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RESEARCH ARTICLE

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Imatinib prevents beta cell death *in vitro* but does not improve islet transplantation outcome

Aileen J. F. King[a], Lisa A. Griffiths[a], Shanta J. Persaud[a], Peter M. Jones[a], Simon L. Howell[a] and Nils Welsh[b]

[a]Diabetes Research Group, Division of Diabetes and Nutritional Sciences, King's College London, London, United Kingdom;
[b]Department of Medical Cell Biology, Uppsala University, Biomedicum, Uppsala, Sweden

ABSTRACT

Introduction Improving islet transplantation outcome could not only bring benefits to individual patients but also widen the patient pool to which this life-changing treatment is available. Imatinib has previously been shown to protect beta cells from apoptosis in a variety of *in vitro* and *in vivo* models. The aim of this study was to investigate whether imatinib could be used to improve islet transplantation outcome.

Methods Islets were isolated from C57Bl/6 mice and pre-cultured with imatinib prior to exposure to streptozotocin and cytokines *in vitro*. Cell viability and glucose-induced insulin secretion were measured. For transplantation experiments, islets were pre-cultured with imatinib for either 72 h or 24 h prior to transplantation into streptozotocin-diabetic C57Bl/6 mice. In one experimental series mice were also administered imatinib after islet transplantation.

Results Imatinib partially protected islets from beta cell death *in vitro*. However, pre-culturing islets in imatinib or administering the drug to the mice in the days following islet transplantation did not improve blood glucose concentrations more than control-cultured islets.

Conclusion Although imatinib protected against beta cell death from cytokines and streptozotocin *in vitro*, it did not significantly improve syngeneic islet transplantation outcome.

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Introduction

Strategies to improve islet transplantation as a therapy for type 1 diabetes have been extensively studied by research groups across the world, including Uppsala University (1–16) and King's College London (17–25). The advantages are apparent; improving islet transplantation outcome could not only bring benefits to individual patients but also widen the patient pool to which this life-changing treatment is available. The foundation on which such strategies are built is thorough knowledge of islet biology. This is the legacy of Professor Claes Hellerström and the common interest which has led to collaborations between King's College London and Uppsala University spanning the last 40 years (17,26–31). In the current collaboration we have studied the effect of imatinib mesylate (imatinib) on islet transplantation outcome which builds on data generated by the Department of Medical Cell Biology, Uppsala (32–37). Imatinib is an inhibitor of the non-receptor tyrosine kinase c-Abl (38). Activated c-Abl promotes apoptosis through activation of downstream effectors such as the stress-activated protein kinases (JNK and p38 MAP-kinases) (39), the tumour suppressor p73 (40), and caspase 9 (41). As an inhibitor, imatinib therefore has the potential to prevent apoptosis in beta cells and indeed has been shown to protect islets from pro-inflammatory cytokines through an NF-κB-mediated pathway (36). Pre-treatment of the islets was necessary for the protective effect, suggesting a pre-conditioning effect of imatinib. Pre-conditioning of islets for islet transplantation may protect islets against the initial inflammation and hypoxia, which occurs immediately after islet transplantation. The aim of the study was to investigate whether pre-conditioning the islets for transplantation with imatinib improved islet transplantation outcome.

Materials and methods

Animals

All mice were 8–10-week-old males sourced from Harlan (Huntingdon, UK). Mice were housed in 12 h light/dark cycles and had access to pelleted food and water *ad libitum*. C57Bl/6 or ICR mice were used for islet isolation for *in vivo* and *in vitro* experiments, respectively. To induce diabetes, C57Bl/6 mice were injected with 180 mg/kg streptozotocin (Sigma-Aldrich, Poole, UK) 5–7 days prior to islet transplantation. Blood glucose concentrations were monitored using Accu-Chek blood glucose meter and strips (Accu-Chek Aviva, Roche Diagnostics, Burgess Hill, UK), and mice with blood glucose concentrations over 20 mM were considered diabetic. All animal experiments were ethically approved by our institution and were carried out under

CONTACT Aileen King aileen.king@kcl.ac.uk Diabetes Research Group, Division of Diabetes and Nutritional Sciences, King's College London, Guy's Campus, London SE1 1UL, United Kingdom

licence in accordance with the UK Home Office Animals (Scientific Procedures) Act 1986.

