Slow action potentials were obtained either by K^+ depolarization of the resting potential (**A**) or by Gaussian shaped stimulation pulses with a duration of 30 ms (**B**). The amplitude of the stimulation pulses (see lower parts) was adjusted to the rheobase and the frequency amounted to 18 Hz in **A** and 11 Hz in **B**. The irregular pattern is characterized by the fact that no number of stimuli can be given after which the action potential pattern repeats. Representative sections are shown. Analyzing longer traces by Fourier transformation revealed a broad band noise

regular *i*-cycles. In contrast, for slow action potentials, windows with increasing rotation numbers were interpolated by domains of chaotic sequences where no distinct levels of membrane potential amplitude could be recognized. A cycle with the rotation number 1:2 was seen in the frequency range between 3.7 and 6.8 Hz, 1:3-cycles between 10.7 and 13 Hz, 1:4-cycles between 14.7 and 15.7 Hz and 1:5-cycles between 17.7 and 18.6 Hz. The chaotic bands occurred in the frequency ranges 6.8 to 10.7 Hz, 13 to 14.7 Hz, 15.7 to 17.7 Hz and 18.6 to 20 Hz. Again, at higher frequencies, the membrane potential remained depolarized.

While the transition from regular *i*-cycles to chaos seemed to be very fast in the experiment of Fig. 5A, some other experiments, where we stimulated the cells at a smaller frequency range, yielded a better resolution. Fig. 5B illustrates such an experiment with visible structure between cycles with the rotation numbers 1:2 and 1:3. In this experiment, an increased K^+ concentration depolarized the membrane potential to -60 mV. At a frequency of 5.7 Hz, the 1:2-cycle turned into a 2:4-cycle, i.e. a bifurcation took place. The next bifurcation (into a cycle with the rotation

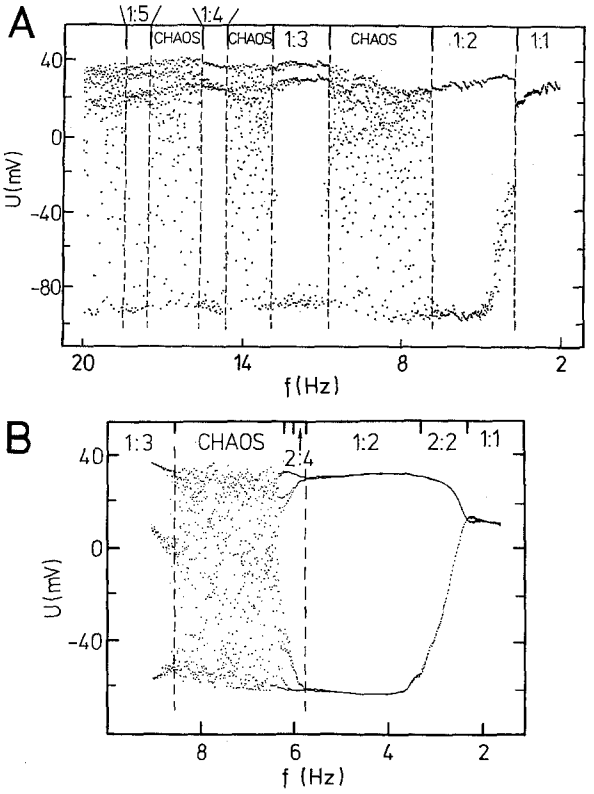

Fig. 5 A and B. Feigenbaum plots of slow action potentials measured with the same experimental protocol as described for Fig. 3, except that the Na^+ current was suppressed. In **A**, Gaussian shaped stimulation pulses were applied; In **B**, the Na^+ current was electrically inactivated due to the depolarized resting potential (around -60 mV). **A** The stimulation frequency decreased from 20 to 2 Hz. Windows with rotation numbers 1:2, 1:3, 1:4 and 1:5 were interpolated by chaotic domains. The 4- and 5-cycles are not well resolved because of superpositions. **B** Higher resolution of the x-axis than in **A**. The frequency varied from 9 to 2 Hz. Bifurcations, i.e. doublings of cycle number, were observed. At 6.3 Hz, the cycles turned into chaos

number 4:8) was only very weakly developed, passing over into the chaotic domain. From that chaos, the 1:3-window developed (at 8.5 Hz).

