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IAPP DOES NOT CAUSE PERIPHERAL OR HEPATIC INSULIN RESISTANCE IN CONSCIOUS DOGS, BUT DOES HAVE A HYPOCALCEMIC EFFECT*

A A Kassir*; A K Upadhyay*; T J Lim*; A R Moossa*; J M Olefsky**

*Department of Medicine** and Surgery*, University of California, San Diego, La Jolla, CA 92093.*

INTRODUCTION

Since the first description by Opei (1, 2), it has been known that proteinaceous amyloid deposits are commonly found in the interstitial space of islets from NIDDM subjects. These deposits can also occasionally be found in islets of non-diabetic elderly or obese individuals, but their frequency in NIDDM is much higher with some estimates as high as 90% (3, 4). Recently, two groups (5, 6) have succeeded in isolating a 37 amino acid peptide from the amyloid deposits and this peptide has been termed amylin or islet associated polypeptide (IAPP). IAPP is a 37 amino acid peptide with 46% amino acid identity to calcitonin gene related peptide (7). The gene for IAPP has now been cloned by several groups (8-11) and the sequence of this peptide is relatively conserved across several species (7). Like calcitonin gene related peptide, IAPP is amidated at the carboxy terminus, and the c-terminal amidation is essential for biolgic potency. It has also been established that IAPP colocalizes with insulin to β cells (12), and the content of IAPP relative to insulin has been reported in the range of 0.2-3 percent (7, 8); the relative content of IAPP mRNA to insulin mRNA is reported at 1-9% (7, 8, 11). IAPP appears to be co-secreted with insulin in response to glucose and protein stimuli (13-15), and the reported circulating concentrations of IAPP are in the 10^{-12}-10^{-11}M range (16-18), which is 1-3% of circulating peripheral insulin levels on a molar basis.

With respect to biologic activity, an important initial study by Leighton et al. (19) demonstrated that IAPP was able to inhibit basal and insulin stimulated glycogen synthesis in rat soleus muscle in vitro. The observations that IAPP is present in β cells and is co-secreted with insulin action in vitro, raised the possibility that this peptide might be hypersecreted in NIDDM leading to the insulin resistance which characterizes this syndrome. Indeed, we have recently observed that when pharmacologic levels of IAPP given intravenously to rats, a state of severe insulin resistance can be produces (20), as measured by the euglycemic clamp technique. In the current studies, we have utilized the conscious dog model to carry out euglycemic glucose clamp studies with or without IAPP at infusion rates of the peptide which more closely approximate the physiologic range. These studies indicate that at these infusion rates of IAPP, no detectable biologic effects on glucose metabolism can be observed.

MATERIALS AND METHODS

Animals: 8 adult, male mongrel dogs (19-34kg)

* 이 논문은 문교부 대학교수국비 해외파견 연구비로 이루어졌음.

were studied. For 10 days prior to operation, animals were fed a high protein chow diet (25% protein; 25% fat; 35% carbohydrate, ad libitum) while their general health status was evaluated. Following an overnight fast, anesthesia was induced using 20mg/kg I. V. surital (Parke-Davis, NJ) and maintained by 50-100mg intermittent bolus injection. Animals were intubated and ventilated using a Harvard Apparatus pressure cycled ventilator with 5 liter/minute oxygen supplementation.

Operative Procedures: In each animal, the left internal carotid artery and external jugular vein were introduced, one to the internal carotid artery for sampling and one to the external jugular vein for infusate delivery. The free end of each catheter was tunneled subcutaneously and exteriorized in the dorsal midline of the neck approximately 10cm below the base of the skull. Each catheter was securely anchored with a non-absorbable (silk) suture and filled with a 300 unit/ml heparin lock. The free end of each catheter was occluded with a capped blunt needle and an umbilical tape ligature. Post-operatively each catheter was flushed at 48 hour intervals using 300 units/ml heparin-saline solution.