Islet isolation

Islets were isolated using collagenase digestion and gradient purification as previously described. Briefly, mice were killed by cervical dislocation and the pancreatic duct was clamped at the ampulla of Vater. A volume of 2 mL of collagenase (Type XI, 1 mg/mL, Sigma-Aldrich) were injected into the pancreatic duct before removal of the distended pancreas and incubation for 10 min at 37 °C. Islets were purified from the pancreatic digest using a Histopaque-1077 (Sigma-Aldrich) gradient. Islets were washed and subsequently cultured in RPMI 1640 (Sigma-Aldrich) supplemented with 10% foetal calf serum (FCS; Sigma-Aldrich), 2 mM L-glutamine, and antibiotics (100 units/mL penicillin + 100 ng/mL streptomycin; Sigma-Aldrich).

Cytokine treatment *in vitro*

Islets from ICR mice were pre-cultured for 24 h in the presence or absence of 10 μM imatinib (Selleckchem, Suffolk, UK) prior to the exposure of the islets to 50 U/mL IL-1β (PeproTech, London, UK), 1,000 U/mL TNF-α (PeproTech), and 1,000 U/mL IFN-γ (PeproTech) for 24 hours. Apoptosis in the islets was then measured by Caspase-Glo 3/7 (Promega, Southampton, UK), and viability was measured by Cell-titer Glo (Promega) which detects ATP.

Streptozotocin treatment *in vitro*

Islets from ICR mice were pre-cultured for 24 h in the presence or absence of 10 μM imatinib prior to the exposure of the islets to 1.5 mM streptozotocin in serum-free RPMI media containing 5.6 mM glucose. After 30 min the islets were washed and placed in normal culture conditions overnight (RPMI 1640 with 11.1 mM glucose and 10% FCS). Apoptosis in the islets was then measured by Caspase-Glo 3/7. Islet function was assessed by measuring glucose-induced insulin secretion.

Glucose-induced insulin secretion

Insulin secretion was measured as previously described in detail (18). Islets were pre-incubated for 2 h in RPMI media containing 2 mM glucose and 10% foetal calf serum. For each experiment, eight to ten groups of three islets were picked into 1.5 mL Eppendorf tubes containing a bicarbonate-buffered physiological salt solution, containing 2 mM $CaCl_2$ and 0.5 mg/mL BSA with 2 mM or 20 mM glucose. The islets were incubated at 37 °C for 1 hour at each glucose concentration. Supernatants were removed and frozen until insulin was measured by an in-house radioimmunoassay (42).

Islet transplantation

Donor islets were isolated from C57Bl/6 mice and pre-cultured in the presence or absence of 10 μM imatinib. A minimal mass of 200 islets were syngeneically implanted under the kidney capsule of streptozotocin-diabetic C57Bl/6 recipients. Briefly, animals were anaesthetized using isoflurane (1%–5% isoflurane, 95% oxygen). Buprenorphine, 30 μg/kg, was administered as an analgesic at the start of surgery. Once the animal was anaesthetized, an incision was made on the left flank. The kidney was externalized and an incision made in the kidney capsule. Islets were centrifuged into PE50 tubing (Becton Dickinson, Sparks, MD, USA), and a Hamilton syringe (Fisher, Pittsburg, PA, USA) was used to deliver the islets under the kidney capsule. Three series of transplantation experiments were carried out. In the first experimental series islets were pre-cultured for 3 days in the presence or absence of 10 μM imatinib, and in the second experimental series the islets were pre-cultured for 24 h in the presence or absence of 10 μM imatinib. In both cases the mice were monitored for 14 days. In the third experimental series, we focused on the immediate post-transplantation period. Islets were pre-cultured for 24 h in the presence or absence of 10 μM imatinib, and imatinib was also administered by gavage to the recipient mice (200 mg/kg) 1 h prior to transplantation and daily thereafter. The mice were killed, and the islet graft-bearing kidneys were removed to measure insulin content as previously described (20).

