The role of the sympathetic nervous system in hypoglycaemia-stimulated gastric secretion

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SUMMARY The gastric secretory response to insulin is mediated predominantly by the vagus. The associated hypoglycaemia stress response is mediated by the sympathetic nervous system.

Inhibition of the sympathetic response by simultaneous alpha and beta receptor blockade was studied in five healthy young adults.

No appreciable modification of gastric secretory output resulted.

Insulin-induced hypoglycaemia leads to vagally mediated stimulation of gastric secretion (Hollander, 1946). Insulin-induced hypoglycaemia also produces a stress response mediated by the sympathetic nervous system (Cannon, McIver, and Bliss, 1924; von Euler and Luft, 1952; Duner, 1954; Cantu, Wise, Goldfien, Gullixson, Fischer, and Ganong, 1963). Adrenaline and l-noradrenaline reduce basal and stimulated gastric secretion (Baronofsky and Wangenstein, 1945; Forrest and Code, 1954; Leonsins and Waddell, 1958; Nicoloff, Peter, Stone, and Wangenstein, 1964; Haigh, Moffitt, and Steedman, 1967). It appears therefore that the effects on secretion of the parasympathetic and sympathetic nervous systems are mutually antagonistic.

This study was undertaken to determine whether inhibition of the sympathetic component leads to a rise in human secretion during insulin-induced hypoglycaemia. In order to achieve adequate inhibition of this sympathetic component it is necessary to block specifically both alpha and beta sympathetic receptors (Ahlquist, 1948) simultaneously, and this was done.

Methods and Materials

Five healthy informed volunteers between the ages of 20 and 26 years each underwent two studies in random order. The intervals between studies were seven, 12, 14, 38, and 54 days. An electrocardiogram was performed on all subjects before the experiments to exclude the presence of any cardiac conduction defects.

CONTROL INSULIN STUDY

After a 12-hour fast from nine o'clock the previous evening a 14FG gastric tube was passed into the stomach and the opaque tube tip fluoroscopically positioned so that it lay in the most dependent part of the stomach with the subject lying on his left-hand side.

Following four 15-minute basal collections of gastric secretion, aspiration being performed continuously by hand, an intravenous infusion of 0.9% saline was set up and continued for the remainder of the experiment. The total volume infused did not exceed 1 litre.

Thirty minutes after beginning this infusion, the stomach was aspirated and the specimen discarded. Crystalline insulin¹, 0.15 units per kilogram body weight, was then injected intravenously as a bolus, and eight further 15-minute gastric samples were obtained.

Blood sugar levels were measured before and after the basal collection, immediately before giving the insulin, and afterwards, at 15, 30, 45, 75, and 105 minutes. Blood pressure and pulse rate were recorded at 15-minute intervals throughout, and more often when indicated.

INSULIN STUDY WITH SYMPATHETIC BLOCKADE

A similar procedure to that described above was followed with the exception that the infusion contained phentolamine², 0.5 mg per ml. A loading injection of 10 mg phentolamine was first given intravenously and then the infusion run in at the rate of 2 ml per minute. Alpha receptor blockade

¹Insulin BP 20 units per ml (CSL Australia) glucagon less than 0.69%

²Phentolamine mesylate (Regitine ®, Ciba, Australia)

was indicated by a consistent rise in pulse rate of 20 beats per minute, usually accompanied by a fall in diastolic blood pressure. Once achieved, the infusion rate was adjusted to maintain this steady state. Blockade was always achieved within 30 minutes of commencement of the phentolamine and then maintained for a further 75 to 120 minutes. A total of 120 mg phentolamine was not exceeded in any experiment.

When a steady state of alpha blockade was achieved, propranolol³ was given intravenously, not more rapidly than 1 mg per minute, until the pulse rate returned to basal levels while the phentolamine continued to run at a blocking dose rate. This required a dosage of 4 to 8 mg of propranolol.

We found this procedure safe in every case. There were no after effects, although during the period of alpha blockade nasal congestion was uncomfortable.

On each gastric sample, volume was measured directly by volumetric cylinder, pH by glass electrode, and titratable acidity by the addition of N/10 NaOH to an electrode pH of 7.40.

Blood sugar levels were measured by an Auto-Analyzer using the ferricyanide method (Technicon Methodology N2A) on blood obtained by repeated venepuncture.

