Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 8920–8924, September 1994
Neurobiology

Brain-derived neurotrophic factor increases the electrical activity of pars compacta dopamine neurons *in vivo*

(substantia nigra/burst activity/neurotrophin/single unit recording/Parkinson disease)

ROH-YU SHEN*†, C. ANTHONY ALTAR‡, AND LOUIS A. CHIODO*§

*Department of Psychiatry, Wayne State University School of Medicine, Detroit, MI 48201; and ‡Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591

Communicated by Ann Graybiel¶, May 23, 1994

ABSTRACT **Chronic infusions of brain-derived neurotrophic factor (BDNF) immediately above the substantia nigra augment spontaneous locomotion, rotational behavior, and striatal dopamine (DA) turnover, indicating that BDNF increases functions of the nigrostriatal DA system. Because the function of the nigrostriatal DA system is related to the electrical activity of DA neurons, we investigated the effect of BDNF on the electrical activity of DA neurons in the substantia nigra pars compacta *in vivo*. Chronic supranigral infusions of BDNF (12 μg/day), nerve growth factor (11 μg/day), or phosphate-buffered saline were started 2 weeks before the electrophysiological recordings. BDNF increased the number of spontaneously active DA neurons by 65–98%, increased the average firing rate by 32%, and increased the number of action potentials contained within bursts. Neither nerve growth factor nor phosphate-buffered saline infusions altered any of these properties relative to unoperated animals. In addition, extremely fast-firing DA neurons (>10 spikes per sec) were commonly found only in the BDNF-infused animals. These results demonstrate neurotrophin effects on the electrical activity of intact central nervous system neurons *in vivo* and suggest that the increases in locomotor behavior and striatal dopamine turnover obtained during supranigral BDNF infusions may result from increases in the electrical activity of DA neurons.**

It has been demonstrated that neurotrophic factors play important roles in development and maintenance of the mammalian central nervous system. A potential for neurotrophic factors in the etiology or treatment of Parkinson disease has been suggested by several lines of research (1–3). The *in vitro* survival, differentiation, and function of dopamine (DA) neurons are promoted by brain-derived neurotrophic factor (BDNF; refs. 4–9), a member of the neurotrophin family. BDNF increases the number of DA neurons that survive in mesencephalic cultures, promotes their neurite outgrowth, and increases high-affinity DA uptake and tyrosine hydroxylase (TH) activity (5–8). In addition, BDNF protects cultured DA neurons against toxic effects of 6-hydroxydopamine or *N*-methyl-4-phenylpyridinium ion (6, 9).

Recent *in vivo* studies demonstrate potentiating effects of BDNF on nigrostriatal DA neurons. In adult rats, chronic infusions (12 μg/day) of BDNF above the substantia nigra pars compacta (SNC) increase the metabolism of DA in the striatum, as indicated by elevations in the ratios of the DA metabolites homovanillic acid and dihydroxyphenylacetic acid to DA (10, 11). In contrast to supranigral infusions, similar chronic intrastriatal infusions of BDNF produce less of an elevation in DA turnover and far fewer contraversive rotations following (+)-amphetamine administration (10), probably due to a limited diffusion of BDNF within the infused striatum (12). The function enhancing effects of BDNF on DA neurons has also been shown by the ability of supranigral BDNF infusions to decrease the number of (+)-amphetamine-induced ipsiversive rotations in animals with partial DA lesions, to induce many more contraversive rotations in these animals, and to greatly increase DA metabolism in the surviving neurons (13).

The ability of supranigral infusions of BDNF to increase locomotor activity (11) and to induce rotational behavior that is directed contralaterally to the BDNF-infused hemisphere after systemic injections of (+)-amphetamine (10) also suggests that supranigral BDNF infusions produce an elevation of DA release in the ipsilateral striatum. However, while supranigral infusions of BDNF reliably elevate striatal DA metabolism, they produce only small increases in striatal DA release, as determined by increases in the ratio of 3-methoxytyramine to DA. *In vivo* microdialysis within the neostriatum of the BDNF-infused hemisphere has also shown small but inconsistent elevations in extracellular DA before or after systemic (+)-amphetamine injections (C.A.A. and M. Fritsche, unpublished data). Thus, a more sensitive measure of DA neuron activity may be required to reveal whether these neurons are functionally activated by BDNF. Because increased striatal DA synthesis, metabolism, and release are observed with increased DA neuron impulse flow (14–16), it is possible that the potentiating effects of chronic BDNF infusions on DA functions are mediated by the increased impulse flow within SNC DA neurons. To test this possibility, we have used extracellular single unit recording techniques to study the spontaneous electrical activity of DA neurons in the substantia nigra after chronic infusions of BDNF in the rat.

