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Action of dopamine on the exocrine pancreatic secretion of the intact dog

R. Delcenserie, M.A., Devaux & H. Sarles

Unité de recherches de Pathologie Digestive, INSERM U 31, 46, Bd de la Gaye, 13009 Marseille, France

1 The effects of dopamine and domperidone, a dopamine antagonist, have been studied on the exocrine secretion of the dog pancreas. The purpose of this study was to see if dopamine acted on enzyme secretion and if its action was merely 'pharmacological' or had a physiological role.

2 Conscious Beagle dogs, fitted with Thomas cannulae were studied following infusions of dopamine 125–1000 $\mu g\,kg^{-1}\,h^{-1}$.

3 During dopamine infusion, a secretory peak lasting 10 min was observed. This was followed by a stable plateau which was approximately 1/3 of the peak. The pattern of water, bicarbonate and protein secretion was similar. The maximum effect was obtained with 500 $\mu g\,kg^{-1}\,h^{-1}$ dopamine.

4 The stimulatory action of dopamine was blocked by domperidone, without any detected effect on the central nervous system, but not by propranolol or phenoxybenzamine. Domperidone 10 $\mu g\,kg^{-1}$ almost completely suppressed the secretory response to the maximally effective dose of dopamine. This inhibition was not competitive. Atropine decreased the secretory response to dopamine.

5 The protein response was not observed when dopamine was infused against a background infusion of secretin. This suggests that the effect of dopamine on protein secretion could be due to a wash-out phenomenon.

6 The maximally effective dose of domperidone, 10 $\mu g\,kg^{-1}$, did not modify the pancreatic response to a solid meal.

7 Thus, in the non-anaesthetized dog, the effect of dopamine on water and bicarbonate secretion has been confirmed. It is concluded that dopamine had no detectable action on protein secretion and that the physiological role of dopamine with respect to pancreatic secretion is still questionable.

Introduction

Dopamine accounts for 30 to 50% of catecholamines present in the pancreas (Schümann & Heller, 1959; Furuta *et al.*, 1974). It is found in the small, intensively fluorescent fibres of the intrapancreatic nerves, ganglia and zymogen granules (Alm, 1971; Alm *et al.*, 1971; 1972). Greengard *et al.* (1942) were the first to show that dopamine stimulated pancreatic secretion of water and bicarbonate in anaesthetized dogs. This has been confirmed in the isolated, perfused pancreas (Hashimoto *et al.*, 1971; Takeuchi *et al.*, 1971; Furuta *et al.*, 1973; 1974; Iwatsuki *et al.*, 1974; 1980; Bastie *et al.*, 1977; Vaysse, 1977; Vaysse *et al.*, 1978).

Although it is clear that dopamine stimulates water and bicarbonate secretion, its action on protein secretion has been found to be weak (Furuta *et al.*, 1972) or absent (Bastie *et al.*, 1977; Vaysse, 1977; Vaysse *et al.*, 1978).

The purpose of this paper is to re-examine the effect of dopamine on the exocrine pancreatic secretion of conscious dogs in order to answer two questions. Does dopamine act on protein secretion? Does dopamine play a role in the physiological regulation of pancreatic secretion? A summary of a part of this work has already been published (Delcenserie *et al.*, 1982).

Methods

Animal model

Eight Beagle dogs weighing 15 to 25 kg, fed a standard diet (Frolic Unisabi, 45520 St Denis de l'Hotel), were

prepared with gastric and duodenal Thomas cannulae under fluothane anaesthesia. The accessory pancreatic duct was ligated.

Treatment of animals

During the experiments, pancreatic juice was collected in 10 min fractions using a Scott cannula inserted into the main pancreatic duct. The gastric cannula was kept open. Drugs were infused into the dogs via catheters inserted into different leg veins. The experiments terminated after 2 h of stimulation.

In certain cases solid meal consisting of 450 g of a proprietary dog food (U.A.R., 91360 Villemoisson sur Orge, France), containing a mixture of beef and pork meat, cereals, vegetables, minerals and vitamins, was given. In such situations only, the gastric cannula was closed.

Animals were never studied before four months after surgery. Experiments were performed no more than twice a week, in conscious animals, fasted for 18 h and standing in Pavlov harnesses. After each experiment, a supplement of meat was given.

Each test was performed once in each dog.

