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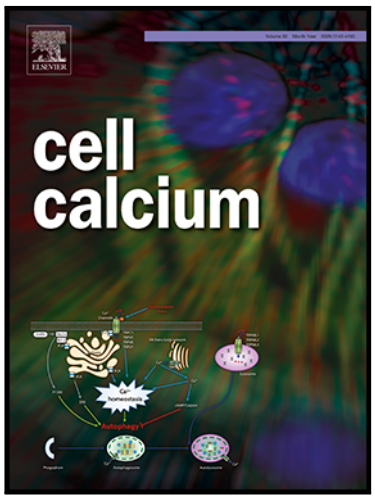

GPR30 IS A POTENTIAL PLAYER BETWEEN ISLET CELLS AND DUCTAL HCO_3^- SECRETION

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PII: S0143-4160(24)00080-0
DOI: https://doi.org/10.1016/j.ceca.2024.102922
Reference: YCECA 102922

To appear in: *Cell Calcium*

Received date: 28 May 2024
Revised date: 11 June 2024
Accepted date: 12 June 2024

Please cite this article as: Viktória Venglovecz , Péter Hegyi , GPR30 IS A POTENTIAL PLAYER BETWEEN ISLET CELLS AND DUCTAL HCO_3^- SECRETION, *Cell Calcium* (2024), doi: https://doi.org/10.1016/j.ceca.2024.102922

Highlights

- Pancreatic ductal epithelial cells secrete high amount of HCO_3^- into the pancreatic juice
- G protein-coupled oestrogen receptor, GPR30 can be activated by HCO_3^- in the brain
- GPR30 is highly expressed in the endocrine pancreas
- HCO_3^-, secreted by ductal cells may regulate endocrine function through activation of GPR30
- This regulatory mechanism presumably occurs at the level of small intralobular ducts, where the endocrine cells are in direct contact with the ductal lumen

GPR30 IS A POTENTIAL PLAYER BETWEEN ISLET CELLS AND DUCTAL HCO_3^- SECRETION

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Abstract

The primary role of pancreatic ductal HCO_3^- secretion is to prevent premature activation of digestive enzymes and to provide a vehicle for the delivery of enzymes to the duodenum. In addition, HCO_3^- is responsible for the neutralization of gastric juice and protect against the formation of protein plugs and viscous mucus. Due to this multifaceted role of HCO_3^- in the pancreas, its altered functioning can greatly contribute to the development of various exocrine diseases. It is well known that the exocrine and endocrine pancreas interact lively with each other, but not all details of this relationship are known. An interesting finding of a recent study by Jo-Watanabe et al. is that the G protein-coupled oestrogen receptor, GPR30, which is expressed in the endocrine pancreas, can be also activated by HCO_3^-. This raises the possibility that ductal cells play a key role not only in the exocrine pancreas, but presumably also in endocrine function through HCO_3^- secretion.

GPR30 is a G protein-coupled oestrogen receptor that is primarily activated by oestradiol (E2) [1]. A recent study by Jo-Watanabe et al. described a previously unknown mechanism that enables HCO_3^- ions to control the activity of GPR30 [2]. Binding of HCO_3^- to the receptor increases the intracellular Ca^{2+} level in a dose-dependent manner that is coupled with the activation of a Gq protein. They showed that GPR30 is expressed in brain vascular smooth muscle cells (SMCs) and pericytes, where it detects serum HCO_3^- levels and induces vasoconstriction through a signalling cascade, including phosphorylation of the ERK1/2 at Thr202/Tyr204 and also activation of phospholipase C. Therefore, GPR30 plays an important

role in the regulation of cerebral blood flow. One of the most important findings of this study was that the degree of ischemia-reperfusion injury (IRI) was smaller in GPR30-deficient mice compared to wild-type mice, indicating that activation of GPR30 contribute to neurological damage during IRI. They also showed that the concentration of HCO_3^- increases in the blood within 5 min of reperfusion, that does not depend on the presence of GPR30. In contrast, the concentrations of other ions, such as Ca^{2+}, Mg^{2+} or Na^+ did not change due to reperfusion. GPR30 knock out mice showed decreased neurological defect and infarct volumes and milder damage of the blood-brain barrier. In addition, GPR30-deficient mice had faster and better recovery of cerebral circulation, suggesting that inhibition of GPR30 may be beneficial in mitigating ischemia-reperfusion injury. Their hypothesis regarding the role of GPR30 in neurological damage is that HCO_3^- ions activate the GPR30 receptor, as a result of which the intracellular Ca^{2+} level increases in vascular SMCs and pericytes leading to vasoconstriction, thereby reduced blood flow, which aggregates neurological damage.

