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European Journal of Pharmacology 451 (2002) 217–225

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NN2211: a long-acting glucagon-like peptide-1 derivative with anti-diabetic effects in glucose-intolerant pigs

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Received 26 June 2002; accepted 30 July 2002

Abstract

Glucagon-like peptide-1 (GLP-1) is an effective anti-diabetic agent, but its metabolic instability makes it therapeutically unsuitable. This study investigated the pharmacodynamics of a long-acting GLP-1 derivative (NN2211: ($Arg^{34}Lys^{26}$-(*N*-ε-(γ-Glu(*N*-α-hexadecanoyl)))-GLP-1(7–37)), after acute and chronic treatment in hyperglycaemic minipigs. During hyperglycaemic glucose clamps, NN2211 (2 μg kg^{-1} i.v.) treated pigs required more ($P<0.005$) glucose than control animals (5.8 ± 2.1 vs. 2.9 ± 1.8 mg kg^{-1} min^{-1}). Insulin excursions were higher ($P<0.01$) after NN2211 (15367 ± 5438 vs. 9014 ± 2952 pmol l^{-1} min), and glucagon levels were suppressed ($P<0.05$). Once-daily injections of NN2211 (3.3 μg kg^{-1} s.c.) reduced the glucose excursion during an oral glucose tolerance test, to $59 \pm 15\%$ of pre-treatment values by 4 weeks ($P<0.05$), without measurable changes in insulin responses. Fructosamine concentrations were unaltered by vehicle, but decreased (from 366 ± 187 to 302 ± 114 μmol l^{-1}, $P=0.14$) after 4 weeks of NN2211. Gastric emptying was reduced ($P<0.05$) by NN2211. NN2211 acutely increases glucose utilization during a hyperglycaemic glucose clamp and chronic treatment results in better daily metabolic control. Therefore, NN2211, a GLP-1 derivative that can be administered once daily, holds promise as a new anti-diabetic drug with a minimal risk of hypoglycaemia.

Keywords: GLP-1 glucagon-like peptide-1 derivative; Minipig; Diabetes type 2; Glucose tolerance; Insulin sensitivity; Gastric emptying; Glucagon

1. Introduction

Glucagon-like peptide 1 (GLP-1), a potent incretin hormone secreted from the intestinal L-cells after ingestion of carbohydrate and fat (Holst, 1997; Kreymann et al., 1987; Ørskov, 1978), has a variety of physiological effects which support its potential use as an anti-hyperglycaemic agent. Firstly, it stimulates insulin and decreases glucagon secretion in a glucose-dependent manner (Gromada et al., 1998). Secondly, the hormone potently inhibits gastric emptying (Nauck et al., 1997) and suppresses appetite (Flint et al., 1998), and, lately, it has been shown that GLP-1 stimulates beta-cell growth (Buteau et al., 1999; Edvell and Lindström, 1999; Gang et al., 1999) and inhibits apoptosis (Hansotia et al., 2001). This unique combination of properties provides an unprecedented opportunity to develop an effective and safe anti-diabetic compound, particularly since both the insulinotropic and glucagonostatic effects are glucose-dependent (Qualmann et al., 1995). Consequently, since its discovery in 1984, GLP-1 has received much attention as a possible new treatment for type 2 diabetes (Gutniak et al., 1994; Larsen et al., 2001; Nauck et al., 1993, 1996; Rachman et al., 1997). However, the native sequence of GLP-1 is rapidly degraded and deactivated by dipeptidyl peptidase IV (DPPIV; EC 3.4.15.5) (Mentlein et al., 1993; Deacon et al., 1995) and eliminated through the kidneys (Deacon et al., 1996). These degradation pathways preclude the use of the native form of the GLP-1 molecule therapeutically. Therefore, we have designed derivatives of GLP-1, which have a protracted pharmacodynamic profile due to binding to serum albumin, resistance towards DPPIV degradation and slow release from the injection site. NN2211 [($Arg^{34}Lys^{26}$-(*N*-ε-(γ-Glu(*N*-α-hexadecanoyl)))-GLP-1(7–37)] is derivatised with a fatty acid side chain and a spacer

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adding charge and solubility (Knudsen et al., 2000). The compound has a maintained affinity for the GLP-1 receptor, affinity for serum albumin and resistance to degradation by DPPIV (Knudsen et al., 2000), giving it a unique pharmacokinetic and pharmacodynamic profile suitable for once-daily subcutaneous administration to humans.

