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Letter to the editor

Diabetes in rats is cured by islet transplantation.....but only during daytime.

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Running header: Continuous blood glucose monitoring in rats.

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To the editor,

Rats and mice are commonly used as animal models in diabetes research with blood glucose concentrations often used as endpoints of the study. Most islet transplantation studies assess blood glucose levels during the day, primarily for practical reasons. However, blood glucose concentrations can vary depending on food intake and activity, both of which peak during the night in these nocturnal animals (1,2). Indeed, it has been shown that blood glucose concentrations in normal non-diabetic rats peak during the night (3). Most studies carried out in diabetic animals do not report the time of day at which blood glucose is measured and whether this is kept constant throughout the study. We here present evidence obtained using continuous glucose monitoring in rat islet graft recipients which suggests that the perceived outcome of the islet transplantation may depend upon the timing of the monitoring of glycemic control.

We used HD-XG continuous glucose telemetry implants (Data Sciences International, St Paul, MN, USA) to observe large circadian variations in blood glucose in streptozotocin-induced diabetic male Lewis rats receiving islet grafts to normalize glycemic control. At the time of transplantation, rats weighed between 250-275g. Blood glucose concentrations in the descending aorta were recorded every 10 seconds for 19 days in conscious unrestrained rats maintained in a 12h:12h light:dark cycle to allow detailed analysis of circadian changes in blood glucose concentrations in unrestrained, undisturbed rats. Each rat generated over 164,000 individual blood glucose measurements, so for statistical analysis average blood glucose concentrations for each day (7am-7pm) and night cycle (7pm-7am) were calculated.

We noted that under normal conditions before streptozotocin administration there was minimal fluctuation in blood glucose concentrations when comparing average day time values to average night time values (day: 6.9 ± 0.6 mM vs night: 7.2 ± 0.7 mmol/l, $p=0.764$, t-test. Average day-night difference: 0.42 ± 0.1 mmol/l). However, after streptozotocin treatment to induce experimental diabetes, the circadian variations in average blood glucose concentrations were much more pronounced (day: 24.7 ± 2.8 mmol/l vs night: 33.0 ± 4.8 mmol/l; average excursion: 8.3 ± 1.2 mmol/l, $p < 0.0001$ vs pre-STZ, t-test. Data within 5 hours of an insulin injection were excluded). In two animals, subsequent islet transplantation (2,000 and 3,000 islets respectively transplanted under the kidney capsule) markedly improved glycaemia, with day time means of 10.5 mmol/l and 11.0 mmol/l. Different doses of islets were used in order to compare a minimal mass model (7,500 islets/kg) to a considerably higher dose of islets (12,000 islets/kg). However, despite this difference significant night excursions in blood glucose remained in both rats, with night time means of 14.6 mmol/l and 14.8 mmol/l respectively ($p < 0.0001$ vs respective mean day glucose concentrations, t-test. Mean excursions: 3.8 mmol/l and 4.2 mmol/l respectively). A third rat implanted with a minimal mass of 2,000 islets remained hyperglycaemic after receiving the islet graft and showed substantial day vs night glucose excursions, similar to that seen after STZ-treatment (mean day blood glucose: 25.2 mmol/l vs night blood glucose 38.1 mmol/l, $p < 0.0001$, t-test. Mean excursion 12.0 mmol/l). Figure 1 shows representative traces of blood glucose concentrations over the 19 days of the study in a rat with improved glycaemia after transplantation (Fig. 1A) and a rat with a non-functional graft (Fig. 1B). In both cases it is clear that, after the induction of diabetes, there is a considerable increase in the circadian variation in blood glucose concentrations (Fig 1 A,B) irrespective of whether the islet graft maintains day-time glycemic control. Figure 1 (C,D) shows blood glucose concentrations over the course of 24h (on day 15), in the “cured” graft recipient (panel C) and “uncured” graft recipient

(panel D). Although the y-axes are scaled differently to reflect the very different blood glucose levels in animals with functional and non-functional grafts, the circadian patterns of glycemic control are remarkably similar in both animals, with a rapid reduction in blood glucose concentrations between 7am and 10am and a rapid increase from 7pm to 10pm in both cases.

These observations raise two important points about glycemic control in rodents following streptozotocin-induced diabetes and subsequent islet transplantation. First, there are substantial circadian rhythms in glycemic control after islet transplantation irrespective of whether the islet grafts are deemed effective (Fig 1 A,C) or ineffective (Fig 1 B,D). The mechanisms underlying these post-transplantation circadian excursions in blood glucose are unknown, but it may be caused by the anatomical relocation of the functional islet mass from the pancreas to the kidney capsule, or to the loss of islet innervation, or both. Second, and most importantly, the reproducible observation that the day time blood glucose concentration is significantly lower than the night time blood glucose concentration in both “cured” and “non-cured” graft recipients suggests that the efficacy of experimental interventions are most likely over-estimated in many animal studies in which blood glucose levels are assessed during the day, often at the beginning of the working day when blood glucose concentrations are changing rapidly.

