DOPAMINE AGONIST-INDUCED HYPERGLYCEMIA IN RATS: STRUCTURE-ACTIVITY RELATIONSHIPS AND MECHANISMS OF ACTION

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The concentration of blood glucose was measured in rats after administration of a number of drugs characterized as dopamine agonists. Compounds that cause release of dopamine, or agents that block the reuptake of dopamine, did not elevate blood glucose. Some direct dopamine receptor stimulants (lergotrile, bromocriptine, apomorphine) caused hyperglycemia, but other agonists (e.g. pergolide) did not. Further experiments with lergotrile, the most active hyperglycemic dopamine agonist, revealed that the blood glucose increase was accompanied by a marked elevation in liver glycogen, indicating a gluconeogenic effect of the compound. This hypothesis was supported by using inhibitors of gluconeogenesis (L-tryptophan or 3-mercaptopicolinic acid) to block lergotrile's hyperglycemic action. Structure-activity relationships among close analogues of lergotrile suggest that the cyano moiety in the lergotrile molecule may be of importance in the hyperglycemic action of lergotrile. These results indicate that central dopamine stimulation per se does not cause hyperglycemia in rats.

Hyperglycemia Blood glucose Dopamine agonists Lergotrile Gluconeogenesis

1. Introduction

An elevation of blood glucose has been observed in humans following administration of dopamine (Leblanc et al., 1977) or L-dopa (Rayfield et al., 1975). L-Dopa also causes hyperglycemia in dogs (Hampshire et al., 1978) and mice (Håkanson et al., 1967). We reported (Schmidt, 1979) that lergotrile, a dopamine agonist in the ergoline class, caused a significant increase in blood glucose in rats. Apomorphine, another direct-acting dopamine agonist, also increased blood glucose, but changes in glucose were not observed with dopamine agonists such as amphetamine or methylphenidate, which release dopamine, or LR5182, a dopamine-uptake inhibitor. These observations led to the conclusion that hyperglycemia perhaps was not a property of central dopaminergic stimulation, although the mechanisms of action involved in the phenomenon were not understood.

The purposes of the present studies were to expand the number of dopamine agonists studied and to define the structural requirements for the hyperglycemia effect, specifically within the ergoline dopamine agonist category. Special emphasis was placed on lergotrile and pergolide, the newest and most potent dopamine agonists in this category (Fuller and Perry, 1978; Clemens and Smalstig, 1978) since these compounds have been found to be efficacious in clinical trials in Parkinson's disease (Lieberman et al., 1975, 1980; Lemberger et al., 1980). Attempts were also made to establish the biochemical mechanism by which lergotrile elevates blood glucose in the rat.

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The data reported here will illustrate that compounds that block dopamine uptake or agents which release dopamine do not produce hyperglycemia, while some, but not all, direct-acting dopamine agonists cause hyperglycemia. Pergolide, a close analogue of lergotrile, does not cause a significant increase in blood glucose, perhaps relating to the fact that pergolide does not contain a cyano group in the molecule. Mechanistically, it will be shown that lergotrile hyperglycemia is associated with a dramatic increase in liver glycogen, suggestive of a gluconeogenic response to the compound. Evidence will be presented to document that this in fact is the case since the effects of lergotrile can be blocked by pretreatment with L-tryptophan or 3-mercaptopicolinic acid, two compounds that inhibit phosphoenolpyruvate carboxykinase (PEPCK) (EC 4.1, 1.32), a main branch point enzyme in the gluconeogenic pathway.

2. Materials and methods

2.1. General

Male Sprague-Dawley rats (Laboratory Supply Company, Indianapolis, IN), 150 g, were used throughout the studies. When indicated, rats were fasted 18 h prior to use, otherwise they were allowed free access to food (Purina Rodent Chow) and water until the start of the experiment. Studies were conducted between 8 a.m. and 3 p.m.

Rats were injected i.m. with 200 units of heparin 5-15 min before drawing the first blood samples. Blood was obtained by cutting off the tip of the tail and aspirating 0.05 ml of blood into a micropipette. Duplicate samples were then diluted in 24 mM NaF and stored at room temperature for the remainder of the day until analyzed for glucose.