The present study was undertaken to investigate the insulinotropic and glucagonostatic effects of NN2211, both acutely (hyperglycaemic clamp) and chronically (4-week dosing study), in nicotinamide and streptozotocin (STZ) treated beta-cell-reduced minipigs (Larsen et al., 2000). This is a new model which was developed to mimic more closely the human conditions of impaired glucose tolerance (IGT) and mild type 2 diabetes. In addition, minipigs provide the additional advantage of resembling humans in terms of gastrointestinal (Miller and Ullrey, 1987; Tumbleson, 1986) and skin physiology (Quist et al., 2000), which are important considerations in terms of nutrition and drug absorption from the skin.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with animal welfare guidelines provided by the Animal Experiments Inspectorate, Ministry of Justice Denmark.

Male Göttingen Minipigs, purchased from Ellegaard Göttingen Minipigs, Denmark were used in the study. The pigs were housed in single pens, and fed a diet as recommended by the supplier: 245 g twice daily of Special Diet Sciences (SDS, Witham, Essex, UK) pelleted fodder. After 2 weeks of acclimatization, the pigs were anaesthetised with a combination of zolazepam 0.8 mg kg^{-1}, tiletamin 0.8 mg kg^{-1}, methadone 0.2 mg kg^{-1}, ketamin 0.8 mg kg^{-1} and xylazin 0.9 mg kg^{-1} i.m., and maintained on anaesthesia with isoflurane 1–3%, after tracheal intubation. During anaesthesia, the animals were instrumented with two venous catheters (Certo 455, B. Braun, Melsungen, Germany) inserted in the external jugular vein and advanced to the superior vena cava. The catheters were exteriorised to the back of the neck and filled with saline containing 1000 U l^{-1} heparin. Animals were allowed to recover from the anaesthesia, and were given post-operative analgesia (buprenorphine 0.03 mg kg^{-1} i.m. and carprophene 4 mg kg^{-1} i.m. once daily) for 3 days. Catheters were flushed twice a week with saline.

One to two weeks after surgery, the pigs underwent an oral glucoce tolerance test (OGTT), in which glucose (2 g kg^{-1}) was mixed with 25 g pelleted fodder. This was offered to unrestrained pigs in a bowl ($t=0$ min), and the animals were carefully supervised while eating the mixture. Blood samples for measurement of plasma glucose, insulin, and glucagon were taken at the following time points: − 15, − 10, 0, 15, 30, 45, 60, 90, 120, 150 and 180 min. All blood samples were drawn from the indwelling catheters while the pigs were moving freely in their pens.

2.2. Induction of diabetes

Animals had a body weight of 24–29 kg, at the time, they had their beta-cell mass reduced with two separate i.v. injections of either 100 mg kg^{-1} (protocol 1) nicotinamide (which prevents cellular energy depletion caused by STZ-induced DNA damage) or 45 mg kg^{-1} (protocol 2) and streptozotocin 125 mg kg^{-1} i.v. (Larsen et al., 2000). After 8 days, a second OGTT was carried out as described above, in order to assess the severity of diabetes, according to the human criteria defined by the American Diabetes Association: impaired glucose tolerance (IGT), 2-h plasma glucose during OGTT >7.8 mmol l^{-1}, type 2 diabetic, fasting plasma glucose >7.0 mmol l^{-1} and/or 2-h plasma glucose during OGTT >11.1 mmol l^{-1}.

2.3. Experimental designs

2.3.1. Protocol 1: hyperglycaemic clamp

One month after nicotinamide and STZ treatment, a hyperglycaemic clamp was carried out in six animals. Prior to the experimental day, the animals were fasted for 18 h and had free access to water. The study was conducted in fasted animals, since it is known that GLP-1 infusion carried out during ingestion of a meal results in a diminished insulin response due to delayed intestinal absorption (Nauck et al., 1997).

