Paraplegia 17 (1979-80) 314-318

RECOVERY MECHANISMS FROM ACUTE HYPOGLYCAEMIA IN COMPLETE TETRAPLEGIA

By R. J. M. CORRALL, B.Sc., M.B.Ch.B., M.R.C.P., M.D., B. M. FRIER, B.Sc., M.B.Ch.B., M.R.C.P., E. J. W. MCCLEMONT, M.B.Ch.B., D.C.H., S. J. TAYLOR and N. E. CHRISTIE

Spinal Unit, Edenhall Hospital, Musselburgh, and Metabolic Unit, University Department of Medicine, Western General Hospital, Edinburgh

Abstract. Acute hypoglycaemia has been achieved in tetraplegic subjects and in healthy controls using insulin. The recovery from hypoglycaemia has been followed by measuring appropriate substrate levels in blood. Abnormal responses of lactate and free fatty acid concentrations were observed; blood glucose recovery proceeded at a normal rate.

Key words: Hypoglycaemia; Tetraplegia; Blood lactate; Free fatty acids.

Introduction

IN the tetraplegic patient, transection of the cervical cord above the first thoracic segment interrupts the major motor and sensory tracts and also disrupts the efferent sympathetic pathway. In effect this produces a total pre-ganglionic sympathectomy. This can result in characteristic clinical problems such as reflex hypertension following bladder distension. Metabolic consequences of this autonomic denervation have received little attention, and could be of practical significance in situations such as prolonged fasting during general anaesthesia. We have therefore examined the metabolic response to acute hypoglycaemia in tetraplegia.

Methods

Six normal male subjects (age range 22–64 years) and four male tetraplegic patients (age range 20–44 years) with complete post-traumatic cervical cord transections at the C5/6 level, were studied after an overnight fast. All subjects gave informed consent to the study and none were greater than 10 per cent over their ideal body weight. After resting supine in bed for at least 30 minutes an intravenous teflon catheter was inserted for blood sampling. Soluble insulin (0·15 units/kg body weight) was given intravenously; blood samples were withdrawn in control subjects at regular intervals for 180 minutes after the onset of the hypoglycaemic reaction. This was manifested as a sudden tachycardia coinciding with the symptoms of hypoglycaemia in the normal group. In the tetraplegic subjects blood samples were taken for 210 minutes after the administration of insulin.

Continuous heart rate was monitored by pulse and ECG tape recording, and skin surface sweating was measured in all of the normal and two of the teiraplegic subjects (Cohen, 1966). Serial estimates of blood glucose (Hill & Kessler, 1961), blood lactate (Hohorst, 1970) and plasma non-esterified fatty acids (NEFA'S) (Baird *et al.*, 1967) were made. Results are expressed as mean vlaues $\pm$ one standard error of the mean (S.E.M.).

Results

In the normal subjects the autonomic hypoglycaemic reaction occurred between 20 and 44 minutes (mean 30 minutes) after the administration of insulin. Pulse rate rose from 60 ± 2 to 89 ± 3 beats per min at the time of the initial hypoglycaemic symptoms. In all the control subjects sweating occurred coincidentally with the tachycardia and the onset of subjective hypoglycaemia. In the tetraplegic group no change in resting pulse (63 ± 5 beats/min) was observed, and in the two subjects in whom skin sweating was monitored, there was no detectable increase with hypoglycaemia. Both groups experienced mild degrees of typical neuroglycopenic symptoms of hunger and drowsiness.

The changes in the metabolic parameters measured in both groups are shown in Figures 1–3. Blood glucose fell rapidly from similar mean basal levels in control and tetraplegic subjects following the administration of insulin with a more profound fall in the normal group (Fig. 1). The rate of recovery of blood glucose was parallel in the two groups and in the tetraplegic subjects the mean basal fasting level was attained by 150 minutes after insulin injection.

In the control group mean blood lactate levels doubled after hypoglycaemia with a subsequent steady decline to normal fasting values (Fig. 2). In the tetraplegic subjects the mean basal lactate level was similar, but the striking increase after hypoglycaemia was not observed.

