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Hypoglycaemic effects of the novel antidiabetic agent repaglinide in rats and dogs

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1 Repaglinide, a novel compound with a nonsulphonylurea structure, is currently being clinically tested as a therapeutic agent. In the present study, the hypoglycaemic effects of repaglinide in rats and dogs were investigated.

2 Whereas the **R**-enantiomer, AG-EE 624 ZW, showed only weak hypoglycaemic activity, the **S**-enantiomer, repaglinide, turned out to be a potent hypoglycaemic compound in rats after oral as well as after intravenous administration. Only 50% of the dose of repaglinide was needed to be equieffective with the racemic mixture AG-EE 388 ZW. The corresponding ED50 values calculated for the effects after 120 min p.a. (intravenous administration) were 3.4 μg kg^{-1} (repaglinide) and 6 μg kg^{-1} (AG-EE 388 ZW).

3 When compared to glimepiride or glibenclamide, repaglinide displayed a 18 to 25 times higher potency in fasted rats. The ED50 values calculated for the effects after 120 min p.a. (oral administration) were 10 μg kg^{-1} (repaglinide), 182 μg kg^{-1} (glimepiride) and 255 μg kg^{-1} (glibenclamide).

4 In glucose loaded rats (0.5, 1.0, 2.0 and 3.0 g kg^{-1} glucose, p.o.) repaglinide exerted a very strong antihyperglycaemic activity which was even more pronounced than under normoglycaemic conditions. So for a reduction in blood glucose of 1 mmol l^{-1}, 10.3, 9.3, 7.0 8.4 and 7.2 μg kg^{-1} repaglinide were needed after glucose loads of 0.0, 0.5, 1.0, 2.0 and 3.0 g kg^{-1}, respectively.

5 In beagle dogs repaglinide again showed a pronounced hypoglycaemic effect (ED50 28.3 μg kg^{-1}) which lasted for up to 24 h. However, insulin levels were only transiently increased.

6 The *in vivo* data presented are well supported by recently published *in vitro* findings. From its activity profile, repaglinide appears to be a promising new therapeutic agent.

Keywords: Repaglinide; antidiabetic agents; hypoglycaemic effects; antihyperglycaemic effects

Introduction

Standard therapy for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), besides diet and exercise, consists of drug treatment, mainly with sulphonylureas. Since the introduction of tolbutamide in 1956, this class of compounds has been widely used for the treatment of type II diabetic patients. However, with the limitations of oral antidiabetic therapy in mind, major efforts have been attributed to the search for alternative antidiabetic compounds, to both novel insulin secretagogues and compounds able to enhance insulin action in target tissues.

One such approach involved the study of a series of benzoic acid derivatives (Geisen *et al*., 1978). However, meglitinide (HB699), as the lead compound, displayed only weak hypoglycaemic activity when compared to the most potent sulphonylureas exemplified by glibenclamide or glipizide (Ribes *et al*., 1983; Garrino *et al*., 1985; Panten *et al*., 1989). Within another series of benzoic acid derivatives, the racemic AG-EE 388 ZW and moreover its **S**-enantiomer AG-EE 623 ZW (=repaglinide) were found to be potent hypoglycaemic compounds when tested *in vivo* or in isolated pancreatic islets (Verspohl *et al*., 1990; Fuhlendorff *et al*., 1995a). Repaglinide, currently undergoing phase III clinical trials, represents one of the most potent antidiabetic compounds of this series described so far.

Like the sulphonylureas, repaglinide is an insulinotropic agent, as evidenced by *in vitro* studies with mouse and rat pancreatic islets (Frøkjaer-Jensen *et al*., 1992; Gromada *et al*., 1995; Malaisse, 1995). Similar to the sulphonylureas, repaglinide also inhibits adenosine 5′-triphosphate (ATP)-sensitive potassium channels thus leading to an increase in intracellular Ca^{2+} concentration (Gromada *et al*., 1995). This has been further substantiated in islet studies where Ca^{2+} in the medium was replaced by Ba^{2+}. Repaglinide failed to affect insulin release under these conditions (van Onderbergen *et al*., 1995). However, the binding characteristics of repaglinide to whole mouse βTC3 cells are found to be different from those of the sulphonylurea glibenclamide (Fuhlendorff *et al*., 1995b). Tolbutamide, glipizide and glibenclamide, but not repaglinide, stimulate insulin exocytosis in voltage-clamped mouse β cells, unrelated to their effect on ATP-sensitive potassium channels (Fuhlendorff *et al*., 1995a). In addition, in mouse perifused islets repaglinide is 3–5 times more efficient at releasing insulin than glibenclamide and this effect is more dependent on the presence of D-glucose (Kofod & Fuhlendorff, 1995).

In the present study the hypoglycaemic activities of repaglinide in rats and dogs are described, and comparative data with glibenclamide and glimepiride in rats are presented.

Methods

Adult female Wistar rats, strain Chbb: THOM (SPF) with a body weight of 200–220 g were used. Animals were fed *ad libitum* with standard pelleted diets and were housed under a 12/12 h light/dark cycle with 7 h 00 min to 19 h 00 min being the light phase. In studies with fasted animals, food was withdrawn 24 h before the start of the studies between 8 h 00 min and 10 h 00 min.

Female Beagle dogs, strain Chbb: Beagle, with a body weight of 10–16 kg were used. Animals were fed with 400 g standard dog diet (Nafag NO9405) daily at 10 h 00 min. The studies were performed in fasted animals and started between 7 h 00 min–8 h 00 min.