MATERIALS AND METHODS

Animal Surgery. Male Sprague–Dawley rats (240–300 g; n = 9–15 per group) were housed individually and maintained in compliance with National Institutes of Health guidelines. Each animal was anesthetized by an i.p. injection of chloropent (148.75 mg of chloral hydrate per kg of body weight and 30.8 mg of sodium pentobarbital per kg of body weight). A 6.4- or 6.8-mm-long, 28-gauge stainless steel cannula (Plastics One, Roanoke, VA) was connected to an Alzet 2002 osmotic minipump (Alza; flow rate, 0.5 μl/hr) containing the sterile filtered phosphate-buffered saline vehicle (PBS; 0.1 M), BDNF (1 mg/ml; Amgen–Regeneron Partners, Thousand Oaks, CA, and Tarrytown, NY), or recombinant human

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: BDNF, brain-derived neurotrophic factor; DA, dopamine; NGF, nerve growth factor; SNC, substantia nigra pars compacta; TH, tyrosine hydroxylase; ISI, interspike interval.

†To whom reprint requests should be addressed.
§Present address: Department of Pharmacology, Texas Tech University Health Science Center, Lubbock, TX 79430.

¶Communication of this paper was initiated by Walle J. H. Nauta and, after his death, completed by Ann Graybiel.

nerve growth factor (NGF; 0.9 mg/ml; Amgen). The cannula was implanted as described (10) to terminate above the right substantia nigra (interaural coordinates: anterior, 2.5 mm; lateral, 2.7 mm). A separate control group of animals received the same surgical procedures but without cannula implantation.

Electrophysiological Recording. Fourteen to 15 days after the implantation, animals were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic apparatus. Body temperature was monitored and maintained at 36–37°C. The cannula and the skull overlaying the midbrain were removed. Single unit extracellular neuronal activity was recorded with single barrel glass micropipettes (World Precision Instruments, Sarasota, FL) filled with 2 M NaCl (*in vitro* impedance, 2–7 MΩ at 135 Hz). Single unit activity was monitored with a high-input impedance amplifier (bandpass filter settings, 0.3–3 kHz). The output was sent to an analog oscilloscope, audiomonitor, window discriminator, and a personal computer. Spontaneously active DA neurons were identified by their characteristic waveforms and firing patterns (17). The recording electrode was passed systematically through a stereotaxically defined block of SNC tissue (32 electrode tracks: 3.0–4.4 mm anterior to interaural line, 1.8–2.4 mm lateral, and 6.0–8.0 mm ventral to brain surface; ref. 18). Electrode tracks were separated by 200 μm. Each DA neuron was recorded for 1–5 min. The average numbers of spontaneously active DA neurons per electrode track (cells per track) were determined in each rat. Average firing rates of DA neurons were determined for all DA neurons sampled within each group.

Interspike intervals (ISIs) of individual DA neurons were determined from 500 consecutive action potentials obtained from each DA neuron to analyze the firing pattern (17, 19). Firing pattern analysis was performed on the ISI files with the Burstan program (19). The onset of a burst was defined by an ISI of <80 msec and a burst termination with the next ISI of 160 msec or greater. Firing patterns were analyzed by the following parameters for each individual DA neuron: coefficient of variation (SD/mean), burst number (percentage of action potentials that were present within the bursts), within-burst ISI (average ISI within individual bursts), postburst inhibitory period (average period between the offset of a burst and the next action potential), burst length (average number of action potentials within bursts), and percentage of within-burst action potentials grouped as doublets (a burst containing two action potentials).

To examine cannula placement after electrophysiological recording, 20 animals implanted with either a 6.4- or a 6.8-mm cannula were perfused with 0.9% saline and 4% paraformaldehyde (in 0.1 M PBS), and the brains were removed for TH immunohistochemistry as described (13). Histological data revealed that the cannulae were placed consistently in the area above the right substantia nigra. The tips of the 6.4-mm cannulae were typically seen 0.1–0.5 mm above the lateral SNC. The tips of the 6.8-mm cannulae were usually closer (0.2 mm to contact) to the SNC cell layer and 60% of them contacted the layer of TH-positive neurons in the SNC. A minor decrease in TH immunostaining was also observed in tissue immediately adjacent to the 6.8-mm cannula tip.

