



# Effects of pancreatic denervation on secretion of pancreatic hormones in rats

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## Abstract

**Aim:** The aim of this study was to determine whether experimentally pancreatic denervation (PD) injury caused effects on pancreatic tissue and endocrine secretions.

**Materials and Methods:** A total of 50 adult male Wistar Albino rats (8 weeks old, 280-300 g) were randomly divided into five groups (n=10) as Control, Sham acute, PD acute, Sham chronic, PD chronic. The PD procedure was performed by cutting the pancreatic vagal and splenic nerves. Sham acute and PD acute groups were sacrificed 120 minutes after the PD procedure, while Control, Sham chronic, and PD chronic groups were sacrificed 7 days after the PD procedure. Pancreatic tissues were collected after the rats were sacrificed. Tissue samples were homogenized, and insulin, glucagon and norepinephrine levels were measured using commercial ELISA kits. Statistical analysis of the data was conducted using the Bonferroni-corrected Mann-Whitney U test in the IBM SPSS Statistics 24.0 Windows program.

**Results:** The decrease in norepinephrine level of pancreas tissue was found to be significant PD groups compared to Control and Sham groups. The decrease of glucagon and insulin level was found to be significant in PD acute and PD chronic compared to Control and Sham groups.

**Conclusion:** According to our findings, pancreatic denervation short and long term effects were effective in insulin and glucagon secretion in the model which examined in pancreatic denervation groups.



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## Introduction

Pancreas; It is the second largest secretory organ of the digestive system after the liver, which has exocrine-endocrine functions. While the exocrine pancreas secretes digestive enzymes into the small intestine, the endocrine pancreas secretes many hormones into the circulation, especially the hormones that regulate glucose metabolism. Pancreatic biology is quite complex and involves both endocrine and exocrine functions, regulated by a series of integrated neural and hormonal processes [1].

Exocrine pancreas structure: acinus and ducts secrete the fluid necessary for digestion into the duodenum and constitute 75-90% of the cells. Pancreatic ductal structure: It contains the acini, has a secretory function, and also forms the carrier ductal structure within the pancreas. It has the capacity to secrete HCO<sub>3</sub><sup>-</sup> at a concentration five or six times higher than plasma. Some diseases, such as cystic fibrosis, are caused by disorders of ductal secretion.

Additionally, the majority of pancreatic cancers are of ductal origin [2].

Endocrine pancreas structure: They release the hormones they secrete directly into the blood. In the human pancreas, there are around a million islets of Langerhans, each about 100 microns in diameter, located around small capillaries and contain cells with different secretion properties. Glucagon is secreted from alpha cells and they constitute 25% of the total cells. Beta cells secrete insulin, proinsulin, C peptide, and amylin and constitute 60% of the total cells. Somatostatin is secreted from delta cells, which make up approximately 10% of the endocrine pancreas. In addition, some of the islets contain PP cells (F cells) that secrete pancreatic polypeptide. Moreover; D1, which secretes VIP, enterochromaffin cells, which secrete serotonin, and epsilon cells, which secrete ghrelin, are located in the pancreatic tissue. Endocrine secretion both participates in the systemic circulation and controls exocrine secretion (paracrine effect) [2].

Blood glucose levels are maintained within narrow physiological limits. Whenever glucose levels deviate from their defended level, adaptive metabolic responses are engaged

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to ensure glucose levels return to the normal range. Critical to these responses are the capacities of pancreatic islet alpha and beta cells to coordinately adjust glucagon and insulin secretion, respectively, in response to changes in blood glucose concentrations. However, accumulating evidence suggests that the central nervous system (CNS) works in tandem with the islet to maintain glucose homeostasis [3]. Here, we review key evidence suggesting that: the brain can regulate islet function directly via innervation by parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) branches of the autonomic nervous system (ANS), and indirectly via neuroendocrine mechanisms [4]; the brain senses circulating glucose levels both directly and indirectly, transducing glycaemic information into adaptive glucoregulatory responses [5]; and interventions targeting the brain can regulate glycaemic control, in part, by modulating islet function [6].

