

Terguride But Not Bromocriptine Alleviated Glucose Tolerance Abnormalities and Hyperlipidaemia in Obese and Lean Genetically Hypertensive Koletsky Rats

V. GOLDA, L. CVAK¹

Institute of Experimental Neurosurgery, Hradec Králové and ¹GALENA, Komárov, Czech Republic

Received October 11, 1993

Accepted July 18, 1994

Summary

Glucose tolerance, total plasma cholesterol and plasma triglycerides were studied in the genetically hypertensive obese Koletsky rats (SHR/N-cp) and in their lean siblings. The initial part of the glucose tolerance curve was substantially elevated in both obese and lean Koletsky animals compared to normotensive Wistar rats. The abnormal glucose tolerance in hypertensive rats was accompanied by increased total plasma cholesterol and plasma triglycerides. Long-term treatment with dopaminergic agonists terguride or bromocriptine (0.2 and 2.0 mg/kg/day, respectively) exerted similar effects on lipid metabolism but both drugs differed in their influence on glucose tolerance. Terguride lowered plasma lipids and normalized glucose tolerance in both obese and lean Koletsky rats. Bromocriptine reduced hyperlipidaemia but did not attenuate the abnormalities of glucose tolerance in either lean or obese Koletsky animals.

Key words

Glucose tolerance abnormalities – Hyperlipidaemia – Koletsky SHR/N-cp rats – Terguride – Bromocriptine

Introduction

Golda and Petr (1989) found the abnormalities of glucose tolerance in the obese genetically hypertensive Koletsky (SHR/N-cp) rats as well as in their lean siblings. The abnormalities were present predominantly in the initial part of the glucose tolerance curve. It is worthwhile to note that the genetic abnormalities of the glucose tolerance were accompanied by alterations of insulin binding to erythrocytes and hepatocytes (Hilgertová et al. 1988). Insulin binding was decreased in both obese and lean SHR/N-cp rats when compared to the normotensive Wistar rats. On the other hand, the basal plasma insulin was elevated only in the obese animals.

Cincotta and Meier (1989) suggested that prolactin has a primary role in supporting the hepatic lipogenic activities of insulin and that bromocriptine, a dopaminergic antagonist which inhibits prolactin secretion, can be used to reduce lipogenesis. The aim of our experiments was to examine the effects of two different dopaminergic agonists (terguride and

bromocriptine) in animals with genetic alterations of glucose tolerance, insulin binding and plasma lipids.

Material and Methods

Animals

Experiments were carried out in normotensive Wistar rats as well as in obese and lean genetically hypertensive SHR/N-cp rats (Koletsky 1975) of both sexes. Lean SHR/N-cp rats represent dominant non-obese homozygotes and heterozygotes whereas their obese siblings are recessive homozygotes (cp/cp). The abnormal animals were obtained by Koletsky (1975) when mating a female spontaneously hypertensive rat (Okamoto-Aoki strain) with a normotensive Sprague-Dawley male rat. The genetically obese animals appeared after several generations of selective

inbreeding of hypertensive offsprings of the original cross.

The blood pressure (measured by an indirect method) attained in lean genetically hypertensive SHR/N-cp males 24.61 ± 2.22 kPa ($n=15$), 17.60 ± 1.32 kPa ($n=8$) in females (Golda and Petr 1982). The obese genetically hypertensive SHR/N-cp rats show comparable blood pressure (Koletsky 1975). After weaning at the age of 30 days the animals were kept in groups of four and supplied with water and DOS-2b pelleted diet *ad libitum*. During the experiment the animals were kept in groups of two. Body weight, water and pellet intake was daily controlled (except Saturdays and Sundays).

Plasma lipids

Blood sampled after the decapitation (without anaesthesia at 07.00 after 14 h starvation) was centrifuged and the serum was stored in plastic tubes at -20 °C. Total plasma cholesterol and plasma triglycerides were estimated enzymatically by Hitachi analyzer.

Glucose tolerance

Blood was sampled to heparinized capillaries (from the retrobulbar plexus under light ether anaesthesia) before glucose loading (basal glycaemia) as well as 30, 60, 120 and 180 min after glucose loading. Glucose (3 g/kg b.w., 30% solution) was applied intragastrically after 14 h starvation. Glycaemia was estimated enzymatically.

