Hypothalamic-Pituitary Dopaminergic System in Patients with Myotonic Dystrophy

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Sakuma, H., Takase, S., Mizuno, Y., Teramura, K. and Hanew, K. Hypothalamic-Pituitary Dopaminergic System in Patients with Myotonic Dystrophy. Tohoku J. exp. Med., 1988, 156 (3), 291-298 — We studied the function of hypothalamic-pituitary dopaminergic system in 15 myotonic dystrophy (MyD) patients whose growth hormone (GH) responses to insulin or arginine had been normal. We obtained the following findings: (1) basal levels of plasma GH and prolactin (PRL) were normal, although the latter levels were slightly lower than controls, (2) both GH and PRL responses to L-dopa or bromocriptine were significantly blunted compared with controls, (3) PRL response to sulpiride was also significantly low compared with controls. These results indicate that hypothalamic dopaminergic neuron and its postsynaptic dopamine receptors relating to GH secretion might be impaired. It was also suggested that the dopamine receptors of pituitary PRL cells might be impaired and the PRL reserve of pituitary cells might be decreased in some case. — — myotonic dystrophy; hypothalamic-pituitary dopaminergic system; growth hormone; prolactin

It is well-known that patients with myotonic muscular dystrophy (MyD) show complications of endocrine disorders (Roses et al. 1979), including the hypothalamic-pituitary system (Yamamoto et al. 1974; Culebras et al. 1977; Narita et al. 1977; Henriksen et al. 1978; Barreca et al. 1980; Mahler and Parizel 1982). However, the exact sites of lesion in hypothalamus or pituitary gland are not clarified well. Takase (1983) have reported that MyD patients showed more blunted GH responses to L-dopa compared with those to insulin induced hypoglycemia. To clarify this, we examined plasma GH and prolactin (PRL) responses to L-dopa, bromocriptine (dopamine agonist), and sulpiride (dopamine antagonist) in MyD patients who had normal GH responses to insulin and arginine.

SUBJECTS and METHODS

Fifteen patients with MyD (12 males and 3 females), aged 16-49 years (mean 30.9) were examined. Each patient had clinical manifestations and typical electromyographic
findings of MyD. The degree of muscle impairment ranged from mild to moderate and everybody was ambulatory. All patients were considered to have normal pituitary GH reserve, based on the results from insulin tolerance test (ITT: regular insulin 0.1 U/kg body weight, i.v.) or arginine tolerance test (ATT: L-arginine-HCl 0.5 g/kg body weight, i.v.) (peak GH: ITT, 13.0-71.7 ng/ml; ATT, 10.2-22.6 ng/ml). Healthy young adult volunteers were employed as controls, and performed L-dopa test (5 males and 3 females), bromocriptine test (3 males and 3 females), and sulpiride test (7 males and 7 females).

Each test was started at 9:00 a.m. after an overnight fast. Blood samples were drawn via an indwelling needle inserted into an antecubital vein. The plasma was separated promptly and kept at -20°C until assayed. The each test was performed as follows.

**L-Dopa test**

All patients and 8 controls were given L-dopa 500 mg orally. Blood samples were taken before and 30, 60, 90, 120 and 150 min after the administration for the measurements of GH and PRL.

**Bromocriptine test**

All patients and 6 controls were given bromocriptine 2.5 mg orally. Blood samples were taken before and 30, 60, 90, 120, 150 and 240 min after the administration for the measurements of GH and PRL.

**Sulpiride test**

All patients and 14 controls were injected with sulpiride (100 mg) intramuscularly. Blood samples were taken before and 30, 60, 90, 120 and 150 min after the injection for the measurement of PRL.

The level of plasma GH and PRL was determined by radioimmunoassay using commercially available kits (GH, Dainabot, Tokyo; PRL, Daiichi RI, Tokyo) and given in terms of mean ± s.e. Student’s t-test was employed for statistical analysis.

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**Fig. 1.** Effect of L-dopa (500 mg p.o.) on plasma GH levels (mean ± s.e.) in 15 MyD and 8 controls.

- ••••, MyD; ○○○○, controls; *p < 0.05; **p < 0.01; †, n = 13.
RESULTS

Growth hormone (GH)

There were no differences in basal levels of plasma GH between MyD patients and controls (Figs. 1 and 2). MyD patients showed a slight increase in plasma GH levels after the administration of L-dopa. Compared with controls, plasma GH response to L-dopa in MyD patients were significantly low at 60, 90 and 150 min ($p<0.01$, $p<0.01$ and $p<0.05$, respectively, Fig. 1). To the administration

![Figure 2. Effect of bromocriptine (2.5 mg p.o.) on plasma GH levels (mean±s.e.) in 15 MyD and 6 controls.](image)

- - - , MyD; ○-○, controls; **$p<0.01$; †, $n=14$.