Data Analysis. The comparisons between groups for numbers of spontaneously active DA neurons and firing rates were made by a one-way ANOVA followed by Tukey HSD post hoc tests (CSS Software, Tulsa, OH). Because DA neurons in animals infused with BDNF discharged at much higher rates than normally observed in control group animals (see below), and burst activities were correlated with firing rate, the analysis of firing pattern parameters between these two groups was performed only in neurons with firing rates between 3 and 8 spikes per sec; to further control the group differences in firing rates, random block design analysis was used in which the burst parameters were compared in different firing rate ranges (3–4, 4–5, 5–6, 6–7, and 7–8 spikes per sec). Two-way multivariate ANOVA or univariate ANOVA was performed to analyze the intercorrelated firing pattern parameters. The comparisons between correlation coefficients were performed with Z tests following Fisher's r-to-Z transformation (20).

RESULTS

Body Weight. The chronic supranigral infusions of BDNF or NGF significantly decreased the percentage gain in body weight during the 2-week infusion period. The average percentage gain in body weight from preoperative levels was 1% and 6% in the NGF- and BDNF-infused animals, compared to 19% and 18% in the nonimplanted and PBS-infused animals, respectively.

Number of Spontaneously Active DA Neurons and Firing Rates. Animals implanted with the 6.4-mm cannulae and infused with BDNF demonstrated a 98% increase in the numbers of spontaneously active DA neurons (1.13 ± 0.10 cells per track; mean ± SEM; $n = 10$) compared with animals infused with PBS (0.57 ± 0.10 cell per track; $n = 9$; Fig. 1). The numbers of spontaneously active DA neurons did not differ among the PBS-infused animals (0.57 ± 0.10 cell per track; $n = 9$) and nonimplant control animals (0.56 ± 0.09 cell per track; $n = 10$) or NGF-infused animals (0.57 ± 0.09 cell per track; $n = 9$; Fig. 1).‖ Similar results were obtained from the animals implanted with the 6.8-mm cannulae. In these animals, the number of spontaneously active DA neurons in the BDNF-infused animals was increased by 65% (0.80 ± 0.07 cell per track; $n = 15$) when compared to the number of spontaneously active DA neurons in PBS-infused animals (0.48 ± 0.05 cell per track; $n = 12$; Fig. 2).

In animals implanted with the 6.4-mm cannulae, there were no differences in the average firing rates among the nonimplanted control animals (4.6 ± 0.1 spikes per sec; $n = 179$ cells from 10 animals), PBS-infused (4.8 ± 0.2 spikes per sec; $n = 160$ cells from 9 animals), or NGF-infused (4.7 ± 0.2 spikes per sec; $n = 167$ cells from 9 animals) animals. In contrast, BDNF increased the average firing rate to 6.3 ± 0.2 spikes per sec ($n = 351$ cells from 10 animals), which represented a 32% increase compared to the average firing rate in PBS-infused animals. Compared to infusions of PBS (4.5 ± 0.1 spikes per sec; $n = 186$ cells from 12 animals), BDNF infusions via the 6.8-mm cannula increased the firing rate by 33% to 6.0 ± 0.2 spikes per sec ($n = 380$ cells from 15 animals; Fig. 1).

The frequency distributions of the DA neuronal firing rates observed in non-BDNF-infused animals (data combined from nonimplanted control animals, NGF-, and all PBS-infused animals) and all BDNF-infused animals are presented in Fig. 2. In non-BDNF-infused animals, only 10% of the SNC DA neurons had firing rates of >8 spikes per sec, while in BDNF-infused animals, 34% of the DA neurons sampled discharged at rates of >8 spikes per sec. Firing rates of >10

‖The numbers of spontaneously active DA neurons (0.56–0.57 cell per track) in these groups are lower than the numbers observed in previous studies (0.80–0.83 cell per track; refs. 21 and 22). This is most likely due to the difference in sampling procedures. In the present study, 32 electrode penetrations were made in order to cover the entire rostral–caudal extent of the medial SNC (18), while in previous studies, the 12 electrode penetrations usually covered the caudal to central portion of the medial SNC. The SNC contains distinct populations of DA neurons that display different electrical activities and responses to DA agonists throughout its rostral–caudal extent (23). The use of 32 electrode tracks in the present study represents a more complete sampling of SNC DA neurons than previously reported.

