Rapid Stimulation by Nerve Growth Factor of Amino Acid Uptake by Clonal PC12 Pheochromocytoma Cells*

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The clonal PC12 pheochromocytoma cell line responds to nerve growth factor (NGF) by ceasing cell division, extending long neurite-like processes, and becoming electrically excitable. It is reported here that NGF treatment stimulates uptake of amino acids, but not nucleosides or norepinephrine, by PC12 cells. The effects of NGF on the rate of uptake of the nonmetabolized amino acid a-aminoisobutyric acid (AIB) were studied in detail. Stimulation of AIB uptake is detectable within 15 min after addition of NGF to PC12 cultures. Stimulation with 50 ng/ml of NGF reaches about 60% by 24 h of treatment and continues to increase for at least another 24 h. Uptake returns to near basal levels within 24 h after removal of NGF from cultures pretreated with the factor. Stimulation is accompanied by an increase in the apparent $V_{max}$ for AIB uptake, while the apparent $K_m$ remains unchanged. Half-maximal stimulation of uptake requires about 10 ng/ml of NGF, and maximal stimulation is attained at 100 to 300 ng/ml of NGF. NGF stimulation of AIB transport is not blocked by the RNA synthesis inhibitor camptothecin at doses which completely block initiation of NGF-induced process outgrowth by PC12 cells. Treatment of PC12 cells with elevated concentrations of serum also stimulates AIB uptake, while treatment with serum free medium reduces uptake; the stimulatory effects of NGF are apparent at all serum concentrations. AIB uptake is depressed by the synthetic corticosteroid dexamethasone; however, dexamethasone does not block the stimulatory effects of simultaneously added NGF. NGF does not stimulate uptake by other cell types that have no known responses to the factor. These results are discussed with regard to the possible role(s) of stimulated uptake of small molecules in the mechanism(s) of action of NGF.

Nerve growth factor (NGF) is a polypeptide required for the survival and maturation of sympathetic and dorsal root sensory neurons (1). NGF* exerts a number of effects on these cells, including stimulation of neurite outgrowth, maintenance of survival (1), hypertrophy (1), induction of tyrosine hydroxylase activity (2), and maintenance of the ability to take up precursor compounds such as nucleosides and amino acids (3). The effect of NGF on precursor uptake is of particular interest due to its rapidity. Readdition of NGF to cultures of chick embryo dorsal root ganglionic neurons previously deprived of the factor for up to 6 h restores uptake to control (i.e. NGF nondeprived) levels within 10 min (3). It has been suggested (3) that this effect on uptake may, therefore, be closely related to the primary mechanism(s) of NGF's action.

Recently, a clonal line of rat pheochromocytoma cells, designated PC12, that responds to NGF, has been described (4). When grown in the absence of NGF, PC12 cells divide and display many of the characteristics of normal adrenal chromaffin cells (4, 5). However, after several days of treatment with nanogram levels of NGF, PC12 cells cease dividing, extend long, microtubule-containing processes (4), and begin to elaborate processes and form (7).

**MATERIALS AND METHODS**

*Cell Culture—PC12 cells or their A1 subclone (8) were maintained as previously reported (4) on 100 mm tissue culture dishes in medium consisting of 85% RPMI 1640, 10% heat-inactivated horse serum, 5% fetal calf serum, 50 units/ml of penicillin, and 25 units/ml of streptomycin. For uptake experiments, cells were subcultured onto 35 mm tissue culture dishes coated with rat tail collagen and were grown in the same medium. Uptake—Cultures were moved to a 37°C constant temperature room, washed three times with a Hepes-buffered (pH 7.4) modified Krebs-Ringer solution (KRH) (9), and incubated in 1 ml of KRH for a 10-min adaptation period. The medium was then removed and replaced with 1 ml of KRH containing the radioactive compound whose uptake was to be measured. Unless otherwise indicated, AIB was used at 50 μCi/ml, 2.5 μCi/ml of other compounds used are given in Table I. After the uptake period (generally 5 min), the radioactive medium was removed by aspiration and cultures were rapidly washed three times with KRH. Radioactivity was extracted.
at room temperature, first for 5 min in 0.5 ml of 1 N HCl and then for 5 min in 0.5 ml of 1 N NaOH. Extracts were transferred directly to scintillation vials which, after addition of 10 ml/vial of Aquasol scintillation fluid (New England Nuclear Co.), were counted in a Packard scintillation counter. For cell counts, duplicate sister cultures were washed and treated with 0.1% trypsin (Difco 1250) for 40 min at 37°C. Cells were dispersed by trituration with a Pasteur pipette and counted in a hemacytometer.

