Therapy of Malignant Hamster Insulinomas with Monoamine Precursors

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Summary. The hyperinsulinaemia and hypoglycaemia produced by malignant insulinomas pose a difficult therapeutic problem. The non-polar monoamine precursors 5-hydroxytryptophan, L-3,4-dihydroxyphenylalanine and DL-threo-dihydroxyphenylserine are readily taken up by normal hamster pancreatic islets and are converted intracellularly to serotonin, dopamine and norepinephrine. These intracellular monoamines then inhibit glucose-stimulated insulin secretion. In the present study we have determined if the monoamine oxidase inhibitor pargyline, and monoamine precursors, could modify the severe hypoglycaemia of hamsters bearing a rapidly growing transplantable insulinoma. One hour after receiving the respective precursor there was an 11, 18, and 54-fold increase in the concentration of serotonin, dopamine or norepinephrine in the insulinomas. Twenty four hours after the administration of the respective precursors there were the following increases in plasma glucose in the respective groups: 5-hydroxytryptophan, 1.9 ± 0.5 to 4.9 ± 0.3 mmol/l (mean $\pm$ SEM); L-3,4-dihydroxyphenylalanine, 1.5 ± 0.3 to 3.4 ± 0.6 mmol/l; and DL-threo-dihydroxyphenylserine, 1.5 ± 0.2 to 6.4 ± 0.7 mmol/l. The change in plasma insulin concentration was statistically significant only in the group receiving DL-threo-dihydroxyphenylserine (229 ± 59 to 81 ± 42 mU/l). To determine if this therapeutic approach could modify the rapidly fatal outcome of the tumour-bearing hamsters, they received 0.154 mol/l saline, DL-threo-dihydroxyphenylserine or pargyline plus DL-threo-dihydroxyphenylserine every two days. The survival of the groups (mean $\pm$ SEM) was: saline 8.4 ± 1.1 d; DL-threo-dihydroxyphenylserine 17.9 ± 3.5 d; and pargyline plus DL-threo-dihydroxyphenylserine 24.4 ± 5.5 d. The present study suggests that increasing the monoamine content of malignant insulinomas may favourably modify the course of these devastating tumours.

Key words: Insulinoma, monoamine oxidase, hypoglycaemia, norepinephrine, dopamine, serotonin, pargyline, neoplasm, insulin

Benign and non-metastatic malignant insulin-producing islet cell tumours of the pancreas (insulinomas) are usually successfully treated by surgical excision. However, the hyperinsulinaemia and hypoglycaemia produced by metastatic malignant insulinomas presents a more difficult therapeutic problem. Agents used to treat this condition with varying degrees of success have included diazoxide, ACTH, glucocorticoids, human growth hormone, glucagon and streptozotocin [1].

Histochemical fluorescence data indicates that normal pancreatic islets of some species and some insulinomas contain dopamine and serotonin [2, 5]. Pharmacological doses of these monoamines inhibit insulin secretion from normal pancreatic islets [6, 7]. We recently demonstrated that a transplantable malignant islet cell tumour of the golden hamster contains a low concentration of dopamine and norepinephrine and a higher concentration of serotonin [8, 9], together with high activity of the monoamine inactivating enzymes monoamine oxidase (monoamine: oxygen oxidoreductase, EC 1.4.3.4.) and catechol-o-methyltransferase (S-adenosyl-L-methionine: catechol-o-methyltransferase, EC 2.1.1.6.).

Normal hamster pancreatic islets also have high monoamine oxidase (MAO) activity. If this MAO is inhibited with the MAO inhibitor tranlycypromine and the norepinephrine precursor DL-threo-dihydroxyphenylserine (DOPS), the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) or the serotonin precursor 5-hydroxytryptophan (5-HTP) administered, the concentration of the respective

monoamine was markedly increased in the pancreatic islets [10]. The increase in islet monoamines was associated with marked inhibition of *in vivo* and *in vitro* glucose-stimulated insulin secretion [10].

The purpose of the present study was to determine if the monoamine concentration of insulinomas could be increased by increasing the synthesis of monoamines with monoamine precursors and inhibiting the degradation of monoamines with the MAO inhibitor pargyline. We also wanted to determine if an increase in the concentration of monoamines in the insulinoma would decrease the insulin secretion from the tumour and ameliorate the hypoglycaemia of the hamsters.

