Neurotrophic paths in the treatment of depression

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Psychiatric disorders were once attributed primarily to neurotransmitter and hormone disturbances, but in the last decade increasing attention has been devoted to growth factors that could affect neurogenesis and neuroplasticity. In this regard, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), glial-derived neurotrophic factor, vascular endothelial growth factor, and neurotrophin-3 and 4 have all been implicated in major depressive illness.[1,2] Among other sources of evidence supporting this perspective were the findings that depressive disorders were associated with structural brain changes indicative of disturbed neuroplasticity, including reductions of hippocampal neurogenesis as well as disturbances of cortical and subcortical synaptogenesis and dendritic branching.[3,4] Coupled with the findings that BDNF is often reduced in depressed patients and in response to stressful events, whereas chronic antidepressant treatments antagonized such effects,[5] a strong case was made that deficiencies of trophic factor might contribute to neuroplastic changes that render individuals vulnerable to depression. Hence, finding novel means of stimulating endogenous neurotrophic mechanisms or administration of trophic factors themselves could constitute the next wave of antidepressants.

As impressive as the data have been regarding the role of BDNF in depression, they have not been uniformly supportive of this perspective,[6] and there are several unresolved issues that need to be considered. Specifically, BDNF and FGF-2 alterations have not only been associated with depressive disorders, but have also been observed in relation to schizophrenia[7] and neurodegenerative disorders,[8] indicating their lack of specificity in relation to brain and behavioural pathology. This is not altogether surprising given the general importance of neurotrophic factors, such as BDNF, in essential processes, including neuronal survival and plasticity (e.g., neurogenesis, synaptogenesis). Hence, disturbances of trophic factors might impart vulnerabilities that could dispose individuals toward several psychiatric and/or neurologic conditions. That said, the very fact that several different growth factors in addition to BDNF have also been associated with depression begs the question of whether they have additive or interactive effects with respect to pathology, and whether changes of one growth factor might compensate for that of another. There is also the question of how and when BDNF might interact with environmental triggers in promoting depression. Moreover, even if it is accepted that BDNF disturbances contribute to the evolution of depressive disorders, how can this information currently be used in the development of treatments for these disorders?

One line of research that might be pertinent in this regard concerns the possibility that genetic biomarkers might be able to predict the occurrence of illness and the efficacy of treatment strategies. Indeed, a single nucleotide polymorphism, in which a valine (val) to methionine (met) substitution occurred in the 5′ proregion of the human BDNF protein (Val66Met), was identified that might be related to the occurrence of depressive disorders.[9] However, the data concerning whether this polymorphism was related to treatment responses have been inconsistent, and a meta-analysis indicated that Val66Met heterozygous individuals displayed a better response to antidepressant treatment than did Val/Val depressed patients, particularly in Asian populations.[10] Yet, it is possible that the influence of the BDNF polymorphism in relation to depressive disorders might depend on the presence of stressful events, as observed with respect to the presence of the short allele of the serotonin transporter gene, 5-HTTLPR.[11]

Consistent with this perspective, early-life stressful events, which have been associated with elevated vulnerability to later depressive disorders, also affect BDNF.[12] It is of significance that such effects were particularly pronounced among Met carriers of the BDNF polymorphism,[13] as was the negative mood associated with early-life adversity.[14] However, it was also reported that despite the Met allele being associated with increased depression, BDNF itself was less affected by early adversity in Met carriers.[15] Adding still further complexity, it was reported that the BDNF Met allele actually had a protective effect among individuals who carried the short (ss) alleles for 5-HTTLPR and who had experienced childhood abuse.[16]

Despite the challenges to the perspective regarding BDNF involvement in depression, the available data clearly indicate that BDNF and its related processes are involved in certain

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aspects of depression, and likely play an important role in its treatment. A particularly interesting perspective regarding the role of the serotonin transporter in relation to depression has been provided that might also be relevant to BDNF.[17] Belsky and colleagues[17] suggested that 5-HTTLPR shouldn't simply be viewed as a "vulnerability factor," but ought to be considered as a "plasticity factor" that "for better or for worse" influences developmental trajectories that might lead to positive or negative well-being, depending on the nature of the early experiences. In a similar fashion, the status of the BDNF Val/Met mutation could also, for better or worse, determine how and whether early experiences would shape later behaviour. From this vantage, the presence of the BDNF polymorphism might be associated with elevated depression, in part, because individuals might not gain from positive experiences. But, it also means that this mutation might limit the negative effects that can be accrued as a result of childhood adversity. In effect, alterations of BDNF processing, which limits the plasticity of emotion-related circuitry, might limit the negative influences otherwise provoked by adverse early-life experiences.[18]

