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Repaglinide, glibenclamide and glimepiride administration to normal and hereditarily diabetic rats

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Abstract

Repaglinide (1 μg/g body wt), glibenclamide (10 μg/g) or glimepiride (10 μg/g) were administered orally to either fed or overnight fasted normal rats and hereditarily diabetic animals (GK rats). In both fed and starved normal rats, repaglinide provoked a greater and more rapid increase in plasma insulin concentration and an earlier fall in glycemia than those observed after administration of the hypoglycemic sulfonylureas. Likewise, in fed GK rats, the plasma insulin concentration was already increased by 30.0 ± 1.6% 15 min after administration of repaglinide, whilst a sizeable insulinotropic action of the sulfonylureas was only recorded at much later times. Except for a lower glycemia at the 240th min of the test, there was little to distinguish, in starved GK rats, between control experiments including the oral administration of the solution of carboxymethylcellulose used as vehicle and the experiments conducted with the antidiabetic agents. Several converging observations indicated that glimepiride stimulated insulin release more promptly than glibenclamide. It is proposed that advantage can be taken from these vastly different time-courses of the hormonal and metabolic response to distinct hypoglycemic agents to optimize the control of glucose homeostasis in non-insulin-dependent diabetic subjects. © 1997 Elsevier Science B.V.

Keywords: Repaglinide; Glibenclamide; Glimepiride; Insulin secretion; (GK rat)

1. Introduction

The restoration of glucose homeostasis in non-insulin-dependent diabetic subjects remains a challenge, the modality of treatment by antidiabetic agents requiring to be adjusted in each individual case. In this perspective, the present study draws attention to the vastly different pattern of the plasma insulin and glucose responses evoked, in both normal and hereditarily diabetic rats examined either in the fed state or after an overnight fasting, by the oral administration of three distinct hypoglycemic agents, namely the meglitinide analogue repaglinide and the sulfonylureas glibenclamide and glimepiride.

2. Materials and methods

Female Wistar rats (Proefdierencentrum, Heverlee, Belgium) and female or male GK rats from our local colony were given free access to food (AO3; Animalabo, Brussels, Belgium) and tap water up to the time of experimentation.

Normal female rats, all about 2 months old, were examined either in the fed state (205 ± 3 g body wt; $n = 16$) or after overnight starvation (186 ± 3 g; $n = 16$). Sixteen GK rats (2 to 3 months old), including 8 males (285 ± 8 g) and 8 females (190 ± 2 g) were tested in the fed state. Twenty four male GK rats (4 to 5 months old) were investigated after overnight fasting (321 ± 5 g).

All drugs used in the present study were solubilized in a 0.5% solution of carboxymethylcellulose sodium salt (Merck, Darmstadt, Germany). Repaglinide was provided by Dr. Karl Thomae (Biberach, Germany) and glimepiride by Hoechst (Frankfurt am Main, Germany). Glibenclamide was purchased from Sigma (St. Louis, MO, USA).

A 2 ml volume of the solution of carboxymethylcellulose containing, as required, either repaglinide (1 μg/g body wt), glibenclamide (10 μg/g body wt) or glimepiride (10 μg/g body wt), was injected via a plastic catheter fitted to a syringe and gently introduced into the stomach.

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Blood samples (0.5 ml) were collected from the severed tip of the tail in heparinized tubes before and at time intervals after the intragastric administration of the tested drugs. The plasma was separated by centrifugation and stored at −20°C until assay. The plasma concentrations of D-glucose (Bergmeyer and Berndt, 1974) and insulin (Leclercq-Meyer et al., 1985) were measured by methods described in the cited references.

All results are expressed as mean values (±S.E.M.) together with the number of individual observations (n). The statistical significance of differences between mean values was assessed by use of Student's t-test.

3. Results

3.1. Basal values

In normal rats, the plasma glucose and insulin concentrations, as well as the paired plasma insulin/glucose ratio were all significantly lower ($P < 0.001$) in overnight fasted than fed animals (Table 1). Such was also the case ($P < 0.001$) in GK rats. Whether in fed or starved animals, the plasma glucose and insulin concentrations were higher ($P < 0.001$) in diabetic than normal rats. The insulin/glucose ratio was not significantly different in normal and GK rats, when examined in the fed state, but was higher in GK than normal animals ($P < 0.001$) after overnight starvation.