Statistics

Data were analysed using Sigmaplot (Systat Software Inc., Hounslow, UK). Two groups were compared using an unpaired *t* test, whereas three or more groups were analysed using a one-way ANOVA. Blood glucose data were analysed using two-way repeated measures (rm) ANOVA.

Results

Pre-treatment of islets with imatinib partially protects islets from cytokine-induced damage *in vitro*

Pre-treatment of islets with 10 μM imatinib for 24 h partially protected from cytokine-induced apoptosis (Figure 1A). In addition, viability was increased in islets pre-treated with 10 μM imatinib prior to exposure to cytokines (Figure 1B).

Pre-treatment of islets with imatinib partially protects islets from streptozotocin-induced damage *in vitro*

Pre-treatment of islets with 10 μM imatinib for 24 h partially protected from streptozotocin-induced apoptosis (Figure 2A). This was also shown to be protective against streptozotocin-induced disruption to glucose-induced insulin release (Figure 2B). Imatinib per se had no effect on glucose-induced insulin secretion.

Pre-treatment of islets with imatinib does not affect islet transplantation outcome

Pre-treatment of islets with imatinib for 3 days prior to transplantation did not affect islet transplantation outcome (Figure 3A). A similar pattern was seen when islets were

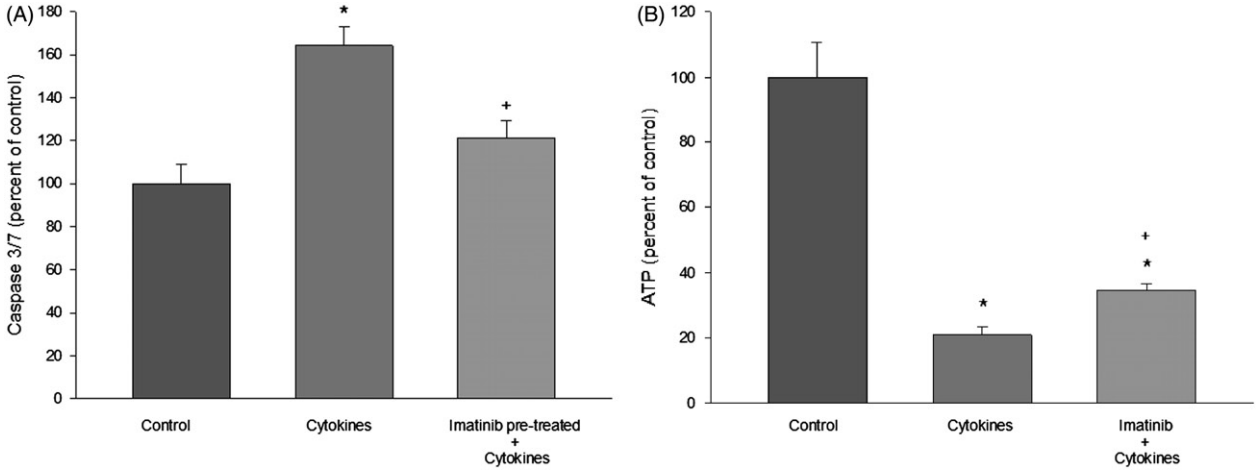

Figure 1. Islets pre-treated with imatinib are partially protected against cytokine-induced damage as shown by reduced levels of apoptosis (A) and increased ATP contents (B). $^{*}P < 0.05$ versus control; $^{+}P < 0.05$ versus cytokines. One-way ANOVA, $n = 5$–8.

