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Enhancement of rectal absorption of insulin in polyacrylic acid aqueous gel bases containing long chain fatty acid in rats

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Summary

The effect of the polyacrylic acid aqueous gel base containing one of 3 kinds of long-chain fatty acids (LCFA (oleic acid, linolic acid and linolenic acid) at various concentrations (none, 0.1, 1, 2 and 5%, v/v) was investigated by a rectal administration of insulin to rats. The hypoglycemic effects of insulin in gel bases containing each LCFA were stronger than that of simple gel (none containing LCFA) at an insulin dose of 1 I.U./kg. The maximum hypoglycemic effect was obtained with gel base containing each LCFA at 1% v/v at 1 h after administration. The hypoglycemic effects, in order of strength, were 1% > 0.1% > 2% > 5% (v/v) > none of each LCFA, and were similar between the 3 kinds of LCFA. Plasma insulin levels reached a peak during the first 30 min and were dose-dependent for the gel base containing LCFA at 1% v/v. The results indicate that when insulin was administered with a polyacrylic acid aqueous gel base containing LCFA, the absorption of insulin was promoted.

Introduction

Treatment of diabetes with a daily injection of insulin constitutes inconvenience for diabetic patients It is generally accepted that for therapeutic use, a proteinous hormone such as insulin cannot be given orally to a patient as it will be destroyed by the digestive juices. Therefore, in recent years, many developments of the new parenteral methods such as the rectal (Morimoto et al., 1980; Touitou et al., 1978), vaginal (Morimoto et al., 1982a), oral mucosal (Ishida et al., 1981), nasal (Hirai et

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al., 1978, 1981) and lung (Yoshida et al., 1979) routes have been attempted. Their routes have the advantage that there is no "first-pass effect" for drugs. In particular, rectal administration has been considered to be of value.

The bioavailability of poorly absorbable drugs, such as insulin, need to be increased by pharmaceutical modification for application. We have previously reported on the use of polyacrylic acid aqueous gel base for the rectal administration of insulin (Morimoto et al., 1980). The hypoglycemic effect was obtained by the small dosing of insulin in gel base at 3 I.U./kg in diabetic rats and rabbits. The gel base has the advantage of adjusting the pH and viscosity over a wide range according to type of drugs to be used (Hirano et al., 1980). The rheological properties of gels (Carbopol gels) were described in detail by Barry and Meyer (1979a and b). However, there have been no reports containing application of the suppository other than our reports (Morimoto et al., 1980, 1982a and b; Hirano et al., 1980).

The purpose of the present study was to investigate in detail the rectal absorption of insulin with polyacrylic acid aqueous gel bases containing one of 3 kinds of long-chain fatty acids (LCFA) (oleic acid, linolic acid and linolenic acid) in rats.

Materials and Methods

Materials

Polyacrylic acid (Hiviswako 105) was obtained from Wako Pure Chemical Industries (Japan). Crystalline bovine insulin (24.6 I.U./mg) from Sigma, St Louis, MO. Oleic acid, linolic acid and linolenic acid were commercial products.

Preparation

The gel base was prepared by adding 10% NaOH solution to adjust to pH 6.5 into 1% (w/v) polyacrylic acid presoaked in distilled water for 15 h at room temperature. Oleic acid, linolic acid or linolenic acid was emulsified in gel base at concentrations of 0.1, 1, 2 and 5% v/v. Insulin was suspended in each gel base according to insulin doses. The viscosity of gel preparation was measured with a cone and plate viscometer (E type, Tokyo Keiki, Japan) at 37°C. The preparations were stored in the dark at 6°C.

Administrations

Wistar strain male rats, weighing 200–250 g, were used. Rats were fasted for 20 h prior to the experiments but water was given freely. The animals were anesthetized with sodium pentobarbital (50 mg/kg) by intraperitoneal injection. The insulin gel preparations, which were warmed to 30°C, were administered into the rectal loop (5 cm section above anus) at the preparation volume of 1 ml/200 g body weight. Blood in a volume 0.4 ml was sampled in heparinized syringe from the femoral veins 10 min before, and 0.5, 1, 2, 3 and 5 h after the administration, and the plasma was separated by centrifugation at 3000 rpm.

