IN VITRO ENHANCEMENT OF INSULIN SECRETION BY GROWTH HORMONE

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SUMMARY: Using the isolated perfused hamster pancreas bovine growth hormone at a concentration of 7.5 ug per ml was recycled for 1 hour prior to stimulation by glucose. Under these conditions the total insulin secreted was roughly doubled compared to the controls during 1 hour of glucose stimulation.

It is thought that some biological activity of growth hormone (GH) may not be a consequence of the GH molecule per se, but may be due to a subsequent product such as sulfation factor (1), currently called somatomedin (2). We have recently reported that hypophysectomized rats have a depressed insulin response to glucose, and that a daily injection of GH to hypophysectomized rats will partially restore this response (3). Those experiments, however, did not exclude the possibility that a product of GH, such as somatomedin, might have been the active molecule. This is due to the fact that organs such as the liver (4) and the kidneys (5) possess the ability to produce somatomedin following GH administration. The experiments reported in this paper were performed in an *in vitro* perfusion system in the absence of either liver or kidneys, thus strongly indicating that the observed effect is due to GH rather than somatomedin. This is further substantiated by the fact that somatomedin production *in vivo* becomes significant only after a lag time of 3 hours following GH infusion (6), whereas in our experiments the lag time was only 1 hour.

The pancreases of golden Syrian hamsters were perfused in the isolated organ perfusion system by the procedures previously described (7), the essential differences being scaling down the size of the cannulae. The

perfusion medium is that previously described for the rat pancreas. Bovine GH (8) was added directly to the perfusate to produce a concentration of 7.5 ug per ml (a concentration considerably higher than that in fasting rat plasma) and this was recycled through the preparation for 1 hour prior to stimulation by glucose. Control pancreases were recycled for 1 hour with the same medium without GH having been added. The insulin assay was done by the immunochemical method of Grodsky and Forsham (9) using rat insulin as a standard, since no hamster insulin was available for such purpose.

The pertinent data from control pancreases are shown in Fig. I. They

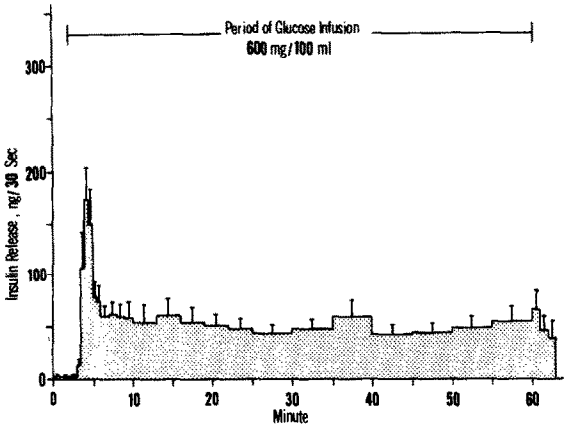

Figure I: Time course of mean insulin release by five normal hamster pancreases during 1 hour of glucose stimulation. The perfusing medium without growth hormone was recycled for 1 hour prior to zero time. Standard error for each collection period is shown.

demonstrate a biphasic insulin secretory pattern. There is an initial rapid response as in the rat pancreas but no rising second phase as occurs in the rat (7). Instead, the second phase is characterized by a steadily maintained release of insulin well above the baseline level. The data from pancreases of hamsters through which GH has been recycled for 1 hour are shown in Fig. II. They show a much larger first phase as well as a

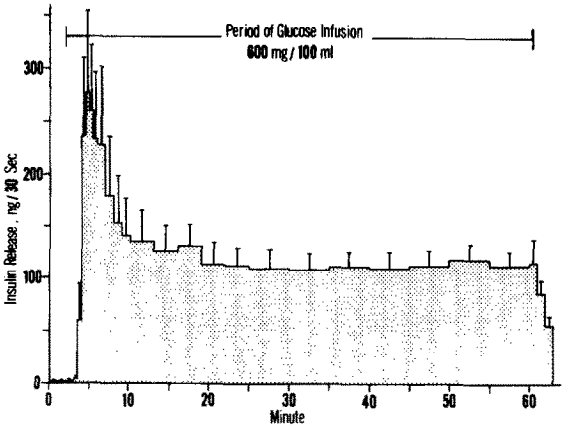

Figure II: Time course of mean insulin release by five normal hamster pancreases exposed to growth hormone. The perfusing medium containing 7.5 ug of growth hormone per ml was recycled for 1 hour prior to zero time. Standard error for each collection period is shown.

much higher level of the steady release second phase. The total insulin released by the control pancreases during the first phase (minutes 2-10) was 1.08 ± 0.19 (n=5) ug as compared to 2.48 ± 0.56 (n=5) ug from the pancreases through which the GH was recycled ($p < .05$). For the second phase (minutes 30-60) the total insulin released was 2.99 ± 0.64 ug and 6.77 ± 0.86 ug respectively for the control pancreases and the pancreases exposed to GH ($p < .01$).

One can only speculate upon the mechanism of action of GH in this system. It is possible that GH increases the ability of the beta cells to synthesize insulin in response to a glucose stimulus and/or enhances transport to the cell periphery from which it is secreted. It is not necessary that newly synthesized insulin be a component of the insulin actually secreted by the cells during this 1 hour period (10). Another mechanism which may be operating, perhaps in combination with the previous one, is that GH increases the number of glucoreceptor sites on beta cell membranes. Such receptor sites have been postulated by Matschinsky and co-workers (11). Regardless of its mechanism of action, this report

illustrates that GH has an *in vitro* insulinotropic effect on the pancreas which requires only a short exposure.

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