On 2 days, separated by 1 week, the animals were dosed i.v. via the implanted catheter, with either vehicle or with the GLP-1 derivative NN2211 (2 μg kg^{-1}, corresponding to 0.6 nmol kg^{-1}), with each animal receiving both treatments in random order. The injected volume was 1 ml and the catheter was flushed with saline. Two basal blood samples were collected at − 30 and − 1 min, after which NN2211 or vehicle were administered ($t=0$ min). An i.v. glucose bolus load (0.1 g kg^{-1}) was given at $t=30$ min, followed by an i.v. infusion of a 20% glucose solution at a variable rate, which aimed to clamp the plasma glucose at a level 1.5–2 mmol l^{-1} above the basal level of the individual animals. Blood samples were thereafter drawn at 5-min intervals until $t=60$ min followed by 10-min intervals until $t=110$ min, after which the glucose infusion was terminated and further blood samples were collected until $t=130$ min. Plasma glucose was measured on the Yellow Springs Instruments glucose analyser (YSI, Ohio, USA). Blood (3 ml) for determination of plasma glucose, insulin, glucagon and NN2211 concentrations was collected into tubes containing the relevant additives for the specific assays, as described below. Samples were centrifuged (4 °C, 3000 × g, 10 min) and plasma separated and stored at − 20 °C until analysed.

In order to study the glucose-dependence of NN2211 further, data from another set of experiments carried out in a parallel group of pigs were analysed. These experiments

were identical in design except for the fact that they utilized a constant low dose i.v. glucoce infusion (3.3 mg kg^{-1} min^{-1}), without clamping the blood glucose.

2.3.2. Protocol 2: chronic dosing study

The effects of chronic (4 weeks) treatment with NN2211 were examined in a second group of animals. OGTTs (as described above, but with the addition of 500 mg paracetamol) were carried out prior to (=pre-STZ) and 1 week after (=post-STZ) induction of diabetes. A further two OGTTs were performed after 2- and 4-week treatment with once-daily s.c. injections (0.33 ml) of NN2211 (3.3 μg kg^{-1} dissolved in phosphate-buffered saline; $n=6$) or vehicle alone ($n=6$). On OGTT days, animals were fasted overnight, but allowed free access to water. Animals received their usual injection of vehicle or NN2211 at 07.30 h ($t=-270$ min), and the OGTT was performed at 12:00 h ($t=0$ min). Blood samples (4 ml) were taken at −15, 0, 15, 30, 45, 60, 90, 120, and 180 min for determination of plasma glucose, insulin, glucagon, and paracetamol. Blood samples for determination of fructosamine and NN2211 concentrations were collected once a week at 12:00 h.

2.4. Formulation of compound

NN2211 is an acylated GLP-1(7–37): ($Arg^{34}Lys^{26}$-(*N*-ε-(γ-Glu(*N*-α-hexadecanoyl)))-GLP-1(7–37) (Knudsen et al., 2000). NN2211 (4.91 mg ml^{-1}) was dissolved in 4 mmol l^{-1} phosphate buffer, containing 38 mg ml^{-1} mannitol, and 5.5 mg ml^{-1} phenol in water. The preparation was stored at 4 °C, and diluted for the clamp experiment (1+99) in saline immediately before dosing. For the chronic dosing study, a solution of NN2211 (284 μg ml^{-1}) was prepared in isotonic 0.2 mol l^{-1} phosphate buffer.

2.5. Analytical procedures

The glucose concentration was measured by the glucose hexokinase method using a Cobas Mira auto-analyser Plus (Roche Diagnostic Systems, Basel, Switzerland) following the procedures as described by the manufacturer. Fructosamine was measured by a reduction test with nitrobluetetrazolium (ABX Diagnostics, Montpellier, France), and paracetamol concentrations were determined by high pressure liquid chromatrography (Hewlett Packard HP1090, C_8 column) with UV detection at 245 nm following extraction from plasma with ethyl acetate.

