The Functional Importance of Sympathetic Nerves to the Liver and Endocrine Pancreas

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Sympathetic noradrenergic nerves, with their wellknown cardiovascular effects, have recently been found to influence several metabolic and hormone-releasing processes. Morphological investigations in man have revealed a dense sympathetic innervation of the liver parenchyma as well as sympathetic fibers among the endocrine cells in the islets of Langerhans. Functional studies both in animals and man have shown that electrical or reflex activation of the hepatic and pancreatic sympathetic nerve fibers causes an increased output of glucose from the liver as well as a stimulation of glucagon and an inhibition of insulin release from the pancreas. From these results we conclude that damage to sympathetic nerves should be avoided in abdominal surgery.

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IF SYMPATHETIC NERVES are mentioned in surgical textbooks at all, they are discussed in connection with shock and trauma, where they are known to participate in the vitally important adjustments of the heart and the peripheral blood vessels. However, studies during the last ten years have clearly demonstrated that sympathetic nerves can also directly influence metabolic processes in liver and fat tissue as well as hormone release from the pancreas (Fig. 1). This report briefly summarizes our knowledge of this sympathetic control of the metabolism in animal and man with a focus on the liver and endocrine pancreas. We conclude with some remarks about these nerves with regard to abdominal surgery.

Sympathetic Nerves to the Liver Parenchyma

Previous Studies

The possibility that the sympathetic nerve fibers to the liver could influence not only vascular tone but also different metabolic functions was first suggested in 1968 by Shimazu and Amakawa.[24] They reported that stimulation of the splanchnic nerves in adrenalectomized rabbits caused a prompt increase in the activity of several enzymes involved in the hepatic glycogenolysis resulting in an augmented release of glucose from the liver into the systemic circulation. Later on, detailed animal studies were made by Edwards and coworkers on the function of the sympathetic nerves in the regulation of blood glucose.[6,7] They demonstrated that activation of the sympathetic nerves to the liver in cats, dogs, calves and pigs caused a pronounced hepatic liberation of glucose and, further, that the amount of glucose released was related to the stimulation frequency. Concomitant to the increase in blood glucose concentration, and in close correlation to the magnitude of evoked hyperglycemia, the hepatic glycogen concentration was diminished. This effect of nerve stimulation on the blood glucose level in fact seemed to be as effective as that caused by blood-borne catecholamines from the maximally stimulated adrenal medulla.[7] Additional support for the importance of sympathetic nerve fibers in the glucose hemostasis was presented by Järhult,[11] who showed that the normal hyperglycemic response to bleeding in cats was depressed if the hepatic sympathetic nerve plexus was cut before hemorrhage.

Recent Studies

We have recently investigated the morphological and physiological function of the hepatic sympathetic nerves in man.[10,20,21] With the Falck-Hillarp histofluorescence technique for visualization of catecholamines on the cellular level,[8,9] it was demonstrated that the human liver parenchyma receives an abundant supply of nerve fibers displaying the typical catecholamine fluorescence and that several hepatocytes in fact were surrounded by a dense network of such adrenergic axons (Fig. 2a). Quantitative determinations revealed that the noradrenaline content of the human liver is about 1 μg/g wet weight which leaves little doubt

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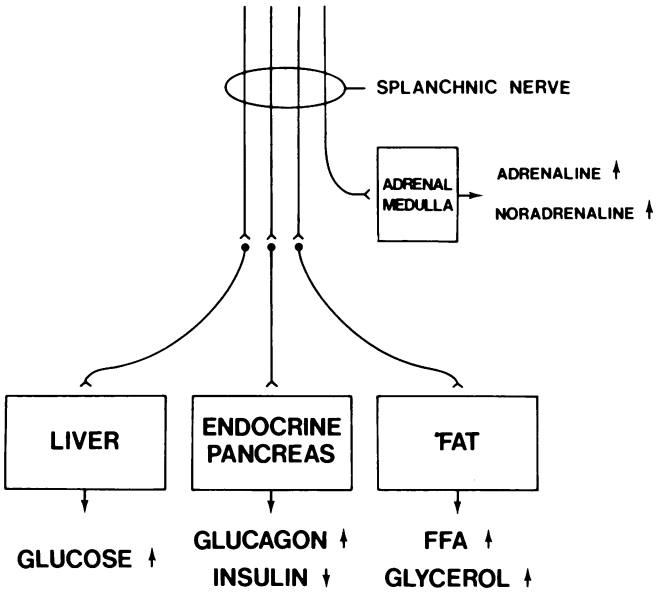