3.2. Plasma glucose concentration

In fed normal rats, the administration of the solution of carboxymethylcellulose containing no hypoglycemic agent (control experiments) provoked a modest rise in plasma glucose concentration (Fig. 1) peaking at the 15–30th min at a level 1.67 ± 0.35 mM ($n = 4$; $P < 0.01$) higher than the paired initial value (min −30). At the 240th min, the hexose concentration was no more significantly different (paired change: -0.17 ± 0.38 mM; $n = 4$) from its initial value. A comparable pattern was observed in overnight fasted rats. The peak value reached at the 15–30th min was 1.73 ± 0.21 mM ($n = 4$; $P < 0.005$) higher than the paired initial measurement, and the plasma glucose concentration at min 240 had returned to such an initial value (paired change: $+0.11 \pm 0.19$ mM; $n = 4$).

In the fed normal rats receiving repaglinide, the rise in plasma glucose concentrations initiated between min −30 and time zero (paired change: $+0.24 \pm 0.12$ mM; $n = 4$) was soon interrupted, the hexose concentration reached at min 30 being already 2.79 ± 0.24 mM ($n = 4$; $P < 0.005$) lower than the paired value at time zero. Thereafter, the sugar concentration remained at a low level up to the 240th min. Similar changes were recorded in the overnight starved animals. Whilst the hexose concentration increased by 0.67 ± 0.13 mM ($n = 4$; $P < 0.02$) between min −30 and time zero, it fell by 0.65 ± 0.12 mM ($n = 4$; $P < 0.02$) over the ensuing 15 min and, thereafter, further decreased, eventually reaching at the 240th min a level 3.92 ± 0.31 mM ($n = 4$; $P < 0.005$) lower than the paired reading at time zero.

Whether in fed or fasted normal rats, the administration of glibenclamide or glimepiride also provoked a significant and sustained lowering of plasma glucose concentration. For instance, in fed animals, the paired difference in hexose concentration between time zero and min 240 corresponded to a fall of 3.51 ± 0.33 and 3.52 ± 0.35 mM ($n = 4$; $P < 0.005$ in both cases) after administration of glibenclamide and glimepiride, respectively, as compared ($P > 0.4$) to 3.85 ± 0.22 mM ($n = 4$; $P < 0.001$) after repaglinide delivery. Likewise, in overnight fasted rats, the paired difference between time zero and min 240 averaged 3.52 ± 0.22 mM ($n = 4$; $P < 0.001$) and 3.43 ± 0.20 mM ($n = 4$; $P < 0.001$) in the case of glibenclamide and glimepiride, respectively, such decreases being again not significantly different from those observed in the animals receiving repaglinide.

The hypoglycemic response to the sulfonylureas differed, however, from that evoked by repaglinide by its time-course. Indeed, in the former case, a significant decrease in plasma glucose concentration below the paired value at time zero was first detected at min 60 in fed rats receiving glibenclamide (2.06 ± 0.30 mM; $n = 4$; $P < 0.01$), at min 30 in fed animals administered with glimepiride (0.52 ± 0.14 mM; $n = 4$; $P < 0.05$), at min 90 after delivery of glibenclamide to overnight fasted rats (2.20 ± 0.46 mM; $n = 4$; $P < 0.02$), and at min 60 after administration of glimepiride to starved animals (1.51 ± 0.23 mM; $n = 4$; $P < 0.01$). The fall in sugar concentration thus occurred later in the animals receiving a hypoglycemic sulfonylurea than after administration of repaglinide or, when first detected at the same time, was less pronounced ($P < 0.001$) in the former than latter situation.

The changes in plasma glucose concentration resulting from the administration of the solution of carboxymethylcellulose, whether containing or not a hypoglycemic agent, differed vastly in GK rats from those found in normal animals (Fig. 2).

