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Glucose Tolerance and Pancreatic Islet Blood Flow in Rats after Intraperitoneal Administration of Different Anesthetic Drugs

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ABSTRACT

A comparision of the effects of different anesthetics on the pancreatic islet blood flow as measured with a microsphere technique and the blood sugar homeostasis in rats was made in rats anesthetized with an IP injection of either thiobutabarbital sodium (TB), pentobarbital sodium (PB), chloral hydrate (CH), chloral hydrate + pentobarbital (CP) or ketamine + xylazine (KX). The mean arterial blood pressure was similar (approximately 100 mm Hg) in all animals except those given KX in which a 20-30% increase was observed. The serum insulin concentrations were increased in rats given CH and CP, but not in the other groups, when compared with TB rats. An intraperitoneal glucose tolerance test (2 g glucose/kg BW 15 min after induction of anesthesia) showed a marked glucose intolerance in the KZ rats, in which the glucose concentrations were elevated for 5 h. Also animals anesthetized with CP and CH were glucose intolerant when compared with TB animals. The whole pancreatic blood flow was similar in TB, PB and CP rats, but was almost doubled in CH-rats and markedly decreased in KX rats. Islet blood flow was also increased by CH and decreased by KX when compared with TB rats, whilst PB and CP did not affect the islet blood flow. It is concluded that TB and PB are suitable anesthetics for the study of pancreatic islet blood flow.

INTRODUCTION

The regulation of blood perfusion of the whole pancreas and the islets have many features in common with those of the other splanchnic organs (15), but nevertheless the pancreas possesses some unique features. One of these is the existence of a complex portal system of blood vessels, with up to 3 capillary systems connected both in series and in parallel, each of which have different morphological and functional characteristics (2,16,17). Furthermore, the blood perfusions of the endocrine and exocrine parenchyma respectively seem to be regulated, at least partially, by different mechanisms (10,13,14). Most in vivo-studies on the regulation of islet blood flow

referred to above have been performed in animals anesthetized with thiobutabarbital. Since this drug is no longer commercially available it was mandatory to evaluate to what extent other anesthetic drugs influence the blood perfusion of both the whole pancreas and the pancreatic islets when compared with thiobutabarbital. Also the effects of the different anesthetics on the blood glucose homeostasis were of interest in this context, since it is known that the ambient glucose concentration markedly affects islet blood flow (13).

MATERIALS AND METHODS

Animals:

Male Sprague-Dawley rats weighing approximately 325 g from a local breeding colony at the Biomedical Center, Uppsala, Sweden were used in all experiments. The animals were housed in rooms with constant temperature (20°C) and humidity (70%), and had free access to tap water and pelleted food (Type R34, Ewos, Anticimex, Södertälje, Sweden) before the experiments.

Induction of anesthesia:

The animals were injected intraperitoneally with either 1.5 ml thiobutabarbital sodium (120 mg/kg BW; Inactin®, Byk Gulden, Konstanz, FRG), ≈0.2 ml pentobarbital sodium (40 mg/kg BW; Mebumal Vet®, NordVacc, Stockholm, Sweden), ≈1.5 ml chloral hydrate (360 mg/kg BW), ≈1.3 ml of a mixture of chloral hydrate (50 mg/kg BW) + pentobarbital (12 mg/kg BW), or ≈0.3 ml ketamine (50 mg/kg BW; Ketalar®, Parke-Davis SA, Barcelona, Spain) + ≈ 0.2 ml xylazine (20 mg/kg BW; Rompun Vet®, Bayer AB, Malmö, Sweden). After this, the animals were placed on a heated operating table and their rectal temperature was maintained at 37.5°C. Polyethylene catheters (outer diameter ≈ 0.40 mm) were inserted into the ascending aorta via the right carotid artery and into the abdominal aorta via the left femoral artery. The former catheter was connected to a pressure transducer (PDCR/751; Druck Ltd., Groby, UK) to allow continuous monitoring of the mean arterial blood pressure.

Measurements of serum glucose and serum insulin concentrations:

Arterial blood samples were collected from the abdominal aorta immediately after the blood flow measurements (see below) and later analyzed for their serum glucose content with an automated glucose oxidase technique (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA, USA), and for their insulin content with radioimmunoassay (8).