2.2. Experimental design

Studies were conducted using groups of 5–12 rats per treatment condition. A saline-treated control group was run along with each set of drug-treated rats. Compounds were dissolved in water or 0.1 percent ascorbic acid and injected i.p. Shortly after heparin was administered, a blood sample was taken which served as the 'control' point for subsequent samples. Drugs were administered 30 min after the initial sampling and blood was then drawn at various times depending on the purpose of specific experiments. In some experiments animals were sacrificed by decapitation and samples of liver and muscle were taken for analysis of glycogen content. Blood was also drawn at these times for measurement of serum insulin and glucagon levels. Inhibitors of gluconeogenesis were administered 2 h (3-mercaptopicolinic acid) or 3 h (L-tryptophan) prior to administration of lergotrile. Doses of compounds were maximal effective doses based on reports in the literature.

2.3. Analytical methods

Blood glucose was measured in a Technicon Autoanalyzer using a modification of the ferricyanide reduction method of Hoffman (1963). Several series of glucose standards were run intermittently during the day with each set of plasma samples. Unknown samples were usually assayed in duplicate. Data are expressed as mg glucose per dl of blood. When tissue glycogen concentrations were to be measured the rats were killed by decapitation, the tissues were removed, and samples frozen between slabs of dry ice and stored in the freezer. Tissue glycogen concentrations were measured by the method of Good et al. (1933) with the glucose measured in the Autoanalyzer (Hoffman, 1963). Serum insulin concentration was measured by radioimmunoassay using ethanol to precipitate the antibody-bound insulin (Heding, 1966). The antiserum, produced in guinea pigs by the injection of procine insulin, binds most mammalian insulins. The standard curve for the measurement of serum insulin concentrations was prepared with highly purified rat insulin. The assay was sensitive to 0.05 ng/ml of rat insulin. Serum glucagon was determined by the radioimmunoassay method of Unger et al. (1970) using antiserum, developed in our laboratories, which is highly specific for pancreatic glucagon and does not cross react with canine gut glucagon at physiological concentrations.

2.4. Drugs used

Drugs used were lergotrile mesylate, pergolide mesylate and LR5182, cis-3-(3,4-dichlorophenyl)-2-N,N-dimethylaminomethyl-bicyclo-[2,2,2]- octane hydrochloride (Eli Lilly and Company), methylphenidate (Ciba-Geigy), apomorphine hydrochloride (Merck), amfonelic acid (Sterling-Winthrop), nomifensin (Hoechst), and mazindol, LSD and bromocriptine (Sandoz). Ergoline derivatives were synthesized at The Lilly Research Laboratories by Dr. E. Kornfeld and Mr. N. Bach. L-Tryptophan was purchased from Sigma Chemical Company. Mr. N. Di Tullio kindly supplied 3-mercaptopicolinic acid from Smith-Kline and French. All other chemicals were from standard commercial sources. All dopaminergic agents were dissolved in 0.1 percent ascorbic acid immediately before use.

3. Results

3.1. The effects of various compounds on blood glucose levels (fig. 1)

Agents known to block the reuptake of dopamine (LR5182 and nomifensin) did not cause a statistically significant increase in blood glucose. No hyperglycemia was observed following administration of compounds which stimulate the release of endogenous dopamine stores (mazindol,