In the control experiments conducted in fed GK rats, the plasma glucose reached its peak value between min 30 and 90. The paired increment above initial value was much higher ($P < 0.001$) in GK rats (15.05 ± 1.16 mM; $n = 4$) than in control animals (1.67 ± 0.35 mM; $n = 4$). Nevertheless, at the 240th min, the sugar concentration was no more significantly different from the initial measurement (paired change: $+0.06 \pm 0.57$ mM; $n = 4$). Likewise, in starved GK rats, the peak value was reached between the 30th and 90th min and corresponded to a paired increment above the initial measurement of 9.73 ± 0.43 mM ($n = 6$), as distinct ($P < 0.001$) from 1.73 ± 0.21 mM ($n = 4$) in normal starved rats. In the overnight fasted GK rats, the

Table 1
Initial values for plasma glucose and insulin concentrations and insulin/glucose ratio in normal and GK rats

Metabolic status	Nutritional status			
	normal rats		diabetic rats	
	fed	starved	fed	starved
Plasma glucose (mM)	8.13 ± 0.12 (16)	6.08 ± 0.16 (16)	15.84 ± 1.00 (16)	10.65 ± 0.45 (24)
Plasma insulin (μU/ml)	24.0 ± 1.8 (16)	6.4 ± 1.0 (16)	61.5 ± 8.5 (16)	21.7 ± 1.9 (24)
Insulin/glucose ratio (U/mol)	2.95 ± 0.22 (16)	1.03 ± 0.14 (16)	4.27 ± 0.71 (16)	2.17 ± 0.16 (24)

plasma glucose concentration at min 240 even remained somewhat higher than its initial value (paired change: +1.44 ± 0.22 mM; $n = 6$; $P < 0.005$).

When the fed GK rats received at time zero a solution containing a hypoglycemic agent, two major differences were observed by comparison with the control experiments. First, the peak value for plasma glucose concentration, which was reached at the 15th or 30th min, yielded a

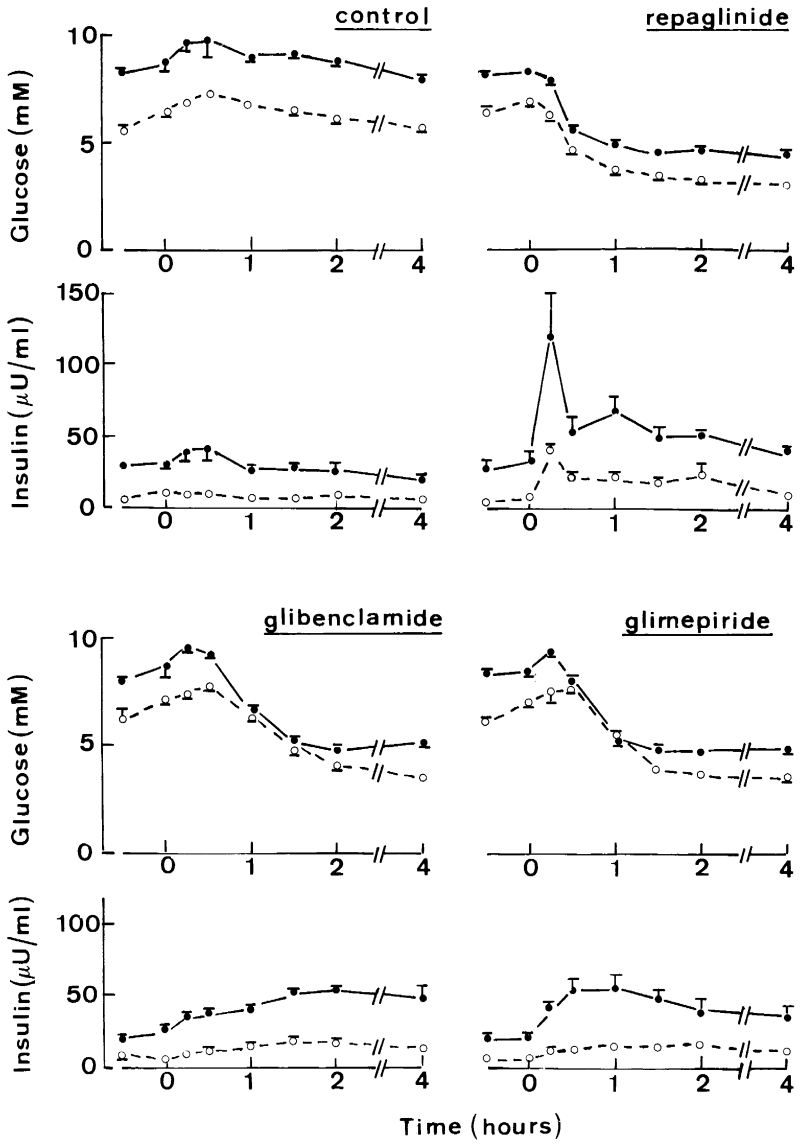

Fig. 1. Time-course for the changes in plasma glucose and insulin concentrations in fed (closed circles and solid lines) or overnight fasted (open circles and dotted lines) normal rats injected intragastrically at time zero with 2.0 ml of a solution of carboxymethylcellulose containing, as required, repaglinide, glibenclamide or glimepiride. Mean values (±S.E.M.) refer to 4 individual experiments in all cases.

