Tranylcypromine: A Potent Insulin Secretagogue and Hypoglycemic Agent

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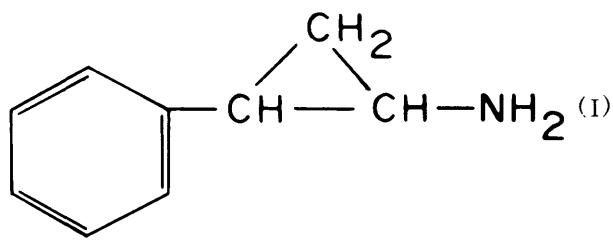
SUMMARY

The intraperitoneal administration of tranylcypromine, a nonhydrazine monoamine oxidase inhibitor, to mice resulted in a rapid and marked stimulation of insulin secretion, which was followed at 60 to 90 min. by profound hypoglycemia. The conversion of lactate to blood glucose was markedly depressed by the drug. Other monoamine oxidase inhibitors tested had no effect on insulin secretion or blood glucose. The tranylcypromine stimulated insulin secretion was not affected by prior administration of reserpine but was inhibited by prior administration of MJ 1999, a β-adrenergic receptor blocker. Tranylcypromine stimulated insulin secretion was augmented by prior administration of phentolamine, an α-adrenergic receptor blocker. Prostaglandin E_1 administration stimulated insulin secretion and this effect was also inhibited by MJ 1999. Tranylcypromine stimulation of insulin secretion from the pancreas was also obtained in vitro. The role of α and β-adrenergic receptors in the control of insulin secretion in the pancreatic islets is discussed. DIABETES *17*:617-24, October, 1968.

Porte has recently found that β-adrenergic stimulation in man by means of isoproterenol (isopropylnorepinephrine) infusion results in stimulation of insulin secretion, and that β-adrenergic blocking agents inhibit this response.[1] Porte and his coworkers have also shown that epinephrine and norepinephrine are potent inhibitors of insulin secretion in man and that this inhibitory effect is mediated via an alpha adrenergic receptor mechanism.[1-3] Studies from the laboratory of Kipnis have shown that the effects of epinephrine on insulin secretion in rats are also mediated via alpha and beta adrenergic receptors in the pancreatic islets.[4-5] Kipnis and Turtle demonstrated that stimulation of alpha receptors inhibits, whereas stimulation of beta receptors stimulates secretion in the rat.[5] Moreover, Turtle and Kipnis found that β-adrenergic stimulation of isolated rat pancreatic islets resulted in a profound rise in the cyclic 3′5′ AMP concentrations in the islets in vitro, and a rise in insulin secretion in vivo.[5] Sussman and Vaughan have shown the stimulatory effect of cyclic 3′5′ AMP on insulin secretion in the isolated perfused pancreas,[6] and Levine has demonstrated that the administration of the cyclic nucleotide to man also stimulates insulin secretion.[7] These data have led to the hypothesis that the effects of a number of pharmacologic agents on insulin secretion are mediated via alpha and beta adrenergic receptors in pancreatic islet cells. Stimulation of beta adrenergic receptors increases cyclic 3′5′ AMP levels which in turn stimulate insulin secretion from the pancreas, whereas stimulation of alpha adrenergic receptors decreases cyclic 3′5′ AMP levels and inhibits insulin secretion.[5-7]

In this communication data are presented which show that tranylcypromine[8] (trans-2-phenylcyclopropylamine) (I), a nonhydrazine monoamine oxidase inhibitor,[9] is a potent hypoglycemic agent, which markedly stimulates insulin secretion from the pancreas. The insulin secretion was ascertained to result from the β-adrenergic stimulatory effect of the drug and not from its capacity to inhibit monoamine oxidase.



