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# Imatinib mesylate improves insulin sensitivity and glucose disposal rates in high-fat diet fed rats

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Key words: imatinib mesylate, high-fat diet, glucose disposal, insulin sensitivity

#### Abstract

The aim of the present study was to investigate whether imatinib affects the insulin sensitivity and glucose disposal of high-fat fed rats. Sprague-Dawley rats were fed either a standard pelleted rat food or a high-fat (60%) diet for 8 weeks. During the ten last days of the high-fat diet regime rats were gavaged daily with 0, 50 or 100 mg/kg of imatinib. The higher dose of imatinib resulted in a decreased psoas fat pad weight of the high-fat treated rats. At euglycemic, hyperinsulinemic clamp conditions high-fat fed rats exhibited increased insulin concentrations and a decreased glucose disposal. The moderate dose of imatinib, but not the high, normalized insulin sensitivity and glucose disposal without affecting the glucose metabolism in control rats. The hepatic glucose production at both fasting and hyperinsulinemic conditions was only weakly affected by imatinib. We conclude that a moderate dose of imatinib efficiently counteracts high-fat induced peripheral insulin resistance and that further studies on the mechanisms by which imatinib increases insulin action in muscle and fat tissues might generate novel strategies for the treatment of Type 2 diabetes.

#### Introduction

Imatinib mesylate, also known as Gleevec or STI571, is a selective tyrosine kinase inhibitor that specifically inhibits the cellular Abelson tyrosine kinase (c-Abl), the platelet derived growth factor receptor (PDGFR), the transmembrane receptor tyrosine kinase (c-Kit), and the Abl related gene (Arg) [1,2]. Imatinib is successfully used in the clinic to treat malignancies such as chronic myeloid leukemia and gastrointestinal stromal tumors [3,4]. Furthermore, it has recently been observed that a modest number of patients, suffering from both chronic myeloid leukemia and Type 2 diabetes, were successfully treated for not only their leukemia, but also for diabetes, when given imatinib [5,6]. Although the beneficial effect of imatinib in Type 2 diabetes were not reported in a third study also with modest number of cases [7], two additional case report have observed a blood glucose lowering effect of imatinib in patients with gastrointestinal stromal tumor [8] and paraneoplastic insulin resistance syndrome [9]. The molecular mechanisms underlying the beneficial effects of imatinib in these cases are unknown, but we have recently observed that imatinib may counteract diabetes by preserving beta-cell viability and mass [10,11]. It appears that imatinib decreases c-Jun N-terminal kinase (JNK)-activation in beta-cells, which leads to protection against apoptosis [11]. However, as these findings were observed in animal models for Type 1 diabetes, namely the NOD mouse and the streptozotocininjected mouse, it is possible that imatinib in Type 2 diabetes also acts by affecting peripheral insulin sensitivity and/or hepatic glucose production. Interestingly, JNKactivation, which occurs in peripheral tissues in response to oxidative stress, has been implicated in the pathogenesis of insulin resistance and Type 2 diabetes [12]. Thus, it might be that imatinib, by preventing JNK-activation, not only protects beta-cells from apoptosis, but also decreases insulin resistance.

Rats given a high-fat diet are known to develop obesity, mild hyperglycemia and decreased insulin sensitivity in muscle, fat and liver [13], and are therefore used as a model of diet-induced obesity and glucose intolerance in humans. We presently exposed high-fat fed rats to imatinib for 10 days and analyzed whole body insulin action. Our findings indicate that a moderate dose of imatinib efficiently counteracts the metabolic consequences of the high-fat diet by lowering the whole body insulin resistance.

#### Materials and methods

Animals: Male Sprague-Dawley rats aged 4 weeks were purchased from B&M, Ry, Denmark. Animals were weighed at the start of the experiment and weekly thereafter. Blood glucose concentrations were measured each week using the ExacTech blood glucose meter (Medisense AB, Stockholm, Sweden). All animal experiments were approved by the local animal ethics committee for Uppsala University.