mean increment above paired initial value not exceeding 10.91 ± 2.35, 9.23 ± 1.04 and 9.34 ± 1.66 mM, as compared to 15.05 ± 1.16 mM ($n = 4$ in all cases) in the control experiments. This difference achieved statistical significance ($P < 0.05$ or less) in the case of the hypoglycemic sulfonylureas, but not so ($P > 0.1$) in the case of repaglinide. Second, between the 30th and 120th min, the fall in hexose concentration was much more pronounced ($P < 0.025$ or less) in the animals receiving repaglinide (paired change: -12.56 ± 1.35 mM), glibenclamide (paired change: -13.78 ± 2.54 mM) or glimepiride (paired change: -15.04 ± 0.88 mM) than in the control experiments (paired change: -4.24 ± 1.79 mM).

In starved GK rats, no significant difference was found between control experiments and those conducted with a hypoglycemic agent as far as the time and magnitude for the increment in plasma glucose concentration are concerned. For instance, the peak value corresponded to a paired increase above the initial reading of 8.17 ± 1.29, 11.10 ± 0.82 and 9.01 ± 0.81 mM in the case of repaglinide, glibenclamide and glimepiride, respectively, as compared to 9.73 ± 0.43 mM in the control experiments ($n = 6$ in all cases). The sole significant effect of the hypoglycemic drugs was to slightly lower the plasma glucose level at the 240th min. The paired difference between the measurements made at such a time and the initial value was indeed significantly lower ($P < 0.025$ or less) in the case of repaglinide (-0.98 ± 0.76 mM), glibenclamide (-0.98 ± 0.82 mM) and glimepiride (-2.23 ± 1.06 mM) than in the control experiments ($+1.44 \pm 0.22$ mM).