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MATERIAL AND METHODS

White male mice, weighing 20 to 25 gm., were offered a standard diet until 24 hrs. before use. Where myocardial and hepatic in vitro oxidations of fatty acids, glucose and pyruvate were to be determined, the experimental animals received 0.4 mg. of tranylcypromine

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in 0.1 ml. normal saline intraperitoneally 45 min. prior to sacrifice, whereas the controls received only saline. The tissues were homogenized in 5.0 ml. of calcium-free Krebs-Ringer phosphate buffer pH 7.4. In the case of the long chain fatty acid oxidation studies, the endogenous FFA of the tissues of the treated and control groups were equal at the time of sacrifice and no corrections were made for difference in specific activity.[10] In vitro assays of palmitate-1-C-14, glucose-U-C-14 and pyruvate-2-C-14 oxidation were carried out as previously described.[10] Free fatty acids in tissues were determined by the method of Trout, Estes and Friedberg.[11] Protein concentration was measured by a modification of the biuret method.[12]

In vivo oxidation of palmitate-1-C-14, pyruvate-2-C-14 and glucose-U-C-14 to C-14-O_2 was assayed by the intraperitoneal administration of a tracer dose of the labeled substrate to the animals and measurement of the blood levels of the administered substrate and the radioactivity of the expired C-14-O_2 at 10-min. intervals.[13]

In gluconeogenesis experiments, the treated group received the pharmacologic agent at various times prior to the intraperitoneal administration of 100 μmoles of L-(+)-lactate-U-C-14 (6×10^6 cpm), whereas the controls received saline injections prior to the lactate. At the start of the experiment and at 10 to 15 min. intervals thereafter, two 10 μl. aliquots of blood were taken from the tail vein. Blood glucose concentration was determined on one aliquot using the glucose oxidase method modified for microdeterminations.[14] The second aliquot was deionized on a 10 cm. $\times$ 0.2-cm.^{2} mixed-bed resin column, consisting of Dowex-50-X8 (100-200 mesh) in the H+ form and Dowex-1-X8 (100-200 mesh) in the HCO_3 form. The sample was eluted with 2 ml. of water, and the eluate assayed for radioactivity. The eluted material was further characterized by thin-layer chromatography on cellulose plates developed in two different systems.[13,15] Ninety-eight per cent of the eluate radioactivity was in a spot which had the Rf of glucose.[13]

Serum lactate determinations were carried out by the enzymatic procedure of Horn and Brun[16]: Tissue glycogen determinations by the method of Seifter, Dayton, Novic and Muntwyler.[17]

Plasma insulin determinations were carried out by the procedure of Genuth, Frohman and Lebovitz.[18] In vitro pancreas studies were carried out by the method of Genuth and Lebovitz.[19]

Reserpine, α-methyloctopamine, α-methylmetatyrosine, phentolamine, tranylcypromine, iproniazid, nialamide, and pargyline were obtained from commercial sources. Lactate-U-C-14, palmitate-1-C-14, pyruvate-2-C-14, glucose-U-C-14 were obtained from New England Nuclear Corporation, Boston, Massachusetts, and dl-4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide • HCl (MJ 1999) was a gift of the Mead Johnson Company, and Prostaglandin E_1 was a gift of The Upjohn Company.

RESULTS

Effect of tranylcypromine on blood glucose and plasma insulin

The intraperitoneal administration of 0.4 mg. of tranylcypromine to mice resulted in a slight rise in blood glucose at 15 to 30 min., which was then followed by a profound hypoglycemia at 75 to 90 min. These results are shown in figure 1.

In order to ascertain the source of the blood glucose elevation seen in response to tranylcypromine at 15 to 30 min., liver and muscle glycogen was determined at 30 min. The data of table 1 show that tranylcypromine resulted in a marked reduction in liver glycogen but no significant depression of muscle glycogen.

The response of plasma insulin to tranylcypromine administration is shown in figure 2. Tranylcypromine caused a twenty-fold rise in plasma insulin which was maximal at 10 min. and remained elevated (two-fold) at 75 min.

The relationship between tranylcypromine dose and

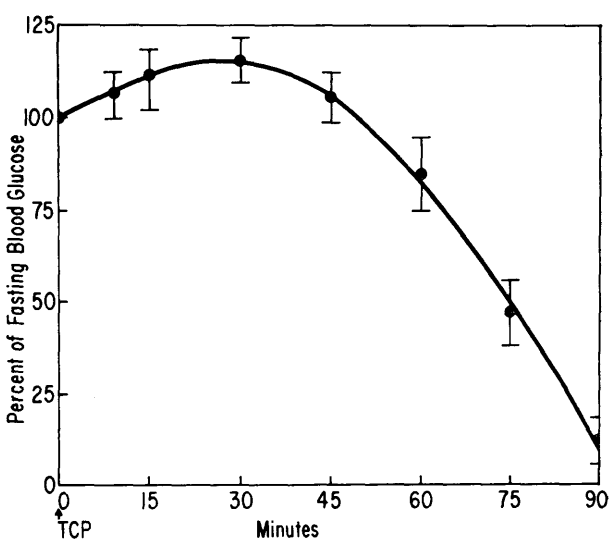

FIG. 1. The effect of tranylcypromine on blood glucose. Mice were given 0.4 gm. of tranylcypromine intraperitoneally and blood glucoses determined at the times indicated. Each time period represents the Mean ± S.E. of fifteen animals.