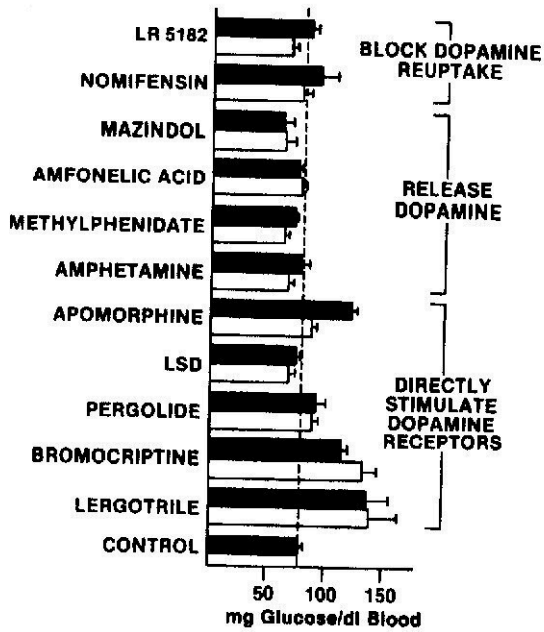

Fig. 1. Effects of dopaminergic stimulants on blood glucose concentrations. Rats were fasted 18 h and administered (i.p.) one of the following compounds at the doses indicated: LR5182, 10 mg/kg; nomifensin, 20 mg/kg; mazindol, 10 mg/kg; amfonelic acid, 5 mg/kg; methylphenidate, 10 mg/kg; amphetamine, 2.5 mg/kg; apomorphine, 10 mg/kg; LSD, 2 mg/kg; pergolide, 2 mg/kg; bromocriptine, 5 mg/kg; lergotrile, 2 mg/kg. Bars represent the mean ±S.E.M. for 5 rats per drug treatment group. The data are from 3 separate experiments, with the control representing 15 ascorbic-treated rats (verticle broken line). One and 2 h data are depicted, which were times of maximal response: solid bar is 1 h and open bars 2 h time points. S.E.M. is shown.

TABLE I

Effect of varying doses of pergolide on blood glucose. Values represent the mean ±S.E.M. of 5 rats per group. Rats were fasted 18 h and administered (i.p.) pergolide at one of the following doses indicated (0.1 mg/kg to 2 mg/kg). A control group received 0.1 percent ascorbic acid. Blood glucose concentrations were measured at 30 min, 1, 2, 4 and 6 h after injection of drug. Data are mg glucose/dl blood.

Treatment group	Hours postinjection					
	0	0.5	1	2	4	6
Ascorbic acid	87±3	90±6	88±5	82±2	90±4	88±3
Pergolide						
0.1 mg/kg	78±2	84±1	83±3	79±2	93±8	94±7
0.4 mg/kg	83±2	96±2	98±3	91±3	92±3	96±4
1.0 mg/kg	79±2	100±5	100±2	95±2	92±5	90±9
2.0 mg/kg	83±2	104±3	98±4	93±8	93±6	91±8

amfonelic acid, methylphenidate, and amphetamine). Four of five drugs known to directly stimulate dopamine receptors elevated blood glucose (apomorphine, pergolide, bromocriptine and lergotrile). LSD did not elevate the blood glucose. The magnitude of the changes within the compound series was variable, with the greatest increase produced by lergotrile and bromocriptine followed by apomorphine. Pergolide did not consistently increase blood glucose in the remaining experiments.

3.2. Relationship between the dose of pergolide and blood glucose concentration (table 1)

Doses of pergolide as low as 0.1 mg/kg or as high as 2 mg/kg failed to elicit a consistent change in blood glucose at any time between 30 min and 6 h after injection. The largest increase seen was at 1 mg/kg, 30-60 min after injection, and this amounted to an increase of only 26 percent. In a subsequent experiment, lergotrile and pergolide were compared directly at a high dose of 5 mg/kg. The maximal increase in blood glucose observed with lergotrile was 104 percent while pergolide at the same dose elicited no change in blood glucose (data not shown).

3.3. Comparison of the effect of structurally related analogues of lergotrile and pergolide on blood glucose concentration (fig. 2, table 2)

Structural analogues of lergotrile and pergolide were compared for their ability to increase blood glucose (fig. 3). Compounds A, B and C all elicited

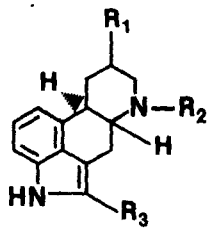

Fig. 2. The ergoline nucleus. R_1, R_2 and R_3 refer to chemical substituents noted in table 2.

50 to 60 percent increases in blood glucose, and all compounds possessed a methylcyano in the R-1 position, with varying substituents in R-3. Compounds D, E and F failed to significantly elevate blood glucose and none of these compounds had a cyano moiety in the structure, although there was correspondence in the R-3 and R-2 positions (table 2).

3.4. Blood glucose, insulin and glucagon and changes in liver and muscle glycogen concentrations following lergotrile (fig. 4)

A number of biochemical parameters were measured in an attempt to determine the reasons for the lergotrile induced elevation of blood glucose in rats. Following administration of 5 mg/kg of lergotrile, blood glucose rose rapidly within 1 h to a value 90 percent above control (fig. 4). Blood glucose concentrations remained elevated for 3 h and then fell towards control values at 5 h (fig. 4). During this same time, plasma insulin increased 500 percent in response to the elevation of blood

TABLE 2

Structures of ergolines examined for hyperglycemic activity.

