Ketotic (Idiopathic Glucagon Unresponsive) Hypoglycaemia

Catecholamine Excretion and Effects of Ephedrine Therapy*

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Rosenbloom, A. L., and Tiwary, C. M. (1972). *Archives of Disease in Childhood*, 47, 924. **Ketotic (idiopathic glucagon unresponsive) hypoglycaemia: catecholamine excretion and effects of ephedrine therapy.** Two children with intermittent hypoglycaemia, associated with vomiting and occurring in the morning after breakfast, were unresponsive to the hyperglycaemic effect of glucagon in the fasting state. Fed-state glucagon response was normal. Urinary catecholamine excretion rate tripled during 18 to 24 hours of fasting. Treatment with ephedrine sulphate 2.5 mg/kg body weight per day divided into 6-hourly doses, much improved fasting tolerance and restored the glycaemic response to glucagon in the fasting state. The ephedrine was without side effects and has completely eradicated hypoglycaemic episodes in one of the children during 22 months use.

The most common form of hypoglycaemia occurring in childhood is characterized by infrequent episodes associated with food deprivation or illness (Colle and Ulstrom, 1964). Though the disorder is called ketotic hypoglycaemia, ketonuria is neither a constant nor a unique feature (Nitzan *et al.*, 1968; Rosenbloom, 1972). This variety of hypoglycaemia is clinically singular in the temporal consistency of spells (early morning), the association of vomiting, and the failure of glucagon to raise circulating glucose levels in the fasting state, despite normal response in the fed state (Colle and Ulstrom, 1964; Rosenbloom, 1972).

The aetiology of this condition is obscure and several observed phenomena have been implicated as causal (Colle and Ulstrom, 1964; Koffler, Schubert, and Hug, 1971; Kogut, Blaskovics, and Donnell, 1969; Pagliara *et al.*, 1971; Sauls, 1966). The purpose of this report is to (1) note urinary catecholamine rises with starvation in two subjects, and (2) document therapeutic responses to oral ephedrine administration in them. These observations contrast with those of a recent report (Koffler *et al.*, 1971).

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Methods

Two children with a history of symptomatic and chemical hypoglycaemia (plasma glucose concentration less than 40 mg/100 ml) were studied in the Clinical Research Center. Glucagon responsiveness in the fed state and unresponsiveness in the fasting state were shown before these studies (Rosenbloom, 1972).

G.D. began having hypoglycaemic episodes at 7 months of age, with a frequency of 1 to 2 per month. They were characterized by crying, trembling, and vomiting in the early morning with tachycardia, pallor, and perspiration, and were relieved by sugar. He had been treated with glucocorticoids for two separate periods of 1 year each. Despite this he had no growth delay. At the time of the present study (age 9½) he had been without treatment for 2 years and was having mild spells 2 to 3 times per year, associated with failure to take a bedtime snack.

P.S. was 7 years old at the time of this study. Her spells began at age 4½ years, and when severe included vomiting, uncontrollable crying, limpness, irrational behaviour, and unconsciousness. These severe episodes occurred approximately once a month, but milder symptoms, relieved readily with orange juice, were seen more often. All episodes were before breakfast.

Neither patient had had a spell within the previous month. P.S. had been taking ephedrine sulphate, 10 mg every 6 hours from age 6, after her initial studies of ephedrine effect (1970). This was stopped one day before the more recent study (1971).

The patients were subjected to a total fast, with

provision of adequate fluid, until either hypoglycaemic symptoms developed or for 24 hours. 3-hour urine aliquots were collected during the fast. The first 3-hour specimen and the last 3-hour specimen before ending the fast were analysed for catecholamines by Bio-Science Laboratories. At the end of the fast, glucagon 1 mg was injected intravenously and plasma glucose measured before and at 15-minute intervals for 1 hour afterwards.

After the glucagon stimulation test, ephedrine sulphate 2.5 mg/kg body weight per 24 hours in 6-hourly doses was started. After 24 hours of refeeding, a repeat fast was carried out with continuation of ephedrine administration. At the end of 24 hours' fasting, a repeat glucagon stimulation test was done.

Results

After a 24-hour fast in 1970 and an 18-hour fast in 1971, P.S. was incoherent, cold, sweaty, crying, and vomiting. Glucagon had no effect on her plasma glucose levels (Fig.). During the more

FIG.—Plasma glucose concentration response to glucagon injection at the end of fasting period in two subjects, P.S. and G.D., on no treatment and with ephedrine sulphate therapy.

recent fast, the hourly urinary catecholamine excretion rose from 0.25 μ g in the first 3 hours to 0.73 μ g during the last 3 hours. Because of her response to ephedrine in the initial study, she was treated with the dose used in these studies during the 16 months between evaluations and had no episodes of hypoglycaemia.

G.D. tolerated the fast without symptoms for 24 hours. Two years earlier (1969) he had developed vomiting at 22 hours of fasting. Catecholamine excretion per hour in the first 3 hours of fasting was 0.67 μ g and in the last 3 hours 1.67 μ g.

Both patients had improved fasting tolerance on ephedrine. P.S. fasted for the full 24 hours without developing any symptoms of hypoglycaemia, in contrast to the marked symptomatology that appeared at 18 hours without treatment. In addition to higher 24-hour fasting glucose levels, ephedrine therapy was associated with a brisk response to glucagon injection in the fasting state (Fig.). There were no side effects of ephedrine administration.

Discussion

The finding of nearly threefold increases in urinary catecholamine excretion during fasting casts doubt on adrenal medullary unresponsiveness as an aetiological mechanism in this condition. Studies by Koffler *et al.* (1971) implicating failure of catecholamine rise with induction of hypoglycaemia by insulin of a ketogenic diet in sporadic hypoglycaemia may not have referred to patients such as ours. No data were given by these authors about glucagon responsiveness, which we consider to be the hallmark of what has been called 'ketotic hypoglycaemia' (Rosenbloom, 1972).

In one of the patients, ephedrine sulphate every 6 hours completely eliminated hypoglycaemic episodes for 16 months before the current studies and for the 6 months after. In a patient with milder symptoms in the morning and proven fasting glucagon unresponsiveness, bedtime ephedrine has been equally effective.

Despite the lack of proof for adrenal medullary unresponsiveness in ketotic (idiopathic glucagon unresponsive) hypoglycaemia, oral ephedrine administration has been seen to provide acute and chronic protection against fasting hypoglycaemia, and to restore fasting glucagon responsiveness.

There is no ready explanation for this observation. Ephedrine should increase lipolysis and glycogenolysis, accelerating the hepatic glycogen exhaustion seen in biopsy specimens of fasting patients (Sauls, 1966). We are presently pursuing more detailed studies of energy substrate utilization and hormonal changes in these subjects and control children, without treatment and while taking ephedrine, in order to clarify the mechanisms involved.

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