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Effects of GABA on Pancreatic Exocrine Secretion of Rats

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Since GABA and its related enzymes had been determined in β-cells of pancreas islets, effects of GABA on pancreatic exocrine secretion were investigated in the isolated perfused rat pancreas. GABA, given intra-arterially at concentrations of 3, 10, 30 and 100 μM, did not exert any influence on spontaneous or secretin (12 pM)-induced pancreatic exocrine secretion. However, GABA further elevated cholecystokinin (10 pM)-, gastrin-releasing peptide (100 pM)- or electrical field stimulation-induced pancreatic secretions of fluid and amylase, dose-dependently. The GABA-enhanced CCK-induced pancreatic secretions were completely blocked by bicuculline (10 μM), a $GABA_A$ receptor antagonist but not affected by saclofen (10 μM), a $GABA_B$ receptor antagonist. The enhancing effects of GABA (30 μM) on CCK-induced pancreatic secretions were not changed by tetrodotoxin (1 μM) but partially reduced by cyclo-(7-aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]) (10 μM), a somatostatin antagonist. In conclusion, GABA enhances pancreatic exocrine secretion induced by secretagogues, which stimulate enzyme secretion predominantly, via $GABA_A$ receptors in the rat pancreas. The enhancing effect of GABA is partially mediated by inhibition of islet somatostatin release. GABA does not modify the activity of intrapancreatic neurons.

γ-Aminobutyric acid (GABA) and its related enzymes have been detected in islet β-cells of the pancreas at a high concentration comparable to that in the brain (1, 2). High affinity binding sites of GABA have been also determined in the exocrine part of the pancreas (3). Although the secretory function of the exocrine pancreas is under influences of the endocrine pancreas via the islet-acinar axis (4, 5), an effect of GABA on pancreatic exocrine function is completely unknown at the present time. Thus, the present study was aimed to investigate if exogenous GABA affects exocrine secretion of the isolated rat pancreas.

The rat pancreas was isolated according to a method described previously (6) and perfused with modified Krebs-Henseleit solution containing 18 mM glucose at a flow rate of 1.2 mL/min. Pancreatic exocrine secretion was stimulated by intra-arterial infusions of synthetic porcine secretin (12 pM), sulfated cholecystokinin-8 (CCK; 10 pM) and porcine gastrin-releasing peptide (GRP; 100 pM) for 60 min, and by application of electrical field stimulation (EFS) with parameters of 15 V, 2 msec and 8 Hz for 45 min, respectively. GABA was added to perfusate at concentrations of 3, 10, 30 and 100 μM. Pancreatic secretions of fluid and amylase were determined by analyzing pancreatic juice collected in 15-min samples.

GABA did not exert any influence on spontaneous pancreatic exocrine secretion. As shown in Table 1 and 2, GABA did not change pancreatic secretions of fluid and amylase induced by secretin but further elevated those induced by CCK dose-dependently. The main function of secretin is water and bicarbonate secretion whereas that of CCK is enzyme secretion. Thus, we investigated whether GABA enhances pancreatic exocrine secretion evoked by secretagogues, which stimulate enzyme secretion predominantly. GABA also dose-dependently enhanced pancreatic secretions of fluid and amylase induced by GRP as well as EFS (Table 1&2). Thus, it is suggested that GABA may exert the enhancing effect on pancreatic exocrine secretion when it is evoked by secretagogues, which stimulate enzyme secretion predominantly.

It has been reported that $GABA_A$ receptors exist on pancreatic exocrine cells of the neonatal rat (3). Thus, it was confirmed that GABA exerts the enhancing effects by acting on the $GABA_A$ receptor in this study. The GABA (30 μM) effects on CCK-induced pancreatic exocrine secretion were effectively inhibited by bicuculline (10 μM), a $GABA_A$ receptor antagonist but not affected by saclofen (10 μM), a $GABA_B$ receptor antagonist (Table 3). The results indicate that GABA acts on pancreatic exocrine cells via the $GABA_A$ receptor.