Materials: Biosynthetic human insulin was provided by Eli Lilly and company, Indianapolis, IN; [3-^{3}H]glucose was obtained from New England Nuclear, Boston, MA. Human IAPP was provided by the Amylin Company, San Diego, CA. On the day of study, all infusates were freshly prepared in normal saline containing 1% human serum. IAPP was dissolved in 30mM HCl then diluted into the infusate solution on the day of study.

Experimental Design: Each animal underwent a series of infusion studies over a 10-12 week period commencing one week after operation. Experiments were performed following an overnight (16 hours) fast, and were conducted in individual animals on separate occasions at intervals of not less than one week Prior to each study, all animals were in general good health, with stable body weight.

Each experiment consisted of a 120 minute infusion of ^{3}H-glucose for tracer equilibration with baseline observations taken between 90-120 minutes. Thereafter, each animal underwent an infusion of insulin. The infusion rates of 5pmol/kg/min and 30 pmol/kg/min were chosen in order to achieve steady state insulin levels which would provide a 1/2 maximal and maximal stimulation of peripheral glucose disposal rate (21). During the initial 10 minutes of insulin infusion, an intravenous priming dose that was given to acutely raise the serum hormone level (21). IAPP infusions were begun 240 minutes after the start of the insulin infusion at an equimolar (5 pmol/kg/min, Study A) or a 10-fold higher (50 pmol/kg/min; Study B) infusion rate.

Measurement of Glucose Turnover: Tritiated [3-^{3}H]glucose was administered in a primed continuous manner (22), (14 uCi prime, o.0 uCi/min constant infusion). glucose turnover rates were quantitated isotopically from the plasma glucose level and the serum glucose specific activity in the basal state and during the period of hormone infusion. A value for baseline R_a and R_d, in each animal, was derived from the mean of the values determined between time points 90, 100, 110, and 120 minutes. Thereafter, paired samples for the measurement of plasma glucose and glucose specific activity were obtained at 20 minute intervals for 2 hours and then at 30 minute intervals. R_a and R_d were calculated with the Steele equations (23) in their modified derivative form (24) since the tracer exhibits non-steady state kinetics under these conditions. Hepatic glucose production rates were calculated from the difference between R_a and the rate of exogenous glucose infusion.

Specimen Collection and Analysis: Specimens for insuin assay were collected in plain glass tubes and allowed to clot at room temperature. IAPP specimens were collected at room temperature in tubes containing 500 I. U./ml trasylol (FBA Pharmaceuticals, N. Y.) and E. D. T. A. Glucagon specimens were collected in chilled tubes also containing 500 I. U./ml trasylol; tritiated [3-^{3}H]glucose specimens were collected in chilled tubes containing NaF. After centrifugation at 4℃, all specimens were stored at -20℃ until analysis. Serum insulin concentrations were measured by a modification of the double-antibody technique (25); glucagon immunoassay was performed using

30k antibody and charcoal separation (26). Blood for the determination of [3-^{3}H]glucose specific activity was deproteinized using perchloric acid before counting as previously described (27), serum IAPP levels were measured by radioimmunoassay according to specifications of Peninsula Laboratories, as previously described (13). Calcium levels were measured by the method described by Moorehead and Biggs (28).

RESULITS

Insulin and IAPP Levels: Euglycemic glucose clamp studies were conducted at an insulin infusions rate of 5 and 30 pmol/kg/min. during the 5 pmol/kg/min studies, IAPP infusions were begun 240 mins after the start of the insulin infusion at an equimolar (5 pmol/kg/min, study A) or a 10-fold higher (50 pmol/kg/min; study B) infusion rate. The plasma insulin levels during the A and B set of studies are presented in Table 1. Insulin levels were comparable in both studies reaching steady state concentrations of ~600 pM which were maintained throughout the study. The facts that insulin levels were the same during studies A and B and did not change after the onset of the IAPP infusion indicate that IAPP does not influence insulin clearance or metabolism. During the glucose clamp studies conducted at an insulin infusion rate of 30 pmol/kg/min steady state insulin levels of ~2800 pmol were achieved which remained unchanged after the onset of the IAPP infusion (50 pmol/kg/min).