Chemical determinations

Volumes were read to the nearest 0.1 ml. Bicarbonate concentration was determined by back titration to pH 7.0 with 0.2 M NaOH solution using automatic titration (TAT-5, Tacussel) of added 0.1 M HCl. Protein concentration was determined, after appropriate dilution, by absorbance at 280 nm using the coefficient E 1%/1 cm = 20 (Holochrom photometer Gibson, Middleton, Wisc.).

From these different parameters, outputs were then calculated. Results were expressed as ml (volume), μEq (HCO_3), mg (protein) per 10 min.

Statistical analysis

Student's t test for paired values was used, comparing one experiment with dopamine infusion to a similar control experiment with saline. Differences were regarded as significant if $P < 0.05$. Results are presented as means ± s.e.mean.

Drugs

The following drugs were used: dopamine (Laboratoire Pierre Fabre, Paris); domperidone (R 33813) (Laboratoire Janssen-Le Brun, Paris); propranolol (Avlocardyl) (Laboratoire ICI Pharma, Reims, France) 0.25 mg kg^{-1} h^{-1}; phenoxybenzamine hydrochloride (Dibenyline; Laboratoires SKF, Paris) 0.20 mg kg^{-1} h^{-1}; atropine sulphate (Laboratoire Aguettant, Lyon 7, France) 20 μg kg^{-1} h^{-1}; secretin (Kabivitrum S.A., France). Domperidone was injected intravenously. All of the drugs were dissolved in saline solution and infused by peristaltic pump (100 ml h^{-1}).

Results

Action of dopamine

In 5 dogs, dopamine was infused over a period of two hours at different doses chosen in a random order: 125, 250, 375, 500 and 1000 μg kg^{-1} h^{-1}, diluted in saline.

Water and bicarbonate secretion started 30–60 s after beginning the 500 μg kg^{-1} h^{-1} infusion. There was an initial secretory peak, lasting approximately 10 min, which was followed by a progressive decrease, leading to a stable plateau; the latter represented approximately 1/3 of the peak value, and lasted as long as the infusion continued (Figure 1).

Increasing doses of dopamine produced a progressive increase in water and bicarbonate secretion during the first 30 min of infusion, the maximum effect being achieved with 500 μg kg^{-1} h^{-1} (Figure 2). The dose 1000 μg kg^{-1} h^{-1} was characterized by a decrease which produced approximately the same effect as 250 μg kg^{-1} h^{-1}, i.e. 1/3 of the maximum effect. Linearisation of the response was not possible but the ED_{50} was estimated to be 320 μg kg^{-1} h^{-1}.

The effect of dopamine on protein secretion was similar to that on water and bicarbonate. Prolonged infusion of 500 μg kg^{-1} h^{-1} dopamine led to a secretory peak during the first 10 min of infusion, followed by a stable secretory plateau representing

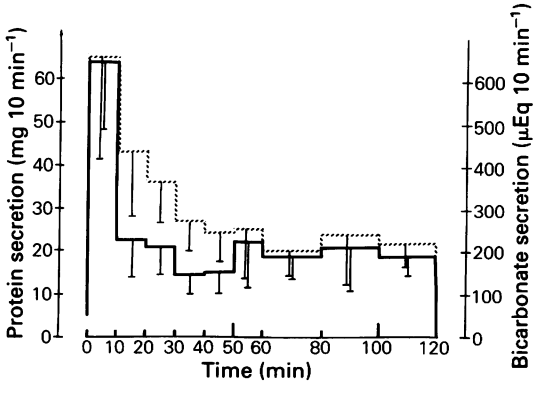

Figure 1 Effect of dopamine (500 μg kg^{-1} h^{-1} for 120 min) on pancreatic bicarbonate (broken line) and protein (solid line) secretion. The stimulatory response to dopamine was immediate but subsequently became less after the initial 10 min period. Results are expressed as means with vertical bars showing s.e.mean (n = 5 dogs).