TABLE 1

The effect of tranylcypromine on liver and muscle glycogen. (Animals were divided into two groups. At zero time one group received 0.4 mg. of tranylcypromine intraperitoneally, whereas the other received saline. Animals were sacrificed 30 min. later and glycogen determination done on liver and gastrocnemius muscle.)

	Glycogen* (gm./100 gm. tissue)	
	Liver	Muscle
Control	0.213±0.032(9)	0.158±0.031(7)
Tranylcypromine	0.028±0.013(9)	0.134±0.045(9)
P	< 0.01	> 0.10

*Mean ± standard deviation. Numbers in parentheses are number of mice used.

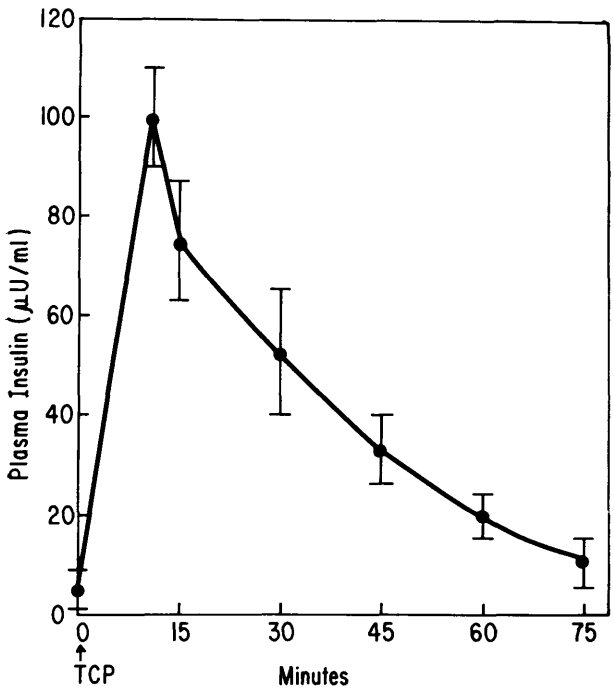

FIG. 2. The effect of tranylcypromine on plasma insulin. Mice were treated as described in figure 1 legend. At the time period indicated the TCP treated mice were decapitated and bled. Each time period represents the Mean ± S.E. of fifteen animals.

plasma insulin response in mice at 15 min. is shown in figure 3. In this plot each point represents the mean of five animals ± the standard error.

Effect of tranylcypromine on in vivo and in vitro substrate oxidations

The conversion of palmitate-1-C-14, glucose-U-C-14 and pyruvate-2-C-14 to C-14-O_2 by mice who were given intraperitoneal tranylcypromine 60 min. prior to the intravenous administration of the radioactive substrates in tracer amounts was the same as that of the controls. In these studies C-14-O_2 was collected at 10-

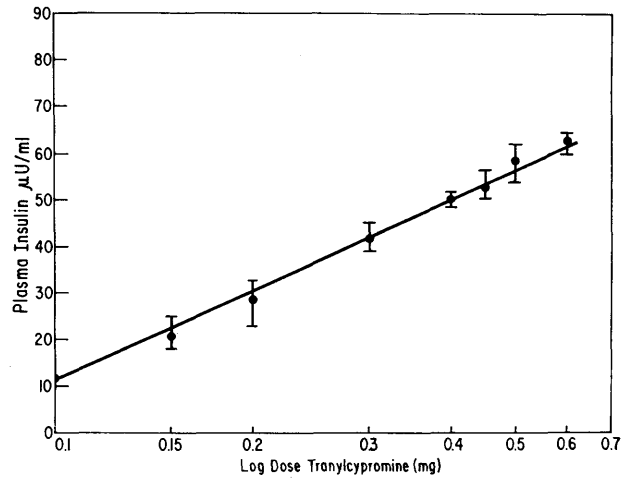

FIG. 3. Tranylcypromine-plasma insulin dose-response curve. Each point represents an average of five determinations per TCP dose.

min. periods for 90 min.