The mean IAPP levels 60 mins after the onset of the IAPP infusion are given in Fig. 1. During study A, IAPP levels increased ~12-fold above basal (~35 pg/ml) to a mean of 424± 130pg/ml (1.15×10^{-10}M); corresponding values during study B were 1855± 297 pg/ml (5×10^{-10M}); or 60-fold above basal.

Glucose Dispsal Rates: Glucose disposal rate (GDR) was assessed by means of a concomitant ^{3}H-glucose infusion, and as can be seen in Fig. 2A, du-

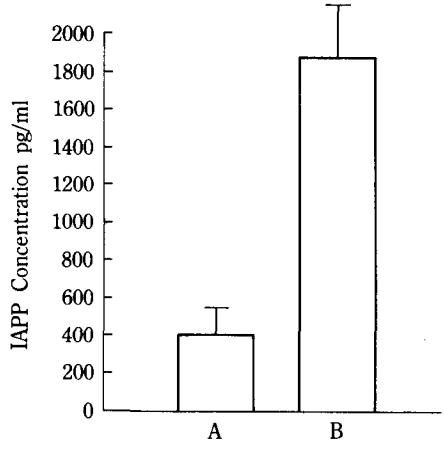

Fig 1. Steady state IAPP levels 60 minutes following initiation of the IAPP infusion: A (5pmol/kg/min) and B (50 pmol/kg/min).

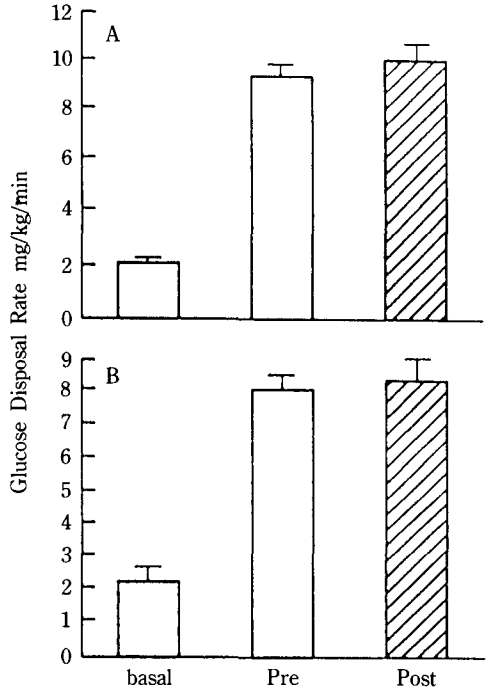

Fig 2. Effect of IAPP infusion on insulin stimulated glucose disposal rate. Data reprsent the mean ± SE glucose disposal rates during the basal state and during the last 40 minutes of the insulin infusions prior to the onset of the IAPP infusion (clear bars); slashed bars represent the steady state glucose disposal rate following 2 hours of IAPP infusion (panel A) or 60 minutes of IAPP infusion (panel B). Panel A represents studies conducted at the 5 pmol/kg/min IAPP infusion rate (n=7). Panel B represents studies conducted at the 5 pmol/kg/min IAPP infusion rate (n=7). Panel B represents studies conducted at the 50 pmol/kg/min IAPP infusion rate (n=6).

ring study A, GDR reached a mean steady state value of 9.4± 0.4mg/kg/min over the last hour of the insulin infusion. At this point, the IAPP infusion was started and continued for 120 mins. No change in GDR was observed at any time after onset of IAPP administration. Comparable results are seen in Study B; i. e., GDR rose to a mean steady state value of 8.1± 0.52 mg/kg/min, with no change following a 60 min IAPP infusion. In 3 of the animals the insulin plus IAPP infusion was continued for an additional 60 minutes and no change in GDR was observed (GDR values were 8.01, 7.63, and 7.77 prior to IAPP and at 60 and 120 minutes of IAPP, respectively, in these 3 dogs). During all studies hepatic glucose production was suppresed by 80-100% and this was unaffected by the IAPP infusion.

