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Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant

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Abstract

Antidepressants and physical exercise have been shown to increase the transcription of hippocampal brain-derived neurotrophic factor (BDNF). Much evidence regarding the initial actions of antidepressant medications as well as exercise leads to the hypothesis that noradrenergic (NE) and/or serotonergic (5-HT) activation is a key element in the BDNF transcriptional elevation common to both interventions. Currently, we used short-term β-adrenergic, 5-HT_{1A}, or 5-$HT_{2A/C}$ receptor blockade to characterize the influence of NE and 5-HT systems on BDNF transcription during physical exercise and antidepressant treatment. In situ hybridization revealed that β-adrenergic blockade significantly blunted the BDNF mRNA elevations due to exercise, and also inhibited the modest elevations in the CA3 and dentate gyrus following short-term treatment with tranylcypromine. In contrast, 5-$HT_{2A/C}$ blockade only minimally altered exercise-induced BDNF mRNA levels, but inhibited up-regulation of BDNF transcription via tranylcypromine. Finally, 5-HT_{1A} blockade did not inhibit exercise-induced BDNF mRNA elevations, but significantly enhanced levels above those achieved with exercise alone in the CA4. These results suggest that NE activation via β-adrenergic receptors may be essential for both exercise and antidepressant-induced BDNF regulation. 5-HT_{1A} and 5-$HT_{2A/C}$ activation, on the other hand, appear to be most important for antidepressant-induced BDNF regulation, but may also participate significantly in exercise-induced regulation in the CA4.

Keywords: Neurotrophins; 5-HT_{1A}; 5-$HT_{2A/2C}$; β-Adrenoceptors; Exercise

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the structurally and functionally homologous neurotrophin family. It is the most widely distributed trophic factor in the brain, and participates in neuronal growth, maintenance, and use-dependent plasticity mechanisms such as long-term potentiation and learning. There are several lines of evidence supporting a role for BDNF in the treatment of depression. Infusion of BDNF into the midbrain of depression-model rats has been followed by recovery of behavioral deficits (Shirayama et al., 2002; Siuciak et al., 1997). In vivo BDNF administration has been reported to produce altered patterns of locomotor behavior (Martin-Iverson et al., 1994), eating and body weight (Lapchak and Hefti, 1992; Pelleymounter et al., 1995), and analgesia (Cirulli et al., 2000; Siuciak et al., 1995). It has been demonstrated that chronic antidepressant administration leads to increased levels of BDNF mRNA and that of its receptor in the rat hippocampus (Nibuya et al., 1995). Furthermore, recent evidence exists that chronic treatment with antidepressants leads to increased neurogenesis in the adult rat hippocampus (Duman et al., 2001).

Evidence from both human and animal studies has implicated monoaminergic hypofunction as a treatable component of depression. Antidepressant medications are therefore designed to enhance serotonergic (5-HT) or noradrenergic (NE) neurotransmission (for review, see Duman et al., 1997). The current treatment model suggests that the long-term, therapeutic action of antidepressants is mediated by intracellular targets following NE or 5-HT stimulation. A major signal transduction pathway mediating 5-HT and NE action utilizes cyclic adenosine 3′,5′-monophosphate (cAMP). Recent evidence indicates that BDNF up-regulation via antidepressant administration occurs through the cAMP signal transduction pathway and the transcription factor, cAMP response element binding protein (CREB) (Jensen

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et al., 2000; Nestler et al., 1989; Nibuya et al., 1996). Taken together, these findings provide strong evidence that increased expression of BDNF is a downstream effect of increased 5-HT/NE neurotransmission, and that this may be responsible for the therapeutic effect of antidepressants.

