MICROCIRCULATION OF THE PANCREAS WITH SPECIAL REFERENCE TO PERIDUCTULAR CIRCULATION. A SCANNING ELECTRON MICROSCOPE STUDY OF VASCULAR CASTS

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ABSTRACT

Microcirculation of the pancreas was studied with special reference to possible short routes conveying islet hormones to the exocrine pancreas including its duct system. Vascular casts of rabbit and rat pancreas were prepared with methyl methacrylate and observed under the scanning electron microscope. The insulo-acinar portal system was clearly demonstrated. The islet receives one or more arterioles and issues many vasa efferentia to the interacinar capillary bed. The vasa efferentia of rat islets close to a ductule may end in a capillary network around the ductule, forming an 'insulo-ductular portal system', which could transport insular secretions from islet to ductule. The periductal or periductular plexus, in addition to having its own arterial supply and venous drainage, is also connected with the capillary bed of the acini by small veins or by capillaries. Most likely blood flows from the lobular parenchyme to the periductular plexus. However, the possible existence of a 'countercurrent portal' vessel, which might drain the periductular plexus back to the lobular capillaries, is not excluded.

KEY WORDS pancreas / microcirculation / insulo-acinar portal system / insulo-ductular portal system / periductular circulation of the pancreas / scanning electron microscopy of vascular casts

The pancreas is a combined endocrine and exocrine organ. Recently special attention has been given to the vascular connection between both portions under the name of insulo-acinar portal vessels (7, 8, 13). The mammalian islet receives a branch of the intralobular artery and releases its hormones into portal vessels (vasa efferentia) so that the acinar portion of the exocrine pancreas receives high concentrations of these hormones. Clues to the significance of this portal system are found in the following

reports: Kanno and Saito (15) demonstrated that insulin markedly potentiates the action of pancreozymin upon pancreatic acini. Fujita and Kobayashi (12) proposed that nerves, terminating in the pericapillary spaces of the islet, may release secretions, which in high concentrations, are conveyed to and stimulate the acinar cells.

Much less attention has been paid to the microcirculation of the duct system. As in many other exocrine glands, the ducts and ductules of the pancreas are surrounded by a basket-like plexus of venules and capillaries but the connections between this periductal or periductular plexus and the capillary bed in the endocrine and exocrine tissues are not known. In

Fig. 1 Surface view of a vascular cast of the rabbit pancreas. Interlobular veins (*V*) are accompanied by thinner interlobular arteries (*A*). The latter branch into intralobular arteries which supply islets (*L*) and the capillary net of the exocrine tissue. *a*, Vas afferens of the islet; *ad*, arteriole directly supplying periacinar capillaries. At the bottom is a periductal plexus (*PdP*) with its connections (arrows) with the capillary bed of the exocrine tissue. $\times 90$

Fig. 2 Vascular cast of a typical islet and its related vessels of the rat pancreas. Note that the vas afferens (*a*) is divided into branches which run in the cortical layer of the islet, and then issue deeper secondary branches. From the islet numerous vasa efferentia (*e*) are emitted, some of which originate from the deep part of the islet. *A*, artery; *V*, veins. $\times 340$

this study we examined the possibility that the periductular plexus might receive directly vasa efferentia from an islet located nearby. If such an 'insulo-ductular portal system' can be demonstrated, it could be direct, short-route for the control of ductular functions by insular hormones and by neurohormones. We also attempted to find a "periductular portal vessel" which might transfer blood from the periductular plexus to the pancreatic lobule, now that a corresponding 'countercurrent portal' route is known in the liver under the name of the peribiliary portal vessels (20, 21, 22).

