

CHAOTIC AND IRREGULAR BURSTING ELECTRICAL ACTIVITY IN MOUSE PANCREATIC B-CELLS

P. LEBRUN AND I. ATWATER

Laboratory of Cell Biology and Genetics, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

ABSTRACT The glucose-induced B-cell electrical activity was recorded in islets of Langerhans isolated from Swiss Webster albino mice originating from different suppliers. 23 out of 25 islets obtained from mice bred at the Charles River Breeding Station (CR mice) exhibited irregular or chaotic burst patterns of electrical activity, while 36 out of 40 islets isolated from mice bred locally at the National Institutes of Health displayed the typical bursting activity. The CR mice tended to recover a regular pattern after 1 mo on the National Institutes of Health mouse diet. The irregular or chaotic bursting electrical activity is proposed to result from changes in B-cell membrane composition or cellular metabolism, possibly induced by differences in diet.

INTRODUCTION

Mouse pancreatic B-cells stimulated by glucose display membrane potential fluctuations that have been proposed to represent an early event in the stimulus secretion coupling of glucose-induced insulin release (1). The general features of the glucose-induced electrical activity consist of a regular succession of depolarized phases with superimposed bursts of spikes (active phase) and silent repolarization periods. Although the absolute duration of a single burst may vary between 5 and 30 s in cells from different islets, the rhythmical burst pattern recorded from one cell usually remains constant over several hours of experimentation (1). Also, within an islet, most of the B-cells exhibit an identical burst pattern in the presence of glucose; this characteristic has been proposed to result from electrical coupling between the different cell domains (2).

Recently, an unusual burst pattern, which consists of a slow (~4 min) modulation in the intensity of the B-cell electrical activity, has been reported to occur in <20% of the islets examined (3, 4). Although several hypotheses have been proposed, at present there is no clear explanation for this irregularity. In the present study, we found that the incidence of the atypical glucose-induced B-cell electrical activity was dependent on the origin of the mice.

MATERIALS AND METHODS

Female Swiss Webster mice, 3–4 mo old, originally from the same strain, were obtained either from Charles River Breeding Station (Kingston, NJ) (CR mice) or from the National Institutes of Health (NIH) general animal house, Bethesda, MD (NIH mice). NIH mice were raised on a standard pellet diet (NIH No. 63-8760) containing 4.5% lipids, 23.5%

proteins, 4.5% fibers, and 54% carbohydrates. The CR mice were raised on another pellet diet (Charles River Breeding Station) containing 6.4% lipids, 21.4% proteins, 3.2% fibers, and 49.5% carbohydrates. Both mouse diets were void of any antibiotic or hormonal activity. Animals from both origins and from several shipments were allowed to settle in for at least 1 wk in the laboratory before use and received the standard NIH diet. Before decapitation, each animal was weighed and the blood glucose measured using a reagent strip in combination with a glucometer (Miles Ames Div., Miles Laboratories, Elkhart, IN).

A single islet of Langerhans was dissected from the tail portion of the pancreas of each mouse. Islets of the same size were isolated from 40 NIH mice and 25 CR mice. The electrical activity was recorded as previously described (2). The experiments were conducted from April through September of 1984.

RESULTS

In the presence of 11.1 mM glucose, a typical, regular, burst pattern of B-cell electrical activity was observed in 36 out of 40 islets isolated from NIH mice (Fig. 1 A). In the remaining islets, the B-cell electrical activity exhibited a slow modulation in the intensity of the burst pattern, which was similar to that described by others (3, 4). In contrast, 23 out of 25 islets isolated from CR mice showed irregular bursting of electrical activity throughout several hours of experimentation (Fig. 1, B and C). However, islets taken from CR mice maintained for 1 mo on NIH mouse diet tended to exhibit a more regular burst pattern (Fig. 1 D).

Two types of irregular pattern of B-cell electrical activity were observed in CR mice; one was chaotic (Fig. 1 B), and the other showed regularly repeating groups of bursts of variable duration (Fig. 1 C). As shown in Fig. 2, the modification in burst duration did not affect the rate of depolarization at the onset of each burst, nor did it affect the spike amplitude. However, the repolarization ending