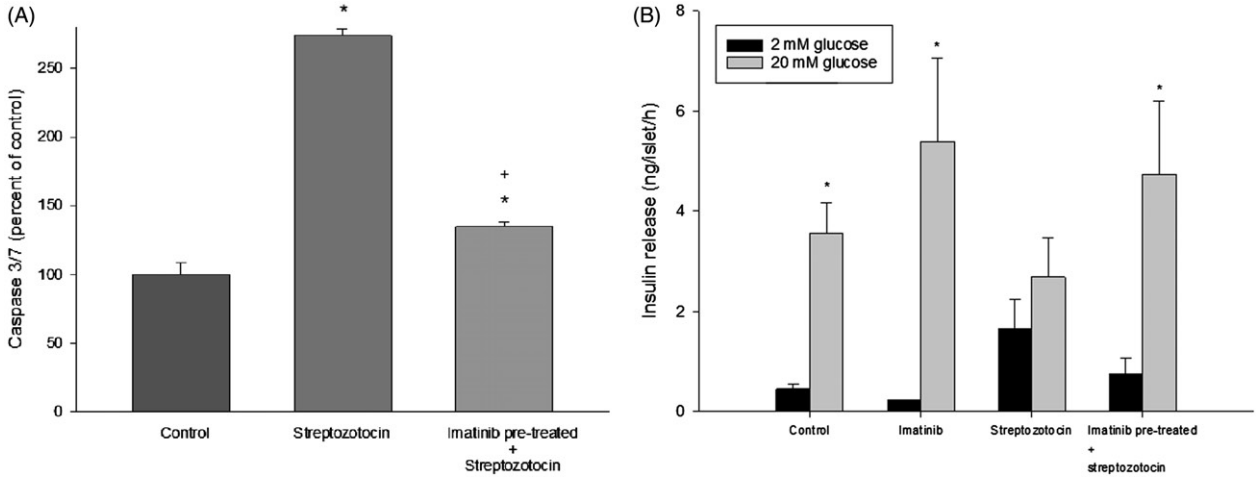

Figure 2. Islets pre-treated with imatinib are partially protected against streptozotocin-induced damage as shown by reduced levels of apoptosis (A) and retaining glucose robust induced insulin secretion (B). A: $^{*}P < 0.05$ versus control; $^{+}P < 0.05$ versus cytokines; one-way ANOVA, $n = 6$–10. B: $^{*}P < 0.05$ versus 2 mM in respective treatment group, t test, $n = 7$.

pre-treated with imatinib for 24 h prior to islet transplantation (Figure 3B).

Pre-treatment of islets with imatinib combined with donor treatment transiently improved islet transplantation outcome in the immediate post-transplantation period

In a third transplantation series we pre-treated the islets with imatinib for 24 h and also administered imatinib to the mice by gavage. In these animals, there was significantly reduced blood glucose concentrations in mice that received imatinib gavage combined with imatinib pre-treated islets on the first 2 days after implantation, but this effect was lost by day three (Figure 4A). Graft insulin content was not significantly different between the treatments (Figure 4B). Mice gavaged with imatinib that did not receive an islet graft remained overtly diabetic.

Discussion

We have shown that pre-treatment of islets with imatinib partially protected islets from both cytokine and streptozotocin-induced damage *in vitro*. This is in agreement with previous studies which have shown the ability of imatinib to inhibit apoptosis in various cell types (43,44) including insulin-producing cells (33,34,45). The mechanism may be dependent on c-Abl rather than c-Kit, which is an alternative target of imatinib (34,46). Pre-incubation of islets with imatinib is necessary to provide protection against streptozotocin, nitric oxide, and cytokines, which indicates a state of preconditioning (33). Exactly how imatinib promotes improved beta-cell survival is not clear, but it has been proposed that altered signalling via the JNK, ERK, PI3K, β-catenin, NF-κB, and PKCδ signalling pathways may alone, or in combinations, mediate the effects of imatinib (33–36,45,47,48). Of these pathways, the NF-κB and JNK pathways have been studied in relation to islet transplantation outcome. Although short-term exposure of islets to imatinib is associated with NF-κB activation, longer incubation periods as used in the current study reduce NF-κB activation in beta cells (36), leading to a lower sensitivity to cytokines. While this effect was seen in the *in vitro* experiments, this did not translate to improved islet transplantation outcomes in our minimal mass transplantation model in mice. The effects of NF-κB activation on islet transplantation outcome are