For intravenous administration, the substances were dissolved in a small amount of 0.1 M sodium hydroxide solution

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and diluted to the desired volume with physiological saline solution. The pH was checked and if necessary adjusted to pH 7.3 with 0.1 M hydrochloric acid. The solutions (volume 1.0 ml kg^{-1}) were administered via the tail vein of the rats. Control animals received physiological saline solution.

For oral administration the substances were suspended in 1.5% Tylose KN 2000 (methylcellulose). The suspension containing the appropriate amount of substance was given either by gavage (rats) or by application of gelatine capsules (dogs). Control animals received Tylose. Administration volume was 10 ml kg^{-1} (rats) and 0.05 ml kg^{-1} (dogs).

Blood for glucose and insulin determination was collected from the retrobulbar venous plexus under light halothane anaesthesia (rats), or from the jugular vein (dogs).

Blood glucose was measured in whole blood by the hexokinase/glucose-6-phosphate dehydrogenase method (Glucoquant, Boehringer Mannheim) after the protein had been precipitated by addition of 0.5 ml 0.33 M HClO4 to 50 μl blood; measurements were carried out with an Eppendorf 5032 automatic substrate analyser.

Insulin was determined in plasma of dogs with a solid phase ^{125}I-radioimmunoassay (Coat-A-Count, Biermann

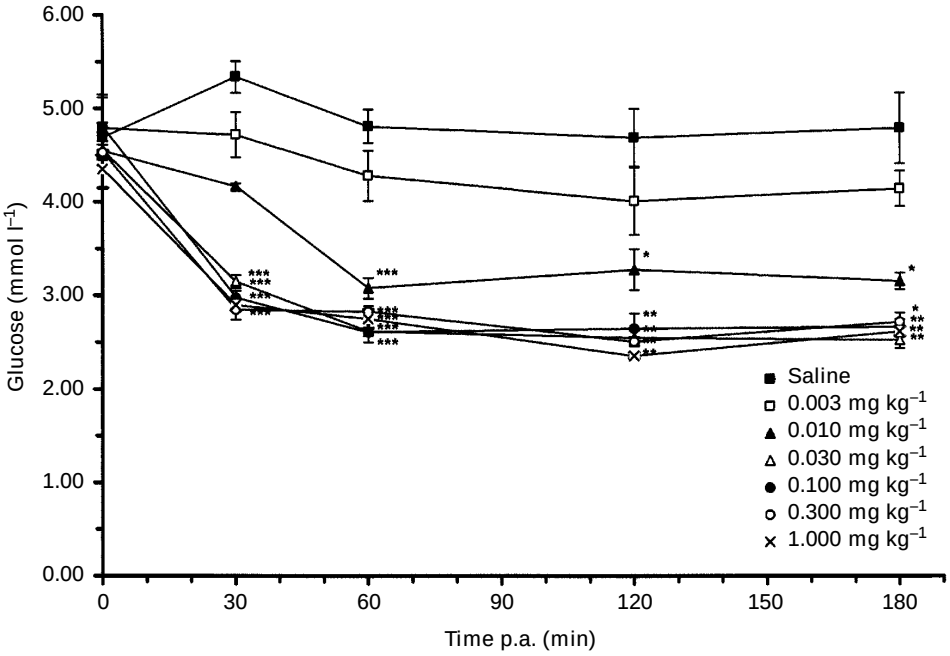


Figure 1 Hypoglycaemic effect of AG-EE 388 ZW in fasted female rats after intravenous dosing. AG-EE 388 ZW 0.003 mg kg^{-1} to 1.0 mg kg^{-1} or saline were administered intravenously via the tail vein. Blood was taken immediately before and 30, 60, 120 and 180 min after administration. Values are means and vertical lines show s.e.mean for 3 to 4 animals. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared to saline controls.

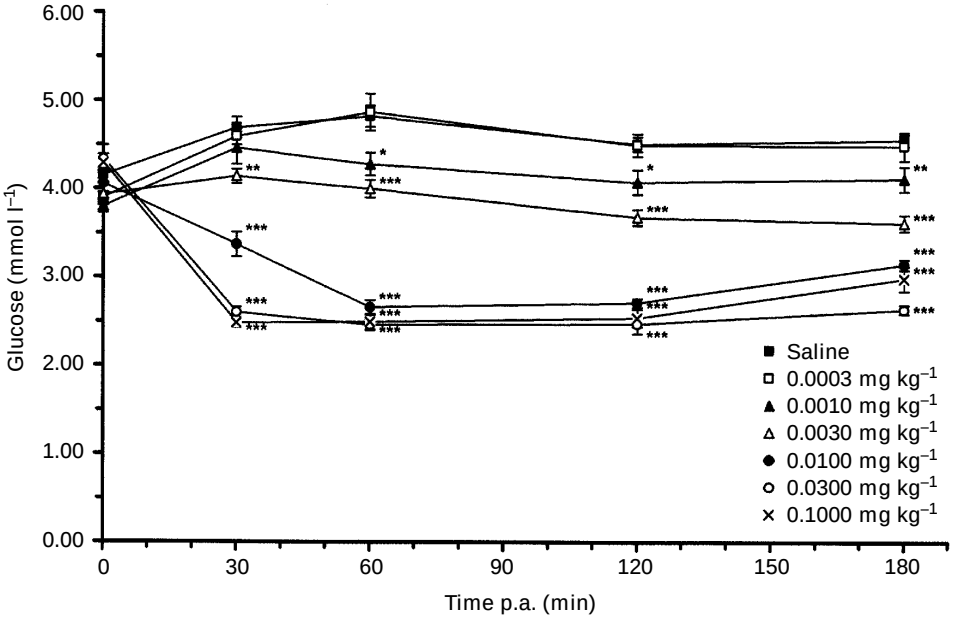


Figure 2 Hypoglycaemic effect of repaglinide in fasted female rats after intravenous dosing. Repaglinide 0.0003 mg kg^{-1} to 0.1 mg kg^{-1} or saline were administered intravenously via the tail vein. Blood was taken immediately before and 30, 60, 120 and 180 min after administration (Values are means and vertical lines show s.e.mean for 4 to 10 animals. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, compared to saline controls.