**High-fat diet and imatinib-treatment:** Animals had free access to either standard pelleted rat food or a high-fat diet (60% fat) from Research Diets, Inc, (New Brunswick, NJ, USA), product number D12492. This high-fat diet lacks corn starch, is low in sucrose and is high in lard (24,5 gm%). The high-fat diet was initiated when rats were 5 weeks of age and continued for a total of 8 weeks. During the last 10 days of the high-fat treatment, imatinib was dissolved in H<sub>2</sub>O and administered daily by gavage at either 0, 50 or 100 mg/kg bodyweight to both control and high-fat treated rats.

**Preparation of animals for clamp study:** The tenth and final imatinib gavage was given to the rats in the morning of the clamp day, after an over-night fast. Three hours later the rats were then anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg; Mebumal; Apotekbolaget, Umeå, Sweden), heparinized and placed on an operating table coupled to thermal pads programmed to maintain body temperature of 38°C. The anesthetized rats were tracheotomized and polyethylene catheters were inserted into both femoral veins (connected to peristaltic pumps), one femoral artery (blood sampling) and one carotid artery (blood pressure monitoring using the PDCR 75/1 (Druck, Groby, UK) pressure transducer). Once the mean arterial blood pressure had stabilized at >90 mm Hg, a 30 min infusion of 0,49  $\mu$ Ci/min D-[3-<sup>3</sup>H]-glucose (Amersham Biosciences) in glucose-free saline was started. During this period blood glucose was analyzed every 10 min and samples were taken for <sup>3</sup>H-glucose determinations every 10 min and for insulin at 0 and 30 min.

Euglycemic and hyperinsulinemic clamp procedure: The clamp was performed essentially as previously described [14,15]. A 30% glucose solution, supplemented with 1  $\mu$ Ci <sup>3</sup>H-glucose/ml, was infused for 60 min at a fixed rate of 27 mg glucose/kg bodyweight x min. Simultaneously, another peristaltic pump delivered human recombinant insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark), at an initial rate

of 18 mU/kg bodyweight x min. The rate of the insulin infusion was adjusted during the beginning of the clamp, in order to keep the blood glucose concentration constant at  $\approx 6$  mM glucose. Blood glucose was analyzed every 5 min and blood samples (100 µl) were taken for <sup>3</sup>H-glucose determinations every 15 min. Insulin was analyzed at 30 and 60 min. After the 60 min clamp, the rats were killed and the pancreas and the psoas fat pad were removed and weighed.

**Determination of <sup>3</sup>H-glucose activity in plasma:** Blood samples were centrifuged, deproteinized and evaporated as previously described [12]. The samples were then dissolved in 100  $\mu$ l of water, followed by the addition of 1 ml of Ultima Gold (Perkin Elmer) scintillant. Tritium counts were quantified in a Wallac 1409 liquid scintillation counter. Glucose disposal rates were calculated using Steeles equation [16].

**Plasma insulin concentration:** Plasma samples were obtained through centrifugation and analysed for insulin content using ultrasensitive rat insulin ELISA (Mercodia, Uppsala, Sweden).

**Statisitcal analysis:** All results are presented as means  $\pm$  SEM. Significant differences were calculated using two-way or one-way ANOVA and the Student Newman Keul post-hoc test.

#### RESULTS

We have previously observed that imatinib counteracts diabetes in mice by promoting beta-cell survival [10,11]. To evaluate whether imatinib also counteracts diabetes by interacting with peripheral insulin sensitivity, we have presently analyzed the effects of imatinib on glucose production and uptake in rats treated with a high-fat diet. Briefly, 47 male Sprague-Dawley rats were given standard rat chow or a high-fat diet for 8 weeks. Out of the total 47 rats 9 were lost or excluded due to gavage to the lung or surgical complications. Among the 9 excluded rats two were low-fat control, three were high-fat imatinib 50, one was low-fat imatinib 100 and three were high-fat

After 6 weeks of high-fat diet, we observed an increased blood glucose concentration in non-fasted rats ( $5.29\pm0.15$  and  $6.07\pm0.19$  mM glucose for control and high-fat treated rats, respectively. P<0.001 using Student's t-test). After 6 weeks of diet the

weight of the control rats was  $445 \pm 6.1$  grams and the weight of the high fat treated rats was  $491 \pm 7.9$  grams (p<0.001 using Student t-test). The high-fat diet increased body weight and psoas fat pad weight also after the full 8 weeks (Fig. 1).