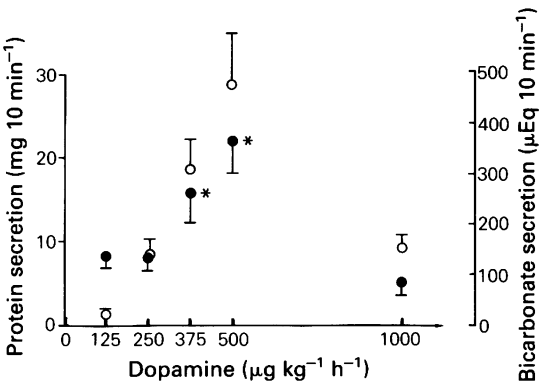

Figure 2 Dose-response curve for the effect of dopamine on bicarbonate (○) and protein (●) secretion. Each point represents the cumulative response over the first 30 min period of stimulation. $*P < 0.05$, significantly different from the plateau response to dopamine 375 and 500 $\mu g\,kg^{-1}\,h^{-1}$. Results are expressed as means, with vertical lines representing s.e.mean ($n = 5$ dogs).

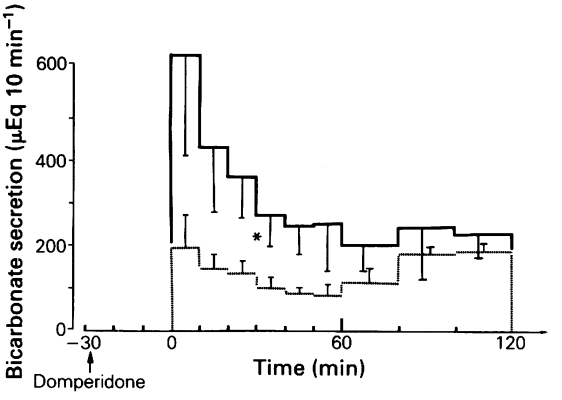

Figure 3 Effect of domperidone (100 $\mu g\,kg^{-1}$, injected on dopamine stimulated bicarbonate secretion 30 min before the dopamine infusion of 500 $\mu g\,kg^{-1}\,h^{-1}$ for 120 min). In the presence of domperidone (broken line) the cumulative values of bicarbonate output were decreased significantly within the first 60 min. $*P < 0.05$, Student's t test for paired values. Results are expressed as means with vertical bars showing s.e.mean ($n = 5$ dogs). The solid line represents dopamine-stimulated bicarbonate secretion in the absence of domperidone.

approximately 1/4 of the peak (Figure 1). There was no significant response to the effect of the two first doses, 125 and 250 $\mu g\,kg^{-1}\,h^{-1}$, but protein secretion was significantly increased by 375 and 500 $\mu g\,kg^{-1}\,h^{-1}$ (Figure 2). As for water and bicarbonate output, protein secretion was less following 1000 $\mu g\,kg^{-1}\,h^{-1}$. This supramaximal inhibition was stronger than for water and bicarbonate, the observed values being of the same order as the basal secretion of approximately 8 mg 10 min^{-1}. The estimated ED_{50} was approximately 350 $\mu g\,kg^{-1}\,h^{-1}$ and the maximum effective dose 500 $\mu g\,kg^{-1}\,h^{-1}$.

Dose-response to domperidone after infusion of dopamine

In order to determine a dose-response relationship to domperidone, a dopamine antagonist (Laduron & Lexsen, 1979; Solokoff *et al.*, 1980; Chevrel, 1981), dopamine was injected intravenously into 5 dogs at various doses (2.5, 5, 10 and 100 $\mu g\,kg^{-1}$) 30 min before a 2 h infusion of 500 $\mu g\,kg^{-1}\,h^{-1}$ dopamine as previously described. This dose was chosen because it was the most effective for water, bicarbonate and protein secretion.

When domperidone was injected 30 min before the infusion of 500 $\mu g\,kg^{-1}\,h^{-1}$ dopamine, there was a significant decrease of both peak and plateau water and bicarbonate secretion ($P < 0.05$) (Figure 3). This inhibitory effect of domperidone on water and bicarbonate output remained unchanged for approximately 80 min and then progressively disappeared.

The relationship between the dose of domperidone and the water and bicarbonate secretion response to 500 $\mu g\,kg^{-1}\,h^{-1}$ dopamine showed that the maximum inhibition was obtained with 10 $\mu g\,kg^{-1}$ domperidone. This inhibition represented 90% of water and 95% of bicarbonate secretion following stimulation by dopamine. Inhibition was significant for all doses of domperidone (Figure 5). The ED_{50} of domperidone calculated according to Hofstee (1952) was 1.44 $\mu g\,kg^{-1}$.