GmbH, Bad Nauheim). Samples were always run in duplicate. Values given are μu ml^{-1} with human insulin as standard reference.

All compounds tested were synthesized in the Department of Chemical Research at Dr Karl Thomae GmbH (Biberach, Germany). AG-EE 388 ZW ((±)-2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid) represents a racemic mixture of the (**S**)(+)-enantiomer AG-EE 623 ZW (=repaglinide) and the (**R**)(−)-enantiomer AG-EE 624 ZW. The repaglinide used contained maximally 0.1% of AG-EE 624 ZW; the AG-EE 624 ZW used contained only 0.005–0.007% of repaglinide. Glibenclamide and glimepiride were used for comparison.

The *t*-test was used for statistical comparison of the data, with $P<0.05$ as the level of significance. Calculation of ED50 values was performed by fitting the function $y=b+[a\times k/(k+x^{nH})]$ to the data by the programme Sigma Plot (Jandel Scientific) where y is the measured glucose value, x is the dose of substance used, nH is the Hill coefficient, a is the difference between the upper and the lower asymptotes of the dose response curve and b is the baseline level. ED50 values were defined as half-maximal effect doses.

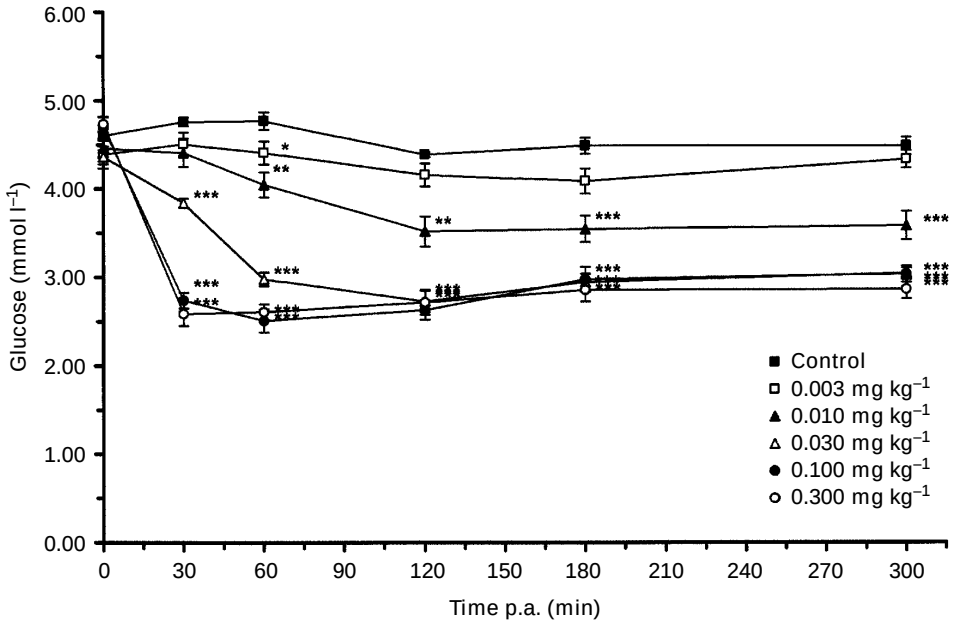


Figure 3 Hypoglycaemic effect of repaglinide in fasted female rats after oral dosing. Repaglinide 0.003 mg kg^{-1} to 0.30 mg kg^{-1}, or methylcellulose were administered orally by gavage. Blood was taken immediately before and 30, 60, 120, 180 and 300 min after administration. Values are means and vertical lines show s.e.mean for 7 animals. *$P<0.05$, **$P<0.01$, ***$P<0.001$, compared to saline controls.

