Are the Islets of Langerhans Neuro-Paraneuronal Control Centers of the Exocrine Pancreas?*

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Summary. The authors investigate whether the islets of Langerhans can actually be regarded as “neuro-paraneuronal control centers of the exocrine pancreas” as was first suggested by Fujita and Kobayashi (1979). The question is discussed on the basis of the authors' electron microscopic findings regarding pancreatic innervation before and after truncular vagotomy.

The results do not seem to support the above hypothesis which advocates that the intra-insular axons are principally engaged in the release of their transmitters into the capillaries in order to regulate, via the insuloacinar portal vessels, the exocrine function of the pancreas. On the contrary, the present data draw attention to the unambiguous assignation of intrainsular axons to endocrine cells, a point of question in line with several findings published in the literature including papers by the first supporters of this hypothesis. No change was observed in the innervation pattern of the effector cells after vagotomy.

The innervation of the islets of Langerhans in the dog and numerous other species can only be described as intensive. The density of the nerves within the endocrine pancreas is so striking that it raises the question of whether these numerous terminal axon bundles and individual axons do in fact serve the endocrine cells alone. The idea that the islets might be a kind of “neuro-paraneuronal control center of the exocrine pancreas” was developed in analogy to the hypothalamohypophyseal neurosecretory system (Bargmann, 1949) by Fujita and Kobayashi (1979). This original concept is based on the hypothesis that the intrainsular nerves belong rather to the numerous capillaries into which the transmitter substances are liberated as neurosecretions than to the endocrine cells. The transmitters are then supposed to be carried with the blood (insulo-acinar portal system) to the exocrine parts of the gland where they directly act on the acinus cells. We wish to state our opinion on the above hypothesis as part of our own studies (Stach, 1974; Radke and Stach, 1982; Stach and Radke, 1982; Radke, 1984; Radke et al., 1985a, b).

MATERIALS AND METHODS

Pancreata of vagotomized and non-vagotomized dogs were studied in the electron microscope. Samples were taken from vagotomized dogs 14 days (Fig. 4) and 5 months after truncular vagotomy. The results do not seem to support the above hypothesis which advocates that the intrainsular axons are principally engaged in the release of their transmitters into the capillaries in order to regulate, via the insuloacinar portal vessels, the exocrine function of the pancreas. On the contrary, the present data draw attention to the unambiguous assignation of intrainsular axons to endocrine cells, a point of question in line with several findings published in the literature including papers by the first supporters of this hypothesis. No change was observed in the innervation pattern of the effector cells after vagotomy.

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RESULTS

The material discussed here was selected specifically in the context of the hypothesis (cf. Discussion). Most intrapancreatic terminal nerve endings are assigned to the endocrine cells themselves (Fig. 1, 2, 3b) with which they definitely form synaptic junctions (RADKE, 1984). This is shown by the small synaptic gaps which are usually narrower than 20 nm, and impressions caused in the membranes of the effector cells by the axon abutting them (Fig. 1, 2, 3b, 4c). Often transmission to an adjacent capillary is simultaneously prevented by Schwann cells on the side facing the vessels (Fig. 1a, c, 2a, b, d). Direct juxtapositions of capillaries and developed axons were observed comparatively rarely (Fig. 3, 4a, b). Some of our findings give the impression that the flow of transmitter could reach both the endocrine cell and the topographically adjacent capillaries (Fig. 1b, 2c, 3b, 4c). In general, however, the neurocellular distance is much shorter than the neurocapillary distance. Some axons even appear to be invaginated by the effector cells (STACH and RADKE, 1982). This applies as well to aminergic axon cylin- ders, which do not merely serve as vascular innervation (Fig. 3), but also form neurocellular synapses (STACH and RADKE, 1982). Simultaneous axonal contact with both endocrine and exocrine cells is often observed (Fig. 2d) at the margins of islets of Langerhans.

Occasionally it is impossible to assign terminal nerve endings to either a capillary or a cell (Fig. 2a). In addition to the relatively wide synaptic gap, the pericapillary synapse often contains basal membranes, colloidal and fibrillar material, which would scarcely make it easier for the transmitter to reach the fenestrated capillary (Fig. 2c, 3, 4), although hormones pass these structures too. Bilateral truncular vagotomy leads, according to subjective assessment, to neither a reduction in the number of intrapancreatic axons nor to a decrease or qualitative change in neurocellular contact zones (Fig. 3, 4). Ultramicroscopic structures that still exist 14 days and 5 months after vagotomy suggest that the intrapancreatic nervous system is anatomically independent (RADKE and STACH, 1986a).