Plasma insulin was analysed using an in-house two site enzyme-linked immunosorbent assay (ELISA) based on two monoclonal antibodies as catcher and detector, respectively. The assay has a detection limit of 3.2 pmol l^{-1} and the inter-assay variations at 87, 235 and 342 pmol l^{-1} of 15.3%, 9.9% and 14.6%, respectively. Intra-assay variations at the same concentration levels are 3.2%, 7.6% and 4.4%, respectively. Cross-reactivities were as follows (all porcine): growth hormone 0.001%, glucagon 0.4%, pancreatic polypeptide 0.2% and C-peptide 0.01%. Plasma NN2211 was analysed using an in-house two-site immunoassay with monoclonal antibodies. The catcher antibody was raised against intact GLP-1(7–37) coupled to KLH and reacted with the C-terminal half of the molecule while the detector antibody raised against an N-terminal fragment of GLP-1 coupled to KLH reacted specifically with the N-terminus and not with elongated or truncated forms of GLP-1. The detector antibody was biotinylated and the detection system was streptavidin-peroxidase in combination with Super-Signal amplifying system (Pierce, cat.no. 37075). (Wilken et al., 2000). The assay measures the sum of free and albumin-bound NN2211, and has a detection limit of 3 pmol l^{-1}. The intra-assay variations at 85, 790 and 3220 pmol l^{-1} are 5.9%, 6.5%, and 2.4%, respectively and inter-assay variations at 95, 840 and 3395 pmol l^{-1} are 10.1%, 6.2% and 3.7%, respectively. Cross-reactivity to endogenous GLP-1 is <4%. Plasma for insulin and NN2211 was stabilised with EDTA (0.18 mol l^{-1}; 35 μl ml^{-1} blood). Plasma glucagon was analysed using a commercial radioimmunoassay kit (GL-32K, Linco Research St Charles, MO, USA). Plasma was stabilised with Trasylol (500 kallikrein inhibitory units ml^{-1} blood) and EDTA (0.18 mol l^{-1}; 35 μl ml^{-1} blood).

2.6. Data analysis

Data were analysed using Statistical Analysis System software (6.11, SAS Institute, Cary, NC, USA). Data are presented as mean ± S.D.; time courses as mean ± S.E.M. Pair-wise group comparisons were performed using a paired *t*-test. In the chronic study, one-way analysis of variance followed by post-hoc analysis was used to demonstrate differences over the course of the study (pre-, post-STZ, 2- and 4-week treatments). Values of $P<0.05$ were considered significant. To investigate the glucose dependency of NN2211's ability to stimulate insulin secretion, corresponding approximate steady-state values of glucose and insulin (mean of time points 15 and 28 min after i.v. bolus of NN2211 and mean of time points 80, 90 and 100 min after i.v. bolus of NN2211) were calculated for each set of experiments. These data points were then plotted (insulin vs. glucose) for each condition (NN2211 or vehicle) and best-fit lines were estimated by linear regression analysis. The slopes of the best-fit lines were statistically compared as described by Zar (1984).

3. Results

3.1. Protocol 1

After 8 days, five of the animals were characterised as IGT and one as type 2 diabetic, according to the human criteria defined by the American Diabetes Association.

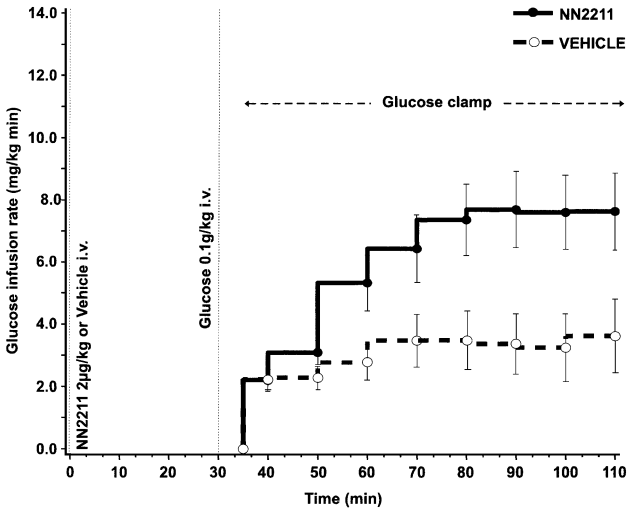

Fig. 1. Hyperglycaemic glucose clamp in β-cell-reduced minipigs. NN2211 (2 μg·kg^{-1} i.v.) treated pigs required a 196 ± 257% increase in the glucose infusion rate compared to vehicle (P < 0.005, mean ± S.E.M., n = 6).