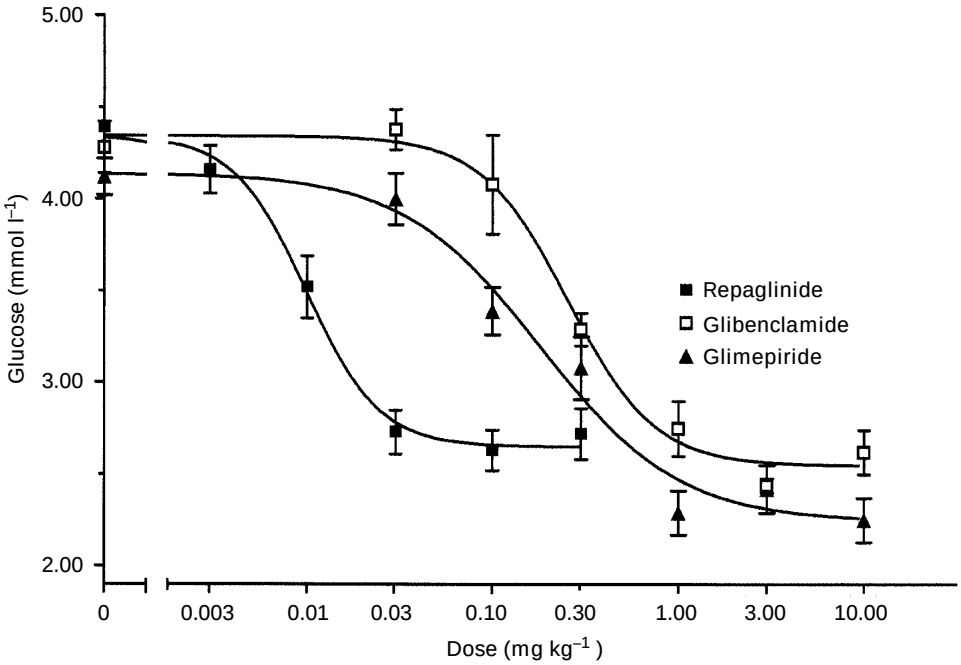
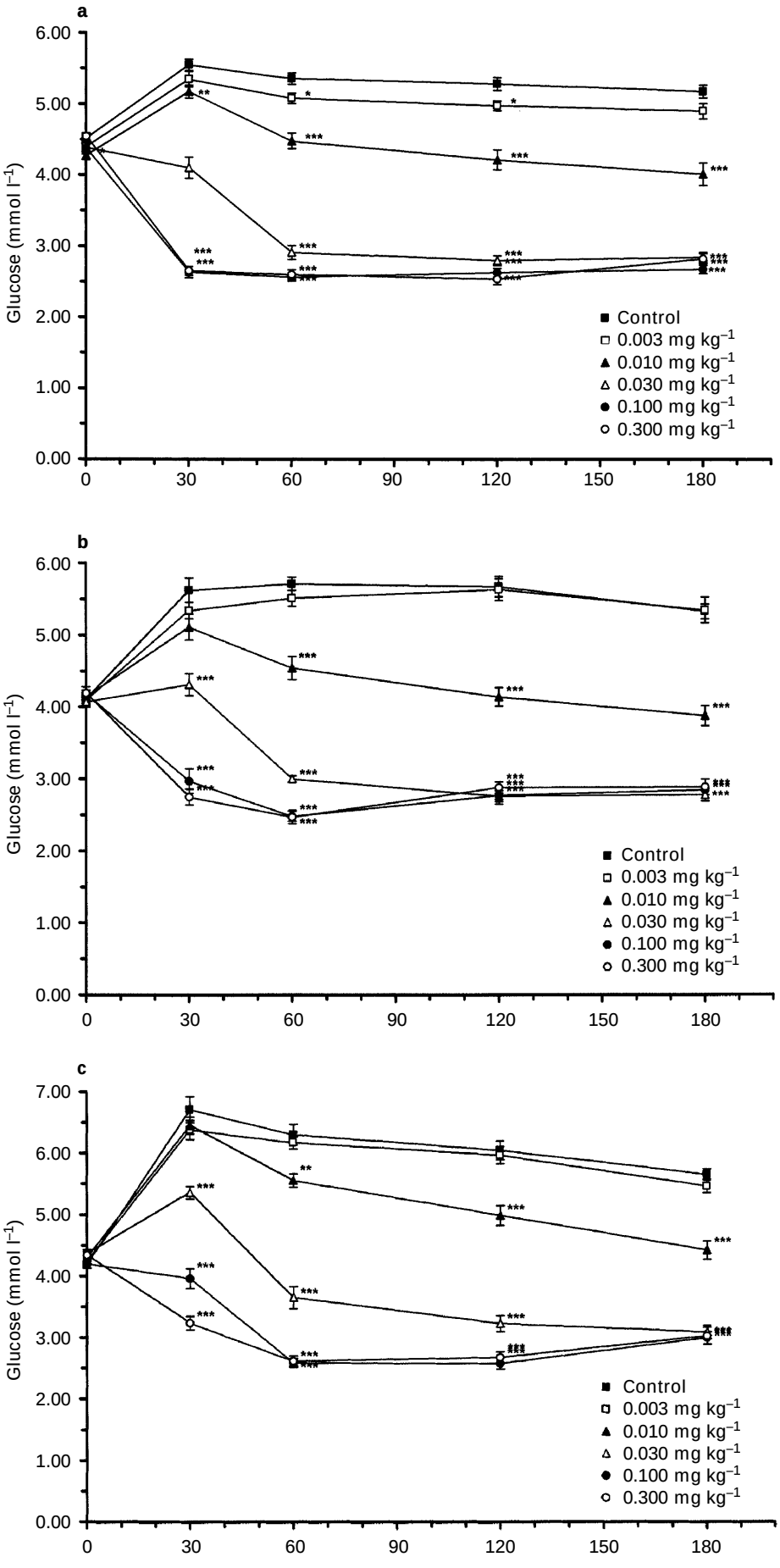


Figure 4 Hypoglycaemic effects of repaglinide, glibenclamide and glimepiride after oral administration to fasted female rats. Repaglinide was administered in doses of 0.003 to 0.3 mg kg^{-1}, glibenclamide and glimepiride in doses of 0.03 to 10.0 mg kg^{-1}. The dose-response curves (mean and vertical lines showing s.e.mean for 6 to 7 animals) for 120 min after oral administration are shown. The ED50 values calculated were 10 (repaglinide), 255 (glibenclamide) and 182 μg kg^{-1} (glimepiride).