Following the injection of insulin, non-esterified fatty acids initially fell in the control group, then rose coincidentally with blood glucose recovery, increasing to above basal levels (Fig. 3). In the tetraplegic subjects the mean fasting N.E.F.A. level was higher and a similar fall was noted following insulin. However, the

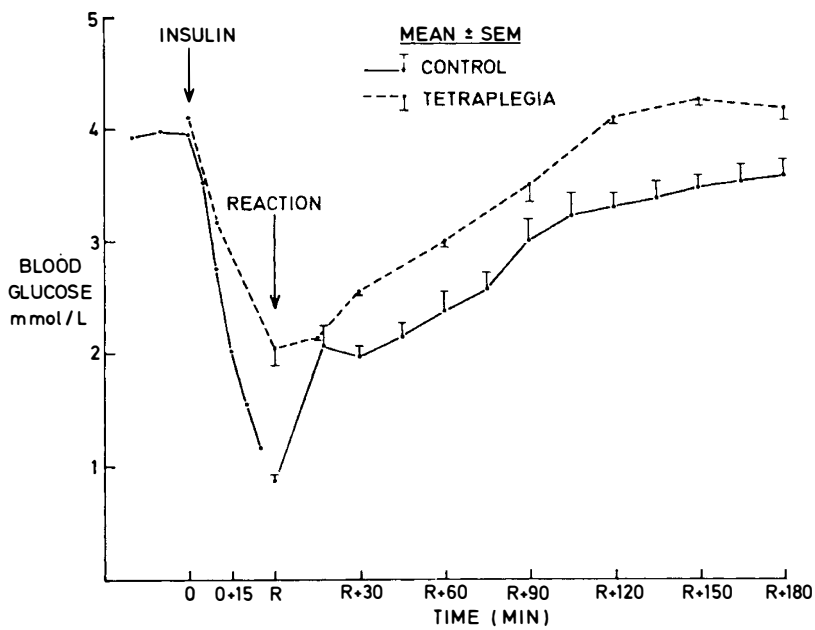

FIG. 1

Changes in blood glucose following injection of insulin in control and tetraplegic subjects.

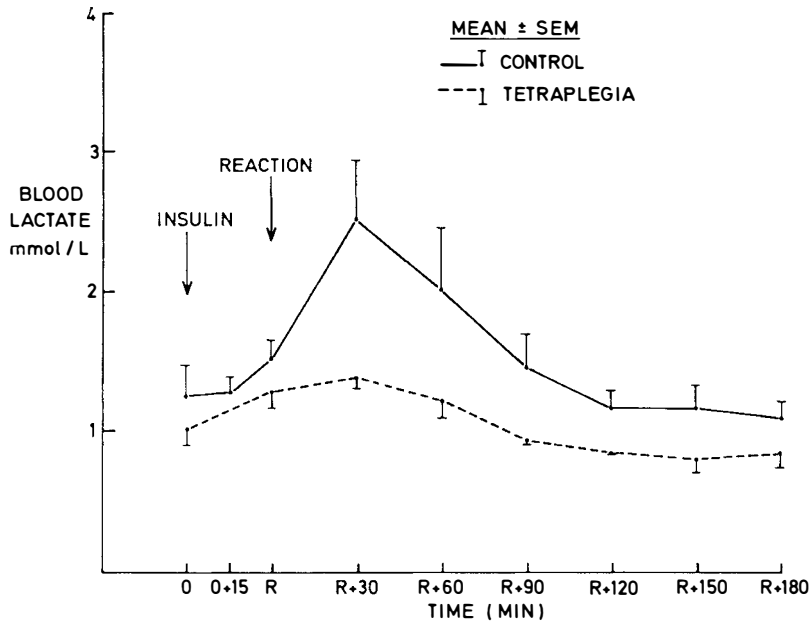

FIG. 2

Changes in blood lactate following injection of insulin in control and tetraplegic subjects.

