The reduction was small but could not be explained in terms of seasonal variation in folate intake and it suggests that small-bowel absorption may be affected by the fibre content of the diet. The mechanism might be similar to that of cholestyramine[21] in lowering serum folate levels.

The colonic flora may be changed by additional fibre. The urinary indican test is a crude indicator of gastrointestinal bacterial activity, but we found no consistent pattern of change.

In the past dietary fibre has been considered physiologically inert. Interest in its metabolic role is now increasing, but research is still at an early stage. We hope that our findings will indicate some further lines of inquiry. In the meantime we conclude that we have not detected any metabolic effect that would contraindicate the use of bran in diverticular disease.

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Cardiovascular effects of insulin

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Summary

Insulin increased the heart rates of seven diabetics with normal cardiovascular reflexes. This effect, which was not due to hypoglycaemia, was greater in the upright than in the supine position and was produced by as little as one unit given intravenously. This increase in heart rate may be a compensatory response to maintain cardiac output.

Introduction

Recent observations have shown that insulin has an effect on the cardiovascular system that is independent of hypoglycaemia[1][2]; it provokes postural hypotension in diabetics with autonomic neuropathy[1][2] and in patients who have had a sympathectomy.[3] We aimed to determine whether a cardiovascular effect of insulin occurs in all diabetics or in only those with neuropathy.

Patients and methods

Seven insulin-dependent diabetics with no evidence of peripheral or autonomic neuropathy were studied (see table). All had normal cardiovascular reflexes—that is, normal beat-to-beat variation of heart rate during deep breathing,[4] response to the Valsalva manoeuvre,[5] and blood pressure and pulse rate responses to standing.[6] Each gave informed consent.

Patients fasted overnight and took no insulin or other medication on the morning of the study. An indwelling polyethylene cannula was inserted into a forearm vein before baseline readings. Serial measurements of blood pressure and pulse rate before and after intravenous insulin were made every quarter hour on a tilt-table with the patient supine and then tilted to 70 standing on a footplate. Tests were performed in a quiet room at near constant temperature (25 C). Radial pulse rate was counted for one minute supine, and after one and a half minutes of tilting. A continuous record of pulse rate was kept with a Hewlett Packard 8025 B cardiotachometer. Blood pressure was recorded with a standard mercury sphygmomanometer three times supine and after half, one, and three minutes of tilting.

Soluble or Actrapid monocomponent insulin was given intravenously as a bolus from a plastic syringe in doses ranging from 1 to 40 IU (see table). Patients were not told of the time of insulin administration. Venous samples were taken every 15 minutes and blood glucose was determined by the autoanalyser ferricyanide method. Blood volume was maintained by replacement with physiological saline.

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Details of treatment, test dose of insulin, and pulse rate in seven diabetic patients

Case No	Age and sex	Duration of insulin treatment	Total daily insulin dose (IU)	Intravenous test dose given (IU)	Mean upright pulse rate/min	
					Before insulin	After insulin
1	29 F	16 years	88	40, soluble	105	122
2	20 M	1 week	72	40, soluble	81	95
3	29 M	1 week	28	10, soluble	83	100
4	18 M	3 years	44	10, soluble	107	135
5	21 M	1 week*	60	1, Actrapid MC	85	102
6	28 M	7 years	56	1, Actrapid MC	84	93
7	23 F	1 week	96	10, Actrapid MC	77	97

*On tablets for three years.   MC = Monocomponent.

Results

The pulse rate rose after insulin in all patients when they were tilted upright (fig 1). There was a smaller and delayed rise in supine pulse rate after insulin (fig 2). That the mean supine heart rate was still rising one hour after insulin, when the mean erect heart rate was falling, was due to the high supine rates in two patients. In both of these patients all subsequent readings were lower. On resumption of the supine posture after tilting a transitory reactive bradycardia usually developed. After insulin this became more pronounced, with increased heart rate variability during normal breathing (fig 3), which indicated an increase in vagal activity. There was no significant change in supine or upright blood pressure after insulin.
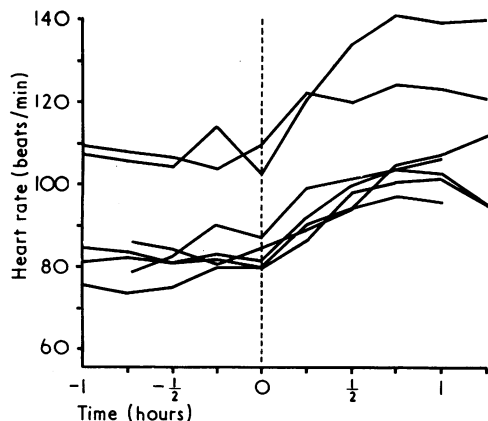

