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Extraction of Epinephrine and Norepinephrine by the Dog Pancreas in Vivo

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This study determined the fractional extraction of epinephrine and norepinephrine by the in situ dog pancreas. Plasma samples for epinephrine measurements were taken simultaneously from the femoral artery and the superior pancreaticoduodenal vein. Pancreatic extraction of epinephrine was 73 ± 5% when basal arterial epinephrine levels were 380 ± 93 pg/mL, 76 ± 4% when arterial levels were 896 ± 123 pg/mL (epinephrine infused intravenously at 20 ng/kg/min), and 84 ± 1% when arterial levels were 2,956 ± 414 pg/mL (epinephrine infused intravenously at 80 ng/kg/min) suggesting that the process of epinephrine extraction by the pancreas is not saturable over this range. During a similar sampling protocol, norepinephrine was infused intravenously at 4 μg/kg/min; pancreatic extraction of norepinephrine was then 65 ± 7% when arterial norepinephrine levels were 107,000 ± 28,000 pg/mL. In separate experiments, lower rates of norepinephrine (12 to 1,200 ng/min) were infused directly into the pancreatic artery and pancreatic norepinephrine extraction was calculated; it ranged between 66% and 75%. Because the pancreas produces as well as extracts norepinephrine, a third technique was required to determine pancreatic norepinephrine extraction at the lower endogenous levels of norepinephrine; ^{3}H-norepinephrine was infused intravenously and the arteriovenous difference of ^{3}H-norepinephrine was measured. Fractional extraction of ^{3}H-norepinephrine was 74 ± 4% both in the basal state (arterial norepinephrine level = 202 ± 44 pg/mL) and during systemic, glucopenic, stress induced by 2-deoxy-glucose (arterial norepinephrine level = 636 ± 70 pg/mL). These data suggest that also the norepinephrine extraction process by the pancreas is not sarurable. Further, since the pancreatic extraction of norepinephrine is so avid, these data suggest that measurement of the arteriovenous concentration difference of endogenous norepinephrine alone will markedly underestimate local norepinephrine spillover. Correcting these measurements for the extraction would, however, provide an index of the endogenous activity of pancreatic adrenergic nerves. Finally, this study also determined whether pancreatic catecholamine extraction is altered by α-or β-adrenoceptor antagonists; phenoxybenzamine was found to reduce the extraction of both epinephrine ($P < .001$) and norepinephrine ($P < .05$) whereas propranolol did not. Thus, one must consider how changes of pancreatic catecholamine extraction might alter the interpretation of experiments using α-adrenoceptor antagonists to study local norepinephrine release or catecholamine effects on pancreatic hormone secretion. In summary, (1) at steady state 60% to 80% of either epinephrine or norepinephrine is extracted in one pass by the dog pancreas, (2) this process of extraction appears nonsaturable, and (3) the pancreatic extraction of catecholamines is impaired by the α-adrenoceptor antagonist phenoxybenzamine, but not by the β-adrenoceptor antagonist propranolol.

CATECHOLAMINES are known to influence islet function,[1-3] yet little is known about their pancreatic metabolism. However, a correct interpretation of studies on catecholamine effects requires a knowledge on pancreatic catecholamine metabolism. For example, knowledge of the fractional extraction of epinephrine by the pancreas would indicate how well pancreatic venous levels reflect the concentration of circulating epinephrine to which the islets are exposed. Further, determination of the fractional rate of norepinephrine extraction would allow a better estimation of the endogenous activity of the noradrenergic nerves within the pancreas. Finally, if autonomic antagonists affect pancreatic catecholamine extraction, then the interpretation of the mechanism of their effects on pancreatic hormone secretion and local adrenergic activity could change significantly.