Protein output was also significantly inhibited ($P < 0.02$) when domperidone was injected 30 min before 500 $\mu g\,kg^{-1}\,h^{-1}$ dopamine (Figure 4). The maximum inhibition was observed with 100 $\mu g\,kg^{-1}$ domperidone (Figure 5). The ED_{50}, calculated according to Hofstee, was 0.7 $\mu g\,kg^{-1}$. Though lower, this was probably not significantly different from the ED_{50} for bicarbonate and water secretion.

Dose-response to dopamine after an injection of domperidone

The dose-response relationship for dopamine after an injection of domperidone was studied in 5 dogs (Figure 6). A submaximal dose (2.5 $\mu g\,kg^{-1}$) of domperidone was injected 30 min before starting a two hour infusion of different doses of dopamine (250, 375, 500 and 750 $\mu g\,kg^{-1}\,h^{-1}$). The dose-response curve to dopamine showed the same pattern in the absence and

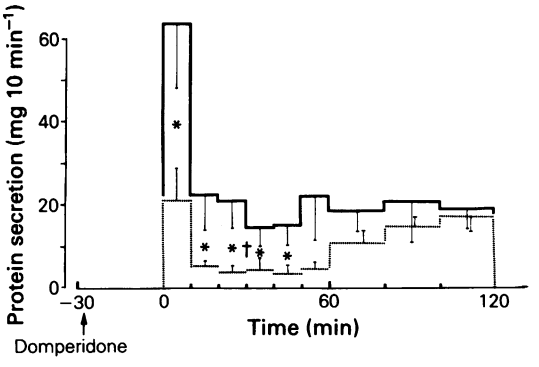

Figure 4 Effect of domperidone, $100\,\mu g\,kg^{-1}$, on dopamine-stimulated protein output. Domperidone was injected 30 min before the dopamine infusion of $500\,\mu g\,kg^{-1}\,h^{-1}$ for 120 min. During the first 50 min of dopamine infusion, protein output was significantly decreased in the presence of domperidone (broken line). $*P<0.05$ for each 10 min value. $\dagger P<0.02$ for cumulative values within the first 60 min. Results are means with vertical bars showing s.e.mean ($n = 5$ dogs). The solid line represents dopamine-stimulated protein secretion in the absence of domperidone.

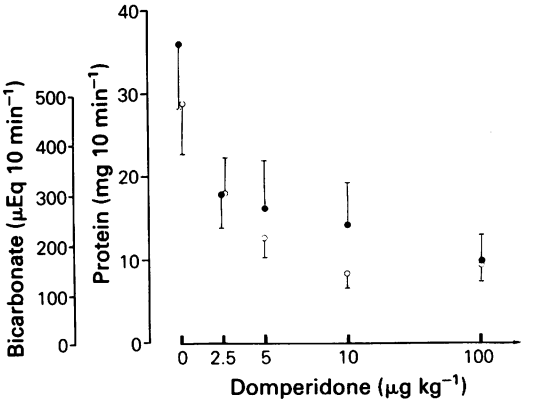

Figure 5 Dose-response curve for the effect of domperidone on dopamine-($500\,\mu g\,kg^{-1}\,h^{-1}$) stimulated bicarbonate (○) and protein (●) outputs. Each point represents cumulative values over the first 30 min periods of domperidone injection. Domperidone progressively decreased both bicarbonate and protein outputs, maximum inhibition being obtained with $10\,\mu g\,kg^{-1}$ for bicarbonate output and $100\,\mu g\,kg^{-1}$ for protein output. Results are means with vertical lines representing s.e.mean ($n = 5$ dogs).