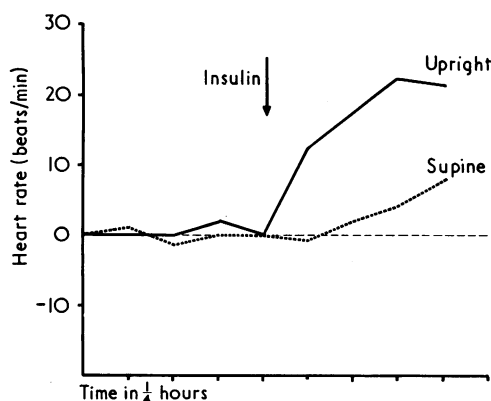FIG 1—Heart rates in upright position before and after insulin, which was given at time 0.

FIG 2—Change from baseline in mean supine and upright heart rates after intravenous insulin (baseline of an individual patient was calculated from average of four readings before insulin).

The blood glucose concentration decreased progressively from a mean of 10·2 mmol/l (184 mg/100 ml) (range 6·4-13·8 mmol/l (115-249 mg/100 ml)) before insulin to a mean of 6·2 mmol/l (112 mg/100 ml) one hour after insulin, but except in one patient concentrations remainded above 3·4 mmol/l (61 mg/100 ml). There was a disparity between the changes in upright heart rate and the blood glucose level: half of the mean total increase in erect heart rate had already occurred 15 minutes after insulin, when blood glucose had declined by a mean of only 0·5 mmol/l (9 mg/100 ml)—an eighth of the eventual fall.

Discussion

Insulin causes an orthostatic increase in heart rate in diabetics without neuropathy. The mechanism of this effect is not known, but it is not due to hypoglycaemia. It seems unlikely to be due to the degree of fall of blood glucose because there is a pronounced early effect of insulin on heart rate when blood glucose has declined little. It is unlikely that impurities of commercial
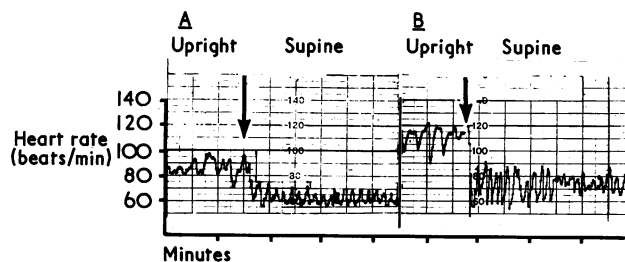

FIG 3—Comparison of pulse rate response on return to the horizontal after tilting (A) before and (B) after insulin. Arrows mark change from upright to supine.

insulin cause the cardiovascular effects, since they are induced equally by soluble and monocomponent insulins. An antigen-antibody interreaction is improbable since the effect is present only one week after the start of insulin treatment. It is also improbable that a cardioactive substance is eluted from the plastic or polyethylene, as has been reported from haemodialysis equipment,[7] since we have observed insulin-induced tachycardia using a glass syringe and metal indwelling needle.

Many different variables affect the heart rate, but we do not believe that the observed pulse rate changes can be interpreted as secondary to psychogenic influences because all except one of the patients were unaware of the time of insulin administration. Analysis of the continuous recordings showed no change in supine heart rate at or immediately after injection.

Insulin lowers the blood pressure in those with abnormal cardiovascular reflexes.[1-3] Maintenance of blood pressure on standing depends on normal afferent impulses from the baroreceptors, and efferent sympathetic cardioaccelerator and peripheral vasoconstrictor impulses. In these diabetics without neuropathy blood pressure changed little after insulin, but on tilting upright the heart rate increased. This could be explained if insulin reduces effective circulating blood volume. This might occur either through a transfer of fluid out of the vascular compartment into the intracellular or interstitial spaces or through a change in venous tone. In either case cardiac output should be reflexly maintained by a compensatory tachycardia and increased peripheral arterial vasoconstriction. The upright posture itself increases venous pooling, reducing venous return and hence cardiac output, and would lead to greater compensatory reflex activity.

An isosmotic shift of fluid and glucose into the cells after insulin seems unlikely in view of the small change in blood glucose levels when heart rate had increased considerably, although blood glucose changes do not represent only alterations in glucose uptake. An effect of insulin on venous tone is therefore the most likely explanation for the tachycardia in diabetics without neuropathy and for the hypotension in those with autonomic neuropathy and why both are more pronounced in the upright position. If so, the change in heart rate would be one of several compensatory mechanisms. An indirect measure of the degree of arterial vasoconstriction induced by tilting was provided by the pulse rate response on resumption of the supine posture (fig 3). A stronger reactive bradycardia often developed after insulin, implying that there was more arterial vasoconstriction in the upright position. This would lead to a transient rise in blood pressure on return to the supine position, causing a reflex slowing of the pulse via the baroreceptors, analagous to the overshoot bradycardia of the Valsalva manoeuvre.[8]

Studies of diurnal variation show that the administration of subcutaneous insulin may lower blood pressure in diabetics with autonomic neuropathy after both morning and evening injections.[1] The implication is that the routine daily insulin injections of any diabetic may cause circulatory stress, and that this might have a long-term effect on the cardiovascular system in insulin-dependent diabetics.