The GDR values during the 5 pmol/kg/min insulin infusions are about 1/2maximal. To determine whether IAPP might have any effect on GDR at higher glucose flux rates, clamp studies were also conducted at an insulin infusion of 30 pmol/kg/min. These results are shown in Fig. 3. Steady state insulin values were ~2800 pM (Table 1), and at these higher insulin levels GDR rose more rapidly to steady state values of ~15 mg/kg/min. An infusion of IAPP (50 pmol/kg/min) was started at 180 mins, and continued for 120 minutes; again, no change in GDR was observed.

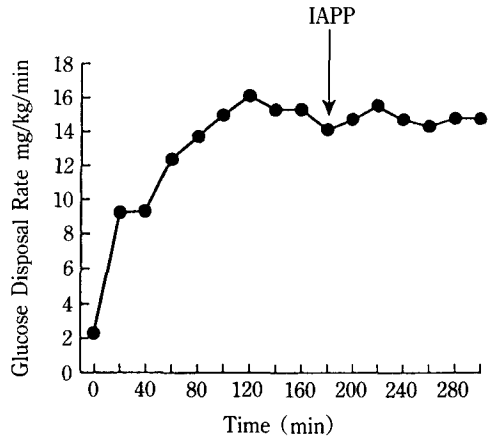

Fig 3. The effect of IAPP (50 pmol/kg/min) on the insulin stimulated glucose disposal rate at an insulin infusion rate of 30 pmol/kg/min. After 180 minutes of insulin infusion, glucose disposal reached steady state and an IAPP infusion (50 pmol/kg/min) was begun and continued along with the insulin infusion for 120 minutes. Data represent the mean of two separate experiments.

Intravenous Glucose Tolerance: In 3 dogs IV glucose was administered on separate days with and without a concomitant IAPP infusion. The order of the studies was randomized and the IAPP (50 pmol/kg/min) was started 30 minutes prior to the IV glucose administration and continued for an additional 90 minutes. Figure 4 shows that intravenous glucose tolerance was unaffected by administration of IAPP.

Table 1.

PLASMA INSULIN LEVELS DURING GLUCOSE CLAMP STUDIES (uU/ml)

		Insulin Infusion Rate (pmol/kg/min) 5			30			
		Time (mins) 0	240	300	0	180	240	300
IAPP Infusion Rate	5	143± 14	617± 93	603± 86	ND	ND	ND	ND
pmol/kg/min	50	150± 14	538± 43	596± 129	100	3049	2511	2691

Values represent the mean insulin concentrations (pM) in the basal state (t=0), after 180 and/or 240 minutes of insulin infusion and after an additional 60minutes of insulin with the IAPP infusion. Insulin was infused at 5 or 30 pmol/kg/min. At the 5 pmol/kg/min insulin infusion, IAPP was given at both 5 or 50 pmol/kg/min (n=7 and 6, respectively, values are mean ± SE); at the 30 pmol/kg/min insulin infusion, IAPP was given only at 50 pmol/kg/min (n=2, values are means).

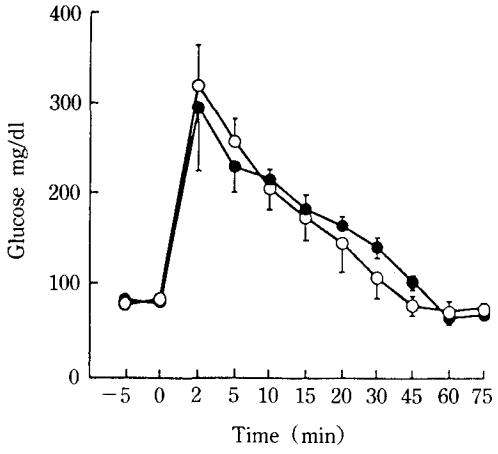

Fig 4. Intravenous glucose tolerance tests without (0) and with (●) a concomitant intravenous IAPP infusion (50 pmol/kg/min). During the IAPP studies, the peptide infusion was begun 30 minutes prior to glucose administration and continued for an additional 90 minutes. Data represent mean± SE of 3 separate studies.

