Phenytoin-induced increase in growth hormone response to levodopa in adult males

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SUMMARY Growth hormone and prolactin response to levodopa were evaluated before and after long-term phenytoin treatment in five men with previously untreated partial epilepsy. After phenytoin treatment, growth hormone response to levodopa increased. There was a close relationship between growth hormone response to levodopa and plasma phenytoin concentrations. These findings suggest a phenytoin-induced dopaminergic activity at the hypothalamic-pituitary level in adult males.

Recently, Luoma *et al*¹ reported elevated serum growth hormone (GH) levels in women treated with phenytoin and carbamazepine. London *et al*,² however, reported lowered response of growth hormone to insulin hypoglycaemia, unchanged baseline growth hormone levels, and increased prolactin response to thyrotropin-releasing hormone administration in healthy male volunteers after 7 days of treatment with phenytoin or carbamazepine. Such hormonal changes may be due to interaction of phenytoin or carbamazepine with the monoaminergic systems that control hypothalamic-pituitary function.³

Clinical findings indirectly suggest that phenytoin may interact with the dopaminergic system at the striatal level.⁴ Furthermore, both *in vivo* and *in vitro* laboratory studies indicate that phenytoin changes the dopaminergic activity within the central nervous system. Hadfield⁵ showed that dopamine uptake is inhibited by phenytoin in the striatum but stimulated in the hypothalamus; Elliott *et al*⁶ found that phenytoin reduced dopamine utilisation and induced a neuroleptic-like activity in behavioral tests on mice. Lepore *et al*⁷ suggested that phenytoin may act as a dopaminergic agonist, since it reduces dopamine turnover in rat striatum.

In the present study, we evaluated growth hormone and prolactin response to levodopa in epilep-

tic men before and after long-term administration of phenytoin to determine if the treatment had any effect on hypothalamic-pituitary regulation.

Subjects and methods

The study was performed on five epileptic men (22 to 49 years of age) who had less than a 6 month history of previously untreated cryptogenetic partial epilepsy. All patients gave their informed consent to the study. The levodopa test was performed both before and after 1 month of phenytoin treatment.

The levodopa test always started at 8.00 am, after a whole night fast and a 30 min rest period, and was performed as follows: a 21-gauge scalp vein needle was inserted into a cubital vein and patency was achieved by a slow drip of physiological saline. Blood samples were taken 15 min before (−15), immediately before (0), and 30, 60, 90, 120, and 180 min after oral administration of 500 mg of levodopa. Blood samples, collected in test tubes containing EDTA, were promptly centrifuged and the plasma aliquot was divided into two parts and stored at −20°C for hormone analysis and drug concentration determinations.

Plasma prolactin and growth hormone concentrations were determined in duplicate by radioimmunoassay, using a commercially available kit (Biodata, Sero, Italy). The method is sensitive to 1.0 ng/ml for prolactin and 0.25 ng/ml for growth hormone. Plasma phenytoin concentrations were measured by a gas chromatographic method.⁸

In two patients, the oral dose of phenytoin was increased on the basis of low plasma phenytoin concentrations, and the levodopa test was repeated after 1 month. Thereafter, phenytoin was further increased in one patient and the levodopa test was repeated again 1 month later. (For these two patients, the data reported in tables 1 and 2 refer to

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the levodopa test obtained at the higher plasma phenytoin concentrations).

Statistical analysis

Serum prolactin and growth hormone concentration values (ng/ml) underwent two separate analyses of variance (ANOVA) according to a $2 \times 7 \times 5$ design (phenytoin $\times$ times of levodopa administration $\times$ subjects). Data were submitted to log-transformation in order to achieve the condition of homogeneity of "error" variances. If the interaction "phenytoin treatment $\times$ times of levodopa administration" was significant, ANOVA was followed by single contrasts "before vs after phenytoin" at each of the seven times of the levodopa test.⁹ Further, the relationship between plasma phenytoin levels and growth hormone peak response to levodopa was evaluated by linear regression analysis. The analysis was performed on the differences between the peak growth hormone value obtained before and after antiepileptic drug treatment; eight differences were evaluated since two of the five subjects had more than one test.