DISCUSSION

The contents of FUJITA and KOBAYASHI’s (1979) hypothesis: were essentially that a considerable portion of the intrainsular axons must be regarded as belonging to the vessels of the islets on account of their locations. The muscle-free capillaries, however, do not appear to need innervation, and FUJITA and KOBAYASHI (1979) have interpreted this in an original way (RADKE and STACH, 1982; STACH and RADKE, 1982). The axons concentrated around the capillaries secrete the transmitters (noradrenalin, acetylcholin, VIP, dopamine) directly into the blood of the islet, in which they reach the exocrine pancreas together with the islet hormones of the capillary system where they can act in a similar way to hormones (insular neurosecretion). This hypothesis was developed on the basis of electron microscopic studies of the canine pancreas and were confirmed by similar studies in the snake and mink (FUJI et al., 1980; FUJITA et al., 1981). Only a few axons near the cells exhibit accumulations of vesicles on the side facing the
Fig. 1. Topographical relationships between B-cells ($B$) and terminal nerve endings ($ax$) near capillaries ($c$) in the pancreas of the dog. 

a. The B-cell ($B_1$) is surrounded by several axons ($ax$). This results in an extensive transmission area (arrows) between cell and axon. An axon ($ax_1$) is in contact with two insulin-producing cells ($B_1$ and $B_2$). Transfer to the capillaries is blocked. 

b. The axon ($ax$) beside the B-cell is completely exposed from the Schwann cell ($s$) on the cell side. A small gap free from Schwann cytoplasm is present on the capillary side. 

c. On the capillary side the axon ($ax$) is completely enclosed by the Schwan cell ($s$) and the basal membrane ($bm$). The axon lies directly against the B-cell. Glutaraldehyde perfusion. 

a: $\times 12,000$, b: $\times 25,000$, c: $\times 48,000$
effector and thus show the qualitative features of synapses (Fujita et al., 1981). The definition of the islet cell as a paraneuron (Fujita et al., 1978, 1981; Fujita and Kobayashi, 1979) owing to its cell-biological relationship with the neuron is another basis for the hypothesis. The islet cell is therefore not necessarily subjected to neuronal control, but could act in parallel with the nerves literally as a paraneuron.

The unification of the islets of Langerhans and the exocrine pancreas into a single

Fig. 2. Single axons (ax) in the pericapillary gap of the canine islet of Langerhans with a distinct topographical relationship (arrows) to B-cells (a, b, d). c. The axons lying against the process of the B-cell (B,) could influence the endothelial cell (e) as well. d. At the margin of the islets of Langerhans an axon may be in simultaneous contact with both B- and acinar cells (ex). Glutaraldehyde perfusion. a: ×35,000, b: ×30,000, c: ×48,000, d: ×56,000
organ does not appear to be a fortuitous anatomical coincidence. On the contrary, functional interactions have been found (HENDERSON et al., 1981). Such relationships obviously also exist in the microcirculation of the hormone synthesizing and the enzyme producing parts of the organ. Scanning electron micrographs of corrosion sections taken from apes clearly show that the vasa efferentia leaving the islet radially connect directly with the capillary region of the surrounding acinar cells before opening into the draining veins (FUJITA and MURAKAMI, 1973). The pancreas of the horse receives almost the whole of its blood supply via the islets of Langerhans (FUJITA, 1973). Studies performed on the dog, the cat and the rat corroborate the existence of an insulo-acinar portal system with the following path: interlobular artery—vas afferens—sinusoidal capillary (islets)—vasa efferentia—intraacinar capillary region—vein system.

The whole (FRASER and HENDERSON, 1979) blood supplies the exocrine part of the gland via islets (FUJITA et al., 1976; OHTANI and FUJITA, 1980). Not even once did the blood from the islets of the rabbit drain directly into a vein (FRASER and HENDERSON, 1980). Exocrine follows endocrine circulation (FRASER and HENDERSON, 1979).
accounts for about a quarter of the whole blood flowing through the pancreas. The vascular architecture described above does indeed appear suitable for transporting islet hormones to the acini in high concentrations (Fujita et al., 1976; Fraser and Henderson, 1980; Lifson et al., 1980).

What evidence, then, speaks contrary to this hypothesis?

Firstly, according to the numerous findings available, there can be no doubt that genuine synaptic connections exist between intrainsular nerves and hormone producing cells (Woods and Porte, 1974; Radke, 1984). Such findings were also extensively reported by the inaugurators of the hypothesis (Kobayashi and Fujita, 1969; Fujita and Kobayashi, 1979). However, it must be stressed that the endocrine cells or paraneurons are assumed to be not so much under the control of neurons as their working parallel with neurons (Fujita et al., 1981).

The islet cells of the dog are decidedly densely innervated. That synaptic gaps of

Fig. 4. Micrograph of intrainsular axons near a capillary 14 days after vagotomy. Doubtful (a, c) and definite (b) neurocapillary relationships. A A-cell, co colloidal material, fi fibrillar material. Glutaraldehyde immersion, a: ×50,000, b: ×28,000, c: ×40,000
about 20 nm and axon-induced depressions on cells make a purely coincidental topographic relationship appears very improbable, even though signs of membrane specialization are regularly absent. Only Orci et al. (1973), using an extracellular tracer (lanthanum), were able to show a zone of greater density between the axon and B-cell. Contacts between nerve endings and non-neural cells, such as endocrine cells, must also be called synapses—in this case so called peripheral synapses (Kirsch, 1960) are involved—even if pre- and postsynaptic membrane specialization cannot be demonstrated (Bargmann, 1975).