One of the interesting findings of Jo-Watanabe et al. is that the GPR30 receptor is also highly expressed in the pancreas. The pancreas is a dual gland that plays a vital role in digestion and carbohydrate metabolism. Digestive enzymes are produced by the acini and secreted into the centroacinar lumen in a plasma-like fluid, whereas ductal cells secrete HCO_3^--rich fluid that provides most of the volume of the pancreatic juice and play essential role in the conveyance of digestive enzymes. This fluid also performs an important protective function by providing pH conditions that protect against the formation of protein plugs and viscous mucus, and prevent the premature activation of digestive enzymes [3, 4]. Furthermore, ductal HCO_3^- secretion also plays a prominent role under pathological conditions, as shown by numerous studies [5-11]. The endocrine pancreas is composed of hormone secreting cells, among them the most important are the insulin-secreting beta cells and the glucagon-secreting alpha cells. Insulin decreases blood sugar level, by promoting the uptake of glucose from the blood; whereas, glucagon promotes the release of glucose from glycogen if the blood sugar level is too low. The two parts of the pancreas lively interact with each other, not only in physiological but also in pathological conditions [12].

The presence of the GPR30 receptor in the pancreas was previously detected in both the exocrine and endocrine pancreas. In relation to the exocrine pancreas, its function was primarily investigated in pancreatic cancer. High levels of GPR30 have been found both in human and mice pancreatic ductal adenocarcinoma (PDAC), regardless the stage of cancer. The presence of GPR30 has been also detected in the normal pancreas although its expression was

significantly lower compare to PDAC [13, 14]. Natale et al. have shown that specific activation of GPR30 decreased tumour grow, prolonged survival and improved the response to immune therapy *in vivo* in mice, suggesting that the pharmacological activation of GPR30 receptor may have therapeutic importance in pancreatic cancer [14]. The role of GPR30 has been more widely investigated in the endocrine pancreas. Previous studies have shown that the receptor plays an important role in oestradiol-stimulated insulin release [15-17]. Binding of oestradiol to GPR30 triggers calcium release and ERK and phosphatidylinositol 3-kinase activation in beta cells that leads to insulin release [17]. The importance of GPR30 in insulin secretion has been also confirmed in GPR30 knock out mice, where the absence of GPR30 induced hyperglycaemia and decreased glucose tolerance as a result of decreased insulin expression and release [16]. Moreover, it has been also demonstrated that the specific GPR30 activator, G-1 improved glucose homeostasis and metabolic abnormalities in ovariectomized or diet-induced obese mice [18]. Beside the beta cells, the presence of GPR30 has been also detected on alpha and delta cells, both in mice and human [15, 19]. Administration of G-1 inhibited glucagon and somatostatin secretion, which presumably also contributes to the regulation and maintenance of normal carbohydrate homeostasis. Protective effect of GPR30 has been also shown in streptozotocin and cytokine-induced islet apoptosis, where the survival of islet cells significantly increased due to receptor activation [19, 20]. These results indicate that oestrogen plays a beneficial role in metabolic processes, primarily through the regulation of islet hormone release.

The discovery by Jo-Watanabe et al. that the GPR30 receptor can be activated by HCO_3^- assumes that ductal cells are able to influence endocrine hormone secretion through HCO_3^- secretion. Ductal HCO_3^- secretion is a strictly regulated process, in which Cl^-/HCO_3^- exchangers and Cl^- channels, especially the cystic fibrosis transmembrane conductance regulator (CFTR), play a central role [21-23]. According to the current view, HCO_3^- accumulates in the cell via the basally located Na^+/HCO_3^- cotransporter (NBC) [24]. In HCO_3^- accumulation, the Na^+/H^+ exchange activity is also an important driving force, through which H^+ is discharged into the blood [21]. In the secretion of HCO_3^- both the exchanger and the CFTR Cl^- channel participate, but under stimulated conditions, HCO_3^- secretion is more dominant through CFTR, as a result of which up to 140 mM HCO_3^- can be secreted in guinea pigs and humans [25]. In addition to the Cl^-/HCO_3^- exchanger and CFTR, other transporters are also found on the apical membrane of intercalated ducts, such as TMEM16A (Anoctamine-1) or the large conductance Ca^{2+}-activated K^+ channel,[9, 26] which presumably also contribute to HCO_3^- secretion, by