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Thyroid disease and sebaceous function

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Summary

Sebum excretion rates (SER) were measured before and after treatment in patients with hypothyroidism and thyrotoxicosis. The mean SER in the former was significantly less than that in normal controls but there was no correlation between SER and the severity of the disease as indicated by serum thyroid-stimulating hormone levels. After treatment with L-thyroxine the SER increased but remained subnormal. By contrast the SER was not increased in patients with thyrotoxicosis and it was unaffected by treatment. The human sebaceous gland seems to respond to thyroid hormone mainly in the hypothyroid range

Introduction

The endocrine control of the sebaceous glands has been less well established in man than in the rodent.[1] [2] In particular, the influence of the thyroid is unknown although thyroidectomy decreases and thyroid hormones increase sebum secretion in the rat.[3] We therefore measured the sebum excretion rate (SER) before and after treatment in patients with hypothyroidism and thyrotoxicosis.

Patients and methods

We studied 25 female and three male patients aged 11-72 years with primary hypothyroidism and 13 women and nine men aged 21-65 years with thyrotoxicosis. In each patient the clinical diagnosis was confirmed by the appropriate endocrine investigations. Serum thyroid-stimulating hormone (TSH) concentration was measured by radioimmunoassay[4] in 23 of the hypothyroid patients before treatment. The patients with hypothyroidism received L-thyroxine as replacement therapy and all those with thyrotoxicosis were treated with carbimazole apart from two men who were given ^{131}I treatment. The SER was measured on the forehead by the method of Strauss and Pochi[5] as modified by Cunliffe and Shuster.[6] The measurements were made before and after treatment (6-42 weeks in hypothyroid patients and 6-35 weeks in thyrotoxic patients); the results were expressed as a percentage of the age- and sex-matched means from 105 female and 70 male controls.

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Results

In hypothyroidism the mean SER ($\pm$ SE of mean), was $61.7\pm9.2\%$ in the women and $31.1\pm2.4\%$ in the men (fig 1) with a group mean of $58.5\pm8.4\%$ (P<0.001). Serum TSH ranged from 5.9 to 115 mU/l (mean 39.7 ± 5.7 mU/l) and there was no correlation between TSH and SER values in the 23 patients in whom both measurements were made. After treatment with L-thyroxine the SER increased in most of the 20 patients in whom it was again measured (fig 2). Although the mean increased significantly (P<0.02), the SER remained lower than normal, rising from $66.1\pm10.6\%$ of normal before treatment to $82.2\pm10\%$ after treatment. The size of the increase after treatment was not related to the size of the decrease before treatment.
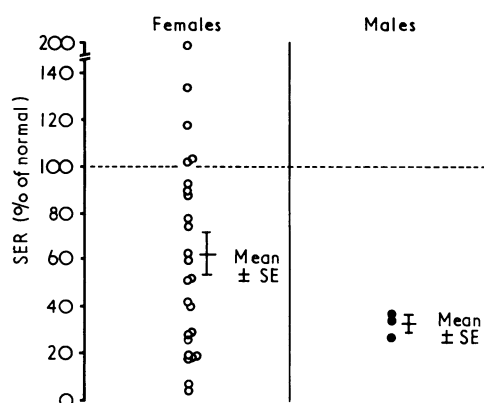

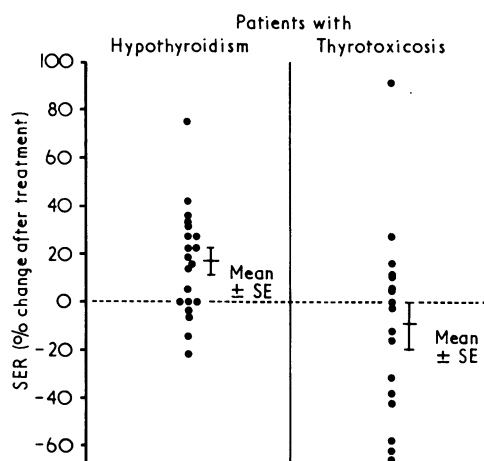FIG 1—Sebum excretion rate in patients with hypothyroidism.

FIG 2—Percentage change in sebum excretion with treatment in patients with hypothyroidism and thyrotoxicosis.