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Antidepressant-Like Effect of Brain-derived Neurotrophic Factor (BDNF)

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SIUCIAK, J. A., D. R. LEWIS, S. J. WIEGAND AND R. M. LINDSAY. *Antidepressant-like effect of brain-derived neurotrophic factor (BDNF).* PHARMACOL BIOCHEM BEHAV **56**(1) 131–137, 1997.— Previous studies have shown that infusion of brain-derived neurotrophic factor (BDNF) into the midbrain, near the PAG and dorsal/median raphe nuclei, produced analgesia and increased activity in monoaminergic systems. Alterations in monoaminergic activity have also been implicated in the pathogenesis and treatment of depression. The present studies examined the ability of centrally administered BDNF to produce antidepressant-like activity in two animal models of depression, learned helplessness following exposure to inescapable shock and the forced swim test. In the learned helplessness paradigm, vehicle-infused rats pre-exposed to inescapable shock (*veh/shock*) showed severe impairments in escape behavior during subsequent conditioned avoidance trials, including a 47% decrease in the number of escapes and a 5 fold increase in escape latency, as compared to vehicle-infused rats which received no pre-shock treatment (*veh/no shock*). Midbrain BDNF infusion (12–24 μg/day) reversed these deficits, and in fact, BDNF-infused rats pre-exposed to inescapable shock (*BDNF/shock*) showed escape latencies similar to *veh/no shock* and *BDNF/no shock* rats. In the forced swim test, BDNF infusion decreased the immobility time by 70% as compared to vehicle-infused controls. Non-specific increases in activity could not account for these effects since general locomotor activity of BDNF- and vehicle-infused animals was not different. These findings demonstrate an antidepressant-like property of BDNF in two animal models of depression, which may be mediated by increased activity in monoaminergic systems. **Copyright © 1997 Elsevier Science Inc.**

Learned helplessness Forced-swim test Serotonin Dorsal raphe Periaqueductal gray Depression Rat

ALTERATIONS in monoaminergic activity have been implicated in the pathogenesis and treatment of depression (3,6,42), with various studies examining the contributions of serotonergic (4,25,26,51), dopaminergic (5,8,61–63,66) and noradrenergic systems (2,40,53). For example, numerous biochemical abnormalities in the serotonergic system have been reported (4,25,26). Furthermore, recent studies have demonstrated the clinical efficacy of selective serotonin reuptake inhibitors in treating depression and other psychiatric disorders (51). Brain dopaminergic systems, particularly the mesolimbic projection from the ventral tegmental area of the midbrain to the limbic forebrain, are involved in motivated behavior/reward processes and there is evidence that clinical depression may be successfully treated by drug regimes that enhance the functioning of this system (8,66).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of nerve growth factor related proteins (for review see 19). Several recent studies have demonstrated neuromodulatory effects of BDNF on monoamines, (1,17,21,32,41,48,50), neuropeptides (7,30,49), and behavior (16,21,32,48-50). We recently reported that infusion of BDNF either intracerebroventricularly or directly into the rat midbrain, near the PAG, and dorsal and median raphe nuclei, increased activity within serotonin, dopamine, and/or norepinephrine pathways in various forebrain areas including the cortex, hippocampus, striatum, and nucleus accumbens (50). Thus, central BDNF administration has been shown to modulate the activity of the neurochemical and anatomical systems thought to be involved in depression.

A wide variety of animal models of depression have been proposed and critically assessed (for reviews see 64 and 65). Two of the most commonly used paradigms are learned helplessness and the forced swim test. The learned helplessness model of depression derives from the work of Seligman and colleagues (43,44). In this paradigm, an animal is initially exposed to uncontrollable stress, such as inescapable shock.