Fig. 3	Compound No.	R_1	R_2	R_3
A	Lergotrile	CH_2CN	CH_3	Cl
B	LY79344	CH_2CN	CH_3	H
C	LY89788	CH_2CN	CH_3	Br
D	Pergolide	CH_2SCH_3	$CH_2CH_2CH_3$	H
E	LY60722	CH_2OH	CH_3	H
F	LY110057	CH_2OH	CH_3	Cl

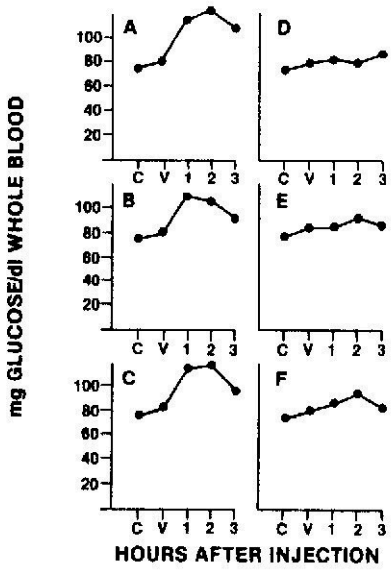

Fig. 3. Comparison of the effects of structurally related analogues of lergotrile and pergolide on blood glucose concentration. Initial blood samples were drawn from rats (C) and animals were then administered either 0.1 percent ascorbic acid or vehicle (1 mM hydrochloric acid) and another sample was taken 1 h thereafter (V). Compounds were then administered and blood glucose measured at 1, 2 and 3 h after i.p. injection. All compounds were administered at 5 mg/kg. The data represent a summary of two separate experiments with 5 animals/group in each experiment. The structures of the compounds are shown in table 2, indicating variations at key points (R-1, R-2 and R-3). The basal concentration of blood glucose varied between 68 and 77 mg/dl for all rats and variability within an experiment was less than 10 percent.

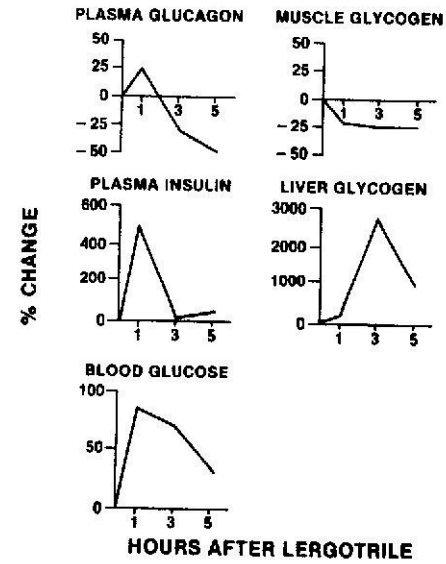

Fig. 4. Changes in blood glucose, insulin, and glucagon, and liver and muscle glycogen concentrations following lergotrile. Rats were fasted 18 h and administered 0.1 percent ascorbic acid or 5 mg/kg of lergotrile i.p. Parameters were measured at 1, 3 and 5 h after administration of drug. Values represent the mean ±S.E.M. for 12 determinations at each time point for glucose and glycogen and 6 determinations for insulin and glucagon.

glucose, with insulin falling rapidly to control levels at 3 h. Plasma glucagon increased slightly at 1 h and then fell precipitously to 50 percent below control at 5 h. Throughout the experiment there was a slight decrease in muscle glycogen. The change in liver glycogen concentration following lergotrile was remarkable. Although no alteration was seen 1 h after administration of lergotrile, liver glycogen thereafter increased markedly to nearly 3000 percent above control values at 3 h, with concentrations then declining to 1000 percent over control at the 5 h time point (fig. 4). Liver glycogen concentrations in 18-h fasted rats were 0.33 mg/g of liver and this value remained constant during the 5 h period in control animals. At the 3 h peak, liver glycogen levels were 8.44 mg/g of liver in lergotrile-treated rats. Considerable variability was encountered in liver glycogen values, with values ranging as high as 17.21 mg/g of liver in some animals receiving lergotrile. Table 3 summarizes the concentrations measured at the 1 and 3 h time point.