a
b
c
Glucose (mmol l⁻¹)
Control
0.003 mg kg⁻¹
0.010 mg kg⁻¹
0.030 mg kg⁻¹
0.100 mg kg⁻¹
0.300 mg kg⁻¹

Results

Comparison of the enantiomers AG-EE 623 ZW and AG-EE 624 ZW with the racemate AG-EE 388 ZW

After intravenous administration to rats, the racemic AG-EE 388 ZW lowered the blood glucose level in a dose-dependent manner (Figure 1). Whereas a trend to lower blood glucose levels was found with 0.003 mg kg^{-1}, a statistically significant decrease was observed with 0.01 mg kg^{-1} AG-EE 388 ZW. It was remarkable that only with a ten fold higher dose (0.03 mg kg^{-1}) the maximal hypoglycaemic effect was already obtained. Such steep dose-response relationships have also been described for other hypoglycaemic agents, like glibenclamide and glimepiride (Geisen, 1988). The ED50 value calculated for the effect after 120 min (when steady-state was reached with all doses) was 6 μg kg^{-1}, i.v., ED50 values for the other time points were: 30 min: 9 μg kg^{-1}; 60 min: 4 μg kg^{-1}; 180 min: 5 μg kg^{-1}. As often seen in intravenously dosed conscious animals, possibly due to stress, glucose levels rose in the control group after 30 min (+14%, $P<0.05$).

The **S**-enantiomer AG-EE 623 ZW (repaglinide) lowered the blood glucose level significantly at all doses $\geqslant$0.003 mg kg^{-1} and at all time-points measured (Figure 2); the ED50 value calculated for the effect after 120 min was 3.4 μg kg^{-1}, i.v., approximately half the value obtained with the racemic AG-EE 388 ZW. As in Figure 1, blood glucose levels in control animals and in the lowest dose group, increased at 30 and 60 min p.a. (30 min + 13%, $P<0.01$; 60 min + 16%, $P<0.001$). An inconsistent blood glucose lowering effect of the various dose groups at later time points could be detected. Whereas the group dosed with 0.003 mg kg^{-1} repaglinide still showed a trend towards lower glucose levels after 60 and 120 min, both the 0.01 and 0.1 mg kg^{-1} dose groups showed increased glucose levels after 180 min when compared to the effect seen after 120 min. A stable effect was seen with 0.03 mg kg^{-1} repaglinide. Whether or not this decrease of the glucose lowering effect reflects some counter regulatory mechanisms cannot be judged from this experiment.

To evaluate further the potency of repaglinide and the racemic AG-EE 388 ZW, direct comparison studies were performed. After intravenous administration, repaglinide (0.01 mg kg^{-1}) and AG-EE 388 ZW (0.02 mg kg^{-1}) exerted similar effects on the blood glucose levels at all time-points measured. This experiment was further supported by a study where both compounds were administered orally. Again, half of the dose of repaglinide (0.015 mg kg^{-1}) was equipotent with AG-EE 388 ZW (0.030 mg kg^{-1}) throughout the time course of the experiment (data not shown).

The **R**-enantiomer AG-EE 624 ZW was also administered intravenously to rats at 10 to 100 fold higher doses than AG-EE 623 ZW. At a dose of 0.1 mg kg^{-1}, AG-EE 624 ZW was inactive. At 1.0 mg kg^{-1}, medium range activity was found i.e. glucose lowering effect 30 min p.a.: −29.4% (vs control), 60 min p.a.: −29.5%, 120 min p.a.: −15.2%, 180 min p.a.: −4.1%. The area under the blood glucose curve (area between the respective curve and the abscissa scale) was clearly smaller after 0.01 mg kg^{-1} AG-EE 623 ZW than after 1.0 mg kg^{-1} AG-EE 624 ZW (538.8 ± 7.9 and 694.2 ± 6.2 mmol × 180 min l^{-1}, $P<0.001$, respectively).

AG-EE 624 ZW at doses of 0.1, 0.3 and 1.0 mg kg^{-1} body weight had no effect on blood glucose levels after oral administration to rats (data not shown).

Experiments so far clearly demonstrate that the **S**-enantiomer, repaglinide, is a very potent hypoglycaemic compound, whereas the **R**-enantiomer, AG-EE 624 ZW, is more than 100 fold less active and contributes, at most, only marginally to the blood sugar lowering effect seen with AG-EE 388 ZW. Based on these results, further studies were carried out only with repaglinide.

Glucose lowering activity of repaglinide in rats

After oral administration to fasted rats repaglinide lowered the blood glucose levels in a dose-dependent manner (Figure 3), the effects reaching significance at a dose of 0.01 mg kg^{-1}. Repaglinide 0.03 mg kg^{-1} was equieffective with 0.1 and 0.3 mg kg^{-1} at the later time points, whereas it was significantly less active at 30 and 60 min p.a.. So the onset of action seemed to be somewhat slower with lower doses as was also seen with the 0.01 mg kg^{-1} dose. Glucose levels in treated animals did not return to control values within the duration of the experiment (5 h). The ED50 value for the effect after 120 min was calculated to be 10 μg kg^{-1}, whereas the ED50

