MINI REVIEW

The Role of Bone Morphogenetic Protein Signalling in Functioning and Adult Neurogenesis of the Hippocampus

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ABSTRACT

Depression and anxiety are widely prevalent disabling psychiatric disorders. Stressful experiences can contribute to the development and pathogenesis of these disorders. However, current antidepressants still show a delayed onset of action and lack of efficacy. Hence, a deeper understanding of the molecular and cellular mechanisms involved in the pathophysiology of these disorders, as well as the action of antidepressants, may provide further insight into the development of novel fast-acting and more effective therapies. The subgranular zone of the hippocampal dentate gyrus is one of the regions where adult neurogenesis occurs in mammals, including humans, and is well known for its involvement in emotion and stress responses. Adult hippocampal neurogenesis decreases due to stress and increases by the chronic usage of antidepressants, the change in adult hippocampal neurogenesis is involved in the stress-related pathophysiology of depression and anxiety disorders and plays a role in the activity of antidepressants and anxiolytics. The Bone Morphogenetic Protein (BMP) signalling pathway in the hippocampus is a key regulator of adult hippocampal neurogenesis, and affects hippocampal function. Herein, we aimed to summarize the current literature on the involvement of the hippocampal BMP signalling pathway in adult neurogenesis, and the pathophysiology and treatment of depression and anxiety.

Keywords: Depression, Anxiety, Stress, Bone morphogenetic protein, Noggin, Chordin, Hippocampus, Neurogenesis

Abbreviations: BMP: Bone Morphogenetic Protein; DG: Dentate Gyrus; SGZ: Subgranular Zone; SSRIs: Selective Serotonin Reuptake Inhibitors; CSDS: Chronic Social Defeat Stress; TNF: Tumour Necrosis Factor-α; IL-1: Interleukin-1

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INTRODUCTION

Depression and anxiety are widely prevalent and disabling psychiatric disorders [1,2]. Although antidepressants alleviate depressive and anxiety symptoms, they require weeks or months to exert their therapeutic effects and only half of the treated patients achieve remission [3-5]. The lack of mechanistic studies that may explain the pathophysiology of these disorders is a bottleneck in clinical practice. Therefore, elucidation of novel pharmacological targets that mediate psychiatric symptoms is necessary.

Adult neurogenesis in the Subgranular Zone (SGZ) of the hippocampal Dentate Gyrus (DG) is well known for its involvement in stress-related pathophysiology of depression and anxiety disorders and for its role in the activity of antidepressants and anxiolytics [6,7]. Accumulating evidence suggests that the Bone Morphogenetic Proteins (BMPs) signalling pathway is involved in the regulation of hippocampal neurogenesis. Our understanding of the role of BMP signalling has recently expanded beyond its role in the skeletal system and in regulating numerous processes of adult hippocampal neurogenesis, aging, and inflammation in both homeostasis and disease states. In this review, we aimed to summarize the findings on the effects of the BMP signalling pathway on adult hippocampal neurogenesis under physiological and pathological conditions.

LITERATURE REVIEW

Role of BMP signalling pathway in adult neurogenesis of hippocampus under physiological conditions

The hippocampus is a brain region that regulates not only learning and spatial memory, but also emotion and stress responses, which are regulated by neurogenesis [8]. Adult neurogenesis is a process by which new granule cell neurons are added to the SGZ of the DG in the hippocampus throughout life. Adult hippocampal neurogenesis has been demonstrated in birds, [9] rodents, [10] and primates, including humans [11,12]. Adult hippocampal neurogenesis, including rate of proliferation, maturation, and survival of neurons, is affected by environmental factors, such as stress and antidepressants [13]. Therefore, the impairment of adult hippocampal neurogenesis may be related to the pathophysiology of depressive and anxiety disorders and the beneficial effects of antidepressant treatment [6,7].