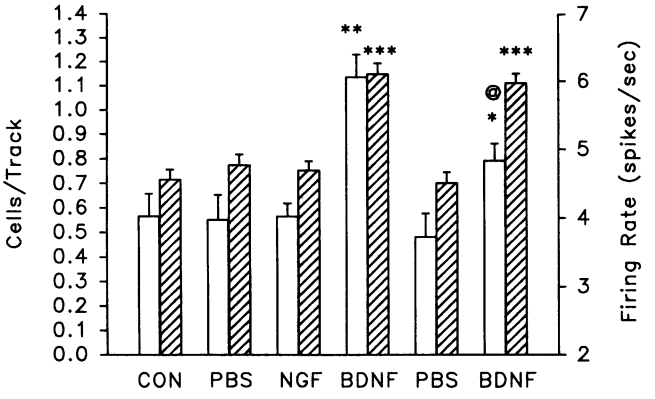

FIG. 1. Number of spontaneously active SNC DA neurons (□) and their firing rates (▨) in nonimplanted control (CON), PBS-, NGF-, and BDNF-infused rats. Male rats were implanted with a 6.4-mm (first four groups) or a 6.8-mm cannula (last two groups) that delivered PBS (0.5 μl/hr), NGF (0.45 μg/hr), or BDNF (0.5 μg/hr) for 14–15 days. Nonimplanted control animals underwent the same surgical procedures but were not implanted with a cannula. The numbers of spontaneously active SNC DA neurons are shown as cells per track (average number of DA neurons encountered from each electrode penetration) ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; BDNF vs. PBS groups compared at equal cannula length; @, $P < 0.05$ BDNF with 6.8-mm cannulae vs. BDNF with 6.4-mm cannulae.

spikes per sec were obtained in 24% of DA neurons sampled in BDNF-infused animals and in only 3% of control animals.

Changes in Burst-Firing Pattern After BDNF Treatment. The six burst parameters studied did not differ among the nonimplanted controls, animals infused with PBS (two groups implanted with the 6.4- or 6.8-mm cannulae), or NGF-infused animals (one group with the 6.4-mm cannulae), and these data were combined for statistical purposes. There was also no difference in any of the burst parameters between the two BDNF-infused groups implanted with 6.4- or 6.8-mm cannulae, and these data were combined to form the BDNF group. BDNF infusions increased the number of bursts and length of individual bursts. A significant positive correlation ($r = +0.73$, $n = 292$, from 40 animals; $P < 0.01$) was obtained between the firing rate and burst number in the control group. This correlation in the BDNF-infused group ($r = +0.87$, $n = 250$, from 25 animals; $P < 0.01$) was enhanced (Z test; $P < 0.001$) compared to the control group (Fig. 3). To obtain a better linear relationship between firing rate and burst length, the correlations were calculated between the firing rate and the logarithmic value of burst length. A positive correlation between the firing rate and log burst length was also observed in both the control ($r = +0.71$, $n = 261$, from 40 animals; $P < 0.01$) and, to an even greater extent, in the BDNF-infused group ($r = +0.85$, $n = 244$, from 25 animals; $P < 0.01$; Fig. 3). The clustering of cells was much more prominent in the low end of firing rate/burst number for controls and in the high end for BDNF-infused animals (Fig. 3).

DA neurons from the control and BDNF-infused groups were significantly different in firing pattern parameters (Table 1). In BDNF-infused animals, DA neurons with firing rates between 3 and 8 spikes per sec displayed a higher coefficient of variation ($P < 0.001$; ANOVA) and higher burst numbers ($P < 0.001$; ANOVA). Differences in the coefficient of variation and burst number between control and BDNF-infused animals diminished in cells with higher firing rates. For example, burst number of DA neurons between 3 and 6 spikes per sec was increased by 90% in BDNF-infused animals. This increase was reduced to 10% for DA neurons with firing rates between 6 and 8 spikes per sec. When DA neurons displaying burst activity (at least 3 doublets or one burst with 3 or more action potentials) were examined,