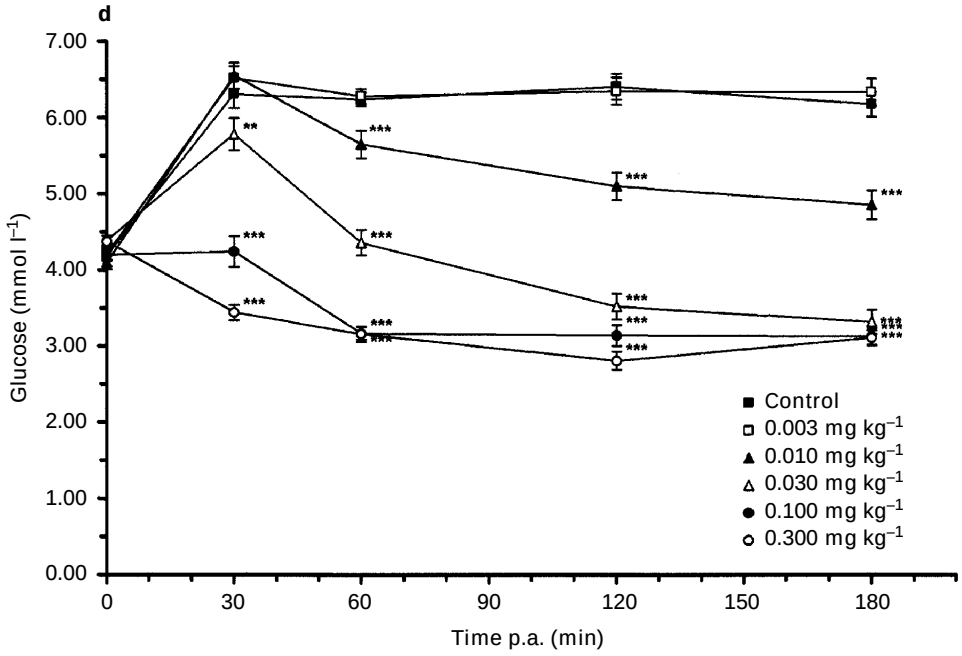


Figure 5 Antihyperglycaemic effects of repaglinide after oral administration to fasted female rats. Repaglinide 0.003 mg kg^{-1} to 0.30 mg kg^{-1} or methylcellulose were administered orally simultaneously together with 0.5 g kg^{-1} (a), 1.0 g kg^{-1} (b), 2.0 g kg^{-1} (c) and 3.0 g kg^{-1} (d) glucose. Blood was taken immediately before and 30, 60, 120 and 180 min after administration. Values are means and vertical lines show s.e.mean for 13 to 14 animals. *$P<0.05$, **$P<0.01$, ***$P<0.001$, compared to controls.