The stimulatory effect on mixed pancreatic nerves shows that this innervation found by ultramorphological methods is functional. The nerve impulses that are triggered lead to hormone liberation by all four endocrine cell populations of the islets of Langerhans (cf. Radke, 1984).

Secondly, nerve fibers ramify over the entire capillary bed in various tissues and organs (Burnstock and Griffith, 1983), including the pancreas (Radke, 1984). Contrary to the hypothesis, the perivascular nerves might easily serve the innervation of the capillaries (Radke, 1984), because the capillaries contain contractile elements (Burnstock and Griffith, 1983). The capillary endothelium has been discussed as a possible receptor in addition to the pericytes (Burnstock and Griffith, 1983).

Third, light (rat, cat) and electron microscopic studies have shown that the exocrine pancreas is also densely innervated. Acinar cells can be innervated directly, indirectly, amnergically, cholinergically and probably peptidergically (Radke, 1984). In the dog, nerves are conspicuously concentrated on the islets (Fujita and Kobayashi, 1979; Kobayashi and Fujita, 1969). However, numerous axons were found in close connection with acinar cells nearest the islets (Radke et al., 1985a; Radke and Stach, 1986b).

Fourth, the observation that the “whole” of the insular blood flows off via exocrine capillary system (Fraser and Henderson, 1979, 1980; Lifson et al., 1980) must definitely be reviewed in the light of recent studies with the scanning electron microscope (Bonner-Weir and Orci, 1982; Ohtani, 1983). Figure 4 in Ohtani (1983) shows on the contrary that some of the efferent insular vessels have a considerably larger caliber, drain directly into venules and, over this relatively short distance, also act as receivers for capillaries from the exocrine pancreas. In other words, the assumption that all efferent insular vessels are capillaries (Fraser and Henderson, 1980) is false. The vessels are partly those of the venous path that drain directly into venules. In many islets, the efferent capillaries coalesce at the edge of the islet and pass along the mantle of non-B-cells as collecting venules before draining into a vein (Bonner-Weir and Orci, 1982). In other words, the blood enriched with hormones and trigger substances flowing through these veins can no longer reach the acinar cells. Judging from the Figures presented by the authors (Fujita, 1973; Fujita and Murakami, 1973; Fujita et al., 1976, 1981) it does not seem at all impossible that some of the small caliber insular vessels drain directly into the venous system. Bonner-Weir and Orci (1982) showed that direct venous drainage is present in rat islets and even predominates in the larger islets.

Fifth, the results altogether give a very good idea of the vascular supply of the islets of Langerhans. The character of the vessels from the adjacent exocrine parenchymatous tissue is not clearly determined by the Figures, however. Furthermore, only a few Figures in Fujita and Kobayashi’s decisive publication (Fujita and Kobayashi, 1979) permit clear assignment of nerves to the capillaries. Most of their excellent micrographs show a direct juxtaposition of nerves and endocrine effector.

Sixth, “... the hormonal concentration in the exocrine microcirculation is several
hundred times greater than if the islets had an independent venous drainage...” (FRASER and HENDERSON, 1980). One wonders whether this can be functionally intended and advantageous mechanism.

Finally, stimulation of the vagus nerve leads to liberation of islet hormones. This fact seems to contradict the opinion that islet cells represent paraneurons. “These appear not necessarily under the regulation of neurons” (FUJITA et al., 1981). The cephalic phase of, say, insulin secretion (HOMMEL et al., 1972) is eliminated after vagotomy (RADKE et al., 1985b). The influence of the intrinsic nervous system of the organ is therefore not definitely switched off (RADKE and STACH, 1986a), as indicated by morphologically intact axons and neuro-cellular relationships (Fig. 3, 4).

In conclusion, the endocrine pancreas is a densely innervated organ. At the margins of the canine islets of Langerhans, almost every endocrine cell is in contact with axons. On the basis of the small synaptic gap of about 20 nm, fusions of basal membranes, and axon-induced depressions in the effector membranes, we are convinced that relations between the two are definitely synaptic. From the ultramorphological findings it must be assumed that the intrapancreatic and extrinsic vegetative nervous system have a major influence on the production and liberation of islet hormones. These anatomical findings are supported by functional results that electrical stimulation of the vagus nerve and of mixed pancreatic nerves leads to the liberation of the four islet hormones. 

FUJITA and KOBAYASHI’s (1979) interesting hypothesis which postulates insular neurosecretion and ascribes to the endocrine pancreas a “neuro-paraneuronal control function” over the exocrine gland obviously underestimates the direct influence of the nervous system on hormone-producing cells. Moreover, it fails to take into account the independent innervation of the exocrine pancreas and intrainsular capillaries. However, it cannot be fully denied that at least a certain portion of the exocrine pancreas is under the control of the insulo-acinar portal vessels. The most attractive and likely candidate of the insular neurosecretions seems to be VIP as it has a secretin-like activity upon the exocrine pancreas (FUJITA and KOBAYASHI 1979).

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REFERENCES

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