From studies in various other tissues it is apparent that catecholamine extraction is substantial and occurs by at least two different mechanisms: the uptake$_1$ mechanism, involving adrenergic nerve terminals; and the uptake$_2$ mechanism, involving extraneuronal cells.[4-7] The degree of catecholamine extraction seems, however, to vary between tissues[8-15] as may the mechanisms regulating catecholamine extraction. For example, in response to β-adrenoceptor antagonism, the uptake$_2$ mechanism is increased in salivary gland slices but decreased in heart tissue.[16-18] α-Adrenoceptor antagonists also influence catecholamine extraction, and phenoxybenzamine has been reported to block both uptake$_1$ and uptake$_2$ mechanisms in vitro.[16-18] Therefore, we studied the dog pancreas to determine its fractional extraction rate of epinephrine and norepinephrine and the effects of autonomic antagonists thereon. To determine the rate of epinephrine extraction by the pancreas, we measured the arteriovenous concentration difference of epinephrine across the pancreas in the basal state and during low and high rates of intravenous epinephrine infusion. Determination of the rate of norepinephrine extraction is more complicated because adrenergic nerves within the pancreas can release norepinephrine. Thus, pancreatic norepinephrine extraction was determined using rates of intravenous or pancreatic intraarterial norepinephrine infusions that far exceeded the rate of pancreatic norepinephrine production. Finally, to calculate pancreatic norepinephrine extraction during the basal state,

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^{3}H-norepinephrine was infused intravenously and the arteriovenous concentration difference of ^{3}H-norepinephrine was measured.

MATERIALS AND METHODS

Animals and Surgical Procedures

Adult dogs of mixed breed, weighing 24 to 36 kg, were used. They were fasted for 18 hours before the experiments. The experiments were carried out under either pentobarbital or halothane (0.8%)/oxygen or halothane (0.8%)/nitrous oxide (70%)/oxygen (30%) anesthesia. A midline laparotomy was performed to gain access to the superior pancreaticoduodenal vein (SPDV). Blood was routed from SPDV via a silastic catheter through an electromagnetic flowmeter, past a sampling port, and then into the portal vein. The circuit allowed blood flow to be measured continuously and SPDV blood to be sampled intermittently. In addition, the femoral artery and vein were cannulated for blood sampling and for intravenous infusions, respectively. In one experimental series, the superior pancreatic artery was isolated and a 22-gauge teflon cannula was inserted. The catheter, which did not affect the pancreatic blood flow, was then connected to an infusion pump delivering a saline infusion (0.9 mL/min). All experiments were performed one hour after these surgical procedures.

Experimental Protocols

Five different experimental series were performed:

1. In the first experimental series, the pancreatic extraction of epinephrine was studied. Epinephrine (Park-Davis, Morris Plains, NJ) was infused intravenously at 20 ng/kg/min or 80 ng/kg/min for 40 minutes.

2. In the second experimental series, the influences of adrenergic blockade on the pancreatic fractional extraction rate of epinephrine were studied. Dogs were, therefore, treated with the α-adrenoceptor antagonist phenoxybenzamine (SK & F Laboratories Ltd, Welwyn Garden City, Hertfordshire, England), which was infused into the pancreatic artery at 100 μg/min or the β-adrenoceptor antagonist propranolol (ICI Ltd, Macclesfield, England), which was infused into the pancreatic artery at 2.4 μg/min.

3. In the third experimental series, the pancreatic extraction of norepinephrine was studied. Norepinephrine bitartrate (Breon Laboratories Inc, New York) was infused into the pancreatic artery at three different doses (12, 120, and 1,200 ng/min) at a volume rate of 0.9 mL/min.

4. In the fourth experimental series, the influences of α- and β-adrenoceptor blockade on the pancreatic extraction of norepinephrine were studied. Norepinephrine bitartrate was infused intravenously (1 or 4 μg/kg/min) alone or together with phenoxybenzamine and/or propranolol. Phenoxybenzamine was given as an intravenous injection of 2.5 mg/kg followed by infusion of 50 μg/kg/min, and propranolol was given as an intravenous injection of 300 μg/kg followed by an infusion of 5 μg/kg/min. The infusions of adrenoceptor blockers were started 15 minutes before the norepinephrine infusion and continued during it.

5. In the fifth experimental series, the pancreatic fractional extraction rate of norepinephrine at low circulating levels of norepinephrine was studied. ^{3}H-Norepinephrine (specific activity 47.7 Ci/mmol, New England Nuclear) was therefore injected intravenously at the dose of 30 μCi followed by an intravenous infusion at 1.2 μCi/min. After 45 min of infusion, 2-deoxy-glucose (Sigma Chemical Co, St Louis) was injected intravenously at 600 mg/kg followed by infusion at 13.56 μg/kg/min. The infusion of ^{3}H-norepinephrine continued throughout.

