

Somatostatin damage on the pancreatic islets

Nahed H. Koura, Ph.D.

ABSTRACT

Objective: To study the histological appearance of the pancreatic islets consequent to prolonged regular daily treatment with somatostatin.

Methods: Thirty albino rats of each sex were divided into controls and another 2 groups; the first received the hormone somatostatin for 21 days and the second for 42 days. Pancreatic specimens were taken from the sacrificed animals by the end of these periods. Examination by light microscopy of these specimens was carried out. Insulin and glucose were regularly measured through out the course of treatment.

Results: Showed irreversible damage of the alpha and beta cells of the islets. All animals developed gradually

and continuously deteriorating diabetes mellitus. All the animals perished within a few days after cessation of treatment.

Conclusion: A relatively long term treatment with somatostatin had an everlasting killing effect on both of the pancreatic islets and the animals themselves. A recommendation has been put forward to seriously request the clinical therapy of this hormone.

Keywords: Pancreatic islets, somatostatin, insulin, diabetes mellitus.

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There has been no satisfactory picture of the suppressive effect of somatostatin hormone on the endocrinal function of the alpha and beta cells of the pancreatic islets. As it currently stands many reports described a highly significant inhibitory effect of this hormone on the endocrinal secretion of both of the alpha and the beta cells.^{1,2} On the other hand, Reichlins in 1993 measured higher levels of blood somatostatin following experimental insulin deficiency,³ but interestingly enough higher blood insulin levels did not influence blood somatostatin. The last author also stated the existence of a somatostatin-glucagon negative feedback mechanism. Strangely enough, histological study of the pancreatic islets consequent to somatostatin treatment is almost entirely lacking in the literature, in particular there have been no reports of the long

term histological effect as a result.

Clinically, the endocrinal pancreas has also been shown to develop a catastrophic downhill course as illustrated with the appearance of clinical diabetes mellitus.⁴ The last disorder was always a consequence of therapeutic long-term employment of somatostatin in many clinical contexts such as endocrinal tumors.^{5,6}

In view of the above mentioned poor understanding of the problem, the present study looked for the probable impact of a long term treatment with somatostatin on the histological integrity of the endocrinal pancreas. The assumption is that such a treatment may produce a detrimental effect on the alpha and beta cells of the pancreatic islets.

From the Department of Anatomy, Faculty of Medicine & King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Nahed H. Koura, Department of Anatomy, Faculty of Medicine & King Khalid University Hospital, King Saud University, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Tel. 467 0809/4671300.

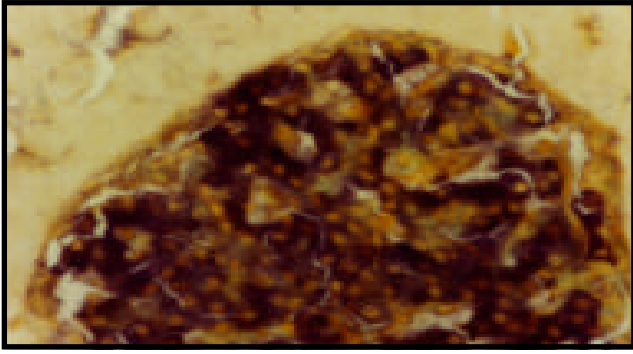


Figure 1 - A photomicrograph of microscopic section of the pancreatic islets presenting the normal appearance. The β -cells appear stained purple-violet and form the vast majority of the cellular element while the δ -cells took a yellowish color and a few in number. *Gomori modified aldehyde fuchsin stain x 640.*

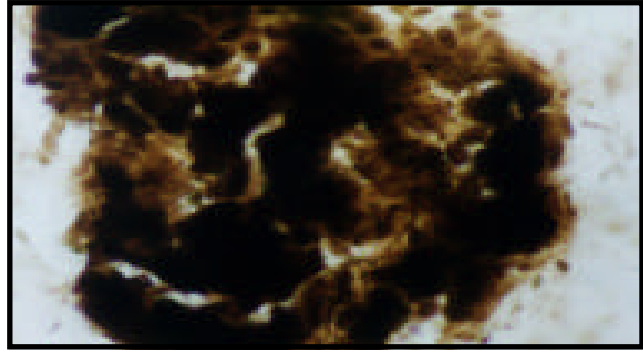


Figure 4 - A photomicrograph of microscopic section of the pancreatic islets in the control rats. There is a strong qualitative activity of acid phosphatase enzyme. *Histochemical technique x 640.*