Oxidation of the aforementioned radioactive substrates to C-14-O_2 by myocardial and hepatic homogenates from mice which had been given tranylcypromine 60 min. prior to sacrifice was not different from that of the controls.

Effect of tranylcypromine on gluconeogenesis

Because of the evidence supporting a rapid suppressive effect of insulin on hepatic gluconeogenesis,[20-22] the effect of tranylcypromine on the conversion of lactate-U-C-14 to C-14-glucose was studied. Mice received tranylcypromine at zero time, and both treated and control groups received 100 μmoles of lactate at 60 min. Although the tranylcypromine-treated animals showed a rise in serum lactate at 15 and 30 min., the levels returned to those of the control group at 60 min. These results are shown in table 2.

The administration of lactate-U-C-14 to control animals resulted in a rise of blood glucose (and C-14-glucose) which were maximal at 15 to 30 min. The administration of tranylcypromine markedly inhibited

TABLE 2

The effect of tranylcypromine on serum lactate

	Serum lactate* (μmoles/ml.)
Controls	1.9(1.9, 2.3, 1.6, 1.8)
Tranylcypromine:	
15 min.	4.2(4.2, 4.7, 3.9, 4.3)
30 min.	3.1(2.6, 3.2, 3.0, 3.4)
45 min.	2.1(1.8, 2.0, 2.4, 2.3)
60 min.	1.9(1.8, 2.3, 2.1, 1.4)

*Means with individual values in parentheses.

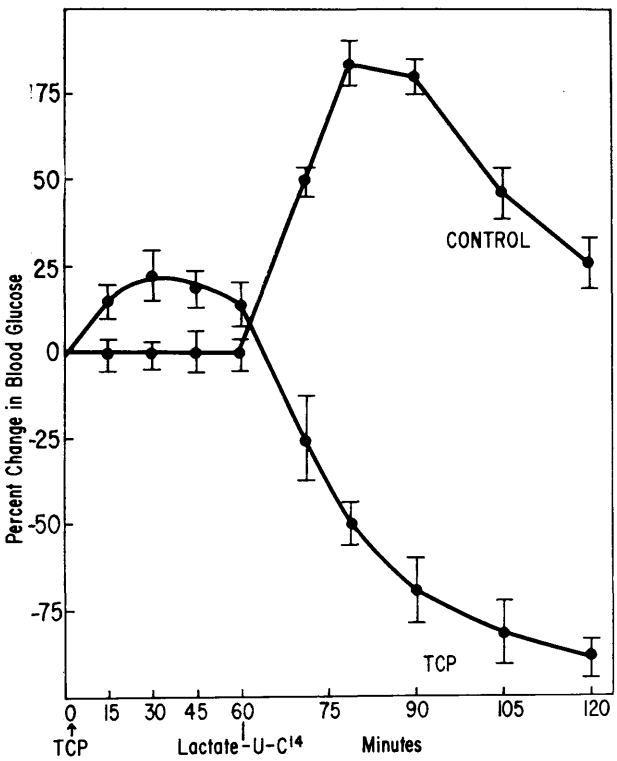

FIG. 4. The effect of tranylcypromine on gluconeogenesis. The animals were divided into two groups. At zero time, one group received 0.4 mg. of tranylcypromine intraperitoneally, whereas the control group received only saline. One hour later the animals all received 100 μmoles of lactate-U-C-14 (6 × 10^6 cpm) intraperitoneally. Blood glucose was assayed every 15 min. and the conversion of lactate-U-C-14 to C-14-glucose was determined at 15-min. intervals after administration of the lactate-U-C-14. Each time period represents the mean ± S.E. of twelve animals.

the conversion of lactate to blood glucose and caused profound hypoglycemia. These results are shown in figure 4.

