noephedrine, and its enantiomer afforded 11S and 11R-[^{2}H]-porphobilinogen (66% e.e.) respectively; our findings are in accord with these results as the use of R-1-phenylethylamine and R-2-amino-2-phenylethanol both afforded 11R-[^{2}H]-porphobilinogen (40 and 88% e.e. respectively).

Acknowledgments. We thank the S.E.R.C. for support of this work and especially for assistance with the purchase of the high field NMR spectrometer.

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0014-4754/87/080892-03$1.50 + 0.20/0

Reversible reduction in bone blood flow in streptozotocin-diabetic rats

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25 November 1986

Summary. Tibial growth and blood flow were both found to be markedly reduced in anaesthetised streptozotocin-diabetic rats compared to controls. Insulin treatment restored tibial growth to approximately control values and increased tibial blood flow to above control values. The observations are likely to be related to reduced bone turnover in uncontrolled diabetes.
Key words. Streptozotocin; diabetes; rat; insulin; bone; blood flow.

The normal development of bone is impaired in human diabetes. Deficits in bone mass[1] and height[2] may be demonstrated in insulin dependent diabetes after several years of the disease. The incidence of osteoporosis is also higher in sex and age matched diabetics[3,4]. Decreased bone formation has been demonstrated in animal models of diabetes[5,6]. Reduced bone turnover has been reported to occur in streptozotocin-diabetic rats with calcium deposition being more severely depressed than calcium loss so that the balance may approach zero[7,8]. A study of regional blood flow in pithed rats has reported a decrease in bone flow in streptozotocin treated animals compared to controls[9]. Autonomic control of the cardiovascular system has been reported to be abnormal by numerous studies in human and experimental animal diabetes[10]. Since pithing suppresses autonomic control of the cardiovascular system, it cannot be assumed that changes in regional blood flow observed in pithed rats will also occur in intact animals. We, therefore, considered it of interest to measure regional blood flow, including bone blood flow, in intact anaesthetised streptozotocin-diabetic rats and to see if any changes observed were modified by insulin treatment.

Materials and methods. Male Wistar rats (200–250 g) received 1 ml · kg^{-1} of freshly prepared solution of streptozotocin (55 mg × ml^{-1}, pH 4.5 citrate buffer) or buffer alone via a tail vein. The animals receiving buffer only served as controls. 14, 28 and 56 days later streptozotocin-treated and control rats were anaesthetised with pentobarbitone (60 mg · kg^{-1}). Cardiac output and its distribution to a number of tissues, including the left tibia was then estimated using ^{46}Sc labelled 15-μm diameter polystyrene microspheres (New England Nuclear Chemicals, Drieich, FRG). The method has been described in detail elsewhere[9]. Briefly, cannulae were placed in the left ventrical of the heart for microsphere injection, in the right femoral artery for blood withdrawal. Approximately 150,000 microspheres suspended in 0.15 ml were injected slowly over about 10 s. Blood withdrawal (0.43 ml · min^{-1}) was started 5 s before the injection of microspheres and continued for 20 s after its completion. Cardiac output (ml · 100 g^{-1} min^{-1}) was estimated as withdrawal rate (0.43 ml · min^{-1}) × dpm injected × 100/b. wt (g) × dpm with withdrawn arterial blood sample. Tissues were removed within 20 min of the microsphere injection and their blood flows (ml · 100 g · min^{-1}) estimated as cardiac output × b.wt (g) × dmp of tissue × 100/wet wt of tissue (g) × dpm, injected.

The above procedure was also carried out using a diabetic group which had received 4U protamine Zn insulin. Kg^{-1} s.c. at 9.00 and 17.00 h each day from 3 days after the streptozotocin dose until use on day 14 (they received the morning insulin dose on this day). Blood flow estimations were all carried out at approximately 13.00 h. The length as well as the weight of each tibia was noted. Blood glucose was determined in 0.1-ml samples of whole blood taken approximately 30 s after the microsphere injection by a micro-colorimetric copper reduction method[11]. The rats were each weighed at the start of the experiment and again just before the blood flow measurements. At no time were they denied access to food or water.

Results. Diabetes was confirmed in the streptozotocin treated animals by their raised blood glucose concentrations and negative growth rates. Insulin treatment returned both variables in approximately control values.