Terguride and/or bromocriptine treatment

The drugs were applied i.p. in two daily doses (07.00 and 14.00) for 21 days (when lipaemia was investigated) or for 11 days only (when glucose tolerance was monitored). Terguride maleate was administered at a dose of 0.1 mg/kg, bromocriptine maleate at a dose of 1.0 mg/kg (or 10 mg/kg in lean SHR/N-cp females only).

Statistics

The data were analyzed by the Student t-test.

Results

Strain and sex dependence of hyperlipidaemia

Total plasma cholesterol (Table 1) showed a clear-cut strain dependence. The obese genetically hypertensive SHR/N-cp males had elevated plasma cholesterol compared to both the lean ones and normotensive Wistar males. On the other hand, the

lean SHR/N-cp females had higher values than the obese ones or normotensive Wistar females. The most pronounced strain dependence was demonstrated in plasma triglycerides which were markedly elevated in the obese SHR/N-cp animals of both sexes (Table 1).

Total plasma cholesterol (Table 1) also showed sex dependence in the normotensive as well as in the lean SHR/N-cp rats; the values being always higher in the females. Sex dependence in plasma triglycerides was found only in the lean SHR/N-cp rats; the levels being also increased in the females.

The effects of terguride and bromocriptine on plasma lipids

Terguride (Table 1) decreased total plasma cholesterol in the normotensive females as well as in the obese and lean SHR/N-cp rats of both sexes. Plasma triglycerides were decreased by this drug only in obese and lean SHR/N-cp females.

Bromocriptine (Table 2) lowered significantly plasma cholesterol and plasma triglycerides in female but not in male obese and lean SHR/N-cp rats.

The effects of terguride and bromocriptine on body weight gain

Terguride decreased the gain of body weight during 21 days (Table 1) in the normotensive males, in the normotensive females as well as in the lean and obese SHR/N-cp females.

Bromocriptine decreased the gain of body weight (Table 2) in the obese SHR/N-cp males and females as well as in the lean SHR/N-cp females.

The effect of terguride and bromocriptine on pellet intake

Terguride (Table 1) reduced pellet intake during the first week of treatment in the normotensive males as well as in the lean SHR/N-cp males and females; in the third week the decrease was found in the normotensive males.

Bromocriptine lowered pellet intake only in obese SHR/N-cp males during the first week of treatment (Table 2).

Strain and sex dependence of glucose tolerance

There was a considerable strain dependence in the glucose tolerance (Fig. 1). At all intervals after glucose loading SHR/N-cp rats of both sexes reached higher glucose levels than the normotensive Wistar rats. In addition, the genetically hypertensive obese SHR/N-cp males had higher values than their lean siblings. This was not true in SHR/N-cp females in which the response of plasma glucose to glucose loading was similar in the lean and obese animals (Fig. 1).

Table 1

Body weight (BW), pellet intake as well as total plasma cholesterol and plasma triglycerides in control and terguride-treated normotensive Wistar rats (NR), genetically hypertensive non-obese Koletsky rats (lean SHR/N-cp) and their obese siblings (obese SHR/N-cp).

Strain	Treatment	n	Age (months)	Initial BW (g)	BW gain (in %) during 21 days	Triglycerides (mmol/l)	Cholesterol	Pellet intake (g/100 g b.w./day) 1st week	3rd week
<i>Males</i>									
<i>NR</i>									
	Controls	8	5	337±24	+8.10±5.37	0.69±0.07	1.66±0.21	5.60±0.33	6.25±0.11
	Terguride	8	5	340±43	+3.80±2.15*	0.66±0.07	1.67±0.19	4.83±0.18**	6.44±0.26
<i>Lean SHR/N-cp</i>									
	Controls	8	4	311±18	+3.88±2.15#	0.60±0.10	1.62±0.10	6.83±0.51	6.63±0.43
	Terguride	8	4	314±20	+3.50±2.50	0.70±0.12	1.90±0.20**	5.86±0.37*	6.35±0.28
<i>Obese SHR/N-cp</i>									
	Controls	7	3	393±29###§§	+20.00±4.14###§§	4.60±1.51###§§	2.26±0.55#§	9.69±0.26###§§	7.04±1.01
	Terguride	8	3	365±34	+18.76±4.05	3.80±0.30	1.48±0.13*	9.35±0.50	7.81±0.87
<i>Females</i>									
<i>NR</i>									
	Controls	8	7	207±19++	+9.25±3.03	0.74±0.12	2.13±0.37+	6.33±0.39+	6.44±0.34
	Terguride	8	7	215±9	+4.75±2.05*	0.72±0.12	1.26±0.20**	6.20±0.26	5.94±0.27*
<i>Lean SHR/N-cp</i>									
	Controls	8	3	192±11++	+7.10±2.10++	1.29±0.27+##	3.27±0.26++##	7.39±0.20##	7.97±0.50++
	Terguride	8	3	222±13	-4.33±2.87*	0.61±0.08**	2.17±0.41**	6.64±0.32**	7.66±0.51
<i>Obese SHR/N-cp</i>									
	Controls	10	3	353±20++###§§	+23.83±6.85++###§§	4.70±0.55###§§	2.47±0.50§§	8.66±0.90##§	7.70±0.82
	Terguride	9	3	314±11	+18.78±2.97*	3.25±0.39**	1.71±0.19**	8.31±0.62	8.57±0.49