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When the animal is later placed in a situation in which shock is controllable, i.e. escapable, the animal fails to respond appropriately. For example, in a conditioned one-way avoidance paradigm, a naive rat rapidly learns that crossing through a doorway terminates a shock. However, a rat pre-exposed to inescapable shock not only fails to acquire the escape response, but often makes no effort to escape the shock at all. This learned helplessness was reversed by several classes of antidepressant treatments including tricyclic antidepressants (imipramine, desipramine, amitryptyline, nortryptyline or doxepin), atypical antidepressants (iprindole or mianserin), monoamine oxidase inhibitors (iproniazid or pargyline), serotonin uptake blockers (fluvoxamine or citalopram) or electroconvulsive shock (18,23,24,45–47), whereas other classes of drugs which lack antidepressant properties, such as haloperidol, amphetamine and diazepam, had no effect on escape behavior (29). Furthermore, animals exposed to inescapable shock present with a series of symptoms similar to those observed in depressed patients, such as weight loss, lethargy, and ulcer formation (64).

In the forced swim test (36–39), rats are forced to swim in a restricted space from which they cannot escape. After an initial period of vigorous activity, animals assume an immobile posture, making only the minimal movements required to keep their heads above water. As with the learned helplessness model, a variety of antidepressant drugs have been found to reduce immobility time in the forced swim test in rats (15,36–39,60).

The aim of the present experiments was to determine whether centrally administered BDNF could produce antidepressant-like effects, possibly related to the increased activity in monoaminergic systems previously observed. To assess this possibility, the effects of midbrain-infused of BDNF was evaluated in two animal models of depression, the forced swim test and learned helplessness following inescapable shock.

MATERIALS AND METHODS

Animal Surgery

Male Sprague–Dawley rats were housed and treated in compliance with AALAC and NIH guidelines. All animal experiments were conducted according to protocols approved by the Institutional Animal Care and Use Committee at Regeneron. Rats were maintained on a 12:12 light/dark cycle and allowed food and water ad lib. Surgery was performed as previously described (48–50). Briefly, animals were anesthetized with chloropent (149 mg/kg chloral hydrate and 30.8 mg/kg sodium pentobarbital, IP) and mounted in a small animal stereotaxic apparatus (Kopf, Tijunga, CA). For midbrain infusions, a 6.8 mm cannulae was inserted 7.6 mm posterior to bregma and l mm lateral to the saggital suture. Each cannula was attached via a 2 cm length of tubing to an osmotic pump which was implanted subcutaneously between the shoulder blades. Animals received infusions of either phosphate buffered saline (veh, 12 μl/day) or recombinant human BDNF (dissolved in PBS, 12 or 24 μg/day, obtained from Amgen-Regeneron Partnership) for 6-7 days prior to final behavioral testing. Separate groups of rats were used for the learned helplessness and forced swim studies. Verification of cannula placement took place at the time of sacrifice. Except for a transient weight loss or lack of weight gain as previously reported (50), animals appeared healthy and no significant morbidity or mortality was observed.

Learned Helplessness

Apparatus. Four automated two-way shuttle boxes (Coulbourn Instruments, Allentown, PA), with inside dimensions of 30 × 20 × 20 cm were used. Shuttle boxes were divided into two equal chambers by a removable stainless steel partition. The floor was constructed of stainless steel rods spaced l cm apart. Walls were constructed of clear Plexiglas to permit observation during experiments. Shuttle boxes were equipped with automated house lights and tone modules and were enclosed in a sound-attenuated environmental chamber with a viewing hole to permit remote observations.

Procedure. Experimental groups were as follows: PBS vehicle-infused rats which received no shock pretreatment (*veh/no shock*), VEH-infused rats pre-exposed to inescapable shock (*veh/shock*), BDNF-infused rats which received no shock (*BDNF/no shock*) and BDNF-infused rats pre-exposed to inescapable shock (*BDNF/shock*). Animals received inescapable shock on day 1, cannulae and pumps were implanted on day 7, and conditioned avoidance testing was performed on day 14 (7 days after the onset of vehicle or BDNF infusion). When surgery to implant the pumps was performed immediately after inescapable shock pretreatment (i.e. surgery on day 2, as was done for the forced swim test), the subsequent impairment in the conditioned avoidance paradigm was not obtained in veh/shock rats. Pump implantation performed 7 days after inescapable shock pretreatment did not interfere with the development of learned helplessness in veh/shock animals and was therefore used for studies addressing the effects of BDNF administration. An additional 7 days was allowed to pass between pump implantation and conditioned avoidance testing thus allowing for full recovery from surgery as well as a relatively long-term infusion of BDNF into the midbrain.