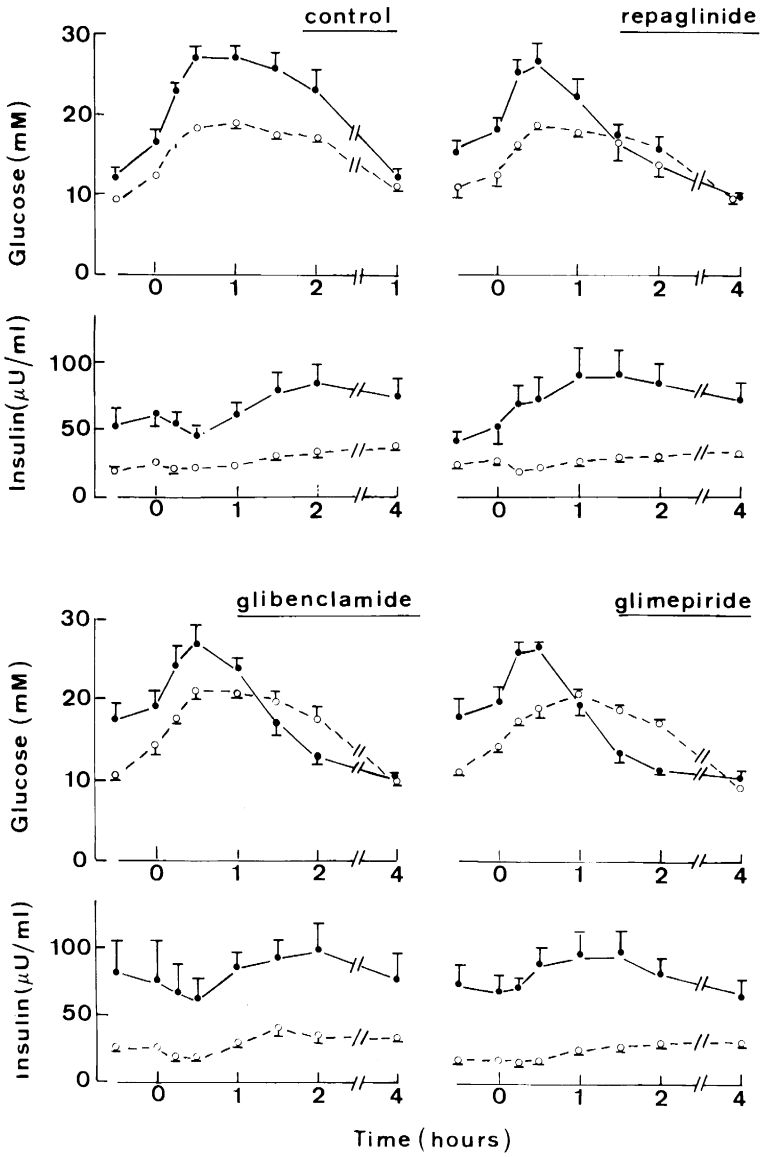

Fig. 2. Time-course for the changes in plasma glucose and insulin concentrations in fed (closed circles and solid lines) or overnight fasted (open circles and dotted lines) GK rats injected intragastrically at time zero with 2.0 ml of a solution of carboxymethylcellulose containing, as required, repaglinide, glibenclamide or glimepiride. Mean values (±S.E.M.) refer to 4 (fed rats) and 6 (fasted animals) individual experiments.

3.3. Plasma insulin concentration

In fed normal rats, the administration of the solution of carboxymethylcellulose first provoked a modest but significant rise in plasma insulin concentration. The peak value was reached at the 15th–30th min, and corresponded to a paired increment above the initial measurements of 14.8 ± 4.5 μU/ml ($n = 4$; $P < 0.05$). Thereafter, the hormone concentration returned to its initial value. Likewise, in overnight starved normal rats, the insulin concentration at the 15–30th min was somewhat higher than its initial value, with paired increments not exceeding 3.8 ± 1.3 μU/ml ($n = 4$; $P < 0.06$). Later measurements were essentially indistinguishable from the initial value.

Both in fed and starved normal rats, the administration of repaglinide caused a pronounced and sustained increase in plasma insulin concentration. The peak value was always reached at the 15th min, it corresponding to a paired increment above the time zero readings of 88.9 ± 20.9 and 34.5 ± 3.6 μU/ml ($n = 4$ in both cases; $P < 0.025$ or less) in fed and fasted animals, respectively. Even at the 240th min, the mean hormonal concentration remained higher than the value at time zero, with paired increments averaging 6.2 ± 5.3 μU/ml ($n = 4$; $P > 0.3$) in fed rats and 4.9 ± 0.9 μU/ml ($n = 4$; $P < 0.02$) in starved rats.

A vastly different pattern characterized the secretory response of the B-cell to the hypoglycemic sulfonylureas, as distinct from the meglitinide analogue. Indeed, in the former case, the plasma insulin concentration increased progressively, reaching its peak value only 90–240 min (mean 154 ± 26 min; $n = 8$) after administration of glibenclamide and 15–120 min (mean 51 ± 12 min; $n = 8$) after