Assays and Data Analysis

Blood was taken in tubes containing EGTA and glutathione, placed on ice, and centrifuged at 4°C after the end of the experiments. Plasma was separated and frozen at −20°C until assay. Epinephrine and norepinephrine were measured using a single-isotope radioenzymatic assay.[19] In the experimental series where the catecholamines were infused intravenously, the pancreatic extraction of epinephrine and norepinephrine was calculated by dividing the pancreatic arteriovenous plasma concentration differences by the arterial plasma levels. In the experimental series employing pancreatic arterial infusions of norepinephrine, the amount of arterially infused norepinephrine escaping pancreatic extraction was calculated by multiplying the pancreatic venous level of norepinephrine by the plasma flow. Since the rate of arterial infusion of norepinephrine was known, the extraction of norepinephrine was calculated by subtracting the difference between the output before and during norepinephrine infusion from the infused rate of norepinephrine divided by the rate infused. In the experimental series with intravenous infusion of ^{3}H-norepinephrine, intact ^{3}H-norepinephrine was separated from its metabolites in plasma using an alumina extraction procedure. Thereafter, the concentration of plasma ^{3}H-norepinephrine was determined by liquid scintillation counting of radiolabeled norepinephrine. The pancreatic fractional extraction rate was calculated by dividing the pancreatic arteriovenous differences of radioactivity by the arterial level.

Statistics

The data is reported as mean ±SEM. Statistical comparisons of means between groups were made with Student's nonpaired t-test and within a group with Student's paired t-test. For calculating correlations between arteriovenous concentration differences and arterial levels, linear regression analysis was performed.

RESULTS

Pancreatic Extraction of Epinephrine

The pancreatic extraction of epinephrine was calculated in the basal state and during the intravenous infusion of epinephrine at 2 different doses (n = 4). Before the infusions, the arterial levels of epinephrine were 380 ± 93 pg/mL; pancreatic venous levels of epinephrine were 88 ± 9 pg/mL (Fig 1A). 73 ± 5% of arterial epinephrine was extracted by

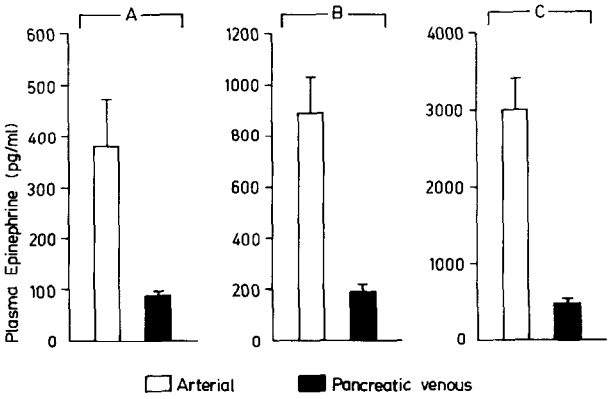

Fig 1. Arterial and pancreatic venous levels of epinephrine in dogs in the basal state (A) (n = 4), and during intravenous infusion of epinephrine at 20 ng/kg/min (B) (n = 4) or 80 ng/kg/min (C) (n = 4). Mean ±SEM is given. Note different scales on the *Y*-axis.

the pancreas in the basal state. During infusion of epinephrine at a dose of 20 ng/kg/min, arterial epinephrine levels increased to 896 ± 133 pg/mL and pancreatic venous levels increased to 193 ± 22 pg/mL (Fig 1B). The mean extraction rate in the pancreas was unchanged at 76 ± 4%. During infusion of epinephrine at a dose of 80 ng/kg/min, arterial epinephrine levels increased to 2,956 ± 414 pg/mL. Pancreatic venous levels of epinephrine were 461 ± 84 pg/mL (Fig 1C). The degree of pancreatic extraction of epinephrine during this high dose infusion of epinephrine was 84 ± 1%.

Figure 2 shows the relationship between arterial epinephrine level and the arterio-venous concentration difference of epinephrine across the pancreas. The close correlation ($r = +.998$, $P < .001$) over the wide range of arterial epinephrine levels suggests an unsaturable extraction process.