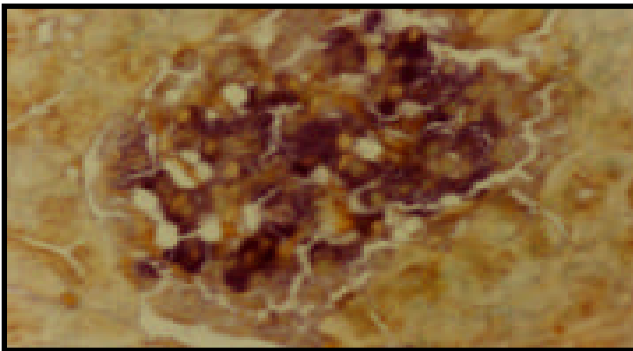


Figure 2 - A photomicrograph of microscopic section of the pancreatic islets taken 21 days after daily treatment with somatostatin. The β -cells became degranulated to various degrees and their nuclei were faintly stained. The δ -cells were very scanty. *Gomori modified aldehyde fuchsin stain x 640.*

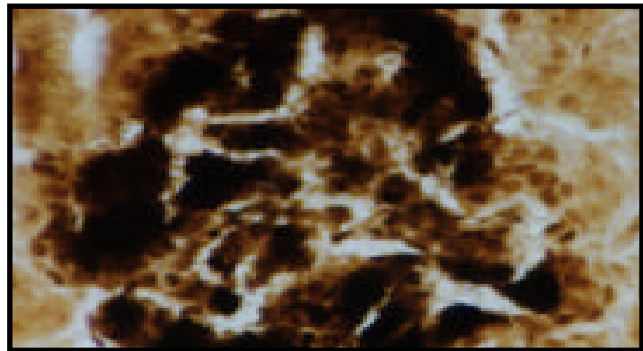


Figure 5 - A photomicrograph of microscopic section of the pancreatic islets treated with a daily single dose of somatostatin for 21 days. There is a moderate qualitative activity of acid phosphatase enzyme. *Histochemical technique x 640.*

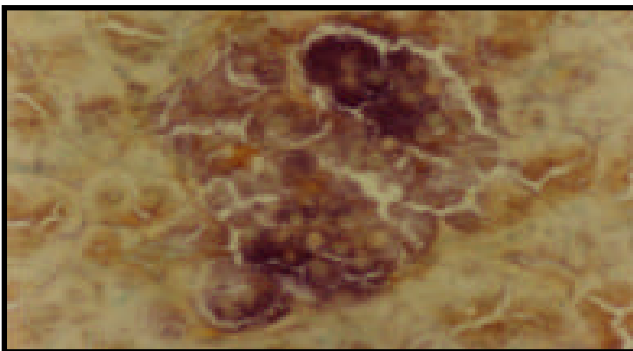


Figure 3 - A photomicrograph of microscopic section of the pancreatic islets 42 days after daily treatment with somatostatin. The β -cells do not show a clear boundary and appeared to coalesce in relatively large faint masses. The δ -cells almost entirely disappeared. *Gomori modified aldehyde fuchsin x 640.*

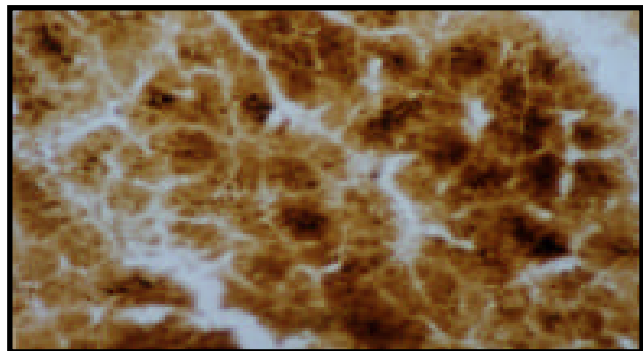


Figure 6 - A photomicrograph of microscopic section of the pancreatic islets treated with a daily single dose of somatostatin for 42 days. There is almost complete missing of any activity of the acid phosphatase enzyme. *Histochemical technique x 640.*