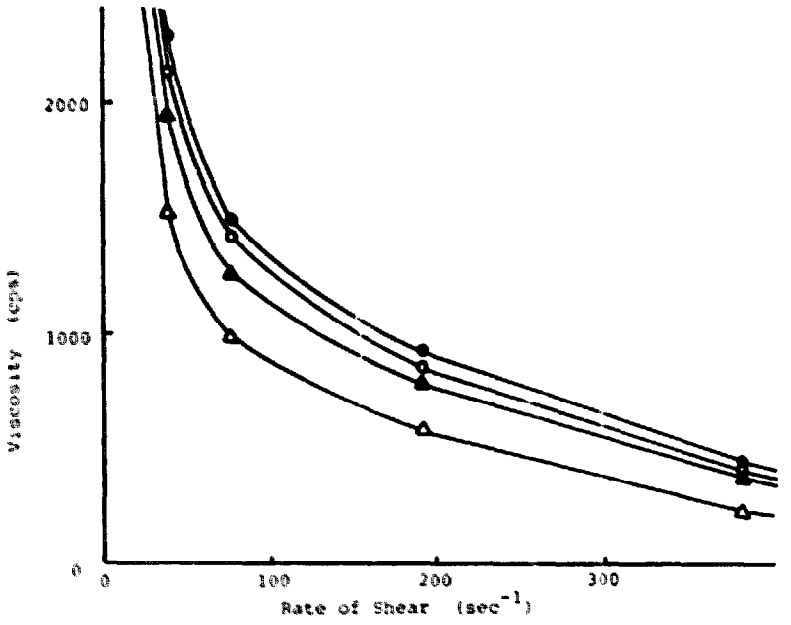

Fig. 1. Viscosity curves of gel (Hiviswaka 105) bases containing oleic acid at various concentrations. Apparent viscosity was measured with cone and plate viscometer at 37°C. Gel concentration is 1% w/v at pH 6.5. Each point represent the mean of three experiments. ●, gel; ○, gel + 0.1% v/v oleic acid; ▲, gel + 1% v/v oleic acid; △, gel + 5% v/v oleic acid.

In the comparative study, insulin was administered rectally with Witepsol H-15 base, and intramuscularly to separate groups of rats.

Analytical methods

Plasma glucose was determined by the glucose-oxidase/peroxidase method (Kiang,

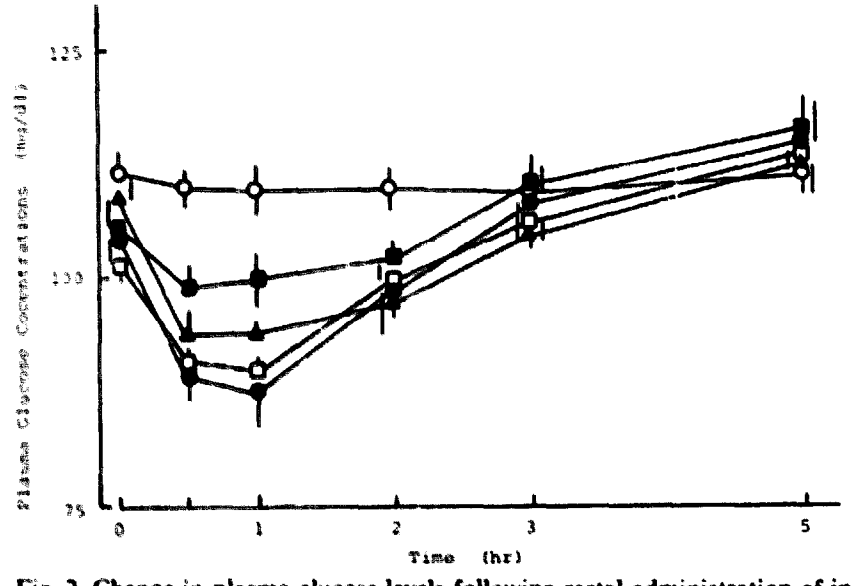

Fig. 2. Change in plasma glucose levels following rectal administration of insulin (dose 1 I.U./kg) in gel base (1% w/v; pH 6.5) containing oleic acid at various concentrations in rats. Each point is a mean ± S.E.M. of 5 animals. ○, gel; □, gel + 0.1% v/v oleic acid; ●, gel + 1% v/v oleic acid, ▲, gel + 2% v/v oleic acid; ■, gel + 5% v/v oleic acid.