Influence of α and β-Adrenoceptor Antagonists on the Pancreatic Extraction of Epinephrine

α-Adrenoceptor Antagonist: Phenoxybenzamine. The α-adrenoceptor antagonist phenoxybenzamine was infused directly into the pancreatic artery at 100 μg/min (n = 19) (Fig 3A). Before the infusion, femoral arterial levels of epinephrine were 267 ± 56 pg/mL and pancreatic venous epinephrine concentrations were 90 ± 14 pg/mL. The pancreatic extraction of epinephrine in these dogs was 58 ± 5%. After 20 minutes of phenoxybenzamine infusion, pancreatic venous levels of epinephrine had increased to 188 ± 32 pg/mL, ie, by 98 ± 21 pg/mL ($P < .001$), but the arterial levels of epinephrine did not change significantly, being 305 ± 70 pg/mL. The pancreatic extraction of epinephrine during infusion of phenoxybenzamine was therefore decreased to 23 ± 4% ($P < .001$).

β-Adrenoceptor Antagonist: Propranolol. The β-adrenoceptor antagonist propranolol was infused into the pancreatic artery at 2.4 μg/min (n = 10) (Fig 3B). Before the infusion, arterial levels of epinephrine were 358 ± 90 pg/mL, pancreatic venous levels were 104 ± 18 pg/mL, and pancreatic extraction of epinephrine was 67 ± 4%. After 20 minutes of pancreatic propranolol infusion, the arterial epinephrine levels were 326 ± 87 pg/mL, the pancreatic venous levels were 78 ± 18 pg/mL, and the pancreatic extraction of epinephrine was 74 ± 3%. This value was not significantly different from before propranolol infusion.

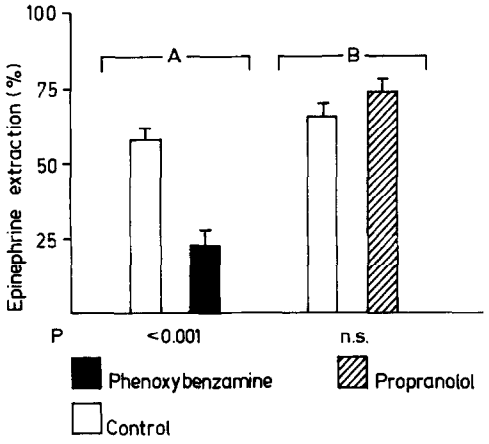

Fig 3. Fractional extraction of epinephrine in the dog pancreas before and during pancreatic arterial infusion of phenoxybenzamine (A) (n = 19) or propranolol (B) (n = 10). Mean ± SEM is given. *P* indicates the significant levels.

Pancreatic Extraction of Norepinephrine

Norepinephrine was infused into the pancreatic artery at three different rates (Fig 4). During a ten-minute infusion of norepinephrine at the low dose of 12 ng/min (n = 6), pancreatic output of norepinephrine increased by only 3.3 ± 0.6 ng/min. Thus, of the 12 ng/min infused, 8.7 ng/min was extracted by the pancreas. The exact fractional extraction rate was 75 ± 7%. During pancreatic infusion of norepinephrine at 120 ng/min (n = 6), the pancreatic output of norepinephrine increased by only 38 ± 17 ng/min. The pancreatic extraction of norepinephrine was again 75 ± 9%. During

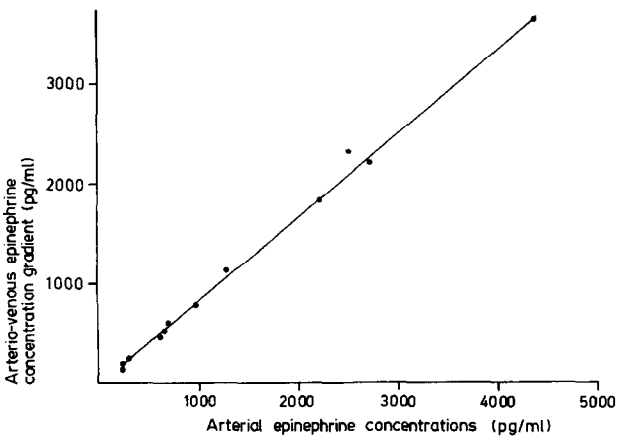

Fig 2. Correlation between the arterial plasma epinephrine levels and the arteriovenous concentration gradient of epinephrine across the dog pancreas in the basal state and during intravenous infusion of epinephrine at 20 ng/kg/min or 80 ng/kg/min (n = 4).

