Received: 2 November 2023 | Revised: 28 December 2023 | Accepted: 21 January 2024

DOI: 10.1002/ddr.22157

REVIEW ARTICLE

DRUG DEVELOPMENT RESEARCH WILEY

Influence of β-catenin signaling on neurogenesis in neuropsychiatric disorders: Anxiety and depression

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Abstract

It has been proven that stress, mainly in the early years of life, can lead to anxiety and mood problems. Current treatments for psychiatric disorders are not enough, and some of them show intolerable side effects, emphasizing the urgent need for new treatment targets. Hence, a better understanding of the different brain networks, which are involved in the response to anxiety and depression, may evoke treatments with more specific targets. One of these targets is β-catenin that regulates brain circuits. β-Catenin has a dual response toward stress, which may influence coping or vulnerability to stress response. Indeed, β-catenin signaling involves several processes such as inflammation-directed brain repair, inflammation-induced brain damage, and neurogenesis. Interestingly, β-catenin reduction is accompanied by low neurogenesis, which leads to anxiety and depression. However, in another state, this reduction activates a compensatory mechanism that enhances neurogenesis to protect against depression but may precipitate anxiety. Thus, understanding the molecular mechanism of β-catenin could enhance our knowledge about anxiety and depression's pathophysiology, potentially improving clinical results by targeting it. Herein, the different states of β-catenin were discussed, shedding light on possible drugs that showed action on psychiatric disorders through β-catenin.

KEYWORDS

anxiety, depression, neurogenesis, stress, Wnt/β-catenin

1 | INTRODUCTION

Stress is an unavoidable aspect of human life; nearly everyone encounters stressful circumstances at some point. Stressful life events can lead to psychopathology (Mutiso et al., 2023). Mental illnesses significantly contribute to the world's growing disease burden. Almost one billion people worldwide are affected by mental illnesses. Notably, depression and anxiety are the most prevalent debilitating mental disorders (Health, 2020). Clinically, there is a strong correlation between anxiety and depressive disorders, with both showing higher vulnerability, especially in women (Kalin, 2020). Women exhibit different neuronal circuits that make them more vulnerable to depression and anxiety, thus emphasizing the importance of sex differences for advancing psychotherapy (Bangasser & Cuarenta, 2021). While the Wnt/β-catenin signaling has been implicated in anxiety and depressive disorders, its exact role and influence remain to be fully understood. The influence of this pathway on psychopathological diseases needs more clarification, especially regarding its link to neurogenesis. To uncover the complexity between psychotropic diseases and neurogenesis, it is

Abbreviations: APC, adenomatous polyposis coli; BDNF, brain-derived neurotrophic factor; BDZ, benzodiazepine.; DG, dentate gyrus; DKK, Dickkopf; Erk 1/2, extracellular signal-regulated kinases ½; GSK-3β, glycogen synthase kinase-3; miRNAs, microRNAs; Sfrp, secreted Fzd-related protein; SSRIs, selective serotonin reuptake inhibitors; TCF, T-cell factor.

important to elucidate the physiological and pathological status of Wnt/β-catenin signaling.