FIG. 1. Schematic illustration to show the effects of activation of the sympathetic nervous system on liver, endocrine pancreas, fat and adrenal medulla.

that these nerves contain noradrenaline. It should be mentioned that the noradrenaline concentration of the human liver is about five to ten times higher than that obtained from the liver of all other species investigated so far.

Electron microscopy revealed the presence of small nerve bundles penetrating into the human liver lobuli. From these bundles, nerve fibers branched off and made direct contact with the liver parenchymal cells. Membrane specialization was not seen in the contact areas, but this is not considered as a necessary prerequisite for synaptic transmission in peripheral tissues. Identification of the neurons was made after incubation of the liver specimen with 5-hydroxydopamine. After such incubation, vesicles with a highly electron-dense core and a diameter of about 400 Å have been observed in adrenergic nerve terminals, and the nerve endings which were observed to have contacts with the human liver cells fulfilled these criteria for adrenergic terminals.[21]

These morphological findings suggest that the sympathetic nerves should also be able to play a role in the human liver physiology. We recently studied the changes of plasma glucose concentration evoked by activation of the hepatic sympathetic nerves in man.[20] This study was performed on seven patients undergoing surgery for gallstones, but otherwise in good health and with a normal glucose tolerance test before the operation. The patients were fully informed about the protocol and agreed to participate in the investigation. A slow infusion of saline was given during the operation and atropine (1.0 mg) was given before the start of nerve stimulation. The sympathetic nerve