Physical exercise is also known to increase hippocampal BDNF expression, and is able to do so very rapidly. Animal studies have provided evidence that voluntary wheel running increases BDNF mRNA levels in the rat hippocampus in as little as 6 h (Oliff et al., 1998). We have demonstrated that physical activity greatly potentiates the up-regulation of BDNF occurring with antidepressant treatments alone (Russo-Neustadt et al., 1999). Also, specific transcript forms of BDNF mRNA (exons I, II) have been shown to increase as much as 250% after both exercise and antidepressant administration, suggesting that both treatments synergistically elevate BDNF transcription and also accelerate the response (Russo-Neustadt et al., 2000). Chronically exercised animals have shown increased levels of NE and 5-HT in most brain areas, as compared to sedentary controls (Brown et al., 1979; Dey et al., 1992; Samorajski et al., 1987). Taken together, this evidence leads to the hypothesis that the pathway of increased BDNF mRNA expression occurring with exercise may also be initiated by monoaminergic activation (the same mechanism proposed for antidepressant action).

The primary aim of these studies is to test the hypothesis that exercise increases hippocampal BDNF mRNA expression through enhanced 5-HT and/or NE neurotransmission. This hypothesis was tested via short-term blockade of NE or 5-HT receptors during the animals' active period. We have conducted short-term (2–3 days) experiments because receptor antagonist administration for longer than 4 days is known to induce receptor supersensitivity (Goodman et al., 1990). In parallel with these experiments, receptor blockade was also employed with short-term antidepressant treatment. The antidepressant used for this study (tranylcypromine, Sigma, St. Louis, MO) led to increased BDNF mRNA levels in some hippocampal areas in as little as 2 days (Russo-Neustadt et al., 2000). Through the current experiment, we wished to determine whether inhibition of NE or 5-HT activation via receptor blockade would have an inhibitory effect on the BDNF mRNA increase occurring with tranylcypromine treatment, as is suggested by the current model of antidepressant mechanisms.

2. Materials and methods

2.1. Animal subjects

Male Sprague–Dawley rats approximately 3 months of age were obtained from Charles River. Rats were housed singly with wood chips for bedding and with food and water available ad libitum. Animal cages (polyethylene, 48 × 27 × 20 cm) were kept in a temperature- and humidity-controlled room and a 12:12 h (0600–1800 h) light/dark cycle. All rats were allowed to acclimate to the vivarium for a week prior to the start of the experiments. All animal handling procedures described below were conducted in strict accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals (1996) and our University's Institutional Animal Care and Use Committee. Great efforts were made to minimize the number of animals and any potential pain or distress.

As outlined in the Introduction, two separate groups of experiments were conducted in which animals received specific receptor antagonists prior to voluntary physical activity, or in conjunction with short-term antidepressant treatment (described below).

2.2. Exercise (voluntary running)

Exercising animals engaged in physical activity via free access to running wheels throughout the experiment. After a week of initial acclimation to their environment, rats were placed in polyethylene cages equipped with running wheels (34.5 cm diameter; Nalgene, OR) at the start of the experiment. The number of exercising animals used per group is presented in Table 1. Control animals remained in standard (no wheel) cages throughout the experiment. Distance run per 24 h was recorded by computer using Ratrun software (C. Hage Associates, CA). Animals were allowed to run for a total of 3 days while receiving receptor antagonists prior to each evening (see below). Rats were sacrificed at 0600 h following their last running period, a time previously reported for peak diurnal baseline expression of BDNF (Berchtold et al., 1999). All animals were rapidly decapitated and their brains quickly removed and quick-frozen in cold 2-methylbutane. Whole brains were stored at −70 °C prior to use.

2.3. Drug treatments

2.3.1. Exercise experiments

For three consecutive evenings, animals received intraperitoneal injections of the β-adrenergic antagonist, 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol (DL-propranolol,

Table 1
Wheel-running activity of animals after treatment with saline or specific antagonists

Treatment	*n*	Average distance (km)
Activity only	7	1.978 ± 0.477
Propranolol + activity	6	1.779 ± 0.392
Ketanserin + activity	7	1.499 ± 0.241
WAY100635 + activity	6	1.841 ± 0.205

Average total distance run per 24 h (expressed in kilometers ± S.E.M.) is shown for each of the active animal groups. Running distance was monitored by computer as described in Section 2. Physical activity was not significantly altered by drug treatments.