The effect of tranylcypromine on the suppression of gluconeogenesis was discernible in advance of the hypoglycemia. When lactate-U-C-14 was administered 30 min. after tranylcypromine there was a decreased conversion of lactate-U-C-14 to C-14-glucose 15 min. after the lactate was given. This decrease in gluconeogenesis was evident, despite elevated blood glucose levels in the treated group (table 3). Although the serum lactate concentrations of the treated mice were greater at 30 min. (cf. table 2), the administration of a large pool of lactate-U-C-14 (100 μmoles) obviated any significant differences in lactate pool size between the treated and control groups. The data of table 3 show a large decrease in the conversion of lactate-U-C-14 to C-14-blood glucose in advance of the hypoglycemia. The failure of

TABLE 3

The temporal course of tranylcypromine on gluconeogenesis and blood glucose. (Animals were divided into two groups. At zero time one group received 0.4 mg. tranylcypromine intraperitoneally, whereas the other group received saline. Thirty minutes later all animals received 100 μmoles of lactate-U-C-14 (6 × 10^6 cpm) intraperitoneally. Blood samples were taken 15 min. after the administration of the lactate load.)

	Blood glucose			
	Controls		Tranylcypromine	
	cpm	mg. per 100 ml.	cpm	mg. per 100 ml.
1	98,400	135	38,200	123
2	113,700	151	41,800	137
3	89,300	137	29,700	121
4	93,800	143	33,400	145
5	108,500	146	36,500	118

tranylcypromine to augment glucose oxidation suggests that the decrease in gluconeogenesis is causally related to the hypoglycemia.

The effect of epinephrine and norepinephrine depletion on gluconeogenesis

In recent years a number of investigators have reported on the hypoglycemic action of a number of hydrazine and nonhydrazine monoamine oxidase inhibitors (MAOIs) in man and animals.[23-25] Cooper and Ashcroft have suggested that the monoamine oxidase inhibition might result in a replacement of epinephrine and norepinephrine in tissues by less potent adrenergic amines.[23] This could result in an inadequacy of homeostatic adrenergic mechanisms which control blood glucose (glycogenolysis and gluconeogenesis). Diabetic patients on oral sulfonylurea compounds or insulin would thus be more prone to hypoglycemic episodes because of an impaired capacity to respond to the fall in blood glucose.

To assess the effect of replacing the norepinephrine and epinephrine stores in mice on their capacity to convert lactate to glucose, α-methyloctopamine and α-methylmetatyrosine were administered for two days. Alpha-methyloctopamine results in a replacement of norepinephrine in the peripheral nerve stores.[26,27] Alpha-methylmetatyrosine penetrates the central nervous system as well as the peripheral nerves where it is converted to metaraminol (3-hydroxyphenylisopropanolamine) which replaces norepinephrine stores.[27,28] Both agents could replace adrenal medulla epinephrine stores.

Figure 5 shows that treatment of mice for two days with either of these agents did not impair the capacity of the animals to convert lactate to blood glucose. The treated mice demonstrated normal to augmented gluconeogenesis.

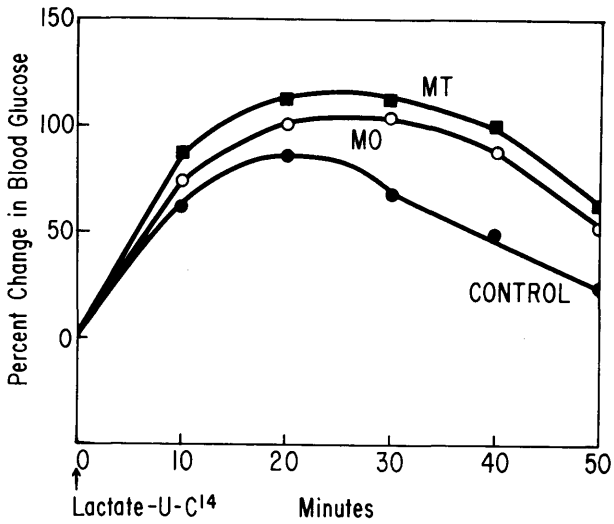

FIG. 5. The effect of α-methyloctopamine and α-methylmetatyrosine on gluconeogenesis. One group of mice received α-methyloctopamine (3 mg./kg.) intraperitoneally every twelve hours for three days prior to the start of the experiment, whereas the other group received α-methylmetatyrosine (100 mg./kg.) on the same schedule. The control groups received only saline. At the start of the experiment all groups received 100 μmoles of lactate-U-C-14 (6×10^6 cpm) intraperitoneally. Blood glucose and C-14-glucose were determined at the times indicated. Each time period represents the average of four determinations per group.