Materials and methods

Materials

The following chemicals were purchased from commercial sources: DL-threo-dihydroxyphenylserine (DOPS), L-3,4-dihydroxyphenylalanine (L-DOPA), 5-hydroxytryptophan (5-HTP), S-acetyl coenzyme A, N-acetyl-5-methoxytryptamine (melatonin) (Sigma Chemical Co., St. Louis, MO); pargyline HCl (Saber Labs, Morton Grove, IL); tryptamine bisuccinate (side chain-2-¹⁴C) with specific activity of 60 mCi/mmol and S-adenosyl-L-(³H-methyl)-methionine (³H-SAM) with specific activity of 7.5 to 10 Ci/mmol (New England Nuclear, Boston, MA); Insulin Radioimmunoassay Kits (Amersham Corporation, Arlington Heights, IL); and male golden hamsters (100–125 g) (Engel Laboratory, Inc., Farmersburg, IN).

Experimental Procedure

The hamster insulinoma was removed from host animals under sterile conditions, minced and transplanted into the SC tissues of the recipient animals. As described below, by 2 weeks after transplantation the insulinoma-bearing hamsters had an elevation in plasma insulin and a fall in plasma glucose levels. Blood samples for glucose and insulin assay were usually obtained from the orbital sinus. Following this procedure there may be a rise in plasma glucose for the next hour. Therefore, the pre-treatment blood samples were obtained 24 to 25 h prior to the post-treatment samples. When evaluating the MAO activity and monoamine and insulin concentration in the tumour, animals were sacrificed by decapitation and blood from the cervical wound collected into heparin. Preliminary studies indicated that there was no difference in the glucose and insulin concentration in blood obtained by orbital puncture or decapitation. After removal the insulinomas were weighed, cut into multiple pieces and stored in individual vials in the freezer (–30°C) until analysis.

The hamsters had access to food and water until the time of sacrifice. All medications were administered IP. The dose of drugs administered was: pargyline 8 mg/kg body weight; DOPS 120 mg/kg; L-DOPA 65 mg/kg; and 5-HTP 30 mg/kg. In the acute studies, after blood samples were obtained, the hamsters received either 0.154 mol/l saline or pargyline at time 0. Twenty four hours later they received either saline or a monoamine precursor (DOPS, L-DOPA, 5-HTP). They were sacrificed either 1 or 24 h after the monoamine precursor was given. In chronic studies, to determine the long term effect of pargyline and monoamine precursors on tumour bearing animals, blood samples were obtained

at time 0. The animals then received 0.154 mol/l saline or pargyline IP. Twenty four hours after the start of the experiment they received either saline or DOPS. Forty eight hours after the start of the experiment, blood samples were again obtained. The animals then received saline or pargyline. Immediately afterwards, they received saline or DOPS. Thereafter, orbital blood samples were obtained and saline or DOPS were administered at 48 h intervals until the animals died from hypoglycaemia. The animals were examined at least once a day.

Analytical Methods

The insulinomas were homogenised with a ground-glass homogeniser at 3°C. When MAO activity was determined, the tissue was homogenised in potassium chloride (11 g/l) and the assay performed on the total homogenate. The MAO assay uses ¹⁴C-tryptamine (1 mmol/l) as substrate [11]. MAO activity is equal to the amount of ¹⁴C-labelled indoleacetaldehyde and indoleacetic acid formed. These metabolites were isolated by differential solvent extraction and counted in a liquid scintillation counter. The lower limits of sensitivity are 50 pmol product/mg tissue/min. The protein content of the homogenate was determined with a colorimetric method [12]. The enzyme activity was expressed as pmol product formed/mg of tumour homogenate/min of incubation.

The insulinomas for norepinephrine and dopamine analysis were homogenised in 0.1 mol/l perchloric acid and the tissues for serotonin were homogenised in 0.1 mmol/l HCl. The perchloric acid homogenate was centrifuged at 4000 X g and the supernatant analysed for norepinephrine and dopamine. As serotonin binds to particulate matter the serotonin analysis was done on the total HCl homogenate. The norepinephrine [13, 14], dopamine [15, 16], and serotonin [17, 18] concentrations in the insulinomas were determined with previously described sensitive and specific radioassays in which a ³H-labelled methyl group is transferred from ³H-S-adenosylmethionine to the monoamine under investigation by a semipurified enzyme. After appropriate insolation, the amount of purified radioactive derivative that was generated was determined in a liquid scintillation counter. The lower limit of sensitivity of the norepinephrine assay was 0.3 to 0.6 pmol norepinephrine/assay tube and there was less than 2% cross reactivity with dopamine and serotonin or DOPS. The lower limit of sensitivity of the dopamine assay was 1 to 2 pmol dopamine/assay tube and there was less than 3% cross reactivity with norepinephrine, serotonin or L-DOPA. The lower limit of sensitivity of the serotonin assay was 4 to 8 pmol of serotonin/assay tube and there was less than 1% cross reactivity with norepinephrine, dopamine or 5-hydroxytryptophan. The monoamine content of the insulinomas is expressed as $\mu\text{mol/kg}$ wet weight.

