INTRODUCTION

The tight glycaemic control in type 1 diabetes which requires comfortable multiple insulin injections is associated with patients’ non-compliance. Therefore, methods which can deliver sustained therapeutic insulin concentrations into the bloodstream may be beneficial with glycemic control. Studies in our laboratory are concerned with methods that sustain controlled insulin release into the bloodstream based on the newly applied pectin hydrogel insulin (PI) matrix patch. In the present study, we were mainly interested in determining whether transdermally applied pectin hydrogel insulin can minimize risk of diabetic complications.

OBJECTIVES

The objectives of this study were to investigate whether topically applied pectin-insulin (PI) amidated matrix patch can:

i. sustain controlled insulin release into the bloodstream.
ii. control some selected diabetes-related metabolic parameters in STZ-induced diabetic rats.
iii. influence the expression of insulin-stimulated enzymes and facilitative glucose transporters in STZ-induced diabetic rats.

MATERIALS AND METHODS

Patch preparation

The amidated pectin hydrogel matrix patch was prepared using a previously described protocol described by Munjeri et al. 2003 with slight modifications. Amidated PI patches with specified pectin/insulin concentrations were prepared by adding 4g of pectin to 1000 ml of presoaked water in a petri dish with subsequent solidification with 2% CaCl2 to give various amounts (11.01, 17.81, 42.64 and 74.98 µg). Patches with measured widths containing 0.74, 1.20, 2.87 and 5.04 µg of insulin including a dose of 2.47, 3.99, 9.57 and 16.80 µg/kg, respectively were cut out and placed on hydrofilm that served as backing material.

Dissolution studies

Rats were divided into groups of six: seven days untreated STZ-induced diabetic (STZ) animals served as control animals and positive control animals, respectively. Blood glucose was measured before glucose loading and at 15 minutes intervals for the first hour and then hourly for the subsequent 3 hours after glucose loading.

Study design

The study was designed to establish the effects of PI hydrogel matrix patch formulation on selected metabolic parameters in experimental diabetic rats.

Acute studies

Oral glucose tolerance (OGT) responses

OGT responses were evaluated in separate groups of non-diabetic and STZ-induced diabetic groups of rats following topical application of insulin patches on the back of the neck. At the end of the OGT experiment, the rats were bled overnight (18 h), followed by measuring blood glucose concentration (mmol/L). Subsequently, OGT responses to topically applied insulin (PI) hydrogel matrix patches of various doses of insulin (2.47, 3.99, 9.57, 16.80 µg/kg) were recorded. Blood samples were collected at baseline and 15 minutes after insulin application for determination of plasma glucose concentrations.

Pharmacodynamic studies

To investigate whether PI matrix patches applied topically onto the skin delivered insulin into the bloodstream, plasma insulin concentrations were measured in separate parallel groups of STZ-induced diabetic rats as prepared for OGT responses.

Short-term effects

Short-term (5 weeks) effects were assessed in animals applied thrice daily 8 hours apart with topical PI patches containing various doses of insulin (2.47, 3.99, 9.57, 16.80 µg/kg). Animals treated with drug free pectin hydrogel matrix patches and insulin (175 µg/kg, s.c.) served as control animals and positive control animals, respectively. Blood glucose was measured before glucose loading and at 15 minutes intervals for the first hour and then hourly for the subsequent 3 hours after glucose loading.

Statistical analysis

All data were expressed as means ± standard error of means (SEM). The AUC 0-360 min values were calculated using blood glucose levels in the animal groups. The AUC 0-360 min values were compared with control animals. Values are presented as means, and vertical bars indicate SEM of means (n=6 in each group).

RESULTS

Dissolution studies

Table 1 shows the amount of insulin in insulin-pectin hydrogel patches. The theoretical amount of insulin in each patch was calculated from the known amount of insulin added to each petri dish during patch preparation and the area of the patch cut out of the petri dish. The insulin incorporation into each patch ranged from 76% to 96%.

Table 2: Comparison of hepatic and muscle glycogen concentrations of STZ-induced diabetic rats treated with amidated PI hydrogel patches applied onto the skin with control animals. Values are presented as means, and vertical bars indicate SEM (n=6 in each group).

GOAT responses

OGT responses of groups and the area under the glucose curve (AUC) of STZ-induced diabetic rats topically applied Pectin hydrogel patches on the skin at various doses of insulin are shown in Figure 3. As can be seen in Figure 3, PI patch treated diabetic rats resulted in a statistically significant decrease in blood glucose at all three times.

In addition, the blood glucose AUC was smaller in PI treated treated animals compared with respective control diabetic rats.

A dose-dependent effect on the magnitude of PI-induced blood glucose lowering was not statistically significant.

Administration of insulin demonstrated blood glucose-lowering effects in STZ-induced diabetic rats. However, the effect of insulin achieved was not statistically significant.

Statistical analysis

The plasma insulin concentration remained very low in the STZ-induced diabetic group (Figure 2).

Conversely, the plasma insulin concentrations were elevated in the non-diabetic and transdermally treated groups for the duration of the experiment.

The plasma insulin concentrations in the animals treated with the high insulin doses (9.57, 16.80 µg/kg) were significantly higher (p < 0.05) than those found in all the other groups.

DISCUSSION

The aim of the study was to develop a transdermal delivery formulation for controlled sustained insulin release into the bloodstream with good control of hyperglycaemia and consequent reduction of diabetic complications. A novel pectin hydrogel insulin matrix patch was developed to deliver insulin in a controlled manner. A strip of the transdermally released insulin was inserted into the skin of the dorsal area and the AUC of the transdermally delivered insulin was monitored. The results of this study show that a pectin/hydrogel insulin compound can be an alternative to insulin pumps and insulin implant for the treatment of type 1 diabetes.

CONCLUSION

Pectin hydrogel insulin patches lower blood glucose concentration in diabetic rats with consequent amelioration of some metabolic parameters and insulin is transported through the skin using the pectin patches. We suggest that the formulation may freely deliver insulin from multiple insulin injections thereby improving patient compliance.

REFERENCES