The rich autonomic innervation of the islet, first described in 1869 by Langerhans, has been characterised in multiple species by several independent research groups [4,7]. While rodent islets are extensively innervated by both efferent cholinergic PNS and adrenergic SNS fibres, initial reports in human islets suggested sparse PNS and less SNS innervation than seen in mice [8]. However, using state-of-the-art tissue clearing and 3D-reconstructive imaging to reduce background and improve clarity and resolution of islet morphology, more-recent work [9,10] revealed dense PNS innervation of the human islet and more SNS fibres than previously reported [8].

The pancreas has both sympathetic and parasympathetic innervation. Pancreatic secretion occurs directly as a result of stimulation of the vagus by parasympathetic effect or indirectly due to increased acid secretion from the stomach. The dorsal vagal complex, located in the brainstem, consists of the dorsal motor nucleus of the vagus and the solitary tract solitarius and provides parasympathetic control of pancreatic secretion. Preganglionic vagal efferent fibers innervate the postganglionic nerves that innervate the pancreas via acetylcholine (ACh). Group II/III metabotropic glutamate and GABA receptors have also been shown to be involved in vagus-mediated stimulation. The dorsal motor nucleus is also open to stimuli from other parts of the brain, such as the hypothalamus, and to the effects of different hormones, peptides, electrical and chemical stimulation. Sympathetic innervation of the pancreas occurs through splenic nerves and originates from T5-10. Since many organs that make up the gastrointestinal system have bilaterally symmetrical neural innervation depending on embryological development, the visceral pain of these organs is felt in the middle parts of the abdomen. Visceral pain is transmitted mainly via unmyelinated thin C fibers. It is usually not well localized and is described as a dull or cramping pain, soreness or discomfort in the middle part of the abdomen. In pathologies related to the pancreas, pain is felt as reflected pain in different areas such as the abdomen and back [11].

New data suggest that cholecystokinin stimulates the nerves in the dorsal motor nucleus of the vagus. While a controversial issue, recent evidence suggests that cholecystokinin has direct secretory effects in human acinar cells. The concept that has been developing recently; some hor-

mones such as melatonin, ghrelin, obestatin and leptin have a dual effect in maintaining metabolic balance and regulating pancreatic secretion. Additionally, regulation of pancreatic secretion of various appetite-controlling neuropeptides such as ghrelin, orexin A, and neuropeptide Y is also discussed. Recent data underline that hormone action mechanisms may differ between species, possibly due to distinct metabolic stimulation pathways during developmental processes [12].

The regulation of the secretory functions of the pancreas by many hormones suggests that this important organ is under the control of a large number of stimulations, perhaps more than necessary. Understanding these various metabolic pathways is important in understanding pancreatitis, diabetes and obesity. This study examines the activities of brain tissue on pancreatic endocrine secretions and examines whether brain tissue can be used as a target organ in the treatment of diseases that develop due to disruptions in blood glucose homeostasis in the future.

## Materials and Methods

### *PD and experimental design of groups*

A total of 50 adult male Wistar Albino rats (8 weeks old, 280-300 g) were purchased from Experimental Animal Research Center of Inonu University, Malatya, Turkey. All the animals were handled in accordance with the Guidelines for the Care and Use of Experimental Animals. All animals were randomly assigned to cohorts and approved by the Animal Research Ethics Committee of Inonu University Faculty of Medicine (License No: 2019/A-42). The rats were housed at  $21 \pm 2^\circ\text{C}$  with a 12/12-hour light-dark cycle with free access to water and food ad libitum with a standard laboratory chow diet. The number of groups and rats in each group (sample size) were determined according to the power analysis based on the values specified. Accordingly, the amount of Type I error ( $\alpha$ ) was 0.05, the power of the test ( $1 - \beta$ ) was 0.8, and the effect size was 0.82 (large). While the number of groups was 5, the minimum sample size required to find a significant difference between the groups was at least 10 in each group for analyzes the total number was determined as 50 [13]. The animals were placed in individual cages before 3 days to accustomed to cage stress. All the weight-matched male rats were randomly divided into five groups ( $n = 10$ ) as Control, Sham acute, PD acute, Sham chronic, PD chronic.