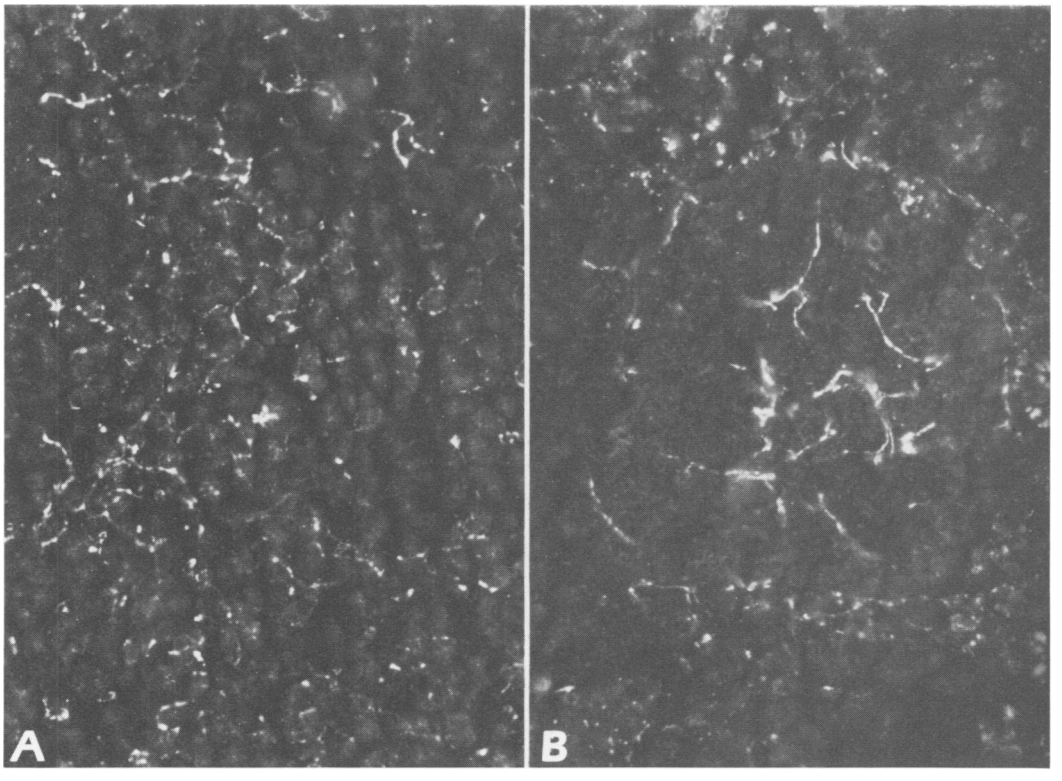

FIG. 2. (a, left) Fluorescence photomicrograph of normal human liver tissue. Numerous fluorescent adrenergic nerve terminals are seen in the parenchyma and some fibers are surrounding individual hepatocytes. ×180. (b, right) Fluorescence photomicrograph of an islet of Langerhans in adult man containing adrenergic nerves in the vicinity of blood vessels and endocrine cells. ×170.

fibers were dissected free on the common hepatic artery, placed on a bipolar platinum electrode with the cathode nearest to the liver and stimulated with a Grass stimulator for ten minutes (20 Hz, 50 V, 1 msec). Arterial blood was withdrawn from a small omental artery at intervals before, during and after stimulation for determination of glucose with the glucose–oxidase method.

As can be seen from Figure 3, stimulation of the sympathetic nerves caused a prompt and clearcut increase in the arterial plasma glucose concentration reaching a significant peak increase of about 2 mM above the control level at the end of stimulation. The plasma glucose concentration then gradually decreased but did not reach the control level within the 45 minutes of observation. The shape and time course of this curve is similar to that obtained by Edwards in calves, cats and dogs,[6,7] but the magnitude of the response is less pronounced than in the animal experiments. This quantitative difference can be partly ascribed to the technical difficulties inherent to the present human experiments.

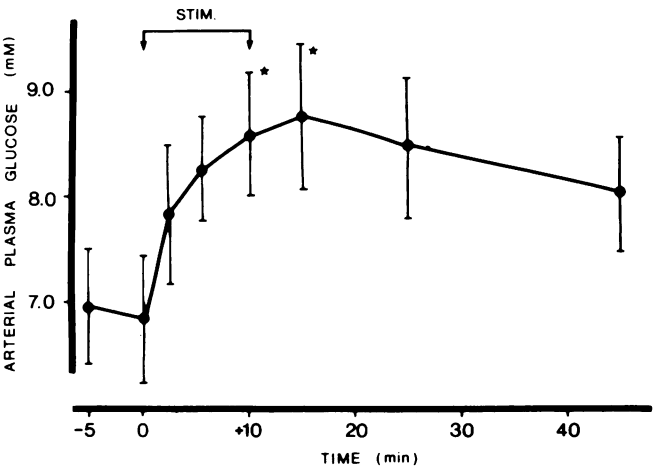

FIG. 3. Changes of arterial plasma glucose concentration in response to stimulation (20 Hz, 50 V, 1 msec) of the hepatic sympathetic nerves in man. Mean values ± S.E.M. from seven experiments are given. * indicates a statistically significant increase above the control value ($p < 0.05$).

Sympathetic Nerves to the Endocrine Pancreas

Previous Studies

In 1964 Coore and Randle discovered that adrenaline could markedly suppress the insulin response to glucose *in vitro*[5] and since then the effects of different catecholamines on the insulin and glucagon release have been repeatedly studied.[17,26] It is well established by now that catecholamines increase the release of pancreatic glucagon, whereas the effect on insulin release depends on which receptor on the β-cell that is activated. Thus, the α-receptors mediate an inhibition of the insulin release whereas the β-receptors mediate an enhanced insulin release.

