



จุฬาลงกรณ์มหาวิทยาลัย  
ทุนวิจัย  
กองทุนรัชดาภิเษกสมโภช

รายงานผลการวิจัย  
เรื่อง

บทบาทของฮอร์โมนวาสโซเพรสซินต่อการกระตุ้นการหลั่ง  
ฮอร์โมนกลูคาگونในหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวาน

โดย

ศิรินทร หยิบโชคนันต์  
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เมษายน ๒๕๔๕



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## กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนจาก โครงการวิจัย ทุนวิจัย กองทุนรัชดาภิเษกสมโภช จุฬาลง  
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สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย

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ชื่อโครงการวิจัย	บทบาทของฮอร์โมนวาซโอเพรสซินต่อการกระตุ้นการหลั่ง ฮอร์โมนกลูคาگونในหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวาน
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### บทคัดย่อ

วัตถุประสงค์ของการศึกษาครั้งนี้ คือ 1) เพื่อศึกษาระดับของฮอร์โมนกลูคาگونที่เป็นผลมาจาก การได้รับฮอร์โมน AVP ระดับต่างๆ ในหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวานเทียบกับหนูปกติ และ 2) เพื่อศึกษาเปรียบเทียบระดับของการหลั่งฮอร์โมน AVP จากตับอ่อนในหนูปกติและหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวาน โดยใช้เทคนิค *In Situ* Pancreatic Perfusion ทำการเหนี่ยวนำหนูให้เป็นเบาหวานโดยการฉีดสาร alloxan HCl ขนาด 200 มก./กก. เข้าช่องท้อง ตรวจวัดระดับฮอร์โมน AVP และ กลูคาگون จากตัวอย่างของสารละลายที่ผ่านจากตับอ่อน โดยวิธี radioimmunoassay จากผลการทดลองพบว่า หนูเบาหวานมีระดับฮอร์โมนกลูคาگونในระยะพักสูงกว่าหนูปกติ ฮอร์โมน AVP ที่ระดับความเข้มข้น 10-100 pM กระตุ้นการหลั่งฮอร์โมนกลูคาгонจากตับอ่อนของหนูปกติ และหนูเบาหวาน ได้เพิ่มขึ้นตามความเข้มข้นของฮอร์โมน AVP ที่สูงขึ้น อย่างไรก็ตาม หนูเบาหวาน มีความไวต่อฮอร์โมน AVP สูงกว่าหนูปกติ และจากการเปรียบเทียบพื้นที่ได้กราฟพบว่า ฮอร์โมน AVP กระตุ้นการหลั่งฮอร์โมนกลูคาгонจากตับอ่อนของหนูเบาหวาน ได้สูงกว่าหนูปกติ 2 เท่า และ ฮอร์โมน AVP ที่ระดับความเข้มข้น 1 pM ไม่สามารถกระตุ้นการหลั่งฮอร์โมนกลูคาгонจากตับอ่อนของหนูปกติ แต่มีผลกระตุ้นการหลั่งฮอร์โมนกลูคาгонจากตับอ่อนของหนูเบาหวานได้อย่าง มีนัยสำคัญทางสถิติ นอกจากนี้คณะผู้วิจัยยังพบว่า ตับอ่อนสามารถหลั่งฮอร์โมน AVP ได้ และหนูเบาหวานหลั่งฮอร์โมน AVP จากตับอ่อนสูงกว่าหนูปกติ 2 เท่า จากการศึกษาครั้งนี้สามารถสรุปได้ว่า ฮอร์โมน AVP ถูกหลั่งได้จากตับอ่อน โดยหนูเบาหวานจะมีการหลั่งฮอร์โมน AVP ได้มากกว่า หนูปกติ และฮอร์โมน AVP ที่ถูกหลั่งออกมาอาจ มีบทบาทสำคัญในการกระตุ้นให้ฮอร์โมนกลูคา กอนหลั่งมากผิดปกติในหนูที่เป็นเบาหวาน ส่งผลให้ภาวะน้ำตาลในกระแสเลือดสูงรุนแรงเพิ่มมากขึ้นในหนูที่เป็นเบาหวานได้