Sigma) at 2 mg/kg. For 5-HT receptor blockade, the 5-$HT_{2A/C}$ and 5-HT_{1A} specific antagonists 3-(2-[4-fluorobenzoyl-1-piperidinyl]ethyl)-2,4-(1*H*,3*H*)-quinazolinedione (ketanserin) and *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY100635, Sigma) were used at 5 and 0.5 mg/kg, respectively. Drugs were dissolved in normal (0.9%) saline and administered at 1700 h (5 p.m.). Control animals received equivalent volumes of saline (vehicle) injections.

2.3.2. Antidepressant experiment

For two consecutive mornings (at 0900 h), animals received intraperitoneal injections of the antidepressant tranylcypromine (*trans*-2-phenylcyclopropylamine, 7.5 mg/kg, Sigma). These animals subsequently received one of the receptor antagonists (described above) or saline vehicle each evening at 1700 h (5 p.m.). During this experiment, animals were housed singly in polyethylene cages (described above) containing no running wheels.

2.4. cRNA probes, in situ hybridization, and data analyses

Construction of cRNA probes, in situ hybridization, and data analyses was performed as previously described (Russo-Neustadt et al., 2001).

3. Results

3.1. Exercise experiments

Animals running voluntarily for three nights with no antagonist treatment (physical activity only) demonstrated a significant up-regulation of BDNF mRNA levels in all hippocampal regions examined, compared to control (sedentary, saline) animals. The enhancement of BDNF mRNA occurring with physical activity was prevented in rats receiving propranolol prior to their active periods (Fig. 1A) [CA1, $F(3,24)=6.33$, $P=.003$; CA2, $F(3,24)=3.09$, $P=.046$; CA3, $F(3,24)=5.11$, $P=.007$; CA4, $F(3,24)=5.18$, $P=.007$; DG, $F(3,24)=3.91$, $P=.021$]. This attenuation was significant as compared to the exercise/saline group in the CA1 CA3 and CA4 hippocampal subregions. Inactive rats receiving propranolol did not exhibit significant attenuation of BDNF mRNA expression below baseline (control) levels.

Treatment with ketanserin eliminated the up-regulation of BDNF mRNA message occurring with exercise in CA4 only (Fig. 1B) [CA1, $F(3,23)=4.67$, $P=.011$; CA2, $F(3,23)=4.92$, $P=.009$; CA3, $F(3,23)=2.43$, $P=.091$; CA4, $F(3,23)=8.58$,