Methods. Experimental animals. Thirty animals of each sex western strain albino rats were 12-18 months of age and separately kept at room temperature. This was to avoid mating among these animals. The animals were given a meal of the same kind of food every 8 hours. Each of the sexes were divided into 3 groups, one used as a control and the others were subcutaneously injected at noon-time daily by $8\mu\text{g}/\text{kg}$ body weight of somatostatin (Synthetic SRIF, OVINE, by FLUKA AG SWITZERLAND). The first group was treated for 21 days and the second group was treated by the same dose for 42 days. The animals of each group were sacrificed at the end of the corresponding period.

The above dose was accepted in this work on the aim that it may well produce an evident effect.⁷ This dose was first employed by the previous author, as the least dose to produce damage of the exocrine pancreas. This dose is justified by the comparable understanding between 2 scopes, the first is the lower rat normal somatostatin blood level of 35 ± 4 the pancreas of all experimental animals.⁸ The histochemical technique⁹ to detect acid phosphatase enzyme activity of the pancreas of all animals, was conducted. The blood level of both glucose and insulin was measured daily at 11 am.

Results. The 21 days period of treatment revealed moderate damage of the islets cells. Modified Gomori stained histological sections (Figure 2) showed faintly stained cytoplasm (compare with the normal appearance in Figure 1) of the beta cells, which indicates degranulation. The alpha cells in the same sections were grossly absent which points out to severe damage and ultimate removal of these cells (compare with Figure 1). Histochemical study of the same sections expressed a moderate acid phosphatase activity of the islets (Figure 5), (compare with normal acid phosphatase activity in Figure 4).

The 42 days prolonged treatment illustrated further devastation, using the same histological technique. The islets were generally shrank and the cellular elements appeared less numerous. The beta cells (Figure 3) greatly lost their contour and most of them came together forming faintly stained bodies with irregular boundaries. This is although some nuclei preserved their configuration. The alpha cells completely disappeared. Histochemistry of the same period brought up the appearance of nearly total loss of the presence of active acid phosphatase enzyme (Figure 6). Biochemical search gave the picture of higher blood glucose ($29.7\text{ mmol}\pm 4.1$ compared with control of $5.6\text{ mmol}\pm 0.2$) and a great decrease of insulin ($10\pm 3\text{ pmol}/\text{L}$ compared with control of $100\pm 60\text{ pmol}/\text{L}$).

Clinical observation of the treated animals highlighted a steady loss of weight that progressed to cachexia and development of skin ulcers by the end of the drug administration time. Mortality rate among the long-term treatment group came to 50% by the last day of treatment. All survivors died within the first few days after cessation of treatment. There was no sex difference shown in all of the above procedures.

Discussion. The results obtained from this work were only directed in one way, that is the ability of somatostatin to produce permanent damage of both the alpha and beta cells of the pancreatic islets. This is supported by the extensive cell destruction, the disappeared acid phosphatase activity and equally important the clinical outcome of the experimental animals as shown by the lethal effect of somatostatin administration in the present work. However it is obviously difficult to explain this histological degradation of the pancreatic cells. Further biochemical investigation is strongly suggested to establish the underlying mechanism behind the present results. Other endocrinal secretions are probably involved in addition to the above mentioned hormones. Exogenous somatostatin may also have an extra-pancreatic influence.

The implication of the irreversible effect of somatostatin on the pancreatic islets raises the important question of the safety of clinical use of this hormone as a therapy in certain pathological conditions. This can be aggravated further in the light of absence of reasonable understanding of the true interaction between this hormone and other hormones.³ Somatostatin therapy has been applied in many disorders such as pituitary tumors associated with acromegaly,⁶ Insulin dependant diabetes mellitus to reduce the insulin dose,⁵ and many other conditions. In the above therapeutic reports, 2 main serious side actions of somatostatin are worth considering in the present context. The first is the development of diabetic manifestations and the second is the inhibition of the gastrointestinal and pancreatic juices. However, although the present work investigating the damaging effect of somatostatin in rats, the possible life long destruction of the pancreas and the digestive function in human must be strongly scrutinized.

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