NEWER INSULINS

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The aim of the present survey is to review the developments in the synthesis of human insulin and to look a little more into newer insulin preparations which may offer advantages to diabetics in the future.

Human Insulin

Human insulin was produced from cadaver pancreas approximately 25 years ago[1] and full chemical synthesis of human insulin was accomplished by Sieber and co-workers[2]. Only one amino-acid differ between porcine and human insulin and in the late seventies it became possible to replace alanine in the porcine insulin molecule with that of threonine thus producing human insulin[3]. This insulin preparation was called semisynthetic human insulin. Recently insulin was produced by means of microorganism after modification of their genome, so called genetic engineering. By this method biosynthetic human insulin is produced. Genetic engineering is defined as a process whereby a gene coding for a specific substance is inserted into an organism in such way that the organism under the right circumstances will express this foreign gene. Biosynthetic insulin was prepared from E. coli firstly by combining the two independently synthesized A and B polypeptide chains[4] and later by converting proinsulin precursor to insulin[5]. Biosynthetic human insulin has also been produced from Baker's yeast, Saccharomyces cerevisiae[6]. By series of complicated processes the insulin gene is incorporated into yeast which will now start to secrete insulin under the proper circumstances and biosynthetic human insulin can be extracted from the secretion product[6]. One of the advantages of biosynthetic human insulin is that no impurities with proinsulin, glucagon, pancreatic polypeptide, somatostatin or VIP exists. No impurities with the insulin precursor, yeast, or bacteria polypeptides has so far been detected. In trials comparing biosynthetic human insulin[7,8,9] no differences were found. Thus, it seems that patients can be changed from semi-synthetic human insulin to genetic engineered insulin without changing the doses of insulin.

Intranasal Insulin

Recent studies using intranasal insulin as the application form has been reported. Salzman and co-workers found a dose dependent decrease in blood glucose by administering intranasal insulin to fasting diabetes[11]. Surfactants have to be used in order that insulin is absorbed from the nasal mucosa. This causes nasal irritation which seems to be proportional to the concentration of surfactant[10]. Salzman and co-workers also evaluated the effect on long-term home use of intranasal insulin on glycemic control, as evaluated by Haemoglobin A1c, home glucose measurements and hypoglycemic reactions. No difference in glycemic control compared to that during a subsequent 3 months period of conventional subcutaneous insulin treatment was found[10]. In another study by Frauman and co-workers the efficacy of insulin administered by nasal spray compared with an intensified subcutaneous insulin therapy in 9 type I

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diabetics on baseline therapy with ultralente insulin was examined for 4 months[11]. In this study a significant rise in glycosylated haemoglobin was found during intranasal insulin administration[11]. However, evaluated by plasma glucose concentrations and glucosuria no difference between the two treatments was found[11].

Examined by euglycemic clamps in eight normal volunteers the onset of effect of intranasal administered insulin was not significantly different from that of IV insulin namely 9 and 8 minutes respectively, and the duration of the effect too was not different, 82 and 100 minutes respectively[12]. Thus, the advantage of nasal insulin seems too be that the absorption kinetics mimic the insulin response to a meal in non-diabetics, that it is a convenient and painless to administer, and that there is no time delay between meal and insulin administration. Like other administration forms, it offers the patients a flexible life-style, However, the problems with nasal insulin is that the bioavailability is low. In the hitherto reported studies it seems to be approximately 2-10% which increases the daily dose of insulin considerably and thereby the cost of the treatment. Further draw-backs are nasal irritation by absorbtion promoters and a great interindividual variation in absorption.

Insulin Analogues

The most recently reported change in insulin preparation has been the insulin analogues[13]. Normally, insulin molecules, due to the high concentrations in the injected insulin preparations, will form hexamers consisting of 6 insulin molecules. On absorption these hexamers have to be changed to monomers before insulin reaches the circulation. This is probably one of the explanations for the slow absorbtion of insulin. It has now been found that by changing some of the amino acids in the binding region between the insulin molecules, these molecules will repulse each other whereby hexamers will not be formed. This increases the absorbtion rate of insulin, considerably (approx. 3 times). It is there-fore possible that these new insulin analogues will be better imitators of the natural insulin response to a meal seen in non-diabetics. Studies are presently being performed to evaluate the metabolic effects of these new insulin analogues[14].

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