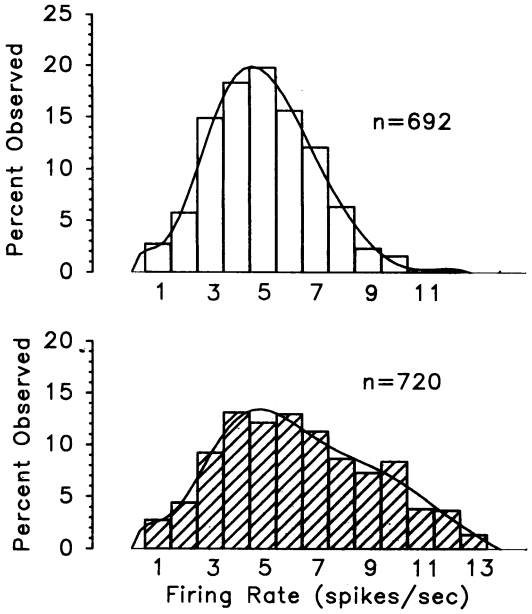

FIG. 2. Frequency distribution histograms of average firing rates of SNC DA neurons in control animals (*Upper*) (combination of data from nonimplanted controls, animals infused with NGF, and animals infused with PBS and implanted with 6.4- or 6.8-mm cannulae) and all BDNF-infused animals (*Lower*). In the BDNF-infused animals, 24% of DA neurons discharged at rates of ≥10 spikes per sec where only 3% of DA neurons in control animals showed firing rates of ≥10 spikes per sec.

neurons in BDNF-infused animals had shortened within-burst ISIs and increased postburst inhibitory period and burst length (Table 1). The percentage of within-burst action potentials grouped as doublets was also decreased in BDNF-infused animals (Table 1).

DISCUSSION

The results from the present study show that the spontaneous electrical activity of SNC DA neurons is substantially increased by chronic BDNF infusions in the area above the substantia nigra. It has been estimated that only 40–50% of SNC DA neurons normally display spontaneous activity (17). The remaining "silent" DA neurons do not generate action potentials due to excessive hyperpolarization of their cell membranes (24). The increases in the number of spontaneously active DA neurons and their firing rate by chronic infusions of BDNF indicate that BDNF can initiate action potentials in these normally silent DA neurons. The increase in firing rate did not appear to disrupt the basic firing pattern of SNC DA neurons, since the positive correlations between the firing rate and either the burst number or burst length were preserved in both control and BDNF-infused animals. The higher correlations in BDNF-infused animals reflect the ability of BDNF to induce a higher range of firing rate, burst number, and burst length. However, when the firing patterns are compared at equal firing rates, an increase in burst activity is still observed in the BDNF-infused animals. Such an increase in burst activity reflects an increased number of action potentials within each burst, increased postburst inhibitory period, and shortened ISIs within each burst.

Our results also indicate that the placement of cannula tips can optimize the potentiating effects of BDNF on the spontaneous activity of SNC DA neurons. The 98% increase in the number of spontaneously active DA neurons obtained with the shorter, 6.4-mm cannulae was greater than the 65% increase observed when the longer, 6.8-mm cannulae were used. The reason for this difference may involve a contact of

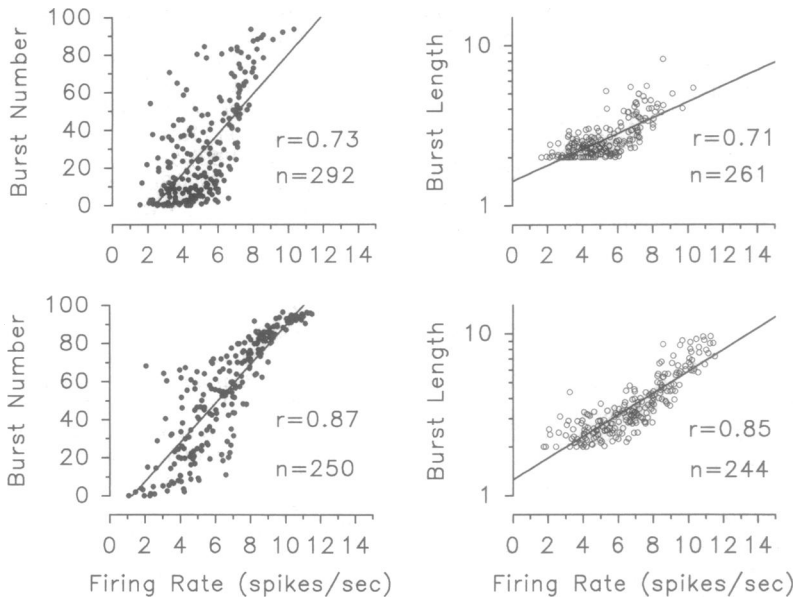

FIG. 3. Scatter plots for relationships between firing rate and two firing pattern parameters: burst number (percentage of action potentials present within bursts) and burst length (average number of action potentials within each burst) in control and BDNF-infused animals. Burst length was converted to logarithmic values to obtain linearity. Significant positive correlation coefficients were observed between firing rate and burst number or burst length. DA neurons in BDNF-infused animals (*Lower*) showed higher correlation between firing rate and burst number ($P < 0.001$) and between firing rate and burst length ($P < 0.01$) than obtained with control animals (*Upper*).

