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THE SOMOGYI PHENOMENON. A SHORT REVIEW

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Hypotheses

SOMOGYI's theory [24] was that, both in diabetic and non-diabetic subjects, hypoglycemia was a stimulus for adrenaline release and this acted on the anterior pituitary to produce ACTH and consequently corticosteroids. There have been many physiological studies, both in animals and humans, to show that hypoglycemia stimulates the release of blood glucose raising hormones such as *a)* adrenaline [14], *b)* corticosteroids [3], *c)* growth hormone [12] and *d)* glucagon [12, 28]. It may be that glucagon acts to prime the adrenal medulla for later adrenaline secretion and then both could act synergistically to raise the level of blood glucose [11]. SOMOGYI [25] showed that hypoglycemia induced hyperglycemia by means of quantitative urine glucose measurements, demonstrating characteristic 'ebb and tide in the extent of glycosuria, the highest glycosuric tides always occurring in the wake of frank hypoglycemic reactions'.

The previously widely accepted role of adrenaline in glucose homeostasis has recently come under attack. The action of adrenaline decreasing glucose utilization peripherally [22] has been challenged by contradictory evidence [2]. The inhibition of insulin secretion after infusion of adrenaline is only seen during the injection period and, after the latter is over, there is increased insulin secretion [20]. Other evidence supports the shortlived elevation of adrenaline following hypoglycemia [29]. Classical teaching has been to associate the clinical symptoms of hypoglycemia with adrenaline release but WALLACE and HARLAN [29] have shown that an infusion of adrenaline associated with insulin-induced hypoglycemia is associated with the disappearance of these symptoms.

Controversy

Initially, and even now, SOMOGYI's concepts were not universally accepted. The clinical significance of the phenomenon has been denied by ALLEN [1] and minimized by CHESTER et al. [9] who were unable to augment hyperglycemia or glycosuria following *single* episodes of insulin-induced hypoglycemia in diabetic patients. They implied that the rebound hyperglycemia and glycosuria seen in other studies may have been due to additional carbohydrate given to counteract

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the hypoglycemic episodes. However, 9 out of their 10 patients were 'maturity-onset' diabetics, mostly obese (2 were on diet alone) and not the 'juvenile-onset' type in whom SOMOGYI described this phenomenon.

Historical aspects

Soon after the introduction of insulin therapy in 1922, it was recognized that after a fall in blood sugar an equally rapid rise could occur and periods of hyperglycemia could alternate with periods of aglycosuria [15]. However, more detailed documentation did not come till 1938 when SOMOGYI and KIRSTEIN [26] reported that, in a group of 'brittle' (unstable) diabetics, overinsulinization could be a cause of extreme hyperglycemia and instability of control. This paradoxical situation that 'hypoglycemia begets hyperglycemia' [21] came to be known as the 'Somogyi phenomenon' or 'Somogyi effect'. From the extensive laboratory and clinical data he accumulated over the subsequent twenty years, SOMOGYI documented in great detail 'the exacerbation of diabetes by excess insulin action' [23]. Although this phenomenon has been debated in the literature for many years, controversy still exists whether it is clinically significant or even exists at all.

Clinical situation

The paradoxical situation arises in insulin-treated diabetics where hypoglycemia, often asymptomatic and unrecognized, is postulated to act as a trigger for the physiological release of insulin antagonists which give rise to a 'rebound' hyperglycemia and glycosuria which leads the patient, or doctor, to increase the insulin dose still more, and further hypoglycemic episodes may result (see fig. 1). A vicious circle leading to higher and higher insulin doses ensues with extremely unstable and unmanageable diabetes. This situation should always be borne in mind when there is deteriorating diabetic control on increasing insulin dosages. Clinical clues [4] that the Somogyi phenomenon is present are: *a)* asymptomatic periods with urine tests negative for sugar and ketones followed, with no intermediate graduation, by heavy glycosuria and ketonuria, as early as 4 hrs later; *b)* wide fluctuations unrelated

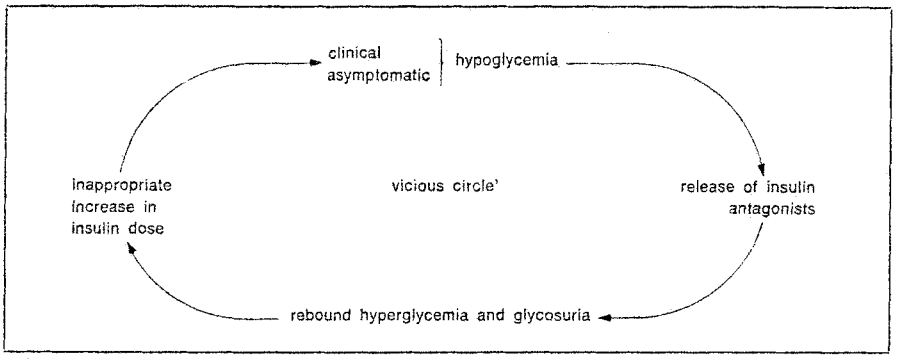

Fig. 1 - Mechanism of Somogyi phenomenon.

to meals in blood sugar values, over several hours; *c)* heavy glycosuria all day with nocturnal sweating, morning hypothermia, or headaches.