regulating Cl^- transport or the membrane potential. Ductal HCO_3^- is secreted into the pancreatic tree then enters the duodenum where it takes part in the digestion. Consequently, this raises the question of how does HCO_3^- reach the islet cells? In the past, the exocrine and endocrine pancreas were considered independent entities, with only a structural connection between them. However, this view is now obsolete, especially since the discovery of the insulo-acinar axis. Hormones released from the islets of Langerhans reach the acinar cells directly through the insulo-acinar portal system and play essential role in the regulation of pancreatic enzyme secretion.[27] Beside the acinar cells, ductal cells can also directly interact with islets, although less data are available on the ductal-islet interactions. Bertelli et al. have identified several connection points between islet and ductal cells in the rat pancreas by immunostaining and transmission electron microscopy.[28, 29] They showed that more than 70% of the islets are associated with the ductal system. Among the islet cells some of the beta and delta cells face the ductal lumen, thereby coming into direct contact with the pancreatic juice. In contrast, alpha and pancreatic polypeptide cells were always separated from the lumen due to the cytoplasmic expansion of ductal or centroacinar cells. This ductal-islet interaction was observed in the case of smaller ducts and centroacinar cells. The connection between ducts and islet cells has also been demonstrated in the human pancreas.[30] Zhao et al. have shown that 10.9% of beta cells and 8.9% of alpha cells are connected to ducts, primarily in the distal region of the ductal tree. They also identified individual, insulin-producing beta cells located in the wall of the ducts and this finding was later confirmed by other studies also. [31-34] It is conceivable that these extra-islet insulin-producing beta cells arose from ductal cells that retained their stem cell characteristics and are able to transdifferentiate into islet cells as a result of pancreatic injury. Further evidence that beta and delta cells are directly connected to the ductal lumen is that rat, canine and human pancreatic juice contains insulin and somatostatin.[35-38] These results indicate that ductal secretion, including HCO_3^-, is able to influence the function of those islet cells that face the ductal lumen, in a paracrine manner. Since beta cells are electrically coupled via the gap junctions, the activation of a beta cell by GPR30 can spread to neighbouring cells or can activates the whole islet. Based on the electron microscopic studies, the alpha cells do not come into direct contact with the ductal lumen, however, it is possible that HCO_3^- can access the alpha cells through other mechanisms and activate them as well. During stimulated secretion, the pressure and HCO_3^- concentration in the ductal lumen increase significantly and it is conceivable, that under these conditions HCO_3^- can enter the pancreatic interstitium via a paracellular pathway, as seen in airways [39].

Our workgroup has recently shown that experimental type-1 diabetes mellitus increases fluid and HCO_3^- secretion in ductal cells [26]. The increased fluid and HCO_3^- secretion is presumably the consequence of the increased ion transporter activity, especially the CFTR Cl^- channel. The exact role of this stimulated HCO_3^- secretion during diabetes is not clear, but a recent study by Zhang et al. suggest that it plays a protective role in the disease [40]. Zhang et al. showed that HCO_3^- promotes glucose-induced insulin secretion by enhancing Ca^{2+} influx and increases intracellular pH and cAMP levels in beta cells. It has been also shown that the effect of HCO_3^- is dose-dependent. At low concentrations (ranging from 6.5 to 12.5 mM) decreased insulin secretion, whereas at high concentrations (ranging from 20 to 30 mM) HCO_3^- increased it. The authors also showed that the effect of HCO_3^- on beta cells is mediated by NBC, through which HCO_3^- enters the cell. This study indicates that ductal HCO_3^- secretion regulates insulin secretion and may represent a new therapeutic target in the treatment of diabetes.