Rats to be subjected to surgery were anesthetized with 70 mg/kg ketamine and 8 mg/kg xylazine ip and PD was performed by cutting the pancreatic vagal and splanchnic nerves [14-16]. PD operation was performed in accordance with the experimental model description described in the literature. The PD procedure was performed with the midline laparotomy technique (Figure 1). Pancreatic nerves extend along the splenic artery and the superior and inferior pancreatic arteries. To identify the splenic artery, the large and small intestines were wrapped in moistened gauze and shifted to the right outside the abdominal cavity. The spleen was mobilized, wrapped in moist gauze, and made visible by rotating it  $180^\circ$  from its position on the left side to the right, around the horizontal axis. The first bifurcation of the splenic artery is approximately 5 mm after the origin. To increase the visibility of the splenic

neurovascular bundle, two drops of 1% toluidine blue solution were placed on it. The nerves were stained dark blue and were resected when they became clearly visible to the left of the artery. The spleen was then placed in the abdominal cavity. A little more omentum was cut, and the nerves located in the superior pancorticoduodenal artery and gastroduodenal artery origin areas were stained with toluidine blue, and the nerves between the artery and vein were visualized and resected. Finally, the inferior pancorticoduodenal nerve was resected in parallel with the artery and vein in the mesentery, along with the stained nerves. The operation was completed with minimal blood loss. The intestines were placed in the abdominal cavity, then the abdomen was closed in two layers with interrupted sutures [16].

*Termination of experiment and collection tissues*

At the end of the required period, Sham acute and PD acute 120 minutes after reperfusion; Control, Sham chronic, PD chronic groups 7 days after reperfusion the rats were sacrificed under anesthesia and pancreas tissues were collected. The pancreas tissues were frozen on dry ice were stored at -80 C under suitable conditions until the day of the analysis for ELISA analyse.

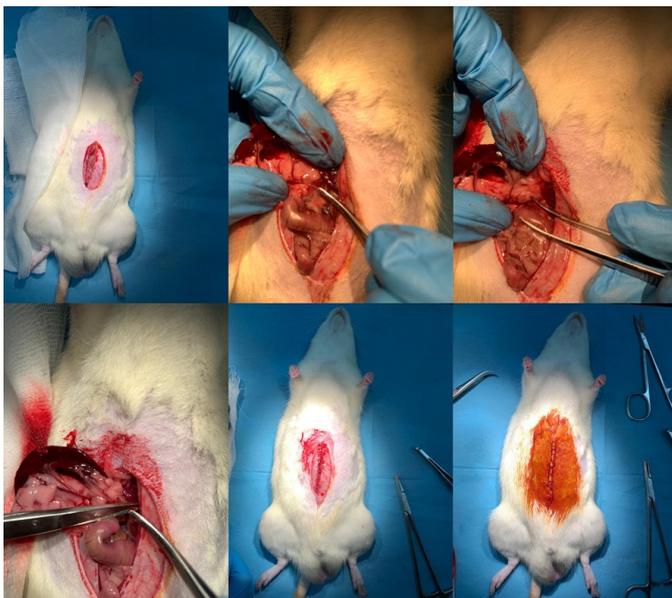
*Statistical analysis*

The Kruskal-Wallis test was used to compare the differences between the groups in statistical evaluations. Bonferroni corrected Mann Whitney U test was used for pairwise comparison of the groups. A value of  $p < 0.05$  was considered statistically significant. IBM SPSS Statistics 22.0 program was utilized in the analysis.

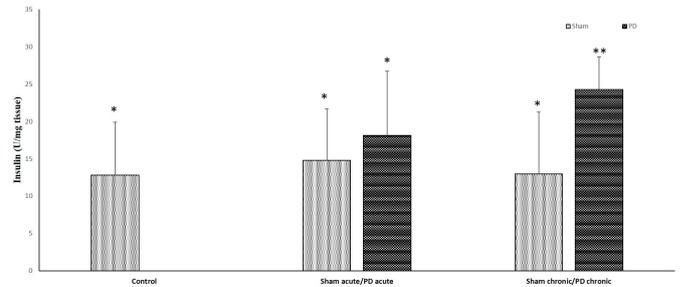
**Results**

*Evaluation of the insulin levels in pancreatic tissues*

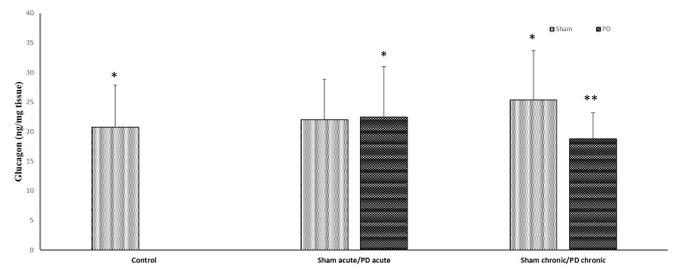
Insulin levels of pancreatic tissues are given in Figure 2. According to our findings, the decrease in pancreas insulin