2 | Wnt/β-CATENIN SIGNALING AND ITS DOWNSTREAM TARGETS

The Wnt/β-catenin signaling is involved in the cell cycle, proliferation, and tissue homeostasis, where its dysfunction is associated with neurogenesis and neurotransmitters release (Mishra et al., 2021). β-Catenin is a vital regulator of spine formation, dendritic growth, survival of newly generated neurons, and aging-related deficits in adult neurogenesis in the hippocampus (Heppt et al., 2020). Caracci et al. supported the role of Wnt/β-catenin signaling in regulating neuronal progenitor cell proliferation, survival, and differentiation (Caracci et al., 2021). In addition, Briona et al. emphasized the role of Wnt/β-catenin signaling in promoting neurogenesis and neuronal differentiation following spinal cord injury (Briona et al., 2015). Also, Gao et al. showed the role of active β-catenin in promoting neural stem cell self-renewal; however, its overstimulation can inhibit normal retinal differentiation (Gao et al., 2021). Increased β-catenin can induce uncontrollable cell division (Liu et al., 2021; Ye et al., 2020). A reduction in β-catenin phosphorylation at Ser45, causing β-catenin accumulation, promoted uncontrollable cell division with a significant relation to the degree of cell differentiation (Pan et al., 2019). β-Catenin can beneficially promote tissue regeneration and homeostasis (Reilly et al., 2023). In addition, overexpressing β-catenin mediates anxiolytic, antidepressant, and stress resilience effects (Dias et al., 2014; Larosa & Wong, 2022). Also, inhibiting glycogen synthase kinase-3 (GSK-3β), promoting β-catenin activity, exhibits resilience to depression. On the contrary, GSK-3β knockout mice can exhibit exaggerated anxiety and aberrant social interaction (Gozal et al., 2021; Nisar et al., 2019). Moreover, single GSK-3β allele deletion exhibits anxiety and aggressive actions (Jaworski et al., 2019). β-Catenin is influenced by stress and is thought to be a mediator in the abused drugs' effect, which contributes to later susceptibility to addiction and relapse (Torres-Berrio et al., 2018). Boosting β-catenin can implicate mood disturbance (Abd-Elmawla et al., 2023). Also, it can impair social interaction and raise repetitive behavior. In addition, β-catenin can contribute to premature astrocyte senescence (Kritsilis et al., 2018). Indeed, increased β-catenin expression is a contributor in autism spectrum disorders. High levels of β-catenin are linked to bipolar disorders and schizophrenia, whereas low levels are associated with epilepsy, Huntington's disease, Parkinson's disease, and Alzheimer's disease. Therefore, treatment interventions that raise β-catenin in disorders like bipolar disorders, cancer, epilepsy, and schizophrenia may exacerbate the case (Ahmed et al., 2017; Gao et al., 2021). The foregoing may in part explain the role of β-catenin toward beneficial or harmful outcomes in different body states. Furthermore, both excessive and insufficient activity of the Wnt/β-catenin pathway is harmful, leading to cognitive performance impairment (Gozal et al., 2021), as summarized in Figure 1. Hence, balanced β-catenin signaling rather than its overexpression or reduction is pivotal.

β-Catenin has different phosphorylation states which in turn may influence the fate of the body state. The phosphorylation sites p^{Ser45}, p^{Thr41}, and $p^{Ser37/33}$-β-catenin can reduce β-catenin signaling (Li et al., 2020). Moreover, p^{Tyr30}, p^{Tyr64}, and p^{Tyr86}-β-catenin are potentially essential to brake proliferation, unlike the active form p^{Tyr654}-β-catenin (Mishra et al., 2017). A dual mutation of $p^{Tyr142E}$ and $p^{Tyr120E}$-β-catenin promotes several tens of fold reduction in lifetime compared with a single mutation (Le et al., 2019). Together, p^{Tyr654} and p^{Tyr142}-β-catenin elicit the accumulation of β-catenin in the cytoplasm (Li et al., 2020). In addition, p^{Ser522} and p^{Ser552}-β-catenin enhance β-catenin signaling (Chang et al., 2020; Choi et al., 2021). Moreover, active p^{Ser675}-β-catenin is a measure for Wnt signaling efficacy (Pinto et al., 2020). This may partly explain the crucial role of β-catenin and its balance depending on its precise phosphorylation site and the present body state (Figure 2). Therefore, β-catenin regulation plays a crucial role in determining β-catenin activity.

