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MINI REVIEW

Alterations in Striatal Neurotrophic Activity Induced by Dopaminergic Drugs

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CARVEY, P. M., L. R. PTAK, D. LIN, E. S. LO, C. M. BUHRFIEND, G. E. DRUCKER AND J. Z. FIELDS. *Mini review: Alterations in striatal neurotrophic activity induced by dopaminergic drugs.* PHARMACOL BIOCHEM BEHAV 46(1) 195–204, 1993.—The administration of dopaminergic drugs induces a variety of compensatory responses ostensibly designed to reinstate normal dopamine (DA) tone. We have hypothesized that drug-induced alterations in striatal-derived neurotrophic activity contributes to these compensatory processes. This phenomenon has been studied by examining the growth of mesencephalic cultures incubated with cell-free extracts of striatal tissue taken from patients or rats treated with various drugs. Our results reveal that reducing striatal DA tone by administering the DA antagonist haloperidol, the DA neurotoxin 6-hydroxydopamine, or as occurs naturally in Parkinson's disease, increases striatal trophic activity. Conversely, increasing striatal DA tone by administering the indirect DA agonists amphetamine or levodopa reduces trophic activity in the striatum. Kainic acid lesions of the striatum similarly reduce this trophic activity. The implications of these drug-induced alterations in trophic activity are discussed and reviewed.

Trophic factor Dopamine Haloperidol Levodopa Amphetamine Culture Review Striatum

WITHIN the nigrostriatal dopamine (DA) projection system, numerous adaptive, compensatory processes accompany the systemic administration of dopaminergic drugs. Following the administration of the DA antagonist haloperidol, the DA neuron increases its firing rate, DA synthesis, and DA release (2,83,84). Following the administration of DA agonists such as amphetamine, the DA neuron decreases its firing rate, DA synthesis, and DA release (25,69). These compensatory processes appear to act to reestablish normal DA tone (85) (the net effect of DA neuron activation and postsynaptic effect). Thus, DA antagonists reduce DA tone and invoke compensatory processes that serve to reinstate normal DA tone. The converse is true of DA agonists. These compensatory processes can occur very quickly following systemic injection (46,47).

Although the DA neuron possesses a number of mechanisms that can compensate for the continued presence of DA drugs following acute administration, additional adaptational changes in the neuronal networks postsynaptic to the DA synapse accompany chronic treatment. The number of D_2 DA receptors are up- and downregulated in the striatum (9–11, 14,19,69,70) as is DA receptor-mediated second messenger production (36,58). These compensatory processes in the "target cells" of the DA neuron, in turn, induce adaptational changes in the action of their neurotransmitters on their respective target cells, as evidenced by the fact that alterations in muscarinic receptor number have been observed in response to chronic DA drug treatment (29). Therefore, a variety of compensatory changes that are both intrinsic and extrinsic to the DA neuron work in concert to reestablish normal DA tone despite the continuous presence of DA drugs.

These adaptive, compensatory mechanisms can have long-term consequences that can influence behaviors associated with the DA system (11,14,69). Although many of the features of these adaptive changes have been explained by characterizing DA turnover or DA receptor number, several inconsistencies exist, suggesting that additional, unknown adaptive mechanisms might be at work (11,14). Examination of the brains of transplant recipients may suggest that neurotrophic factors may participate in this adaptive process.

One of the more popular hypotheses invoked to explain the antiparkinsonian efficacy of adrenal medulla-to-brain transplantation is that it increases neurotrophic activity in the striatum (5). The tissue surrounding the implant site in rodents

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(6), nonhuman primates (32), as well as humans (43), exhibits an increase in DA that is associated with an increase in tyrosine hydroxylase immunoreactivity (TH-IR), suggesting DA terminal sprouting. Several investigators have suggested that the increased TH-IR surrounding the implant site is the result of a host sprouting response (5,27,28). Although it could be argued that adrenal chromaffin cells, which are a rich source of neurotrophic substances (61,63), are producing the trophic effects, several reports have documented the poor viability of these cells following implantation (28,43), and further, tissue implants other than adrenal chromaffin cells have also been observed to induce an increase in host TH-IR (3). These data suggest that trophic factors resulting from the invasion of inflammatory cells into the transplant site or factors intrinsic to the striatum are responsible for the increase in TH-IR. Although the factor(s) responsible for this effect have not been identified, transplantation research has greatly contributed to the notion that neurotrophic factors play a role not only in development, but in the damaged adult brain as well.

Our laboratory has assumed that neurotrophic factors capable of stimulating the sprouting of DA terminals exist within the striatum. Moreover, we have assumed that an increase in these factors participates, at least in part, in the antiparkinsonian efficacy of adrenal medulla-to-brain transplantation. The presence of intrinsic striatal trophic factors capable of stimulating a sprouting response in DA neuron terminals might suggest that this activity plays a role in the normal physiological function of the nigrostriatal pathway. If this were the case, then DA-mediated alterations in striatal neurotrophic activity might also participate in the adaptive processes that accompany alterations in DA neurotransmission. We have begun to explore this possibillity by manipulating DA neurotransmission with drugs.