Chemicals—Dexamethasone acetate, uridine, thymidine, and α-aminoisobutyric acid were purchased from Sigma Chemical Co. Camptothecin was generously supplied by Dr. Harry B. Wood of the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute and was converted to the sodium salt before use according to a protocol prepared by the Research Triangle Institute, Research Triangle Park, North Carolina.

Radiochemicals from New England Nuclear Co. were as follows: α-amino[methyl-3H]isobutyric acid (10 Ci/mmol); [methyl-3H]thymidine (20 Ci/mmol); aminocyclopentane-1-C-carboxylic acid (30 Ci/mmol); [5,6-3H]uridine (38 Ci/mmol); and 1-[3H]norepinephrine (6 Ci/mmol).

Horse serum and fetal calf serum were from KC Biologicals, Inc.

RESULTS

Stimulation of Amino Acid Uptake by NGF—We tested the ability of PC12 cells treated or untreated with a physiological level of NGF (50 ng/ml) for 24 h to take up several small molecules. Uptake was expressed on a per cell basis since 24 h of NGF treatment affected neither the number of cells nor the amount of protein per culture. Table I shows that uptake of the nonmetabolized amino acids α-aminoisobutyric acid and aminocyclopentane-1-carboxylic acid was significantly greater in NGF-treated cultures, while uptake of uridine, thymidine, and norepinephrine (for which PC12 cells have been shown (5) to have a specific transport system) was unaffected.

Since AIB has been used as a convenient model substrate to study amino acid uptake (10-12), the effects of NGF treatment on uptake of this compound by PC12 cells were studied in greater detail. AIB uptake by PC12 cells proceeded at a linear rate for about 10 min (Fig. 1A) and accumulation was, therefore, used in subsequent experiments. As shown in Table II, AIB uptake by PC12 cells was temperature- and sodium-dependent. This is in agreement with other results with other types of cells (10-12). AIB uptake was nearly saturable (see Fig. 2), but a certain amount of radioactivity was retained by cultures even when uptake was in the presence of 100 mM unlabeled AIB. This noncompetitive “uptake” amounted to 616 ± 65 cpm/culture (n = 20) and was independent of the number of cells per culture, the presence or absence of NGF, and the uptake activity of the culture measured at 50 μM AIB. At least part of this “uptake” occurred immediately upon addition of AIB to cultures, as shown by extrapolation of the uptake versus time curve of Fig. 1A to a positive value at zero time. We considered this noncompetitive radioactivity to be “background” and, where indicated, it was subtracted from the total uptake.

The kinetic data of AIB uptake by PC12 cells were compared before and after 24 h treatment with 50 ng/ml of NGF. Fig. 2 shows an example of the relation between uptake velocity and AIB concentration. When plotted according to Hofste (13), the data may be fitted to a straight line (r² = 0.99 for untreated cells, r² = 0.88 for NGF-treated cells) and thus appear to conform to the Michaelis-Menten equation (Fig. 2). In the experiment shown in Fig. 2, NGF treatment increased both the apparent Kₘ (from 2.7 to 3.5 mM) and apparent Vₘₐₓ (from 1.0 fmol/cell/min to 2.1 fmol/cell/min) of AIB uptake. However, when data from five separate experiments were considered, the effect of NGF on the apparent Kₘ for AIB transport was not significant (no NGF, Kₘ = 1.9 ± 0.3 mM; +NGF, Kₘ = 2.6 ± 0.3 mM), while NGF treatment increased the apparent Vₘₐₓ by 71% (p < 0.025). Stimulation of AIB uptake by NGF was also apparent when longer times of uptake were studied (Fig. 1B), suggesting that the more rapid initial rate of AIB uptake led to greater accumulation of this compound.