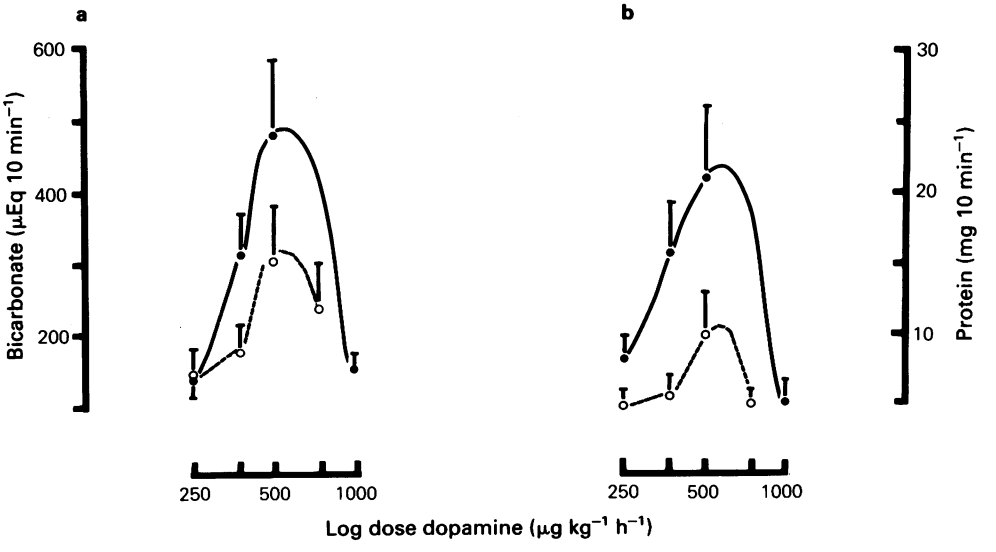

Figure 6 Inhibition of dopamine stimulated pancreatic secretion of (a) bicarbonate and (b) protein by a low dose of domperidone ($2.5\,\mu g\,kg^{-1}$). (●—●): Control (dopamine alone); (○---○): dopamine in the presence of domperidone. Each point represents the cumulative value over the first 30 min. Results are means with vertical lines representing s.e.means ($n = 5$ dogs).

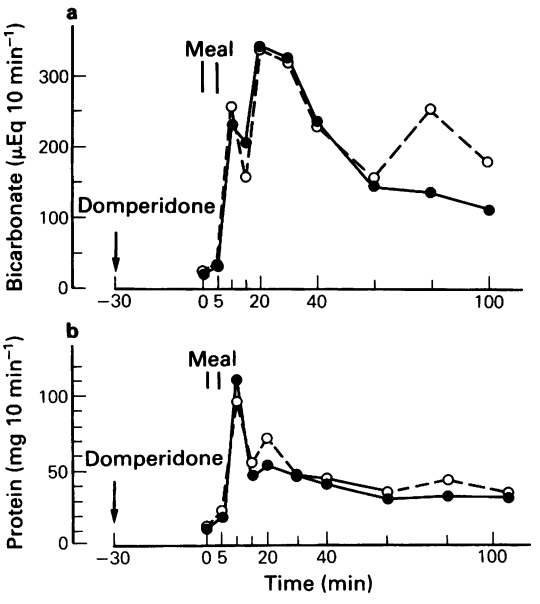

Figure 7 Postprandial secretion of (a) bicarbonate and (b) protein output in the absence (●—●) and presence (O---O) of domperidone (10 μg kg^{-1}) demonstrates that domperidone has no effect on pancreatic exocrine secretion.

presence of the antagonist. In each case the maximum stimulation was observed with 500 μg kg^{-1} h^{-1}, followed by a sharp decrease with 750 μg kg^{-1} h^{-1}. There was a marked inhibition of the water and bicarbonate response. Inhibition was even more obvious for the protein response (20% of the control response in the absence of domperidone). Domperidone decreased the apparent maximal response to dopamine but not the estimated ED_{50}.

Action of domperidone on the pancreatic response to a normal meal

Domperidone 10 μg kg^{-1}, considered to be the maximally effective secretion dose, for bicarbonate secretion and near maximal dose for protein secretion, was injected intravenously in 5 dogs before a solid meal. Neither the flow, bicarbonate nor protein outputs were significantly depressed in response to a meal (Figure 7).

Effect of an α-adrenoceptor antagonist on the response to dopamine

After 80 min of basal secretion, phenoxybenzamine (0.20 mg kg^{-1} h^{-1}), an α-adrenoceptor blocking drug was infused throughout the 2 h test period in 8 dogs. One hour after starting the phenoxybenzamine infusion, 500 μg kg^{-1} h^{-1} dopamine was infused through another vein. The immediate stimulation of volume and bicarbonate response by dopamine was observed in the presence of phenoxybenzamine (Figure 8) but the secondary decrease after the initial secretory peak was no longer observed and secretion was sustained. The cumulative response of protein secretion at 60 min was significantly increased by dopamine plus phenoxybenzamine compared to controls in the absence of dopamine (Figure 9a).