NN2211-treated animals required more glucose during the hyperglycaemic clamp period (cumulated amount infused $_{30-110\ min}$; 462 ± 152 mg kg^{-1}) compared to the vehicle-treated group (233 ± 132 mg kg^{-1}) (Fig. 1), representing a 196 ± 257% increase during NN2211 treatment (P < 0.005). Despite this, plasma glucose concentrations during the clamp (70–110 min) tended to be slightly lower during NN2211 treatment (6.1 ± 0.5 mmol l^{-1}) than in the vehicle group (6.4 ± 0.3 mmol l^{-1}; n.s.; Fig. 2A). In spite of this trend, the corresponding plasma insulin concentration profile (Fig. 2B) was markedly higher in the NN2211-treated animals (area under the plasma insulin curve ($AUC_{30-110\ min}$), 15367 ± 5438 pmol l^{-1} min for NN2211 compared to 9014 ± 2952 pmol l^{-1} min) representing a 72 ± 28% increase (P < 0.01). After NN2211 injection, plasma glucagon was suppressed during the hyperglycaemic clamp (glucagon $AUC_{70-110\ min}$ decreased by 31 ± 14%, from 832 ± 360 pmol l min^{-1} (vehicle group) to 531 ± 82 pmol l^{-1} min P < 0.05), but the suppression was lifted immediately after the glucose infusion was terminated and plasma glucose fell below fasting levels (Fig. 2C). Plasma NN2211 immunoreactivity remained relatively constant during the test period, 6825 ± 1155, 6603 ± 1198 and 6318 ± 1103 pmol l^{-1} at 45, 60, and 130 min, respectively, reflecting a prolonged half-life of the compound also after i.v. administration (Fig. 2D). For both NN2211 (r^2 = 0.97, P < 0.05) and