NEUROTRANSMISSION AND NEUROTROPHIC ACTIVITY

A considerable literature exists in support of the hypothesis that alterations in neurotransmitter activity influence the growth of neurons. As reviewed by Mattson (52), ACh, DA, GABA, glutamate, 5-HT, and somatostatin have all been shown to influence neuron growth in both invertebrate and vertebrate model systems (44,53-56). For instance, iontophoresed glutamate, at subtoxic levels, reduced dendritic sprouting without influencing axonal growth in culture, suggesting that glutamate, in effect, contours the architecture of the pyramidal neuron (53). It has also been shown that incubation of these cultures with GABA prevents axon extension, and further, that GABA incubation could reverse the selective contouring effect of glutamate. This finding is significant, since glutamate and GABA represent the primary excitatory and inhibitory inputs, respectively, to pyramidal cells in the hippocampus. This would suggest that the advent of glutaminergic afferents into the pyramidal cell field, inhibits process extension of the pyramidal neuron without interfering with axon extension. The subsequent growth of GABA-secreting afferents into the vicinity of the pyramidal cell then inhibits axon extension and promotes dendritic growth of the pyramidal cell. ACh and NE have also been shown to influence pyramidal cell growth, but not until the receptors for these transmitters are present on the pyramidal cell (52). This suggests that receptor/transmitter interaction is a necessary prerequisite for the observed growth effects.

These studies do not suggest that the neurotransmitters act as "the" growth promoting or inhibiting factors themselves, but rather, that they influence a function of the target cell that, in turn, influences cell growth. These data are most consistent with the notion that the effect of neurotransmitters on cell growth revolves around alterations in neuronal excitability [i.e., electrical activity of the cell (20)]. Alterations in cell excitability are therefore thought to be, in part, the regulators of a neuron's growth potential. Excitability may also regulate the production of neurotrophic factors or the response of neurons to these factors by regulating receptor expression (4). The observations that demonstrate that the growth-promoting effects of glutamate in the hippocampus are antagonized with receptor subtype antagonists [i.e., gamma-*d*-glutamylglycine (DGG)], but not by others [i.e., 2-amino-5-phosphonovaleric acid (APV)], and mimicked by appropriate receptor-specific agonists like kainate, but not by others (NMDA) (52), suggest that drug treatment may potentially influence this growth effect in vivo as well.

Other investigators have characterized the ability of drugs to alter programmed motor neuron death in the periphery (50), neuromuscular junction innervation (60), and ganglion cell outgrowth (48). In the adult CNS, blockade of muscarinic receptors using atropine results in an increase in the mRNA for brain-derived neurotrophic factor (BDNF) in much the same fashion that fimbria-fornix transection induces increased mRNA for BDNF (45). This suggests that drugs can influence trophic factor production, and further, that drug-induced alterations in synaptic activity in the adult similarly have neurotrophic consequences. It is therefore becoming clear that drug-induced alterations in neurotransmitter tone alter excitability that, in turn, influences trophic activity. In the adult, where synaptic architecture is already well established, postsynaptic-derived growth-promoting and growth-inhibiting factors could strengthen and weaken synaptic connectivity, respectively (66). If dopaminergic drugs were capable of regulating the production of NTFs in the striatum, then drug-induced alterations in these NTFs might compliment the compensatory mechanisms already known to occur in response to chronic DA drug treatment. We have been studying this possibility in the laboratory rat by analyzing the effect striatal homogenates have on the growth of rostral mesencephalic tegmentum (RMT) cultures containing DA neurons. Our results indicate the involvement of neurotrophic effects in the actions of dopaminergic drugs.

GENERAL METHOD

There are several candidate neurotrophic substances in the adult brain that have been shown to stimulate the growth of RMT cultures. These include basic fibroblast growth factor (bFGF) (26), epidermal growth factor, insulin-like growth factor (42), platelet-derived growth factor (59), and BDNF (39). Since it is possible that any one of these factor, some unknown factor, or combination thereof could be influenced by DA drugs, we have chosen to characterize the overall growth-promoting effects of the striatum by examining extracts from the striatum for the presence of growth-promoting activity (GPA). GPA therefore represents the overall growth-promoting effect that striatal extracts have on RMT cultures. Since neuroinhibitory factors have also been found in the CNS (71), GPA could also reflect alterations in the presence of factors that inhibit the growth of neurons. We have developed several assay systems to examine GPA.

CULTURE PREPARATION

RMT cultures are established from precisely timed E-15.5 rat embryos (Sprague–Dawley; Zivic Miller) using standard

methodology with minor modifications (21,22,65,79). The details of this technique have been published elsewhere (15,17). Two approaches are employed that utilize two different RMT plating densities. High cell density cultures are plated out at 40,000 cells per well (Falcon 96-well plates; poly-*l*-lysine coated; 12,500 cells/mm^2) in 200 μl of media containing 10% fetal calf serum for 24 h. The cells are then washed and incubated in a defined media described elsewhere (15). In some studies, the cells are then incubated for 24 h with 5-fluorouracil/uracil (5FU; 52.8 and 135 μM, respectively), an antimitotic agent that kills off glia. These cultures are then maintained in defined media.

Low cell density cultures (3500 cells/well; 96-well plate; 1250 cells/mm^2) are also employed to examine cell survival and neurite extension (17). Poly-*l*-lysine-coated plates are preincubated for 4 h at 37°C with 20% fetal calf serum. This plate conditioning is critical in promoting cell viability. The cells are then plated out in defined media. The basic premise of this procedure is that cells plated out at this density do not survive for more the 48 h without the addition of exogenous trophic factors (51,80). Under these conditions, the plates can be quickly scanned for the presence of viable cells with fine, nontapering processes (neuron-specific enolase immunoreactive cells) and, because of the low plating density, cell counts and the length of their processes can be determined.