Results

GROWTH HORMONE RESPONSE TO LEVODOPA TEST

Table 1 shows the individual values obtained at each of the seven levodopa test times before and after 1 month of phenytoin treatment; the table also contains the mean ($\pm$ SEM) on the original scale (ng/ml). ANOVA of log-transformed values yielded a highly significant interaction "phenytoin treatment $\times$ times of levodopa test" ($F = 3.296$; $DF = 6/52$; $p < 0.01$), indicating that growth hormone response exhibited a different trend after phenytoin treatment. Single "before vs after" contrasts (see Table 1) showed no differences at test times -15 and 0

(unchanged baseline values), whereas significantly higher mean values were seen at 60, 90 and 120 min after levodopa administration in comparison with the respective values obtained before anticonvulsant therapy.

Linear regression analysis (fig) showed a highly significant correlation between peak growth hormone changes and plasma phenytoin concentrations ($r = 0.96$; $F = 69.82$; $DF = 1/6$; $p < 0.001$).

PROLACTIN RESPONSE TO LEVODOPA TEST

Table 2 shows the single values obtained from the observations as well as the means ($\pm$ SEM) on the original scale (ng/ml). As in growth hormone response, ANOVA of log-transformed values yielded a significant interaction "phenytoin treatment $\times$ times of levodopa test" ($F = 2.766$; $DF = 6/52$; $p < 0.025$), indicating that prolactin response to levodopa also displayed a different pattern after phenytoin treatment. In this case, too, "before vs after" contrasts (see table 2) did not show any difference in baseline values at -15 and 0 test times, but revealed changes in the response to dopaminergic stimulation after phenytoin therapy. The mean prolactin values were lower at 120 and 180 min after levodopa administration.

Discussion

Our study showed that chronic phenytoin administration enhanced growth hormone and prolactin responses to levodopa. However the effect of phenytoin on prolactin response, although statistically significant, must be considered with caution since the magnitude of the differences in prolactin levels

Table 1 Plasma growth hormone concentration in response to administration of 500 mg of levodopa before (B) and after (A) phenytoin treatment

Patients		Plasma growth hormone concentration (ng/ml)						
		Min -15 levodopa	Min 0 levodopa	Min 30 levodopa	Min 60 levodopa	Min 90 levodopa	Min 120 levodopa	Min 180 levodopa
1	B	0.95	0.08	6.00	18.00	3.80	1.90	1.00
	A	1.20	1.10	16.00	42.00	30.00	7.00	1.90
2	B	0.36	0.30	0.40	0.40	0.46	0.50	0.65
	A	0.48	0.38	0.60	5.00	27.00	9.00	0.60
3	B	1.20	1.00	2.80	1.50	1.00	1.10	1.00
	A	0.42	0.38	0.65	8.50	5.60	2.60	0.65
4	B	0.55	0.95	2.90	3.90	0.95	0.70	0.57
	A	0.82	0.48	15.00	16.00	1.35	0.75	0.48
5	B	0.85	0.90	0.82	0.80	0.85	0.70	0.82
	A	0.70	0.82	1.00	2.50	7.80	3.00	0.90
B Mean ($\pm$ SEM)		0.78 $\pm$ 0.15	0.79 $\pm$ 0.13	2.58 $\pm$ 0.99	4.92 $\pm$ 3.32	1.41 $\pm$ 0.60	0.98 $\pm$ 0.25	0.81 $\pm$ 0.09
A Mean ($\pm$ SEM)		0.72 $\pm$ 0.14	0.63 $\pm$ 0.14	6.65 $\pm$ 3.62	14.80 $\pm$ 7.17	14.35 $\pm$ 5.89	4.47 $\pm$ 1.52	0.91 $\pm$ 0.03
B vs A*		NS	NS	NS	$p < 0.005$	$p < 0.0001$	$p < 0.02$	NS

*From ANOVA on log-transformed values

Fig Linear regression of peak growth hormone changes on plasma phenytoin concentrations. Peak growth hormone changes were calculated as differences (Δp) between peak growth hormone response to levodopa before and after phenytoin treatment.

before and after phenytoin treatment does not exceed the range of error of the assay. Secretion of growth hormone and prolactin is controlled by monoaminergic pathways in the hypothalamic-infundibular region. Growth hormone secretion is

increased by dopaminergic, adrenergic, and serotonergic activity,¹⁰⁻¹² whereas prolactin secretion is increased by serotonergic but inhibited by dopaminergic activity.¹³⁻¹⁶ Hormonal changes reported by other authors, both in baseline values¹