MATERIALS AND METHOD

Commercially available methacrylate medium

(Mercox; Oken Shyoji, Tokyo, Japan) was arterially injected in the pancreas of rabbits weighing 1.5–2.0 kg and Wistar rats weighing 250–300 g. After polymerization was completed, the injected tissue was corroded in NaOH or KOH aqueous solution to obtain the vascular casts (18, 19, 21, 22), which were frozen in water; trimmed with a razor blade; and dissected under a stereoscopic microscope with sharpened needles and forceps, to expose the various portions of the gland. The specimens were then coated with gold or platinum-palladium in a sputter coater and observed in a scanning electron microscope (JSM-U3, JEOL) with an accelerating voltage of 5 kV. After observation in the scanning electron microscope, some casts were further dissected to remove vessels,

which obscured the deeper structures. The specimens were coated again and observed in the scanning electron microscope. This procedure of microdissection, coating and scanning was repeated until the parts of interest could be observed (7).

RESULTS

There is no essential difference between rabbit and rat pancreatic microcirculation.

The interlobular artery branches into intralobular arteries and then into arterioles which are mainly destined to reach islets. However, some of the arteriolar twigs connect directly with the capillary bed of the acini and still others join the capillary network surrounding the duct system (the periductal and periductular plexus).

Insulo-Acinar Portal System

The islet of Langerhans is supplied by an arteriole, vas afferens, which arises from the interlobular artery (Figs. 1 and 2). The vas afferens, after reaching the islet, divides into swollen sinusoidal capillaries which form a glomerular-like capillary network. Occasionally in the rat two vasa afferentia supply a single islet. The vas afferens terminates at the periphery of the islet, where A cells are known to be located in

the rat and rabbit pancreas, and breaks up into branches which run in the cortical layer of the islet, and which issue secondary branches to the deeper parts of the islet (Fig. 2).

Numerous vessels, vasa efferentia, smaller in caliber than the islet capillaries, radiate from the peripheral capillary net of the islet to connect with the capillary net of the acini to form a round or polygonal mesh, which enclosed spaces originally filled by individual acini (Figs. 2 and 3). In the rat and rabbit pancreas, some of the vasa efferentia are thick and considerably long. After running a straight or wavy course and often after bifurcating, they break up into the acinar capillary net (Figs. 2 and 3). These large vasa efferentia better deserve the name of the insulo-acinar 'portal' vessels than the weaker vessels in other animals.

In the rat the vasa efferentia from islets located close to ducts are partly connected directly with the periductular plexuses. This 'insulo-ductular portal system' will be described in detail later.

In the rabbit and especially in the rat, there are many branches of intralobular arteries which do not end in an islet but break up into the capillary network of the acini (Figs. 1 and 9). Thus, in these species, the acini are only partly supplied by blood from the islets.

The capillary net of the acini drains into venules, which ultimately form the intralobular

Fig. 3 Stereomicrographs (6° tilt) of a rabbit islet (closer view of the right upper part of Fig. 6). Among several thin vasa efferentia, the one labeled *ed* is thick and long, originates from the deep part of the islet and, after bifurcation, extends its branches to a large portion of the exocrine pancreas. The vas afferens (*a*) is seen behind other vessels. An arrow indicates the connecting vessel between the peri-acinar capillary net and the periductular plexus. At the left is a periductular plexus. $\times 200$

vein or into a venule, which is connected with the periductular vascular plexus (*vide infra*). The intralobular veins take irregular courses, preferring more or less the peripheral part of the lobule (Fig. 7), and they usually do not accompany an intralobular artery at all. On the other hand, the interlobular vein is usually accompanied by the interlobular artery (Figs. 1 and 5).

Periductular Circulation

The ducts and ductules are surrounded by a sinusoidal capillary network, the periductal and periductular plexus. Branches from the inter- or intralobular artery form polygonal meshes of capillaries around the duct system, and these are gradually collected to thicker venules,

which anastomose with each other and accompany the ducts to form the intra- or interlobular veins (Figs. 4-8).

Noteworthy, connections are found between the blood vessels of the exocrine lobule and the plexus around the duct system. First, blood in the venules of lobular portions may flow into the periductal vessels of larger caliber, probably of venular nature (Figs. 6 and 8). Second, the periductal or periductular plexus may be connected with the capillaries of the lobule by one or a few thin vessels probably of capillary nature (Figs. 5, 6 and 8). In both cases the blood flow presumably is from lobule to duct, although a vascular connection which might allow blood to flow from the periductular plexus to the lobular plexus is not excluded.