Given the assumption that variations of BDNF, as well as other neurotrophins, contribute to depressive disorders, and that this might depend on stressful encounters in childhood, it follows that administration of BDNF to correct neuroplasticity abnormalities in depressed individuals would be a useful treatment strategy. Indeed, in one study peripheral BDNF administration was found to reduce the signs of anxiety in several behavioural tests coincident with increased hippocampal neurogenesis and BDNF levels.[19] However, it is generally believed that BDNF does not appreciably cross the blood–brain barrier, hampering its use as a clinical agent. In fact, recent efforts to circumvent such problems have used delivery methods that included focused ultrasonography, to temporarily disrupt the blood–brain barrier, thereby allowing BDNF better access to the brain,[20] but it should be considered that BDNF treatment might have untoward side effects on pain circuits.[21] It is also the case that "overloading" BDNF receptors with exogenous ligand holds the inherent risk of inducing negative neuroplasticity, such as increasing anxiogenic connections within the amygdala,[22] or even provoking apoptotic consequences, owing to activation of the promiscuous p75 receptor. Thus, using alternative strategies that affect the production of "reasonable" endogenous levels of BDNF and other neurotrophins would be desirable.

Strategies to increase BDNF through other routes have recently involved using the *N*-methyl-D-aspartate antagonist, ketamine, to rapidly provoke BDNF and synaptogenesis in animals, and have been employed successfully in a subset of treatment-resistant patients.[23] However, finding novel trophic factors that cross the blood–brain barrier and have more limited side effects would obviously be desirable. In this regard, there is reason to believe that riluzole and memantine, which differ from ketamine but have several common features with respect to their effects on glutamatergic functioning, might turn out to be effective in treating depression, although there have also been negative reports regarding their actions as an adjunctive therapy.[24] Yet another neurotrophic agent, erythropoietin (EPO), a hematopoietic trophic cytokine produced predominately by the kidney, may have potential in treating human brain diseases. Erythropoietin and its receptors are abundant in the developing brain and persist in the adult hypothalamus, hippocampus and neocortex.[25] Unlike BDNF, EPO crosses the blood–brain barrier[26] to impart neuroprotective effects, and EPO was found to have such actions in models of stroke and traumatic brain injury.[27] Indeed, EPO is already routinely used to help repopulate immune cells following chemotherapy and generally is considered to be well tolerated and safe, although careful titration of doses is essential given its ability to mobilize large numbers of red blood cells that could have negative vascular effects.

In addition to directing the trafficking of immune cells and having antiapoptotic actions, EPO provoked antidepressant-like effects in animal models,[28] and in human imaging studies EPO modulated brain responses to emotional stimuli.[29] Taken together with the fact that the nonhematopoietic, carbamylated form of EPO, also has robust effects on the central nervous sytem, it seems that the actions of EPO on brain functioning are independent of variations of red blood cells.[30] Perhaps most importantly in regard to neuroplasticity and depression, EPO may increase BDNF expression and adult hippocampal neurogenesis[31] and hippocampal EPO levels were elevated after antidepressant or electroconvulsive shock treatments.[25,30] Thus, EPO could promote antidepressant effects by inducing BDNF expression or alternatively, by directly stimulating trophic pathways involving phosphatidylinositol-3-kinase (PI3-K), Akt/protein kinase-B, MAP kinases and STAT5.[32] It is also possible that EPO-induced BDNF could act synergistically with exogenously applied EPO to reinforce antidepressant-like actions, since both factors act through PI3-K and MAP kinase pathways. Whatever the case, EPO itself could have appreciable clinical utility as an adjunct or add-on treatment for certain subsets of depressed patients.

Erythropoietin has achieved notoriety because of its illicit use by athletes involved in endurance sports, such as long-distance cycling, in an effort to increase their red blood cell count and thus increase their oxygen levels. Interestingly, exercise itself may act as an antidepressant, possibly through its effects on BDNF,[33] which could develop as a result of elevated EPO.[31] In this regard, exercise has been suggested as an adjunct treatment to diminish depressive symptoms,[34] although this could occur owing to factors other than EPO variations, including the value of exercise as a distraction (avoidant coping) or because it might foster social support. For more severe depression, where fatigue and social isolation are common, recommending an exercise regimen might not be practical. Even though one would hardly suggest that EPO is a good substitute for exercise, in general, it could potentially serve as an adjunctive treatment for depression.

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