In 1972 Marliss and collaborators showed that electrical stimulation of the dog's mixed autonomic pancreatic nerve evoked a pronounced liberation of glucagon from the pancreas[18] and it was soon demonstrated by others that stimulation of this nerve (or of the splanchnic nerves in adrenalectomized animals) caused an inhibition of the insulin release as well.[1,14,22] This sympathetic inhibitory influence was so powerful that the normal insulin release in response to glucose infusion was eradicated.[2] It has also been shown recently (Fig. 4) that these direct adrenergic fibers are involved in the reflex hyperglucagonemia and hypoinsulinemia which occur in response to a blood pressure drop in cats[12] and, also, that they participate in the regulation of glucagon and insulin during hemorrhage and hemorrhagic shock (Järhult, unpublished).

Recent Studies

Fluorescence microscopic examination of human islets has revealed that the endocrine cells are reached by adrenergic nerve terminals both in fetuses[4] and adults (Fig. 2b). In some preliminary experiments we have found that stimulation of the splanchnic nerves in man causes the same pattern of response as in animals, *i.e.* a decrease of the insulin and an increase of the glucagon concentration in portal blood. Moreover, indirect evidence of the importance of these direct sympathetic nerves in man has been obtained from experiments in bilaterally adrenalectomized patients.[13] When these patients were exposed to stress in terms of exercise until exhaustion, they responded with the same adrenergic adjustment of endocrine pancreas as normal controls. It has also been shown by Carey's group that hemorrhagic and/or traumatic shock in man is associated with hyperglycemia and depressed insulin levels in the blood,[3] adjustments which in all probability are caused by an adrenergic control of the β-cells and hepatocytes. Similar changes of the glucagon and insulin levels have been reported also in patients with severe burn injuries.[25]

It should be added that many pancreatic endocrine cells in mammals carry intracellular catecholamines or 5-hydroxytryptamine.[4] In human islets processed according to the Falck-Hillarp method we have observed a few cells displaying the fluorescence characteristics of catecholamines. In *in vitro* experiments we have, however, demonstrated that a dominating population of islet cells can take up L-dopa and decarboxylate it, the resulting catecholamine being accumulated in a cytoplasmic granular fraction. These observations indi-

cate that also in human islets, adrenergic intracellular mechanisms may operate which add to the complexity in the interpretation of the effects of catecholamines on endocrine pancreas.

Surgical Implications

The sympathetic nerves no doubt participate in the control of vascular tone and capillary exchange in the liver and pancreas.[15,19] In addition, the above mentioned studies suggest an important role of the sympathetic noradrenergic fibers also in the regulation of blood glucose, both via direct influence on the hepatocytes and, indirectly, via an influence on the pancreatic hormone release.

The sympathetic nerves to the liver and pancreas emerge mainly from the coeliac and superior mesenteric plexus and reach the liver along the hepatic artery, and the pancreas along the gastroduodenal and splenic arteries. It follows that these sympathetic nerves are easily damaged during surgery of the pancreas, stomach and biliary tract. It has even been proposed that the coeliac plexus should be destroyed in connection with major abdominal surgery in order to relieve the patient of postoperative pain, in analogy with the percutaneous destruction of the coeliac plexus with alcohol sometimes used to treat patients with intractable abdominal pains.

It is reasonable to assume that sectioning of some, or even all of these sympathetic fibers does not interfere with the normal carbohydrate metabolism at rest, even if it has been proposed that adrenergic mechanisms partly control the release of glucagon and insulin during basal conditions in man.[23] Thus, in the resting state the vascular and metabolic effects of the sympathetic nerves can be easily compensated for by other control mechanisms such as the adrenal catecholamines. However, it seems likely that intact sympathetic nerves are necessary during bleeding, trauma, exercise and starvation in order to fully adapt the organism to the stress situation. It might be speculated for instance that the severe attacks of hypoglycemia which frequently occur during the postoperative care of patients with total pancreatectomy partly depend on the absence of sympathetic nerves to the liver parenchyma. This hypothesis is now being tested in our departments.