Effect of reserpine on the response to tranylcypromine

In order to ascertain whether the stimulation of insulin secretion by tranylcypromine was mediated by the release of endogenous catecholamines the epinephrine and norepinephrine stores were depleted by reserpine.[29] The data of table 4 show that the prior administration of reserpine to mice did not alter the stimulatory effect of tranylcypromine on insulin secretion. The reserpinized

TABLE 4

The effect of reserpine on the response of the blood glucose and plasma insulin to tranylcypromine. (Animals were divided into four groups. Eighteen hours prior to the start of the experiment two groups received 0.75 μg. of reserpine intraperitoneally, whereas the other two groups received saline. At zero time one group which had received reserpine and one group which had not received reserpine, was given 0.4 mg. of tranylcypromine intraperitoneally. Blood glucose and plasma insulins were determined at 15 min.)

Treatment	Blood glucose (mg. per 100 ml.)	Plasma insulin* (μU./ml.)
None	76±9(6)	4 ±2.8(6)
Reserpine	88±6(6)	3.8±1.5(6)
Tranylcypromine	91±4(6)	53. ±8.5(6)
Reserpine then tranylcypromine	98±10(6)	56. ±6.4(6)

*Mean ± standard deviation. Numbers in parentheses are number of mice used.

animals had higher levels of blood glucose but not of such magnitude as to elevate the insulin response.

Effect of monoamine oxidase inhibitors on insulin secretion

In order to ascertain whether the stimulation of insulin secretion by tranylcypromine was a property of its capacity to inhibit monoamine oxidase a number of other MAOIs were assayed. Marsalid is a hydrazine-type MAOI, whereas the others are not. Tolbutamide was used to assess the response of the animals. Table 5 shows the blood glucose and plasma insulin responses

TABLE 5

The effect of monoamine oxidase inhibitors on insulin secretion. (Animals were divided into six groups. The mice received either saline, 0.5 mg. tranylcypromine, 0.5 mg. pargyline, 1.25 mg. nialamide, 1.25 mg. marsalid or 5.0 mg. tolbutamide intraperitoneally. Samples of blood were obtained at 15 min. for assays of glucose and insulin.)

Control	Blood glucose* (mg. per 100 ml.)	Plasma insulin* (μU./ml.)
Control	75(76, 65, 77, 81)	5.7(7, 3, 9, 4)
Tranylcypromine	96(104, 94, 100, 86)	88.5(100, 94, 76, 84)
Pargyline	84(86, 96, 78, 76)	7.5(9, 7, 4, 10)
Nialamid	81(71, 83, 90, 80)	2.5(2, 1, 3, 3)
Marsalid	76(64, 78, 68, 94)	4.2(5, 3, 2, 7)
Tolbutamide	68(61, 76, 65, 78)	31.0(23, 41, 28, 32)

*Means with individual values in parentheses.

to these compounds. Tranylcypromine was the only MAOI which caused insulin secretion, and on a milligram basis was over thirty times as potent as tolbutamide. The data indicate that the secretion of insulin due to tranylcypromine is not related to its property of MAO inhibition.

Effect of β-adrenergic receptor blockade on the response to tranylcypromine

Because tranylcypromine resulted in an early rise in blood glucose and fall in liver glycogen (cf. figure 1 and table 1), a β-adrenergic effect of the drug was suggested. Animals were treated with a β-adrenergic receptor blocker, MJ 1999,[30] and the response to tranylcypromine ascertained. MJ 1999 markedly diminished both insulin secretion in response to tranylcypromine and the hypoglycemia (table 6). These data suggest that the stimulatory effect of tranylcypromine on insulin secretion is mediated via β-adrenergic receptor stimulation.

Effect of α-adrenergic receptor blockade on the response to tranylcypromine

Since it has been postulated that α and β receptors mediate divergent influences on insulin secretion,[1,5]

TABLE 6

The effect of MJ 1999 on the response of the blood glucose and plasma insulin to tranylcypromine. (Animals were divided into four groups. One hour prior to the start of the experiment two of the groups received 0.5 mg. of MJ 1999 intraperitoneally whereas the other two groups received saline. At zero time, one of the groups which had received MJ 1999 and one of the groups which had not, was given 0.4 mg. tranylcypromine intraperitoneally. Blood glucose and plasma insulins were determined at 15 and 75 min.)