Plasma glucose was measured with a glucose analyser (Beckman Instruments, Fullerton, CA) that uses a modified glucose oxidase method [19]. After the insulin was extracted from the insulinomas with acid-ethanol, the acid-ethanol was diluted with an appropriate amount of 0.01 mmol/l sodium phosphate buffer (pH = 7.3) [20]. Plasma and tumour insulin concentrations were determined with a double antibody radioimmunoassay method [21]. Beef insulin was used as the insulin standard. To minimise the problem that the binding curves for hamster and beef insulin are not perfectly parallel, aliquots of plasma and medium were selected that would fall in the midportion of the standard curve. The plasma insulin glucose ratios (I/G) was calculated to determine if the plasma insulin concentration is appropriate to the plasma glucose concentration [22].

Statistical Methods

Unless otherwise stated, data are given as mean $\pm$ SEM. The statistical significance of differences between two groups was

Table 1. Alteration in plasma glucose, plasma insulin and tumour monoamine concentration in insulinoma-bearing hamsters 24 h after the injection of pargyline and/or a monoamine precursor

Monoamine precursor	Pargyline administration	Tumour monoamine assayed	Tumour monoamine ($\mu\text{mol/kg}$)		Plasma glucose (mmol/l)		Plasma insulin (mU/l)	
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
0	0	c	c	c	2.5 ± 0.5	2.0 ± 0.4	299 ± 52	333 ± 40
0	+	c	c	c	3.0 ± 0.5	3.0 ± 0.6	233 ± 79	173 ± 41
DOPS	0	Norepinephrine	0.6 (<0.2 – 2.6)	0.3 (<0.2 – 0.8)	2.5 ± 0.6	5.7 ± 0.4^b	273 ± 93	152 ± 36
DOPS	+	Norepinephrine	0.6 (<0.2 – 2.6)	0.6 (<0.2 – 1.1)	1.5 ± 0.2	6.4 ± 0.7^b	229 ± 59	81 ± 42^a
L-DOPA	+	Dopamine	0.3 (<0.2 – 1.0)	1.3 (<0.2 – 4.7)	1.5 ± 0.3	3.4 ± 0.6^b	190 ± 27	151 ± 38
5-HTP	+	Serotonin	5.2 (<0.6 – 26.5)	5.9 (1.3 – 12.4)	1.9 ± 0.5	4.9 ± 0.3^b	368 ± 132	188 ± 35

Plasma glucose and insulin and tumour monoamine concentration were determined in insulinoma-bearing hamsters before (pre-treatment) and after (post-treatment) the hamsters received the norepinephrine precursor DL-threo-dihydroxyphenylserine (DOPS), the dopamine precursor L-3, 4 dihydroxyphenylalanine (L-DOPA) or the serotonin precursor 5-hydroxytryptophan (5-HTP) 24 h before. Some hamsters were treated with the monoamine oxidase inhibitor pargyline 48 h before. Values are given as the mean $\pm$ SEM or mean (range) of specimens from 6 to 10 different hamsters. The pre-treatment monoamine concentrations were established on another group of insulinomas obtained from 6 to 8 untreated hamsters

^a $p < 0.05$ compared with pre-treatment

^b $p < 0.01$ compared with pre-treatment

^c not measured

sought with Student's *t* test if only a single determination was made in an animal [23]. If more than one determination was made in an animal the post-treatment value was expressed as a percentage of the pre-treatment and the data analysed by the paired *t* test [23]. When more than one experimental group was being compared to the control group, the data was subjected to analysis of variance. The significance of the differences between mean values was then estimated with the single-tailed multiple comparisons test of Scheffe [23].