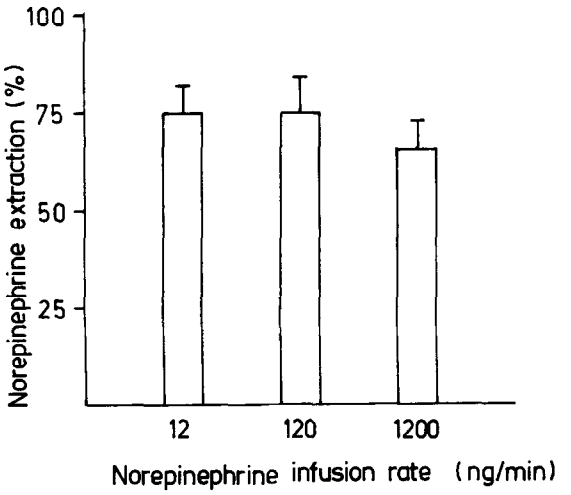

Fig 4. Fractional extraction of norepinephrine in the dog pancreas during infusion into the pancreatic artery of norepinephrine at either 12 ng/min (n = 6), 120 ng/min (n = 6), or 1,200 ng/min (n = 6). Mean ±SEM is given.

infusion of norepinephrine at 1,200 ng/min (n = 6), pancreatic output of norepinephrine increased by 407 ± 76 ng/min. The pancreatic extraction of the infused norepinephrine was 66 ± 7%, not significantly different from the extraction rates at the 2 lower doses of norepinephrine infusion.

Influence of α- and β-Adrenoceptor Antagonists on the Pancreatic Extraction of Norepinephrine

Infusion of norepinephrine intravenously at 4 μg/kg/min (n = 8) increased the arterial levels of norepinephrine from 0.12 ± 0.03 ng/ml to 107 ± 28 ng/mL and increased the pancreatic venous levels of norepinephrine from 0.08 ± 0.02 ng/mL to 42 ± 12 ng/mL after ten minutes of infusion (Fig 5). The pancreatic extraction of norepinephrine at these elevated norepinephrine levels was 65 ± 7%. When the β-adrenoceptor antagonist propranolol was infused intravenously from 15 minutes before an intravenous norepinephrine infusion for 60 minutes (n = 4), the pancreatic extraction rate of norepinephrine was 72 ± 7%. This value did not differ significantly from that in the previous experiments without propranolol. Thereafter, the α-adrenoceptor antagonist phenoxybenzamine was added to the infusion for another 60 minutes, (n = 4), the fractional extraction rate for norepinephrine decreased to 58 ± 2% ($P < .05$).

Pancreatic Extraction Rate at Endogenous Norepinephrine Levels

To determine the extraction of norepinephrine when the pancreas is exposed to baseline norepinephrine levels, ^{3}H-norepinephrine was infused for 45 minutes (n = 6) in the basal state. Arterial levels of norepinephrine were 253 + 41 pg/mL and pancreatic venous norepinephrine levels were 202 ± 44 pg/mL. The baseline extraction rate of norepinephrine was calculated from the arteriovenous difference of alumina-extracted ^{3}H-norepinephrine and found to be 73 ± 3%. Intravenous injection of 2-deoxy-glucose during the ^{3}H-norepinephrine infusion increased arterial norepinephrine levels to 636 ± 70 pg/mL and increased pancreatic venous levels of norepinephrine to 561 ± 112 pg/mL, but did not change the fractional extraction rate of ^{3}H-norepinephrine (73 ± 4%).

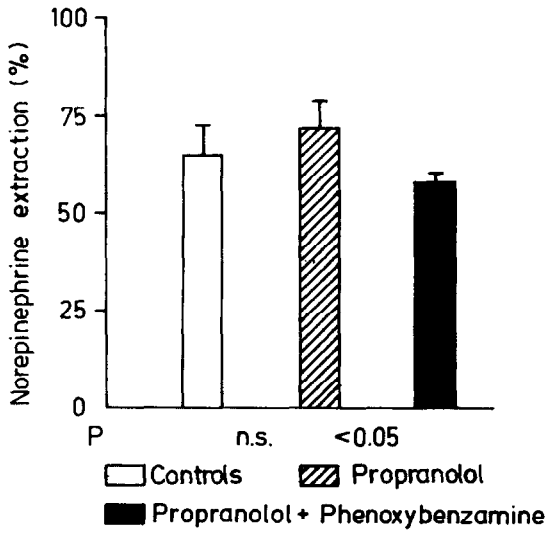

Fig 5. Fractional extraction of norepinephrine in the dog pancreas during intravenous infusion of norepinephrine (4 μg/kg/min) (controls, n = 8), or during intravenous infusion of norepinephrine (1 μg/kg/min) after pretreatment with propranolol (n = 6) or propranolol together with phenoxybenzamine (n = 6). Mean ± SEM is given.