Time Course of Effect of NGF on AIB Uptake—As shown in Fig. 3, a significant stimulation of AIB uptake could be detected as early as 15 min after addition of NGF to PC12 cultures. However, stimulation was less than 10% if NGF was present only during the uptake period. With 50 ng/ml of NGF, uptake was stimulated by about 30% during the first 18 h of treatment and by about 60% at 24 h. There was considerable variability in NGF stimulation of AIB uptake from experiment to experiment. For example, in 13 separate experiments with cultures treated with 50 ng/ml of NGF for 24 h, stimulation of uptake ranged from 18% to 106%. The cause of this variability is not known.

Reversibility of Effect of NGF on AIB Uptake—PC12 cultures were treated with NGF for 24 h and then for an additional 24 h with or without the factor. Fig. 4 shows that within 24 h after removal of NGF, AIB uptake returned nearly to that in untreated cultures. Note that cultures treated with NGF for 48 h exhibited even higher AIB uptake levels than those treated with NGF for 24 h.

Dependence of Stimulation of AIB Uptake on NGF Concentration—Fig. 5 shows that 24-h treatment with as little as 3 ng/ml of 2.5 S NGF significantly stimulated AIB uptake (p < 0.05, Student’s t test). Half maximal stimulation was attained at about 10 ng/ml of NGF, and stimulation reached a plateau at about 300 ng/ml of NGF.

Effect of Camptothecin—The reversible RNA synthesis inhibitor camptothecin (14) has been shown to block NGF-induced initiation of neurite outgrowth by PC12 cells (15). Fig. 6 shows the effects of this drug on NGF stimulation of AIB uptake. At 0.1 μg/ml, a dose that completely and reversibly

| Compound        | Concentration | No NGF | +NGF | +NGF/no NGF |
|-----------------|---------------|--------|------|-------------|
| AIB             | 50 μM; 2.5 μCi/ml | 2.4 ± 0.3 | 3.9 ± 0.1 | 1.60ab |
| ACPC            | 34 μM; 1 μCi/ml | 13.1 ± 0.7 | 13.9 ± 0.6 | 1.04ab |
| Uridine         | 50 μM; 2.5 μCi/ml | 5.2 ± 0.2 | 4.8 ± 0.2 | 0.93 |
| Thymidine       | 50 μM; 2.5 μCi/ml | 0.89 ± 0.01 | 0.89 ± 0.09 | 1.09 |
| Norepinephrine  | 0.14 μM; 0.8 μCi/ml | 2.9 ± 0.1 | 2.7 ± 0.2 | 0.94 |

ab p < 0.005; all other values were p > 0.2 (Student’s t test).
Stimulation of Amino Acid Uptake by Nerve Growth Factor

**FIG. 1 (left and center).** Time course of [3H]AIB uptake (A) and accumulation (B) by PC12 cells. PC12 cultures were maintained without NGF (○—○) or for 24 h with 50 ng/ml of NGF (□—□). Uptake was measured as described under "Materials and Methods" but at the indicated times. Values are means ± S.E. of determinations on quadruplicate sister cultures.