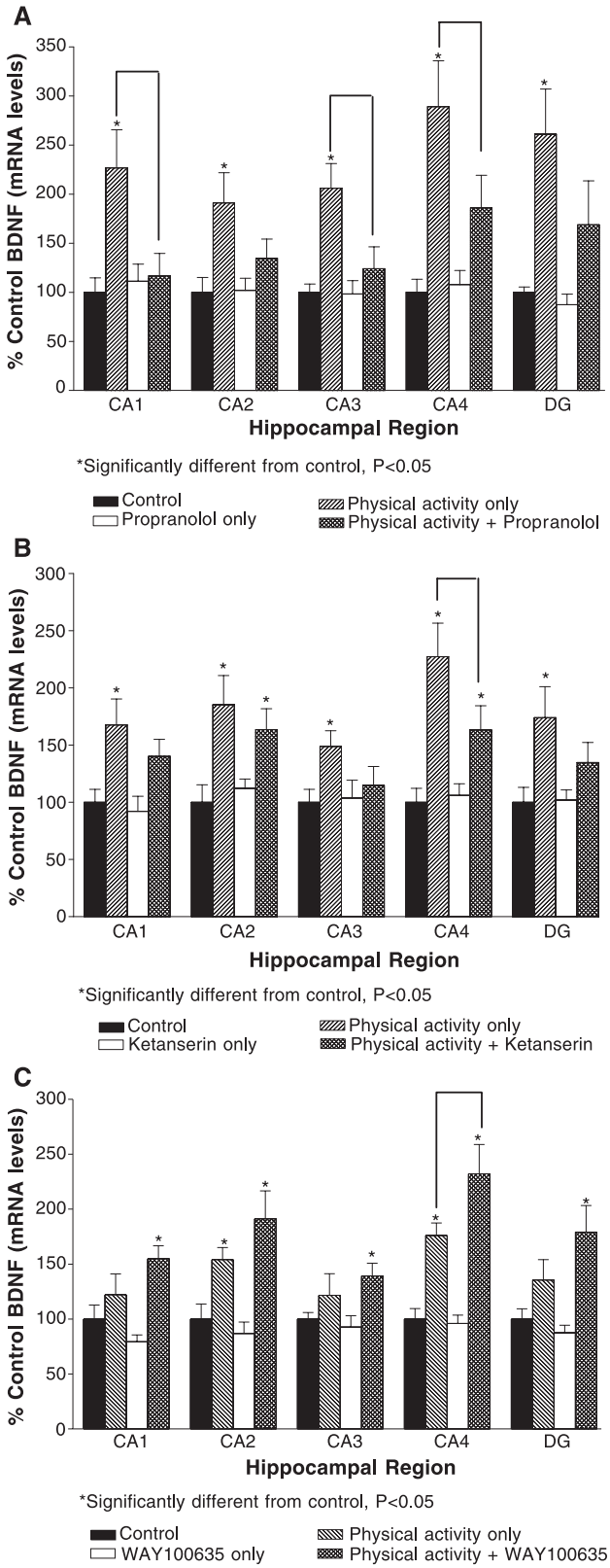

Fig. 1. Effects of receptor antagonists on BDNF expression occurring with physical activity. Rats were treated with either 2 mg/kg propranolol ip (A), 5 mg/kg ketanserin ip (B), or 0.5 mg/kg WAY100635 sc (C), immediately prior to their active period (5 p.m.). Results are expressed as percent of control and are the mean ± S.E.M. ($n=7$). Bar graphs represent analysis of variance (ANOVA) comparing BDNF levels in CA1, CA2, CA3, CA4 (hilus) and dentate gyrus regions of control, exercise alone, receptor antagonist treatment alone, and receptor antagonist + exercise groups. * $P<.05$ from control (sedentary, saline-treated) animals (one-way ANOVA with Fisher's PLSD). Bridges between bars indicate statistical significance ($P<.05$) from the exercise-alone group.

P=.0005; DG, $F(3,23)=3.57$, P=.029]. Otherwise, both active groups (with and without ketanserin) showed equal BDNF mRNA levels in each of the remaining hippocampal subregions.

Administration of the 5-HT_{1A} receptor antagonist WAY100635 did not attenuate exercise-induced BDNF mRNA levels resulting from short-term exercise in any hippocampal region. In fact, BDNF mRNA up-regulation was enhanced significantly in the CA4 (Fig. 1C) [CA1, $F(3,24)=5.95$, P=.004; CA2, $F(3,24)=8.82$, P=.0004; CA3, $F(3,24)=2.73$, P=.066; CA4, $F(3,24)=17.20$, $P<.0001$; DG, $F(3,24)=6.40$, P=.002]. Administration of WAY100635 without exercise did not affect baseline BDNF mRNA expression. Activity levels (total distance run per night) were not altered by treatment with any of the antagonists, as shown in Table 1.

3.2. Antidepressant experiment

Tranylcypromine significantly up-regulated BDNF mRNA levels in the CA3 and the DG during the brief 2-day treatment period. This up-regulation of BDNF mRNA by tranylcypromine treatment was attenuated when the antidepressant was administered in conjunction with propranolol (Fig. 2A) [CA1, $F(3,24)=1.68$, P=.197; CA2, $F(3,24)=1.49$, P=.244; CA3, $F(3,24)=4.77$, P=.009; CA4, $F(3,24)=2.05$, P=.133; DG, $F(3,24)=12.12$, $P<.0001$]. As in the exercise experiment, there was no attenuation of BDNF mRNA below baseline levels with propranolol treatment.