Counter Regulatory Hormone Levels: Serum levels of glucagon, and norepinephrine were measured. Just prior to the onset of the IAPP infusion, norepinephrine levels were 214± 37 pg/ml and were 244± 73 pg/ml 60 minutes later. Basal glucagon values were 290± 65 pg/ml, falling to 178± 47 pg/ml just prior to the IAPP infusion and remaining at 181± 37 pg/ml at the end of the IAPP infusion.

In earlier studies, we showed that very high pharmacological levels of IAPP (5,000 pmol/kg/min) can induce in vivo insulin resistance in rats (20). Although the purpose of the current study was to determine whether more reasonable doses of IAPP (5 or 50 pmol/kg/min) could cause similar biologic effects, at the end of 4 of the infusion B studies, IAPP was given as a rapid bolus over 1 minute while the insulin and glucose infusions were continued. This led to a prompt 20-50 mg/ml rise in the plasma glucose level. These studies indicate that, as in rats, high pharmacologic levels of IAPP are capable of causing a rapid insulin resistant state in dogs.

Effects of IAPP on Serum Calcium Levels: It has previously been shown that IAPP administration can lead to a prompt reduction of serum calcium levels in rabbits (29), and our results demonstrate the same phenomena in the conscious dog model. Serum calcium was measured during the glucose clamp A and B studies and these results are summarized in Fig 5. Figure 5 shows the time course of the fall in serum calcium during a 50 pmol/kg/min IAPP infusion. Calcium levels fell by 10-15% at 10 minutes after IAPP onset and remained relatively constant until the end of the infusion. The mean calcium levels just prior to and 60 mins after the onset of IAPP in studies A and B are given in bar graph form in the inset to Figure 5. Values were slightly reduced after the lower dose IAPP infusion, but these differences were

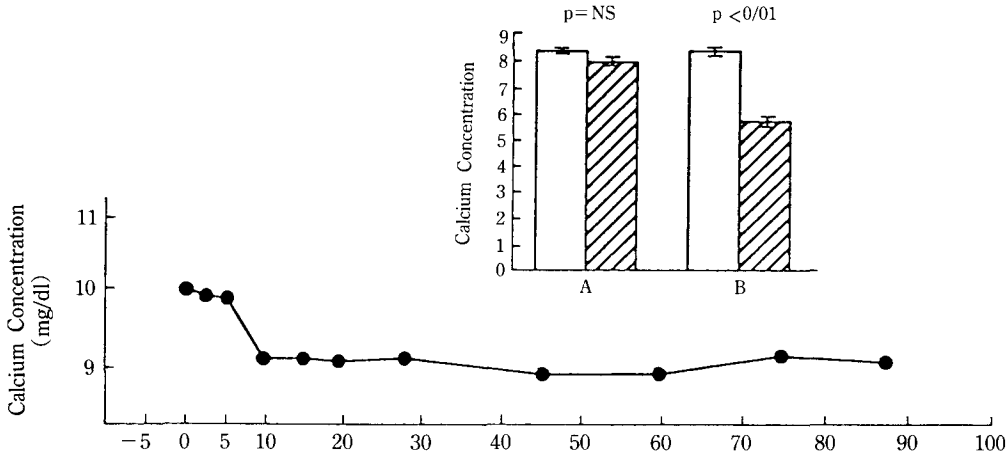

Fig 5. The effect of IAPP infusion on serum calcium levels. The line graph represents the time course of the fall in serum calcium level following the onset (at time zero) or an IAPP infusion at 50 pmol/kg/min. The bar graphs after (slashed bars) the IAPP infusions at either 5 pmol/kg/min (A) or 50 pmol/kg/min (B).

not statisticaly significant. A highly significant decrease in serum calcium was observed during study B.

DISCUSSION

IAPP is a polypeptide made in pancreatic β cells which can be found in the extracellular amyloid deposits within islets of NIDDM subjects (5, 6). This peptide is co-secreted with insulin from β cells (13-15) and in virto studies have shown that this material can lead to reduced rates of insulin stimulated glucose metabolism in rat soleus muscle (19). These findings have led to the hypothesis that excessive levels of IAPP (or increased tissue sensitivity to IAPP) leads to insulin resistance in NIDDM.

