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DOES NEUROTROPIN-3 HAVE A THERAPEUTIC IMPLICATION IN MAJOR DEPRESSION?

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Although several classes of antidepressants are used to treat major depression, there is an unmet need in real clinical practice because not all patients treated with an antidepressant fully recover from their functional impairment. Hence, the development of new antidepressants based on a novel therapeutic mechanism may help in the development of more effective and ideal antidepressive agents. There is emerging evidence suggesting that the etiopathogenesis of depression involves transmitters other than the major neurotransmitters such as serotonin, norepinephrine, and dopamine. Therefore, it has consistently been suggested that an alteration in neuroprotection and synaptic plasticity is associated with the pathogenesis and therapeutic mechanism of depression. Neurotropin-3 (NT3) is an interesting protein that regulates neuronal survival, synaptic plasticity, and neurotransmission. It is widely expressed in the hippocampus and facilitates hippocampal plasticity by regulating neurogenesis. It has been also reported that an infusion of NT3 increases the level of brain-derived neurotrophic factor (BDNF) mRNA expression in the cerebral cortex and produces BDNF-like effects that induce cortical tyrosine kinase B phosphorylation. BDNF has been consistently implicated in the pathogenesis of depression and the therapeutic mechanism of antidepressants. It has also been implicated in the treatment effect of mood stabilizers such as lithium. NT3 has demonstrated its possible antidepressant effect in a learned helpless animal model. Animal studies have shown that it also modulates the neurotransmitters, serotonin and noradrenaline, which are essential in the development and treatment of depression. Therefore, further studies on the therapeutic implications of NT3 for depression are warranted and are expected for the development of newer, effective antidepressants.

Keywords neurotropin-3, depression, therapeutic implication

INTRODUCTION

Despite antidepressants being the gold standard for the treatment of depression, only one third of patients treated with an antidepressant completely recover from their functional impairment (Crown et al., 2002). The mechanism for the action of antidepressants is not completely understood. However, a number of behavioral, electrophysiological, and microdialysis studies have shown that serotonin (5-HT) receptors play an important role in modulating the antidepressant activity (Bourin, David, Jolliet, & Gardier 2002). The

indirect activation of neurotransmitter receptors by antidepressants can also lead to the activation of various G proteins coupled with a receptor, a transduction signal, transcription factors, and neurotrophic factors through increases in the endogenous levels of serotonin in the synapses of specific brain regions (Bourin et al., 2002; Tardito et al., 2006). Therefore, a further examination of the mechanism for the action of antidepressants will help facilitate the development of new action mechanism–based antidepressant that will overcome the limitation of contemporary antidepressants. Indeed the novel pathogenetic theories for depression include a change in the neuronal plasticity (Duman, 2002) and disturbances in neurogenesis (Kempermann & Kronenberg, 2003), which suggests a putative role of neurotrophic factors in depression.

As a new approach to the mechanism of antidepressants, neuroptophin-3 (NT3), an authentic neurotrophic factor with an important role in the development and maintenance of the nervous system, may be an interesting molecule. This is because it stimulates and controls neurogenesis by activating tyrosine kinase neurotrophin receptors (TrkC and TrkB), is associated with the regulation of monoamine neurotransmitters such as serotonin and noradrenaline, enhances other neurotrophic factors such as nerve growth factors (NGFs) and brain-derived neurotrophic factor (BDNF), and is also involved in the treatment effects of mood stabilizers. This paper discusses the potential role of NT3 in the treatment of depression based on the currently available evidences.

EVIDENCE FROM CURRENTLY AVAILABLE DATA

It should be noted that the cerebral cortex and hippocampus are essential for the modulation of emotion and anxiety along with being important targets in the therapeutic mechanism of contemporary antidepressants (Fumagalli et al., 2005). NT3 is widely expressed in the dentate gyrus of the hippocampus and facilitates hippocampal plasticity by regulating neurogenesis through the activation of tyrosine kinase neurotrophin receptors such as TrkC and TrkB. It has been reported that NT3 has a direct role in the proliferation, survival, or differentiation of hippocampal progenitor cells in vivo (Shimazu et al., 2006). Indeed, hippocampal atrophy as well as atrophic changes in the frontal cortex have been consistently demonstrated as one of the eminent pathophysiological findings in depression, which have also been correlated with clinical variables such as duration of depression (Sheline, Wang, Gado, Csernansky, & Vannier, 1996). Therefore, the currently available findings suggest that NT3 is involved in the mechanism of antidepressants at least as a critical modulator in certain

phases of synaptic plasticity and neurogenesis in the critical neuronal structures such as the hippocampus.