**FIG. 2 (right).** Effect of NGF on kinetics of AIB uptake by PC12 cells. PC12 cells were maintained without NGF (W) or for 24 h with 50 ng/ml of NGF (○—○). The initial rate of AIB uptake (v) was measured as described under "Materials and Methods." The concentration of [3H]AIB was 2.5 μCi/ml, and the concentration of unlabeled AIB ranged from 0.05 to 15 mM. Uptake at each concentration (S) was corrected for nonsaturable uptake measured at 100 mM unlabeled AIB. Each point represents the mean of determinations on quadruplicate sister cultures. Data were plotted as shown according to Hofstee (13). Lines were calculated by the least squares method. Abscissa, v = initial velocity of AIB uptake as femtomoles/cell/min; ordinate, S = concentration of AIB and the units of v/S are expressed in picoliters/cell/min.

**TABLE II**

| Condition               | AIB uptake |
|-------------------------|------------|
|                        | cpm/culture/5 min | Experimental/Control |
| 1                      | 37°C (control) | 28,858; 20,990 |
| 0°C (experimental)     | 3,094; 1,576    | 0.09          |
| 2                      | 125.5 mM Na⁺ (control) | 7,327; 7,113 |
| 9 mM Na⁺, 125.5 mM choline (experimental) | 3,280; 3,919 | 0.50 |

**FIG. 3.** Time course of the effect of NGF on [3H]AIB uptake by PC12 cells. PC12 cells were cultured without NGF or for the indicated lengths of time with 50 ng/ml of NGF. [3H]AIB uptake was determined in this (and in subsequent) figure as described under "Materials and Methods" and was corrected for nonsaturable uptake measured in the presence of 100 mM unlabeled AIB. In each experiment, AIB uptake by NGF-treated cultures (two to four sister cultures/experiment) was compared with AIB uptake by sister NGF-untreated cultures (two to four cultures/experiment). Values given are means ± S.E. with the numbers of experiments in parentheses.

with 10^{-5} M dexamethasone for 24 h significantly depressed AIB uptake but did not prevent stimulation of AIB uptake by simultaneously added NGF (Fig. 8). Similar results were observed when dexamethasone was present at 10^{-6} M. In agreement with previous findings (20) these doses of dexamethasone neither stimulated neurite outgrowth nor blocked NGF-induced neurite outgrowth; moreover, 24 h of dexamethasone treatment did not affect cell viability.

**Specificity of Stimulation with Respect to Cell Type**—The effect of NGF on AIB uptake was tested on several other cell lines that have no known biological response to the factor. The data in Table III show that while 24 h of NGF treatment stimulated AIB uptake by PC12 cells, it did not affect uptake by 3T3 fibroblasts (21), C6 glioma cells (22), neuro-2a neuro-
blastoma cells (23), T28 neuroblastoma x sympathetic ganglion cell hybrids (24), or F4 NGF-unresponsive pheochromocytoma-derived cells.

**DISCUSSION**

**Effects of NGF on Substrate Accumulation in Responsive Cells**—Early studies with explanted chick embryo dorsal root ganglia were interpreted to indicate that NGF stimulated incorporation of a variety of precursors into macromolecules (1). Subsequent work has, however, suggested that such apparent stimulation was, rather, due to a decrease in incorporation by NGF-deprived “controls” which require the factor for their survival (25, 26). Horii and Varon (26) demonstrated that NGF-deprived dissociated chick embryo dorsal root ganglia underwent a progressive decline in rate of incorporation of uridine into RNA while incorporation in NGF-treated cells was unaltered. Moreover, these workers found that for up to 6 h of NGF deprivation, incorporation could be restored to its original level by readdition of the factor. This restoration was rapid, reaching completion within 10 min of NGF treatment. More recently, Horii and Varon (3) showed that such changes in incorporation were entirely due to changes in accumulation of precursor. That is, NGF maintained or rapidly restored the ability of dissociated ganglia to accumulate uridine, cytidine, guanosine, 2-deoxyglucose, or AIB. It was not established, however, whether such changes in accumulation were due to changes in the rate of uptake.