CELL-FREE EXTRACT PREPARATION

Animals are perfusion exsanguinated with cold saline under light halothane anesthesia. The brain is removed and snap-frozen in liquid 2-methyl-butane for 1 min. Brains are stored at −80°C until dissection. The striatum and cerebellum are dissected from coronal sections, weighed, and immediately homogenized in Hanks balanced salt solution (HBSS; 40 mg wet weight/ml of HBSS). The samples are then spun down at 12,000 × *g* for 45 min at 4°C. The supernatants (referred to as the "extract") are removed, and in the early studies, pooled by tissue section and treatment group. In later studies, extracts from individual animals were studied. Extracts are always assessed for total protein using the Bio-Rad protein assay kit. All extracts are diluted with HBSS to yield an equivalent protein content. The stability of these extracts have been studied and they were shown to retain activity for 8 months when stored at −80°C, although freshly prepared, unfrozen extracts had approximately 10% higher activity (unpublished observation).

GPA IN STRIATAL EXTRACTS WITH REDUCED DA TONE

As previously reported (12,13,15), rats were pretested for apomorphine-induced stereotypic behavior (SB), group-matched by SB behavioral scores, and then treated daily with 0.75 or 1.25 mg/kg haloperidol (IP) for 24 days. SB is a continuum of behaviors consisting of increased locomotion, sniffing, and rearing at low doses of apomorphine, and chewing and gnawing at higher doses. This behavior was quantified by grading these behaviors (0+ not present to 5+ continuously present) at 5-min intervals following apomorphine injection. Following treatment, the animals were withdrawn from haloperidol for 96 h, retested for SB using apomorphine, and sacrificed 48 h later. Extracts from the striata and cerebellums of these animals were generated as described above and then added to high cell density RMT cultures.

Striatal extracts from vehicle-treated controls stimulated the growth of RMT cultures (Fig. 1a) relative to the effect of cerebellar extracts (data not shown). This effect is consistent with the findings of Heller and his colleagues (34,35,37), and suggests that target cells that normally receive dopaminergic innervation possess a factor(s) that stimulates the growth of DA neurons. Striatal extracts from haloperidol-treated animals had a profound effect on the growth of high cell density RMT cultures relative to the effect of extracts from saline-treated controls (Fig. 1b).

There are various cell types present in RMT cultures. These include glia as well as neurons. Tyrosine hydroxylase immunoreactive (TH-IR) cell counts of these cultures from our lab suggest that DA neurons represent approximately 1% of the neurons present in these cultures, with the majority of the remaining neurons being glutamic acid decarboxylase immunoreactive (GAD-IR), suggesting GABA. The GPA present in striatal extracts could therefore be directed at any, or all, of these cell types. It is also important to appreciate that although cultures incubated with striatal extracts from haloperidol-treated animals contain more cells, this does not mean that these extracts stimulated mitosis, but rather, that striatal extracts prevent the cell death that normally occurs in cultures growing in defined media. Glial cells, which can undergo mitotic proliferation in culture, could represent the stimulated cell growth observed in cultures incubated with striatal extracts. However, defined media does not readily support glial cell growth, and neurons have a characteristic structure that differentiates them from the various types of glia found in these cultures. Moreover, we have demonstrated that cultures pretreated with the antimitotic agent 5FU exhibit a similar response to striatal extracts from haloperidol-treated animals (15). This suggests that striatal extracts possess a GPA that acts directly on neurons in culture.

That striatal extracts from haloperidol-treated animals possess a GPA directed at neurons was further evaluated by examining ^{14}C-DA and ^{3}H-GABA uptake in cultures incubated with various extracts. Both DA and GABA uptake were increased in cultures following incubation with striatal extracts from haloperidol-treated animals relative to the effect of extracts from vehicle-treated controls (13,15). That these changes in GPA were related to alterations in DA tone was supported by the fact that cerebellar extracts from haloperidol- or vehicle-treated controls possessed an equivalent amount of GPA that was reduced relative to the effect of striatal extracts from vehicle-treated controls. Haloperidol treatment thus increased GPA in the striatum, a normal target structure of the DA-containing cells of the mesencephalon, but did not enhance uptake in cultures incubated with cerebellar extracts, a structure that does not contain a significant dopaminergic innervation. Furthermore, the effect striatal extracts had on DA uptake was not altered when the cultures were pretreated with 5FU, whereas 5FU pretreatment dramatically attenuated GABA uptake (15). This suggests that the factor(s) responsible for stimulating increased DA uptake works directly on the DA neuron, whereas the factor(s) stimulating an increase in GABA uptake involve glia. This observation expands upon that of Tomozawa and Appel, who similarly reported GPA present in the striatum, and further, that fractionation of the extract could partially segregate the GPA directed at DA neurons from that directed at GABA neurons (79).