Results

In a group of 12 normal fed hamsters, the plasma glucose concentration was 6.0 ± 0.3 mmol/l, the plasma insulin concentration was 48 ± 7 mU/l and the plasma insulin glucose ratio was 8.1 ± 1.3 . Fourteen (range 13 to 15) days after receiving a transplantation of the insulinoma, a second group of 12 hamsters had a plasma glucose concentration 4.5 ± 0.4 mmol/l ($p < 0.05$), a plasma insulin concentration of 170 ± 31 mU/l ($p < 0.05$) and a plasma insulin glucose ratio of 63 ± 21 ($p < 0.05$) compared with normal group. Twenty one (range 20 to 24) days after receiving the transplantation of the insulinoma this second experimental group had the following values: plasma glucose 1.7 ± 0.3 mmol/l; plasma insulin 230 ± 43 mU/l and plasma insulin glucose ratio of 156 ± 27 . In the absence of therapy the

hamsters usually developed hypoglycaemic signs (diaphoresis, seizures) between 24 and 34 days after tumour transplantation.

Table 1 shows attempts to decrease insulin secretion from the insulinomas by increasing the monoamine concentration of the tumour by administering pargyline at 0 h and DOPS, L-DOPA or 5-HTP 24 h later. Twenty-four hours after the monoamine precursor, the animals were sacrificed. There was no change in the low plasma glucose and the high plasma insulin concentration in the group receiving saline and in the group receiving pargyline and saline. There was a significant increase in the plasma glucose concentration in the groups receiving DOPS alone, pargyline plus DOPS, pargyline plus L-DOPA and pargyline plus 5-HTP. However, only the pargyline plus DOPS group had a significant fall in the elevated plasma insulin concentration.

At the time of sacrifice the SC insulinoma in the control group weighed 4.4 ± 0.45 g and had an insulin content 0.118 ± 0.029 mU/g. There was no significant difference in the weight or in the insulin concentration of the insulinomas in the other experimental groups. There was 67% inhibition of MAO in the insulinoma in the animals receiving pargyline (control MAO activity 2331 ± 158 pmol/mg/min and pargyline treated MAO activity 772 ± 64 pmol/mg/min). However none of the groups had an increase in

Table 2. Alteration in plasma glucose and tumour monoamine concentration of insulinoma-bearing hamsters 1 h after the injection of pargyline and/or monoamine precursors

Monoamine precursor	Pargyline administration	Tumour monoamine assayed	Tumour monoamine ($\mu\text{mol/kg}$)		Plasma glucose (mmol/l)	
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
DOPS	0	Norepinephrine	0.6 (<0.2 – 2.6)	23.6 (21.2 – 36.4)	2.0 ± 0.3	2.7 ± 0.4
DOPS	+	Norepinephrine	0.6 (<0.2 – 2.6)	29.5 (5.8 – 52.5)	1.8 ± 0.7	7.3 ± 2.1^a
L-DOPA	+	Dopamine	0.3 (<0.2 – 1.0)	6.1 (1.7 – 11.9)	2.4 ± 0.5	5.0 ± 1.8
5-HTP	+	Serotonin	5.2 (<0.6 – 26.5)	59.3 (34.8 – 77.8)	2.4 ± 0.6	1.7 ± 0.6

Plasma glucose and tumour monoamine concentration were determined in insulinoma-bearing hamsters before (pre-treatment) and after (post-treatment) the hamsters received the norepinephrine precursor DL-threo-dihydroxyphenylserine (DOPS), the dopamine precursor L-3, 4 dihydroxyphenylalanine (L-DOPA) or the serotonin precursor 5-hydroxytryptophan (5-HTP) 1 h before. Some hamsters received the monoamine oxidase inhibitor pargyline 24 to 25 h before. Values are given as the mean $\pm$ SEM or mean (range) of specimens from 6 to 10 different hamsters. The pre-treatment monoamine concentrations were established on another group of insulinomas obtained from 6 to 8 untreated hamsters

^a $p < 0.01$ compared with pre-treatment

the concentration of the appropriate monoamine, 24 h after administration of the monoamine precursors (Table 1).

To determine if the administration of pargyline and monoamine precursors resulted in an initial elevation in the monoamine concentration of the insulinomas pargyline was administered at 0 h and DOPS, L-DOPA or 5-HTP at 24 h. The animals were sacrificed 1 h later. At the time of sacrifice, there was an 84% inhibition of MAO in the insulinoma (control MAO activity 2331 ± 158 pmol/mg/min and pargyline treated MAO activity 377 ± 31 pmol/mg/min). Table 2 demonstrates that DOPS alone resulted in a 43 fold increase in norepinephrine, pargyline plus DOPS in a 53 fold increase in norepinephrine, pargyline plus L-DOPA in an 18 fold increase in dopamine and pargyline plus 5-HTP in an 11 fold increase in serotonin. Only the pargyline plus DOPS group had a significant increase in plasma glucose (Table 2). DOPS alone reduced the plasma insulin from 461 ± 69 mU/l to 222 ± 42 mU/l ($p < 0.05$).