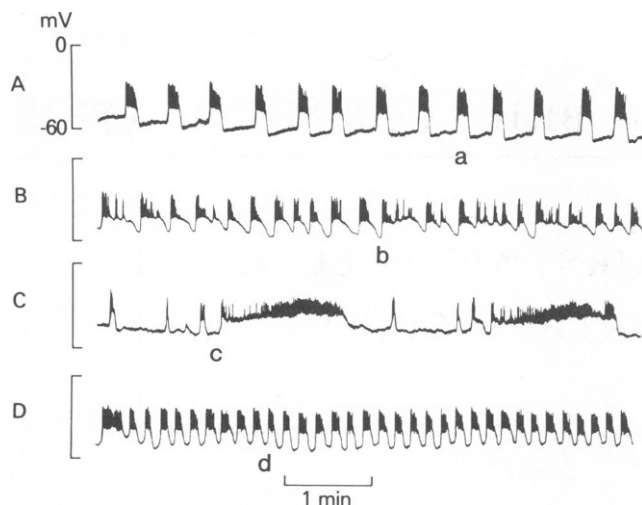


FIGURE 1 Steady-state bursting activity from four different mouse islets of Langerhans after 30-min exposure to 11.1 mM glucose. (A) NIH mouse islet; (B, C) CR mouse islets. (D) CR mouse islet after 1 mo on the NIH mouse diet. *a-d* indicate portions of the trace illustrated in Fig. 2.

each burst was much slower in the CR mice, even in those maintained for 1 mo in our laboratory. Also, the spike frequency distribution along the active phase of the bursts was altered with respect to the control experiments. In NIH mice (Fig. 2 *a*) spike frequency was always high at the beginning and decreased gradually during the active phase, as is usually described in pancreatic B-cell electrophysiology. In contrast, in the CR mice, spike frequency was uneven throughout the bursts (Fig. 2 *b*) or increased along the active phase (Fig. 2 *c*). Even in the islets that showed a tendency to recover a regular burst pattern (Fig. 2 *d*), the overall spike frequency was usually lower than in typical islets (Fig. 2 *a*).

In islets isolated from either CR mice or NIH mice, the removal of glucose induced the expected hyperpolarization with cessation of the electrical activity, whereas increasing the glucose concentration to 22.2 mM induced continuous spiking activity (data not shown).

Blood glucose levels in mice from both origins were not significantly different; their averages were 6.87 ± 0.76 mM (mean \pm SEM; $n = 40$) and 7.17 ± 1.08 mM (mean \pm SEM; $n = 25$) in NIH and CR mice, respectively. However, body weight differed significantly, averaging 22.75 ± 1.25 g (mean \pm SEM; $n = 40$) and 28.45 ± 1.05 g (mean \pm SEM; $n = 25$) for NIH and CR mice, respectively ($P < 0.005$).

DISCUSSION

The present data show that 23 out of 25 (~90%) islets of Langerhans isolated from CR mice exhibit an irregular or chaotic bursting electrical activity in the presence of 11.1 mM glucose. This high incidence of irregular or chaotic activity sharply contrasts with our observation of slow modulations in burst intensity in only 4 out of 40 (10%) islets obtained from NIH mice. Previous reports have described a similar pattern in <20% of the islets isolated from albino mice (3, 4).

The modifications in the repolarization rate of the burst, in the duration of the active phase and in the spike frequency distribution suggest that islets isolated from the CR mice present alterations in membrane ionic permeabilities. Interestingly, when using a mathematical model that simulates the typical B-cell electrical activity and that contains no stochastic components, chaotic bursting electrical activity, similar to that depicted in Fig. 1 *B*, was reproduced. This chaotic electrical activity was simulated by reducing the rate constants of the ionic permeabilities, and by varying the uptake rate of cytosolic calcium (5). This latter parameter specifically affects the potassium permeability (1). Thus, as the glucose-induced periodic oscillations in B-cell membrane potential have been shown to be correlated with cyclic variations in potassium permeability, the chaotic electrical activity observed in islets isolated from CR mice could reflect alterations in the potassium conductance (1).

On the other hand, the occurrence of an irregular bursting activity could also result from alterations in