Effect of a β-adrenoceptor antagonist on the response to dopamine

Propranolol (0.25 mg kg^{-1} h^{-1}), a β-adrenoceptor blocker, was infused following a similar protocol to that used for phenoxybenzamine ($n = 8$ dogs). The immediate response to dopamine was not modified. The delayed decrease of the response to dopamine was less evident than with dopamine alone (Figures 8 and 9b).

Effect of atropine on the response to dopamine

Atropine (20 μg kg^{-1} h^{-1}) was infused into 6 dogs using a similar protocol to that described for phenoxybenzamine. No basal secretion was observed with

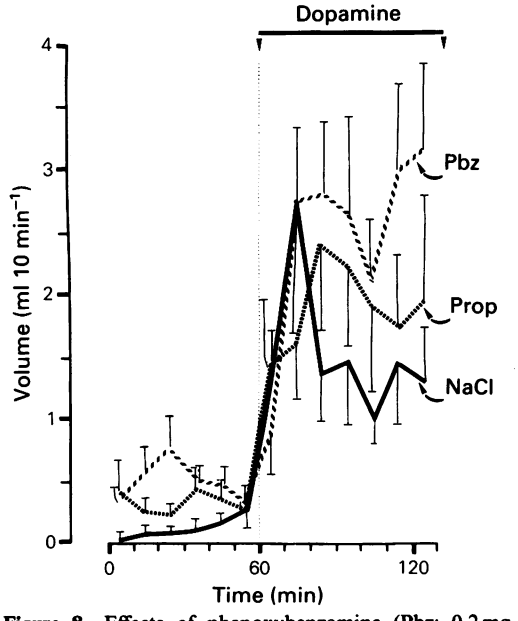

Figure 8 Effects of phenoxybenzamine (Pbz; 0.2 mg kg^{-1} h^{-1}) and propranolol (Prop; 0.25 mg kg^{-1} h^{-1}) on pancreatic secretion before (0–60 min) and during (60–120 min) an infusion of dopamine (500 μg kg^{-1} h^{-1}). NaCl = NaCl infusion as control.

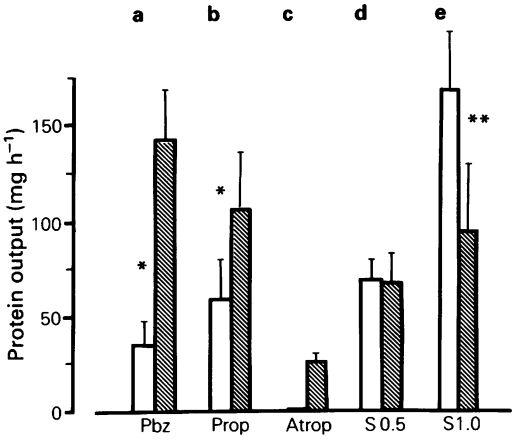

Figure 9 A comparison of the cumulative values for protein secretion at 1 h in the absence (open columns) and presence (shaded columns) of an infusion of dopamine ($500\,\mu g\,kg^{-1}\,h^{-1}$) during various drug infusions. (a) Pbz phenoxybenzamine ($0.20\,mg\,kg^{-1}\,h^{-1}$). (b) Prop, propranolol ($0.25\,mg\,kg^{-1}\,h^{-1}$). (c) Atrop, atropine ($20\,\mu g\,kg^{-1}\,h^{-1}$). (d) S 0.5, secretin ($0.5\,Cu\,kg^{-1}\,h^{-1}$). (e) S 1.0, secretin ($1.0\,Cu\,kg^{-1}\,h^{-1}$). Values are means with vertical bars representing s.e.mean.

atropine alone (control experiment). The response of volume bicarbonate and protein secretion to dopamine was decreased by atropine (Figure 9c).