Prochiantz and his colleagues (21,24,64,65) previously demonstrated that striatal extracts from rats with unilateral lesions of the mesencephalon induced by the DA neurotoxin 6-hydroxydopamine (6-OHDA) possessed increased GPA relative to sham-lesioned controls. We recently reproduced these findings (17). We have also demonstrated that striatal extracts

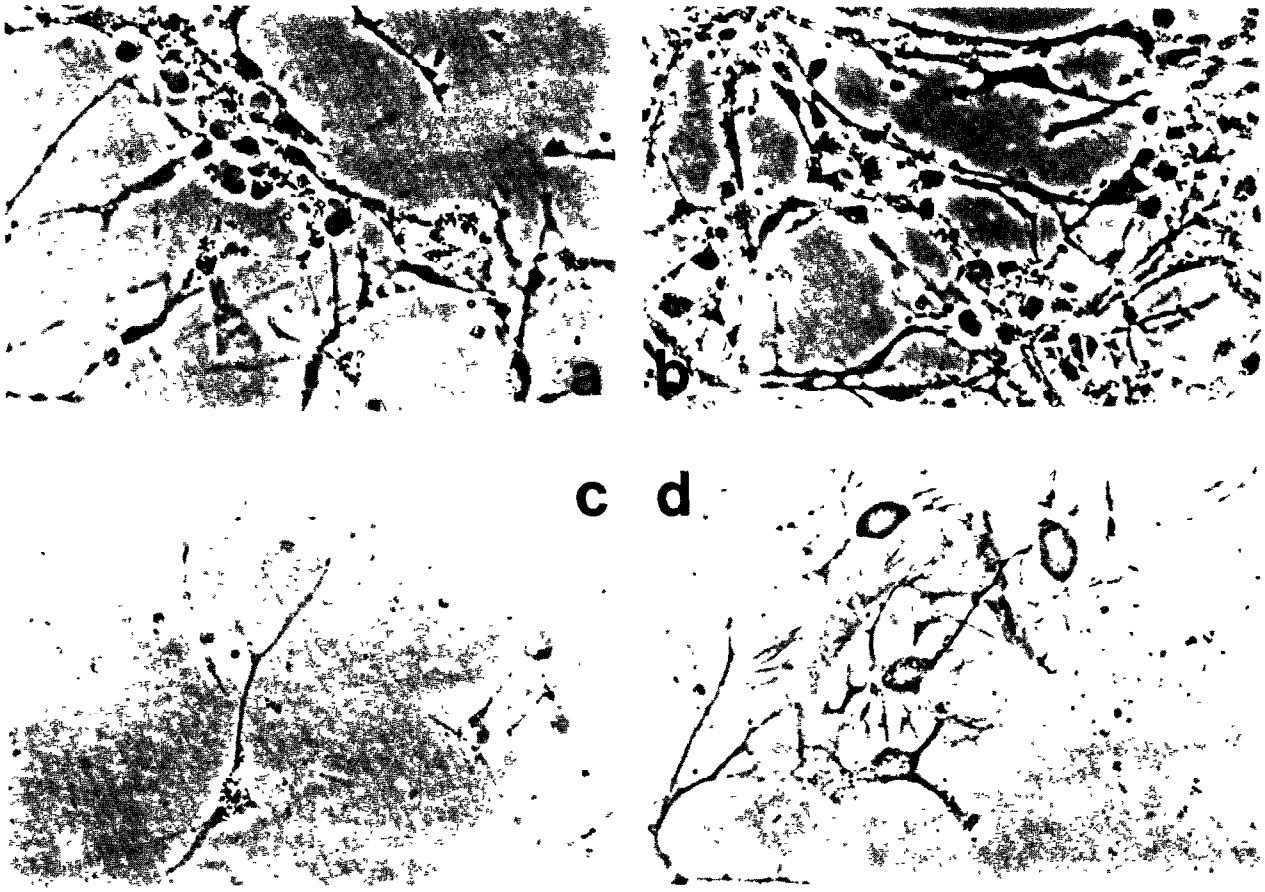

FIG. 1. Phase contrast photomicrographs of rostral mesencephalic cultures incubated with striatal extracts from (a) normal saline, (b) haloperidol (1.25 mg/kg/day), (c) amphetamine (10.0 mg/kg/day), and (d) amphetamine (2.5 mg/kg/day) treated animals. Animals received 24 daily treatments with these drugs followed by 6 drug-free days. The striatal extracts were then incubated with the cultures for 72 h. Magnification ×200.

from patients with Parkinson's disease (PD) possess an increase in GPA relative to neurologically normal, aged controls (16,18,49). Thus, extracts of the putamen and caudate, but not the cerebellum, of PD patients enhanced the number of viable cells with processes in low cell density RMT cultures, and increased DA uptake as well as the number of TH-IR cells in high cell density cultures. Furthermore, the CSF of PD patients similarly contains more GPA than age-matched neurologically normal controls (12). Together with the results from our work with haloperidol, it therefore appears that interruption of DA neurotransmission by physical denervation (6-OHDA lesions or PD) or by pharmacological blockade (haloperidol) elevates trophic activity in the striatum.

The fact that several conditions that reduce DA tone are associated with enhanced striatal GPA might suggest that alterations in neurotrophic activity participate in the compensatory processes that accompany chronic drug treatment. Of course, for this to occur, it must be established that the growth-promoting effects observed in vitro also occur in vivo. We have reported preliminary evidence in support of this possibility (41). Animals chronically treated with haloperidol and exhibiting increased GPA were submitted to electron microscopic analysis of the dorsolateral quadrant of the striatum. Haloperidol-treated animals exhibited a significant increase in synaptic density. This observation is consistent with the findings of Meshul and Casey (57), who similarly reported evidence of increased synaptic plasticity in the striatum following DA antagonist treatment. Numerous neuron types could be contributing to this effect and tyrosine hydroxylase electron microscopic analysis of this finding is proceeding. However, these data are consistent with the notion that the increased GPA present in striatal extracts may induce plastic changes in the striatum of the adult rat in much the same fashion that RMT cultures are stimulated.