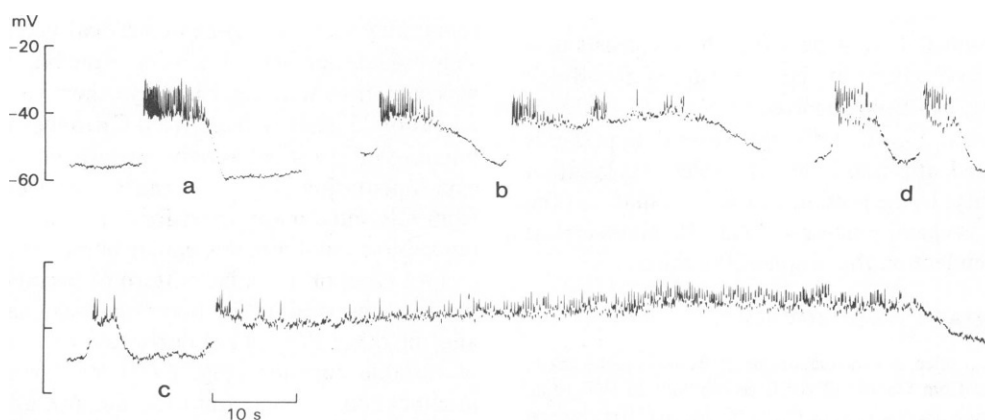


FIGURE 2 Details from Fig. 1, shown with an expanded time base. *a, b, c, and d* correspond, respectively, to the experiments illustrated in Fig. 1, parts A, B, C, and D.

cell-to-cell coupling. This might in turn exaggerate differences in the intrinsic frequency between cell domains and give rise to repeating groups of bursts of different durations (Fig. 1 C). Incidentally, since the insulin-releasing process has been shown to be correlated with the glucose-induced bursting activity, it is probable that the islets isolated from the CR mice exhibit irregular secretory oscillations (6).

At present there is no clear explanation for the origin of this irregular or chaotic electrical-activity exhibited by the islets isolated from CR mice. The mice were obtained from several shipments and the experiments were conducted during a 6 mo period, thus excluding a spurious or seasonal variation. Also, both groups of mice originated from the same strain, had similar blood glucose levels, and were used under the same experimental conditions (see Materials and Methods). However, the CR mice presented a body weight exceeding that of the NIH mice of the same age by ~25%. In healthy rodents, the body weight has been shown to be mainly correlated with the metabolic rate or with the lipid composition of the pellet diet (7, 8). The fatty acid and sterol content of diet can modify the cell membrane composition and has been proposed to affect the cell membrane fluidity and ionic permeability (9). As the CR mice were raised on a diet containing more lipids than the standard NIH diet, the erratic B-cell electrical activity could result from modifications in cell membrane composition induced by the diet. This hypothesis is supported by the finding that the islets isolated from the CR mice, which were fed with the NIH diet for 1 mo, tended to resume a regular bursting pattern. On the other hand, changes in the cytosolic composition due to alteration of cellular metabolism could also generate such irregular or chaotic electrical activity by affecting the channel properties and/or cell-to-cell coupling.

In conclusion, the incidence of erratic bursting pattern

of electrical activity recorded from islets of Langerhans was found to be dependent on the origin of the mice. Alterations in membrane ionic permeabilities or cell-to-cell coupling could result from changes in membrane composition or cellular metabolism. It is tempting to speculate that these changes could result from differences in diet; however, the involvement of some other environmental factors cannot be excluded.

Received for publication 11 February 1985 and in final form 11 May 1985

REFERENCES

1. Atwater, I., C. M. Dawson, A. Scott, G. Eddlestone, and E. Rojas. 1980. The nature of the oscillatory behaviour in electrical activity from the pancreatic B-cell. *Horm. Metab. Res.* 10 (Suppl.):100-107.
2. Meda, P., I. Atwater, A. Goncalves, A. Bangham, L. Orci, and E. Rojas. 1984. The topography of electrical synchrony among B-cells in the mouse islet of Langerhans. *Q. J. Exp. Physiol.* 69:719-735.
3. Cook, D. L. 1983. Isolated islets of Langerhans have slow oscillations of electrical activity. *Metabolism.* 32:681-685.
4. Henquin, J. C., H. P. Meissner, and W. Schmeer. 1982. Cyclic variations of glucose-induced electrical activity in pancreatic B-cells. *Pfluegers Arch. Eur. J. Physiol.* 393:322-327.
5. Chay, T. R., and J. Rinzel. 1985. Bursting, beating and chaos in an excitable membrane model. *Biophys. J.* 47:357-366.
6. Atwater, I., E. Rojas, and A. Scott. 1979. Simultaneous measurements of insulin release and electrical activity from single microdissected mouse islets of Langerhans. *J. Physiol. (Lond.)* 291:57P.
7. Storer, J. B. 1967. Relation of lifespan to brain weight, body weight, and metabolic rate among inbred mouse strains. *Exp. Gerontol.* 2:173-182.
8. Peckham, S. C., C. Entenman, and H. D. Carroll. 1962. The influence of a hypercaloric diet on gross body and adipose tissue composition in the rat. *J. Nutr.* 77:187-197.
9. Kummerow, F. A. 1983. Modification of cell membrane composition by dietary lipids and its implication for atherosclerosis. *Ann. NY Acad. Sci.* 414:29-43.