Figure 1 compares the plasma glucose, insulin and insulin glucose ratio of insulinoma-bearing hamsters receiving saline and hamsters receiving pargyline plus DOPS every 48 h. The plasma glucose concentration was significantly higher and the plasma insulin glucose ration was significantly decreased in the drug treated group from 2 to 8 d. The plasma insulin concentration was significantly lower in the drug treated group at 4 and 8 d. More than half of the animals in the control group died from hypoglycaemia by 10 d so the graph for their group was not carried beyond 8 d. Although there was an increase

in plasma insulin and a decrease in plasma glucose in the PARG/DOPS group between 8 and 10 d the majority of animals survived. The increase in plasma insulin and decrease in plasma glucose may have been due to progressive growth of the insulinomas.

Figure 2 depicts studies designed to determine if it is essential to administer pargyline plus DOPS to ameliorate the hyperinsulinaemia and hypoglycaemia of insulinoma-bearing hamsters. DOPS alone did not significantly modify the hyperinsulinaemia and hypoglycaemia. When pargyline plus DOPS was administered once at the beginning of the experiment, there was a significant increase in plasma glucose and a significant decrease in plasma insulin and the plasma insulin glucose ratio at 2 d. By 4 d, however, this group did not differ from the control group. In the third experimental group the hamsters received pargyline plus DOPS initially and again at 2 d. On the fourth day they received pargyline but the DOPS was omitted. There was a striking decrease in plasma glucose concentration and a striking rise in plasma insulin concentration and in the plasma insulin glucose ratio. Although the hypoglycaemia and hyperinsulinaemia could be ameliorated by administering pargyline and DOPS on the sixth day the omission of the DOPS on the fourth day was associated with death from hypoglycaemia in three of the seven animals in the group between day four and day six.

The mean survival of the hamsters in the various experimental groups from the time of initiation of injections were: control 8.3 ± 1.1 d; pargyline plus DOPS with DOPS omitted on the fourth day only, 12.0 ± 3.6 d; DOPS alone every two days $17.9 \pm$

Fig 1. Effect of the administration of pargyline (PARG) and DL-threo-dihydroxyphenylserine (DOPS) on the plasma glucose, insulin and glucose-insulin ratio of insulinoma-bearing hamsters. The PARG/DOPS group initially received pargyline at 0 days and DOPS at one day. Subsequently they received pargyline and DOPS after blood samples were obtained on days 2, 4, 6, 8, 10 and 14. The control group received saline on days 0, 1, 2, 4, 6, and 8. Initially there was 8 hamsters in the control group and 7 hamsters in the PARG/DOPS group. Each point represents the mean and SEM. The asterisk (*) indicates a significant ($p < 0.05$) difference between the control and PARG/DOPS group

3.5 d; and pargyline plus DOPS every two days 24.4 ± 5.5 d. The survival of the latter group was significantly prolonged over that of control ($p < 0.05$). The survival of insulinoma-bearing animals without treatment would be predicted to be 2.4 to 14.4 days (95% confidence limits). Five of the seven hamsters in the pargyline plus DOPS group lived beyond 14.4 days.

All but one of the hamsters were observed until they died of hypoglycaemia. One hamster in the pargyline plus DOPS group was showing signs of marked hypoglycaemia at 38 d. At sacrifice body weight was reduced to 88 g and the SC insulinoma weighed only

Fig 2. Effect of various dose schedules of pargyline (PARG) and/or DL-threo-dihydroxyphenylserine (DOPS) on the plasma glucose, insulin and insulin-glucose ratio of insulinoma-bearing hamsters. The PARG/DOPS ONCE and the PARG/DOPS INT (intermittent) received pargyline at 0 days and DOPS at one day. The PARG/DOPS INT continued to receive pargyline and DOPS every two days except on day four when they received only pargyline. The DOPS group received DOPS at 1, 2, 4, 6 and 8 days. The control group received saline at these times. There were initially 7 or 8 hamsters in each group. Each point represents the mean and SEM. The solid arrow in the panel depicting plasma glucose indicates the time of DOPS administration. The insulin-glucose ratios that exceed the scale of the figure are: DOPS at 4 days 317; PARG/DOPS ONCE at 6 days 302; and PARG/DOPS at 6 days 616

0.9 g. However gross and microscopic examination revealed extensive intra-abdominal deposits of metastatic insulinoma.