![Figure 3. Effect of sulpiride (100 mg i.m.) on plasma PRL levels (mean±s.e.) in 10 male MyD and 7 male controls.](image)

- - - , MyD; ○-○, controls; *$p<0.05$; **$p<0.01$. 
of bromocriptine, MyD patients showed a slight increase in plasma GH. However, the response was significantly lower than that of normal controls at 120 min ($p < 0.01$, Fig. 2).

**Prolactin (PRL)**

Although basal levels of plasma PRL in all MyD patients were normal (male, 3.7–18.4 ng/ml; female, 5.2–23.8 ng/ml), they were slightly lower compared with
controls. Especially in male MyD patients, their basal levels of plasma PRL were significantly lower than those of controls (Fig. 3). The administration of sulpiride was followed by sharp increases in plasma PRL levels in both male and female MyD patients, and like in normal subjects, the PRL response to this drug was slightly greater in female patients than in male patients (Figs. 3 and 4). Compared with controls, however, both male and female MyD patients showed significantly lower responses (Figs. 3 and 4). After the administration of L-dopa, MyD patients showed a clear decrease of plasma PRL levels. However, the response was significantly lower than controls at 120 min \( (p < 0.05, \text{Fig. 5}) \). Bromocriptine also caused a clear decrease in plasma PRL levels in MyD patients. The PRL response in MyD patients was significantly blunted compared with controls at 120, 180 and 240 min \( (p < 0.01, \text{on each occasion, Fig. 6}) \).

Regarding the relationship between hormonal responses and the severity of MyD, impairment of GH responses were somewhat correlated with age and duration of the disease, whereas impairment of PRL responses were not.

**DISCUSSION**

In this study, we obtained the following findings: 1) basal levels of plasma GH and PRL were within normal ranges, although the PRL levels were slightly lower than controls, 2) both GH and PRL responses to L-dopa and bromocriptine were significantly impaired compared with controls, 3) PRL response to sulpiride was also significantly blunted compared with controls.

Although we examined MyD patients with normal GH response to insulin or
arginine, their plasma GH responses to L-dopa or bromocriptine were significantly lower than those in normal subjects. It is thought that hypothalamic dopaminergic neuron (DA neuron) regulates growth hormone releasing hormone (GHRH) secretion (Martin 1973). It is postulated that central nervous system (CNS) may be the main site of actions for dopaminergic agents (Liuzzi et al. 1978). L-Dopa can cross blood brain barrier (BBB) and converts to dopamine (DA) in DA neuron. Bromocriptine, one of DA agonists, can also cross BBB and seems likely to stimulate DA receptors in CNS “loci” responsible for GH secretion in the normal subject (Camanni et al. 1975), that is, bromocriptine may facilitate GHRH secretion via the stimulation of postsynaptic hypothalamic DA receptors (Konagaya et al. 1983). Therefore, the impaired GH response to dopaminergic agents might be due to the defect of hypothalamic DA neuron and/or postsynaptic DA receptors of GHRH neuron.

Pituitary PRL secretion is regulated by hypothalamic PRL inhibitory factor (PIF), which is assumed to be DA itself (MacLeod and Lehmeyer 1974). Sulpiride, the DA(D2) receptor blocker, has a direct effect on the lactotroph cells (Iwasaki et al. 1976; Morgan and Benedetti 1977) and releases the PRL by blocking DA action. In our results, plasma PRL response to sulpiride was significantly lower than normal controls. This result might be due to the possibility that pituitary PRL reserve is decreased, whereas the possible defect of DA neuron mentioned above may give us the other clue, that is, as the magnitude of PRL response to sulpiride is proportionate to the degree of hypothalamic DA tone exerting to pituitary gland (Hanew et al. 1983), it seems likely that dopaminergic inhibition on the lactotrophs is decreasing.

Despite the possible defect of DA neuron and DA receptors mentioned above, the basal PRL levels in MyD patients were rather decreased. Furthermore it differed from previous reports (Henriksen et al. 1978; Mahler and Parizel 1982). The reason for decreased PRL secretion from lactotrophs is not clear. However, following two explanations might be offered, 1) there exist some defects of the DA receptors in the lactotrophs, 2) the lactotroph cells in MyD patients possess some abnormalities.

The impaired PRL responses to L-dopa and bromocriptine might support these explanations. After L-dopa converts into DA peripherally, DA inhibits the pituitary PRL release directly (Yoshinaga and Sato 1978). Bromocriptine has also direct effects on the pituitary DA receptors (Schams 1972; Tashijian and Hoyt 1972; Nagasawa et al. 1973; Calabro and MacLeod 1978; Kurachi et al. 1983). Therefore, the impaired PRL responses to L-dopa and bromocriptine might be derived from the impairment of pituitary DA receptors on lactotrophs and/or lactotroph itself.

In conclusion, MyD patients have some derangement either in the hypothalamic DA neuron and postsynaptic DA receptors for GHRH secretion or in the pituitary DA receptors on lactotrophs and lactotrophs itself.
References