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Figure Legend

Figure 1. Blood glucose concentrations in rats implanted with continuous glucose telemetry devices. Basal measurements were taken for five days before streptozotocin (STZ) injection and subsequent islet transplantation under the kidney capsule. Examples of rats with functional (A) and non-functional (B) islet grafts are shown. The lower panel shows blood glucose concentrations over a 24h period (on day 15) in rats with functional (C) and non-functional (D) islet grafts. Note the differences in y-axis scaling between panels C and D.

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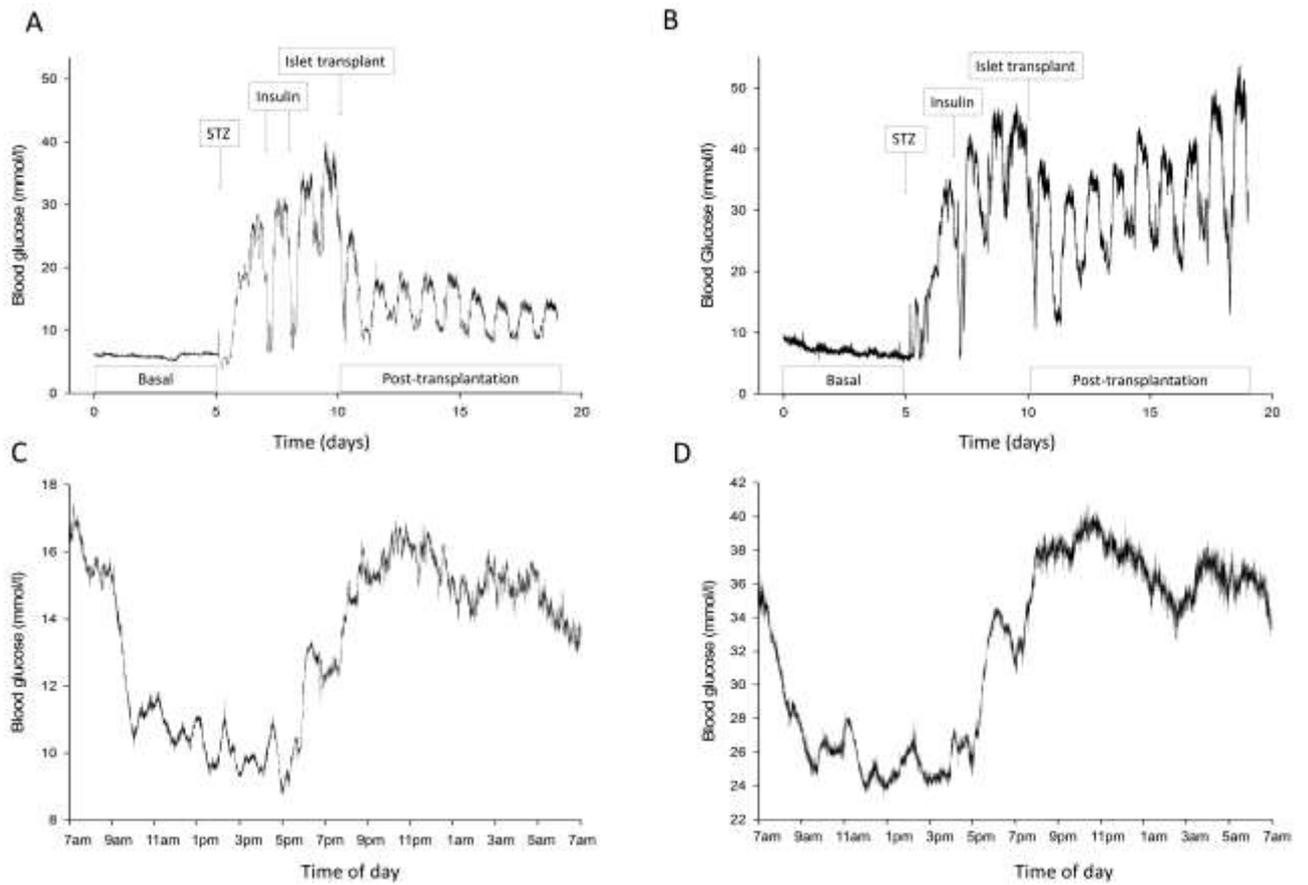


Figure 1