Special attention must be called to the fre-

Fig. 4 Periductal plexus (PdP) of the rabbit pancreas is supplied by a branch (arrow) of an artery (A). Note a venule (v) connecting the periacinar capillary bed with the periductal plexus. $\times 100$

quently close relation of an islet to the periductular plexus. In the rat an islet often occurs close to the duct system (Figs. 7-9). Such islets usually receive a short branch (vas afferens) from an interlobular artery, and their vasa efferentia partly enter the periductal (Fig. 7)

or periductular plexus (Fig. 9). As suggested in Fig. 7 and clearly demonstrated in Fig. 9, a part of this vascular connection is represented by one or a few thick capillaries which may deserve the name of insulo-ductular (or ductal) portal vessels.

Fig. 5 Vascular cast of the rat pancreas showing a periductal plexus and its connecting vessels. Arrows indicate venules draining the plexus. *A*, *V* interlobular arteries and veins, *a* arteriole supplying the periductal plexus, *v* venule. $\times 100$

DISCUSSION

Insulo-Acinar Portal System

The existence of an insulo-acinar portal system has been demonstrated by one of the authors (T. F.) in an India ink injected pancreas of horse (6), rabbit and some other animals (8). A scanning electron microscope study of vascular casts of a monkey pancreas made the finding more convincing (7). Such a microcirculation pattern had been correctly reported by earlier investigators (23, 24) but was ignored, until Henderson (13) proposed that this insulo-acinar vascular system could transport islet hormones, in high concentrations, to the acini where they would play a significant role in the metabolism of the exocrine pancreas.

This hypothesis has been further advanced by

Fujita and his associates (8, 9) who proposed more concrete possibilities of the effects of islet secretions upon the exocrine pancreas. Experimental studies by Kanno and his associates (15-17) demonstrated that insulin markedly potentiates the effect of pancreozymin upon the exocrine pancreas in the rat.

Furthermore, Fujita and Kobayashi (12) proposed that, at least in the dog, numerous nerves in the islets might release their neurosecretions, such as noradrenaline, dopamine, acetylcholine and VIP, into the capillaries. Through the insulo-acinar portal vessels these neurosecretions could then affect the exocrine pancreas.

The present observation confirmed that, unlike rhesus monkey, dog and horse, in the rat and rabbit the vas afferens does not penetrate deeply into the islet but divides into branches

Fig. 6 Periductal plexus (PdP) and its connecting vessels of the rabbit pancreas. The periacinar capillaries are connected to the periductal plexus by capillaries and venules (arrows). A, V interlobular arteries and veins, L islet. $\times 125$

Fig. 7 Periductal plexus (PdP) and its related vessels in the rat pancreas. The plexus is supplied by branches from an artery (A). In the upper right, an islet (L) is located very close to the periductal plexus. It receives a vas afferens (a), and possible vasa efferentia (e) appear to drain the insular blood to the periductal plexus. $\times 150$

which run in the cortical layer of the islet, the deeper portion of the islet being supplied by secondary branches of these arcuate, cortical vessels. This finding seems to support the hypothesis proposed by Fujita (9) that the blood in the islet generally flows in such a way that it takes up hormones from A and D cells and transports them to B cells. In the rat and rabbit the cortical portion of the islet is the site of A and D cells, whereas the core is occupied by B cells. It is widely accepted that the release of insulin from the B cells is stimulated by glucagon (produced in the A cells) and inhibited by somatostatin (produced in the D cells).