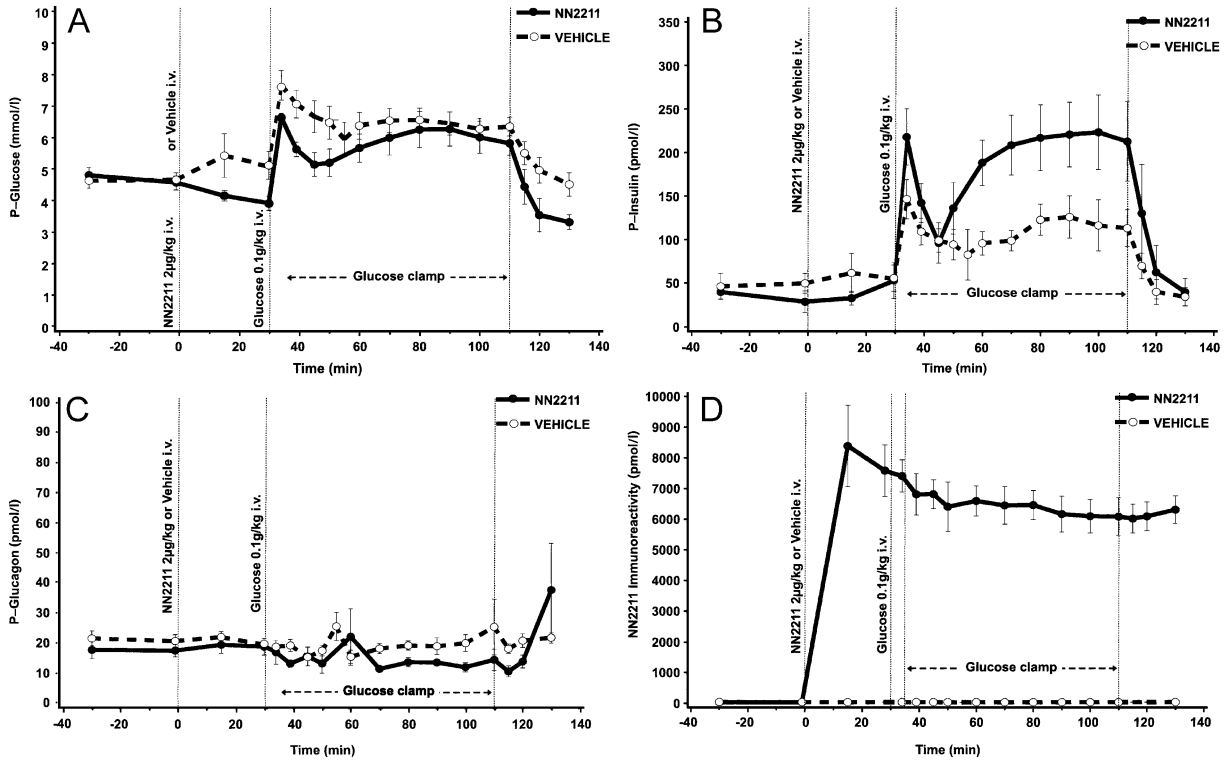

Fig. 2. (A) Plasma glucose profile before, during and after hyperglycaemic glucose clamp. The plasma glucose clamp level tends to be slightly lower during NN2211 (2 μg·kg^{-1} i.v.) treatment (6.1 ± 0.5 vs. 6.4 ± 0.3 mmol·l^{-1}, n.s., mean ± S.E.M., n = 6). (B) Plasma insulin profiles show the area under the curve to be 72 ± 28% higher after NN2211 (2 μg·kg^{-1} i.v.) compared to vehicle (P < 0.01, mean ± S.E.M., n = 6). (C) Plasma glucagon is suppressed during hyperglycaemic clamp by 31 ± 14% after NN2211 (2 μg·kg^{-1} i.v.) compared to vehicle (P < 0.05, mean ± S.E.M., n = 6). (D) Plasma concentrations of NN2211 after i.v. injection of 2 μg·kg^{-1} remained constant during the clamp period (mean ± S.E.M., n = 6).

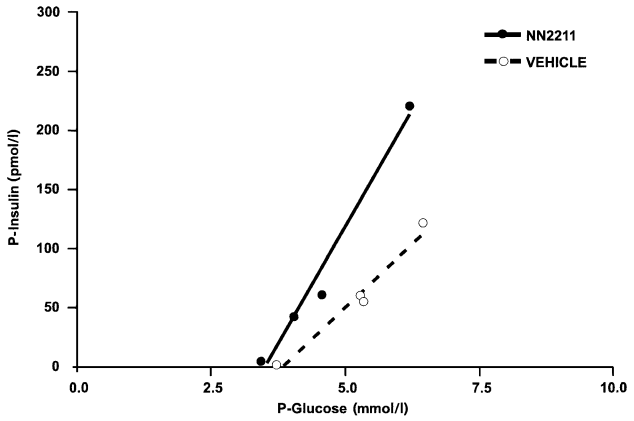

Fig. 3. Correlation between mean plasma glucose and plasma insulin at steady state. The slope of the best-fit line is significantly steeper after NN2211 treatment (2 μg·kg^{-1}, i.v.) after vehicle ($P<0.05$) demonstrating that NN2211 stimulation of insulin secretion is glucose dependent. Two points from each condition (NN2211 or vehicle) are from a low-dose glucose infusion study in a separate group of pigs.

vehicle ($r^2=0.96$, $P<0.05$) conditions, there was a significant linear correlation between plasma insulin and glucose values. There was, however, a significant difference in slope of the best-fit lines between the NN2211 and vehicle treated animals ($P<0.05$), demonstrating that NN2211 stimulation of insulin secretion is glucose dependent (Fig. 3).

3.2. Protocol 2

After treatment with nicotinamide and STZ, 2 animals were characterised as diabetic and 10 as IGT. Because of the severity of diabetes in the two diabetic animals (fasting plasma glucose above 11 mmol l^{-1}), it was considered unethical to randomly allocate the animals to receive vehicle or NN2211 treatment. Therefore, these animals were assigned to receive NN2211, with random allocation of the remainder. The NN2211-treated group was statistically treated as one group ($n=6$, four IGT pigs and two diabetic pigs). In addition, for the glucose and insulin responses, the NN2211-treated animals were further subdivided into those with IGT and those with diabetes, although because of the small number of diabetic animals, further statistical analysis was not possible.