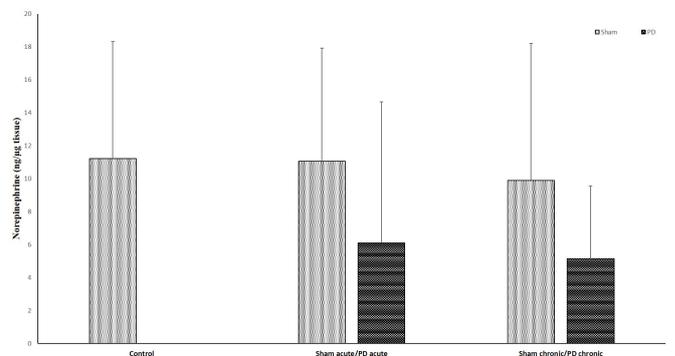
**Figure 1.** The PD procedure with the midline laparotomy technique.



**Figure 2.** Insulin level of pancreatic tissue. \* refers to the statistical same, \*\* refers to the statistical difference between groups  $p < 0.05$ .



**Figure 3.** Glucagon level of pancreatic tissue. \* refers to the statistical same, \*\* refers to the statistical difference between groups  $p < 0.05$ .



**Figure 4.** Norepinephrine level of pancreatic tissue. \* refers to the statistical same, \*\* refers to the statistical difference between groups  $p < 0.05$ .

levels in PD chronic groups statistically significant compared to the Control and Sham chronic groups ( $p < 0.05$ ).

*Evaluation of the glucagon levels in pancreatic tissues*

Glucagon levels of pancreatic tissues are given in Figure 3. According to our findings, the decrease in pancreas glucagon levels in PD chronic groups statistically significant compared to the Control and Sham chronic groups ( $p < 0.05$ ).

### *Evaluation of the norepinephrine levels in pancreatic tissues*

According to our findings, in the study model in which acute and chronic effects were examined (Figure 4), decrease in pancreas tissue epinephrine levels in PD acute and PD chronic groups were statistically significant compared to the Control, Sham acute and Sham chronic groups ( $p < 0.05$ ).

### **Discussion**

Similar to the brain, nervous tissue, erythrocytes, leukocytes and renal medulla cells also can only meet the energy they need from glucose. Therefore, it is important to keep circulating glucose levels in balance at certain intervals [18]. Glucagon is a hormone that increases blood glucose level through hepatic glucose production, which is synthesized from pancreatic  $\alpha$  cells and released into the blood [19]. In the simplest level, glucagon secretion decreases with increasing circulating blood sugar levels, and glucagon secretion increases when blood glucose level decreases, helping to maintain blood glucose level. Most studies examining the control of glucagon focused on how glucagon secretion responds to changes in glucose, particularly in hypoglycemia. Although it is thought that the brain may play a role in the changes in glucagon level through various stressors (hypoglycemia, leptin, etc.), there is insufficient data on the mechanism [20]. There may be changes in some stress hormones both in the acute period and in the recovery period after a stroke [17]. There are studies indicating that these neurohormonal changes are associated with long-term mortality [18]. It has been reported that hypothalamic-pituitary-adrenal activity increases in patients with ischemic stroke, that the increase in these hormones may increase hypoxic damage to neurons, and massive release of these hormones in hyperacute stroke may expand the damaged area in the brain [19]. Increased secretion of stress hormones may also trigger hyperglycemia, which may affect the prognosis. The relationship between the course of stroke and hyperglycemia has been shown in previous studies [20].

It is stated in the literature that hyperglycemia is detected in 1/3 of patients with ischemic stroke at the time of admission to the hospital, and this is associated with a poor clinical course [21]. In another study, it was reported that hyperglycemia detected at admission in nondiabetic patients with intracerebral hemorrhage may be a significant predictor of high mortality during the first 28 days [22].

In our study, while examining the brain interaction of effects on pancreatic tissue were regulated by a neuronal or hormonal interaction was also investigated. In addition, it has been aimed to clarify whether the possible brain activity by changing the sympathetic nervous system activity and affecting the extra pancreatic tissues or by altering the release of these hormones from the pancreas.