The phosphorylation and influence of β-catenin are determined by several proteins. β-Catenin is regulated through the destructive complex GSK-3β, adenomatous polyposis coli (APC), and Axin

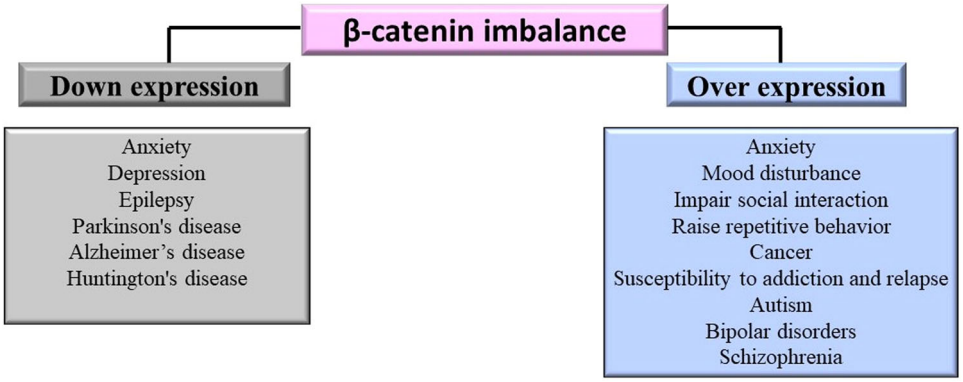

FIGURE 1 The effect of β-catenin imbalance. Balancing β-catenin is pivotal where its dysregulation can cause various diseases such as cancer, anxiety, depression, and so on.