TH-positive SNC neurons with the 6.8-mm cannula. This contact may have attenuated the electrical activity of DA neurons by causing partial damage, as noted by the slightly diminished TH immunohistochemistry and/or local astrocyte proliferation (25). The shorter cannulae produced little or no damage to DA neurons, as determined by their normal TH immunostaining, equivalent spontaneous activity, and equivalent firing rates among the nonimplant controls and PBS- or NGF-infused animals.

Consistent with previous findings (10, 11), supranigral infusions of BDNF were found here to decrease the normal gain in body weight. Although the mechanism for this effect is unknown, it is clearly not due to the increase in DA neuron firing, since NGF, which also decreased the weight gain, did not increase the firing rate of DA neurons. By a similar logic, the elevation of DA neuron firing rates by BDNF was probably not a result of the lower body weight gain, since lower body weights but no changes in SNC electrical activity were obtained with NGF-infused animals. A role for the high-affinity receptor for NGF, TrkA, can also be ruled out. The SNC does not possess high-affinity NGF binding sites (26) or transcripts for TrkA receptors for NGF (27, 28), and NGF infusions here are without neurochemical, behavioral (10, 13), or electrical effects on nigral DA neurons. On the other hand, NGF receptor activation can increase the firing rates of fetal septal neurons grafted to the anterior chamber of the eye (29) presumably via NGF binding sites, which are normally found on rat septohippocampal neurons (e.g., see ref. 26).

Rather than through changes in body weight, the mechanism of BDNF's potentiating effects on DA neuronal activity may involve direct or transynaptic effects on membrane properties through BDNF binding to TrkB receptors located on SNC DA neurons (3, 27, 28, 30). This possibility may be better understood after electrophysiological actions of BDNF are characterized with DA neurons maintained *in vitro*

Table 1. Firing pattern parameters for DA neurons in control and BDNF-infused animals at different firing rates

Firing rate, spikes per sec	CV***	BN,*** %	WB ISI,*** msec	PB INB,* msec	BL**	PD,*** %
			Control			
3–4	0.54 ± 0.03	16 ± 2	62 ± 1	416 ± 18	2.25 ± 0.04	76 ± 3
4–5	0.48 ± 0.03	15 ± 2	66 ± 1	323 ± 6	2.27 ± 0.03	75 ± 3
5–6	0.52 ± 0.03	23 ± 3	72 ± 1	273 ± 8	2.32 ± 0.05	71 ± 3
6–7	0.52 ± 0.04	41 ± 4	80 ± 2	241 ± 6	2.93 ± 0.13	49 ± 4
7–8	0.56 ± 0.03	61 ± 3	81 ± 2	238 ± 7	3.60 ± 0.14	28 ± 3
			BDNF			
3–4	0.68 ± 0.07	25 ± 5	59 ± 3	438 ± 21	2.50 ± 0.10	62 ± 5
4–5	0.64 ± 0.04	32 ± 3	61 ± 2	348 ± 10	2.53 ± 0.06	55 ± 4
5–6	0.66 ± 0.03	42 ± 3	65 ± 2	314 ± 9	2.71 ± 0.08	45 ± 4
6–7	0.57 ± 0.03	50 ± 3	75 ± 2	255 ± 6	3.23 ± 0.11	31 ± 3
7–8	0.60 ± 0.05	65 ± 2	78 ± 2	231 ± 4	3.44 ± 0.10	25 ± 2

CV, coefficient variation; BN, burst number; WB ISI, within-burst ISI; PB INB, postburst inhibitory period; BL, burst length; PD, percentage of within-burst action potentials grouped as doublets. CV and BN were taken from all DA neurons. The rest of the parameters were taken from DA neurons displaying at least three doublets or one burst with three or more action potentials. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ for main effects between control and BDNF-infused animals.