Inescapable Shock Preconditioning. Electric footshock was delivered in shuttle boxes in which the partition used to separate the two compartments was removed. The houselight remained on throughout pretesting. Footshock (0.8 mA) was delivered for l5 s durations, every min ± 15 sec. The training sessions lasted for 60 min, therefore, total shock duration was approximately 15 min. Control rats (*no shock*) were placed in inactive shuttle boxes for l hour with the houselight on but no shock administered. All preconditioning trials were performed in the afternoon on day 1.

Conditioned Avoidance Testing. To evaluate subsequent escape deficits, avoidance training was performed in shuttle boxes which were divided into two chambers of equal size. Animals were individually placed in the shuttle boxes and allowed to habituate to the environment for 5 min. Animals received 30 avoidance trials, using a shock intensity of 0.8 mA, a shock duration of 30 s and an intertrial interval of 30 s. The total test duration was 30 min. A tone (used as a conditioned stimulus) was presented for the first 3 s of each trial. The shock was then initiated and the tone remaining on for the entire duration of the shock (30 s). Both tone and shock terminated together either after an animal crossed to the other side (escaped) or 30 s elapsed (failure), whichever came first. Crossing through into the other compartment of the box during the 3 s "conditioned stimulus only" period was referred to as an avoidance and was considered a successful escape with a latency score of zero seconds. The number of escapes and the latency to escape was measured during the 30 trials and averaged. All conditioned avoidance tests were performed in the afternoon on day 14.

Forced Swim Test

The forced swim test, originally described by Porsolt (36-39), is a standard test used to screen compounds for antidepres-

sant-like activity. Swim sessions are conducted by placing rats in plastic containers containing l6 inches of water (23–25°C), an amount deep enough so that a rat cannot touch the bottom with its hind limbs or tail, nor can it escape. Two swim sessions were conducted, an initial 15 min pretest one day prior to surgery and a second 5 min test on Day 6 after infusion into the midbrain was begun. Each rat's 5 min test session was videotaped for scoring later. The amount of time the animal spends active (swimming, exploring or trying to escape) and the time the rat is immobile (not struggling and making only those movements necessary to keep its head above water) was measured.

Open Field Locomotor Activity

Grid locomotor activity was assessed on day 5 after the onset of PBS or BDNF infusion. Rats were placed on a flat surface divided into 9 equal squares (10 in × 10 in) and the number of grid crossing were quantified for a 10 minute period. Each rats performance was videotaped for scoring at a later time.

Statistical Analysis

For learned helplessness experiments, statistical significance was assessed using a two-way ANOVA comparing infusion treatment (*BDNF or veh*) and shock pretreatment (*shock* or *no shock*) followed by post-hoc analysis with Scheffe's *S* test with $p < 0.05$ considered significant. Possible changes in escape performance during conditioned avoidance testing was assessed using a mixed factorial ANOVA (treatment × shock × 30 trials). A commercial computer software program SuperANOVA (Abacus Concepts Inc., Berkely, CA) was used. For the forced swim test and locomotor tests, a comparison of data from vehicle- and BDNF-infused rats was performed using an unpaired Student's *t*-test with $p < 0.05$ considered to be statistically significant.