GPA IN STRIATAL EXTRACTS WITH INCREASED DA TONE

Figure 1c and d depicts the effect that striatal extracts from animals treated for 24 days with *d*-amphetamine SO_4 (10.0 and 2.5 mg/kg/day, IP, respectively) have on high cell density culture growth. As was true of all of our drug studies, the extracts were generated from these animals 6 days following their last treatment to reduce the possibility that drug carried over from the treatment could directly influence culture growth. Striatal extracts from animals treated with amphetamine contained less GPA than striatal extracts from vehicle-treated controls. Cultures incubated with striatal extracts from amphetamine-treated animals contained fewer neurons, and

overall, the cultures resembled cultures incubated with extracts from the cerebellum or those incubated with an equivalent amount of BSA. This suggests that prolonged elevation of striatal DA tone using amphetamine reduces the GPA present in the striatum.

So-called neurotoxic doses of the amphetamines have been reported to induce DA neuron toxicity. In support of this hypothesis are the observations that neurotoxic doses of amphetamine induce: 1) a long-lasting depletion of DA and its metabolites (30,77); 2) a reduction in striatal DA reuptake sites (82); 3) a decrease in striatal tyrosine hydroxylase activity (38); and 4) silver impregnation changes, suggesting degeneration of DA neuron terminals (68). It has been suggested that amphetamines enhance the production of quinones such as 6-OHDA (72) or that the excess quantities of DA released by amphetamine favor the production of free radicles with subsequent lipid peroxidation (23,67). However, it has also been reported that DA and NMDA receptor antagonists prevent the neurotoxic effects of amphetamine (73–75,78). This suggests that mechanisms postsynaptic to the DA neuron, perhaps involving alterations in GPA, may also be involved in the neurotoxic process as well. We therefore examined this possibility.

Rats received a "cocktail" of *d*-amphetamine SO_4 (9.2 mg/kg) and iprindole (10 mg/kg) delivered daily (IP) for 3 consecutive days. Control animals received iprindole injections via the same injection schedule. Iprindole prevents the catabolism of amphetamine (30), and this treatment regimen has been previously shown to induce neurotoxicity (77). The animals were housed singly to reduce mortality, which was low (<10%). Seven and 14 days following their last treatment, the animals were sacrificed, a striatal punch was taken for HPLC analysis, and striatal and cerebellar extracts were generated as described above. The extracts were then evaluated for GPA using the low cell density assay system (7).

Amphetamine/iprindole treatment reduced the content of DA and its metabolite DOPAC in the striatum relative to iprindole-treated animals [Fig. 2; there were no statistically

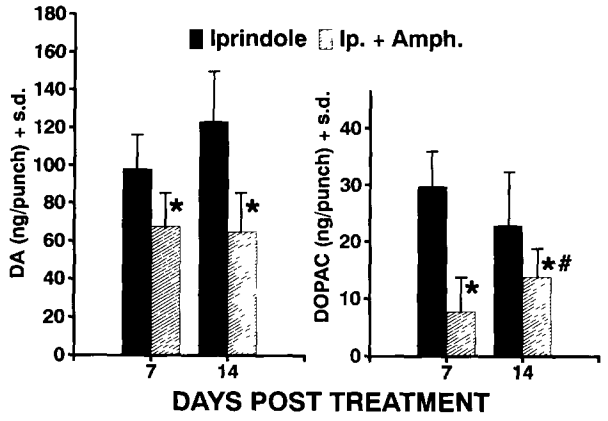

FIG. 2. DA and DOPAC content in punches taken from animals treated with iprindole (10.0 mg/kg/day) or iprindole + amphetamine (9.2 mg/kg/day) for 3 days. The animals were sacrificed 7 and 14 days following their last treatment. *$p < 0.05$ vs. iprindole-treated animals; #$p < 0.05$ vs. 7-day iprindole + amphetamine-treated animals (p values based on Tukey's post hoc comparison test).

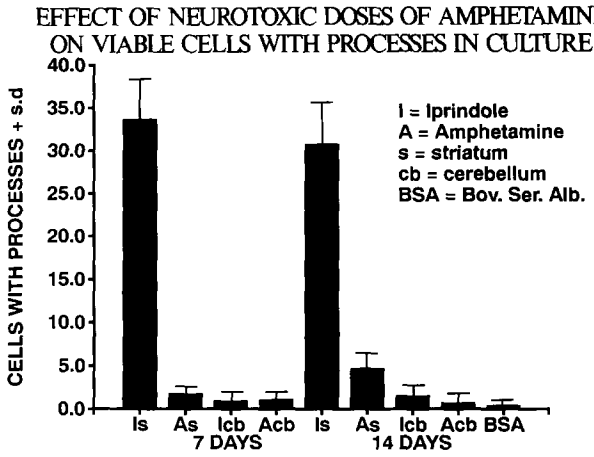

FIG. 3. Number of viable cells with processes in mesencephalic cultures incubated with striatal and cerebellar extracts from animals treated with iprindole (10.0 mg/kg/day) or iprindole + amphetamine (9.2 mg/kg/day) for 3 days. Extracts were generated 7 and 14 days following the last treatment and added to the cultures. The cultures were scored 40 h later. Both Is group means are significantly elevated relative to the effects of all other extracts ($p < 0.05$). No other significant differences were observed using the Tukey post hoc comparison test.

significant differences between DA levels in saline-treated (data not shown) and iprindole-treated animals: $t = 1.08$, $p > 0.05$]. This supports previous studies, which demonstrated that amphetamine/iprindole can induce long-lasting DA depletion (30,77). Figure 3 depicts the effects the various extracts had on the number of viable cells with processes. The incubation of RMT cultures with striatal extracts taken from animals sacrificed 1 and 2 weeks following amphetamine/iprindole treatment resulted in a dramatically reduced rate of culture growth relative to control striatal extracts, $F(9, 83) = 130.40$, $p < 0.0001$. Significantly fewer cells with processes were observed in the cultures incubated with the amphetamine-treated striatal extracts, and the level of culture growth observed was just slightly elevated relative to the effect of cerebellar extracts. This growth effect was replicated with a second set of cultures and the exact same trend was observed, $F(9, 83) = 79.75$, $p < 0.0001$.