BMPs are members of the transforming growth factor-β superfamily [14]. Many different BMPs are expressed in the hippocampus, such as BMP-2, BMP-4, BMP-7, and BMP-10. The functions of BMPs are mediated by interactions with membrane-bound receptors belonging to the serine/threonine kinase family, including BMP receptor I (BMPR Ia, BMPR Ib) and II (BMPR II) [15]. These receptors form heteromeric complexes with BMPR I and BMPR II. Once the BMP binds to BMPR II, which is the ligand binding subunit, BMPR I activates the phosphorylation of the intracellular signal transducer Smad1/5/8 which interacts with co-mediator Smad4 [15,16]. The Smad complex then translocates to the nucleus where it acts as a transcription regulator. In addition, activated BMPRI complexes are also able to initiate Smad-independent signalling pathways, such as extracellular signal-regulated kinase, p38 mitogen-activated protein kinase, C-Jun N-terminal kinase, and nuclear factor kappa beta [14].

With regard to the mammalian brain, the activation of BMP signalling pathway has broadly divergent functions in cell-fate decision, [17] central nervous system patterning, [18] axon pathfinding, [19] and dendrite development [20,21]. BMPs are also regulated by antagonistic factors, such as noggin and chordin, which directly bind to BMPs and prevent their activation [22]. The BMP signalling pathway is involved in the regulation of cognitive function in the hippocampus. For example, mice overexpressing noggin exhibit markedly better performance in hippocampus-dependent cognition than that of control mice [23,24]. Furthermore, chordin-null mice exhibit impairments in spatial memory and novel object recognition performance [25]. Regarding the relationship between BMPs and neurogenesis in the hippocampus, BMP signalling has been reported to play a key role in regulating the balance between quiescence/proliferation of neural stem cells and maturation. BMPs and their receptors are expressed in neural stem cells in the DG of the hippocampus. Viral overexpression of BMP-4 slows the maturation speed of neural stem cells, resulting in a long-term reduction in hippocampal neurogenesis [26]. Transgenic activation of BMP signalling inhibits the maturation of neural stem cells into

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neurons in adult mice and increases astrocyte differentiation, whereas its inhibition enhances hippocampal neurogenesis via the activation of neural progenitor cells at multiple stages of lineage and by accelerating their maturation [26,27]. In addition, it has been reported that the deletion of either BMPRIa or Smad4 in the SGZ, transiently increases the proliferation of neural stem cells in the SGZ, which leads to the reduction of precursors, thereby limiting neurogenesis [28]. In contrast, Withers et al.[29] reported that the treatment of cultured hippocampal neurons BMP-7 stimulated dendritic development and synapse formation. In addition, exposure to BMP-2 and BMP-4 increased neurogenesis in adult hippocampal neural stem and progenitor cells while decreasing oligo dendrogenesis [30]. These studies suggest that the BMP signalling pathway plays a crucial role in regulating functions and adult neurogenesis of the hippocampus under physiological conditions. Therefore, a balance between BMPs and their antagonistic factors is required to control quiescence and proliferation of neural stem cells, and prevent the loss of stem cell activity that supports continuous neurogenesis in the adult hippocampus.

The BMP signalling pathway mediates therapeutic effects of antidepressants

Several studies have demonstrated that the BMP signalling pathway in the hippocampus plays an important role in mood regulation and in exerting the therapeutic effects of antidepressants. It has been reported that chronic administration of fluoxetine, a Selective Serotonin Reuptake Inhibitor (SSRI), increases the production of the BMP inhibitor noggin and suppresses the expression levels of BMP-4, phosphorylated Smad1/5/8, and Id protein, which are considered indicators of an active BMP signalling pathway and regulators of the biological responses to BMPs [31]. The authors also showed that viral overexpression of BMP-4 in the hippocampus completely blocked the therapeutic effects of fluoxetine on depression-and anxiety-like behaviour and neurogenesis in mice. Conversely, viral overexpression of noggin exerts antidepressant-like effects by increasing hippocampal neurogenesis [31]. Recently, Tunc-Ozcan et al. [32] showed that multiple classes of antidepressants, including SSRIs, inhibit the BMP signalling pathway and enhance neurogenesis in the hippocampus. These findings suggest that hippocampal BMP signalling is a common pathway that mediates the therapeutic effects of antidepressants.