We observed bifurcations and chaotic domains in all experiments under conditions favoring slow action potentials ($n = 33$). But again, the results differed in their quantitative behaviour, i.e. the exact length and location of the $1:i$-windows as well as of the chaotic domains varied from one experiment to the other. Furthermore, we observed hysteresis effects. In experiments with the same cell, where we first increased the frequency from 2 to 20 Hz and then decreased it again, we obtained two Feigenbaum plots which differed in the length of their chaotic regions (not shown).

Discussion

Although all investigated cardiocytes differed in their quantitative responses, the present experimental protocol clearly allowed discrimination between two qualitatively different modes of behaviour. In the presence of the fast Na^+ current, which yielded fast (all or nothing) action potentials, chaotic domains never occurred and the transition from the i-cycle to the $(i+1)$-cycle occurred in a devil's staircase pattern. In contrast, when the slower Ca^{2+} inward current initiated the action potentials, they were less exactly determined, and the cell responded at certain stimulation frequencies with chaos, i.e. irregular fluctuations of the membrane potential. The transition from the i-cycle to the chaotic sequence occurred via bifurcations.

Therefore, it is suggested that the fast Na^+ current system causes suppression of irregular action potential sequences and stabilizes a basal rhythmicity of the cardiocyte. Such a mechanism is preferentially expected in the non-spontaneous, ventricular cardiocytes since they have – under physiological conditions – a low resting potential (around -80 mV) which allows the activation of large Na^+ current during depolarization (Hille 1984). On the other hand, the chick embryonic heart cell aggregates, which were used in previous studies, are spontaneous cardiocytes with resting potentials of around -50 mV where the Na^+ current is electrically inactivated (Colizza et al. 1983; Glass et al. 1983). In line with our observations, Guevara and coworkers (1981) described chaotic action potential domains in these cardiac preparations.

Theoretical considerations already predict a distinguishable electrical behaviour in the presence or absence of a fast current system. Reducing the multidimensional describing Beeler-Reuter equations to simple one dimensional models, phase transition curves are obtained (see e.g. Guevara and Glass 1982; Bélair 1986), where the membrane potential after the stimulus $n+1$ (U_{n+1}) is expressed as a nonlinear function of U_n, thus $U_{n+1} = f(U_n)$. The presence of the fast Na^+ current system may cause an invertible (e.g. a strictly monotone) phase transition function. On the other hand, the absence of the Na^+ current system may be described by a non-invertible transition curve (e.g. a function with a smooth extremum). If such one-dimensional functions are examined using the known results on circle maps, there are only two possible patterns of behaviour, namely bifurcations/chaos or devil's staircase transition/suppression of chaos (see Keener 1980; Arnold 1983; Bélair and Glass 1985; MacKay and Tresser 1986). Thus, the present experimental results support the view that one-dimensional transition functions are sufficient to describe the rhythmicity and arrhythmicity of the cardiac membrane potential responses (see also Honerkamp 1983; de Bruin et al. 1983; Strittmatter and Honerkamp 1984).

From a more general point of view, our results obtained with cardiac cells may also have some im-

plications for the electrical activity of other excitable cells, since the presence of both Na^+ and Ca^{2+} current is ubiquitous. For instance, nerve cells may respond, depending on their impulse frequency and their resting potential, with regular as well as with irregular outputs (see e.g. Rapp et al. 1985; Babloyantz et al. 1985; Haken 1985; Connor 1985; Matsumoto et al. 1987). Holden (1982) and Holden et al. (1982) reported that extracellular application of some chemical agonists (e.g. tetra-ethylammonium) to a molluscen neuron produced changes in the periodicity of discharges. Such a processing of chemical or electrical information might also be important in β-cells of the pancreas, where, depending on the glucose concentration (and therefore metabolic factors) chaotic or regular burst patterns could be observed (Atwater et al. 1980; Lebrun and Atwater 1985; see also Sherman et al. 1988).