The results from the low cell density study using extracts from animals receiving neurotoxic doses of amphetamine are similar to those described above, where 24 days of amphetamine treatment was employed. Thus, amphetamine treatment, which elevates DA tone, reduces striatal GPA. These results further suggest that neurotoxic doses of amphetamine may induce a reduction in striatal GPA that lasts at least 14 days. If this GPA is responsible for maintaining the synaptic integrity of the nigrostriatal pathway, continued depression of the GPA present in the striatum might lead to "pruning" of DA neuron terminals with an associated reduction in total DA and its metabolites, as was observed in the present study. Continued depression of GPA would also be expected to lead to a reduction in tyrosine hydroxylase activity and striatal DA reuptake sites, as has been reported previously (30,38, 68,77,82).

Involvement of a postsynaptic-derived trophic activity in the neurotoxic effects of amphetamine might also explain why pretreatment with DA antagonists would prevent the toxicity.

Thus, a direct-acting DA antagonist would ostensibly block the GPA depressing effects amphetamine-induced DA release would have on the striatal neurons responsible for producing the factor(s) contributing to GPA.

The fact that MK-801, an indirect-acting antagonist of the NMDA receptor, similarly prevents amphetamine-induced toxicity (75) is more difficult to reconcile with the possible trophic involvement in the amphetamine toxicity hypothesis, however. One possibility is that excessive activation of the cortico-striate pathway, as has been hypothesized to occur with high-dose amphetamine treatment (8), could, in some way, attenuate the ability of striatal neurons to produce the factor(s) responsible for GPA. We have begun to evaluate this possibility.

We infused the excitotoxin kainic acid unilaterally into the rostral (A = 1.0; L = 3.0; D = 5.5) and caudal (A = −0.4; L = 3.5; D = 5.5) regions of the striatum (4 μg/infusion). Extracts from the ipsi- and contralateral striata generated from these animals 10 days following infusion were then incubated with low cell density RMT cultures. As depicted in Fig. 4, the ipsilateral striatal extracts from these animals had significantly reduced GPA relative to the effects of the contralateral striatum, $F(6, 23) = 10.38$, $p < 0.001$. This suggests that the cells that are responsible for GPA are kainic acid sensitive. It is interesting to note that the contralateral striatal extracts from the kainic acid-lesioned animals had significantly more GPA than all other extracts. This might suggest that the contralateral striatum was attempting to compensate for the loss of GPA in the ipsilateral side. We have seen a similar contralateral effect following the unilateral infusion of 6-OHDA (17).

Since it has been shown that glutamate can regulate the growth of CNS neurons in the hippocampus at noncytotoxic levels (53), glutamate may be able to influence trophic activity in other systems as well. It could then be hypothesized that both DA and glutaminergic afferents to the striatum regulate the "trophic environment" within the striatum. If this were the case, MK-801 might attenuate amphetamine-induced toxicity by preventing the GPA depressing effect the glutaminergic cortico-striate pathway has on striatal GPA. Another possibility is that gliosis or the inflammatory cell invasion that accompanies kainic acid lesions could be affecting the trophic environment of the striatum, producing the results observed here. Thus, kainic acid lesions could be increasing a growth inhibitory activity. However, if free radicle production secondary to neurotoxic doses of amphetamine were to induce gliosis or invasion of inflammatory cells, the net reduction in GPA would still be expected to have a deleterious effect on the growth of DA neurons and therefore still support a role for neurotrophic activity in the amphetamine toxicity phenomenon.