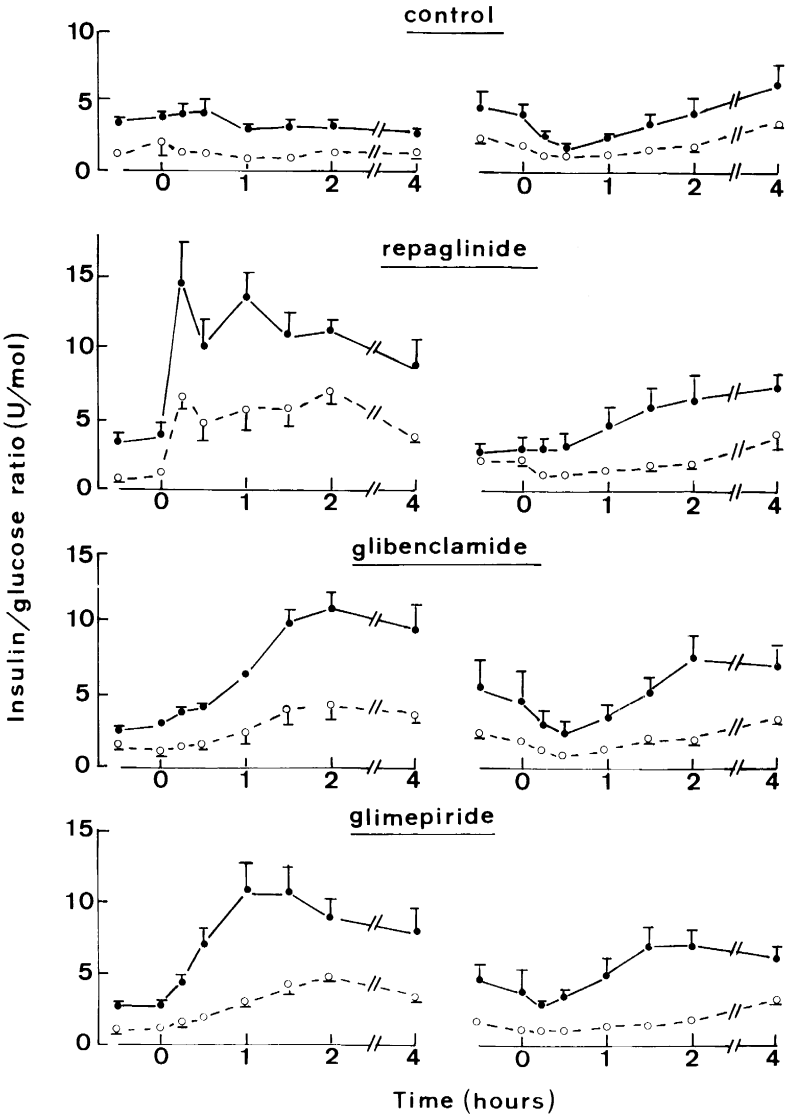

Fig. 3. Time-course for the changes in the plasma insulin/glucose ratio in fed (closed circles and solid lines) and overnight fasted (open circles and dotted lines) normal animals (left panels) or GK rats (right panels) injected intragastrically at time zero with a solution of carboxymethylcellulose containing, as required, repaglinide, glibenclamide or glimepiride. Mean values (±S.E.M.) refer to 4 individual experiments except in the starved GK rats, in which case 6 experiments were performed.

delivery of glimepiride. The highest hormonal concentration reached in each individual experiment corresponded to a paired increment above the time zero determination of 32.4 ± 7.6 and 36.5 ± 9.9 μU/ml ($n = 4$; $P < 0.05$ or less) in fed rats receiving glibenclamide and glimepiride, respectively, as distinct ($P < 0.06$ or less) from corresponding values of no more than 12.4 ± 2.7 and 12.0 ± 1.6 μU/ml ($n = 4$; $P < 0.02$ or less) in starved animals. In all cases, the plasma insulin concentration at the 240th min remained higher than the paired time zero reading, such a difference averaging, in fed rats, 23.9 ± 8.7 ($P < 0.08$) and 16.1 ± 5.1 μU/ml ($P < 0.06$) and, in starved rats, 7.5 ± 4.1 ($P < 0.18$) and 6.5 ± 2.0 ($P < 0.05$) μU/ml in the case of glibenclamide and glimepiride, respectively.

In the control experiments conducted in either fed or starved GK rats, the salient feature of the insulin profile consisted in a progressive increase of hormonal concentration beyond the 30th min after administration of the solution of carboxymethylcellulose. The paired difference in hormone concentration at min 30 and 240 averaged 29.8 ± 5.8 μU/ml ($n = 4$; $P < 0.02$) in fed rats and 15.8 ± 2.0 μU/ml ($n = 6$; $P < 0.001$) in starved animals. This late increase in insulin concentration was often preceded by a modest fall. For instance, between time zero and min 15, the level of circulating insulin decreased in both fed and starved GK rats, with an overall mean fall of 6.3 ± 2.5 μU/ml ($n = 10$; $P < 0.05$).

In fed GK rats, the administration of repaglinide prevented this initial fall in insulinemia and, on the contrary, increased the concentration of insulin by 16.2 ± 4.2 μU/ml ($n = 4$; $P < 0.05$) between time zero and min 15. Moreover, the peak increment in hormone concentration above the paired time zero reading represented a relative increase of 90.2 ± 16.8% in the rats receiving the meglitinide analogue, as distinct from only 37.3 ± 3.8% in the control experiments ($n = 4$ in both cases; $P < 0.02$). In starved GK rats, however, repaglinide did not suppress the early decrease in plasma insulin concentration (paired fall between time zero and min 15: 9.7 ± 1.5 μU/ml; $n = 6$; $P < 0.005$), and failed to provoke a peak increment above the time zero reading significantly different ($P > 0.2$) from that recorded in the control experiments.