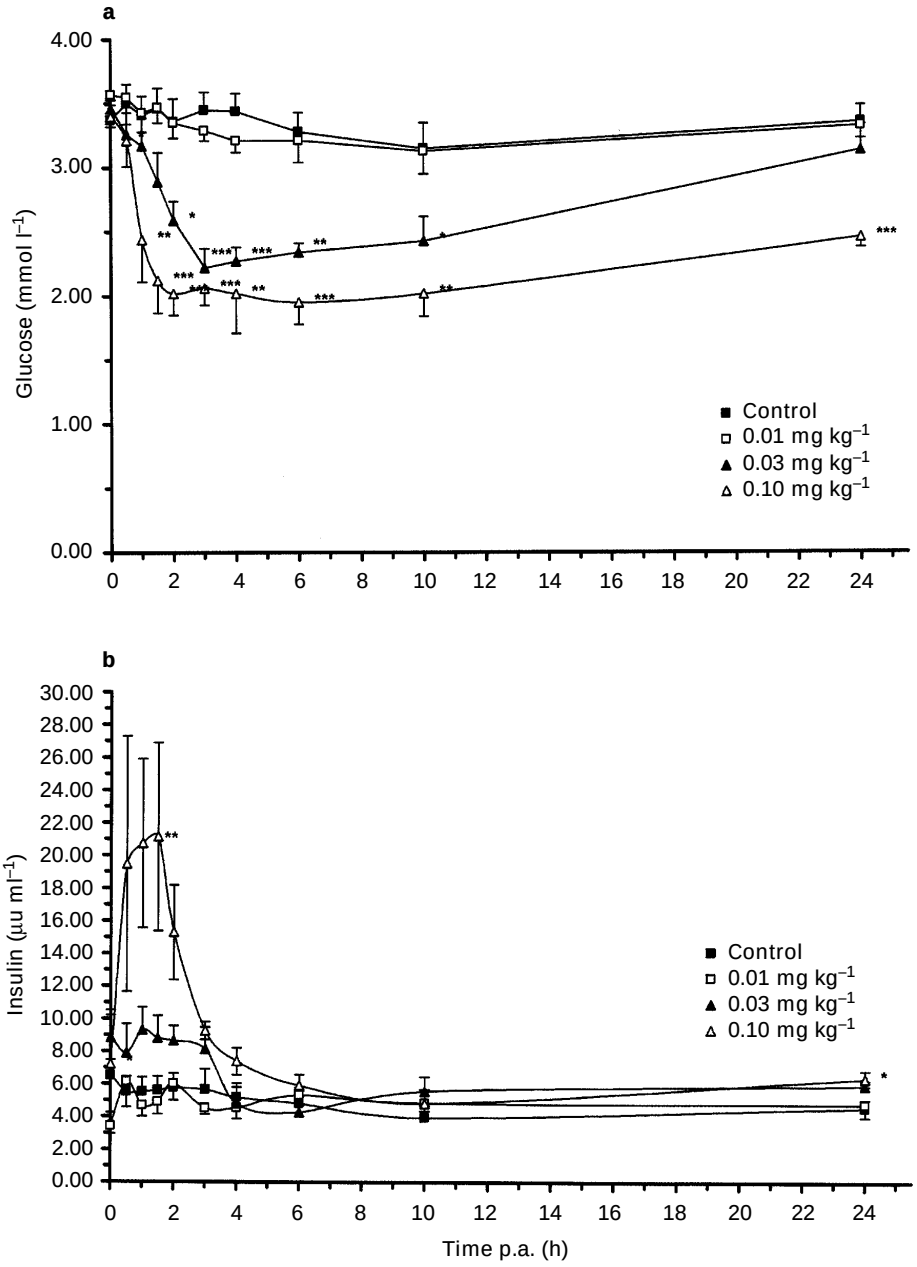


Figure 6 Hypoglycaemic effects of repaglinide after oral administration to fasted female beagle dogs. Repaglinide 0.01 mg kg^{-1}, 0.03 mg kg^{-1} and 0.10 mg kg^{-1} were suspended in methylcellulose and filled into capsules which were administered orally. Controls received methylcellulose alone. Blood was taken immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 h after administration. Glucose (a) and insulin (b) levels were determined. Values are given as means and vertical lines show s.e.mean for 4 to 8 animals. *$P<0.05$, **$P<0.01$, ***$P<0.001$, compared to controls.

value after 30 min was 38 μg kg^{-1}, after 60 min 15 μg kg^{-1} and after 180 min 6 μg kg^{-1}.

Comparison of repaglinide with glibenclamide and glimepiride

Repaglinide was directly compared to glibenclamide and glimepiride. Thus, repaglinide was administered in doses of 0.003 to 0.3 mg kg^{-1}, glibenclamide and glimepiride in doses of 0.03 to 10.0 mg kg^{-1} orally to fasted rats. With all three compounds tested, the maximal blood glucose lowering effects obtained were not statistically different (ANOVA test). The hypoglycaemic potencies of the three compounds were compared by use of the ED50 values calculated for the effects after 120 min, when for each of the compounds a plateau of the blood glucose lowering activity was obtained. Repaglinide (ED50 10 μg kg^{-1}) turned out to be the most potent compound, being almost 20 times more potent than glimepiride (ED50 182 μg kg^{-1}) and about 25 times more potent than glibenclamide (ED50 255 μg kg^{-1}) (Figure 4).

Hypoglycaemic activity of repaglinide in rats under hyperglycaemic conditions

Repaglinide was simultaneously administered with an oral glucose bolus (0.5, 1.0, 2.0 or 3.0 g kg^{-1}) to fasted rats. Increasing doses of glucose led to an increase in plasma glucose Cmax values and also to a longer lasting hyperglycaemic effect. Whereas the lowest dose of repaglinide used (0.003 mg kg^{-1}) exhibited a significant antihyperglycaemic effect only in the presence of 0.5 g kg^{-1} glucose, blood glucose levels were significantly decreased under all experimental settings with doses of $\geqslant$0.01 mg kg^{-1} repaglinide, p.o.. With doses $\geqslant$0.1 mg kg^{-1}, the initial increase in blood glucose, which was seen after

the glucose boli was totally blunted, and glucose levels even fell below starting values (Figure 5a–d). Whereas with 0.01 mg kg^{-1} there was a steady decrease of blood glucose levels also after 180 min, the hypoglycaemic effect with higher doses of repaglinide remained stable once the plateau effect was reached. The ED50 values calculated for the effect after 120 min were: 12.3 (0.5 g glucose kg^{-1}), 9.9 (1.0 g glucose kg^{-1}), 14.5 (2.0 g glucose kg^{-1}) and 12.8 μg kg^{-1}, p.o. (3.0 g glucose kg^{-1}), respectively. Based on the ED50 doses at 120 min p.a. for the various glucose challenges the doses of repaglinide which were needed to decrease the blood glucose levels of animals by 1 mmol l^{-1} were calculated. So this calculation was independent of the actual glucose level. These doses were calculated to be 10.3, 9.3, 7.0, 8.4, and 7.2 μg kg^{-1}, p.o., after glucose loads of 0.0, 0.5, 1.0, 2.0 and 3.0 g kg^{-1}, respectively. This means that the more hyperglycaemic the animals were, the lower the dose of repaglinide needed to achieve the same absolute reduction in blood glucose levels. This trend is in accord with the findings of Kofod & Fuhlendorff (1995), who found, in an *in vitro* situation, a glucose-dependent insulin secretory effect with repaglinide.

Glucose lowering activity of repaglinide in dogs

The hypoglycaemic activity of repaglinide was tested in fasted beagle dogs as a non-rodent model which has been commonly used to demonstrate pharmacodynamic effects of sulphonylureas. After oral administration, repaglinide (0.03 and 0.1 mg kg^{-1}) caused a significant decrease in blood glucose levels in dogs. Onset of action was rapid, reaching its maximum after 3 (0.03 mg kg^{-1}) and 2 (0.1 mg kg^{-1}) h, respectively (Figure 6a). The effect lasted for up to 24 h. Further increases of the dose did not lead to a further reduction in blood glucose levels (data not shown). The ED50 value calculated for the effect after 120 min, p.a., was 28.3 μg kg^{-1}.