It is possible that the reductions in GPA following amphet-

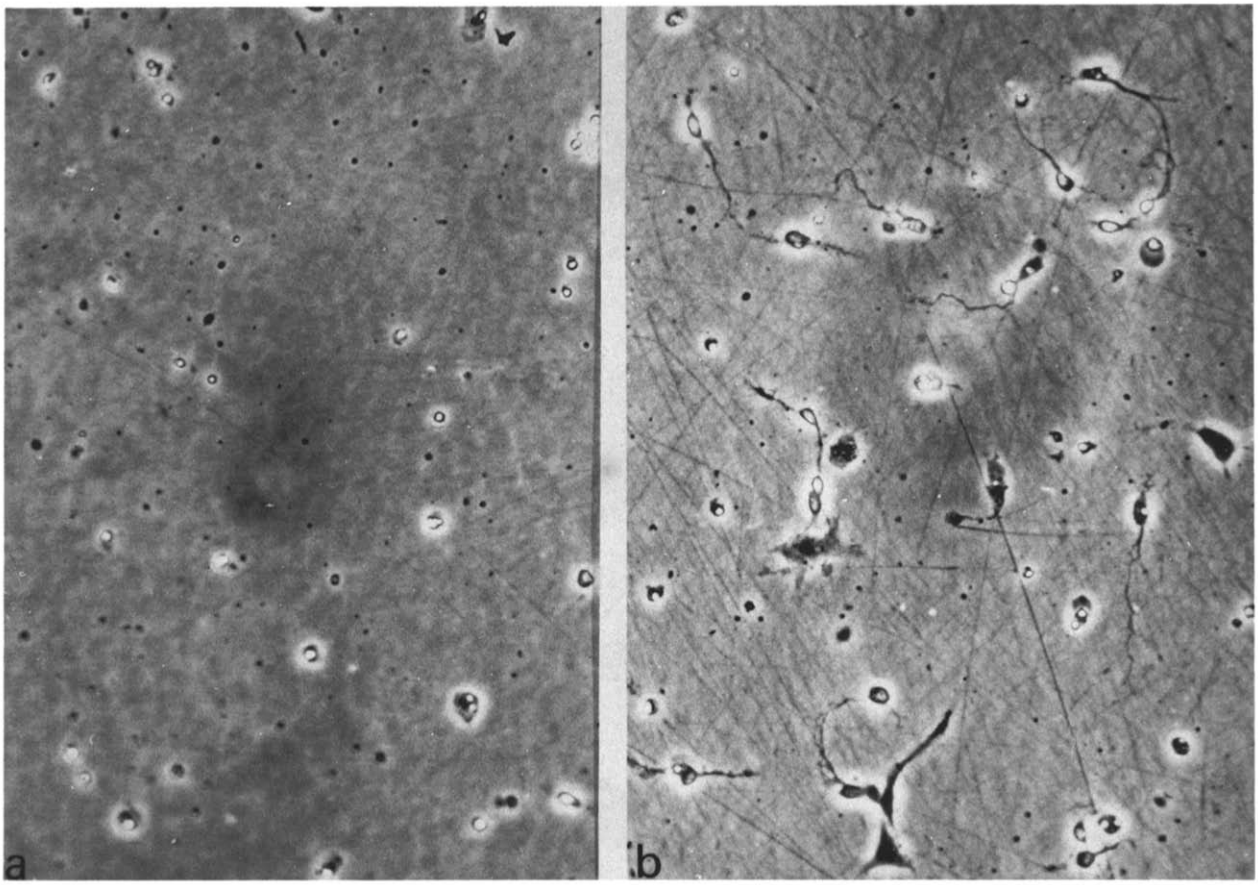

FIG. 4. A phase contrast photomicrograph of mesencephalic cultures incubated 40 h with extracts generated from the ipsilateral (left) or contralateral (right) striatum of a rat that received two ipsilateral striatal infusions of kainic acid. Note the absence of process development in the cultures incubated with extracts from the ipsilateral striatum. Magnification ×200.

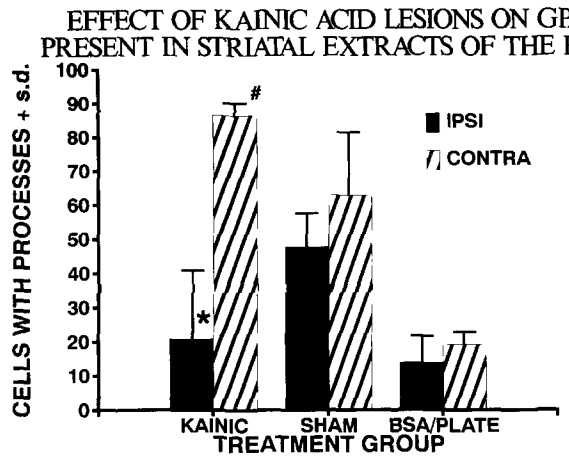

FIG. 5. Number of viable cells with processes in mesencephalic cultures after 40-h incubation with extracts generated from the ipsilateral (ipsi) or contralateral (contra) striata of animals that had received two infusions of kainic acid into the striatum. BSA depicts the cells with processes in cultures incubated with an equivalent amount of bovine serum albumin (1 mg/ml); PLATE depicts the number of cells with processes incubated with defined media only. $*p < 0.05$ vs. kainic contra and both sham effects; $\#p < 0.05$ vs. all other incubation conditions using the Tukey post hoc comparison test.

amine treatment are a unique effect of this drug that is not related to increased DA neurotransmission. However, we have also demonstrated that the increase in GPA induced by 6-OHDA lesions can be reversed with chronic levodopa treatment (17). In this study, sham-lesioned controls and 6-OHDA-lesioned rats were treated with carbidopa alone (50 mg/kg/day), or carbidopa and a low (65 mg/kg/day) or a high (130 mg/kg/day) dose of levodopa delivered in the animals' diet for 21 days. Six days later, the animals were sacrificed and striatal extracts ipsilateral and contralateral to the lesion were generated as described above. Using the low cell density assay system, we observed that 6-OHDA lesions increased GPA relative to the effect of the contralateral striatal extracts, as well as the effect of striatal extracts from the sham controls. Moreover, levodopa decreased the GPA present in the striata of both the sham and lesioned animals in a dose-dependent fashion. Process length was similarly affected. As we have observed with all of the DA manipulations, levodopa treatment did not influence the low-level GPA present in the cerebellar extracts from these animals. These data suggest that the reductions in GPA observed are not unique to amphetamine and therefore probably result from increased DA tone.