1976) and plasma insulin was measured by the enzyme immunoassay using a kit supplied by Toyo Jozo, Japan.

Results

Rheological characteristics of polyacrylic acid aqueous gel

The apparent viscosity characteristics of the gel (Hiviswako 105) bases containing oleic acid at various concentrations, measured with cone and plate viscometer, are shown in Fig. 1. The gel base (1%; pH 6.5) showed a non-Newtonian liquid as the viscosity became infinitely large near the zero shear rate. The apparent viscosity of the gel base itself and the degree of the viscosity reduction became larger as concentration of oleic acid (0–5% v/v) was made higher. The apparent viscosities of the gel base containing linolic acid or linolenic acid were similar to the gel base containing oleic acid (data not presented). Therefore, carboxyl groups of the polymer chain in a polyacrylic acid aqueous gel base became less ionized. The mutual repulsive forces of the electric charges decrease by action of LCFA so that the viscosity of the gel decreases.

Administrations of insulin

Figs. 2, 3 and 4 show the change in plasma glucose levels after rectal administration of the insulin in gel bases containing oleic acid (Fig. 2), linolic acid (Fig. 3) or linolenic acid (Fig. 4) at various concentrations (none, 0.1, 1, 2 and 5% v/v) in rats. The hypoglycemic effects of the insulin in gel base containing each LCFA were

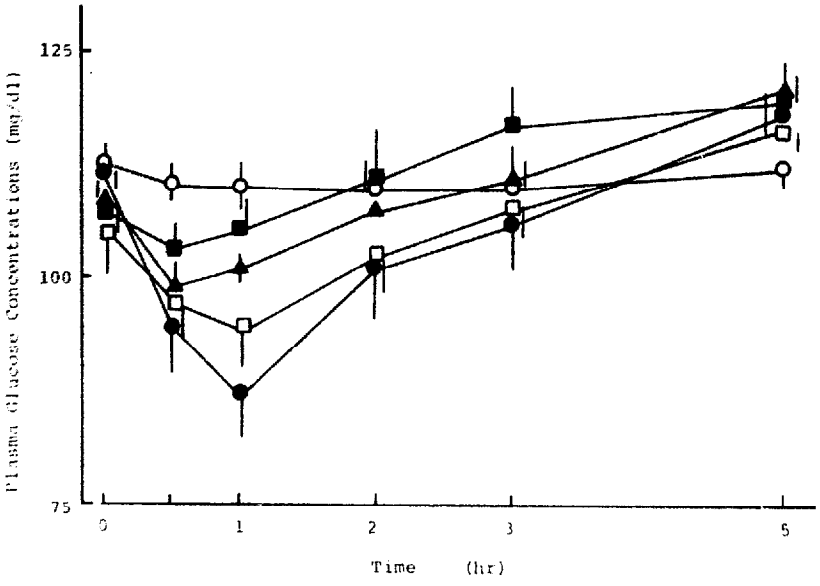

Fig. 3. Change in plasma glucose levels following rectal administration of insulin (dose 1 I.U./kg) in gel base (1% w/v; pH 6.5) containing linolic acid at various concentrations in rats. Each point is a mean ± S.E.M. of 5 animals. ○, gel; □, gel + 0.1% v/v linolic acid; ●, gel + 1% v/v linolic acid; ▲, gel + 2% v/v linolic acid; ■, gel + 5% v/v linolic acid.