RESULTS

Learned Helplessness

Figure 1A summarizes the effect of learned helplessness induction on the number of escapes made during conditioned avoidance testing in vehicle- and BDNF-infused rats. A 2-way ANOVA indicated an overall effect of BDNF administration [*veh* vs. *BDNF*, $F(2, 86) = 16.8$, $p < 0.0001$) and of shock pretreatment (*shock* vs. *no shock*, $F(1, 86) = 19.3$, $p < 0.0001$). The two-way ANOVA also indicated a significant interaction between infusion and shock treatment ($F(2, 86) = 14.4$, $p < 0.0001$), such that *veh/shock* rats showed significantly fewer escapes than all the other treatment groups. Vehicle-infused rats pre-exposed to inescapable shock showed severe impairments in escape behavior during subsequent conditioned avoidance trials as compared to vehicle-infused rats which received no pre-shock treatment (47% decrease in the number of escapes). Post-hoc analysis indicated both concentrations of BDNF reversed this performance deficit (*veh/shock* vs. *BDNF (12 μg/day)/shock*, Scheffe's *S*, $p < 0.0011$ and *veh/shock* vs. *BDNF (24 μg/day)/shock,* Scheffe's *S*, $p < 0.0001$) although the two concentrations of BDNF were not significantly different from each other in their effect on the number of escapes (*BDNF (12 μg/day)/shock* vs. *BDNF (24 5 μg/day)/shock,* Scheffe's *S*, $p = 0.64$, not significant). BDNF administration had no effect on conditioned avoidance performance in rats which were exposed to inactive shuttle boxes (*no shock rats, veh* vs. *BDNF*, 1 way ANOVA, $F(2, 43) = 1.1$, $p = 0.34$, not significant) suggesting no general effect of BDNF administration on locomotor activity or performance.

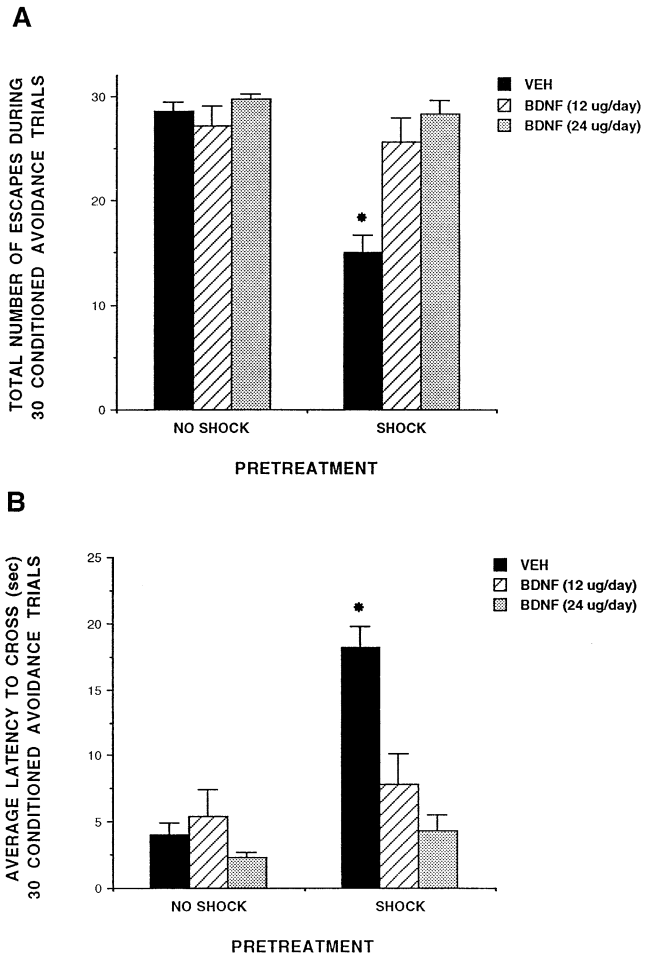

FIG. 1. The effect of learned helplessness induction on (A) the number of escapes and (B) the latency to escape during 30 conditioned avoidance trials. Animals were pre-exposed (Day 1) to either inescapable shock (*shock*) or an inactive shuttlebox apparatus (*no shock*) and then received midbrain infusions of vehicle or BDNF (12–24 5 μg/day) for 7 days. The values shown are mean ± SEM and are summarized from eight independent experiments. The number of animals per group were as follows: *veh/no shock* = 26, *veh/shock* = 24, *BDNF (12 μg/day)/no shock* = 8, *BDNF (12 5 μg/day)/shock* = 8, *BDNF (24 μg/day)/no shock* = 12, *BDNF (24 5 μg/day)/shock* = 14.