Animals receiving ketanserin in conjunction with tranylcypromine treatment also exhibited a significant attenuation of BDNF mRNA, compared to animals receiving tranylcypromine alone. This attenuation was significant in all hippocampal subregions (Fig. 2B) [CA1, $F(3,24)=9.186$, P=.0003; CA2, $F(3,24)=14.662$, $P<.0001$; CA3, $F(3,24)=11.903$, $P<.0001$; CA4, $F(3,24)=16.65$, $P<.0001$; DG, $F(3,24)=18.18$, $P<.0001$]. In addition, animals receiving the ketanserin/tranylcypromine treatment combination exhibited attenuation of BDNF mRNA below baseline in all five hippocampal regions.

Fig. 2C reveals that the modest up-regulation of BDNF mRNA occurring with acute (2 days) antidepressant treatment in the CA3 and DG regions was eliminated with the addition of WAY100635. Baseline BDNF mRNA levels were not affected by this antagonist (Fig. 2C) [CA1, $F(3,24)=3.637$, P=.0271; CA2, $F(3,23)=0.934$, P=.440; CA3, $F(3,24)=4.39$, P=.013; CA4, $F(3,23)=1.49$, P=.241; DG, $F(3,24)=4.69$, P=.010].

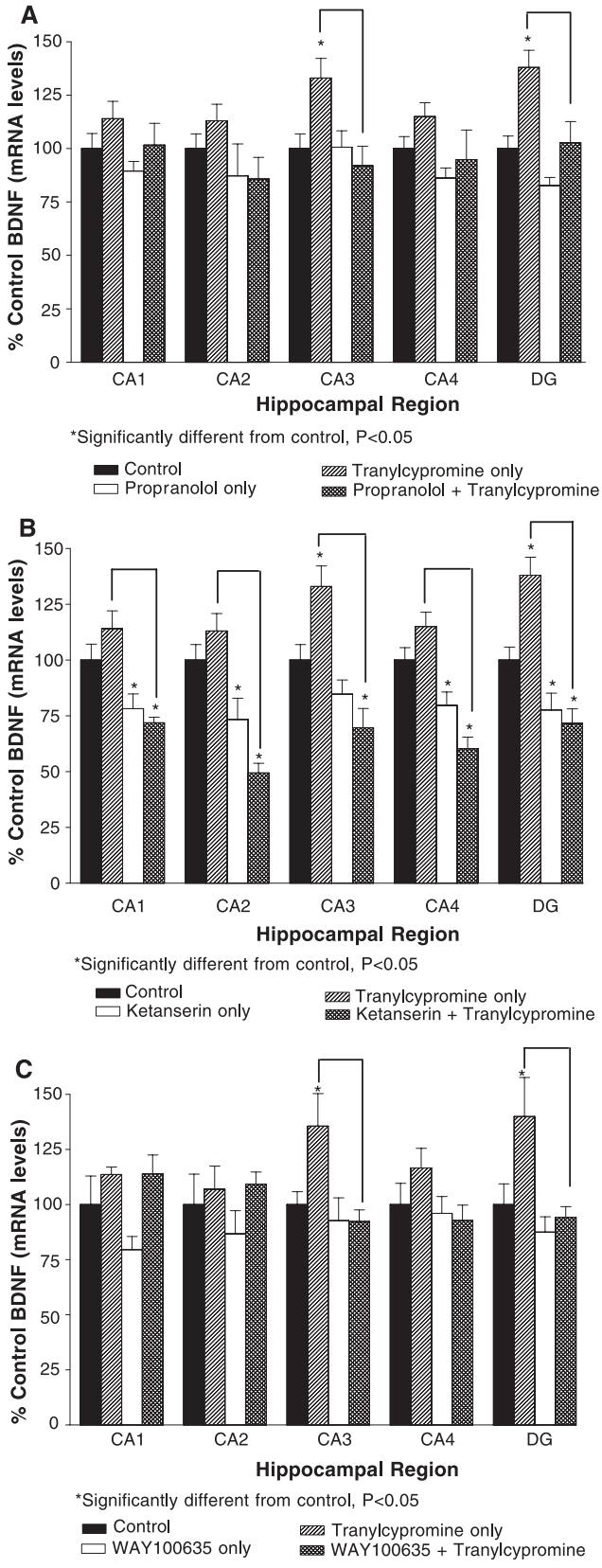

Fig. 2. Effects of receptor antagonists on BDNF expression occurring with short-term tranylcypromine treatment. Rats were treated with 7.5 mg/kg tranylcypromine at 9 a.m., and/or 2 mg/kg propranolol ip (A), 5 mg/kg ketanserin ip (B), or 0.5 mg/kg WAY100635 sc (C), immediately prior to their active period (5 p.m.). Results are expressed as percent of control and are the mean ± S.E.M. ($n=7$). Bar graphs represent ANOVA comparing BDNF levels in CA1, CA2, CA3, CA4 (hilus), and dentate gyrus regions of control, antidepressant treatment alone, receptor antagonist treatment alone, and antidepressant + receptor antagonist groups. * $P<.05$ from control (sedentary, saline treated) animals (one-way ANOVA with Fisher's PLSD). Bridges between bars indicate statistical significance ($P<.05$) from the antidepressant treatment-alone group.

4. Discussion

As noted in the Introduction, much evidence exists for involvement of 5-HT and NE systems (and, more specifically, β-adrenergic, 5-HT_{1A}, and 5-HT_2 receptors) in antidepressant treatment. We have sought to test the hypothesis that activation of one or more of these receptor types is necessary for the observed regulation of hippocampal BDNF expression following short-term exercise or antidepressant treatment.

4.1. Voluntary exercise