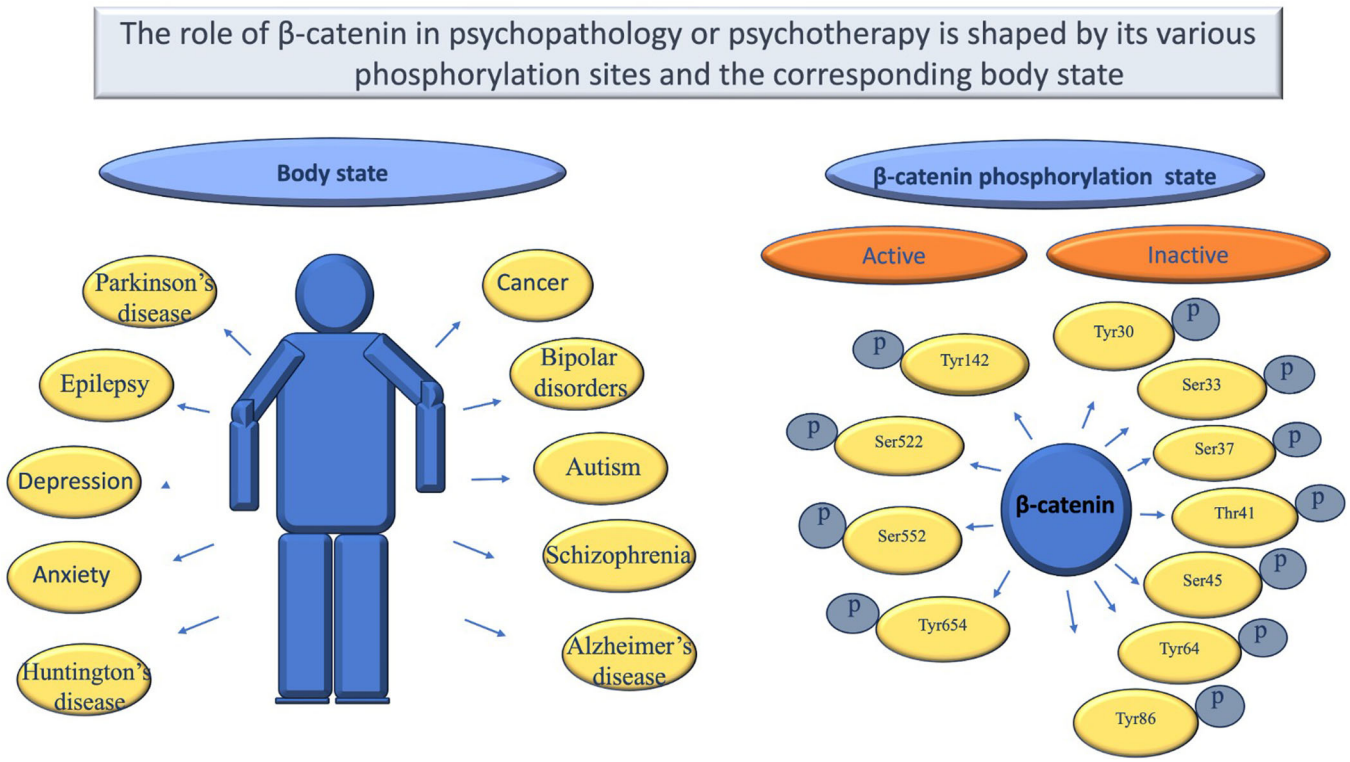

FIGURE 2 Role of β-catenin toward psychopathology or psychotherapy depends on its phosphorylation site and body state. β-catenin can be phosphorylated to be active or inactive. The phosphorylation site alongside different body states like anxiety, depression, epilepsy, Huntington's disease, Parkinson's disease, Alzheimer's disease, autism, bipolar disorders, and schizophrenia can figure out the impact of β-catenin in the pathophysiology.

(Zhang et al., 2021). Moreover, secreted Fzd-related protein (sFRP) and Dickkopf (DKK) are considered Wnt/β-catenin inhibitors that regulate cell survival, proliferation, and fate through monitoring Wnt/β-catenin level (Gómez-Oliva et al., 2020). GSK-3β is a potential therapeutic target for psychiatric disorders due to its critical role in regulating the inflammation process. GSK-3β is a proinflammatory protein that can increase both cytokines and the proinflammatory transcription factor nuclear factor kappa B (NF-κB) (Marques Orellana et al., 2015). In addition, the phosphorylation of GSK-3β is involved in hippocampal neurogenesis that mediates the antidepressant effect of Wnt/β-catenin signaling (Zou et al., 2021). β-Catenin accumulation is a marker for GSK-3β inhibition (Illesca-Matus et al., 2023; Karege et al., 2012). Furthermore, women may be vulnerable to depressive-like behavior because of increased susceptibility to GSK-3β activation (Hasbi et al., 2020). Moreover, β-catenin signaling can be elevated in the inner zone of the adrenal cortex of males compared with females, which is positively influenced by androgens (Dumontet et al., 2018; Lyraki et al., 2023). This may be in part account for the vulnerability of females toward psychopathology. Together, APC is essential for brain growth through neuronal differentiation and axonal growth (Ruane et al., 2016). The precise role of APC in the destructive complex remains obscure, and it was not yet established whether APC promoted Wnt/β-catenin signaling or inhibited it (Parker & Neufeld, 2020). The activation of downstream proteins of this signaling was the determinant of APC role and action.

One of the executive tools of β-catenin is microRNA (miRNA). Besides, miR-155 has a "cleanup" mechanism by inducing apoptosis and regulates hippocampal viability under the dominance of β-catenin signaling (Dai et al., 2020; Woodbury et al., 2015). This enabled Narayanan and Schratt to describe miR-155 as a stress-regulated microRNAs (miRNA) (Narayanan & Schratt, 2020). Moreover, miR-155 controls microglial cells in several processes, such as differentiation, inflammation, and astrocyte association. The knowledge of these determinant proteins anticipates the status of β-catenin signaling and the possible mechanisms that drugs may act on during anxiety and depression.

3 | β-CATENIN AND NEUROGENESIS IN PSYCHIATRIC DISORDERS

The concept of functional neurogenesis began to emerge in the 1990s. Continuous neurogenesis can occur in the hippocampus, subventricular zone, and olfactory bulb. Hippocampus rather than subventricular is pivotal for mood regulation, which is related to anxiety and depression disorders (Dutheil et al., 2009; Zhao et al., 2018). Recently, Chen et al. showed that the olfactory bulb is another neurogenesis niche that relies on the subventricular zone (Chen et al., 2023). Rottstaedt et al. revealed that the olfactory bulb volume may be used as a depression biomarker, however, it is insufficient to