It has been also shown that an infusion of NT3 increases the level of BDNF mRNA expression (Schutte, Yan, Mestres, & Giehl, 2000) and produces BDNF-like effects, inducing cortical tyrosine kinase B phosphorylation (Bothwell, 1995). In addition, NT-3 has been reported to modulate BDNF signaling in differentiating hippocampal neurons (Paul, Gottmann, & Lessmann, 2001). BDNF has been implicated in the pathogenesis of depression and the therapeutic mechanism of antidepressants, as evidenced by the number of preclinical and clinical studies (Sandi & Bisaz, 2007; Gratacos et al., 2007). For example, BDNF significantly increases the level of 5-hydroxyindoleacetic acid (5-HIAA) and/or the 5-HIAA/5-hydroxytryptamine (5-HT) ratio in the hippocampus, cortex, striatum, nucleus accumbens, substantia nigra, and hypothalamus. It also alters the dopaminergic activity, primarily within the striatum and cortex (Siuciak, Boylan, Fritsche, Altar, & Lindsay, 1996). In preclinical studies, antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRI), and monoamine oxidase inhibitors (MAOIs), elevate the BDNF mRNA levels in the hippocampus (Huang, Lee, & Liu, 2007). In addition, BDNF has demonstrated antidepressant-like behavioral effects in the modified rat forced swimming test, by showing reduced immobility and increased swimming (Hoshaw, Malberg, & Lucki, 2005). Therefore, NT3 might be involved in the fundamental molecular events in the treatment of depression by regulating or boosting the important neurotrophic factors such as BDNF.

NT3 increases the turnover of 5-HT and the levels of noradrenaline in the neocortex, basal ganglia, and hippocampus (Celada, Siuciak, Tran, Altar, & Tepper, 1996; Martin-Iverson, Todd, & Altar, 1994). In addition, NT3 promotes the noradrenergic neuronal cells of the locus ceruleus (LC) (Sieber-Blum & Ren, 2000). These findings are particularly intriguing in that the monoamine hypothesis is the prevailing pathogenesis of depression as well as the main therapeutic mechanism of contemporary antidepressants such as tricyclic antidepressants (TCAs), SSRIs, and SNRIs. Preclinical studies have shown that the simultaneous targeting of a subset of 5-HT receptors and α-adrenergic receptors may play a key role in modulating the antidepressant activity. Indirect activation of the neurotransmitter receptors by antidepressants might lead to increases in the endogenous levels of available monoamines in the synapses of specific depression-related brain regions. Furthermore, NT3 is capable of accelerating the regrowth and sparing of 5-HT innervation from various neurotoxic insults (Mamounas, Blue, Siuciak, & Altar, 1995).

NT3 markedly enhances the level of extracellular signal–related kinase (ERK) phosphorylation that is associated with a variety of growth factors, hormones, and neurotransmitters (Cavanaugh et al., 2001). This strongly supports the existence of a specific receptor for NT3 (e.g., G-protein–coupled receptor) and suggests that multiple signal transduction mechanisms might be activated by NT3, which may be involved in the action mechanism of antidepressants. Preclinical studies have shown that antidepressant-induced neurotrophin signaling may trigger the formation and stabilization of the synaptic connectivity, which gradually leads to the clinical antidepressive effects and mood recovery (Saarelainen et al., 2003).

NT3 mRNA has also been found in the ventral tegmental area (VTA), which is important in the reward process. Recent preliminary evidence suggests that NT3 may participate in a certain step in the regulation of the mesoaccumbens dopamine system on the initiation of behavioral sensitization through the activation of the mitogen-activated protein (MAP) kinase signal transduction cascade (Freeman & Pierce, 2002; Pierce, Pierce-Bancroft, & Prasad, 1999). This indicates that NT3 has potential psychostimulant activity. This is interesting when considering the findings that psychostimulants may be effective in augmenting the treatment response in patients who have failed to respond adequately to antidepressants (Fava, Thase, & DeBattista, 2005).

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis after multiple stressors is consistent with the results from previous preclinical and clinical studies in depression (Faure, Uys, Marais, Stein, & Daniels, 2006). In this regard, the compensatory elevation of NT3 after an aberration of the HPA axis may support the potential role of NT3 in the treatment of depression (Faure et al., 2006), which is in line with the antidepressant effect involving the normalization of the HPA feedback loop (Nielsen, 2006).