Separate anesthetized animals, not subjected to any blood flow measurements, were injected intraperitoneally with D-glucose (2 g/kg BW) 15 min after induction of anesthesia as given above. Arterial blood samples were taken from a catheter inserted

into the femoral artery immediately before glucose administration and 10, 30, 60 and 120 min later and analyzed with an ExacTech®-blood glucose meter (Baxter Travenol Labs. Inc., Deerfield, IL, USA). A separate blood glucose sample was also taken from the cut tip of the tail 10 min before induction of anesthesia.

Blood flow measurements:

Approximately 30 min after induction of anesthesia ≈1.5 x 10^5 non-radioactive microspheres (NEN Chemicals, Boston, MA) with a diameter of 11 μm were injected during 15 sec into the catheter with its tip in the ascending aorta. Simultaneously an arterial reference sample was collected from the catheter in the femoral artery at a rate of ≈0.60 ml/min for 60 sec. The exact withdrawal rate was confirmed by weighing the sample in each individual experiment. The animals were then killed and the pancreas and the adrenal glands were removed, blotted and weighed. The microsphere contents of the whole pancreas, the islets, the adrenal glands and the reference sample were then determined with a freeze-thawing technique as previously described in detail (11,12). The blood flow values of the whole pancreas and the pancreatic islets were calculated with the formula $Q_{org} = N_{org} \times Q_{ref}/N_{ref}$ where Q_{org} = organ blood flow (ml/min), Q_{ref} = withdrawal rate of the reference sample (ml/min), N_{org} = number of microspheres counted in the organ and N_{ref} = number of microspheres counted in the reference sample.

The microsphere contents of the adrenal glands were counted and compared to confirm an adequate mixing of the microspheres with the arterial blood circulation, and a difference exceeding 10% between the two glands excluded the animals from the study (a total of 4 animals).

Statistical calculations:

All values are means ± SEM. Probabilities (P) of chance differences between the experimental groups were calculated with Student's unpaired t-test. All comparisons were made with the rats anesthetized with thiobutabarbital.

RESULTS

The mean arterial blood pressure remained stable at approximately 100 mm Hg throughout the experiments in all animals, with the exception of the rats anesthetized with ketamine + xylazine in which a higher blood pressure was consistently recorded (Table 1). In these latter animals the blood pressure was further elevated (to ≈150 mm Hg) when the recordings started, but it decreased during 5-10 min to a level of ≈120-130 mm Hg and then remained constant (data not shown).

In comparison with animals anesthetized with thiobutabarbital the glucose concentrations at the time of the blood flow measurements were increased in the

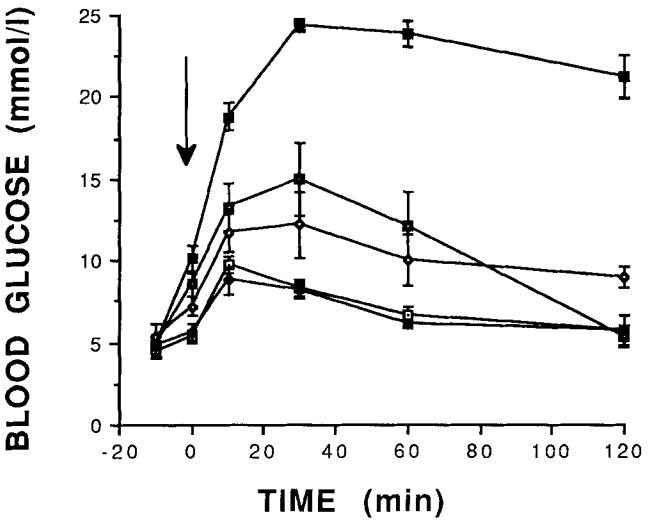

Figure 1: Blood glucose concentrations in samples taken before induction of anesthesia (time -10 min), after 15 min of anesthesia (time 0) and then at different time points after an intraperitoneal injection (arrow) of glucose (2 g/kg BW). The values are means ± SEM for 4 animals anesthetized with either (from top to bottom of the figure at time 10 min) ketamine + xylazine (filled squares), chloral hydrate (open squares), chloral hydrate + pentobarbital (open circles), pentobarbital (open squares) or thiobutabarbital (filled squares).

animals anesthetized with chloral hydrate and chloral hydrate + pentobarbital, whilst there was no effect of pentobarbital (Table 1). The serum insulin concentrations were increased in the animals given chloral hydrate or chloral hydrate + pentobarbital (Table 1).