Data are means ± S.D., n – number of rats. Significantly different ($p < 0.05$, $p < 0.01$) from: controls *, **; males +, ++; NR #, ##; lean SHR/N-cp §, §§.

Table 2

Body weight (BW), pellet intake as well as total plasma cholesterol and plasma triglycerides in control and bromocriptine-treated genetically hypertensive non-obese Koletsky rats (lean SHR/N-cp) and their obese siblings (obese SHR/N-cp).

Strain	Treatment	n	Age (months)	Initial BW (g)	BW gain (in %) during 21 days	Triglycerides (mmol/l)	Cholesterol	Pellet intake (g/100 g b.w./day)	
								1st week	3rd week
<i>Males</i>									
<i>Lean SHR/N-cp</i>									
	Controls	8	4	311±18	+3.88±2.15	0.60±0.10	1.62±0.10	6.83±0.51	6.63±0.43
	Bromocriptine	8	4	335±10	+3.50±2.00	0.70±0.07	1.70±0.07	6.01±0.44	6.76±0.12
<i>Obese SHR/N-cp</i>									
	Controls	7	3	393±29	+20.00±4.14	4.60±1.51	2.26±0.55	9.69±0.26	7.04±1.01
	Bromocriptine	8	3	335±43	+11.78±7.58**	2.71±0.81	2.01±0.43	7.53±0.33**	6.21±0.39
<i>Females</i>									
<i>Lean SHR/N-cp</i>									
	Controls	8	3	192±11	+7.10±2.10	1.29±0.27	3.27±0.26	7.39±0.20	7.97±0.50
	Bromocriptine	8	3	194±5	+2.38±3.16*	0.85±0.13*	2.34±0.17*	7.16±0.28	8.06±0.13
<i>Obese SHR/N-cp</i>									
	Controls	10	3	353±20	+23.83±3.85	4.70±0.55	2.47±0.50	8.66±0.90	7.70±0.82
	Bromocriptine	8	3	316±30	+14.88±4.43**	2.53±0.56**	2.06±0.50*	7.68±0.79	7.26±0.84

Data are means ± SD, n – number of rats. Significant drug effects *, ** ($p < 0.05$, $p < 0.01$).

