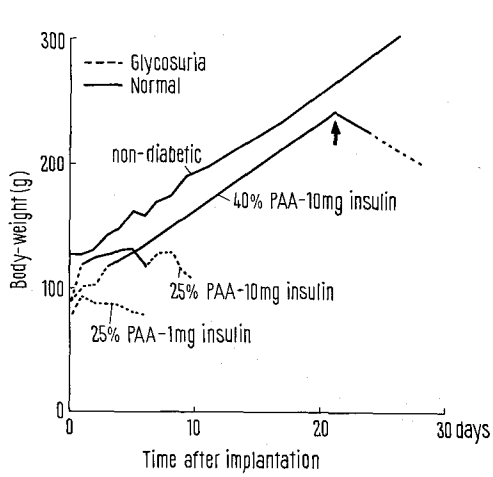
Control of Diabetes with Polyacrylamide Implants Containing Insulin

An attempt to prolong the action of insulin by implantating tablets of the hormone under the skin of rabbits was reported to be unsuccessful, in an early paper by PARKES and YOUNG[1]. The dependence of diabetic animals upon administered insulin furnishes a useful physiological model for testing implant media that permit prolonged continuous administration of protein drugs. In this work, polyacrylamide (PAA) admixed with insulin has been subcutaneously implanted in alloxan diabetic rats and the performance of these animals is described with respect to survival, growth and urinary sugar status. In terms of these standards, diabetic rats responded well to PAA implants containing insulin; the effectiveness of an implant being subject to its porosity and the amount of hormone contained.

Three week old albino rats (CD), fasted overnight, were injected i.p. with 25 mg × 3 alloxan[2] (re-crystallized) to induce diabetes. After 3 days, diabetic animals among the survivors showed emaciation, polyphagia and polyurea associated with elevated urinary sugar levels, which were detected by BENEDICT's test[3]. Comparable with various other mammalian species, rat blood sugar levels, normally around 100 mg/100 ml, roughly double in alloxan diabetes[4,5] and this level exceeds the renal sugar threshold since 4–6 g glucose is excreted daily in the urine[6]. Histological examination of pancreatic tissue sections provided direct evidence of alloxan damage to the islets of Langerhans in treated animals. Implants containing insulin were prepared from 25 and 40% acrylamide (Eastman; recrystallized), with 2% N, N' methylenebisacrylamide serving to cross-link PAA chains. Riboflavin was used to catalyze photo-polymerization[7]. Bovine pancreatic insulin (24 IU/mg; Sigma) was added to the reaction mixture before polymerization and during polymerization this mixture was gently stirred. The resulting slurry was washed with distilled water and implants of 0.2 ml were then ventrally s.c. injected. There were 4 groups in the experiment and each group had 4 rats. Animals in 3 groups received implants; 1 mg insulin in 25% PAA and 10 mg insulin in 25 and 40% PAA. The 4th group was an untreated Control. Body-weight, length of survival and the reaction of urine to BENEDICT's reagent were observed among the experimental animals.

From the results shown in the Figure, it can be seen that the response of alloxan diabetic rats to PAA implants containing insulin is influenced both by implant porosity (PAA concentration) and the amount of hormone present. Animals bearing 1 mg insulin implants of 25% PAA responded relatively poorly; their body-weight increased only briefly, glycosuria was present in this group throughout the experimental period and none of the animals survived for more than 7 days. In contrast, it may be observed (Figure) that diabetic rats given 10 mg insulin, 40% PAA implants grew at a virtually normal rate and had normal (non-glycosuria) urine, until the implants were removed on day 21 following implantation, when the symptoms of diabetes quickly re-emerged. Intermediate in their performance were animals with 10 mg insulin, 25% PAA implants. These rats, as may be noted, recovered body-weight and showed no glycosuria for a few days following implantation. However, glycosuria reappeared on day 6 and they lost body-weight sharply after day 8. Three of the 4 rats in this group did not live beyond day 11.



Response of alloxan diabetic rats to polyacrylamide (PAA) implants containing insulin. The arrow designates when implants were removed from rats in the 10 mg insulin, 40% PAA group.

These results clearly show that insulin in PAA implants, deposited by s.c. injection, can serve to sustain diabetic animals for a period of at least a few weeks. Implant effectiveness is influenced by PAA concentration which is illustrated by the performance of rats that received 10 mg insulin in 25% PAA (pore size about 23 Å) compared to that of rats with this amount of hormone in 40% PAA (pore size about 16 Å). The latter performed better, evidently because 40% PAA releases insulin over a longer interval than does 25% PAA. Since an insulin dimer (prevalent form in solution) is roughly cyclindrical, with dimensions 20 × 40 Å[8], a molecule of insulin should obviously experience a much lower frictional resistance during diffusion in a 25% PAA implant than in a 40% PAA implant and consequently would be released faster from it. Parenthetically, porosity in these implants would increase somewhat due to swelling. Apart from diffusion, insulin release may also reflect its rate of dissolution. Obviously, it would be of value to obtain quantitative information rendering the kinetics of insulin release from PAA implants reasonably predictable. The apparent success of PAA as an implant medium for insulin raises the prospects of it being possible to also implant other drugs in this medium.

Zusammenfassung. Es wurden durch insulinhaltige s.c. injizierte Polyacrylamid-Implantate Glucosurie geheilt sowie Wachstums- und Überlebensrate Alloxan-diabetischer Ratten gefördert.

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