As pointed out by Thiel (23) the blood supply to the exocrine pancreas is almost entirely

via the endocrine portion in the horse. In other animals there is a mixed pattern, with some branches of the intralobular arteries forming periacinar capillary networks directly (9). The present study indicates that this 'incomplete' pattern of microcirculation is most marked in the rat, in which considerably large arterioles may be destined to wide exocrine areas without passing an islet. This finding suggests that in the rat a fairly large portion of the acini is free from the 'neuropancreaurological control' of the islet (12). It is notable that distribution of numerous nerve terminals on the pancreatic acini have been reported only in the rat (2). In other species, since the acinar portion of the pancreas lies downstream to the islets, nervous control of the acini might be mediated by the

Fig. 8 Vascular cast of the rat pancreas showing an islet (L) which is closely associated with the periductular plexus (PdP). The islet is supplied by a vas afferens (a) and its vasa efferentia (e) are directly connected with the periductular plexus. A, V inter lobular artery and veins. $\times 100$

insulo-acinar portal system.

Periductular Circulation

It seems to be a general rule that the ducts of exocrine glands are surrounded by capillary plexuses. This vascular arrangement is consistent with the physiological finding that the exocrine secretions (especially those of salivary glands, pancreas and liver) undergo extensive modification as they pass the duct (14).

In the liver the bile ducts and ductules are surrounded by a capillary net supplied by hepatic artery branches (1). This periductular capillary bed drains into the sinusoids of the hepatic lobule by a relatively thick vessel, the peribiliary portal vessel (20, 21, 22). The significance of this peribiliary portal system has been considered in terms of a countercurrent

mechanism, which facilitates the reabsorption of substances from the bile (14). On the other hand, we have suggested that hormones released from the basal-granulated cells in the bile ductules in response to the chemical information of the bile might be transferred by the peribiliary portal system back to the hepatic lobule (11).

The ducts of the salivary glands are surrounded by a dense network of capillaries. However, whether there is any connection between duct and acinar capillaries is a subject of controversy as is the direction of blood flow. In the canine parotid gland Burgen and Seeman (4) described a 'countercurrent portal system' with blood flowing from the periductal to the acinar capillary bed. However, in the sheep parotid the blood flow was found to be from acini to duct (3). Furthermore, Frazer and

Fig. 9 Vascular cast of the rat pancreas showing an islet (*L*) which is located very close to the periductular plexus (*PdP*). Note that some of the vasa efferentia (*e*) of the islet join the capillary of the periductular plexus. *A*, *V* interlobular arteries and veins, *a* vas afferens, *ad* arterial branch to the exocrine tissue. $\times 250$

Smaje (5) reported in the rabbit submandibular gland that the ductal and acinar circulations are independent from each other.

In the present study the ducts and ductules of the rat and rabbit pancreas are richly covered by a sinusoidal and venular network, which is supplied by its own afferent arterioles and drained by interlobular veins. The connections between the periductal and acinar capillary beds are either by thin capillaries or by thicker vessels of apparent venular nature. Our morphological analysis of vascular casts suggested that the blood flow might be from the acini to the duct. Thus, a 'countercurrent portal system' was not demonstrated in the pancreas, although such a system cannot be excluded. Since the pancreatic duct epithelium contains dispersed basal-granulated (endocrine) cells, it seems that further studies should be done to determine if their secretions might be

transported back to the acinar tissue.

Insulo-Ductular Circulation

Our micrographs suggested that, at least in the rat, vasa efferentia of the islet may drain into the periductal vascular net. This suggests that islet secretions, both neuronal and paraneuronal (*vide supra*) might exert their effects upon the ductal wall in very high concentrations. The vasa efferentia involved in this special route may deserve the name of insulo-ductular (or ductal) portal vessels, in so much as they may be represented by thick, fairly long capillaries. In addition to this direct insulo-ductular system, attention must be paid to the fact that the duct system of the pancreas can also receive acinar blood which contains islet secretions in high concentrations.

Our knowledge is very meager concerning

the effects of islet hormones on the pancreatic duct system, i.e., on the muscular tonus and contraction as well as on epithelial absorptive and secretory functions. The possibility proposed in the present study that insular blood is, either directly through the insulo-ductular route or indirectly through the insulo-acinar circulation, conveyed to the duct wall will hopefully stimulate the study of insular secretions as short-distance hormones which affect the duct system of the pancreas.

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