During the last 10 days of this regime, the rats were gavaged daily with saline (control), 50 mg/kg or 100 mg/kg body weight imatinib. We observed that the high-fat diet-induced increase in body weight and psoas fat weight was significantly attenuated by the high dose of imatinib (Fig. 1).

We also determined hematocrit and mean arterial blood pressure at the beginning of the procedure and the pancreatic weight at the end (Table 1). We observed that the hemoatocrit was decreased by the high dose of imatinib in both low fat and high fat treated rats. The pancreas weight was significantly increased by imatinib in low-fat treated rats (Table 1).

Imatinib treatment did not affect food intake during the last 10 days. A typical food intake during a 3 day period was 144, 144 and 156 grams for two control rats gavaged with 0, 50 and 100 mg/kg imatinib, respectively, and 116, 92 and 119 grams for two high fat rats with 0, 50 and 100 mg/kg imatinib, respectively.

Three hours after the final imatinib administration the over-night fasted rats were anesthetized, tracheostomized and catheterized. A 30 min <sup>3</sup>H-glucose infusion was performed on the rats and plasma insulin, blood glucose and whole body glucose utilization, measured by scintillation counting, was determined. We found that the fasting blood glucose concentrations directly after anesthesia and surgery were unaffected in high-fat rats as compared to control rats (Fig. 2A). This is at variance with the results obtained with non-anesthetized and non-fasted rats (see above), but it is easily envisaged that both over-night fasting and anesthesia could mask the hyperglycemic effect of the high fat diet. It was also observed that imatinib did not affect the fasting blood glucose concentration of the control rats at time 0. However, in high-fat fed rats imatinib increased fasting blood glucose both at time 0 and after 30 min (Fig. 2A). Also in control rats the blood glucose was increased in response to the high imatinib concentration after 30 min of anesthesia. Indeed, the mean arterial blood pressure seemed to be higher in imatinib treated low-fat rats after anesthesia (Table 1). Surprisingly, the mean arterial blood pressure was lowered by the low dose of imatinib in the high-fat treated rats.

The imatinib-induced increase in blood glucose of the high-fat rats at 0 min was paralleled by an increase in plasma insulin levels (Fig. 2B). Also in control rats there

was a modest increase in plasma insulin levels at the high imatinib concentration. However, at 30 min imatinib affected insulin levels neither in control nor in high-fat rats. Instead, insulin levels were higher in the high-fat rats as compared to control rats. The glucose disposal rate before start of the clamp was moderately increased in control rats treated with the high dose of imatinib as compared to no imatinib treatment (19.8±0.7 vs. 13.6±1.7 mg glucose/kg x min for LF100 and LFC rats, respectively, p<0.05). This effect was, however, not observed in high-fat fed rats (12.2±0.7 vs 14.2±1.2 for HF100 and HFC rats, respectively). The glucose disposal rates were not affected in the rats receiving the lower dose of imatinib (16.8±0.8 and 13.9±2.7 mg/kg x min for LF50 and HF50 rats, respectively). As glucose disposal rates equal hepatic glucose output at fasting conditions, it is likely that the imatinibinduced increase in blood glucose resulted, in part, from an increase in hepatic glucose production.

After the 30 min <sup>3</sup>H-glucose infusion at fasting conditions, a hyperinsulinemic, euglycemic ( $\approx 6$  mM glucose) clamp was initiated. Plasma insulin levels during euglycemic equilibrium at the end of clamp were significantly higher in the high-fat treated rats as compared to control rats (Fig. 3A). Interestingly, the low dose of imatinib completely normalized the insulin requirement during the clamp (Fig. 3A). An intermediate effect was observed with the high dose of imatinib. Imatinib did not affect insulin sensitivity in control rats (Fig. 3A).