depend on solely. In addition, the olfactory bulb is involved in emotional regulation, which is connected to the hippocampus (Rottstaedt et al. 2018; Rottstädt et al., 2018). Moreover, the hippocampus is highly connected with the amygdala and higher brain regions like the prefrontal cortex. These areas have been linked to mood and stress-related behaviors, especially the hippocampus, which has been identified as a key regulator of emotional distress and neurogenesis through the dentate gyrus (DG) (Eliwa et al., 2017; Joshi et al., 2020). Neurogenesis is related to psychiatric diseases and is currently embedded in the neuronal networks. While numerous studies suggest that hippocampal neurogenesis plays a significant role in the etiology of anxiety and depression, the exact contribution of neurogenesis to psychiatric disorders remains a topic of debate. The hippocampus provides the path for most information toward stress and adaptation. It is observed that hippocampal DG neurogenesis is mastered by β-catenin signaling, where neurogenesis may influence anxiety and depression (Vidal et al., 2019). Indeed, β-catenin possesses a dual role in the cell, where it can boost or diminish neurogenesis (Al-Dalahmah et al., 2020; Knotek et al., 2020). β-Catenin serves as a point of convergence for directing cell survival, proliferation, and differentiation, where β-catenin promotes neurogenesis (L'Episcopo et al., 2013). In accordance, diminished β-catenin reduce neurogenesis (Shin et al., 2022; Tao et al., 2023; Xiao et al., 2021). In line with these studies, Cuesta et al. showed that the dysregulation of β-catenin is linked to anxiety, and its overexpression promotes stress resilience (Cuesta et al., 2020). Similarly, other studies pointed to the role of β-catenin signaling in anxiety-related behavior by impeding anxiety progression (Wang et al., 2019, 2017). In the same context, β-catenin showed the ability to be involved in the psychopathology of another psychiatric disorder, like depression. Additionally, a decrease in neurogenesis has been linked to the onset of both anxiety and depression. Conversely, an increase in neurogenesis is associated specifically with the emergence of anxiety symptoms (Gomes-Leal, 2021; Morgan et al., 2018). Accordingly, decreased β-catenin may increase neurogenesis and elicit a compensatory mechanism that modifies the activity of positive and negative pathway regulators (Etet et al., 2013; Gao et al., 2021). Furthermore, inhibiting Wnt/β-catenin signaling through the nuclear factor of activated T cells positively regulates neurogenesis (Gamit et al., 2023). Hence, reduced β-catenin signaling may decrease neurogenesis, which may implicate anxiety and depression. On the other side, it may be associated with a coping strategy for increasing neurogenesis for the precipitation of anxiety with an anti-depressant character.

From another point of view, the pathophysiology of depression is associated with inflammatory milieu besides β-catenin signaling activation impacts inflammation control (Vallée et al., 2022; Yang et al., 2017). Moreover, chronic unpredictable mild stress (CUMS) is accompanied by a reduction in hippocampal β-catenin that elicits an inflammatory response, causing psychopathological disorders (El-Kadi et al., 2024; Habib et al., 2020). Eventually, the pathology of depression is significantly influenced by changes in β-catenin. In addition, β-catenin is regarded as a common target for treating stress (Cuesta & Pacchioni, 2017). Koshiyama et al. highlighted the neurogenesis hypothesis as a recent one for explaining the etiology of depression instead of the conventional monoamine theory (Koshiyama et al., 2020). Furthermore, Farioli-Vecchioli and Cutuli provided valuable insights of implementing the neurogenesis hypothesis in the pathophysiology of depression where depression is correlated to neurogenesis reduction and hippocampal DG volume. The neurogenesis hypothesis interpreted the lag of antidepressant action to increase neurogenesis of the atrophied hippocampus. Indeed, the latency of antidepressant efficacy is comparable to the time required for fully maturation and differentiation of newly formed neurons. Moreover, there are several lines of evidence that support the neurogenesis hypothesis such as the reduction of hippocampal neurogenesis upon stress, increasing hippocampal neurogenesis after antidepressant, and the complete elimination of antidepressant effect upon ablation of hippocampal neurogenesis (Farioli-Vecchioli & Cutuli, 2023) Thus, this new hypothesis may be valid an alternate to monoamine hypothesis. Altering neurogenesis levels can significantly impact anxiety, with a decrease tending to exacerbate it, while an increase can have anxiolytic and antidepressant effects. Therefore, these data sum up the necessity to discover new interventions to regulate β-catenin and the preceding neurogenesis processes to manage the resulting anxious and depressed behavior. The influence of β-catenin on anxiety and depression is highlighted in Table 1.