The administration of glibenclamide failed to suppress the early fall in insulinemia. Indeed, in both fed and starved rats, the nadir value for plasma insulin was reached at min 30, being 10.4 ± 5.4 μU/ml ($n = 10$; $P < 0.09$) lower than the paired zero time measurement. In the case of glimepiride, however, the paired difference in hormone concentration between time zero and min 30 indicated a mean increase of 8.7 ± 6.0 μU/ml ($n = 9$; $P > 0.2$). The early response to the two sulfonylureas was thus seemingly different ($P < 0.05$). Thereafter, there was little to distinguish between the results of control experiments and of those including the administration of a sulfonylurea. In fed GK rats, the peak increment in plasma insulin concentration above the zero time reading averaged 25.5 ± 11.6 μU/ml ($n = 4$; $P > 0.1$) and 33.9 ± 7.5 μU/ml ($n = 4$; $P < 0.05$) in rats injected with glibenclamide and glimepiride respectively, as compared to 23.4 ± 5.1 μU/ml ($n = 4$; $P < 0.02$) in the control experiments. Likewise in starved GK rats, the peak increment averaged 19.3 ± 5.1 μU/ml ($n = 6$; $P < 0.02$) and 17.4 ± 1.2 μU/ml ($n = 6$; $P < 0.001$) after administration of glibenclamide and glimepiride, respectively, as compared to 15.7 ± 2.4 μU/ml ($n = 6$; $P < 0.005$) in the control experiments.

3.4. Insulin / glucose ratio

In order to reach a better understanding of the data so far presented, the paired ratio between plasma insulin/glucose concentrations was calculated in each sample (Fig. 3).

In the control experiments conducted in either fed or starved normal rats, this ratio remained fairly stable throughout the period of observation. Whether in fed or fasted normal rats, repaglinide caused a rapid and sustained increase in the insulin/glucose ratio. Likewise, glibenclamide and glimepiride significantly increased the ratio between hormone and hexose concentrations, both in fed and starved animals. In this case, however, the peak value was reached at a later time than in the experiments including the administration of repaglinide. For instance in fed rats, the peak value was reached, in individual experiments, at min 15 with repaglinide, at min 60–90 with glimepiride and only at min 120–240 with glibenclamide. Likewise, in starved rats, the peak measurements were recorded at the 15th min in animals receiving repaglinide, as distinct from 90–120 min after administration of glimepiride and 120–240 min after glibenclamide injection. Pooling the results of the two series of experiments (fed and starved rats), the time corresponding to the peak value averaged 15 ± 0, 97 ± 8 and 180 ± 23 min after administration of repaglinide, glimepiride and glibenclamide, respectively ($n = 8$ in all cases), such mean values being significantly different from one another ($P <$ 0.005 or less).

A different pattern prevailed in GK rats. Except in the fed rats receiving repaglinide, the paired insulin/glucose ratio decreased during the first part of the experiments. Between the initial measurements and min 15, the insulin/glucose ratio decreased by 2.04 ± 0.62 U/mol ($n = 12$; $P < 0.01$) in fed rats and by 1.06 ± 0.16 U/mol ($n = 24$; $P < 0.001$) in starved rats. Thereafter, a progressive reascension of the insulin/glucose ratio was observed in all cases. In fed GK rats, a significant increase in such a ratio above the time zero value was only reached at the 240th min in the control experiments (paired change: 2.31 ± 0.66 U/mol; $P < 0.05$). In the fed rats receiving repaglinide, the increase reached at the 90th min was already significant (paired change: 2.86 ± 0.82 U/mol; $P < 0.05$). After glibenclamide administration, a delay of 120 min was required to detect a significant increase of the insulin/glucose ratio above the zero time value (paired

change: 2.97 ± 0.53 U/mol; $P < 0.02$). Last, in the fed GK rats receiving glimepiride, the increment in the hormone/hexose ratio was already significant at the 60th min (paired change: 1.38 ± 0.43 U/mol; $P < 0.05$) and further increased at the 120th min to 3.46 ± 0.67 U/mol ($P < 0.02$). These comparisons indicate that the administration of the hypoglycemic agents accelerated the reascension of the insulin/glucose ratio, relative to the situation found in the control experiments.