Results

Figure 1 presents the mean blood sugar estimations, with standard errors, during the 'insulin only' and

the 'insulin plus alpha and beta blockade' studies. Although it has been reported that beta receptor blockade delays the return of the blood sugar level towards normal following insulin (Abramson, Arky, and Woeber, 1966) this was not seen with both alpha and beta receptor blockade (Fig. 1).

The mean values of the acid outputs with standard errors were calculated for the five subjects and are presented in Figure 2. Using paired Student's *t* tests there was no significant effect on any of the 15-minute outputs after insulin nor on total 120-minute outputs. There were no significant differences in volume outputs nor acid concentrations using the same statistical procedure.

Peak acid output, calculated as maximum acid output in any two consecutive 15-minute periods, fell as a result of sympathetic blockade in all subjects but one ($M = 17.1 \pm SE 1.60$ to $M = 14.0 \pm SE 0.77$). However, significance was not achieved when paired Student's *t* test was applied ($0.20 > P > 0.10$).

During the study, changes in blood pressure (with limits of ± 20 mm Hg systolic and ± 20 mm Hg diastolic) as a result of experimental manipulations and sympathetic blockade could not be correlated with any changes in gastric secretion. Similarly alterations in pulse rate (with limits of ± 25 beats per minute) could not be shown to be related to secretion.

Discussion

In all subjects there was evidence of both a parasympathetic and sympathetic nervous response when

Fig. 1 Blood sugar level before and after giving insulin. --- without blockade, — with blockade. There is no significant difference between the two curves using paired *t* tests.

³Propranolol hydrochloride (Inderal ®, ICI Australia)

Fig. 2 Acid output per 15 min before and after giving insulin. --- without blockade, — with blockade. Using paired *t* tests, there is no significant difference between the two curves either at each period or over the whole experiment.

blood sugar was appropriately lowered. The rise of gastric secretion indicated the expected parasympathetic response (Fig. 2). The sympathetic nervous response was demonstrated clinically by sweating, palpitation, tachycardia, and a feeling of anxiety by the subject. However, the sympathetic alpha and beta receptor blockade appeared adequate as indicated by the sequential cardiovascular effects.

Although it is believed that there is initial inhibition of gastric secretion by insulin (Olsen and Necheles, 1955; Geziri, Robertson, Plzak, and Woodward, 1958; Hirschowitz and Robbins, 1966; Schapiro, Cummins, and Wruble, 1967; Singleton, 1969), we obtained no significant statistical evidence to support them (Fig. 2).

It was expected that when the sympathetic component of the stress response to insulin was removed in this study, gastric secretion would increase. However, this occurred in only two experiments. It is probably safe to conclude that the effects of the sympathetic nervous system on the vagally driven acid output of hypoglycaemia are of little consequence. The reasons for this can only be speculative.

There seem to be two possibilities. In the first place there seems to be no information available regarding the direct effects of catecholamines on the parietal cell, nor is there any on the effects of phentolamine and propranolol. What effect therefore these agents had in this study is unknown. In the second place, however, there is some information on

the indirect effects of catecholamines on gastric secretion.

Many published reports have indicated that during basal secretion and many varying types of secretory stimulation, catecholamines have an inhibiting effect (Baronofsky and Wangenstein, 1945; Forrest and Code, 1945b; Leonsins and Waddell, 1958; Nicoloff *et al*, 1964; Haigh *et al*, 1967). However Linde (1950), Code (1951), and Karvinen and Karvonen (1953) found them to have no effect. Haigh and Steedman (1968) found inconstant effects while Cumming, Haigh, Harries, and Nutt (1963) believe that they stimulate secretion. These apparently conflicting results may be due to variations induced in mucosal blood flow.

Cutting, Dodds, Noble, and Williams (1937) showed that the effect of parietal cell stimulation is dependent on adequate gastric blood flow, but it has been realized more recently (Thompson and Vane, 1953; Nicoloff *et al*, 1964; Delaney and Grim, 1965; Jacobson, Swan, and Grossman, 1967) that the significant part of gastric blood flow is that to the mucosa. During histamine stimulation total gastric blood flow may be increased with adrenaline by the opening of subserosal and submucosal arteriovenous shunts while simultaneously causing mucosal vasoconstriction; this leads to a fall in secretion (Peters and Womack, 1958; Nicoloff *et al*, 1964). Also, the infusion of catecholamines into the arterial supply of the stomach produces patchy mucosal congestion

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