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Interleukin-2 but not basic fibroblast growth factor is elevated in parkinsonian brain

Short Communication

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Summary. The contents of interleukin (IL)-2 and basic fibroblast growth factor (bFGF) were measured in the brain (caudate nucleus, putamen, and cerebral cortex) from control and parkinsonian patients by highly sensitive enzyme-linked immunosorbent assay (ELISA). The concentrations of IL-2 in the brain were in the order of pg/mg protein, and the values were significantly higher in the caudate and putamen from parkinsonian patients than those from control patients. However, the levels of IL-2 in the cerebral cortex showed no significant difference between parkinsonian and control patients. In contrast to IL-2, the bFGF levels in the brain were high and in the order of ng/mg protein, and there was no significant difference in the caudate and putamen between parkinsonian and control patients. Although both IL-2 and bFGF may play important roles in dopaminergic neurons as neurotrophic factors, IL-2 but not bFGF may relate to the compensatory response in the nigrostriatal dopaminergic regions in parkinsonian brain during progress of neurodegeneration.

Keywords: Interleukin-2, basic fibroblast growth factor, Parkinson's disease, brain.

Introduction

Growth factors and cytokines are soluble proteins or glycoproteins produced by leukocytes and other types of cells, and involved in chemical communication between cells (Sternberg, 1988). As well as having a key role in differentiation and mitosis, they are also involved in the interaction between the immune and nervous system. During the last several years, such growth factors and cytokines have been identified that support the development,

survival, and maturation of dopaminergic neurons in the brain as neurotrophic factors (Morrison et al., 1987; Snyder, 1991).

In addition to having trophic effects on developing dopaminergic neurons in culture, there is evidence that administration of basic fibroblast growth factor (bFGF) is able to restore functional and behavioral deficits resulting from the injury of dopaminergic neurons. Beneficial effects of chromaffin cell grafts to the brains of animals with experiment parkinsonism and in patients with Parkinson's disease (Freed et al., 1981; Goetz et al., 1989), along with evidence that bFGF is contained in chromaffin cells (Grothe and Unsicker, 1989), support the notion that bFGF might have some physiological activity in the maintenance and survival of dopamine neurons in vivo.

On the other hand, there is increasing evidence that cytokines also act as neurotrophic factors in the brain. Interleukin (IL)-2, an important cytokine responsible for the initiation and progression of most immune responses, promotes the long-term proliferation of activated T-cells (Morgan et al., 1976). In the brain, IL-2 induced oligodendrocyte proliferation and enhanced sympathetic neurite outgrowth (Benveniste and Merrill, 1986). Thus, IL-2 may have important regulatory effects on the growth ad differentiation of cells in the brian.

Our previous study demonstrated that the levels of tumor necrosis factor (TNF)-α, IL-1β, IL-6, epidermal growth factor (EGF) and transforming growth factor (TGF)-α were increased in the nigrostriatal dopaminergic regions from parkinsonian brains (Mogi et al., 1994a,b). Cytokine elevation may be closely related to the pathogenesis of Parkinson's disease associated with neurodegeneration in nigro-striatal dopaminergic regions (Greenfield, 1992).

In the present study, we further attempted to compare the contents of two cytokines, IL-2 and bFGF, in the nigrostriatal regions of the brain from control and parkinsonian patients.

Materials and methods

Control human brains (11 bases) from patients without neurological diseases and parkinsonian brains (9 cases) were obtained at autopsy, as described in our previous report (Mogi et al., 1995). They were age- and sex-matched with the patients. The control group consisted of 6 males and 5 females with mean age of 71 (range, 54–99) years. The parkinsonian group included 5 males and 4 females with a mean age of 72 (range, 63–83) years. The mean duration of Parkinson's disease was 17.9 years (5–33 years). The causes of death were: in patients with Parkinson's disease; 5 cases, pneumonia; 1 case, pyothorax; 1 case, congestive heart failure; 1 case, cirrhosis; and 1 case, burn shock; and in control patients; 8 cases, pneumonia; 1 case, gestric cencer; 1 case, renal failure; and 1 case, congestive heart failure. Postmortem times were from 3 to 21 hours. The caudate nucleus, putamen, and cerebral cortex were dissected and stored frozen at −80°C. Brain tissues were homogenized with 0.32 M sucrose containing protease inhibitors (100 μM of phneylmethylsulfonylfluoride; each 50 μg/ml of leupeptin, pepstatin and antipain). IL-2 contents in the samples were measured by enzyme-linked immunosolvent assay (ELISA) utilizing a commercially available ELISA kit (Cayman Chemical Co., U.S.A.). bFGF contents in the brain were also determined utilizing an ELISA kit (R&D System Inc., U.S.A.). Protein concentration was estimated by the method of Bradford (1976) with bovine serum albumin as a standard. Statistical differences between control and parkinsonism patients were subjected to analysis by Student's t-test.