(5–9). The BDNF-induced increases in firing rate and, in particular, burst activity indicate that these changes may also have been mediated indirectly via afferent inputs, because DA neurons in *in vitro* slice preparations do not display burst activity (31, 32). DA neurons may be activated *in vivo* by increases in direct excitatory inputs or decreases in inhibitory inputs. For example, intranigral administration of acetylcholine (33), excitatory amino acids (19), neurotensin (34), or the tachykinins substance P (35) and substance K (36) directly excite DA neurons. Alternatively, enkephalins (37, 38) can activate DA neurons by attenuating their tonic inhibition by nigral γ-aminobutyric acid (GABA)ergic interneurons. The potentiating effects of BDNF on the neuronal activity of DA neurons may be due to its effect on increasing the outputs of one or more of these afferents. This possibility is supported by the observation that BDNF exposure to developing *Xenopus* neuromuscular cultures increases synaptic currents through an increase in the presynaptic release of acetylcholine (39). Future studies with lesion techniques and receptor antagonists to the modulatory systems mentioned above may help define the contributions of these afferents in mediating the effects of BDNF on DA neuronal activity.

BDNF mRNA is found most abundantly in the adult brain (40, 41). It is thus not surprising that BDNF can affect the maintenance and regulation of mature neurons (1–3). The results from the present study support this speculation by demonstrating that BDNF can potentiate the electrical activity of SNC DA neurons in the adult central nervous system *in vivo*. Furthermore, our data suggest that BDNF or other TrkB agonist ligands may possess a therapeutic potential for treating Parkinson disease. Both animal and clinical studies in Parkinson disease have shown that severe movement deficits are associated with large depletions of DA neurons in the substantia nigra (42, 43). By increasing the spontaneous electrical activity of the remaining neurons, BDNF may increase the endogenous synthesis and release of DA (14–16) in otherwise untreated patients or during treatment with the anti-Parkinson drug L-dihydroxyphenylalanine (L-Dopa; refs. 44 and 45).

We appreciate the supply of recombinant human NGF by Dr. Randy Hecht, Amgen Pharmaceuticals.