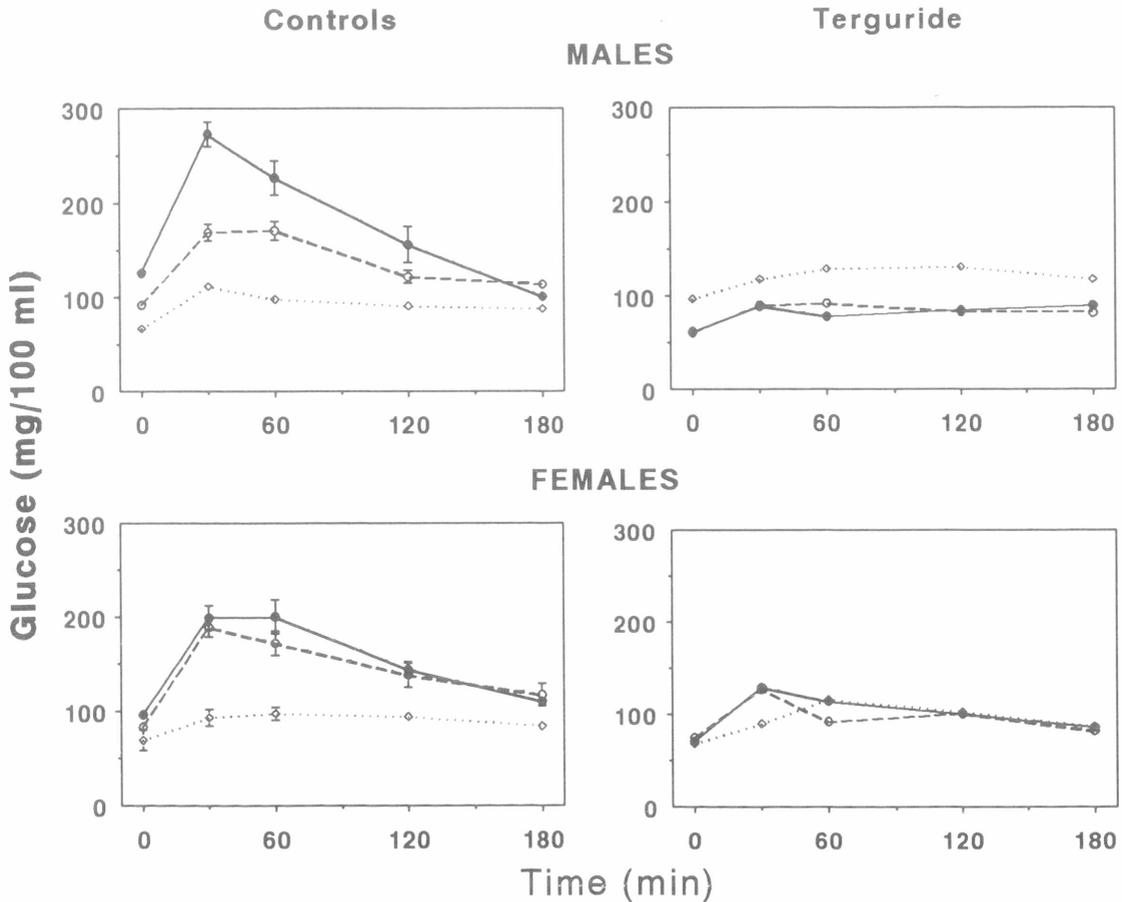


Fig.1
Glucose tolerance test in control and terguride-treated normotensive Wistar rats (NR, dotted lines), genetically hypertensive non-obese Koletsky rats (lean SHR/N-cp, broken lines) and their obese siblings (obese SHR/N-cp, full lines). Plasma glucose levels were determined before (basal glycaemia) as well as 30, 60, 120 and 180 min after oral glucose loading. Data are means \pm S.E.M.

The effects of terguride and bromocriptine on glucose tolerance

Terguride (Fig. 1) increased plasma glucose levels in normotensive Wistar males at all intervals after glucose loading whereas in normotensive females this was observed only at 60 and 120 min after glucose loading. The inverse effect of terguride was found in the obese and lean SHR/N-cp rats of both sexes in which terguride decreased plasma glucose levels at all intervals after glucose loading (Fig. 1). It is evident that terguride normalized abnormal glucose tolerance in both obese and lean genetically hypertensive Koletsky rats.

Bromocriptine effects were studied only in rats with abnormal glucose tolerance curve, i.e. in the obese SHR/N-cp rats and their lean siblings. Considering the effects of the dose of 2 mg/kg/day, there was no

tendency to a normalization of abnormal glucose tolerance curves (Fig. 2). In contrast, bromocriptine treatment increased plasma glucose levels in the lean SHR/N-cp females at 60 min and in the obese SHR/N-cp rats of both sexes at 180 min after glucose loading. The only decrease of plasma glucose occurred in the obese SHR/N-cp males in which both basal glycaemia and plasma glucose levels at 30 min after glucose loading were lower in bromocriptine-treated animals.

A possible dose-dependent effect of bromocriptine was controlled in the lean SHR/N-cp females in which the dose of 20 mg/kg/day was used (Fig. 2). This dose slightly increased basal glycaemia but the glucose tolerance curve was influenced in the same fashion as by the dose of 2 mg/kg/day. At both bromocriptine doses plasma glucose levels were increased at 120 and 180 min after glucose loading.