Overall tissue blood flow (cardiac output) was not significantly different in 14- or 28-day untreated diabetic groups compared to their controls, while in 56-day untreated diabetic animals it was increased by approximately 50%. Tibial blood flow was markedly reduced in all three groups compared to controls. The effect appeared to be maximal by 14

	Blood glucose (mmol l^{-1})	Growth rate (g day^{-1})	Cardiac output (ml·100 g^{-1}·min^{-1})	Mean blood pressure (mmHg)	Tibia blood flow (ml·100 g^{-1}·min^{-1})	Tibia length (mm)	Tibia weight (mg)
Controls (7)	6.25 ± 0.54	2.48 ± 0.42	28.6 ± 2.3	121 ± 7	26.5 ± 2.5	35.8 ± 0.3	554 ± 28
14-day diabetic (6)	25.1 ± 1.4[d]	−1.30 ± 0.45[d]	22.1 ± 2.1	113 ± 8	8.9 ± 1.0[d]	35.0 ± 0.4	480 ± 33
14-day diabetic+insulin (9)	8.9 ± 0.9[d]	2.86 ± 0.12[d]	30.3 ± 2.5[a]	124 ± 8	36.6 ± 2.9[d]	36.1 ± 0.3[a]	558 ± 29
Controls (8)	6.67 ± 0.78	2.25 ± 0.26	23.5 ± 1.9	119 ± 6	23.0 ± 2.4	37.6 ± 0.36	626 ± 22
28-day diabetic (10)	35.8 ± 1.9[d]	−0.96 ± 0.32[d]	28.7 ± 2.5	87 ± 6[c]	13.7 ± 2.2[b]	35.1 ± 0.24[d]	486 ± 25[d]
Controls (13)	6.94 ± 0.47	2.15 ± 0.17	21.7 ± 1.4	121 ± 4	22.6 ± 3.4	38.8 ± 0.21	677 ± 18
56-day diabetic (7)	29.6 ± 2.03[d]	−1.11 ± 0.39[d]	31.9 ± 4.1[b]	102 ± 10[a]	12.1 ± 1.7[a]	34.9 ± 0.26[d]	478 ± 0.24[d]

Values given are of mean ± SEM. The figures in parentheses are the numbers per group. The significance of differences between diabetic groups and their controls and between the insulin-treated diabetic group and the untreated 14-day diabetic group were assessed by t-tests, the probability values obtained being indicated by: [a] $p < 0.05$; [b] $p < 0.02$; [c] $p < 0.005$ and [d] $p < 0.001$.

days since no further depression was evident at 28 or 56 days. In no other tissue was such a marked reduction in blood flow seen. The reduced tibial blood flow was accompanied by a cessation of tibial growth whether measured by length or weight.

The insulin treated 14-day diabetic animals were found to have approximately 36% higher mean cardiac output than the untreated 14-day diabetic group. Since insulin appeared to have no major effect on mean blood pressure a reduction in peripheral resistance is indicated. Tibial blood flow was approximately four times higher in the insulin treated diabetic group than in the untreated 14-day diabetic group and about 38% higher than in the control group.

The results demonstrate a major reduction in tibial blood flow in intact anaesthetised streptozotocin diabetic rats after 14, 28 and 56 days. This is in agreement with data obtained in pithed animals[9]. The change was not due to a general circulatory alteration since cardiac output was not found to be reduced in any of the diabetic groups and was actually increased above that of the controls in the longest term diabetic animals. Similarly the dramatic increase in tibial blood flow resulting from insulin treatment was much too large to be accounted for by the more modest increase in cardiac output. The reversal by insulin of the depressed tibial blood flow of the 14-day diabetic rats strongly suggests that the depression in this diabetic group was due to insulin deficiency rather than to any direct effect of streptozotocin. It would seem likely that this also applies to the two longer term diabetic groups although this was not demonstrated by the present results.

The mechanisms of the above changes require further elucidation. Since depression of tibial flow has also been shown to occur in pithed rats[9] it would appear not to be mediated by autonomic mechanisms. It may be related to the reduced bone turnover which has been demonstrated in this model of diabetes[7,8].

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0014-4754/87/080894-02$1.50 + 0.20/0

Decidua and the control of corpus luteum function, follicular development and pituitary LHRH-responsiveness in pseudopregnant and pregnant rats

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Summary. The mid-pregnancy rescue of corpora lutea can be mimicked in the pseudopregnant rat by induction of decidual tissue in the uterus: in such rats, around day 10, there is neither luteolysis, nor resumption of follicle-development or increase of the pituitary responsiveness to LHRH. The results suggest that the mid-pregnancy rescue of corpora lutea is caused by a maternal factor.

Key words. Mid-pregnancy rescue of corpus luteum function; pseudo-pregnancy; pituitary LHRH-responsiveness; luteolysis; decidua.

Around day 10 of pseudopregnancy (PSP) the LHRH-responsiveness of the rat pituitary gland begins to increase. This increase coincides with functional luteolysis, that is, cessation by the corpora lutea (CL) of the production of progesterone (P) in favor of the production of the P-metabolite 20α-dihydroprogesterone (DHP)[1].

We demonstrated recently that luteolysis and increase of pituitary LHRH-responsiveness did not occur in PSP rats which were treated with exogenous P, if the treatment with P was initiated before the onset of luteolysis. These observations led to the suggestion that pituitary LHRH-responsiveness does not increase as long as the CL are active[2].