The PC12 line provides an opportunity to confirm and extend such findings concerning the effect of NGF on precursor accumulation by normal neurons. If promotion of accumulation (or of uptake) of small molecules is a general effect of NGF, then one might expect this effect to be present in other NGF-responsive systems such as the PC12 line. Also, since PC12 cells respond to NGF but do not require the factor (as do normal neurons) for their survival, the effect of NGF on uptake should be perceived as a stimulation rather than maintenance or restoration. Finally, the homogeneity and ease of obtaining large numbers of PC12 cells should aid in further studies of this phenomenon.

**Effect of NGF on Uptake by PC12 Cells**—The characteristics of AIB uptake by PC12 cells are similar to those reported for other cell types. These characteristics include partial dependence on external Na+ concentration (10–12), inhibition of uptake at low temperature (10), slow approach to equilibrium (10–12), saturability of uptake at high AIB concentrations (10, 11), and an apparent \( K_m \) in the 1 to 10 mM range (10, 11).

One of the major findings reported here is that NGF treatment of PC12 cells causes an increase in their rate of uptake (and apparently accumulation) of AIB. This change appeared to be due to an increase in apparent \( V_{max} \) for AIB uptake. Within the limits of resolution of our system, the apparent \( K_m \) for uptake was not significantly altered. Similar results have been obtained for insulin stimulation of AIB uptake by rat liver parenchymal cells (11), while both \( V_{max} \) and \( K_m \) were reported to be changed in insulin-stimulated rat thymocytes (10). NGF treatment also increased the uptake by PC12 cells of the amino acid analogue ACPC which is reported (12) to be taken up mainly by transport systems distinct from those which transport AIB. On the other hand, the factor did not alter the uptake of all transported small molecules since uptake of several other species (uridine, thymidine, and noradrenaline) was unaffected after 24 h of NGF treatment. The significance of the apparent difference in effects of NGF on uridine uptake in PC12 cells and chick sensory ganglion cells (3) is not clear.

The effects of NGF on uptake also appeared to be selective with respect to cell type. Thus, NGF did not stimulate AIB uptake in a variety of cell types that have no other known responses to the factor. The effects of NGF on AIB uptake were reversible in that removal of NGF from cultures pretreated with the factor resulted in return of the rate of AIB uptake to near unstimulated levels within 24 h. Other effects of NGF on PC12 cells have also been shown to be reversible (4, 17). Such findings suggest that the continued presence of NGF may be a general requirement for expression of NGF-induced characteristics. The dose response relationship between NGF concentration and degree of stimulation of AIB uptake revealed half-maximal stimulation at about 7 to 10 ng/ml (0.2 to 0.4 nM) of NGF. Studies of the binding of \(^{125}\)I-NGF to membranes of rabbit superior cervical sympathetic ganglia (27) have yielded a similar value for the apparent dissociation constant of NGF with a surface receptor. Furthermore, assuming a \( K_a \) of 10 ng/
the reversible 1:1 interaction of NGF and receptor. The basis for uptake is not presently clear.

of "I-NGF to its receptor on membranes of rabbit superior cervical ganglion was reported to reach equilibrium within 10 min of exposure (27). Several other rapid effects of NGF on PC12 cells that involve the cell membrane are also known. These include reorganization of the cell surface (commencing by 1 min) as detected by scanning electron microscopy and changes (detectable within 10 min) in the adhesive properties of the cells to one another and to surfaces (28). The causal relationship, if any, of these rapid events to one another is presently unknown. In contrast to such early events, a number of other responses of PC12 cells to NGF appear with a slower time course. These include induction of ornithine decarboxylase activity (apparent by 2 h and maximal by 5 to 6 h) (29), cell flattening (12 to 24 h) (4, 30), increased synthesis of an 80,000 dalton protein (24 to 48 h), and (after at least 48 h) cessation of cell division, outgrowth of neurites, increase in somatic volume, appearance of synaptic vesicles, acquisition of electrical excitability, enhanced responsiveness to acetylcholine, and increase in synthesis of a 230,000-dalton glycoprotein (31).