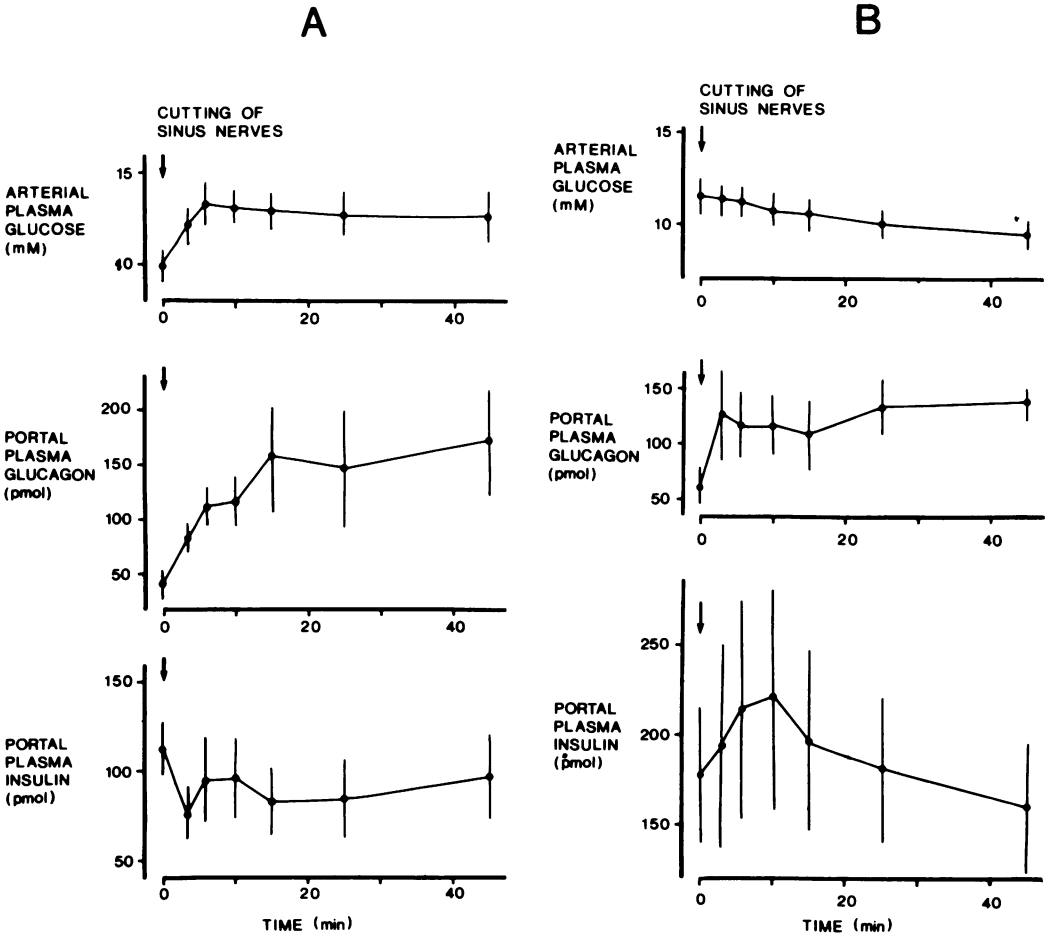

FIG. 4. Changes of arterial plasma glucose concentration and of portal plasma glucagon and insulin concentrations in response to cutting of the bilateral sinus nerves in vagotomized cats. Such nerve sectioning simulates a blood pressure drop to about 50–60 mm Hg. Panel A depicts the responses in adrenalectomized cats and panel B the responses in cats with cut splanchnic nerves and extirpated adrenal glands. The increase in glucose and decrease in insulin concentrations present in the adrenalectomized cats is eliminated by cutting of the sympathetic nerve fibers, whereas the glucagon increase is significantly depressed by the sympathetic denervation.

These findings prompt us to recommend careful handling of the sympathetic nerves during abdominal operations as part of the atraumatic surgery which all of us should perform.

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