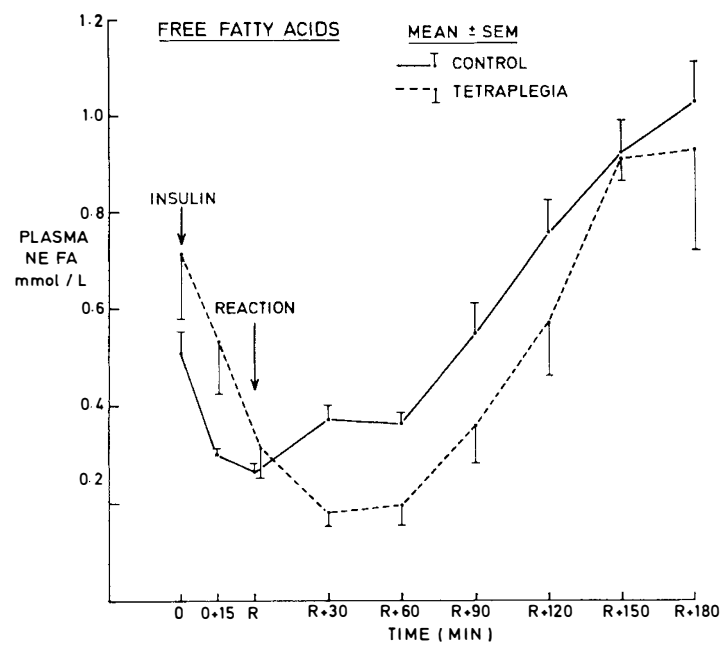

FIG. 3

Changes in plasma free fatty acids following injection of insulin in control and tetraplegic subjects.

subsequent increase in N.E.F.A. levels was delayed compared to the control group.

Discussion

Electrical stimulation experiments in the rat have indicated that the activation of recovery from acute hypoglycaemia originates in the ventromedial nucleus of the hypothalamus (Frohman & Bernardis, 1971). Efferent pathways connect with nerve cell bodies in the thoraco-lumbar grey matter which emerge as the sympathetic outflow and synapse in peripheral ganglia. The adrenal medulla may be considered a modified ganglion, the activation of which causes humoral secretion of adrenaline and noradrenaline (Bloom *et al.*, 1975). The liver with its central role in carbohydrate homeostasis receives a rich sympathetic nerve supply (Holzbauer & Sharman, 1972). Adrenaline and noradrenaline levels rise markedly in peripheral blood following hypoglycaemia and the initiation of recovery from hypoglycaemia bears a close temporal relationship to this acute secretion (Garber *et al.*, 1976). Blood glucose recovery is also impaired by adrenergic blockade (Corrall *et al.*, 1978) and during total autonomic blockade with hexamethonium (Lawrence & Stacey, 1952).

Following the injection of insulin, a lesser fall of blood glucose occurred in the tetraplegic subjects. This relative insulin insensitivity is a recognised consequence of physical inactivity (Lipman *et al.*, 1970). The rate of recovery in the tetraplegic group, however, is similar to that observed in the control subjects, indicating that recovery from hypoglycaemia is relatively normal. This suggests that non-adrenergic mechanisms may be invoked to restore blood glucose to normal. However, it is possible that carbohydrate homeostasis could be severely impaired during the early period following traumatic transection of the cervical cord, and this merits further study.

The lack of response of blood lactate to hypoglycaemia in the tetraplegic group is an interesting finding. The blood lactate rise following hypoglycaemia is thought to result from breakdown of muscle glycogen and this is activated by raised circulating adrenaline levels. Thus it is blocked by hexamethonium which prevents secretion of adrenaline, and also by adrenalectomy (Di Salvo *et al.*, 1956). The formation of glucose from lactate has been implicated as an important factor in the recovery from hypoglycaemia in man (Corrall *et al.*, 1978). It is of interest therefore that recovery proceeds normally in the tetraplegic group where lactate production appears to be impaired.

In both the control and tetraplegic subjects the fall in N.E.F.A. levels following insulin injection results from inhibition of fat cell lipolysis. The subsequent re-activation of lipolysis is delayed in the tetraplegic subjects and probably results from adrenergic denervation. In the later stages of blood glucose recovery, other lipolytic hormones including glucagon, growth hormone and cortisol may be responsible for the raised N.E.F.A. levels which are eventually attained.

These preliminary observations indicate that following cervical cord transection in man significant metabolic dysfunction occurs. Blood lactate and plasma N.E.F.A. responses to hypoglycaemia are abnormal, but restoration of euglycaemia appears to be relatively intact.

Summary

The metabolic response to insulin-induced hypoglycaemia was studied in six normal and four tetraplegic subjects. In the tetraplegic group the normal

autonomic reaction to hypoglycaemia was absent, but blood glucose recovery was not impaired. The normal increase in blood lactate was markedly attenuated and the rise in plasma free fatty acids following hypoglycaemia was delayed. The significance of these metabolic changes in tetraplegia is discussed.