In an earlier study, we found that in vivo administration of pharmacologic levels ($\sim 10^{-8}$M) of IAPP decreased insulin mediated glucose disposal and overcame insulin's suppressive effect on hepatic glucose production during glucose clamp studies in anesthetized rats (20). This provided evidence that short term administration of IAPP can lead to insulin resistance in vivo. At that time, no information on circulating IAPP levels was available and we attempted to achieve levels (10^{-8}M) which were ~10-fold above the presumed physiologic range. Subsequently, it has become clear that IAPP is far less abundant than insulin (7, 8, 11). The β cell content of IAPP mRNA relative to insulin mRNA ranges from 1-9% (7, 8, 11) and this is consistent with measurement of peptide content. Pancreatic perfusion studies, measuring direct secretion of insulin and IAPP, have shown that following various stimuli, IAPP secretion is only 3-10% that of insulin (7, 13, 15, 30). Finally, several laboratories have directly measured circulating insulin and IAPP levels by radioimmunoassay and find that IAPP concentrations are only 1-3% as high as insulin on a molar basis (14, 16-18). Based on these results, our earlier infusion studies were probably conducted at IAPP levels 100-1000 fold above the physiologic range.

To address this issue we have now conducted glucose clamp studies in conscious dogs during which insulin was given at 5 pmol/kg/min and IAPP was infused at either an equimolar dose or 10X the insulin dose (ie., 5 or 50 pmol/kg/min). These IAPP infusion rates are 0.1 and 1% as high as the rate we used in our initial study (5 rmol/kg/min) in rats (20). Measurement of the IAPP levels achieved during the current studies showed concentrations 12-60 fold above basal and can be considered as high physiologic and low pharmacologic concentrations. The major findings from these studies are that over this concentration range, short term administration of IAPP had no effect on insulin mediated glucose disposal or hepatic glucose production on conscious dogs.

The current glucose clamp studies were conducted at 2 different insulin infusion rates (5 and 30 pmol/kg/min) designed to achieve a half maximal and a maximal rate of glucose disposal, respectively. Under either condition, IAPP, even at levels (50 pmol/kg/min) which far exceed the physiologic range, was without effect on either GDR or hepatic glucose production. Combining these results with our earlier study we conclude that while high pharmacologic levels of IAPP can cause in vivo insulin resistance, physiologic and even low pharmacologic concentrations of IAPP are without effect. These results are quite consistent with the literature. Thus, Young et al. (31) and Koopoman et al. (32) have conducted glucose clamp studies with IAPP in rats. Both grorps confirmed our earlier results demonstrating that high infusion rates (5 rmol/kg/min) of IAPP can cause in vivo insulin resistance. Additionally, Koopman et al. (32) showed that at a lower rate of infusion (12.5 pmol/min) no effect of IAPP to decrease GDR could be demonstrated and, in addition, the effect of IAPP to increase hepatic glucose production was markedly reduced. Sowa et al. (33) conducted glucose clamp studies in conscious dogs over a range of IAPP infusion rates. They found that very high levels of IAPP inhibited insulin stimulated glucose disposal, whereas infusion rates below 40 pmol/kg/min had no effect to cause insulin resistance. Lastly, relatively low doses of IAPP were given intravenously to rabbits (34) and to humans using the forearm perfusion technique (35), and in both cases found no effect