There were no significant differences in glucose disposal rates between the different groups during the clamp (results not shown). However, as insulin was delivered at different rates and the plasma insulin levels therefore were significantly different (Fig. 3A), and because glucose disposal rates are known to correlate well with insulin levels [17], we expressed glucose disposal rates per plasma insulin levels normalized to the low-fat control. In this case we observed a lowering effect of a high-fat diet upon glucose disposal rates (Fig. 3B), which is in good agreement with the decreased insulin sensitivity observed in Figure 3A. Interestingly, the low dose of imatinib increased glucose disposal rates both in low-fat and high-fat treated rats (Fig. 3B). No significant effect was exerted by the high dose of imatinib.

Since the hepatic glucose output rate equals the difference between the glucose infusion rate and the glucose disposal rate, we consequently observed that high-fat treated rats exhibited an increased hepatic glucose output as compared to low-fat treated rats (Fig. 4). Again, the low dose of imatinib significantly decreased the

hepatic glucose output rate in low-fat rats, but the effect in high-fat rats did not reach statistical significance.

#### DISCUSSION

In the present investigation, two doses of imatinib were administered, namely 50 or 100 mg/kg. In rats, the lower dose, 50 mg/kg or 0.045 mg/cm<sup>2</sup> for a rat weighing 500 grams, has been reported to result in a peak plasma concentration of approximately 10  $\mu$ M [18]. In humans, the maximal plasma imatinib level reaches 4  $\mu$ M using the conventional 600 mg dose [19], which corresponds to 0.035 mg/cm<sup>2</sup> assuming a body weight of 80 kg. It has been observed in pre-clinical rat toxicological studies that most toxicities start to appear at the clinical dose adjusted for body weight [19], indicating that the 100 mg/kg dose, but probably not the 50 mg/kg dose, may be associated with some toxicity. Indeed, as the high dose provoked a multitude of effects including rather dramatic decreases in hematocrit, body weight and psoas fat pad weight, it is likely that most of these changes occurred as the result of toxicity and that damage to other organs, such as the liver and the kidney, might have taken place as well. The complex metabolic alterations presently observed in response to the high dose of imatinib are therefore not easily interpretable.

The low dose of imatinib did not significantly affect body weight, psoas fat pad weight, hematocrit, blood pressure or fasting blood glucose and insulin levels. Thus, we could not observe any signs of toxicity in response to 50 mg/kg of imatinib. Instead the low dose of imatinib increased blood glucose and insulin levels of anaesthetized and high-fat fed rats. It is not clear why imatinib increases blood glucose and insulin levels during these specific conditions, but it could be speculated that high concentrations of imatinib and a high-fat diet together augment the anesthesia/surgery-induced sympathetic stress response. After 30 min of anesthesia the insulin level was no longer augmented, which may have resulted from a gradual increase in surgery/anesthesia-induced inhibition of insulin release [20], or a diminished stress response.

The high-fat diet given to the rats resulted in increased body weight, poas fat pad weight, blood glucose and serum insulin concentrations - during both fasting anesthesia and euglycemic clamp conditions - and hepatic glucose output, and in decreased glucose disposal rates, all signs typical for diet-induced Type 2 diabetes.

The low dose of imatinib partially or completely counteracted all these high-fat induced effects. These findings suggest that high-fat diet-induced whole body insulin resistance is counteracted by imatinib, and that the drug increases both muscle/fat and liver insulin sensitivity. We cannot exclude a beta-cell protective role of imatinib in the high-fat treated rat, but the rather short treatment period (10 days) argues against dramatic changes in beta-cell mass and function.

