Neuroimmune Imbalance: The Key for the Treatment of Anxiety?

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Anxiety disorder, a common mood disorder, seems associated with neuro-immune aberration on the pathophysiology, revealed by many clinical and preclinical evidences1-5. Furthermore, previous research suggested that the prefrontal cortex (PFC) is a critical brain region involved in anxiety disorders6-9. Now, we show that to keep the balance of pro-inflammatory immune-status and the anti-inflammatory immune-status in the PFC is the key for the treatment of anxiety10.

3’-deoxyadenosine (3’-dA), one of the major bioactive metabolites in the Cordyceps Militaris, possesses multiple beneficial effects of anti-inflammatory, anti-cancer, anti-viral, and anti-fungal activities11,12. In recent study, we found that 3’-dA treatments significantly increased IL-4 expression in neurons, and IL-4 expression strongly correlated with the parameters representing reduced anxiety behaviours, suggesting that expression of the key anti-inflammatory molecule IL-4 is critical for the anxiolytic effect10. In addition, both 3’-dA and traditional anxiolytic imipramine enhanced the expression levels of IL-4 and IL-10, and decreased the expression levels of IL-1β and TNF-α, synchronous with the anxiolytic effects produced after chronic treatment for 5 days. The blockade of IL-4 action using the specific inhibitor RIL-4Rα prevented the anxiolytic effect of both 3’-dA and imipramine, indicating that correction of imbalance of proinflammatory and anti-inflammatory pathways is the common mechanism for the treatment of anxiety disorders10. Other anxiolytics, including diazepam, oryzanol, and chlordiazepoxide were shown enhancing anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines in support of the findings13-16.

It is well established that pro-inflammatory cytokines, such as interleukin (IL)-6, TNF-α and IL-1β, are increased in patients with anxiety disorders1. Conversely, the anti-inflammatory cytokine IL-4 is negatively associated with trait anxiety in adolescent girls2 and with anxiety symptoms in women in mid-pregnancy2,3. In an animal model, IL-4 was reduced in anxious mice4, and an IL-4 injection attenuated anxiety-like behaviour5 and a previous study demonstrated that IL-4-knockout mice exhibited anxiety-like behaviour18. Immobilization stress leads to decreased release of IL-4 from the neurons of the locus coeruleus4. Growing evidence indicates the balance between pro-inflammatory and anti-inflammatory factors is associated with the pathophysiology of anxiety disorder17. Increased inflammatory reactions in the CNS are commonly seen in patients with anxiety disorders.

3’-dA was reported to be able to modulate peripheral immune functions, Downregulating the gene expression of the pro-inflammatory factors IL-1β, TNF-α, and IL-2 and upregulating the
anti-inflammatory factors IL-4, IL-10, IL-1Ra, and TGF-β in macrophages and mononuclear cells in the peripheral immune system, similar to what happened in CNS. The lack of IL-4, a key molecule to modulate neuroimmune status, leads to increased neuroinflammation in response to lipopolysaccharide in mice. The action of IL-4 results from its ability to inhibit the release of pro-inflammatory cytokines, such as IL-1β and TNF-α, by innate immune cells and to upregulate the synthesis of anti-inflammatory factors, such as IL-1β receptor antagonist. In addition, neuronal IL-4 plays a vital role in brain cleanup and repair after ischemic damage. Endogenous IL-4 is expressed mainly in neurons, although small amounts co-localize with GFAP-positive cells and Iba1-immunoreactive cells. Our study shows that 3′-dA exhibited a rapid and stable anxiolytic effect in the mice behavioural tests via activating the IL-4 pathway, regulating the expression levels of the IL-10 IL-1β and TNF-α in PFC, suggesting 3′-dA functions to correct the imbalance between pro-inflammatory factors and anti-inflammatory factors, which is helpful for restraining inflammatory reactions, activating anti-inflammatory factor pathways, and promoting neuronal-functional repair in the CNS.

Furthermore, cumulative studies show that transition of pro-inflammatory to anti-inflammatory status helps to modulate neuronal and synaptic functions. It was previously reported that restoration of IL-4 concentrations in the hippocampus to the levels of those observed in young rats is associated with the successful maintenance of long-term potentiation (LTP), and the downregulation of IL-4-stimulated signalling significantly contributes to the deficit in LTP. LTP is an important indicator of neural synaptic plasticity, which plays a key role in behavioural manifestations, and may be a relevant mechanism in IL-4-mediated anxiolytic effects of 3′-dA and imipramine.

In summary, both 3′-dA and the traditional anti-anxiety medication produced an anxiolytic effect via increasing the IL-4 expression levels to correct the pro-inflammatory/anti-inflammatory balance, subsequently to change the neuronal functions and behaviours, and the IL-4 specific inhibitor RIL-4Ra could prevent the anxiolytic effect of both 3′-dA and imipramine. These results indicate that IL-4 pathway is the key to the treatment of anxiety disorder and provide an innovative drug with a novel neuro-immune mechanism for the treatment of anxiety disorder.

References