Treatment	Blood glucose* mg. per cent	Plasma insulin* μU./ml.
None	73(68, 81, 72, 71)	5.2(7, 3, 6, 5)
MJ 1999	75(76, 88, 58, 78)	3.7(3, 6, 4, 2)
Tranylcypromine:		
15 min.	95(104, 95, 87, 93)	52.2(46, 55, 70, 38)
75 min.	27(36, 16, 24, 32)	7.8(9, 14, 5, 3)
MJ 1999 then Tranylcypromine:		
15 min.	86(71, 83, 94, 97)	17.0(19, 7, 31, 11)
75 min.	62(61, 48, 53, 84)	6.5(8, 10, 5, 3)

*Mean with individual values in parentheses.

TABLE 7

The effect of phentolamine on tranylcypromine stimulated insulin secretion. (Animals were divided into five groups. One group received 0.5 mg. of MJ 1999 intraperitoneally one hour prior to the start of the experiment. The other groups received saline. At zero time the MJ 1999 treated group received 0.4 mg. of phentolamine whereas the other groups received saline, 0.4 mg. tranylcypromine, 0.4 mg. phentolamine or 0.4 mg. tranylcypromine plus 0.4 mg. phentolamine intraperitoneally. Blood glucose and plasma insulins were determined at 15 min.)

Treatment	Blood glucose* (mg. per 100 ml.)	Plasma insulin* (μU./ml.)
None	86(95, 82, 78, 90)	9.2(9, 8, 11, 9)
Tranylcypromine	109(110, 100, 123, 104)	65.6(43, 90, 76, 54)
Phentolamine	92(83, 90, 96, 100)	25.2(21, 34, 29, 17)
Tranylcypromine + phentolamine	98(98, 114, 88, 92)	75.0(83, 66, 78, 73)
MJ 1999 then phentolamine	75(57, 91, 65, 87)	9.7(8, 14, 12, 5)

*Mean with individual values in parentheses.

α-adrenergic blockade was carried out using phentolamine[31] prior to the administration of tranylcypromine. The data of table 7 show that both α-adrenergic blockade (phentolamine) and β-adrenergic stimulation (tranylcypromine) caused an increased secretion of plasma insulin. When mice were first subjected to β-adrenergic blockade (MJ 1999), the insulin response to α-adrenergic blockade (phentolamine) was inhibited (table 6).

Effect of prostaglandin E_1 on the response to tranylcypromine

Because it has been reported that prostaglandin E_1 (PGE_1) elevates levels of cyclic 3'5' AMP in some tissues,[32] the response of plasma insulin to PGE_1 was studied. The data of table 8 show that PGE_1 stimulated the secretion of plasma insulin, and that this effect was additive to that of tranylcypromine when they were given together. The augmentation of insulin secretion caused by PGE_1 was decreased by β-adrenergic receptor blockade with MJ 1999, as was that due to tranylcypromine. These data suggest that PGE_1 increases insulin secretion via a β-adrenergic stimulatory mechanism.

TABLE 8

The effect of prostaglandin E_1 on insulin secretion. (Animals were divided into seven groups. When MJ 1999 was used 0.5 mg. was administered intraperitoneally one hour prior to the other agents. All other agents were administered at zero time. Prostaglandin E_1 was given in the doses indicated, and 0.4 mg. of tranylcypromine was administered where shown. Where tranylcypromine and prostaglandin E_1 were used together they were given at the same time. Blood glucose and plasma insulins were determined at 15 min.)

Treatment	Blood glucose* (mg. per 100 ml.)	Plasma insulin* (μU./ml.)
None	77±8(6)	3.8±1.8(6)
2.5 μg. PGE_1	118±11(6)	17.7±3.6(6)
5.0 μg. PGE_1	133±9(6)	34.5±4.1(6)
MJ 1999 then 2.5 μg. PGE_1	103±8(6)	11.1±1.2(6)
MJ 1999 then 5.0 μg. PGE_1	116±10(6)	12.2±2.4(6)
Tranylcypromine	98±7(6)	43.7±4.2(6)
Tranylcypromine 5.0 μg. PGE_1	127±11(6)	79.8±5.5(6)
MJ 1999 then tranylcypromine	83±8(6)	10.6±2.3(6)

*Mean ± standard deviation. Numbers in parentheses are number of mice used.