Neurotrophic factors figure out the antidepressant effect through the neurogenesis hypothesis (Samuels & Hen, 2011). One of the β-catenin targets is brain-derived neurotrophic factor (BDNF), which heightens neurogenesis, plasticity, and synaptic activity. The increase in its signal is associated with anti-depressant effect along with an enhanced hippocampal neurogenesis process (Eliwa et al., 2017; Zhang et al., 2022). The active form of β-catenin is p^{Ser675}-β-catenin, which triggers T-cell factor (TCF) activation (Ip et al., 2012). The hippocampal β-catenin and TCF regulate mood disorders that are crucial in psychiatric disorders (Zwamborn et al., 2018). Besides, Dicer and c-Myc are other β-catenin downstream targets (To et al., 2017; Xu et al., 2016). Dicer is a micro-RNA-generating-protein in the cell that plays a significant role in neuronal cell-cycle regulation (Mens & Ghanbari, 2018). Dicer is found to be common in stress-related disorders (Haramati et al., 2011), while the Myc family is a super transcription factor that influences essential cell functions such as cell-cycle genes, cell adhesion, viability, protein synthesis (Chen et al., 2018). Cell-cycle-related factors such as c-Myc have been proven to increase proliferation through β-catenin signaling, which affects neurological diseases like Parkinson's disease, Alzheimer's disease, depression, and spinal cord injury (Gao et al., 2021). Moreover, TCF, BDNF, Dicer, and c-Myc, as downstream effectors of β-catenin signaling, primarily impact anxiety and depression. Therefore, assessing these effector proteins is significant in evaluating the efficacy of antidepressant or anxiolytic drugs. Another critical mediator mastered by β-catenin is the extracellular signal-regulated kinases 1 and 2 (Erk1/2). β-Catenin mediates Erk1/2 activation (Jung et al., 2008), which is crucial for stress adaptation (Trollope et al., 2017). The Erk1/2 activation in the hippocampus was noted to be

TABLE 1 Role of β-catenin in anxiety and depression.