The effect of pre-exposure to inescapable shock on the escape latency of both vehicle- and BDNF-infused rats during conditioned avoidance testing is shown in Fig. 1B. A 2-way ANOVA indicated an overall significant effect of BDNF administration (*veh* vs. *BDNF*, $F(2, 86) = 15.3$, $p < 0.0001$) and of shock pretreatment (*shock* vs. *no shock*, $F(1, 86) = 20.6$, $p < 0.0001$). A significant interaction between infusion and shock treatment was found, such that *veh/shock* rats showed significantly longer latencies to escape than all the other treatment groups ($F(2, 86) = 11.8$, $p < 0.0001$). Vehicle-infused rats pre-exposed to inescapable shock showed an increase in the latency to cross as compared to vehicle-infused control rats placed in an inoperable shock box for an equivalent amount of time (356% increase). Post-hoc analysis indicated that both

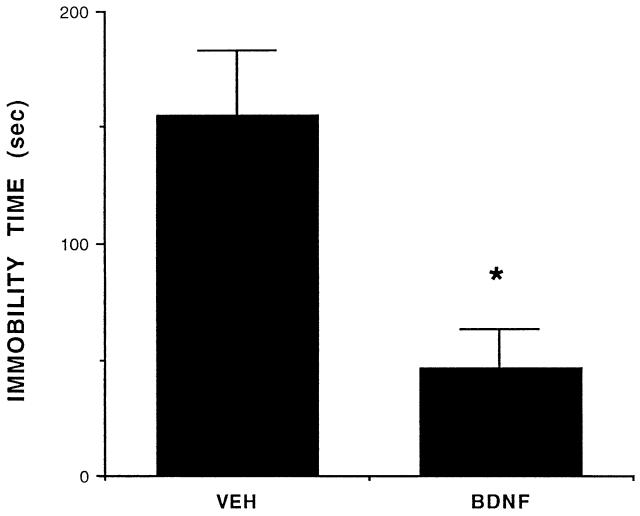

FIG. 2. The effect of BDNF-infusion on duration of immobility in the forced swim test. Animals were pre-exposed to a single 20 min forced swim test (Day 1), then received midbrain infusions of PBS vehicle (12 μl/day) or BDNF (24 μg/day). The values shown are mean ± SEM for 4-5 rats/group. Students *t*-test, $t = 3.52$, $p < 0.01$.

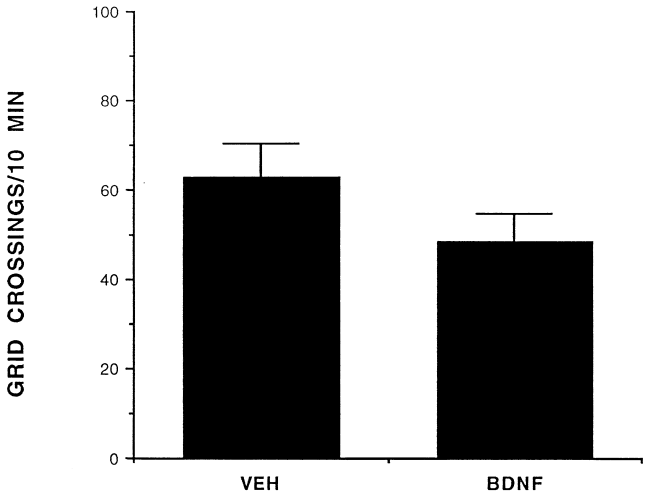

FIG. 3. The effect of midbrain BDNF-infusion on general locomotor activity. Animals received midbrain infusions of PBS vehicle (12 μl/day) or BDNF (24 μg/day) and were tested by grid crossing in open field. Activity was assessed for l0 min. Students *t*-test: $t = 1.6$, $df = 11$, $p < 0.13$, not significant.