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References

Arnold VI (1983) Geometrical methods in the theory of ordinary differential equations. Springer, Berlin Heidelberg New York

Atwater I, Dawson CM, Scott A, Eddlestone G, Rojas E (1980) The nature of the oscillatory behaviour in electrical activity for pancreatic β-cell. In: Biochemistry biophysics of the pancreatic β-cell. Thieme, New York, pp 100–107

Attwell D, Cohen I, Eisner DA (1981) The effects of heart rate on the action potential of guinea-pig and human ventricular muscle. J Physiol 313:439–461

Babloyantz A, Salazar JM, Nicolis C (1985) Evidence of chaotic dynamics of brain activity during the sleep cycle. Phys Lett 111A:152–156

Beeler GW, Reuter H (1977) Reconstruction of the action potential of ventricular myocadial fibres. J Physiol 268:177–210

Bélair J (1986) Periodic pulsatile stimulation of nonlinear oscillator. J Math Biol 24:217–232

Bélair J, Glass L (1985) Universality and self-similarity in the bifurcations of circle maps, Physica 16D:143–154

Chay TR (1985) Chaos in a three-variable model of an excitable cell. Physica 16D:233–242

Chay TR, Lee YS (1985) Phase resetting and bifurcation in the ventricular myocardium. Biophys J 47:641–651

Clay J, DeFelice L, DeHaan R (1979) Current noise parameters derived from voltage noise and impedance in embryonic heart cell aggregates. Biophys J 28:169–184

Clay JR, Guevara MR, Shrier A (1984) Phase resetting of the rhythmic activity of embryonic heart cell aggregates. Biophys J 45:699–714

Colizza D, Guevara MR, Shrier A (1983) A comparative study of collagenase- and trypsin-dissociated embryonic heart cells: reaggregation, electrophysiology, and pharmacology. Can J Physiol Pharmacol 61:408–419

Connor JA (1985) Neuronal pacemakers and rhythmicity. Ann Rev Physiol 47:17–28

Cranefield P, Witt A (1979) Cardiac arrhythmias. Ann Rev Physiol 41:459–472

De Bruin G, Ypey DL, Van Meerwijk WPM (1983) Synchronization in chains of pacemaker cells by phase resetting action potential effects. Biol Cybern 48:175–186

DeHaan R, DeFelice L (1978) Oscillatory properties and excitability of the heart cell membrane. In: Theoretical chemistry: advances and perspectives. Academic Press, New York, pp 181–233

Eckmann JP (1981) Roads to turbulence in dissipative dynamical systems. Rev Mod Phys 53:643–654

Fabiato A, Fabiato F (1979) Calcium and cardiac excitation-contraction coupling. Ann Rev Physiol 41:473–484

Feigenbaum M (1978) Quantitative universality for a class of non-linear transformations. J Stat Phys 19:25–52

Glass L, Guevara MR, Shrier A (1983) Bifurcation and chaos in a periodically stimulated cardiac oscillator. Physica 7D:89–101

Glass L, Guevara MR, Bélair J, Shrier A (1984) Global bifurcations of a periodically forced biological oscillator. Phys Rev A29:1348–1357

Goldberger AL, Bhargava V, West BJ, Mandell AJ (1985) Nonlinear dynamics of the heartbeat. II: Subharmonic bifurcations of the cardiac interbeat intervals in sinus node disease. Physica 17D:207–214

Grassberger P, Procaccia I (1983) Measuring the strangeness of strange attractors. Physica 9D:189–208

Guevara MR, Glass L (1982) Phase locking, period doubling bifurcations and chaos in a mathematical model of a periodically driven oscillator: a theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias. J Math Biol 14:1–23