Stress type	Animal model	β-Catenin effect	β-Catenin role	References
Low anxiety level	Chronic morphine exposure in male Sprague–Dawley rats for 1 week	Anxiolytic	Inhibiting β-catenin may be beneficial in treating this level of low anxiety caused by morphine exposure	Wang et al. (2019,2017)
Anxiety	Social isolation in male Wistar rats	Anxiolytic	β-Catenin is diminished in stress and its overexpression promotes stress resilience and anxiolytic character	Cuesta et al. (2020)
	CTNNB1 (mutations in β-catenin) conditional knockout mice showing autism-associated behavioral defects	Anxiolytic	Mutations in β-catenin in the parvalbumin interneurons cause anxiogenic effect in the open field test and elevated plus maze test but do not exhibit depression-like behaviors	(Dong et al., 2016)
	Chronic unpredictable mild stress-induced anxiety in female Wistar rats	Anxiolytic	Stress lowered β-catenin and downstream proteins: p-Erk, c-Myc, and Dicer-1 besides miR-17-5p and miR-18	El-Kadi et al. (2024)
	Chronic stress-induced anxiety-like behavior in male C57BL/6 mice treated with morphine	Anxiogenic	Morphine treatment stimulated Wnt/β-catenin signaling that enhanced anxiety	Ma et al., (2018)
Depression and anxiety	Activation of dopamine D1-D2 receptor by SKF 83959 in African green monkey and Sprague–Dawley rats	Anxiolytic and Anti-depressant	Females are susceptible for depression-like and anxiety-like behaviors because of increased vulnerability to GSK-3β activation, which promotes β-catenin diminishing	Hasbi et al. (2020)
	Chronic social defeat stress in c57bl/6 male mice	Anxiolytic and Anti-depressant	β-Catenin overexpression promoted resilience with antidepressant and anxiolytic characters through Dicer1/microRNA regulation	Dias et al. (2014)
	Two conditional transgenic C57BL6/J male mice with inactive or stable β-catenin	Anxiolytic and Anti-depressant	Reduction of β-catenin in hippocampal DG shows definite anxiety and depression-like behavior. While animals with stabilized-catenin displayed anxiolytic-like and anti-depressive-like responses and stress resilience	Vidal et al. (2019)
Depression	Unpredictable chronic mild stress in male Sprague–Dawley rats	Anti-depressant	Depression can diminish β-catenin in the nucleus accumbens and ventromedial prefrontal cortex	Bright & Akirav, (2023)
	Chronic stress-induced depressive-like behavior in male Wistar rats	Anti-depressant	Stress is accompanied by a reduction in hippocampal β-catenin that elicited inflammatory response figuring psychopathological disorders	Habib et al. (2020)
	Chronic unpredictable mild stress-induced depression in male Sprague Dawley	Anti-depressant	Hippocampal β-catenin levels may be considered an indicator of antidepressant effects	Yang et al. (2017)
	Subclinical hypothyroidism model in Sprague–Dawley rats	Anti-depressant	β-Catenin upregulation is a marker for antidepressant effect	Ge et al., (2016)
	Chronic unpredictable mild stress model in male C57BL/6 mice	Anti-depressant	β-catenin may figure out depression through neurogenesis and inflammation control	Dai et al. (2020)
	GSK-3-inhibitor in stressed C57/BL6J male mice	Anti-depressant	Raising β-catenin through GSK-3 inhibition can promote neurogenesis and antidepressant effect	Pérez-Domper et al. 2017)
	Chronic unpredictable mild stress with lipopolysaccharide model in C57BL/6 male rats	Provoke depression	Continuous β-catenin activation can lead to depression	Fan et al. (2022)

(Continues)

TABLE 1 (Continued)

Stress type	Animal model	β-Catenin effect	β-Catenin role	References
	In vivo chronic unpredictable mild stress model in Sprague–Dawley rats and the invitro neuroinflammation model of lipopolysaccharide-induced depression in BV2 cells	Provoke depression	Both in vivo and in vitro activation of β-catenin can result in depression	Du et al. (2024)

inhibited in suicidal cases (Wang & Mao, 2019), and this complies with the notion that Erk1/2 exhibits antidepressant and anxious behavior. Pytka et al. suggested the antidepressant effect of Erk in part following the reduction of both Erk and p-Erk in postmortem tissues of depressed patients beside similar changes in an animal model (Pytka et al., 2018). At the same time, Xiang et al. highlighted the anxiogenic effect of serotonin through phosphorylation of both Erk1 and Erk2 (Xiang et al., 2018). At the cellular level, β-catenin partners with Erk1/2. Under stress conditions, the signaling between Erk1/2 and β-catenin impacts miR-17-92 and miR-203 (Chakraborty et al., 2016). Interestingly, miR17-92 can decrease or increase anxiety however, its increase enhances neurogenesis (Murphy & Singewald, 2019). Hence, β-catenin may be involved in neurogenesis through mastering Erk1/2 and miRNA. Accepting the knowledge of this milieu may open new avenues in advancing the treatment options of psychiatric disorders. β-Catenin signaling is highlighted in Figure 3.