As previously reported (Russo-Neustadt et al., 2000), a significant effect of increased BDNF mRNA levels relative to controls was observed in all hippocampal regions examined following short-term voluntary exercise. Propranolol administered alone resulted in no significant change in BDNF mRNA expression. Nevertheless, in the presence of this β-adrenergic receptor antagonist, physical exercise did not lead to increased hippocampal BDNF mRNA, resulting in baseline levels. This result supports the proposal that the BDNF-enhancing effect of exercise is dependent upon NE neurotransmission, and suggests that the previously observed enhanced central NE release with physical exercise (Dishman et al., 2000; Dunn et al., 1996) may be associated with downstream effects on BDNF expression via activation of β-adrenergic receptors. The possibility that other effects of propranolol besides specific β-receptor blockade may have participated in the observed results cannot be ruled out, however. For example, β-adrenergic stimulation of inhibitory interneurons (Bergles et al., 1996) has been shown to enhance GABA receptor-mediated inhibition in dentate granule cells (Bijak and Misgeld, 1995). It is therefore possible that secondarily enhanced GABAergic transmission may have been responsible for the observed diminishment of the exercise effect, rather than reduced NE transmission exclusively.

The exercise effect of enhanced hippocampal BDNF mRNA expression was attenuated in only one hippocampal subregion (the CA4) as a result of pretreatment with ketanserin. This suggests that a smaller portion of the exercise effect may be mediated via activation of 5-HT_2 receptors. Alternatively, the hippocampal CA4 subregion (hilus) may be particularly sensitive to 5-HT activation via these receptor subtypes. It is known that hippocampal granule neurons have a strong GABAergic component, and alterations in GABA transmission may offset the activating exercise effects. Along these lines, evidence exists that physical exercise not only has potent antidepressant effects (Chaouloff, 1989, 1994, 1997; Chaouloff et al., 1986; Dey, 1994; Dey et al., 1992; Meeusen and De Meirleir, 1995), but can also offset the decreased activation of GABAergic interneurons that are thought to increase spontaneous GABA release and lead to increased inhibitory control of hilar granule cells (Dishman, 1997; Piguet and Galvan, 1994).