Guevara MR, Glass L, Shrier A (1981) Phase locking, period-doubling bifurcations, and irregular dynamics in periodically stimulated cardiac cells. Science 214:1350–1353

Guevara MR, Glass L, Mackey MC, Shrier A (1983) Chaos in neurobiology. IEEE Trans Syst Man Cybern SMC-13:790–798

Haken H (1985) Complex systems – operational approaches in neurobiology, physics and computers. Springer, Berlin Heidelberg New York

Hamill OP, Marty A, Neher E, Sakmann B, Sigworth J (1981) Improved patch-clamp technique for high resolution current recording from cells and cell-free membrane patches. Pflügers Arch 391:85–100

Hescheler J, Kameyama M, Trautwein W (1986) On the mechanism of muscarinic inhibition of the cardiac Ca-current Pflügers Arch 407:182–189

Hille B (1984) Ionic channels of excitable membranes. Sinauer, Sunderland

Holden AV (1982) Effects of tetraethylammonium and 4-aminopyradine on the somatic potential of an identified molluscan neuron. Comp Biochem Physiol 73A:303–310

Holden AV, Winlow W, Haydon PG (1983) The induction of perodic and chaotic activity in a molluscan neurone. Biol Cybern 43:169–173

Honerkamp J (1983) The heart as a system of coupled nonlinear oscillators. J Math Biol 18:69–88

Isenberg G, Klöckner U (1982a) Calcium tolerant ventricular myocytes prepared by preincubation in a 'KB medium'. Pflügers Arch 395:6–18

Isenberg G, Klöckner U (1982b) Isolated bovine ventricular myocytes: Characterization of the action potential. Pflügers Arch 395:19–29

Jensen JH, Christiansen PL, Scott AC, Skovgaard O (1984) Chaos in the Beeler-Reuter system for the action potential of ventricular myocardial fibres. Physica 13D:269–277

Keener JP (1980) Chaotic behaviour in piecewise continuous difference equations. Trans Am Math Soc 261:589–604

Lebrun P, Atwater I (1985) Chaotic and irregular bursting electrical activity in mouse pancreatic β-cells. Biophys J 48:529–531

MacKay RS, Tresser C (1986) Transition to topological chaos for circle maps. Physica 19D:206–237

Matsumoto G, Aihara K, Hanyu Y, Takahashi N, Yoshizawa S, Nagumo J (1987) Chaos and phase locking in normal squid axons. Phys Lett 123A:162–166

Nobel D (1986) Ionic mechanics controlling the action potential duration and the timing of the repolarization, Jpn Heart J 27:[Suppl] 3–19

Ott E (1981) Strange attractors and chaotic motions of dynamical systems. Rev Mod Phys 53:655–671

Rajasekar S, Lakshmanan M (1988) Period-doubling bifurcations, chaos, phase-locking and devil's staircase in a Bonhoeffer-Van der Pol oscillator. Physica 32D:146–152

Rapp PE, Zimmerman ID, Albano AM, Deguzman GC, Greenbaun NN (1985) Dynamics of spontaneous neural activity in the simian motor cordex: the dimension of chaotic neurons, Phys Lett 110A:335–338

Sherman A, Rinzel J, Keizer J (1988) Regularization of bursting in pancreatic beta cells by cannel sharing. Biophys J 53: W-Pos 113

Spear J, Moore E (1982) Mechanisms of cardiac arrhythmias. Ann Rev Physiol 44:485–497

Strittmatter W, Honerkamp J (1984) Fibrillation of a cardiac region and the tachycardia mode of a two-oscillator system. J Math Biol 20:171–184

West J, Goldberger AL, Rovner G, Bhargava V (1985) Nonlinear dynamics of the heartbeat. I. The AV junction: passive conduit or active oscillator. Physica 17D:198–206

Wolf A, Swift JB, Swinney HL, Vastano JA (1985) Determining Lyapunov exponents from a time series. Physica 16D:285–317