Calcium antagonists and hormone release. IV.
The role of calcium in glucose-stimulated early phase
insulin release in vivo

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ABSTRACT. Extensive in vitro studies have demonstrated that an increase in the concentration of Ca\(^{2+}\) in the cytosol of the \(\beta\)-cell of islets of Langherhans is essential for the glucose-stimulated insulin release. However, there are controversies as to whether both phases of insulin release are equally dependent upon glucose-stimulated uptake of extracellular calcium. Previous studies performed in vivo, have demonstrated an inhibitory effect of verapamil, an organic antagonist of calcium transport into cells, on the release of insulin induced by an oral glucose load. The present study was designed to investigate whether calcium antagonists are capable of inhibiting the rapid release of insulin that follows the iv infusion of glucose. Verapamil, infused into normal subjects for different periods of time before the iv administration of glucose was ineffective in inhibiting the rapid release of insulin, even when it was infused for 1 h before the glucose stimulus was applied. The present results obtained in vivo confirm some previous in vitro data showing that the first phase insulin release is not inhibited by calcium antagonists, agents known to block the uptake of calcium from extracellular sources.

INTRODUCTION
	Several in vitro and in vivo experiments have demonstrated that constant infusions of glucose result in a biphasic secretion of insulin from the \(\beta\)-cell of islets of Langherhans (1 -4). The response is characterized by a first phase release of insulin lasting a few minutes, followed by a second phase of slowly increasing insulin release.

One of the explanations proposed for this pattern of release has been that constant glucose stimulation sets up a chain of events resulting in a biphasic change in the cytosolic Ca\(^{2+}\) concentrations (5). Although an increase in the concentration of Ca\(^{2+}\) in the cytosol of the \(\beta\)-cell is believed to be essential for the glucose-stimulated insulin release (6-11), there are controversies as to whether both phases of insulin release are equally dependent upon glucose-stimulated uptake of extracellular calcium (12-15). Recently, the importance of extracellular calcium on the release of insulin has been studied by examining in vitro the different effects of organic calcium antagonists on both the glucose-induced calcium uptake and the insulin release from the \(\beta\)-cell (12-15). Although earlier studies had shown that both phases of insulin release were inhibited by organic calcium antagonists (12, 13), more recent studies have indicated that the first phase release is not dependent upon an increased Ca\(^{2+}\) uptake from extracellular sources (14, 15).

We have recently studied and reported an inhibitory effect of verapamil on insulin release induced by an oral glucose load in normal subjects (16). In the present study we investigated whether in normal subjects verapamil infusion influenced the rapid release of insulin which follows the iv injection of glucose.

MATERIALS AND METHODS

Eighteen normal subjects (18-38 yr old, 10 females and 8 males) were invited to participate to this study. None of the subjects was obese, had family history of diabetes mellitus, had any evidence of endocrinopathies, or was receiving drugs of any kind. All subjects participating in the investigation were informed as to the purpose of the study and gave their consent. Before testing, all subjects were given a diet containing a minimum of 250 g of carbohydrate daily for 3 days. All subjects were studied in the fasting state; they were...
Fig. 1 - Mean values (± SE) of blood glucose and serum insulin (IRI) in response to 20 g glucose, injected iv at 0 time over 2 min, in 6 healthy subjects.

Fig. 2 - Mean values (± SE) of blood glucose and serum insulin (IRI) in response to 20 g glucose, injected iv at 0 time over 2 min, during verapamil infusion, in 6 healthy subjects. Verapamil (5 mg/h) was infused between −30 and 60 min.

Fig. 3 - Mean values (± SE) of blood glucose and serum insulin (IRI) in response to 20 g glucose, injected iv at 0 time over 2 min, during verapamil infusion, in 6 healthy subjects. Verapamil (5 mg/h) was infused between −60 and 60 min.