3.5. Hyperglycemic effects of lergotrile in fasted compared to fed rats (table 4)

Eighteen hours of fasting reduced blood glucose levels 33 percent: 120 mg/dl in fed and 80 mg/dl after fasting. Lergotrile elevated blood glucose in fed as well as fasted rats, but the increase was much larger after fasting; a 35 percent (43 mg/dl) increase in fed rats and a 95 percent (75 mg/dl) increase in fasted animals.

TABLE 3

Blood glucose, insulin and glucagon and changes in liver and muscle glycogen concentrations following lergotrile. Rats were fasted 18 h and administered 0.1 percent ascorbic acid or 5 mg/kg of lergotrile i.p. Parameters were measured at 1, 3 and 5 h after administration of drug. Values represent the mean ± S.E.M. of the mean for 12 determinations at each time point for glucose and glycogen and 6 determinations for insulin and glucagon.

	1 h		3 h	
	Control	Lergotrile	Control	Lergotrile
Glucose (mg/dl)	71 ± 2	123 ± 9	70 ± 3	121 ± 15
Liver glycogen (mg/g)	0.33 ± 0.07	0.68 ± 0.20	0.30 ± 0.11	8.44 ± 2.11
Muscle glycogen (mg/g)	1.77 ± 0.38	1.54 ± 0.30	2.26 ± 0.17	1.77 ± 0.12
Insulin (pg/ml)	85 ± 39	525 ± 140	277 ± 75	261 ± 38
Glucagon (pg/ml)	125 ± 20	152 ± 19	109 ± 6	79 ± 8

3.6. Effect of pretreatment with L-tryptophan on the hyperglycemic effects of lergotrile (table 5)

L-Tryptophan, a known inhibitor of gluconeogenesis, was administered to determine if it would alter lergotrile's influence on blood glucose. Administration of 750 mg/kg of L-tryptophan did not alter resting concentrations of blood glucose 3 or 6 h later, but liver glycogen was decreased 68 percent (table 5). Administration of lergotrile increased blood glucose 77 percent in saline-pretreated animals, but in tryptophan pretreated animals the blood glucose change was only 32 percent. A more dramatic effect was seen with respect to liver glycogen, where lergotrile increased liver glycogen 1,075 percent in saline pretreated animals, but glycogen did not change in tryptophan pretreated animals 3 h after administration of lergotrile.

3.7. Effect of pretreatment with 3-mercaptopicolinic acid, a potent inhibitor of gluconeogenesis, on the hyperglycemic effects of lergotrile (table 6)

Administration of 150 mg/kg of 3-mercaptopicolinic acid led to a progressive reduction in resting amounts of blood glucose, evidenced as a

TABLE 4

Hyperglycemic effects of lergotrile in fed compared to fasted rats. Rats were fasted 18 h or not fasted prior to the experiment. Lergotrile (5 mg/kg) was administered i.p. and glucose measured 1 h later. Values represent the mean ± S.E.M. of 6-7 rats per group. Numbers show mg glucose/dl of blood. N.S. indicates not statistically different from fed, control rats or '0' time controls, respectively. The percent changes shown were significant at $P < 0.05$ using Student's t-test.

	Control			Lergotrile		
	0	1 h	Percent Δ	0	1 h	Percent Δ
Fed	120 ± 3	116 ± 3	N.S.	124 ± 3	167 ± 5	+ 35
Fasted	80 ± 2	81 ± 4	N.S.	79 ± 5	154 ± 8	+ 95
Percent difference from fed	− 33	− 30		− 36	N.S.	

TABLE 5

Effect of pretreatment with L-tryptophan on the hyperglycemic effects of lergotrile. Rats were administered 750 mg/kg L-tryptophan or saline (p.o.) 3 h prior to 5 mg/kg lergotrile or 0.1 percent ascorbic acid (i.p.). Blood glucose and liver glycogen were determined 3 h later. Values represent the mean ± S.E.M. of 6 rats per group. Blood glucose is expressed in mg/dl of blood and liver glycogen as mg/g wet wt. The percent changes shown indicate the effects of lergotrile treatment vs appropriate ascorbate-treated control rats. N.S. indicates that no statistically significant change had occured.