Results

The concentrations of IL-2 and bFGF in the brain from control and parkinsonian patients are shown in Table 1. In the control brains, the concentrations of IL-2 were not detectable in the cerebral cortex, and about 1 pg/mg protein in the caudate and putamen. The mean IL-2 contents in the candate and putamen of the parkinsonian brains were about 10–20 pg/mg protein, 20–30 fold higher than the values of control patients. On the other hand, IL-2 contents in the cerebral cortex from the parkinsonian patients were low but detectable, about 1 pg/mg protein.

Table 1 also shows the contents of bFGF in the nigro-striatal dopaminergic regions (caudate nucleus and putamen) and cerebral cortex from control and parkinsonian patients. bFGF contents in the dopaminergic region of control and parkinsonian brains were much higher (ng/mg of protein) than IL-2 contents (pg/mg protein), but there are no significant differences between control and parkinsonian brains. In addition, bFGF contents in the cerebral cortex of control brains were similar to those in the striatum, and to those from parkinsonian cerebral cortex or striatum.

Discussion

Relatively little attention has been given to the determination of neurotrophic factors and cytokines in parkinsonian brains, except our previous works (Mogi et al., 1994a,b). In the present study, we proved immunochemically the increase of IL-2 content in the nigro-striatal dopaminergic region of parkinsonian brain for the first time. IL-2 is produced in astrocyte and microglial cells, and stimulates both proliferation and differentiation of oligodendrocytes (Benveniste and Merrill, 1986).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces extrapyramidal motor dysfunction which mimics major clinical signs of the Parkinson's disease in humans, monkeys, and mice (Davis et al., 1979; Langston et al., 1983; Burns et al., 1983; Chiueh et al., 1985; Heikkila et al., 1984; Mogi et al.,

Table 1. Interleukin-2 (IL-2) and basic fibroblast growth factor (bFGF) contents (mean ± S.E.M.) in the brain from control and parkinsonian patients (*$p < 0.05$, **$p < 0.01$)

Brain regions IL-2	Control patients (pg/mg protein)	Parkinsonian patients (pg/mg protein)
Caudate + Putamen (11)	0.80 ± 0.15 (100%)	15.3 ± 7.1 (1911%)*
Caudate (3)	0.97 ± 0.70 (100%)	17.0 ± 9.8 (1747%)
Putamen (8)	0.34 ± 0.34 (100%)	10.9 ± 1.9 (3197%)**
Cerebral cortex (4)	0.00	0.89 ± 0.89
bFGF	(ng/mg protein)	(ng/mg protein)
Caudate + Putamen (11)	2.72 ± 0.17 (100%)	2.75 ± 0.24 (101%)
Caudate (3)	2.99 ± 0.22 (100%)	2.85 ± 0.23 (95%)
Putamen (8)	2.62 ± 0.22 (100%)	2.71 ± 0.33 (103%)
Cerebral cortex (4)	3.33 ± 0.32 (100%)	4.21 ± 0.47 (126%)

1987). Liang et al. (1989) reported that IL-2 was distributed in the lesion site of MPTP-injured rat brain. This result agrees with the present data.

Interestingly, while both IL-2 and bFGF are candidates for neurotrophic factors in the brain, IL-2 but not bFGF showed a significant elevation in the dopaminergic region of parkinsonian brains. No change in bFGF content in the striatum from parkinsonian patients differs from the data that bFGF reversed chemical and morphological deficits in the nigrostriatal system of MPTP-treated mice (Otto and Unsicker, 1990). bFGF was expressed in both astrocytes and neurons including dopamine neurons of the substantia nigra (Ferrara et al., 1988; Bean et al., 1991; Yoshida and Gage, 1991). Although the reason why bFGF content was unchanged between control and parkinsonian striatum is not clear, the function of IL-2 and bFGF may be different in the striatum in Parkinaon's disease. We previously demonstrated that TNF-α, IL-1β, IL-6, EGF, and TGF-α contents were increased in the dopaminergic region of parkinsonian brains (Mogi et al., 1994a,b). These cytokines were reported as neurotrophic factors in the brain. Taken together with our previous results, it is conceicable that the compensatory increase of cytokines in the nigro-striatal dopaminergic regions in Parkinson's disease may occur in some later stages of the disease while neurodegeneration is in progress.

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