**Project Title** The role of arginine vasopressin in diabetes-associated glucagons secretion

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### Abstract

The purpose of this study was to investigate the role of arginine-vasopressin (AVP) on glucagon secretion in both normal and diabetic rats. Diabetes was induced by intraperitoneal administration of alloxan HCl (200 mg/kg). Both glucagon and AVP were determined in the effluent of the perfused pancreas using radioimmunoassay. Diabetic rats had higher baseline glucagon concentrations than normal rats. AVP (1 pmol/L) failed to change glucagon secretion in normal rats, but significantly increased glucagon secretion in diabetic rats. AVP (10 - 100 pmol/L) increased glucagon secretion from both normal and diabetic rats in a concentration-dependent manner. However, diabetic rats were more sensitive to AVP administration than normal rats with regard to glucagon secretion. By comparison of the areas under the curves, the glucagon secretion induced by AVP in diabetic rats was ~2-fold that of the normal rats. In addition, we determined whether AVP was secreted from the pancreas. Immunoreactive AVP was detected in the effluent of the perfused pancreas, and diabetic rats had 2-fold higher AVP concentrations in the pancreatic effluent than normal rats. We conclude that AVP is secreted from the pancreas and diabetic rats secrete more AVP from the pancreas than normals. Consequently, AVP may have a greater impact on glucagon secretion in diabetic rats than normals. AVP might play an important role in the hypersecretion of glucagon, a hyperglycemic hormone, in diabetic animals.

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สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย

## INTRODUCTION

DIABETES MELLITUS is a serious metabolic disease that affects millions of people. Diabetes is top tenth leading cause of death by disease in the world, costing a great deal of finance in health care and productivity losses. Type 2 diabetic patients may have low insulin secretion in response to glucose challenge, whereas type 1 diabetic patients cannot secrete insulin. In addition, most of these patients have excessive glucagon secretion, and this further aggravates hyperglycemia. Normally, insulin secreted from  $\beta$ -cells of the pancreatic islets inhibits glucagon secretion, and thus insulin deficiency or insufficiency causes an increase in basal glucagon secretion. Hyperglycemia in diabetic patients has been alleviated when plasma glucagon levels are reduced or glucagon receptors are blocked.<sup>1</sup> Therefore, glucagon enhances hyperglycemia in diabetic subjects, and thus the inhibition of glucagon secretion may be beneficial in the control of diabetes.

The neurohypophysial hormone arginine vasopressin (AVP) is synthesized in the hypothalamus and secreted from the posterior pituitary gland. AVP is found in a number of peripheral tissues, including ovary, oviduct, follicular fluid,<sup>2</sup> adrenal,<sup>3</sup> testis,<sup>4</sup> and pancreas.<sup>5</sup> In addition to the regulation of body water homeostasis, AVP induces glycogenolysis,<sup>6</sup> proliferation of the pituitary gland<sup>7</sup> and vascular smooth muscle cells,<sup>8</sup> vasoconstriction,<sup>9</sup> and secretion of catecholamines,<sup>10</sup> glucagon and insulin.<sup>11</sup> AVP stimulates glucagon secretion from  $\alpha$ -cells of the pancreatic islets,<sup>12-14</sup> which can induce hyperglycemia.<sup>3</sup> However, the role of AVP in the physiological regulation of glucagon is controversial, since the concentrations of AVP used in the previous studies were at least 100 times greater than the peripheral plasma concentration of  $\sim 1$  pmol/L.<sup>12</sup> On the other hand, AVP is found in the pancreas at the concentration of 2,000 to 10,000 pmol/L.<sup>15</sup> These findings suggest that the pancreatic AVP, rather than hypophysial AVP, may play a major role in glucagon secretion. We recently found that AVP at  $\geq 3$  pmol/L stimulated glucagon secretion from the normal rat pancreas<sup>16</sup>. These results suggest that AVP (particularly the pancreatic AVP) plays an important role in glucagon secretion.