	Ascorbic acid		Lergotrile	
	Blood glucose	Liver glycogen	Blood glucose	Liver glycogen
Saline pretreatment	70 ± 2	0.59 ± 0.19	124 ± 4 +77 percent	6.93 ± 0.95 +1075 percent
L-Tryptophan pretreatment	78 ± 7	0.10 ± 0.02	103 ± 5 +32 percent	0.12 ± 0.02 N.S.

TABLE 6

Effect of pretreatment with 3-mercaptopicolinic acid on the hyperglycemic effects of lergotrile. Rats were administered 150 mg/kg 3-mercaptopicolinic acid or saline (p.o.) 2 h prior to 5 mg/kg lergotrile or 0.1 percent ascorbic acid (i.p.). Blood glucose and liver glycogen were determined 3 h later. Values represent the mean ± S.E.M. of 6 rats per group. Blood glucose is expressed in mg/dl of blood and liver glycogen as mg/g wet wt. The percent changes shown indicate the effects of lergotrile treatment vs. appropriate ascorbate-treated control rats. N.S. indicates that no statistically significant change had occurred. The percent changes shown in parentheses depict the effects of 3-mercaptopicolinic acid pretreatment.

	Ascorbic acid		Lergotrile	
	Blood glucose	Liver glycogen	Blood glucose	Liver glycogen
Saline pretreatment	74 ± 3	4.65 ± 1.00	153 ± 14 106 percent	16.00 ± 1.79 244 percent
3-Mercaptopicolinic acid pretreatment	55 ± 2 (−66 percent)	0.12 ± 0.01 (−97 percent)	34 ± 8 N.S.	0.11 ± 0.01 N.S.

35 percent decrease at 1 h and a 62 percent decrease 2 h after treatment (table 6). Blood glucose concentrations were stable in saline-pretreated animals. Liver glycogen in saline pretreated animals was higher than in previous experiments (4.65 mg/g) but 3-mercaptopicolinic pretreatment reduced liver glycogen to 0.12 mg/kg. Administration of lergotrile (5 mg/kg) caused a 100 percent increase in blood glucose in saline-pretreated animals and increased liver glycogen 329 percent (table 6). However, in 3-mercaptopicolinic-pretreated animals neither blood glucose nor liver glycogen were elevated.

4. Discussion

The present experiments have confirmed that lergotrile exerts a hyperglycemic effect in rats and this work has provided insights as to possible biochemical mechanisms through which this effect might occur. Earlier suggestions that the hyperglycemic response to lergotrile was elicited through central dopaminergic stimulation (Schmidt, 1979) now appear unfounded (fig. 1). Only 3 of 11 compounds that cause dopaminergic effects in rats caused a significant and consistent elevation of blood glucose; apomorphine, bromocriptine, and lergotrile. Compounds that block the reuptake of dopamine, release dopamine stores, or directly stimulate dopamine receptors failed to change blood glucose concentrations, even though these compounds caused intense behavioral signs of dopamine stimulation such as continuous sniffing, piloerection, and in some cases gnawing. The fact that pergolide, an extremely potent and long-lasting dopamine agonist (Clemens and Smalstig, 1978; Lieberman et al., 1980; Fuller et al., 1979)

did not consistently or markedly increase blood glucose demonstrates this point most decisively. Hyperglycemia has also not been observed during clinical trials with pergolide (L. Lemberger, personal communication), although some moderate fluctuations have been observed during long-term toxicology studies in rats and dogs (N. Owen, personal communication). These latter effects have been small and inconsistent. The marginal change in blood glucose caused by pergolide and the lack of effect of LSD indicates that the hyperglycemic response to lergotrile is not a general property of compounds in the ergoline category; e.g. lergotrile and bromocriptine increase blood glucose while LSD and pergolide failed to increase blood glucose.