DISCUSSION

The present study used measurements of the arteriovenous concentration difference to demonstrate that in vivo 60% to 80% of arterial epinephrine is extracted by the dog pancreas. This rate of fractional extraction is surprisingly high considering those reported for other tissues.[8-12] Such avid extraction implies that measurements of pancreatic venous epinephrine levels would markedly underestimate the concentration of circulating epinephrine to which the pancreatic islets are exposed. The rate of epinephrine extraction did not decrease even when the arterial epinephrine concentration was increased to levels seen during severe stress. These data imply that the epinephrine extraction process in the pancreas is not saturable over most of the physiologic range.

Pancreatic extraction of endogenous norepinephrine can not be calculated solely from measurements of the arteriovenous norepinephrine concentration difference because the pancreatic venous norepinephrine level reflects not only that part of arterial norepinephrine that escapes pancreatic extraction but also the spillover of locally released norepinephrine. Thus, the pancreatic extraction of endogenous norepinephrine was estimated by the arteriovenous difference of infused ^{3}H-norepinephrine. It was found that over 70% of the ^{3}H-norepinephrine was extracted both in the basal state and when endogenous levels of circulating norepinephrine are increased during neuroglucopenic stress. This high fractional extraction contrasts with the arteriovenous concentration difference of unlabeled norepinephrine in the basal state of 253 *v* 202 pg/mL and during glucopenic stress of 636 *v* 561 pg/mL. Thus, these data confirm that the arteriovenous concentration difference of endogenous norepinephrine markedly underestimates the actual pancreatic extraction of the norepinephrine that circulates in systemic plasma.

The high rate of arterial norepinephrine extraction by the pancreas also implies that arteriovenous concentration difference of unlabeled norepinephrine markedly underestimates the degree of activation of pancreatic adrenergic nerves because only a small percentage of arterial norepinephrine actually contributes to the level of norepinephrine measured in the pancreatic venous effluent. Knowledge of the fractional extraction of arterial norepinephrine by the pancreas, however, allows the appropriate correction of the arteriovenous concentration difference and, therefore, a more accurate estimation of pancreatic noradrenergic activity.

Recognition that the pancreas produces as well as extracts norepinephrine indicates that the arteriovenous concentration difference technique can be used to estimate pancreatic norepinephrine extraction only when the arterial norepineph-

rine level is increased to a point that renders pancreatic norepinephrine production negligible by comparison. In the present study, we increased arterial norepinephrine levels into this range by intra-arterial and by intravenous infusion of exogenous norepinephrine. Despite the presence of extremely high arterial norepinephrine levels in some of these experiments, the fractional extraction of arterial norepinephrine by the pancreas remained between 60% to 80%. These data show that the pancreatic extraction process for physiologic levels of circulating arterial norepinephrine is not saturable, and they further imply that the uptake processes responsible for the extraction of the presumably high synaptic levels of locally released norepinephrine probably also do not saturate.

The amount of catecholamines extracted by the pancreas has not been reported before, to our knowledge. Studies in other tissues or of whole body extraction have been reported, however, and they show a variable extraction rate, which is dependent both on the tissue studied and on the experimental conditions. For example, in man, the whole body fractional extraction rate for norepinephrine was calculated to be 45%.[8] In human forearm[9] and in human lung,[10] rates of 40% and 25%, were calculated, respectively. In smooth muscle, the calculated rate of extraction of neuronally released norepinephrine was 50%,[12] and in dog tracheal tissue, dog saphenous venous tissue and in dog pulmonary arterial endothelium, the norepinephrine extraction was calculated as 70% to 75%.[13-15] The fractional extraction of epinephrine in human forearm was reported to depend on the prevailing epinephrine levels and varied between 26% and 51% with the higher extraction values seen at high epinephrine levels.[11] In our study, the extraction rate was between 60-80% with the highest rate at the highest arterial level of epinephrine tested. Thus, our findings suggest that the pancreas has one of the higher fractional extraction rates.