The present study was designed to determine 1) if AVP is secreted from the pancreas and if diabetic animals secrete greater amount of AVP from the pancreas than normal animals and





2) if diabetic subjects are more sensitive to AVP administration than normal subjects with regard to glucagon secretion.

## MATERIALS AND METHODS

Male Wistar rats (250-350 g) were randomly assigned to two groups: 1) control and 2) diabetes. Diabetes were induced by intraperitoneal injection of alloxan HCl (200 mg/kg)<sup>17</sup> and were identified when hyperglycemia ( $\geq 350$  mg/100 ml) was present (by measuring glucose from a drop of blood from the tail vein). Animals were given Ultra-lente insulin injection (1-6 U/rat, SC) to maintain euglycemia.<sup>17</sup> The pancreatic perfusion was performed 14 days after the administration of alloxan HCl, and followed the procedures previously describe.<sup>18</sup> Briefly, the rats were anesthetized with pentobarbital sodium (60 mg/kg ip) and were maintained at 37°C on a hot plate during the experiment. After cannulation of the celiac arteries, the pancreata were immediately perfused with the Krebs-Ringer bicarbonate buffer (KRB) supplemented with 20 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES), 5.5 mM glucose, 1% dextran and 0.2% bovine serum albumin (BSA) as a basal medium. The KRB was continuously aerated with 95% O<sub>2</sub>-5% CO<sub>2</sub> at pH 7.4. The rats were sacrificed immediately after the placement of cannula into the portal vein and beginning of the flow.

### Experimental Design

The perfusion rate was set at 1 ml/min and the effluent fluid which was collected from the portal vein was ~1 ml/min. In the experiment 1, fourteen rats were randomly assigned to control and diabetic groups of seven rats each. After a 20-min equilibration period, 5 effluent samples of 2 ml each were collected from each preparation for AVP radioimmunoassay. In experiment 2, forty rats were randomly assigned to eight groups of five rats: 1) normal basal control, 2) diabetic basal control, 3) AVP 1 pM in normals, 4) AVP 1 pM in diabetics, 5) AVP 10 pM in normals, 6) AVP 10 pM in diabetics, 7) AVP 100 pM in normals, 8) AVP 100 pM in diabetics, according to a 2 (conditions) x 4 (AVP concentrations) design. After a 20-min equilibration period, and another 10 min of the baseline period, each pancreas was treated with AVP or control buffer (KRB) for 10 min, followed by a washout period during which the KRB was administered for 10 minutes. The perfusate containing arginine (1 mM) was administered as a positive control for 5 min at the end



of all experiments. Effluent samples were collected for glucagon radioimmunoassay as previously described<sup>18</sup>.

### Test Agents

AVP and alloxan HCl were purchased from Sigma Chemical (St. Louis, MO). Pentobarbital sodium was purchased from Fort Dodge Laboratories (Fort Dodge, IA). <sup>125</sup>I-glucagon was purchased from Linco Research Inc. (St. Charles, MO). Glucagon antibody and AVP antiserum were donated by Dr. Joseph Dunbar of Wayne State University (Detroit, MI), and Dr. C. Combe-Poncet, Neurobiologie Integrative, Domaine de Carreire, France, respectively. Glucagon standard was donated by Eli Lilly Laboratories (Indianapolis, IN).

### Statistical Analysis

The means effluent AVP concentrations were calculated from 7 rats in each group. Effluent glucagon concentrations data were expressed as a percentage of baseline (mean of last five baseline values). The 10-min perfusion curve was plotted and the areas under the curves (AUCs) were calculated using a SigmaPlot program (SPSS, Chicago, IL). The AUC values were analyzed using ANOVA to determine the effects of diabetes and AVP concentration. Duncan's mean comparison test was used to determine differences between groups. The significance level was set at  $P < .05$ .