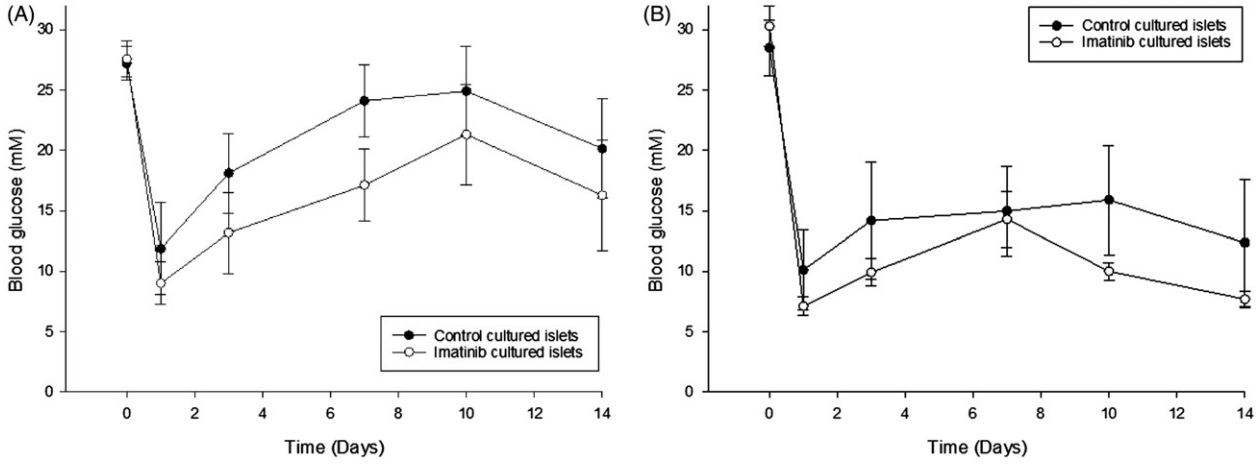

Figure 3. Blood glucose concentrations of diabetic mice after transplantation of 200 islets pre-cultured with imatinib for 3 days (A) or 24 hours (B). Two-way rm ANOVA, effect of imatinib $P = 0.356$ (A), and $P = 0.358$ (B). Effect of time $P < 0.05$ in (A) and (B); $n = 5$ (A) and $n = 5$–7 (B).