on glucose metabolism was found. Thus, the accumulated evidence is fully consistent with the notion that suprapharmacologic levels of IAPP can lead to short term insulin resistance by decreasing peripheral GDR and increasing hepatic glucose production rate by a mechanism which is currently unknown. However, at more physiologic and even lower pharmacologic levels of IAPP no short term effects leading to insulin resistance can be demonstrated. A similar dichotomy, has been shown with respect to IAPP's effects on insulin secretion. Thus, at suprapharmacologic levels IAPP has been reported to inhibit insulin secretion (36), whereas at levels which more closely approximate even the highest concentrations which might be achieved within the islet, no effects of IAPP to inhibit insulin secretion are demonstrated (37). The observations that pharmacologic levels of IAPP exert effects on glucose metabolism, whereas more physiologic levels do not are consistent with several possibilities: (1) pharmacologic levels of IAPP exert effects through non-specific mechanisms, or (2) high levels of IAPP interact with a receptor for some other hormone not normally occupied at physiologic concentrations. Even the in vitro studies which showed an effect of IAPP to inhibit soleus muscle glucose metabolism required concentrations of 10^{-7} to 10^{-9}M to observe effects (19, 38). Given that the reported circulating concentrations of IAPP are in the 10^{-11} to 10^{-12}M range (16-18), clearly the levels reported to be effective in vitro are pharmacologic.

Since our results are essentially negative with respect to IAPP effects on glucose metabolism, certain questions should be addressed. (1) It has been suggested that IAPP is a relatively insoluble peptide and, therefore, is it possible that the actual delivery rates into the dogs were less than we calculated? This is unlikely for several reasons. First, radioimmunoassay measurement of IAPP in the infusate solutions yielded the predicted results based on the amounts added and these levels were unchanged after 2 hours. Second, assay of IAPP concentration in the infusate solution delivered from the end of the infusion line at the termination of the study resulted in 85-100% of the expected concentration. Finally, immunoassay of serum IAPP infusions showed concentrations well above the known physiologic range. (2) Could the IAPP used have been impaired or chemically incorrect? This is unlikely because the material we used migrated as a single peak on HPLC and displayed the correct sequence including carboxy terminal amidation. Furthermore, in vitro bioassay using the soleus muscle system (19, 38) revealed ED_{50} values (2-10nM) for inhibition of glucose incorporation into glycogen comparable to previously reported results (A. Young, personnel communication). Finally, and probably most importantly, the IAPP we infused was quite potent in lowering the serum calcium levels; in a sense, this provides an internal standard for the biologic potency of the material we used. Beyond this, whether there are subtle chemical or conformational differences between synthetic and native IAPP which compromise effects on glucose but not calcium metabolism cannot be determined. (3) We used synthetic human IAPP in dogs and this raises the possibility of a species difference This seems unlikely, since the IAPP infusions were capable of lowering calcium levels as also reported in rodents (29). Furthermore, the sequence of dog IAPP differs by only 2 residues from human.

Since IAPP is is normally secreted directly into the portal system, the question can be raised as to whether it has unique effects on hepatic glucose metabolism. Although a final answer on this must await studies such as direct measurement of portal vs. peripheral levels and liver perfusion experiments, at the current time such an effect seems unlikely. Thus, Sowa et al (33), infused IAPP directly into the portal vein in dogs and found no greater effect than after peripheral administration. Furthermore, in the current studies, peripheral vein IAPP levels were at least 60-fold above basal and, therefore, the portal vein levels were likely to exceed portal IAPP levels achieved in the physiologic state.

Under the experimental conditions used in the current studies, our results clearly show that after 1-2 hours of administration IAPP has no effect to modulate the measured aspects of glucose metabolism. As such, these results argue against a physiolo-

gic role for this peptide to counterregulate insulin action or to cause in vivo states of insulin resistance. It should be cautioned that the current data apply only to short term effects (1-2 hours). Whether chronic IAPP administration can cause insulin resistance over a period of days or weeks is a question for future study. Even in this event, however, it remains quite unlikely that IAPP could be an important cause of insulin resistance in NIDDM. Three papers now exist in which serum levels of IAPP were reported in NIDDM (16, 17, 39); in all 3 studies, circulating levels of IAPP in both the basal and stimulated state were comparable to controls. Thus, excessive IAPP secretion does not appear to be a feature of NIDDM. Therefore, even if chronic IAPP administration causes insulin resistance, whereas short term infusion does not, it would be an unlikely cause of the insulin resistance of NIDDM. Whether chronically elevated levels of IAPP exist in other states, such as obesity or impaired glucose tolerance, and contribute to the insulin resistance remains to be determined.

