

Do insulin injections make you fat?

INTRODUCTION

A locum now, I work in other people's surgeries. It can be most instructive. At one surgery I found that a very dedicated partner with a special interest in diabetes was bringing a middle-aged man with type 2 diabetes back for monthly visits. Each time his sugars were high and each time she increased his insulin. Anybody who has run a diabetes clinic will be familiar with this scenario. Increasing the insulin fails to bring down the blood sugar; it simply makes an already tubby middle-aged man fatter and fatter. But why, it crossed my mind, does insulin make people fat?

We are all on insulin, whether endogenous or, as in this patient's case, injected. So the question is:

'How does insulin injected peripherally and subcutaneously differ from insulin released in the portal circulation?'

To answer this question, two subsidiary questions must be answered. First, is insulin released into the portal circulation metabolised differently from that injected subcutaneously? Second, does insulin reaching the brain stimulate appetite?

INSULIN, ITS METABOLISM, AND ITS EFFECT ON APPETITE

Starting with the first, it is well established that insulin released into the portal circulation is broken down 60% in the liver and 40% in the kidneys. With insulin injected subcutaneously the proportion is reversed.¹ This is a small but significant difference. If more of the same dose of insulin reaches the brain, and insulin stimulates appetite, then we would have an explanation as to why injected insulin tends to make you fat. (It might also be that insulin reaching the liver leads to more gluconeogenesis rather than increased appetite, and that injected insulin has a greater effect on peripheral adipose tissue.)

Turning to the second step, we know a

great deal about the control of appetite, as a review describes.² There are a number of nuclei and pathways controlling appetite in the hypothalamus, and insulin has an effect on many of them. Insulin, then, has a stimulating, if minor, effect on appetite at several different pathways in the brain.

PERITONEAL DIALYSIS

If insulin injected peripherally increases appetite more than the same dose of insulin released into the portal system, why are not all patients with diabetes treated with insulin fat? Many, indeed most, young type 1 patients with diabetes are not fat. I would like to answer this question in two parts.

First, as a sort of natural experiment, a substantial number of patients with diabetes on insulin (though a minute proportion of the whole population of patients with diabetes on insulin) have had their therapeutic insulin delivered via the portal system. I am referring here to those patients with diabetes on peritoneal dialysis who receive their insulin intraperitoneally with the dialysis fluid.

Early studies showed minor advantages in diabetic control with intraperitoneal infusion.³ In practice, however, for patients on peritoneal dialysis, it has turned out that both subcutaneous injection and insulin infusion with the peritoneal dialysis solution work perfectly well, and it has become a matter of choice for individual patients.

In summary, then, this natural experiment shows that intraperitoneal infusion has some small and measurable benefits that are of marginal importance in practice.

CONCLUSION

The reason, then, why not all patients with diabetes become fat on injected insulin is that the effects are small, even if they are measurable. However, where appetite control is already weakened, as in our middle-aged obese man, the extra stimulus of injected insulin may be significant and lead to a progressive increase in weight, in

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other words, to a loss of the homeostatic control of weight. In a young, fit, and active person, the appetite control systems will likely be robust enough to compensate easily for the small extra challenge of injected insulin.

Injected insulin, then, makes fat those people who have marginally effective appetite control. This is because more of the insulin reaches the brain when it is injected subcutaneously than when it is spontaneously released into the portal system, and insulin stimulates appetite centres in the brain.

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