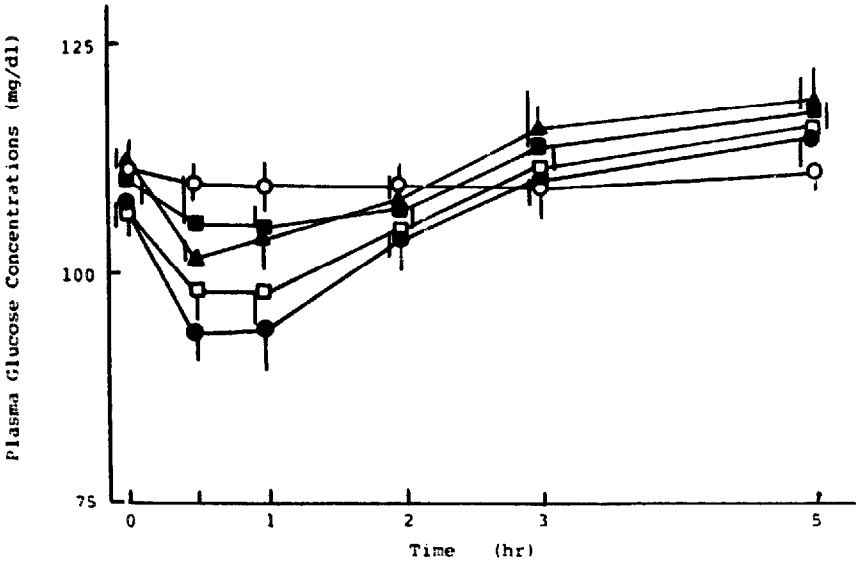

Fig. 4. Change in plasma glucose levels following rectal administration of insulin (dose 1 I.U./kg) in gel base (1% w/v; pH 6.5) containing linolenic acid at various concentrations in rats. Each point is a mean ± S.E.M. of 5 animals. ○, gel; □, gel + 0.1% v/v linolenic acid; ●, gel + 1% v/v linolenic acid; ▲, gel + 2% v/v linolenic acid; ■, gel + 5% v/v linolenic acid.

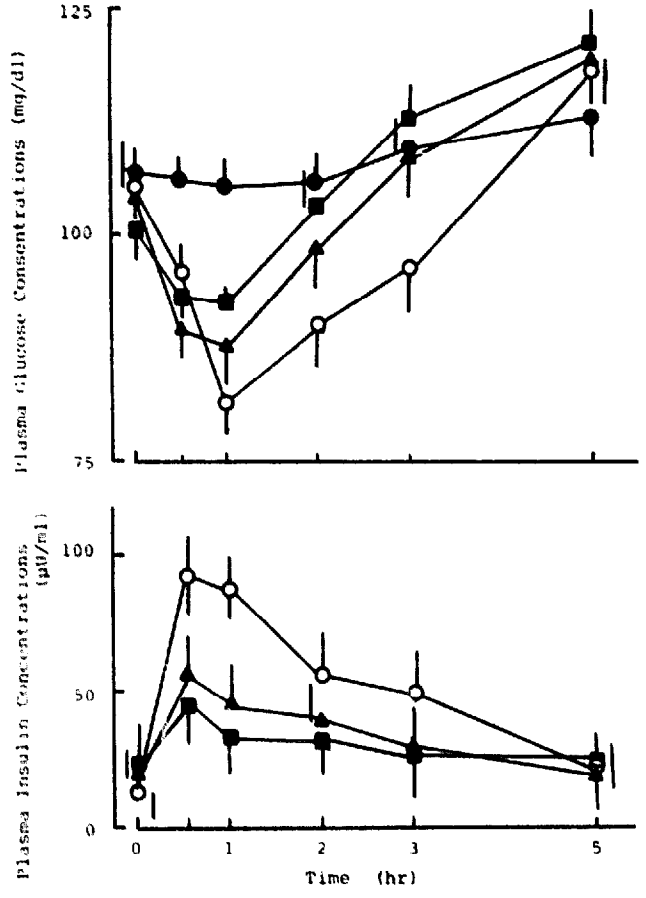

Fig. 5. Dose dependency of plasma insulin levels and plasma glucose levels following rectal administration of insulin in gel base containing 1% v/v oleic acid in rats. Each point is a mean ±S.E.M. of 5 animals. Insulin dose: ●, none; ■, 0.5 I.U./kg; ▲, 1 I.U./kg; ○, 3 I.U./kg