The fact that lergotrile and pergolide are close structural relatives which both induce intense dopaminergic stimulation, yet only lergotrile produces hyperglycemia, prompted a more thorough examination of the chemical differences in the compounds that might account for the hyperglycemic phenomenon. Tests with derivatives of lergotrile and pergolide in which the halogen and cyano groups were added or deleted (table 2) showed (fig. 2) that the cyano group of the molecule was associated with the rise in blood glucose. To our knowledge, the effects on blood glucose of cyano moieties added to other molecular structures have not been studied. However, the fact that free cyanide can uncouple oxidative phosphorylation and arrest mitochondrial respiration indicates that similar but more subtle effects of the cyanide group may occur in the liver of treated animals. Lergotrile did elicit changes in some liver enzymes and cause mitochondrial abnormalities in clinical trials (Jones et al., 1979). Therefore, it was hypothesized that the hyperglycemia observed in rodents might be a reflection of liver malfunction and so further experiments were performed to establish potential mechanisms.

Lergotrile caused an increase in blood glucose within 15 min with a peak effect between 1 and 3 h (Schmidt, 1979). It was not unexpected that glucagon concentrations decreased following lergotrile while plasma insulin was markedly elevated (fig. 4). The decreased muscle glycogen observed (-25 percent) might be explained by the intense motor stimulation elicited by lergotrile which activates dopamine receptors in motor areas of the brain. In the present studies this was manifested by hyperactivity, piloerection, head bobbing and gnawing. The most marked effect of lergotrile was the many-fold increase in liver glycogen stores which occurred between 1 and 3 h after administration of the compound (fig. 4). The fact that liver glycogen levels increased following the blood glucose rise suggested that gluconeogenesis might be the means by which the change was effected. This was supported by subsequent studies (table 4) in which the hyperglycemic effect was greater in fasted rats than in fed rats. The hyperglycemia produced by L-dopa only occurs in fed mice (Håkanson et al., 1967) while hypoglycemia is seen in fasted mice. Thus, the L-dopa hyperglycemia results from the breakdown of liver glycogen. However, lergotrile's effect on blood glucose does not depend upon intact stores of glycogen since the effect is more marked in the fasted animals. Furthermore, fasting enhances gluconeogenesis (Soling et al., 1970) and it would appear that lergotrile potentiates that action.

Definitive evidence that lergotrile elicits hyperglycemia through gluconeogenesis came from studies using inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme in the gluconeogenic pathway. L-Tryptophan (Foster et al., 1966) and 3-mercaptopicolinic acid (Robinson and Oei, 1975; Jomain-Baum et al., 1976) inhibit PEPCK and prevent the production of glucose from aminoacids. These inhibitors led to a substantial fall in liver glycogen concentrations (tables 5 and 6) and caused either partial (L-tryptophan) or complete (3-mercaptopicolinic acid) blockade of the hyperglycemic actions of lergotrile. In neither case were the dopaminergic signs reduced. Thus, it would appear that lergotrile exerts its effects on blood glucose by stimulating gluconeogenesis through PEPCK.

Confirmation of this fact has come from studies of R. Merryfield and H. Lardy (personal communication). These investigators have isolated a 'ferrous activator protein' which is capable of transporting iron to the active site of PEPCK thereby causing an activation of gluconeogenesis in vitro. Studies of lergotrile and pergolide in this

system revealed that while lergotrile was able to elicit an activation of PEPCK in vitro such was not the case with pergolide. Furthermore, a cyano derivative in the ergoline category also activated PEPCK, again pointing to the cyano as a critical moiety. Based on these findings, we hypothesize that the cyano moiety of lergotrile might act in vivo as a ferrous carrier which activates PEPCK and stimulates the synthesis of glucose from non-glucose precusors.

The PEPCK activation rationale would explain the hyperglycemic effects of lergotrile (fig. 1) and the structural modification studies shown in fig. 2 and table 2. It would not, however, explain the hyperglycemic effects of bromocriptine or apomorphine. Therefore, other mechanisms might also exist for this phenomenon. It is possible that the hyperglycemic activity of bromocriptine and apomorphine are being exerted through central nervous stimulation at unique receptor sites. Multiple dopamine receptors have been identified biochemically, but functional or physiological roles for the multiple receptors have yet to be defined. Perhaps some agents may act through central nervous system stimulation to increase blood glucose, possibly through dopamine receptors with which lergotrile does not react, or at discrete anatomical sites (e.g. the hypothalamus).

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