NT3 is also expressed in the noradrenergic neurons of the LC, and recurrent immobilization stress increases the NT3 mRNA levels in the LC (Smith et al., 1995). It was also reported that high levels of endogenous glucocorticoids are involved in the increase in NT-3 mRNA levels in the LC (Smith et al., 1995). Given that NT3 is stress responsive and neurotrophic to LC, NT3 may play a role in the effects of stress and antidepressants on mood.

The effect of NT3 on the vegetative functions such as sleep has been also demonstrated in preclinical studies (Kushikata, Kubota, Fang, & Krueger, 2003). The duration of nonrapid eye movement sleep (NREMS) was increased by an intracerebroventricular injection of two doses of NT3 (50 ng and 500 ng), although only the higher dose produced a statistically significant result (Kushikata et al., 2003).

In a recent animal study, NT3 was found to be involved in the effects of mood stabilizers such as lithium and valproate (Walz et al., in press). Lithium increases the serum and hippocampal NT-3 levels in the reversal and prevention animal model of mania, whereas valproate increases the hippocampal NT-3 level in a prevention model only (Walz et al., in press). This indicates that lithium and valproate have different effects on the intracellular signaling systems that regulate the expression of neurotrophic factors or the differential response of NT3 (Walz et al., in press). Overall, NT3 has a broader mode of action that can be used beyond unipolar depression.

SUMMARY AND CONCLUSION

The currently available findings suggest possible therapeutic implications of NT3 in the treatment of depression, even though the data might not translate directly into clinical applications. It should be noted that NT3 plays an important role in the treatment of depression through several major mechanisms: (1) regulation of synaptic plasticity and neurogenesis; (2) modulation of other neurotrophic factors, such as BDNF, eventually leading to increased neuronal survival and a change in the synaptic neurotransmission positive to the treatment of depression; (3) direct effect on monoamine neurotransmitters such as 5-HT and noradrenaline; (4) neuroprotection from neurotoxic insults; and (5) enhancement of the vegetative function such as sleep.

REFERENCES

Bothwell, M. (1995). Functional interactions of neurotrophins and neurotrophin receptors. *Annual Review of Neuroscience*, *18*, 223–253.

Bourin, M., David, D. J., Jolliet, P., & Gardier, A. (2002). Mechanism of action of antidepressants and therapeutic perspectives. *Therapie*, *57*(4), 385–396.

Cavanaugh, J. E., Ham, J., Hetman, M., Poser, S., Yan, C., & Xia, Z. (2001). Differential regulation of mitogen-activated protein kinases ERK1/2 and ERK5 by neurotrophins, neuronal activity, and cAMP in neurons. *Journal of Neuroscience*, *21*(2), 434–443.

Celada, P., Siuciak, J. A., Tran, T. M., Altar, C. A., & Tepper, J. M. (1996). Local infusion of brain-derived neurotrophic factor modifies the firing pattern of dorsal raphe serotonergic neurons. *Brain Research*, *712*(2), 293–298.

Crown, W. H., Finkelstein, S., Berndt, E. R., Ling, D., Poret, A. W., Rush, A. J., et al. (2002). The impact of treatment-resistant depression on health care utilization and costs. *The Journal of Clinical Psychiatry*, *63*(11), 963–971.

Duman, R. S. (2002). Pathophysiology of depression: The concept of synaptic plasticity. *Euopeanr Psychiatry*, *17*(Suppl. 3), S306–S310.

Faure, J., Uys, J. D., Marais, L., Stein, D. J., & Daniels, W. M. (2006). Early maternal separation followed by later stressors leads to dysregulation of the HPA-axis and increases in hippocampal NGF and NT-3 levels in a rat model. *Metabolic Brain Disease*, *21*(2–3), 181–188.

Fava, M., Thase, M. E., & DeBattista, C. (2005). A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *The Journal of Clinical Psychiatry*, *66*(1), 85–93.

Freeman, A. Y., & Pierce, R. C. (2002). Neutralization of neutrophin-3 in the ventral tegmental area or nucleus accumbens differentially modulates cocaine-induced behavioral plasticity in rats. *Synapse*, *46*(2), 57–65.

Fumagalli, F., Molteni, R., Calabrese, F., Frasca, A., Racagni, G., & Riva, M. A. (2005). Chronic fluoxetine administration inhibits extracellular signal-regulated kinase 1/2 phosphorylation in rat brain. *Journal of Neurochemistry*, *93*(6), 1551–1560.