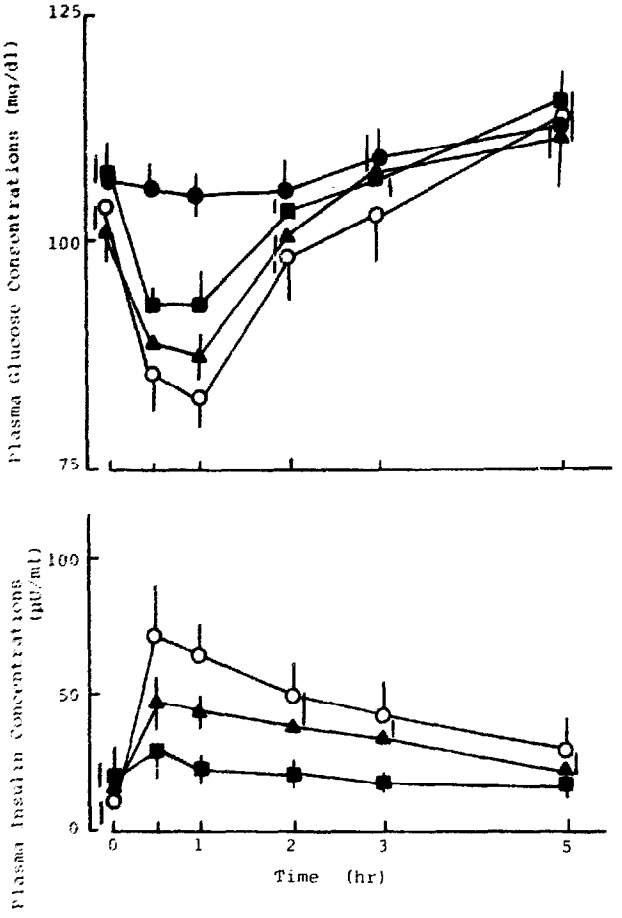

Fig. 6. Dose dependency of plasma insulin levels and plasma glucose levels following rectal administration of insulin in gel base containing 1% v/v linolic acid in rats. Each point is a mean ± S.E.M. of 5 animals. Insulin dose: ●, none; ■, 0.5 I.U./kg; ▲, 1 I.U./kg; ○, 3 I.U./kg

stronger than that of simple gel (none containing LCFA). The maximum hypoglycemic effect was obtained with gel base containing each LCFA at 1% v/v concentration at 1 h after administration. The hypoglycemic effects were in the following order of strength: 1% > 0.1% > 2% > 5% (v/v) > none of each LCFA.

The dose dependency of plasma insulin levels and plasma glucose levels following rectal administrations of the insulin with gel preparations containing oleic acid or linolic acid at 1% v/v concentration are shown in Figs. 5 and 6. Plasma insulin levels reached a peak during the first 30 min at every dose and were dose-dependent on oleic acid and linolic acid. The prominent hypoglycemic effects started during the first 30 min. The maximum effects were recorded at 1 h. The plasma glucose level returned to the initial level after 5 h.

To summarize, a comparison with those subjects observed after intramuscular or rectal administrations is shown in Fig. 7. The maximum decrement of plasma glucose level was plotted versus log dose of insulin. The insulin preparations with the fatty suppository bases (Witepsol H-15) needed a high dose (100 I.U./kg) for hypoglycemic effects following rectal administration. However, the hypoglycemic