Intraperitoneal glucose tolerance tests were performed in separate animals, not subjected to any surgery except for the insertion of a catheter into the femoral artery. Markedly higher blood glucose values were seen in the animals anesthetized with ketamine + xylazine (Figure 1). The blood glucose values did not return to the basal values until 5 h after the glucose injection in this group of animals (data not shown). However, when the same animals were tested unanesthetized 24 h later, the glucose tolerance was normal (data not shown). Also the rats anesthetized with chloral hydrate or chloral hydrate + pentobarbital exhibited increased glucose concentrations at 10, 30 and 60 min after glucose administration when compared with animals given thiobutabarbital (Figure 1). The animals anesthetized with chloral hydrate had glucose concentrations similar to the basal values after 120 min, whereas those of the animals given chloral hydrate + pentobarbital remained elevated at this time point when compared with the thiobutabarbital animals (Figure 1). Pentobarbital alone did not

TABLE 1. Serum glucose and serum insulin concentrations and mean arterial blood pressure in adult rats anesthetized with an intraperitoneal injection of either thiobutabarbital sodium (120 mg/kg BW), pentobarbital sodium (40 mg/kg BW), chloral hydrate (360 mg/kg BW), chloral hydrate + pentobarbital sodium (Ekviticin®; 50 mg/kg BW and 12 mg/kg BW respectively) or ketamine + xylazine (50 mg/kg BW and 5 mg/kg BW respectively). The number of observations in each group is given within parentheses.

Anesthesia	Glucose concentration (mmol/l)	Insulin concentration (ng/ml)	Mean arterial blood pressure (mm Hg)
Thiobutabarbital sodium (7)	9.3 ± 0.6	1.40 ± 0.18	100 ± 4
Pentobarbital sodium (7)	8.5 ± 0.2	1.29 ± 0.27	105 ± 6
Chloral hydrate (9)	19.1 ± 1.0***	4.62 ± 0.24***	91 ± 6
Chloral hydrate + pentobarbital sodium (7)	13.3 ± 1.4*	3.55 ± 0.38**	104 ± 11
Ketamine + xylazine (7)	10.1 ± 0.9	1.88 ± 0.43	128 ± 5**

All values are means ± SEM. * denotes $P<0.05$, ** denote $P<0.01$ and *** denote $P<0.001$ compared with the animals anesthetized with thiobutabarbital sodium. Blood samples for assays of glucose and insulin concentrations were obtained 30 min after induction of anesthesia.

induce any differences in glucose tolerance when compared with rats given thiobutabarbital (Figure 1). The blood glucose concentrations of these two groups of animals were also indistinguishable from those of unanesthetized rats (data not shown).

Both the whole pancreatic blood flow and the islet blood flow were increased by chloral hydrate, whilst pentobarbital and pentobarbital + chloral hydrate had no effects compared with the animals anesthetized with thiobutabarbital (Table 2). Ketamine + xylazine markedly decreased both the whole pancreatic and islet blood flow. The vasoconstriction was more pronounced in the endocrine pancreas, as evidenced by the decrease in fractional islet blood flow in these animals (Table 2). Both pentobarbital

TABLE 2. Whole pancreatic blood flow and islet blood flow in adult rats anesthetized with an intraperitoneal injection of either thiobutabarbital sodium (120 mg/kg BW), pentobarbital sodium (40 mg/kg BW), chloral hydrate (360 mg/kg BW), chloral hydrate + pentobarbital sodium (Ekviticin®; 50 mg/kg BW and 12 mg/kg BW respectively) or ketamine + xylazine (50 mg/kg BW and 5 mg/kg BW respectively). The number of observations in each group is given within parentheses.