Gratacos, M., Soria, V., Urretavizcaya, M., Gonzalez, J. R., Crespo, J. M., Bayes, M., et al. (2007). A brain-derived neurotrophic factor (BDNF) haplotype is associated with antidepressant treatment outcome in mood disorders. *Pharmacogenomics Journal*, *8*(2), 101–112.

Hoshaw, B. A., Malberg, J. E., & Lucki, I. (2005). Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Research*, *1037*(1–2), 204–208.

Huang, T. L., Lee, C. T., & Liu, Y. L. (2008). Serum brain-derived neurotrophic factor levels in patients with major depression: Effects of antidepressants. *Journal of Psychiatric Research*, *42*(7), 521–525.

Kempermann, G., & Kronenberg, G. (2003). Depressed new neurons—Adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biological Psychiatry*, *54*(5), 499–503.

Kushikata, T., Kubota, T., Fang, J., & Krueger, J. M. (2003). Neurotrophins 3 and 4 enhance non-rapid eye movement sleep in rabbits. *Neuroscience Letters*, *346*(3), 161–164.

Mamounas, L. A., Blue, M. E., Siuciak, J. A., & Altar, C. A. (1995). Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *Journal of Neuroscience*, *15*(12), 7929–7939.

Martin-Iverson, M. T., Todd, K. G., & Altar, C. A. (1994). Brain-derived neurotrophic factor and neurotrophin-3 activate striatal dopamine and serotonin metabolism and related behaviors: Interactions with amphetamine. *Journal of Neuroscience*, *14*(3 Pt. 1), 1262–1270.

Nielsen, D. M. (2006). Corticotropin-releasing factor type-1 receptor antagonists: the next class of antidepressants? *Life Sciences*, *78*(9), 909–919.

Paul, J., Gottmann, K., & Lessmann, V. (2001). NT-3 regulates BDNF-induced modulation of synaptic transmission in cultured hippocampal neurons. *Neuroreport*, *12*(12), 2635–2639.

Pierce, R. C., Pierce-Bancroft, A. F., & Prasad, B. M. (1999). Neurotrophin-3 contributes to the initiation of behavioral sensitization to cocaine by activating the Ras/Mitogen-activated protein kinase signal transduction cascade. *Journal of Neuroscience*, *19*(19), 8685–8695.

Saarelainen, T., Hendolin, P., Lucas, G., Koponen, E., Sairanen, M., MacDonald, E., et al. (2003). Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *Journal of Neuroscience*, *23*(1), 349–357.

Sandi, C., & Bisaz, R. (2007). A model for the involvement of neural cell adhesion molecules in stress-related mood disorders. *Neuroendocrinology*, *85*(3), 158–176.

Schutte, A., Yan, Q., Mestres, P., & Giehl, K. M. (2000). The endogenous survival promotion of axotomized rat corticospinal neurons by brain-derived neurotrophic factor is mediated via paracrine, rather than autocrine mechanisms. *Neuroscience Letters*, *290*(3), 185–188.

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(9), 3908–3913.

Shimazu, K., Zhao, M., Sakata, K., Akbarian, S., Bates, B., Jaenisch, R., et al. (2006). NT-3 facilitates hippocampal plasticity and learning and memory by regulating neurogenesis. *Learning & Memory*, *13*(3), 307–315.

Sieber-Blum, M., & Ren, Z. (2000). Norepinephrine transporter expression and function in noradrenergic cell differentiation. *Molecular and Cellular Biochemistry*, *212*(1–2), 61–70.

Siuciak, J. A., Boylan, C., Fritsche, M., Altar, C. A., & Lindsay, R. M. (1996). BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration. *Brain Research*, *710*(1–2), 11–20.

Smith, M. A., Makino, S., Altemus, M., Michelson, D., Hong, S. K., Kvetnansky, R., et al. (1995). Stress and antidepressants differentially regulate neurotrophin 3 mRNA expression in the locus coeruleus. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(19), 8788–8792.

Tardito, D., Perez, J., Tiraboschi, E., Musazzi, L., Racagni, G., & Popoli, M. (2006). Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressants: a critical overview. *Pharmacological Reviews*, *58*(1), 115–134.

Walz, J. C., Frey, B. N., Andreazza, A. C., Cereser, K. M., Cacilhas, A. A., Valvassori, S. S., et al. (in press). Effects of lithium and valproate on serum and hippocampal neurotrophin-3 levels in an animal model of mania. *Journal of Psychiatric Research*.