Table 2 Plasma prolactin concentration in response to administration of 500 mg of levodopa before (B) and after (A) phenytoin treatment

Patients	Plasma prolactin concentration (ng/ml)							
		Min -15 levodopa	Min 0 levodopa	Min 30 levodopa	Min 60 levodopa	Min 90 levodopa	Min 120 levodopa	Min 180 levodopa
1	B	6.0	4.6	4.0	2.1	1.8	1.7	2.0
	A	5.5	5.8	4.0	1.8	1.8	1.5	1.4
2	B	5.6	5.6	4.2	3.2	3.3	2.9	2.2
	A	7.8	7.0	2.8	2.8	2.7	2.2	2.2
3	B	9.2	9.0	6.5	5.8	4.2	3.9	4.0
	A	14.0	10.0	7.5	5.5	3.8	3.2	3.4
4	B	8.2	7.5	7.2	6.5	3.8	3.2	4.4
	A	8.5	7.2	6.6	5.8	4.2	3.4	2.8
5	B	10.0	8.5	9.5	7.0	5.3	3.6	3.0
	A	11.0	9.5	8.0	5.0	3.8	3.2	2.8
B Mean ($\pm$ SEM)		7.8 $\pm$ 0.9	7.0 $\pm$ 0.8	6.3 $\pm$ 1.0	4.9 $\pm$ 1.0	3.7 $\pm$ 0.6	3.1 $\pm$ 0.4	3.1 $\pm$ 0.5
A Mean ($\pm$ SEM)		9.4 $\pm$ 1.5	7.9 $\pm$ 0.8	5.8 $\pm$ 1.0	4.2 $\pm$ 0.8	3.3 $\pm$ 0.4	2.7 $\pm$ 0.4	2.5 $\pm$ 0.3
B vs A*		NS	NS	NS	NS	NS	p < 0.03	p < 0.03

*From ANOVA on log-transformed values.

and under stimulation tests,² may be due to an interaction of phenytoin with these monoaminergic systems. Levodopa may act on growth hormone secretion by increasing both dopaminergic and adrenergic activity.^{10,12} However, clinical⁴ and laboratory studies⁵⁻⁷ indicate dopaminergic activity of phenytoin. Moreover, prolactin changes induced by levodopa in our study, although cautiously interpreted, are consistent with a dopaminergic effect of phenytoin. On this basis we believe that the increased growth hormone response to levodopa after phenytoin administration is mainly due to a dopaminergic effect.

Mendez *et al.*¹⁷ reported that phenytoin worsens the symptoms of patients with Parkinson's disease who are treated with levodopa and of patients with Huntington's chorea. In Huntington's chorea, hypersensitivity to dopamine of neurons in the caudate nucleus has been suggested as a primary defect.¹⁸⁻²⁰ The worsening of Huntington's chorea, as well as mental agitation, supports the hypothesis of a dopaminergic effect of phenytoin, whereas the worsening of Parkinson's disease is probably due to increased levodopa metabolism caused by liver enzyme induction associated with phenytoin administration, as suggested by Lühdorf and Lund.⁴ Previously, London *et al.*² reported diminished growth hormone response to insulin hypoglycaemia after phenytoin treatment, but phenytoin was administered for only 7 days and reached plasma concentrations of less than 1 µg/ml. Furthermore, the insulin hypoglycaemia test is not as specific as the levodopa test because it modifies the activity of systems other than the dopaminergic one.^{10,21} Therefore, our findings are not directly comparable with those of London *et al.*²

Our study supports, as regards hypothalamic-pituitary function, previous findings indicating a dopaminergic effect of phenytoin.⁴⁻⁷ Such dopaminergic effect may play a specific therapeutic role in some possibly dopamine-related types of reflex epilepsy;²² it also may explain human hyperkinesias during phenytoin therapy.⁴ The mechanism by which phenytoin may have dopaminergic activity is uncertain.

Phenytoin has an inhibitory effect on the Ca⁺⁺-calmodulin complex,²³ which could affect the activity or sensitivity of dopamine receptors.²⁴ Acting on the Ca⁺⁺-calmodulin complex, phenytoin may enhance dopamine receptor responsiveness.

Further studies are necessary to assess the dopaminergic effect of phenytoin and to evaluate its clinical implications.

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