Catecholamine extraction presumably involves neural and extraneural uptake, denoted $uptake_1$ and $uptake_2$, respectively. While in earlier studies β-adrenoceptor antagonists were reported to inhibit $uptake_1$[6] or whole body clearance of epinephrine[20] or norepinephrine,[21-23] we found that propranolol had no effect on the pancreatic extraction of catecholamines. This suggests either that pancreatic extraction is mediated only by $uptake_2$ or that the more recent interpretation of β-blocking studies is correct, namely, that propranolol decreases catecholamine clearance by reducing cardiac output rather than by blockade of uptake per se.[9] We also found that phenoxybenzamine reduced pancreatic extraction of catecholamines. However, this study does not allow distinction between $uptake_1$ and $uptake_2$ because previous studies indicate that α-adrenoceptor antagonists can inhibit both mechanisms.[16-18] Whatever the mechanism, synaptic levels of norepinephrine would probably be increased in the presence of phenoxybenzamine. Thus, the effects of α-adrenoceptor antagonists on pancreatic hormone secretion could result not only from blockade of islet α-adrenoceptors but also from increased local concentrations or norepinephrine. Moreover, findings of increased venous norepinephrine levels in presence of α-adrenoceptor antagonists, which have previously been ascribed solely to potentiation of neuronal norepinephrine release via blocking presynaptic α_2-adrenoceptors (compare references 1-3, 24) may reflect, in addition, blockade of extraction.

It might be argued that changes in blood flow during the infusion performed in the study would explain the failure of saturation of the catecholamine extraction process. However, it is highly unlikely that blood flow is a major determinant of catecholamine extraction. Of the 5 different experimental protocols used in the present study, pancreatic venous blood flow was not significantly altered in protocols no. 1 and no. 2, presumably because the systemic effect of the catecholamines on blood pressure counterbalances the presumed vasoconstrictor effect on the pancreas. In protocol no. 3, the intrapancreatic infusions of norepinephrine, there was a progressive decrease of blood flow in response to the graded infusions of norepinephrine. For example, when norepinephrine was infused intraarterially at 12 ng/min, pancreatic venous blood flow decreased by 1.0 ± 0.6 mL/min, at 120 ng/min by 1.5 ± 0.2 mL/min, and at 1,200 ng/min by 3.7 ± 0.7 mL/min. It is unlikely that this progressive decrease in pancreatic venous blood flow by itself produced a higher fractional extraction of norepinephrine and therefore offset an effect of high concentrations of norepinephrine to saturate the extraction mechanisms, since in protocol no. 4, when norepinephrine was given intravenously at very high rates, there was no change in pancreatic blood flow and the pancreatic extraction of norepinephrine was 65 ± 7% *v* 66 ± 7% seen during the highest rate of arterial norepinephrine infusion which had produced a large decrease of pancreatic blood flow. Further, in protocol no. 5, injection of 2-deoxyglucose did produce a significant increase of pancreatic blood flow of 2 mL/min but no change in norepinephrine extraction.

In summary, this study has shown (1) that in vivo 60% to 80% of arterial epinephrine or norepinephrine is extracted by the dog pancreas during one passage, (2) that this extraction process appears non-saturable, and (3) that the extraction of epinephrine or norepinephrine is not affected by the β-adrenoceptor antagonist propranolol, but is impaired by the α-adrenoceptor antagonist phenoxybenzamine.

We make the following conclusions: (1) pancreatic venous levels of epinephrine will markedly underestimate the circulating epinephrine concentrations seen by the islets, (2) arteriovenous concentration differences of endogenous norepinephrine across the pancreas will markedly underestimate both the pancreatic extraction and spillover of norepinephrine, (3) knowledge of percentage of norepinephrine extracted by the pancreas allows one to determine the activity of the adrenergic nerves within the pancreas, and (4) the effects of α-adrenoceptor blockade on islet hormone secretion and pancreatic venous norepinephrine levels are due, in part, to reduction of pancreatic norepinephrine extraction.

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