## RESULTS

### The secretion of AVP from perfused pancreata of diabetic and normal rats.

The result in Fig.1 shows the basal AVP secretion from the perfused rat pancreas, which was obtained by perfusion with KRB alone for 10 min. AVP was detected in the effluent from the perfused pancreata of both normal and diabetic rats. However, the diabetic rats had a 2 folds higher AVP concentration in the pancreatic effluent than normal rats (normal rats =  $36.2 \pm 3.29$  pg/ml; diabetic rats =  $61.42 \pm 6.47$  pg/ml). (n = 7)

### **Effect of AVP on glucagon secretion from perfused pancreata of diabetic and normal rats.**

In the control group receiving KRB alone, glucagon secretion remained constant for the whole experiment (~35 min). The diabetic rats had higher baseline glucagon concentrations than normal rats. Range of baseline glucagon concentrations in the effluents of normal and diabetic rats were 32-109 pg/ml and 320-569 pg/ml, respectively. Administration of 1 mmol/L arginine in normal- and diabetic-control groups increased glucagons secretion by 5.1 and 4.9 folds over the baseline level at the end of experiment (data not shown).

AVP (1-100 pM) increased glucagons secretion from the perfused rat pancreas in a concentration-dependent manner. It increased glucagon secretion in a biphasic pattern: a peak followed by a sustained plateau or a second peak (for AVP 100 pM), in which the peak was started within a few second and reached the maximum within 2 min. In normal rats, AVP (1-100 pM) induced a maximum increase in glucagon secretions by 1.2, 2, and 4.8 folds, respectively, over the baseline level, whereas, in diabetic rats, they induced a peak increase in glucagon secretions by 2.9, 4.4, and 11.8 folds, respectively, over the baseline level (Fig.2).

AVP (1 pM) failed to increase glucagons secretion in normal rats, but significantly increased glucagons secretion in diabetic rats. The sustained phase of glucagon secretion induced by AVP (10 and 100 pM) in normal rats was ~1.5-2 folds over the baseline level. In diabetic rats, the sustained glucagons secretion induced by AVP (1 and 10 pM) was ~ 2-3 folds over the baseline level and the second peak of glucagons secretion induced by AVP (100 pM) was ~8-fold over the baseline level. The effluent glucagons concentrations returned to the baseline during the washing period (on the removal of AVP) and increased to 4.7 (in normal rats) and 5.2 (in diabetic rats) folds over the baseline level on administration of 1 mmol/L arginine (Fig. 2). By comparison of AUCs, AVP (1-100 pM)-induced glucagons secretions in diabetic rats were significantly higher than those in normal rats. (Fig. 3)

## **DISCUSSION**

According to the data of the present study obtained from *in situ* pancreatic perfusions, AVP was secreted from the rat pancreas. This result is consistent with that of Aminoco *et al.*, in which high concentration of AVP has been found in both human and rat pancreas.<sup>15</sup> In addition, we have



found that diabetic rats secreted 2-fold greater amount of AVP from the pancreas than normal rats which is similar to those existing in diabetic patients that the plasma concentration of AVP is higher in diabetic patients than normal persons.<sup>19</sup> A morphometric study also showed that AVP-immunoreactive neuronal somata of the supraoptic nucleus (SON) and the paraventricular nucleus (PVN) in the diabetic rats underwent marked hypertrophy, representing hyperactivity of this peptide in diabetic rats.<sup>20</sup>

AVP (10-100 pM) evoked glucagon secretion from the perfused rat pancreas in a concentration-dependent manner in both normal and diabetic rats, however, the results from our present study showed that diabetic subjects were more sensitive to AVP administration than normal subjects with regard to glucagon secretion. AVP (10-100 pM) increased glucagon secretions in normal rats by 2, and 4.8 folds, respectively, whereas they increased glucagon secretions in diabetic rats by 4.4, and 11.8 folds, respectively. In addition, a very small concentration of AVP (1 pM) increased glucagon secretion by 3 fold in diabetic rats, but failed to do so in normal rats. These findings suggested that AVP played a role in the hypersecretion of glucagon in diabetic subjects. Diabetes Mellitus is one of the most serious metabolic diseases, and insulin secretion is decreased or abolished in diabetic patients, leading to hyperglycemia. Our findings is supported by the finding that most of these patients have excessive glucagons release, which further aggravates hyperglycemia in diabetes.<sup>1</sup>