1. Altar, C. A., Alderson, R. F., Anderson, K. A., Hyman, C., Wiegand, S. J. & Lindsay, R. M. (1994) in *Alzheimer's and Parkinson's Diseases: Recent Advances*, eds. Hanin, I., Fisher, A. & Yoshida, M. (Plenum, New York), in press.
2. Hefti, F. (1994) in *Neurodegenerative Diseases*, ed. Calne, D. B. (Saunders, Philadelphia), pp. 177–194.
3. Lindsay, R. M., Wiegand, S. J., Altar, C. A. & DiStefano, P. S. (1994) *Trends Neurosci.* **17**, 182–190.
4. Barde, Y.-A., Edgar, D. & Thoenen, H. (1982) *EMBO J.* **1**, 549–553.
5. Beck, K., Knüsel, B. & Hefti, F. (1993) *Neuroscience* **52**, 855–866.
6. Hyman, C., Hofer, M., Barde, Y.-A., Juhasz, M., Yancopoulos, G. D., Squinto, S. P. & Lindsay, R. M. (1991) *Nature (London)* **344**, 339–341.
7. Hyman, C., Juhasz, M., Jackson, C., Wright, P., Ip, N. Y. & Lindsay, R. M. (1994) *J. Neurosci.* **14**, 335–347.
8. Knüsel, B., Winslow, J. W., Rosenthal, A., Burton, L. E., Seid, D. P., Nikolics, K. & Hefti, F. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 961–965.
9. Spina, M. B., Squinto, S. P., Miller, J., Lindsay, R. M. & Hyman, C. (1992) *J. Neurochem.* **59**, 99–106.
10. Altar, C. A., Boylan, C. B., Jackson, C., Hershenson, S., Miller, J., Wiegand, S. J., Lindsay, R. M. & Hyman, C. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 11347–11351.
11. Martin-Iverson, M. T., Todd, K. G. & Altar, C. A. (1994) *J. Neurosci.* **14**, 1262–1270.
12. Anderson, R. F., Alterman, A., Morissey, D. & Lindsay, R. M. (1993) *Soc. Neurosci. Abstr.* **19**, 666 (abstr.).
13. Altar, C. A., Boylan, C. B., Fritsche, M. F., Jones, B. E., Jackson, C., Wiegand, S. J., Lindsay, R. M. & Hyman, C. (1994) *J. Neurochem.*, in press.
14. Cheramy, A., Barbeito, L., Godeheu, G., Desce, J. M., Pittaluga, A., Galli, T., Artaud, F. & Glowinski, J. (1992) *J. Neural. Transm.* **S29**, 183–193.
15. Gonon, F. & Buda, M. (1985) *Neuroscience* **14**, 765–774.
16. Murrin, L. C., Morgenroth, V. H., III, & Roth, R. H. (1976) *Mol. Pharmacol.* **12**, 1070–1081.
17. Chiodo, L. A. (1988) *Neurosci. Biobehav. Rev.* **12**, 49–91.
18. Paxinos, G. & Watson, C. (1986) *The Rat Brain in Stereotaxic Coordinates* (Academic, New York), 2nd Ed.
19. Zhang, J., Chiodo, L. A. & Freeman, A. S. (1992) *Brain Res.* **590**, 153–163.
20. Nachmias, D. & Nachmias, C. (1982) *Research Methods in the Social Sciences* (St. Martin's, New York), pp. 463–464.
21. Chiodo, L. A. & Bunney, B. S. (1983) *J. Neurosci.* **3**, 1607–1619.
22. Chiodo, L. A. & Bunney, B. S. (1987) *J. Neurosci.* **7**, 629–633.
23. Shepard, P. D. & German, D. C. (1988) *Neuroscience* **27**, 537–546.
24. Grace, A. A. (1991) *Synapse* **7**, 221–234.
25. Shults, C. W., Matthews, R. T., Altar, C. A. & Langlais, P. J. (1994) *Exp. Neurol.* **125**, 183–194.
26. Altar, C. A., Burton, L. E., Bennet, G. & Dugich-Djordjevic, M. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 281–285.
27. Merlio, J. P., Ernfors, P., Jaber, M. & Persson, H. (1992) *Neuroscience* **51**, 513–532.
28. Gall, C. M., Gold, S. J., Isackson, J. & Seroogy, K. B. (1992) *Mol. Cell. Neurosci.* **3**, 56–63.
29. Palmer, M. R., Eriksdotter-Nilsson, M., Henschen, A., Ebendal, T. & Olson, L. (1993) *Exp. Brain Res.* **93**, 226–230.
30. Altar, C. A., Siuciak, J. A., Wright, P., Ip, N. Y., Lindsay, R. M. & Wiegand, S. J. (1994) *Eur. J. Neurosci.*, in press.
31. Grace, A. A. & Onn, S.-P. (1989) *J. Neurosci.* **9**, 3463–3481.
32. Sanghera, M. K., Trulson, M. E. & German, D. C. (1984) *Neuroscience* **12**, 793–801.
33. Lichtensteiger, W., Felix, D., Lienhart, R. & Hefti, F. (1976) *Brain Res.* **117**, 85–103.
34. Pinnock, R. D. (1985) *Brain Res.* **338**, 153–158.
35. Davies, J. & Dray, A. (1976) *Brain Res.* **107**, 623–627.
36. Innis, R. B., Andrade, R. & Aghajanian, G. K. (1987) *Brain Res.* **411**, 139–143.
37. Hommer, D. W. & Pert, A. (1983) *Peptides* **4**, 603–608.
38. Nowycky, M. C., Walters, J. R. & Roth, R. H. (1978) *J. Neural Transm.* **42**, 99–116.
39. Lohof, A. M., Ip, N. Y. & Poo, M.-M. (1993) *Nature (London)* **363**, 350–353.
40. Leibrock, J., Lottseich, F., Hohn, A., Hengerer, B., Masiakowski, P., Thoenen, H. & Barde, Y.-A. (1989) *Nature (London)* **341**, 149–152.
41. Maisonpierre, P. C., Belluscio, L., Squinto, S., Ip, N. Y., Furth, M. E., Lindsay, R. M. & Barde, Y.-A., Yancopoulos, G. D. (1990) *Science* **247**, 1446–1451.
42. Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K. & Seitelberger, F. (1973) *J. Neurol. Sci.* **20**, 415–455.
43. Zigmond, M. J., Abercrombie, E. D., Berger, T. W., Grace, A. A. & Stricker, E. M. (1990) *Trends Neurosci.* **7**, 290–296.
44. Acquas, E., Carboni, E., de Ree, R. H., Da Prada, M. & Dichiara, G. (1992) *J. Neurochem.* **59**, 326–330.
45. Snyder, G. L. & Zigmond, M. L. (1990) *Brain Res.* **508**, 181–187.