Effect of dopamine on a prolonged secretin infusion

To determine that the protein response to dopamine was not due to a wash-out of preformed protein secretion, dopamine $500\,\mu g\,kg^{-1}\,h^{-1}$ was infused ($n = 5$ dogs) for 90 min after starting the secretin infusion of either $0.5\,Cu\,kg^{-1}\,h^{-1}$ or $1.0\,Cu\,kg^{-1}\,h^{-1}$, by which time a constant stable secretory plateau had been obtained. With $0.5\,Cu\,kg^{-1}\,h^{-1}$ secretin, dopamine significantly stimulated the secretion of fluid and bicarbonate but had no action on protein secretion (Figure 9d). With $1.0\,Cu\,kg^{-1}\,h^{-1}$ secretin, the stimulation of fluid and bicarbonate secretion was not significant but the protein output was significantly inhibited ($P < 0.05$) (Figure 9e).

Discussion

This is the first time that the effect of dopamine and its antagonist domperidone on the exocrine pancreatic secretion following a meal in the conscious dog has been studied. This has been made possible by the finding that this antagonist does not cross the meningeal barrier and therefore has no central action (Laduron & Lexsen, 1979).

Effect of dopamine on water and bicarbonate secretion

Our study confirmed that, in the intact dog, the secretory action of dopamine on pancreatic duct cells is dose-dependent. This effect is apparently maximal with $500\,\mu g\,kg^{-1}\,h^{-1}$ dopamine, 50% maximum being produced by $320\,\mu g\,kg^{-1}\,h^{-1}$. The supramaximal response to $1000\,\mu g\,kg^{-1}\,h^{-1}$ was approximately 30% of the maximum response observed. The effect of $500\,\mu g\,kg^{-1}\,h^{-1}$ was not sustained; an initial 10 min peak was followed by a stable plateau, representing approximately 1/3 of the peak value.

That dopamine acted preferentially on a specific receptor and not on α-and β-adrenoceptors is supported by the observation that domperidone, a specific dopamine antagonist, inhibited almost completely the response to dopamine while, in contrast, phenoxybenzamine, an α-adrenoceptor antagonist and propranolol, a β-adrenoceptor antagonist, did not inhibit the stimulatory effect of dopamine. The action of domperidone on dopamine secretion was not competitive; the maximum effect was decreased but the ED_{50} was not modified.

Singer *et al.* (1981) have shown that basal cholinergic activity potentiated the effect of secretin on bicarbonate secretion. As atropine reduced the action of dopamine, as well as the action of secretin, it is probable that acetylcholine potentiates the effect of dopamine.

Effect of dopamine on protein secretion

Dopamine stimulated the pancreatic protein secretion of the dog in parallel with that of water and bicarbonate. The strict parallelism between the effect of dopamine and drugs on ecbolic and hydrelatic secretions suggests that the protein response could be due to a wash-out by fluid. Indeed, dopamine lost its effect on protein output when a prolonged secretin infusion ($0.5\,cu\,kg^{-1}\,h^{-1}$) was started 90 min before dopamine. When $1.0\,Cu\,kg^{-1}\,h^{-1}$ secretin was infused, the action of dopamine was reversed and pancreatic protein secretion inhibited. This could have been due to suppression of the vasodilatation of pancreatic vessels induced by secretin (Iwatsuki *et al.*, 1974). High doses of dopamine are known to act on α- and β-adrenoceptors (Bastié *et al.*, 1977; Vaysse, 1977). Another possibility is that supramaximal inhibition occurred due to the summation of the effect of a maximal dose of dopamine and a submaximal dose of secretin.

Physiological significance of the pancreatic secretory response to dopamine

Domperidone, which almost completely blocked the effect of dopamine, did not significantly modify the secretory response to a normal, solid meal. However, a

physiological involvement of dopamine has yet to be established.

The mechanism of dopamine action on the pancreas is not known. Case & Scratcherd (1972) were the first to show that adenosine 3′:5′-cyclic monophosphate (cyclic AMP) is the second messenger for the action of secretin on pancreatic water and bicarbonate secretion. Since the type of dopamine receptor which stimulates cyclic AMP is a D_1-receptor (Kebalian & Calne, 1979) it is possible that the action of dopamine on water and bicarbonate secretion is mediated by the D_1- subclass of dopamine receptors.

The biphasic action of dopamine could be due to an immediate effect on the pancreatic cell dopamine receptors followed by vasoconstriction due to a non-specific effect mediated by α- and β-adrenoceptors, as indicated by the finding that this delayed inhibition disappeared when phenoxybenzamine was given and was less evident in the presence of propranolol (Iwatsuki *et al.*, 1974; Bastié *et al.*, 1977).

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