There is much evidence indicating that 5-HT_{1A} receptors are down-regulated in depression (Stahl, 1994) and chronic stress (Lopez et al., 1998) and that expression of this receptor can be up-regulated by antidepressant treatment (Lopez et al., 1998). In spite of the presence of 5-HT_{1A} receptor blockade (WAY100635; Forster et al., 1995), physical exercise still led to a dramatic increase in BDNF mRNA levels in all hippocampal subfields examined. In one hippocampal region (CA4), the exercise/WAY100635 combination led to a significantly higher level of BDNF mRNA than did exercise alone. This result suggests that 5-HT_{1A} receptor blockade potentiated the BDNF-enhancing effects of exercise in the CA4. It is possible that 5-HT_{1A} activation of autoreceptors may normally exert an inhibitory tone on 5-HT neurotransmission in this region. The inhibitory effect of 5-HT_2 blockade (above) in the CA4 also suggests that 5-HT activation is particularly influential for exercise-induced effects in this hippocampal region. The widespread prevalence of the 5-HT_{1A} receptor subtype in the hippocampus (Lopez et al., 1998), the ability of WAY100635 to increase 5-HT neuronal activity in the raphe (Fornal et al., 1996; Gartside et al., 1997), and the putative antidepressant-like effect of physical exercise (Chaouloff, 1989, 1994, 1997; Chaouloff et al., 1986; Dey, 1994; Dey et al., 1992) all provide possible mechanisms behind the BDNF mRNA potentiation resulting from physical exercise-plus-WAY100635 treatment. Consistently, WAY100635 has also been shown not only to potentiate the effects of antidepressants, such as the SSRI, citalopram, in some brain regions (Invernizzi et al., 1997; Romero et al., 1996), but also to reverse the inhibition of 5-HT cell firing caused by a variety of reuptake inhibitors (Gartside et al., 1997).

Our experimental paradigm involved short-term blockade of specific receptors during a portion of the animals' active period. Antagonists were administered just prior to the active (lights out) period in order to maximize this effect. The chosen doses of antagonists were intended to produce full, temporary receptor blockade. However, it is recognized that these treatments could not have produced full and continuous receptor blockade during the entire active period. The absence of effects of ketanserin or WAY100635 treatment in several regions, and the absence of any effects on baseline BDNF mRNA expression may possibly be explained by this limitation. Nevertheless, it is possible that 5-HT and NE activation may be specifically responsible for enhanced transcription due to exercise, and not as vital for baseline (tonic) expression. The latter may be under the control of other neurotransmitter or intracellular signaling systems. In addition, it is possible that some compensation in the form of receptor recruitment or synthesis may have occurred during the 3-day experimental treatment period. As noted above, no antagonist significantly changed activity levels (Table 1), therefore, our experimental results cannot be attributed to altered exercise behavior.

4.2. Antidepressant (tranylcypromine) treatment

As expected, the results of the current study provide further evidence that antidepressant treatment increases the levels of BDNF mRNA in several hippocampal subfields (Altar, 1999; Duman, 1998; Duman et al., 1997, 2000; Nibuya et al., 1995; Russo-Neustadt et al., 1999, 2000), even during the short period of 2 days (Russo-Neustadt et al., 2000). The effect of antidepressant on BDNF expression may be attributed to any one of a large variety of available intracellular targets, such as by inhibiting the breakdown of cAMP (Fujimaki et al., 2000) or stimulating adenylyl cyclase (Morinobu et al., 1999). The net antidepressant effect, then, through a positive feedback loop (see Altar, 1999; Duman, 1998; Duman et al., 1997, 2000, for review) could ultimately result in enhanced survival and sprouting of monoaminergic axons (Mamounas et al., 1995).

Within the hippocampus, both β-adrenergic receptor subtypes are located postsynaptically and are known to stimulate the adenylyl cyclase system, which could then ultimately lead to increased BDNF transcription (Duman et al., 1997, 2000). Consistent with previous results (Russo-Neustadt et al., 2000), a significant increase in BDNF mRNA levels was evident in the CA3 and DG following antidepressant treatment. In the presence of the β-adrenergic receptor antagonist, propranolol, this exercise effect was removed. When propranolol was administered either alone or with tranylcypromine, no significant differences in BDNF mRNA levels relative to controls were observed. This result suggests that the modest, initial effect of antidepressant treatment (following 2 days of treatment) on hippocampal BDNF mRNA transcription may depend upon NE transmission and β-adrenergic receptor activation.