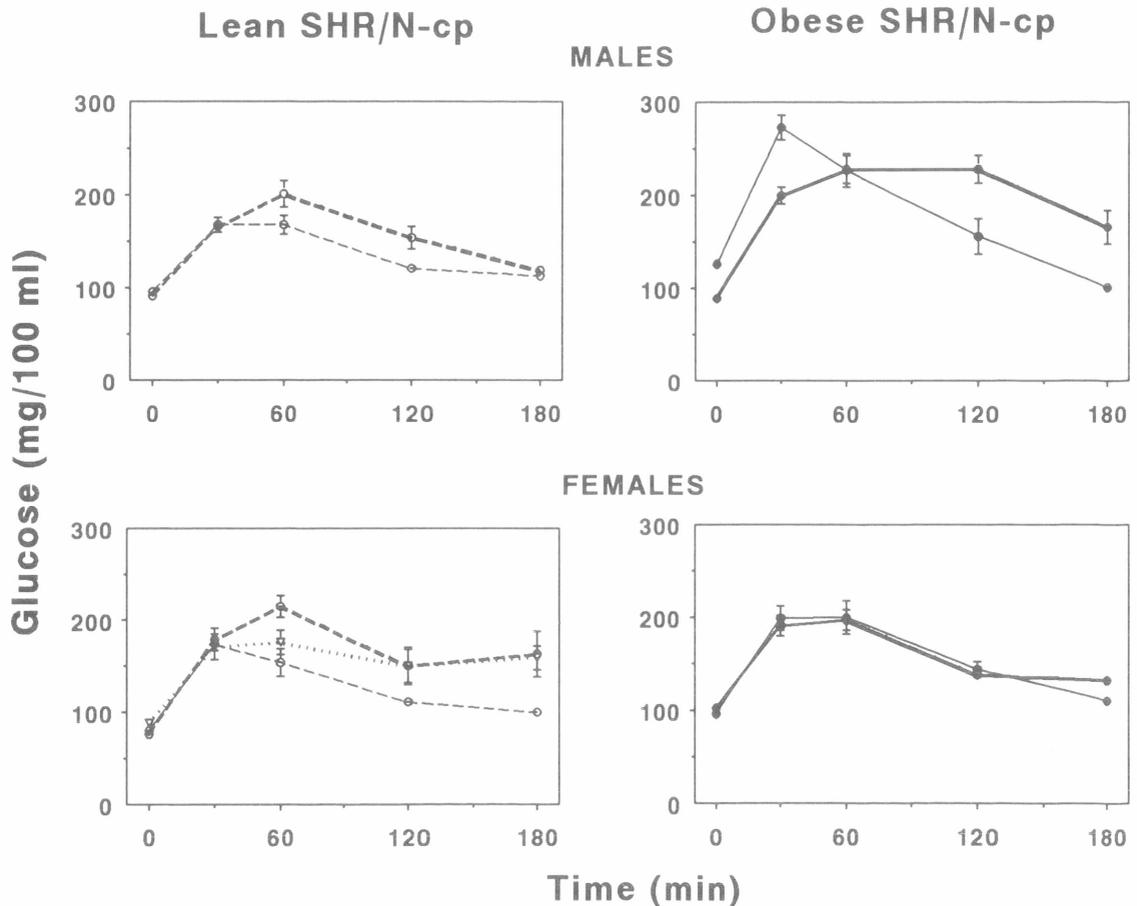


Fig. 2

Glucose tolerance test in control (thin lines) and bromocriptine-treated (thick lines) genetically hypertensive non-obese Koletsky rats (lean SHR/N-cp, broken lines) and their obese siblings (obese SHR/N-cp, full lines). Dotted line represents the effects of higher bromocriptine dose (20 mg/kg/day for 11 days). Data are means \pm S.E.M.

Discussion

Our study documented comparable hypolipaeamic effects of dopaminergic agonists bromocriptine and terguride. Nevertheless, it also indicated different effects of these two drugs on glucose metabolism. Though terguride almost entirely alleviated glucose tolerance abnormalities in both lean and obese Koletsky rats, bromocriptine treatment was without effects or the abnormalities were even emphasized.

The discrepancy between bromocriptine and terguride effects on abnormal glucose tolerance in the obese and lean genetically hypertensive SHR/N-cp rats remains to be solved. Bromocriptine is a dopaminergic agonist which shows an agonistic-antagonistic effect only at higher doses (Rosenfeld *et al.* 1980). Terguride shows a mixed agonistic-antagonistic effect on dopamine receptors even in low doses (Dorow *et al.* 1983). These different characteristics of the two drugs

could be considered as the cause of their different influence on glucose tolerance. Nevertheless, this possibility is weakened by the absence of dose-dependent bromocriptine effect because the effects of 2 and 20 mg/kg/day on glucose tolerance were practically the same.