concentrations of BDNF reversed this performance deficit (*veh/shock* vs. *BDNF (12 μg/day)/shock,* Scheffe's *S*, $p < 0.0033$; *veh/shock* vs. *BDNF (24 μg/day)/shock,* Scheffe's *S*, $p < 0.0001$), although the two concentrations of BDNF did not differ in their effect on escape latency (*BDNF (12 μg/day)/shock* vs. *BDNF (24 μg/day)/shock, Scheffe's S*, $p = 0.54$, not significant). BDNF administration had no effect on latency to escape in rats which were pre-exposed to inactive shuttle boxes (*no shock rats, veh* vs. *BDNF*, 1 way ANOVA, $F(2, 43) = 1.2$, $p = 0.30$, not significant) suggesting no general effect of BDNF administration on locomotor activity or performance. There was a significant overall effect of trial performance ($F(29,2494) = 4.83$, $p < 0.0001$) such that animals escaped significantly more quickly as the trials progressed. Although animals in the *veh/no shock, BDNF/no shock* and *BDNF/shock* groups escaped significantly faster than *veh/shock* rats, the pattern of the latencies for all groups did not differ significantly over the 30 conditioned avoidance trials.

Forced Swim Test

Figure 2 demonstrates the effect of midbrain BDNF administration on immobility time in the forced swim test. The vehicle-infused rats were immobile for 155.5 ± 27.8 s of the 300 s comprising the 5 min post-drug test. In contrast, midbrain BDNF-infused rats remained immobile for only 46.6 ± 16.8 s, a 70% decrease ($t = 3.5$, $p < 0.01$).

Open Field Locomotor Activity

In order to demonstrate that general changes in activity could not account for the reduction of immobility time in the forced swim test, rats receiving midbrain infusions of BDNF were also assessed for changes in locomotor activity. Figure 3 demonstrates that BDNF infusion produced no changes in locomotor activity as measured by grid crossing in an open field test No significant difference between the two infusion groups (*veh,* 62.9 ± 6.2 vs. *BDNF,* 48.6 ±6.1 crossings/10 min, $t = 1.6$, $p = 0.13$, not significant).

DISCUSSION

The present studies demonstrate that administration of BDNF produces an antidepressant-like effect in two animals models of depression. In the learned helplessness paradigm, vehicle-infused rats subjected to inescapable electric footshocks showed escape deficits, i.e., decreased number of escapes and increased latency to escape, when subsequently tested in a conditioned avoidance paradigm. These escape deficits were reversed by chronic administration of BDNF. In the forced swim test, midbrain infusion of BDNF decreased the immobility time as compared to vehicle-infused control animals.

We have also demonstrated that midbrain infusions of BDNF produced no significant changes in locomotor activity, suggesting that the increased escape performance in the learned helplessness paradigm and the decrease in immobility in the forced swim test are not due to nonspecific motor activation. In addition, in rats which received no pre-shock treatment in our learned helplessness studies, BDNF infusion produced no difference in performance in conditioned avoidance behavior as compared to vehicle-infused rats, further suggesting no effect of BDNF on locomotor activity.

One caveat to consider is that we have reported alterations in nociceptive thresholds following midbrain BDNF administration using the tail-flick, hot-plate and formalin tests (48,49). However, several points argue against the interference of analgesia in the present studies. First, reduced pain sensitivity would be predicted to decrease rather than increase the number of escapes and latency to cross from a noxious stimuli such as shock in the learned helplessness test. However, rats receiving infusions of BDNF show an increased number of crosses to avoid the shock and furthermore, spend less time before responding to the shock. Secondly, animals were pre-exposed to inescapable shock prior to drug administration, therefore, the induction of learned helplessness takes place under non-analgesic control conditions. Finally, the use of more than one model, i.e. forced swim test, circumvents this problem entirely. The fact that similar antidepressant-like effects were obtained in both animal models argues against the interference of analgesia in the results.

A wide range of behavioral models have been proposed and utilized for the study of depression. Some of these animal models appear to have similarities to endogenous depression with respect to biochemical changes, including alterations in monoamine and endocrine function. For example, several studies have reported that the induction of learned helplessness in rats results in decreased levels and release of monoamines in the CNS (12,13,27,33–35,45,46). Exposure to inescapable shock decreased the levels and the release of norepinephrine as measured by in vivo microdialysis in the hippocampus (27,33). Decreased levels of serotonin have also been reported following inescapable shock (12,34). Petty and Sherman (34) demonstrated decreased 5HT release in cortical perfusates in rats which developed a behavioral deficit following exposure to inescapable shock. This behavioral deficit was reversed by injection of 5HT in frontal neocorptex, but not after injection of norepinephrine, GABA, acetylcholine, glutamate, and aspartate (45).