The mechanisms by which imatinib decreases insulin resistance and to a modest extent hepatic glucose production are not known. It is possible that the improved insulin sensitivity arises, at least in part, secondary to the slimming effect of imatinib. On the other hand, it appears that the Type 2 diabetes patients that were successfully treated for their diabetes with imatinib did not loose weight during the treatment [5,6]. An alternative explanation could be that imatinib decreases JNK-activation in peripheral tissues, as demonstrated in islets [11]. A high fat diet is known to promote mitochondrial reactive oxygen species production, which in turn leads to increased JNK activity and insulin resistance [21]. Indeed, activation of c-Abl has been demonstrated to result in phosphorylation of the MAP and ERK Kinase-1 (MEKK1), which in turn promotes MKK4 and JNK activation [22]. Thus, it is conceivable that JNK-activation during diet-induced oxidative stress is negatively modulated by the c-Abl inhibitor imatinib. Finally, it has recently been observed that imatinib attenuates PDGFR-induced phosphorylation of the low-density lipoprotein receptor-related protein (LPR) [23], which in turn might lead to an improved lipoprotein metabolism [24] and protection against atherosclerosis [25]. To what extent this mechanism operates in high fat-induced glucose intolerance and the development of Type 2 diabetes remains also to be elucidated.

We have presently observed beneficial effects of a moderate (50 mg/kg) imatinib dose when given to the high-fat diet rats. On the other hand, the high dose of imatinib evoked unclear and complicated actions possibly involving toxicity. The side effects of imatinib in treatment of CML and GIST-tumors preclude imatinib from being used as a treatment of Type 2 diabetes. However, with a better understanding of the mechanisms by which imatinib counteracts diabetes a novel imatinib-like drug could possibly be generated that exhibits a better side-effect profile.

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	LF	LF50	LF100	HF	HF50	HF100
Hemotocrit	49.4±1.0	45.9±0.8	44.8±0.7	47.6±2.6	44.8±0.9	41.6±0.8*
(%)						
Mean	97±5.5	110±4.9	108±4.9	110±5.4	91±1.0*	99±7.4
arterial						
blood						
pressure						
(mm Hg)						
Pancreas	$1.43 \pm 0.04$	1.60±0.04*	1.69±0.04*	1.50±0.,09	$1.42 \pm 0.08$	$1.62 \pm 0.07$
weight (g)						

Table 1. Hematocrit, mean arterial blood pressure and pancreas weight of rats included in the present study. Hematocrit and arterial blood pressure was determined directly after anaesthetization, surgery and catheterization, i.e. at time 0. The pancreas weight was determined directly after end of experiment. Results are means  $\pm$  SEM. \* denotes p<0.05 vs. corresponding control using two-way ANOVA and the Student Newman-Keul test as post-hoc test.

#### Legends to the Figures

Figure 1. A high dose of imatinib counteracted the high-fat induced increase in total body weight (left panel) and psoas fat weight (right panel). LF and HF stand for low-fat diet and high-fat diet, respectively. C, 50 and 100 stand for gavage with 0, 50 or 100 mg/kg imatinib, respectively. Bars are means  $\pm$  SEM for 5-9 rats. \* and \*\* denote p<0.05 and p<0.01, respectively, using one-way ANOVA for repeated measurements and the Student Newman-Keul post-hoc test.

Figure 2. Blood glucose concentrations (A) and plasma insulin levels (B) at 0 and 30 min after anesthesia and surgery. Rats were anesthetized using pentobarbital and surgery was performed. Blood was taken from a catheter after anaesthesia at the time points indicated in the Figure and the glucose concentration was determined using the ExacTech blood glucose meter. Plasma insulin levels were determined using a ultrasensitive rat insulin ELISA. \* denotes p<0.05 vs. respective control using one-way ANOVA for repeated measurements and the Student Newman-Keul post-hoc test.

Figure 3. Imatinib at 50 mg/kg body weight restored insulin sensitivity (A) and whole body glucose disposal (B) in high-fat treated rats. A euglycemic (6 mM), hyperinsulinemic clamp was performed on the anesthetized rats. Blood samples were taken and insulin levels were determined. Glucose disposal rates are corrected for differences in plasma insulin levels by calculating Gd/insulin ratios and using insulin levels normalized to the LF C group. Bars are means  $\pm$  SEM for 5-9 rats. \* denotes p<0.05 using one-way ANOVA for repeated measurements and the Student Newman-Keul post-hoc test.

**Figure 4. Hepatic glucose output.** Hepatic glucose output was calculated from the data in Figure 3 and the glucose infusion rate of 13.6 mg/min per rat. . \* denotes p<0.05 using one-way ANOVA for repeated measurements and the Student Newman-Keul post-hoc test.