In the starved GK rats, the pattern of changes in the plasma insulin/glucose ratio was virtually indistinguishable in the control experiments and those including the administration of a hypoglycemic agent.

4. Discussion

The baseline values for plasma glucose and insulin concentrations found in the present study indicate that starvation lowers, in both normal and GK rats, the insulin/glucose ratio, suggesting a decreased responsiveness of the pancreatic B-cell to glucose, as indeed previously documented in experiments conducted both in vivo and in vitro (Malaisse et al., 1967). The abnormally high values for such a ratio in the GK rats are more likely, however, to reflect insulin resistance, since the secretory response to D-glucose of isolated islets from GK rats is severely decreased (Östenson et al., 1993).

The results of the control experiments conducted in the absence of an antidiabetic agent were rather unexpected. In fed conscious normal rats, the intragastric administration of saline leads to both a decrease in plasma insulin concentration and a rise in glycemia, both phenomena being currently ascribed to the mild stress caused by the handling of the animals and the repeated blood collections from the severed end of the tail (Malaisse-Lagae et al., 1994; Vicent et al., 1994). In the normal rats receiving the solution of carboxymethylcellulose, a modest rise in plasma glucose concentration was also observed, but it failed to coincide with a decrease in insulinemia. On the contrary, both the plasma insulin concentration and insulin/glucose ratio were transiently increased, at least in fed rats. A possible explanation for these findings could consist in a release of insulinotropic gastrointestinal hormones that would counteract the consequences of the postulated stress.

In the GK rats, however, the prevailing changes recorded during the initial part of the control experiments consisted in a decrease of plasma insulin concentration and increase in glycemia. These changes, which were observed in both fed and starved animals, coincided with a decrease in the plasma insulin/glucose ratio indeed supporting the view of an adrenergic stress. In this perspective, the later rise in the insulin/glucose ratio may correspond to the relief from such a stress, when the blood sampling became less frequent.

Repaglinide, although given in an amount 10 times lower than that of either glibenclamide or glimepiride provoked a much earlier and initially greater stimulation of insulin release than the two sulfonylureas. This was quite obvious in normal rats, whether fed or starved. Even in fed GK rats, the plasma insulin concentration was already increased by 16.2 ± 4.2 μU/ml ($n = 4$; $P < 0.05$) 15 min after administration of repaglinide, this representing a 30.0 ± 1.6% increment above the paired measurement at time zero, whereas a comparable rise occurred much later in the animals receiving glimepiride or glibenclamide. The insulinotropic action of repaglinide, as well as that of the hypoglycemic sulfonylureas, only failed to be easily discernible in starved GK rats, the sole effects of the antidiabetic agents being to prevent, on occasion, the early fall in plasma insulin concentration and to decrease glycemia at the 240th min of the test.

The greater sensitivity of fed, as distinct from overnight fasted, GK rats to the hypoglycemic agents resulted in the fact that, about 60 min after their administration, the plasma glucose concentration became lower in fed animals than in the starved rats.

Several converging observations indicate that glimepiride caused a more rapid stimulation of insulin release than glibenclamide. Thus, in normal rats, whether examined in the fed or starved state, a significant decrease in plasma glucose concentration below the paired value at time zero was first detected 30 min earlier in the animals receiving glimepiride rather than glibenclamide. This coincided with an earlier peak in both plasma insulin concentration and insulin/glucose ratio. Likewise, in fed GK rats, a significant increase in the insulin/glucose ratio above the time zero value occurred earlier after glimepiride, rather than glibenclamide, administration. Moreover, both in fed and starved GK rats, glimepiride, but not glibenclamide, suppressed the initial fall in plasma insulin concentration otherwise observed over the first 30 min after oral injection of the solution of carboxymethylcellulose.

In conclusion, the present study documents that distinct hypoglycemic agents, that are all thought to exert their insulinotropic action through the same sequence of biological events in the pancreatic islet B-cell (Lins et al., 1995; Malaisse, 1995), affect both the insulinemia and glycemia according to vastly different time-courses, when administered orally to either normal or diabetic animals. If comparable differences were to prevail in non-insulin-dependent diabetic subjects, it would be the responsibility of the physician to decide which of these patterns is best suited for the control of glucose homeostasis in each patient.

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