The blood sugar lowering effect was preceded by a rise in plasma insulin concentrations. The maxima of these levels were seen at 60 and 90 min after administration. Control levels were reached again after 4 and 6 h, respectively (Figure 6b). It is noteworthy that despite this short-lasting increase in insulin levels, a long lasting hypoglycaemic effect was obtained.

Discussion

Repaglinide is a novel antidiabetic agent currently being investigated in phase III clinical trials. As a benzoic acid derivative, it is structurally different from the insulinotropic sulphonylureas like glibenclamide and glimepiride which are available on the market. Repaglinide can be regarded as a highly potent 'second generation benzoic acid derivative', in contrast to meglitinide (HB 699) which represents the 'first generation' of benzoic acid derivatives. The development of meglitinide has been discontinued, because of its weak potency which was comparable to tolbutamide (Ribes *et al*., 1981; Gutniak & Efendic, 1982).

With the racemic AG-EE 388 ZW, the main hypoglycaemic activity resides in the **S**-enantiomer (repaglinide) which displays, in the rat, a $\geqslant$100 fold higher activity than the **R**-enantiomer (AG-EE 624 ZW). This enantioselectivity of action was also observed in mouse β cells (Fuhlendorff *et al*., 1995b), and is consistent with findings with other related benzoic acid derivatives (Rufer & Losert, 1979; Garrino & Henquin, 1988; Verspohl *et al*., 1990). It is tempting to speculate that the different *in vivo* activities of the enantiomers can be explained by different affinities to the sulphonylurea binding site of the pancreatic β cell (Verspohl *et al*., 1990).

AG-EE 624 ZW must have weak hypoglycaemic activity of its own, because its effects cannot be explained by the residual repaglinide which was maximally 0.007% in the sample used. However, it can be concluded that, at least at low doses, AG-EE 624 ZW does not contribute to the hypoglycaemic activity seen with AG-EE 388 ZW.

In fasted rats, after oral administration repaglinide was 18 times more potent than glimepiride and 25 times more potent than glibenclamide, according to the ED50 (2 h)-values of 10, 182 and 255 μg kg^{-1}. These findings are remarkably consistent with data obtained for glimepiride and glibenclamide by Geisen (1988). In that publication, an activity quotient of 1.4 for glimepiride/glibenclamide for the 2 h time point after oral administration to rats was found, which exactly matches the ratio for the ED50 values obtained in this study. Surprisingly, the relative potency sequence observed in fasted rats seems to be followed by those observed in NIDDM diabetics in whom 4 mg of repaglinide were found to be equipotent with 15 mg of glibenclamide (Wolfenbuttel *et al*., 1993).

Repaglinide is not only effective in fasted rats but also, and even more markedly, in glucose-loaded rats. This is evidenced by a series of studies in rats where various doses of glucose were administered together with repaglinide. In all situations, repaglinide was able to exert its hypoglycaemic activity, and, in higher doses, even to blunt the increase in plasma glucose levels observed after an oral glucose load. Thus, repaglinide was found to be relatively more effective in the presence of higher glucose levels. Its glucose-dependent activity is illustrated best with the doses of 10.3 and 7.2 μg kg^{-1} p.o. needed to achieve a 1 mmol l^{-1}-decrease in blood glucose in the fasted state and after a glucose bolus of 3.0 g kg^{-1}, respectively. Recent findings in mouse perifused pancreatic islets (Kofod & Fuhlendorff, 1995) confirmed the glucose-dependent activity of repaglinide observed *in vivo* and, moreover, showed that the analogous effect of glibenclamide is less glucose-dependent.

In fasted dogs, repaglinide exerted a strong and long lasting hypoglycaemic effect. The potency of repaglinide was higher and its onset of action was faster, compared with the data obtained for glimepiride and glibenclamide in the same animal model (Geisen, 1988). It was surprising to find that the insulin release evoked by repaglinide in dogs was short lasting, despite the very pronounced and long lasting hypoglycaemic effect. This 'insulin sparing effect' was also confirmed in man, when repaglinide was administered to sulphonylurea-treated NIDDM patients (Wolfenbuttel *et al*., 1993). In addition, a similar finding was obtained for the racemic AG-EE 388 ZW when compared with glibenclamide in NIDDM patients (Profozic *et al*., 1993).

In contrast to its long-lasting hypoglycaemic effects in rats and dogs, repaglinide turns out to be surprisingly short acting in man and, therefore, ideally suited for preprandial dosing (Tronier *et al*., 1995). A difference was also observed for glibenclamide and glimepiride. The hypoglycaemic effect in rats was short lasting for glimepiride and long lasting for glibenclamide, whereas the long duration of action in man for glimepiride even exceeds that of glibenclamide (Draeger, 1995). Whether the species differences with respect to duration of action observed for repaglinide are due to different metabolic activities remains to be elucidated.

In conclusion, the data presented clearly demonstrate that the novel non-sulphonylurea compound, repaglinide, is a very potent hypoglycaemic agent in animals. Its potency in rats was 18 and 25 times higher than that of glimepiride and glibenclamide; its hypoglycaemic potency was more pronounced in the hyperglycaemic than in the normoglycaemic state. In dogs, repaglinide also turned out to be more potent than glibenclamide and glimepiride; its pronounced and long lasting glucose lowering effects were accompanied by only shortly increased insulin levels.

The *in vivo* results obtained with repaglinide in rats and dogs are supported by recently published *in vitro* data. The activity profile in rats and dogs suggests repaglinide to be a promising new antidiabetic agent.

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