In vitro effect of tranylcypromine on the pancreas

To ascertain whether the effect of tranylcypromine on insulin secretion was a direct one, more definite evidence was sought by a study of insulin release in vitro. Tranylcypromine caused a significant augmentation of insulin output over that of the controls ($p < 0.02$). These data (table 9) show a direct stimulatory effect of tranylcypromine on insulin output by the pancreas.

DISCUSSION

Tranylcypromine is a potent monoamine oxidase inhibitor which has proved to be an effective antidepressant in man. In recent years a number of MAOI drugs have been found to possess hypoglycemic activity in animals and man. Although the mechanism of the hypoglycemic action of these MAOIs is unknown, one of

TABLE 9

The in vitro effect of tranylcypromine on insulin release. (The tail and body of the mouse pancreas were removed in a single piece under Nembutal anesthesia. The pancreas was cut into quarters, weighed on a torsion balance and preincubated for 30 min. in 2.0 ml. of Krebs-Ringer bicarbonate buffer containing sodium pyruvate 0.005M, sodium fumarate 0.005M, sodium glutamate 0.005M, glucose 60 mg./100 ml., bovine serum albumin 400 mg./100 ml., and gassed with 95% oxygen-5% carbon dioxide. Following the preincubation the medium was removed, the pancreas was rinsed with additional buffer and then incubated for 30 min. in 2.0 ml. of either the same medium, one with 0.4 mg./ml. tranylcypromine added or one with the glucose concentration raised to 300 mg./100 ml. At the conclusion of the incubation, the medium was chilled rapidly and assayed for insulin content. All incubations were performed at 37°C. in stoppered 10 ml. flasks in a gyrorotary shaker.)

Treatment	Insulin release* (μU./100 mg./30 min.)
Control	269±31(15)
Tranylcypromine	402±30(15)
Glucose (3 mg./ml.)	617±36(15)

*Mean ± standard error. Number in parentheses represents number of observations made.

them, tranylcypromine, is a potent stimulator of insulin secretion. Moreover, the insulin stimulating capacity of tranylcypromine appears to be unrelated to its MAOI activity because a number of other MAOI drugs do not stimulate insulin secretion. The hypoglycemic activity of tranylcypromine may be attributed to its stimulation of insulin release which results in a marked depression of gluconeogenesis. The tranylcypromine-induced insulin secretion appears to depend on the β-adrenergic receptor stimulatory activity of the drug. This activity was manifest by its activation of hepatic glycogenolysis, and like isoproterenol, its stimulation of insulin secretion was inhibited by β-adrenergic blockers.[1] These observations support the concept that stimulation of β-adrenergic receptors in the pancreatic islets increases, whereas stimulation of α-adrenergic receptors decreases insulin secretion. Turtle and Kipnis have presented evidence which suggests that the stimulatory and inhibitory influences noted are mediated via increases and decreases in pancreatic islet levels of cyclic 3′5′ AMP. The role of the α-adrenergic receptor is further underlined by studies which have shown that phentolamine can cause hypoglycemia in rabbits, dogs and man.[33] The increased insulin secretion which occurs in response to the administration of α-adrenergic blocking agents is decreased in adrenal demedullated rats[33] suggesting that the action of these drugs is mediated by release of epinephrine from the adrenal medulla.

A direct β-adrenergic receptor stimulatory effect of tranylcypromine on the pancreatic islet cells was supported by the in vitro stimulation of insulin secretion and is consonant with the failure of reserpine to diminish the tranylcypromine stimulated insulin-release in vivo.

The stimulation of insulin secretion by prostaglandin E_1 (PGE_1) and its inhibition by MJ 1999, a β-adrenergic receptor blocker, suggest that PGE_1 is effecting insulin secretion directly or indirectly via stimulation of a β-adrenergic receptor in the pancreatic islets. PGE_1 has been reported to increase levels of 3′5′ cyclic AMP in some tissues and thus could simulate the action of a β-adrenergic receptor stimulator in the pancreatic islets. It has been suggested by Clegg that prostaglandins might not occupy receptor sites themselves but might increase the affinity of sympathomimetic amines for the receptor site.[34] This would result in an enhanced binding of agonist on the receptor site.

These studies do not provide an explanation for the hypoglycemic activity of the MAOI drugs. The data do, however, suggest that Cooper's hypothesis of the hypoglycemic effects being due to an inadequacy of adrenergic homeostatic mechanisms, is not tenable.

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