The midbrain infusion site, near the PAG and dorsal and median raphe nuclei, permits BDNF access to the largest number of serotonergic cell bodies in the brain. The terminal arbors of serotonin containing neurons in the CNS are extensive, with fibers found virtually everywhere in the brain, including the hippocampus, cerebral cortes, striatum, locus coeruleus and hypothalamus (14, 52). Furthermore, the midbrain PAG/DR also receives extensive input from structures such as the hippocampus and locus coeruleus, areas known to be involved in aspects of learned helplessness (20).

We have recently performed a comprehensive regional examination of the neuromodulatory effects of exogenous BDNF on central monoaminergic systems following either midbrain or ICV administration of this trophic factor (48,50). Increases in 5HT were found only at the site of infusion (PAG/DR) and in the cortex. However, significant increases in 5HIAA and/or turnover, as measured by the 5HIAA/5HT ratio, were seen in these two areas as well as in the hippocampus, cortex, striatum, n. accumbens, substantia nigra and hypothalamus following either route of administration. In contrast, changes in dopaminergic activity (DA, DOPAC, and HVA levels and/or DOPAC/DA and HVA/DA ratio) were more restricted, being evident primarily within the striatum and cortex. Finally, BDNF administration produced an increase in norepinephrine in the locus coeruleus, as well as in the cortex and n. accumbens. Therefore, the ability of BDNF to reverse behavioral deficits in these animal models of depression may be attributable to increased monoaminergic activity within the central nervous system which compensates for the decreased levels resulting from the induction of learned helplessness.

In addition to monoamines, several neuropeptides, including opioid peptides (9–11,22,55,57) and neuropeptide Y (54,56,58,59), are thought to play a role in clinical depression or learned helplessness behavior in rats. Several recent papers have examined the effects of central administration of BDNF on neuropeptides (7,30,49). We have found region specific increases in beta-endorphin and neuropeptide Y levels following midbrain infusion of BDNF (49). At the site of infusion, within the PAG and dorsal raphe, BDNF increased the level of beta-endorphin by 63%, but had no effect on met-enkephalin or NPY levels. In contrast, midbrain administration of BDNF produced a 93% increase in NPY levels within the striatum, without concomitant changes in opioid peptide levels. Therefore, the modulation of neuropeptide systems by BD{NF, whether a direct or indirect effect, may contribute to the antidepressant-like effects of this protein.

Although these initial studies have demonstrated an antidepressant-like effect of BDNF after chronic administration in the midbrain, further studies are needed to determine the temporal characteristics of this response, i.e. whether acute administration of BDNF will produce a similar effect, the time to onset of this effect after chronic BDNF infusion has begun and it's loss after termination of the infusion. The anatomical sites capable of mediating this effect remain to be determined. Furthermore, the receptor hypothesis of mood disorders suggests beta-adrenergic and serotonergic receptors may mediate the clinical effects of antidepressant drugs (for review see 3). We have not yet addressed the possibility of BDNF-induced changes in monoamine and/or peptide reUceptors, however, in light of the neurochemical and behavioral effects of BDNF, these studies would be of interest.

In conclusion, midbrain infusion of the neurotrophic factor BDNF produces an antidepressant-like effect in two animal models of depression. Furthermore, recent studies by Duman and colleagues (28,31) have reported that antidepressant administration and electroconvulsive shock regulate the expression of BDNF and TrkB mRNA in rat frontal cortex and hippocampus. Taken together, these studies suggest a possible role for neurotrophic factors in the etiology and/or treatment of depression.

NOMENCLATURE

BDNF, brain-derived neurotrophic factor; PAG/DR, periaqueductal gray/dorsal raphe; VEH, vehicle-infused; 5HT, serotonin; 5HIAA, 5-hydroxyindole acetic acid.

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