If impaired glucose sensing in the brain contributes to elevated blood glucose levels in type 2 diabetes, can the brain be targeted to treat this disease? In support of this, intracerebroventricular (i.c.v.) administration of leptin in both genetic (i.e. ob/ob) and acquired (i.e. severe insulin-deficient type 1 diabetes) rodent models of leptin-

deficiency ameliorates hyperglycaemia suggesting that deficient leptin signalling in the brain contributes to the diabetic phenotype. This effect occurs independently of changes in energy balance and is associated with normalisation of elevated plasma glucagon and corticosterone levels. In addition, i.c.v. leptin administration modulates gastrointestinal neuronal system via the CNS in rodent models of type 2 diabetes [23] and improves glucose homeostasis in high-fat-diet-fed rats [24], while systemic administration of leptin to a polygenic model of type 2 diabetes normalises fasting plasma glucose levels in association with decreased glucagon concentrations and elevated pancreatic insulin content [25]. However, evidence suggests that the degree of hyperleptinaemia necessary to achieve adequate brain signalling can exert effects that paradoxically undermine leptin's central action [26]. This may explain why subcutaneous metreleptin therapy was not efficacious in improving blood glucose levels in patients with type 1 diabetes, although it did reduce daily insulin requirements [27]. Additional work is warranted to investigate whether central leptin administration can ameliorate hyperglycaemia without the need for insulin in patients with type 2 diabetes.

The capacity of the brain to normalise hyperglycaemia in diabetes is also clear from studies examining the glucose-lowering actions of fibroblast growth factor (FGF) peptides [28]. Recent work demonstrates that a single i.c.v. injection of FGF1 is sufficient to induce sustained diabetes remission across several rodent models of type 2 diabetes [29]. This effect involves FGF1 signalling in the ARC-ME [30] and is mediated, in part, by preservation of beta cell mass and function, thus delaying the progressive decline of basal insulin levels that parallels hyperglycaemia in controls [31]. Importantly, rather than simply lowering blood glucose levels, FGF1 appears to act in the brain to lower the defended level of blood glucose, as i.c.v. FGF1 has no effect on blood glucose levels in nondiabetic rodents [29]. This observation suggests that FGF1 resets the glycaemic set-point to normal, without increasing the risk of iatrogenic hypoglycaemia, a critical factor limiting tight glycaemic control in people with diabetes. Although the mechanisms underlying the effects of FGF1 remain uncertain, these findings raise the possibility that therapeutic interventions that target both the brain and islet may be more effective for the treatment of diabetes than current treatments targeting the islet alone, which, though effective acutely, fail to sustainably preserve beta cell function over the long term in either adults or children with type 2 diabetes [32].

In conclusion, cooperation between the brain and islet is fundamental to glucose homeostasis and involves both neuroendocrine and autonomic mechanisms. While the brain contains glucose-sensing neurons and has the capacity to sense circulating glucose levels, it also receives glycaemic information from peripheral glucose sensors [33]. Although the main stimulating factor on pancreatic secretion is blood glucose; our study results provide evidence that neural stimuli can also be effective in the short and long-term regulation of the synthesis and secretion of endocrine secretions in a mutual balance under changing physiological conditions. However, it is hard to esti-

mate on which variable/variables the role of this neural control in glucose homeostasis is to ensure the balance in blood glucose, which one is aimed to be kept in balance as the main regulatory step, or which one is sensitive to the change and creates a response, and how this response is regulated.

#### Author Contributions

T.K. and S.S. conducted experiments and analysed the data.

T.K. data curation.

T.K. wrote the manuscript.

S.S. project administration.

All authors have read and agreed to the published final version of the manuscript. S.S. is the guarantor of this work and takes responsibility for the integrity of the data.

#### Declaration of conflict of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

#### Ethical approval

This study was carried out with approval of Ethical Committee of Experimental Animals of the Faculty of Medicine in Inonu University (2018/A-45). The authors have no ethical conflicts to disclose.

#### Institutional review board statement

All procedures performed in studies involving animals were in accordance with the ethical standards of the Ethical Committee of Experimental Animals of the Faculty of Medicine in Inonu University, at which the studies were conducted.

#### Study approval

All animal procedures were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of the Inonu University. All animals were randomly assigned to cohorts.

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