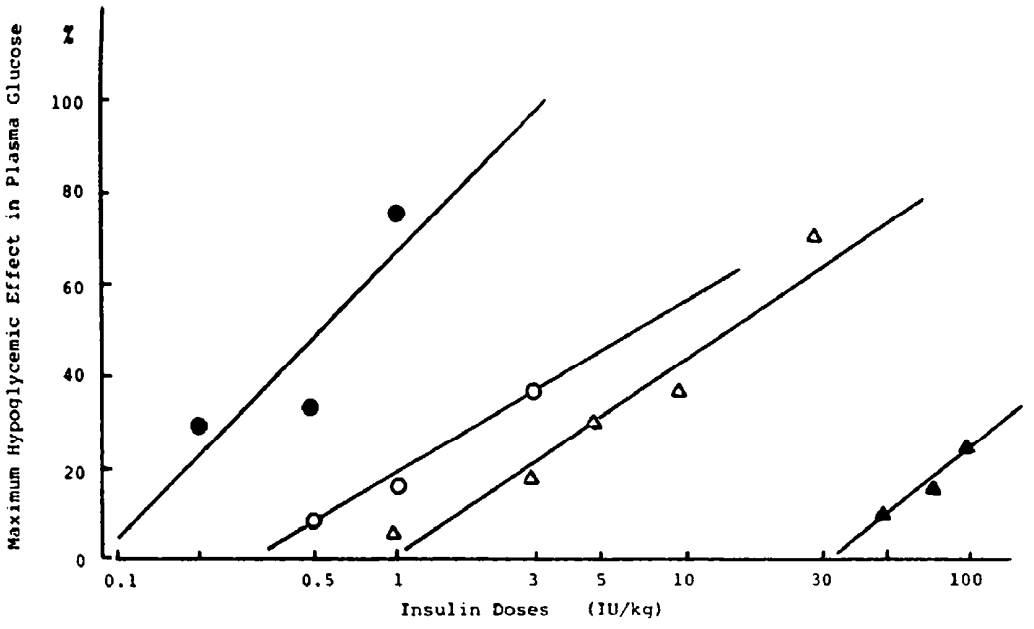

Fig. 7. Dose–response curves following rectal administration (▲, Witepsol H-15; △, 0.1%, w/v gel base; ○, gel containing 1% v/v oleic acid) and intramuscular administration (●) of insulin in rats. Each point is a mean of 5 animals.

effects were produced by rectal administration of insulin with polyacrylic acid aqueous gel base at a low dose (5 I.U./kg) (Morimoto et al., 1980). Thus, promotion of absorption of insulin is due to an accelerating effect of polyacrylic acid aqueous gel. In the present study, the higher hypoglycemic effects were obtained by a polyacrylic acid aqueous gel base containing oleic acid at 1% v/v concentration at a low dose (1 I.U./kg). The dose of this dosage form was near to the dose of intramuscular injection that produced hypoglycemia of similar magnitude.

Discussion

It has been generally considered that a high-molecular weight hormone such as insulin cannot be absorbed through rectal mucosa. Recently, a number of reports have appeared concerning the promoting effect of surfactant (Ichikawa et al., 1979; Touitou et al., 1978), and the emulsion containing surfactant via the rectal absorption of insulin (Shichiri et al., 1978). However, the use of surfactant has considerable problems, such as detectable irritation of rectal mucosa and toxity after long-term administration. In preliminary experiments, this problem was overcome by using a polyacrylic acid aqueous gel base in rectal administration of insulin. Furthermore, the present experiments showed that when insulin was administered with a polyacrylic acid aqueous gel base containing LCFA, rectal absorption of insulin was promoted. This gel caused no mucosal damage and rectal injection of the gel was suitable for treatment of rectal inflammation, as reported by Kakegawa et al. (1981).

When the range of 0.1–5% v/v LCFA was dispersed in the gel, the viscosity of

the gel bases was reduced with increasing concentration of LCFA (Fig. 1). In a previous study (Morimoto et al., 1980), the administration of insulin with the lower viscosity gel bases gave a greater hypoglycemic effect than that of higher viscosity gel bases. However, the strongest hypoglycemic effect was obtained by that of containing LCFA at 1% v/v, independent of the viscosity of the gel base (Figs. 2, 3 and 4).

LCFA has an affinity for the intestinal membrane and is absorbed well through the intestinal mucosa (McDonald et al., 1980; Isselbacher, 1967). Thus, the mechanism of the promotion of absorption of insulin has so far not been clarified, but it seems likely that the membrane absorption mechanism may be changed through affinity to membrane changes, possessed by absorption of LCFA.

It is interesting that this promoted absorption corresponds to the mechanism in which administration of liposome (Patel and Ryman, 1976) or mixed micelles containing micro oil droplets (Muranishi et al., 1979) can induce the absorption of normally poorly absorbable drugs.

In conclusion, the results indicate that the rectal administration of the insulin gel preparation containing a long-chain fatty acid, may be useful as a simple and painless dosage form in the long-term therapy of diabetics.

Acknowledgement

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