It has been reported that intrapancreatic neurons play a stimulatory role in CCK-induced pancreatic exocrine secretion in the rat (7). Thus, it was investigated if intrapancreatic neurons mediated the GABA action in this

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Table 1. Effects of GABA on pancreatic fluid secretion (μL/60 min in peptides and μL/45 min in EFS) induced by various stimulants (mean±SE of 7 experiments)

	Concentrations of GABA (μM)				
	0	3	10	30	100
Secretin	15.6±1.1	15.4±1.9	16.1±1.3	16.8±2.2	15.9±1.5
CCK	24.6±1.0	26.7±1.9	34.4±2.3*	37.4±3.9*	31.6±3.0*
GRP	17.9±1.5	24.4±2.8	38.6±5.7*	34.7±3.2*	28.6±2.9*
EFS	16.2±0.5	17.2±1.4	21.7±2.0*	22.9±1.7*	25.5±1.5*

Asterisks indicate significant difference form the corresponding value without GABA

Table 2. Effects of GABA on pancreatic amylase secretion (U/60 min in peptides and U/45 min in EFS) induced by various stimulants (mean±SE of 7 experiments)

	Concentrations of GABA (μM)				
	0	3	10	30	100
Secretin	77.6±7.2	76.7±6.1	81.6±10.6	90.3±11.5	86.2±12.5
CCK	359.4±29.3	511.4±55.6*	699.0±62.7*	792.4±102.4*	661.8±45.5*
GRP	265.7±31.4	512.9±52.7*	758.1±76.6*	744.9±72.8*	573.0±40.7*
EFS	237.2±18.5	293.3±41.8	320.4±36.5*	484.1±70.6*	632.2±50.7*

Asterisks indicate significant difference form the corresponding value without GABA

Table 3. Effects of GABA antagonists on GABA (30 μM)-enhanced CCK-induced pancreatic exocrine secretion (mean±SE of 7 experiments)

	CCK+GABA		
	Control	+Bicuculline	+Saclofen
Fluid (μL/ 60 min)	37.4±3.9	23.8±1.6*	33.9±1.8
Amylase (U/60 min)	792.4±102.4	401.3±84.1*	678.6±59.3

Asterisks indicate significant difference form the corresponding value without bicuculline

Table 4. Effects of tetrodotoxin and a somatostatin antagonist on GABA (30 μM)-enhanced CCK-induced pancreatic exocrine secretion (mean±SE of 7 experiments)

	Tetrodotoxin		Somatostatin antagonist	
	CCK	CCK+GABA	CCK	CCK+GABA
Fluid (μL/ 60 min)	14.4±1.2	21.8±1.6*	29.5±1.4	35.3±1.7*
Amylase (U/60 min)	202.8±27.9	434.2±34.7*	514.7±29.6	776.7±84.7*

Asterisks indicate significant difference form the corresponding value without GABA

study. Even if intrapancreatic neuronal activity was inhibited by tetrodotoxin (1 μM), GABA still remarkably elevated the CCK-induced pancreatic exocrine secretion (Table 4). The result suggests that GABA does not modify the intrapancreatic neuronal activity to elevate CCK-induced pancreatic exocrine secretion.

It has been reported that GABA and its agonist reduce pancreatic release of somatostatin (8), which inhibits CCK-induced pancreatic exocrine secretion (9). Thus, it was also examined if GABA elevated CCK-induced pancreatic exocrine secretion by inhibiting somatostatin release. When cyclo-(7-aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]), a somatostatin antagonist (7) was infused at a concentration of 10 nM in this study, GABA still elevated the CCK-induced pancreatic exocrine secretion (Table 4) but the incremental rate was less than half of that obtained without the somatostatin antagonist. Thus, it is suggested that GABA may elevate CCK-induced pancreatic exocrine secretion, in part, by inhibition of pancreatic somatostatin release.

In conclusion, exogenous GABA enhances pancreatic exocrine secretion induced by enzyme-secreting stimulants via the $GABA_A$ receptor in the rat pancreas. The enhancing effect of GABA is also partially mediated by inhibition of pancreatic somatostatin release. GABA does not modify the activity of intrapancreatic neurons.

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