The BMP signalling pathway is related to the regulation of adult neurogenesis in hippocampus during stress and in psychiatric disorders

Alterations in hippocampal BMP signalling pathway activity have been studied in rodent models of depression and anxiety. Chronic Social Defeat Stress (CSDS) is considered useful for assessing anxiety and depressive disorders in humans and significantly increased BMP-4 signalling pathway activity and decreased chordin expression levels in the hippocampus in mice model of depression, but not in other depression-related brain regions such as the amygdala and hypothalamus. Moreover, both pharmacological and genetic overexpression of hippocampal chordin completely blocked the CSDS-induced detrimental effects in mice [33]. Similarly, a previous study demonstrated that repeated social defeat stress activated BMP-4 and phosphorylated Smad1/5/9 expression levels concomitant with impaired cell proliferation and neurogenesis in the dorsal hippocampus in a rat model of anxiety [34]. These studies suggest that the hippocampal BMP signalling pathway is involved in the modulation of adult neurogenesis under stress and pathological conditions.

Accumulating evidence suggests that hippocampal BMP signalling activity is affected by environmental factors, such as stress and antidepressants, as well as hippocampal adult neurogenesis. In addition to these factors, various other factors, such as aging and inflammation, could induce activation of the BMP signalling pathway. With aging, the expression levels of BMP-4 increase gradually, while the levels of its inhibitor noggin decrease in the DG of the hippocampus, which results in decreased neurogenesis and enhanced gliogenesis in the hippocampus [35]. In contrast, inhibition of the BMP signalling pathway in aging mice increases hippocampal neurogenesis and prevents age-related cognitive dysfunction [36]. Therefore, the age-dependent increase in BMP-4 expression levels is attributed to the development of age-related neurodegenerative disorders such as Alzheimer's disease. Interestingly, the neurogenic effects of antidepressant fluoxetine treatment decline with age [36]. It has also been reported that the BMP signalling pathway is a key mediator of inflammatory processes [37]. Many studies have shown that neuro inflammation plays crucial roles in the onset and development of psychiatric disorders including depression [38]. Inflammatory cytokines, such as Tumour Necrosis Factor (TNF)-α and Interleukin (IL)-1 are released during inflammation and induce impairment of hippocampal neurogenesis [39,40]. For instance, a previous study showed that TNF-α and IL-1 stimulated expression of BMPs in endothelial cells [41]. BMP-4 is upregulated in endothelial cells in response to shear stress and promotes inflammatory processes [42,43]. Given that neuronal stem cells in the DG of the hippocampus are located close to blood vessels [44], stress-induced elevation of inflammatory cytokine levels may affect hippocampal function and neurogenesis in the DG. In fact, it was recently reported that synovial BMP-4 and BMP-7 signalling mediates systemic inflammation, resulting in decreased adult neurogenesis in the hippocampus in a rat model of rheumatoid arthritis [45]. These results suggest that the BMP signalling pathway plays a leading role in aging and inflammation, and is involved in both direct and indirect blunting of the normal process of adult neurogenesis.

Finally, BMP signalling affects not only neurogenesis of neural stem cells in the hippocampus but also gliogenesis in astrocytes. It is well known that astrocytes play a key role in controlling the environment in the neurogenic niche [46]. They release growth factors and various soluble factors such as brain-derived neurotrophic factor and interleukins that are essential for maintaining environmental homeostasis in the hippocampus. One study showed that BMP-4 was upregulated in reactive astrocytes of the spinal ventral horns in a rodent model of amyotrophic lateral sclerosis [47]. Moreover, intrathecal infusion of Bmp-4 targeted antisense oligonucleotides and selective Bmp-4 knockdown suppressed astrocyte activation and neuro inflammation [47]. It is unclear whether BMP signalling affects the function of astrocytes in the hippocampus; thus, the involvement of BMP signalling in the function of astrocytes in the hippocampus requires further study.

CONCLUSION

In this review, we mainly focused on the effects of BMP signalling on the neurogenesis of neural stem cells in the hippocampus. An increasing number of studies have suggested the involvement of the BMP signalling pathway in abnormal neurogenesis in the diseased hippocampus and the action of antidepressants, which strongly highlights the importance of the BMP signalling pathway as a potential target for a new therapeutic strategy for psychiatric disorders, such as depression and anxiety.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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