Possible Significance of the Effect of NGF on Uptake—A natural question raised by the present and other similar findings is the relationship between the effect of NGF on uptake of small molecules and its effects on neuronal survival and differentiation. One possibility is that enhancement of uptake is merely a secondary event (reflecting, for example, reorganization of the membrane after interaction with NGF) that is without further consequences for neuronal function. Of relevance to this possibility, we have recently found evidence that NGF treatment causes a 20-fold induction of ornithine decarboxylase in PC12 cultures, but that this effect can be dissociated from the effects of the factor on neurite outgrowth, cell survival in serum-free medium, and increase in somatic size (29). A second possibility is that increased uptake of small molecules could play a direct role in certain responses to NGF. For example, increased uptake could (at least in part) be responsible for the increase in somatic volume and protein per cell which occurs in the presence of NGF (1, 4, 30). It is also attractive to consider that NGF-dependent uptake may not be a consequence, but rather a cause, of the effect of NGF on survival of responsive normal neurons or serum-deprived PC12 cells. Yet another viewpoint, as suggested by Horii and Varon (3), is that a change in membrane permeability is the primary means through which NGF exerts its effects, i.e. that a molecule whose uptake is increased in response to NGF serves as a "second messenger" and triggers further events in the sequence of action of the factor. However, since serum

### Table III

| Cell type             | [3H]AIB uptake | +NGF | +NGF/no NGF |
|-----------------------|----------------|------|-------------|
|                       | cpm/culture/5 min |     |             |
| PC12 pheochromocytoma | 8,893 ± 429 | 13,165 ± 558 | 1.48* |
| T3 fibroblast         | 4,722 ± 181 | 5,093 ± 284 | 1.07* |
| Neuro-2a neuroblastoma| 77,553 ± 5,684 | 77,523 ± 3,420 | 1.00* |
| C6 glia               | 24,884 ± 1,052 | 26,366 ± 1,145 | 1.06* |
| T28 neuroblastoma x   | 62,546,54,666 | 52,480,54,501 | 0.91 |
| sympathetic neuron     |                 |     |             |
| hybrid                 |                 |     |             |
| F4 pheochromocytoma-  | 1,960 ± 63 | 1,944 ± 63 | 0.99* |
| derived               |                 |     |             |

* p < 0.005.

* p > 0.2 (Student's t test).

ml, the present dose-response curve is in reasonable (but not exact) agreement with the degree of occupancy predicted from the reversible 1:1 interaction of NGF and receptor. The basis for the somewhat broader range of the dose-response curve for uptake is not presently clear.

The effect of NGF on AIB uptake was detectable after 15 min of treatment and thus is one of the most rapid effects of NGF. Of other responses of PC12 cells to NGF appear with a slower time course. These include induction of ornithine decarboxylase activity (apparent by 2 h and maximal by 5 to 6 h) (29), cell flattening (12 to 24 h) (4, 30), increased synthesis of an 80,000 dalton protein (24 to 48 h), and (after at least 48 h) cessation of cell division, outgrowth of neurites, increase in somatic volume, appearance of synaptic vesicles (4), acquisition of electrical excitability, enhanced responsiveness to acetylcholine (6), and increase in synthesis of a 230,000-dalton glycoprotein (31).

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was found here to enhance uptake by PC12 cells, but does not induce morphological differentiation, stimulated uptake of amino acids in itself does not appear to be sufficient as a mediator for all other responses to NGF. Finally, recent studies (15) suggest that stimulation of neurite outgrowth from PC12 cells has two required roles for NGF. One of these is independent of RNA synthesis and is camptothecin-insensitive, while the other requires RNA synthesis and is blocked by low levels of camptothecin. Thus, it is conceivable that the NGF-dependent increases in uptake (which were shown here to occur even in the presence of camptothecin) could be associated with the former role. Further work with the PC12 line should be useful for refining and testing such possibilities.

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