Discussion

In the present study we have demonstrated that the norepinephrine concentration of transplantable hamster insulinomas is increased by the administration of pargyline and DOPS. This was associated with a decrease in plasma insulin concentration, an

increase in plasma glucose concentration with a resulting decrease but not complete correction of the markedly abnormal insulin glucose ratio. Our data suggests that the increase in plasma glucose is due to inhibition of insulin secretion from the insulinoma. However administration of the dopamine precursor L-DOPA or the serotonin precursor 5-HTP resulted in a statistically significant increase in plasma glucose despite a statistically nonsignificant decrease in plasma insulin. Thus it is possible that extrapancreatic effects may also contribute to the amelioration of the hypoglycaemia by the monoamine precursors. The monoamines may antagonise insulin action in peripheral tissues or stimulate hepatic glycogenolysis or gluconeogenesis. It is also conceivable that the monoamine precursors stimulate the release of hormones such as glucagon, glucocorticoids or growth hormone that are known to antagonise the action of insulin. Finally the monoamine precursors may act as general inhibitors of tumour growth, rather than specific inhibitors of insulin secretion. This is unlikely for the insulinoma growth rate does not seem to be decreased by chronic administration of monoamine precursors.

Although there are occasional insulinomas that are glucose responsive, most benign and malignant human insulinomas do not secrete insulin in response to a glucose challenge [24–27]. The hamster insulinoma has either sluggish or absent insulin secretion in response to a glucose challenge [27, 28]. However, the insulinoma has an adenylcyclase system that can be activated by glucagon [28]. Glucagon, N⁶ 0²-dibutyl-adenosine 3'5'-monophosphate, potassium and calcium can increase insulin secretion from the hamster insulinoma [28, 29]. These stimuli are also effective in increasing insulin secretion from normal pancreatic B cells. The exact mechanism by which monoamines inhibit insulin secretion from normal pancreatic B cells or from the hamster insulinoma is not clear at this time.

Previous studies of the effects of catecholamines on insulin secretion from insulinomas have varied depending on the experimental design used. Shen [30] found that an acute infusion of propranolol and epinephrine inhibited insulin secretion in five normal subjects, but did not alter the increased insulin secretion in two patients with insulinomas. Lins and Effen-dic noted that an epinephrine infusion inhibited glucose-stimulated insulin secretion in patients harbouring glucose responsive insulinomas [27]. However, epinephrine did not inhibit glucagon-stimulated insulin secretion from insulinomas. Scandellari et al found that chronic propranolol administration ameliorated the hypoglycaemia of patients with insulinomas [31]. Propranolol did not alter the

increased levels of plasma insulin in the basal state suggesting it was acting by an extra pancreatic mechanism. However, it did decrease the insulin response to a challenge with glucose, tolbutamide or glucagon.

The approach used in the present study differs in a number of respects from approaches used in the past. Monoamines such as epinephrine are polar compounds that do not penetrate cell membranes well [7, 32]. Such "exogenous" monoamines probably inhibit insulin secretion by acting at the cell membrane. There is pharmacological evidence that non-polar monoamine precursors such as DOPS, L-DOPA and 5-HTP effectively penetrate the cell membrane. Intracellularly they are converted to their respective "endogenous" monoamines. It is in this location that they may inhibit insulin secretion [7, 32].

The present animal study suggests that it may be worthwhile to try to ameliorate the hypoglycaemia of patients with malignant insulinomas by utilising monoamine precursors and/or inhibitors. We selected DOPS and pargyline for long term evaluation for several different reasons. Some animals who received pargyline and L-DOPA or 5-HTP acutely, became hyperkinetic, due probably to increased brain monoamine levels. In contrast, the animals who received pargyline and DOPS acutely, did not have any change in behaviour. The threo-isomer of DOPS used in these studies does not penetrate the central nervous system well and so does not increase the concentration of norepinephrine in the brain [13]. In the acute studies, DOPS also seemed to be a more effective inhibitor of insulin secretion from the insulinoma than L-DOPA or 5-HTP. However, there are species difference in the response of the B cells to stimulators and inhibitors of insulin release [33]. Thus L-DOPA may be as effective in ameliorating the hypoglycaemia of patients with insulinoma than is DOPS. L-DOPA has been given in conjunction with the MAO inhibitor deprenyl to increase the dopamine concentration in the basal ganglia of the brain of patients with Parkinson's Disease [34]. Perhaps drugs such as these might ameliorate the hypoglycaemia of patients with nonresectable insulinomas.

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