OPERATIONAL HYPOTHESIS

In every single culture evaluation performed over the last 4 years, we have always observed that striatal extracts contain more GPA directed at RMT cultures than extracts of the cerebellum. This suggests that the normal, intact striatum of the adult contains a specific factor(s) that stimulates RMT growth. Furthermore, cerebellar extracts contain only low-level GPA, which has consistently been only slightly elevated relative to RMT cultures incubated with an equivalent amount of BSA. The data summarized above further demonstrate that striatal GPA is directed at both DA and GABA neurons, although the later effect appears to be mediated via glia.

Table 1 summarizes the effects alterations in DA tone have on striatal GPA. Haloperidol and 6-OHDA lesions of the

TABLE 1
OPERATIONAL HYPOTHESIS CONFIRMATION

Condition	DA Tone	GPA
Haloperidol	↓	↑
6-OHDA lesion	↓	↑
Parkinsonism	↓	↑
Amphetamine	↑	↓
Levodopa	↑	↓

mesencephalon reduce DA tone and increase GPA. Natural conditions associated with reductions in DA tone, as occurs in PD, similarly elevate striatal GPA. In contrast, chronic treatment with levodopa and amphetamine, which elevate DA tone, reduce GPA. As described above, extremely high doses of amphetamine may even be able to reduce striatal GPA so dramatically that the loss of this activity may actually participate in the neurotoxic effects amphetamines have on DA nerve terminals. That these alterations in GPA are mediated by the action of DA is supported by the fact that the various DA drug treatments or conditions we have studied alter the GPA present in the striatum but not in the cerebellum. Furthermore, the fact that several different conditions associated with changes in DA tone consistently alter striatal GPA in a predictable fashion strongly suggests a causal relationship with DA and not an epiphenomenon associated with drug treatment in general. We have therefore hypothesized that, "the production of a striatal-derived neurotrophic factor(s) is inversely related to striatal DA tone" (13).

IMPLICATIONS OF DRUG-SENSITIVE NEUROTROPHIC FACTORS

We propose an adaptive, homeostatic, regulatory, feedback system involving DA neurotransmission and "target-derived" neurotrophic factor(s) production (Fig. 6). Following the development of a functional nigrostriatal pathway, this homeostatic system is viewed as being responsible for maintaining, at least in part, the architectural and synaptic integrity of this pathway. Reductions in DA tone, as might occur with normal alterations in synaptic traffic within the system, drug

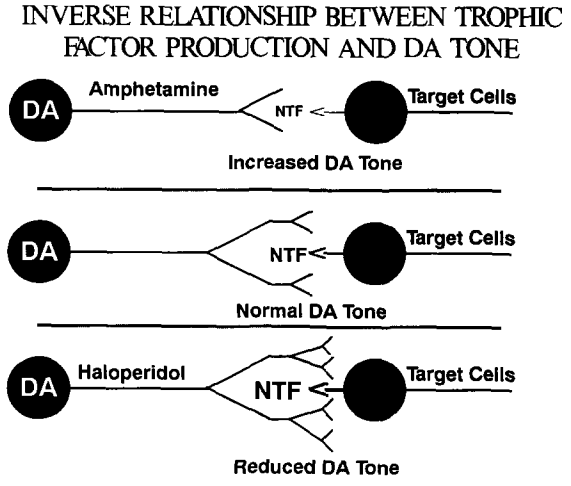

FIG. 6. Depiction of the relationship between DA tone and neurotrophic factor (NTF) production.

treatment, or pathophysiological changes, would result in increased neurotrophic activity directed at DA neurons. Working directly on DA neurons, this increased neurotrophic activity would stimulate the sprouting of DA neurons and reinstate normal DA tone. Conversely, increased DA tone, as might occur with normal alterations in synaptic traffic, drug treatment, or pathophysiological changes, would reduce the normal level of neurotrophic activity, leading to a reduction in the density of DA terminals within the striatum. Since the cells that produce this factor(s) are kainic acid sensitive, it is also possible that neuronal activity outside the nigrostriatal pathway (e.g., cortico-striate pathway) could similarly influence the ability of striatal cells to produce these trophic substances, thereby producing a transynaptic effect on DA neurons.

Neurotrophic and neuroinhibitory factors may play an important role in neuronal plasticity in the adult brain. Neurotransmitters have been shown to influence neuronal growth in several studies (40,45,48,50,53,76). Numerous behavioral paradigms have similarly been shown to be associated with plastic changes in the CNS (1,31,33,62,81). The data presented here strongly suggest that the DA system also appears capable of undergoing plastic changes. If our operational hypothesis is correct and DA drug treatment does induce trophic alterations that influence synaptic architecture, the interpretation of behavioral, biochemical, and receptor data following chronic DA drug treatment should consider the possibility that underlying structural changes accompany the various indices that have been developed to explain these drug effects. Thus, the development of hypersensitivity behaviors following chronic DA antagonist treatment may involve an increased density of DA terminals. The DA neurodegeneration of PD could involve an enhanced sprouting of remaining DA neurons, which may delay the onset of clinical symptoms by inducing the spread of one DA terminal field into that of another to maintain DA tone in totally denervated areas. Since DA drugs have been shown to influence this trophic activity, it may be possible to develop pharmacological agents that are not necessarily formulated to reestablish DA tone, but rather, to establish a desired trophic environment to acheive a clinical effect. Numerous studies are needed to clarify the role that drug-induced alterations in trophic activity have on the pharmacodynamics of dopaminergic agents. However, it is hoped that the operational hypothesis presented here will provide the conceptual framework in which to initiate these studies.

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