Our results demonstrate a calcium lowering effect of IAPP in dogs (Fig. 5). This confirms previous reports demonstrating a hypocalcemic effect of IAPP in rabbits and rats (29). This effect is of interest and its mechanism is unknown. Morkshita et al. (40) have recently shown that IAPP can cross react with receptors for calcitonin gene related polypeptide (CGRP); possibly the hypocalcemic actions of IAPP are mediated through crossover into bone CGRP receptors. Patients with IDDM should be deficient in IAPP due to β cell destruction. Although abonormal serum calcium levels are not a feature of IDDM, osteomalacia and/or osteoporosis has been reported (41). Regardless of the mechanisms or possible physiologic significance of this hypocalcemic effect, it does raise a note of caution. Should IAPP eventually find its way into human investigation, the possible adverse consequences of this calcium lowering effect should be carefully considered in any study design.

In summary, our results show that administration of IAPP to conscious dogs at levels which span and exceed the physiologic concentration range has no short term effect on GDR or hepatic glucose production in the glucose production in the glucose clamp setting. Intravenous glucose tolerance tests were also uneffected. These results argue against a physiologic effect of IAPP as an acute counterregulator of insulin action. Coupled with the reports (16, 17, 39) of normal serum IAPP levels in NIDDM, these results also argue against a role for IAPP in the insulin resistance of this state. Since IAPP is co-secreted with insulin, increased IAPP secretion might be expected in hyperinsulinemic states. Whether elevated levels of IAPP exist in obesity and contribute to the insulin resistance of this and other conditions; what is the true physiologic role of this peptide; what are the consequences (if any) of its excess or deficiency, and what is the significance of its hypocalcemic effect, are all questions for future study.

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=ABSTRACT=

In this study we have administered constant intravenous infusions of IAPP, to conscious dogs during the euglycemic glucose clamp setting. The doses of IAPP used (5 and 50 pmol/kg/min) raised the circulating IAPP levels approxomately 12-fold and 50-fold above basal, respectively. Studies were conducted at two different insulin infusion rates, resulting in steady state plasma insulin levels of ~610 and 2600 pmol. our results showed that the IAPP infusions did not lead to any measurable change in the insulin stimulated glucose disposal rate, at either insulin infusion rate. Additionally, no effect of IAPP on hepatic glucose production was observed. Intravenous glucose tolerance tests were also performed with and without a concomitant IAPP infusion and we found that IAPP had no influence on the glucose profile. Although we could not observe any effect of IAPP on any of the measured aspects of glucose or insulin metabolism, we did find a consistent hypocalcemic effect of this peptide. Shortly after the onset of IAPP on any of the measured aspects of glucose or insulin metabolism, we did find a consistent hypocalcemic effect of this peptide. Shortly after the onset of IAPP infusion, serum calcium levels fell by 10-15% and remained at these levels throughout the course of the IAPP infusion. In summary: (1) infusion of IAPP at doses of 5 or 50 pmol/kg/min in conscious dogs raises the circulating IAPP level 12- to 50-fold above basal (2) During these infusion studies, no effect of IAPP was observed on any of the measured aspects of glucose or insulin homeostasis. (3) IAPP leads to a prompt reduction in plasma calcium concentrations upon intravenous administration.

=국문초록=

동물실험에서 IAPP는 말초또는 간 인슐린 저항에는 영향을 미치지 못하나 저칼슘증을 초래한다.

계명대학교 의과대학 외과학 교실

임 태 진

Peptide의 일종인 IAPP (islet associated polypeptide)의 glucose metabolism에 대한 영향을 관찰하기 위해 8마리의 성숙한 잡종개를 사용 동물실험을 하여 다음과 같은 결론을 얻었다.

의식이 있는 개에서 5-50pmol/kg/min의 IAPP의 infusion으로 순환 IAPP치가 basal보다 12-50배 상승을 보였다.

실험중 IAPP치가 glucose 또는 insulin homeostasis에 대해서는 영향을 미치지 않았다.

IAPP의 정맥주사로 혈장 칼슘농도는 신속한 감소를 보였다.

Key Word : Glucose metabolism, IAPP.