RÉSUMÉ

L'hypoglycémie aigüe a été provoquée chez les sujets tétraplégiques et les cas contrôles sains par l'utilisation de l'insuline. Le rétablissement de l'hypoglycémie a été étudié en mesurant les niveaux substratums appropriés dans le sang. Des réactions anormales de lactate et de concentrations acides gras libre étaient observées. La guérison du glucose du sang continua à un cours normal.

ZUSAMMENFASSUNG

Die akute Hypoglykämie ist in den tetraplegien Patienten und gesunden Kontrollen durch die Benutzung des Insulins untersucht worden. Die Heilung der Hypoglykämie ist in der Blutglukose studiert worden. Abnormale Werte von Lacticaecid und von freien, fettigen Säuren wurden gemessen.

Acknowledgements. We thank Mr D. Shirling for valuable technical assistance, the nursing staff of the Spinal Unit at Edenhall Hospital for helpful cooperation, Professor J. A. Strong and Dr J. D. Baird for advice and encouragement and the secretarial staff of the Department of Medicine for typing the manuscript.

REFERENCES

BAIRD, J. D., BLACK, M. W. & FAULKNER, D. E. (1967). Semi-automated method for the determination of free fatty acids in plasma. *J. Clin. Path.*, **20**, 905–909.

BLOOM, S. R., EDWARDS, A. V., HARDY, R. N., MALINOWSKA, K. W. & SILVER, M. (1975). Endocrine responses to insulin hypoglycaemia in the young calf. *J. Physiol.*, **224**, 783–803.

COHEN, S. (1966). An investigation and fractional assessment of the evaporative water loss through normal skin and burn eschars using a microhygrometer. *Plastic reconstr. Surg.*, **37**, 475–485.

CORRALL, R. J. M., DAVIDSON, N. McD. & FRENCH, E. B. (1978). Recovery from acute hypoglycaemia in man: Adrenergic Mechanisms. *Clin. Sci. and Mol. Med.*, **55**, 3P.

DI SALVO, R. J., BLOOM, W. L., BRUST, A. A., FERGUSON, R. W. & FERRIS, E. B. (1956). A comparison on the metabolic and circulatory effects of epinephrine and norepinephrine and insulin hypoglycaemia with observations on the influence of autonomic blocking drugs. *J. Clin. Invest.*, **35**, 568–577.

FROHMAN, L. A. & BERNARDIS, L. L. (1971). Effect of hypothalamic stimulation on plasma glucose insulin and glucagon levels. *Am. J. Physiol.*, **221**, 1596–1602.

GARBER, A. J., CRYER, P. E., SANTIAGO, J. V., HAMMOND, M. W., PAGLIARA, A. S. & KIPNIS, D. M. (1976). The Role of Adrenergic mechanisms in the substrate and hormonal response to insulin-induced Hypoglycaemia in man. *J. Clin. Invest.*, **58**, 7–14.

HILL, J. B. & KESSLER, G. (1961). An automated determination of glucose utilising a glucose-oxidase-peroxidase system. *J. Lab. Clin. Med.*, **57**, 970–980.

HOHORST, H. J. (1970). In H. U. BERGMEYER (ed.), *Methods in Enzymatic Analysis*, 2nd ed., vol. ii, p. 1425. Verlag Chemie, Weinheim.

HOLZBAUER, M. & SHARMAN, D. F. (1972. The distribution of catecholamines in vertebrates. In H. C. BLASCHKO & E. MUSCHOLL (eds.), *Handbook of Experimental Pharmacology XXXIII Catecholamines*, pp. 110–185. Springer-Verlag, Berlin.

LAURENCE, D. R. & STACEY, R. S. (1952). Effect of Hexamethonium on the response to insulin in animals and man. *Brit. J. Pharmacol.*, **7**, 255–260.

LIPMAN, R. L., SCHNURE, J. J., BRADLEY, E. M., LECOCQ, E. R. (1970). Impairment of peripheral glucose utilisation in normal subjects by prolonged bed rest. *J. Lab. Clin. Med.*, **76**, 221–230.