One reason the Somogyi phenomenon has not been more widely accepted is related to the fact that hypoglycemia may be asymptomatic. The clinical symptoms of hypoglycemia need not occur at a level of *absolute* hypoglycemia (by definition less than 40 mg/100 ml) but may be related to the *fall* in blood glucose. Clinical and physiological signs of hypoglycemia may be present when the blood glucose value is actually in the hyperglycemic range [5]. Asymptomatic hypoglycemia may require for its detection hourly blood sugar determinations, very often at times different from routine hospital practice *e.g.* through the night [4], and the determinations should be done for at least 48 hrs since the blood glucose pattern is never the same 2 days in a row [7]. Perhaps more attention should be paid in trying to detect hypoglycemia by hypothermia, a little recognized clue to the presence of hypoglycemia [16, 18, 27]. In BLOOM's series [4], 5 out of 6 patients had morning hypothermia when 'somogying'.

'Nearing the truth'

Many of the objections to SOMOGYI's concepts were based on the absence of suitable laboratory measurement of 'hormonal factors' antagonistic to insulin. With the recent development and refinement of hormonal immunoassay techniques, there are now clinical studies demonstrating hormonal factors principally responsible for the Somogyi phenomenon.

MINTZ et al. [17] have demonstrated in normal control subjects that post-hypoglycemic glucose intolerance persisted despite inhibition of the insulin-induced elevation of cortisol by metyrapone. Their observations showed HGH was primarily responsible for post-hypoglycemic glucose intolerance. They demonstrated, during insulin glucose tolerance tests, with and without pharmacological blockade of α-receptors and cortisol production, that the disposal rate of p.o. administered glucose was impaired, insulin secretion reduced and HGH enhanced. The rebound increase in FFA in response to hypoglycemia was inhibited by oral ingestion of glucose, showing elevated FFA were not inducing the post-hypoglycemic glucose tolerance. To distinguish whether the latter was due to endogenous hypoinsulinism or enhanced HGH secretion, the disposal rate of p.o. administered glucose following insulin-induced hypoglycemia was measured in patients with hypopituitarism and despite poor insulin responses in these patients, the disposal rate of the glucose was considered normal.

In an 11-year-old diabetic child with post-hypoglycemic hyperglycemia, BRUCK and MACGILLIVRAY [6] made serial measurements of HGH, cortisol and catecholamines. The plasma cortisol appeared to fluctuate without any particular relationship to the blood sugar. Excessive catecholamine excretion was variable and it was only where it coincided with elevation of HGH that it was followed by rises in blood sugar. The HGH levels showed very high peaks following every sharp fall in blood glucose. The HGH values were sometimes 3 times as high as those that can usually be provoked in normal people by insulin stimulation. These peaks in HGH were then followed by a sharp rise in blood glucose which often lasted for many hours, sometimes a day.

Both MINTZ et al. [17] and BRUCK and MACGILLIVRAY [6] concluded that an increase in HGH is the major consequence of hypoglycemia and this rise in HGH is the major hormonal factor in the etiology of the Somogyi phenomenon. Hypoglycemia produces a rapid rise in plasma glucagon which precedes the elevation in cortisol and HGH [12] and glucagon would appear to play a major role in the Somogyi phenomenon although as yet its role is not accurately defined.

Clinical management

Although the Somogyi phenomenon is not mentioned in many of the standard text books in internal medicine and often glossed over in the more specialized ones, it may be more common than many doctors believe [7, 8]. COLWELL [10] estimated that approximately 10% of insulin-treated diabetics, mostly juveniles, fall into the category of 'brittle' or unstable diabetics. CHANCE [3] reports that failure to recognize Somogyi phenomenon in diabetic children may be one cause of 'brittleness' in children. In fact, the Somogyi phenomenon is probably more common in young children than in adults [7].

Unless the paradoxical fact is appreciated that hyperglycemia may follow hypoglycemia, the insulin dosage may be incorrectly increased and that unstable diabetic control aggravated. However, once hypoglycemia has been demonstrated or been suspected clinically, treatment is based on the reduction of the insulin dose to correct the overinsulinization and 'break up the vicious circle'. SOMOGYI, himself, recommended a gradual reduction in the insulin dose to get more stable blood sugars, decreased urinary glucose excretion and better diabetic control. The insulin dosage was gradually decreased over a period of many months in some of his patients [23]. BLOOM et al.[4] support SOMOGYI's view that too rapid a reduction in insulin dose can cause persistent severe hyperglycemia and ketonuria. Our own practice, however, as with others [19] is to arbitrarily reduce the insulin dose to approximately half its peak value and then to make further minor adjustments as required. This practice has proved successful in our experience in reestablishing good diabetic control.

The ultimate proof of the Somogyi phenomenon depends upon better glycemic control and decrease in glycosuria on a reduced insulin dose. If the diagnosis is wrong, reduction in insulin dose will aggravate the hyperglycemia, glycosuria, ketosis and ketonuria. Further proof of the amelioration of the post-hypoglycemic hyperglycemia can be shown by a dramatic reduction in quantitative 24-h glycosuria with the decreased insulin dose.

The future

Further clinical studies measuring hormones especially glucagon (when immunoassay more readily available) before and after treatment of patients with the Somogyi phenomenon are required to delineate the true underlying factors responsible for the post-hypoglycemic hyperglycemia. With this will come a wider appreciation of this phenomenon and its clinical significance especially in relation to 'brittle' diabetic patients.

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SUMMARY

The Somogyi phenomenon or effect is a paradoxical situation of insulin-induced post-hypoglycemic hyperglycemia. The historical aspects of this phenomenon and the subsequent hypotheses and controversy are reviewed. The clinical situation is explained, with regard to its recognition, management and importance as an etiological factor in 'brittle' diabetes. Hormone immunoassay techniques at present show human growth hormone (HGH) to be the major consequence of insulin-induced hypoglycemia leading to post-hypoglycemia glucose intolerance, but further studies will probably show glucagon to have a major role.

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