## CONCLUSION

The present findings suggest that AVP was secreted from the rat pancreas and diabetic rats secreted higher amount of AVP concentration than normal rats. The pancreatic AVP, rather than hypophysial AVP, exerted a paracrine function to physiologically increase glucagon release. In diabetic condition, AVP played a major pathological role in hypersecretion of glucagon release. These findings greatly contributed to the understanding of the physiological and pathophysiological role of AVP on glucagon secretion. From our previous studies, AVP evokes glucagon release by activating  $V_{1b}$  receptor in  $\alpha$ -cells of the rat pancreas<sup>16</sup> and hamster glucagonoma cell In-R1-G9 cells.<sup>21</sup> Further studies utilizing  $V_{1b}$  receptor antagonists may be useful for treating diabetes-associated hyperglycemia.

### Suggestion for future work

To determine whether  $V_{1b}$  receptor antagonist blocks AVP-induced glucagon secretion in diabetic rats using *in situ* pancreatic perfusion technique. If the hypothesis is proved, diabetic rats will be tested in the future experiments to determine whether this  $V_{1b}$  receptor antagonist reduces hyperglycemia.

### การเผยแพร่ผลงานวิจัย

1. นำเสนอในงานประชุมวิชาการประจำปี 2545 ของคณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ซึ่งจะจัดขึ้น ระหว่างวันที่ 18-19 เมษายน 2545
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3. นำส่งตีพิมพ์ในวารสารนานาชาติ “Metabolism” มีค่า impact factor เท่ากับ 1.652

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**FIGURE LEGEND**

Fig. 1. The secretion of AVP from the perfused rat pancreata of normal and diabetic rats. In these experiments, after a 20-min equilibration period, 5 effluent samples of 2 ml each were collected from each preparation for AVP radioimmunoassay. Values are the mean  $\pm$  SE (n=7). Normal rats (●); Diabetic rats (▼). \*  $P < .05$  vs normal rats.

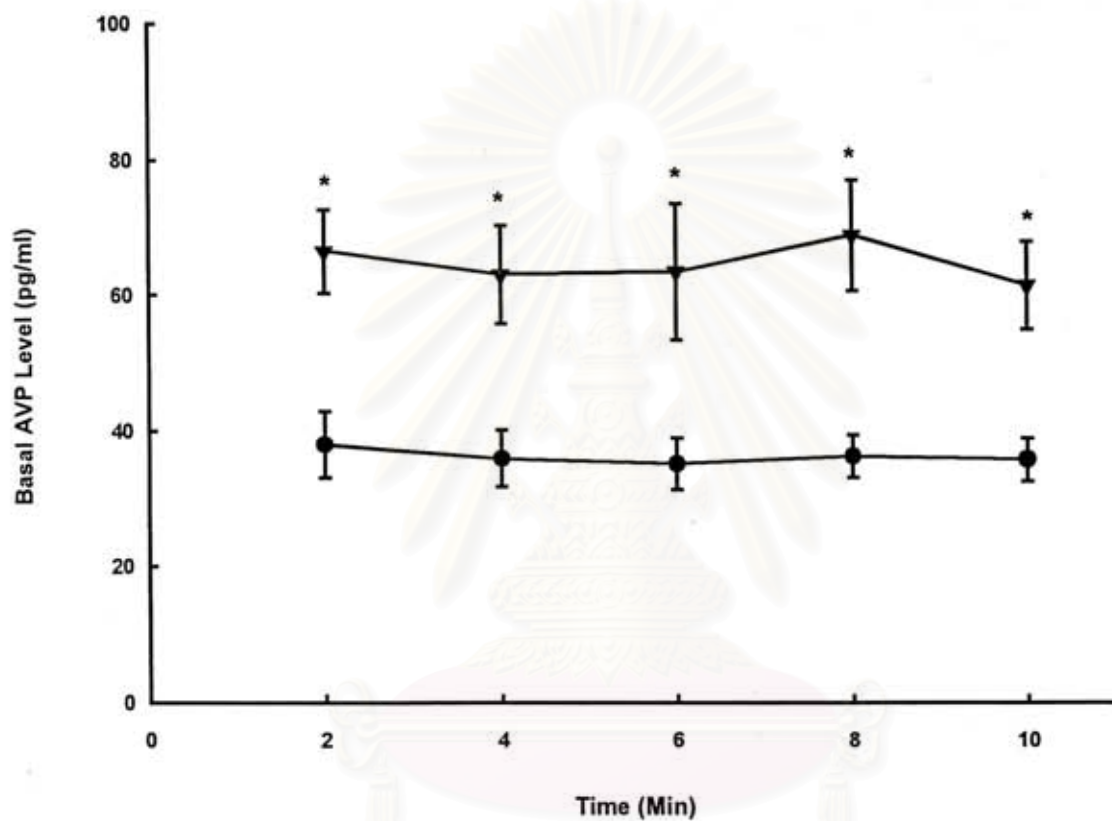
Fig.2. Effect of AVP on glucagons secretion from the perfused rat pancreata or normal and diabetic rats. After a 20 minutes equilibration period, and another 10 min of the baseline period, AVP was given for 10 minutes. AVP concentrations were 1 (A), 10 (B) and 100 pM (C), respectively. Values are mean  $\pm$  SE (n=5). Normal rats (●); Diabetic rats (▼).