Although Zhang et al. assumes the role of NBC in the effect of HCO_3^-, it is conceivable that HCO_3^- also activates the GPR30 receptors on beta cells, through which insulin secretion is also stimulated (**Figure 1**). Based on this, it is hypothesized that during a meal, when the concentration of HCO_3^- in the pancreatic juice increases, in addition to ensuring suitable pH conditions for digestion, HCO_3^- also regulates the release of pancreatic hormones through the activation of GPR30 that leads to increased insulin and decreased glucagon and somatostatin secretion. Insulin and glucagon oppositely regulate blood glucose levels, while somatostatin inhibits fluid and HCO_3^- secretion, suggesting that regulation of islet hormone secretion by HCO_3^- may represent an important physiological mechanism which promotes normal digestion. In terms of intracellular mechanisms, it is conceivable that the binding of HCO_3^- triggers calcium release in beta cells, similarly to oestrogen or the GPR30 agonist, G-1. Jo-Watanabe et al. also found that HCO_3^--induced GPR30 activation also increases intracellular calcium levels. Additional mechanisms probably involve different signalling pathways, such as the activation of certain kinases or an increase in cAMP levels, but further studies are needed to clarify whether GPR30 on islet cells can be activated by HCO_3^-, and if so, what is the intracellular mechanism through which the effect is exerted.

In summary, it is hypothesized that GPR30 provides a link between increased HCO_3^- secretion and the glucose-induced insulin secretion. This raises the possibility that ductal cells have a protective role not only in the neutralization of acidic pH but also in the regulation of glucose homeostasis.

This study was supported by the CF-Trust CFRD-SRC Grant (No.: SRC 007) and the National Research, Development and Innovation Office (SNN134497 to VV and K131996 to PH).

Declarations of interest: none

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FIGURE LEGEND

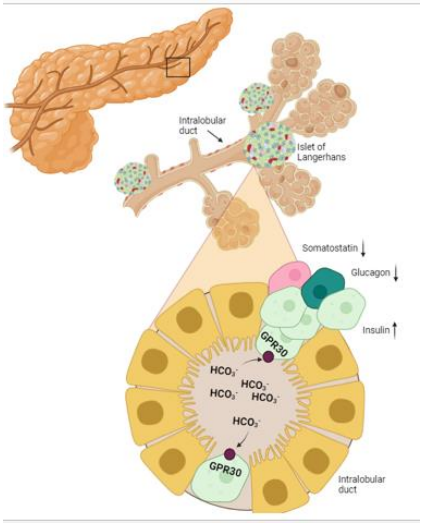
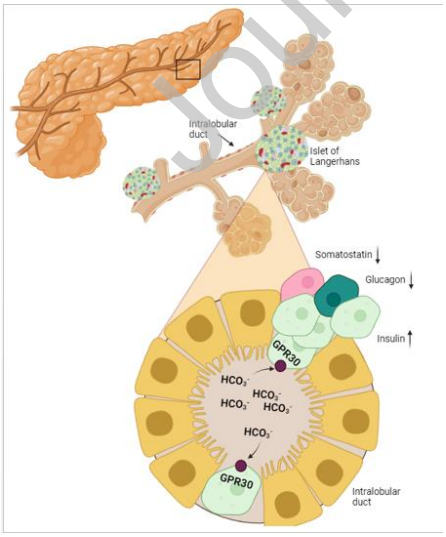


Figure 1: Hypothetical mechanism for the stimulation of islet secretion by pancreatic ductal HCO_3^- secretion. In the smaller pancreatic ducts, some islets are in direct contact with the ductal lumen, and individual beta cells also occur in the ductal wall. HCO_3^- binds to the GPR30 receptor on the surface of beta cells (light green), activates it, which probably triggers Ca^{2+} oscillations and other intracellular pathways. As a result, insulin secretion in the beta cells increases. Presumably, HCO_3^- also binds to the GPR30 receptors of alpha (dark green) and delta (pink) cells, where it causes a decrease in glucagon and somatostatin secretion.

Graphical Abstract



Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Peter Hegyi reports financial support was provided by CF-Trust. Viktoria Venglovecz reports financial support was provided by National Research Development and Innovation Office. Peter Hegyi reports a relationship with National Research Development and Innovation Office that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.