Comparing the effects of terguride on body weight gain and on the lipidaemia, there was more tight relationship between changes of total plasma cholesterol and body weight gain than between plasma triglycerides and the latter parameter. Body weight gain and terguride-induced changes of plasma triglycerides were independent in the normotensive males and females. The same was true for changes of total plasma cholesterol in the normotensive males and in the obese SHR/N-cp males. The independence between the above mentioned variables can also be shown under the bromocriptine treatment in the obese SHR/N-cp males.

It is useful to consider the effects of bromocriptine and terguride treatment on pellet intake. Nevertheless, the coincidence between drug-induced decrease in the gain of body weight and decrease in pellet intake was found only in some groups of rats.

Thus our findings resemble the data of Cincotta and Meier (1989). When tracing the effect of bromocriptine on total plasma cholesterol and plasma triglycerides, they found that food consumption was unchanged (hamsters and rats) or only modestly reduced (pigs and mice) in the bromocriptine-treated animals. Furthermore, the same was true for body weight which was not altered or slightly reduced.

Our data as well as the findings of Cincotta and Meier (1989) suggest that the possible drug-

induced changes in pellet intake and/or changes in body weight gain cannot be used as the only explanation of hypolipaeamic effect of dopaminergic agonists.

The abnormalities demonstrated in the obese genetically hypertensive Koletsky rats and in their lean siblings indicate that these rats can be used for the study of the relationships between altered glucose tolerance, hyperinsulinism, hyperlipoproteinaemia and arterial hypertension (Reaven 1988, 1991).

Acknowledgement

The authors wish to thank Carl T. Hansen, Animal Genetics Division, National Institute of Health, Bethesda, USA, for providing the genetically hypertensive rats of Koletsky type.

References

- CINCOTTA A.H., MEIER A.H.: Reduction of body fat stores and total plasma cholesterol and triglycerides concentrations in several species by bromocriptine treatment. *Life Sci.* **45**: 2247–2254, 1989.
- DOROW R., BREITKOPF M., GRÄF K.J., HOROWSKI R.: Neuroendocrine effects of lisuride and its 9,10-dihydrogenated analog in healthy volunteers. In: *Lisuride and Other Dopamine Agonists*, D.B. CLANE, R.J. McDONALD, R. HOROWSKI, W. WUTTKE (eds), Raven Press, New York, 1983, pp.161–174.
- GOLDA V., PETR R.: Dopaminergic mechanism and genetic factor in blood pressure regulation. *Sborník věd. prací LF UK, Hradec Králové*, suppl. **25**: 419–427, 1982.
- GOLDA V., PETR R.: A genetically based animal model of Cushing's disease: glucose tolerance. *Physiol. Bohemoslov.* **36**: 366, 1988.
- HILGERTOVÁ J., KÜMMEL L., HOVORKA R., GOLDA V.: Decreased insulin binding and internalization in hepatocytes and erythrocytes of SHR Koletsky rats depend on the presence of "f" gene and on sex. Metabolic characteristics of hepatocytes from obese rats. In: *Insulin and the Cell Membrane*. I. KLIMEŠ, B.V. HOWARD, R.C. KAHN (eds), Harwood Academic Publishers, London, 1989, pp. 81–92.
- KOLETSKY S.: Pathologic findings and laboratory data in a new strain of obese hypertensive rats. *Am. J. Pathol.* **80**: 129–140, 1975.
- REAVEN G.M.: Role of insulin resistance in human disease. *Diabetes* **37**. 1595–1607, 1988.
- REAVEN G.M.: Insulin resistance, hyperinsulinemia and hypertriglyceridemia in the etiology and clinical course of hypertension. *Am. J. Med.* **90** (Suppl. 24): 7–12, 1981
- ROSENFELD M.R., MAKMAN H.S., AHN H.S., THAL L.J., HISHRA R.K., KATZMAN R.: Selective influence of ergot alkaloids on cortical and striatal dopaminergic and serotonergic receptors. In: *Ergot Compounds and Brain Functions*. M. GOLDSTEIN, D.B. CALNE, A. LIEBERMAN, M.-O. THORNER (eds), Raven Press, New York, 1980, pp.83–93.

Reprint Requests

V. Golda, M.D., Institute of Experimental Neurosurgery, 500 36 Hradec Králové, Czech Republic.