Fig.3. Effect of AVP-induced glucagons secretion from the perfused rat pancreata of normal and diabetic rats. Values are mean  $\pm$  SE (n=5), obtained by calculating areas under 10-min glucagons secretion curve and expressed as a percentage of baseline. \*  $P < .05$  vs normal rats.

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Figure 1



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Figure 2

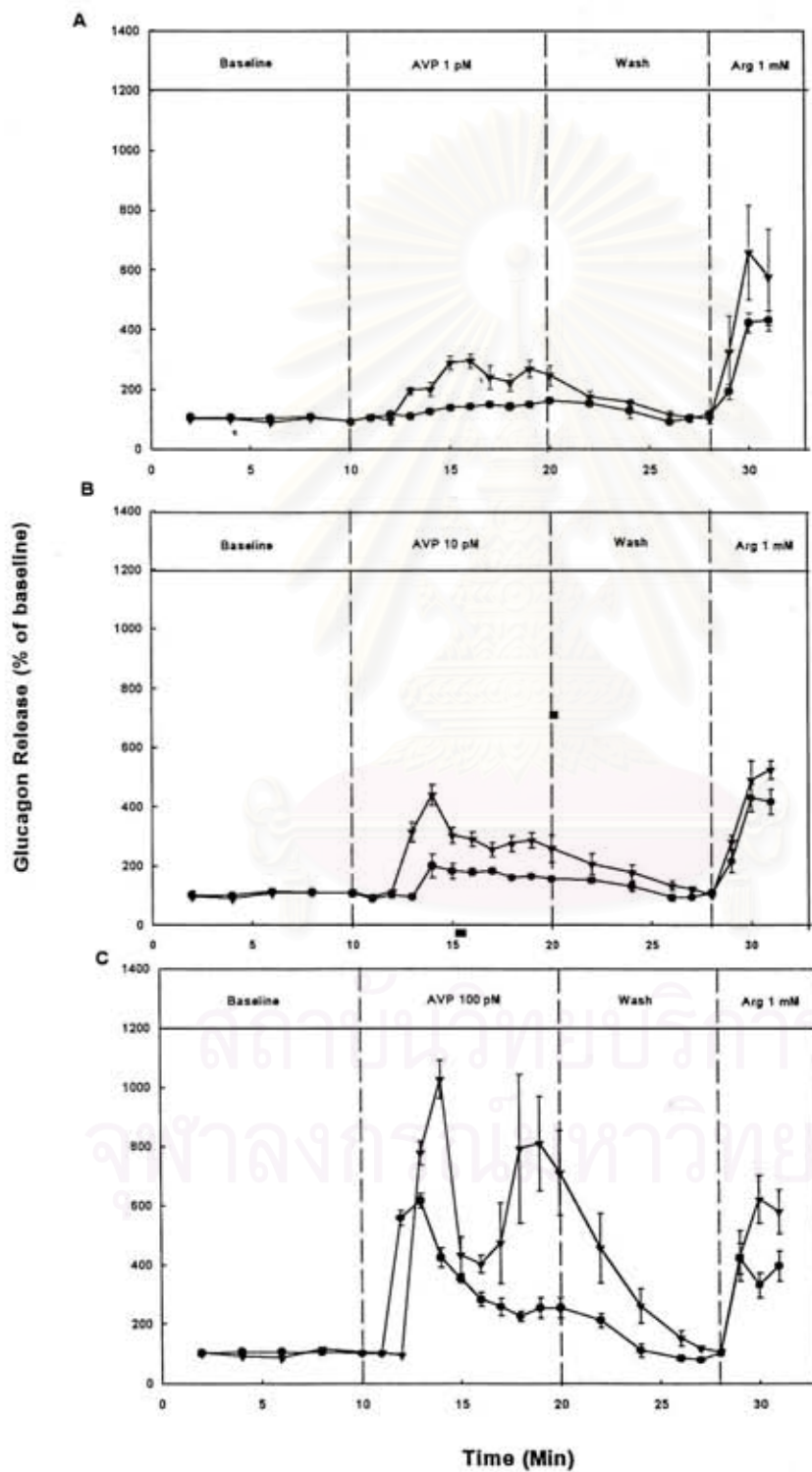
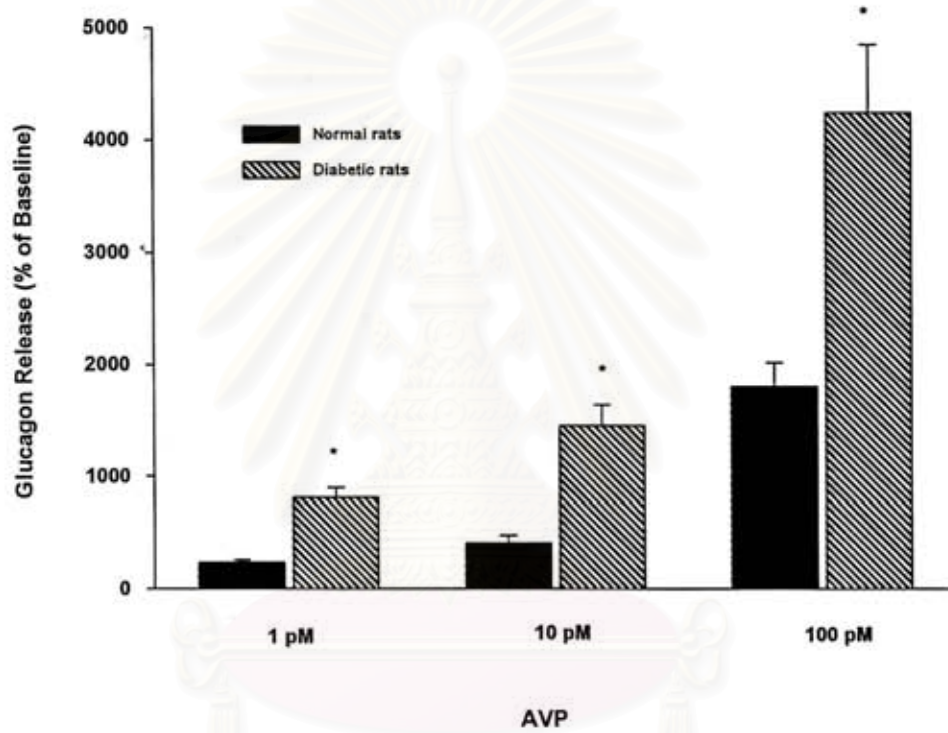


Figure 3



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