Treatment with ketanserin in conjunction with tranylcypromine led to a removal of the BDNF enhancement seen with antidepressant administration, and also reduced BDNF mRNA levels significantly below baseline. This result suggests that 5-HT_{2A} receptor activation may be essential for the enhanced BDNF transcription following tranylcypromine treatment, and may also participate in baseline expression. Alternatively, ketanserin-induced BDNF mRNA reduction might be attributed to the fact that 5-HT_{2A} receptors are highly expressed on GABAergic interneurons, hilar cells, and hippocampal granule cells (Pompeiano et al., 1994; Wright et al., 1995). The inhibition of these 5-HT_2 autoreceptors on GABAergic interneurons may impose a counteracting inhibitory tone on DG granule cells with the net effect of decreasing or blunting BDNF transcription. Secondly, it is also possible that because ketanserin is a relatively nonselective drug, which also binds histamine, β-adrenergic, and dopamine receptors (Janssen, 1983), blockade of other receptors' stimulatory subtypes (e.g., dopamine) could down-regulate BDNF mRNA levels. Also, since ketanserin was administered systemically, it cannot be assumed that all effects arose from hippocampal receptor blockade, but possibly via effects on presynaptic nuclei (Gorea and Adrien, 1988).

Similar to the results obtained with propranolol, the addition of WAY100635 to the animals' treatment led to a return of BDNF mRNA levels to baseline. The modest elevation of BDNF mRNA levels in the CA3 and DG resulting from tranylcypromine treatment was thus removed following short-term 5-HT_{1A} blockade. This result suggests that 5-HT_{1A} function may be important for the effect of short-term antidepressant treatment on hippocampal BDNF expression.

The 5-HT_{1A} receptor subtype is the most abundant 5-HT receptor in the hippocampus, where a significant proportion is postsynaptic. Animal models of depression have exhibited behavioral improvements when treated with 5-HT_{1A} agonists with an associated down-regulation of 5-HT_2 receptors in some preclinical trials, and these changes are correlated with the antidepressant response (Stahl, 1994). These results are consistent with the idea that 5-HT projections from the dorsal raphe exert global control over the hippocampus via modulation of local inhibitory interneurons (Freund et al., 1990). The efficacy of antidepressant treatment appears to depend upon a balance between 5-HT receptor subtypes in various regions of the brain. For example, a balance between functional down-regulation of 5-HT_{1A} receptors in the neocortex and a concomitant up-regulation of 5-HT_{1A} in the hippocampus seems to be essential for effective antidepressant action (Lopez et al., 1998).

BDNF is known for its ability to enhance survival of denervated monoaminergic axons (Mamounas et al., 1995), its antidepressant-like properties (Siuciak et al., 1996, 1997), and its ameliorative effects on stress (Altar, 1999; McEwen, 1999, 2000; Smith et al., 1995) and depression (Duman et al., 1997, 2000). We have previously shown that physical exercise and/or antidepressant treatment robustly increase the transcription of BDNF (Russo-Neustadt et al., 1999, 2000). In keeping with our current understanding of the cellular and molecular mechanisms of depression (Duman et al., 1997, 2000), monoaminergic neurotransmitter function may be an important component of these interventions. Taken together, our results suggest that NE stimulation is an important initial event in the cellular mechanisms leading to enhanced BDNF transcription following physical exercise. Both NE and 5-HT mechanisms appear to be essential for the initial actions of the MAO inhibitor, tranylcypromine in its ability to enhance BDNF mRNA expression in the hippocampus. It is apparent that these two interventions, exercise and antidepressant treatment, exert distinct but complementary effects on the mammalian brain. Distinct and sometimes region-specific effects following manipulation of individual receptor subtypes have revealed that an intricate interaction between multiple neurotransmitter systems participates in the regulation of growth factor expression.

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