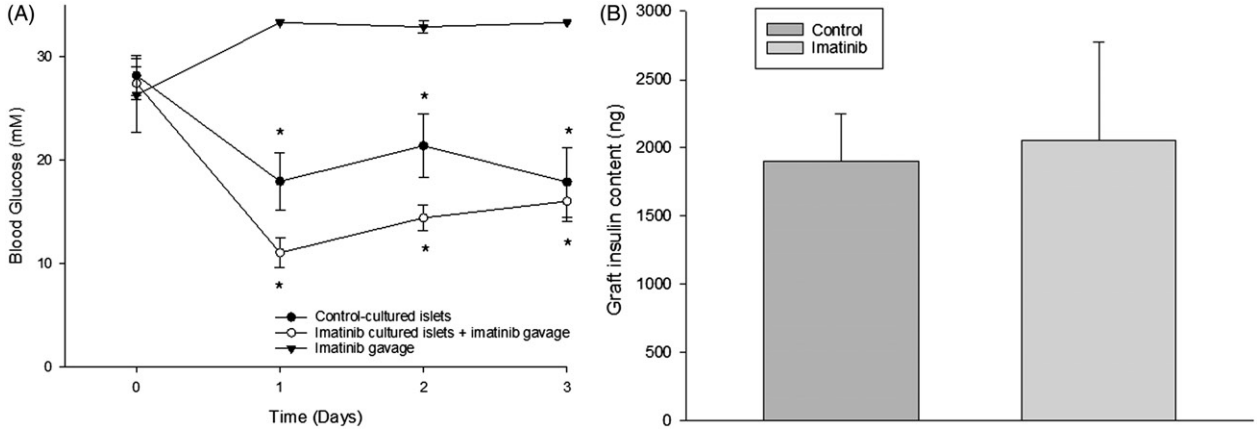

Figure 4. A: Blood glucose concentrations of diabetic mice after transplantation of 200 control-cultured islets or 200 islets pre-cultured with imatinib for 24 hours combined with the recipient receiving imatinib by gavage. A separate group of non-transplanted animals received imatinib gavage. $^{*}P < 0.01$ versus non-transplanted imatinib gavage; $^{+}P < 0.05$ versus control-cultured islet graft. Two-way rm ANOVA, $n = 6$–7. B: Insulin content of islet grafts on day three after transplantation. $P = 0.873$, t test, $n = 5$–7.

ambiguous, with studies suggesting that acute inactivation may be beneficial (49–51), whereas chronic inactivation may be ineffective (52). The role of JNK in islet transplantation has also been investigated. Inhibition of JNK during human or pig islet isolation (53–55) and culture (54) improves transplantation outcome in a mouse model.

One reason for the differing results *in vivo* compared with *in vitro* could be that the *in vitro* environment does not reflect the stresses that islets face in the post-transplantation period. One important difference may be the levels of oxygen available, which has previously been implicated as an important factor in islet NF-κB activation in response to transplantation (49). Also it should be noted that only partial protection was seen *in vitro*, which may not be sufficient to change the outcome of transplantation. However, it is worth noting that, although not reaching statistical significance, in every experimental series the imatinib-treated islets performed marginally better than the control islets, which may be indicative of a subtle effect. This is similar to our previous study where inhibition of NF-κB in islets prior to implantation using salicylate had a subtle but non-significant effect ($P < 0.072$) (52). However, subtle effects mediated by other pathways such as JNK, ERK, beta-catenin, and PKCδ cannot be ruled out. We have previously noted that promising results in islets *in vitro* do not always lead to improved function after transplantation; for example, prevention of endothelial cell death in islets *in vitro* did not improve islet transplantation outcome (19). One factor which may be of importance is the ability of the protective compound to sustain beneficial effects after islet transplantation. Although imatinib seems to be able to protect islets *in vitro* after its removal, its ability to be effective *in vivo* may require further exposure. Indeed, when we administered imatinib to the mice immediately before and for 3 days after implantation a significant improvement was seen in blood glucose concentrations. However, this effect was lost by day three, which is evident by no difference in insulin content of the grafts upon removal.

We have previously improved islet transplantation outcome by pre-treating the islets *in vitro* with either cells (21,22) or compounds (24,56). Interestingly, these interventions, which have been successful, have all improved glucose-induced insulin secretion in the islets prior to transplantation. It is perhaps not surprising that implanting well-functioning islets may be the key to successful transplantation outcome.

The superior outcome of islet transplantation outcome when islets were only cultured for 1 day (Figures 3B and 4A) rather than 3 days (Figure 3A) may also reflect this point, with cultured islets losing beta cell mass. Although it has been well documented that inflammation around the time of transplantation leads to loss of a substantial amount of the islets (57,58), pre-treatment of islets against inflammation may not be sufficient to protect them against the harsh *in vivo* environment. We are therefore currently focusing on strategies that will deliver anti-inflammatory agents to the site of implantation. To do this we have applied a layer-by-layer nanoencapsulation method which can incorporate anti-inflammatory peptides such as α1-anti-trypsin (59). It is possible that this strategy combined with using insulinotropic peptides will lead to better function and survival of islets in a transplantation setting.

Disclosure statement

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