The dose of NN2211 used for s.c. administration was selected because it resulted in plasma levels similar to those obtained after i.v. administration of 2 μg kg^{-1}, which was shown to be effective in the acute study (protocol 1). This dose (3.3 μg kg^{-1}) was well tolerated, with all signs of well-being and behaviour being normal. Animals ate and drank normally, and there were no incidences of vomiting.

Despite the fact that the animals were not randomly allocated to receive NN2211 or vehicle, there was no significant difference in their response to the pre-STZ OGTT (Table 1). Glucose tolerance was significantly worsened by nicotinamide and STZ treatment in animals assigned to receive vehicle treatment, and remained constant over the 4-week vehicle treatment (Table 1). In animals allocated to receive NN2211, the deterioration of glucose tolerance was more pronounced, reflecting the fact that this group included animals with severe diabetes. However, in contrast to vehicle, treatment with NN2211 significantly improved glucose tolerance at both 2 and 4 weeks (Table 1), corresponding to reductions in the glucose excursion to 74 ± 12% and 59 ± 15% of the post-STZ values at 2 and 4 weeks, respectively. When the two subgroups of NN2211-treated animals were examined, the respective values were 73 ± 14% and 68 ± 3% for the IGT group and 65% and 51% for the diabetic group.

Induction of diabetes resulted in an impairment of the insulin response to the OGTT in both vehicle and NN2211 groups. The insulin response remained impaired over the 4-week study period in both groups (Table 2).

The glucose to insulin ratios (calculated from the $AUC_{0-120\ min}$) did not differ between the groups prior to the induction of diabetes (Table 3). In the vehicle group, the ratio increased after STZ treatment and thereafter was unchanged over the 4-week period (Table 3). ANOVA analysis revealed an overall difference ($P<0.05$) between vehicle treatment and the NN2211 (IGT) subgroup, although post hoc analysis to compare the individual time points failed to reach statistical significance. However, NN2211 treatment did result in a reduction of the glucose to insulin ratio, corresponding to falls to 53% ($P<0.001$) and 60% ($P<0.05$) in the IGTs and 20% and 17% in the diabetic animals at 2 and 4 weeks, compared to their respective post-STZ values. Taking the NN2211 as a whole, the corresponding values were 25% at 2 weeks (n.s.) and 20% at 4 weeks ($P<0.05$) compared to NN2211 (all) post-STZ values.

Table 1
Effect of NN2211 (3.3 μg kg^{-1} s.c. once daily) treatment on glucose tolerance during an OGTT (2 g kg^{-1}) before and after induction of diabetes in Göttingen minipigs

	Glucose $AUC_{0-120\ min}$ (mmol l^{-1} min)			
	Pre-STZ	Post-STZ	2 Weeks	4 Weeks
Vehicle	689 ± 21	982 ± 69[a]	974 ± 75[b]	879 ± 111[b]
NN2211(All)	787 ± 53[c]	1950 ± 46[d]	1437 ± 797[e]	1149 ± 287[e]
NN2211(IGT)	777 ± 82[c]	1237 ± 133[f]	914 ± 150[e]	837 ± 107[g]
NN2211(Dia)	806	3375	2222	1774

Data are mean ± S.D., $n=6$ in Vehicle and NN2211(All) groups, $n=4$ in NN2211(IGT) group and $n=2$ in NN2211(Diabetic) group. No statistics is applied with diabetic group because of the low number of animals.

[a] $P<0.01$ vs. vehicle pre-STZ.
[b] n.s. vs. vehicle post-STZ.
[c] n.s. vs. vehicle pre-STZ.
[d] $P<0.05$ vs. NN2211 pre-STZ.
[e] $P<0.05$ vs. NN2211 post-STZ.
[f] $P<0.001$ vs. NN2211 pre-STZ.
[g] $P<0.001$ vs. NN2211 post-STZ.

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