Anesthesia	Pancreatic blood flow (PBF) (ml/min x g)	Islet blood flow (µl/min x g)	Islet blood flow (% of PBF)
Thiobutabarbital sodium (7)	0.60 ± 0.05	62 ± 5	9.8 ± 0.7
Pentobarbital sodium (7)	0.44 ± 0.07	53 ± 6	12.5 ± 0.9*
Chloral hydrate (9)	1.16 ± 0.12***	119 ± 13**	10.1 ± 0.4
Chloral hydrate + pentobarbital sodium (7)	0.51 ± 0.08	62 ± 12	13.2 ± 1.4*
Ketamine + xylazine (7)	0.33 ± 0.04***	21 ± 3***	6.4 ± 0.9**

All values are means ± SEM. * denote $P<0.05$, ** denote $P<0.01$ and *** denote $P<0.001$ compared with the corresponding value for the animals anesthetized with thiobutabarbital sodium.

and chloral hydrate + pentobarbital slightly increased the fraction of the whole pancreatic blood flow diverted through the islets (Table 2).

DISCUSSION

The glucose concentrations measured after an intraperitoneal glucose injection in the animals anesthetized with pentobarbital or thiobutabarbital were similar to that of unanesthetized control animals. This suggests that barbiturates induce small or negligible short-term effects on glucose homeostasis (cf. 1,12), despite their suppression of neurotransmission in autonomic ganglia (6,18). However, there are also some reports on glucose intolerance or disturbed islet hormonal release caused by

pentobarbital (4,7,19). These discrepancies may reflect differences in age and strain of the animals as well as differences in the duration of anesthesia in the studies.

Administration of chloral hydrate, most markedly when given alone but also when administered in combination with pentobarbital, produced a glucose intolerance. An even more pronounced glucose intolerance was seen after administration of the combination of ketamine and xylazine. This is somewhat surprising since ketamine only has minor effects on glucose homeostasis (1). It is therefore likely that xylazine by itself or, more probable, a synergistic action of ketamine and xylazine causes the glucose intolerance. It is of interest in this context that the hyperglycemia is maintained for up to 5 h, even though the animals are fully recovered from anesthesia already after 1-1.5 h. This may indicate either that one or several metabolites of the drugs cause the glucose intolerance, or that the drugs induce more long lasting effects on some other organs or enzymes of importance for the carbohydrate metabolism. It is for instance known that several anesthetics may influence liver enzymes which are of importance for glucose homeostasis (3), and it is possible that similar mechanisms are involved in the observed ketamine/xylazine-induced glucose intolerance.

The mean arterial blood pressure was similar in all animals with the exception of those given ketamine + xylazine. The reasons for this are unknown, but taken together with the findings of the glucose intolerance and the low pancreatic blood flow-values this could be due to a more pronounced hyperactivity of the sympatho-adrenal system, than generally encountered in anesthetized animals.

With regard to the pancreatic blood perfusion thiobutabarbital, pentobarbital and chloral hydrate + pentobarbital all demonstrated similar values with the exception of a slight increase in the fractional islet blood flow in the two latter groups. The reasons for this increase are unknown. Chloral hydrate on the other hand, markedly increased both whole pancreatic blood flow and islet blood flow, but did not change the intra-pancreatic distribution of the blood flow. This is unexpected, since the elevated glucose concentrations seen in these animals would be supposed to selectively increase the islet blood flow (cf. 12,13). However, since the blood flow values are already markedly elevated, and well above the islet blood perfusion seen after glucose stimulation in barbiturate-anesthetized rats, it is possible that the blood flow cannot be further elevated. The increase may also be an unspecific response to the local irritation within the abdominal cavity induced by the high dose of chloral hydrate. Ketamine + xylazine produced a drastic decrease in the pancreatic blood perfusion, especially in the islets. The reasons are unknown, but it should be noted that ketamine in itself has no marked effects on the splanchnic circulation (5,9). It could be that the combination of ketamine and xylazine, as discussed above, causes an excessive sympatho-adrenal stimulation.

In summary, it seems as if thiobutabarbital and pentobarbital influence both the glucose tolerance and the pancreatic blood perfusion to the same degree in rats, that is pentobarbital seems to be the drug of choice to replace thiobutabarbital with regard to studies on pancreatic islet blood flow in anesthetized rats. Chloral hydrate increases

the pancreatic blood flow and causes a glucose intolerance. A combination of chloral hydrate and pentobarbital only has minor effects on the pancreatic blood perfusion when compared with the barbiturates, but causes a glucose intolerance. Ketamine + xylazine induces both a glucose intolerance, changes in the mean arterial blood pressure and a marked decrease in the pancreatic and islet blood flow. Thus, none of these three latter anesthetics are suitable for studies of either pancreatic islet blood flow or glucose homeostasis of anesthetized animals.

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