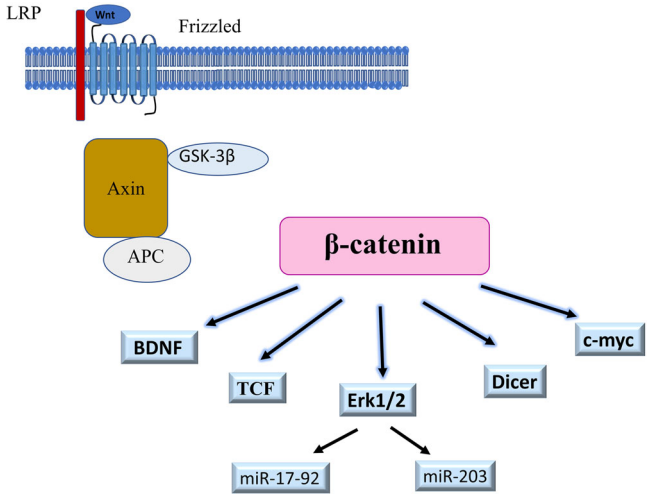

FIGURE 3 Overview of β-catenin signaling. Reduction in the activity of the destructive complex promotes β-catenin signaling where it can figure neurogenesis through its downstream targets. β-catenin can regulate the neurotrophic factor (brain-derived neurotrophic factor [BDNF]), T-cell factor (TCF), c-myc, and dicer-1. In addition, β-catenin can master extracellular signal-regulated kinases 1 and 2 (Erk1/2) activation that influences miR-17-92 and miR-203.

4 | PSYCHOTROPIC DRUGS AND NEUROGENESIS

It has been suggested that β-catenin mediates the effects of various psychotropic drugs, especially antidepressants, anxiolytics, and mood stabilizers (Mishra et al., 2021). Regarding anxiolytics, the benzodiazepine (BDZ) class is one of the most effective anxiolytics. Of note, benzothiazepines like diazepam are GSK-3β allosteric inhibitors that influence β-catenin activity (Shri et al., 2023). The JM-20, a BDZ derivative, protects against neuronal damage and counteracts cognitive and memory impairments by normalizing phosphorylated GSK-3β (Wong-Guerra et al., 2021). Treatment by 2,3-BDZ derivatives, rather than the classical 1,4-BDZ, increases hippocampal proliferation and synaptic transmission, which may improve cognitive performance (Carli et al., 2020). However, the common anxiolytic drug, buspirone, effectively boosts mammalian hippocampal neurogenesis without extensive data on its action on β-catenin signaling (Baptista & Andrade, 2018). Cilostazol is an antiplatelet drug that experimentally showed antidepressant effect by different mechanisms; however, there is no study pointed to its significance in increasing β-catenin levels that mediated neurogenesis and reversed anxious and depressive symptoms in different animal models (Kim et al., 2016). Alijanpour and Rezayof recorded that ketamine can increase hippocampal neuronal activity and boost BDNF, a β-catenin downstream, figuring its anxiogenic character (Alijanpour & Rezayof, 2023). Therefore, β-catenin signaling, particularly its neurogenesis role, is of great importance in the pathophysiology of psychotherapy. In addition, research on this signaling may broaden our understanding of psychopathology and clinical outcomes.

Regarding major depressive disorder (MDD), there is a relationship between neurogenesis and antidepressants, where antidepressants can promote hippocampal neurogenesis to restore normal hippocampal functions (Taniguchi et al., 2021). Moreover, selective serotonin reuptake inhibitors (SSRIs) and lithium may support cellular survival and brain function through modulation of Wnt/β-catenin signaling alongside increasing BDNF signals as neurogenesis markers (Bersani et al., 2015; Liu et al., 2016). In addition, it has been found that citalopram can promote the proliferation and survival of the hippocampal DG, the primary site of neurogenesis (Vega-Rivera et al., 2020). Besides, citalopram can normalize hippocampal GSK-3β and β-catenin in chronically stressed rats to rescue depression (Teo et al., 2019); this may, in part, support the therapeutic value of normalizing β-catenin signaling in mood disorders. Lithium is a Wnt agonist that can boost hippocampal neurogenesis in neurodegenerative diseases

TABLE 2 The role of β-catenin in the action of antidepressant medications.

Drug	Animal model	Conclusion	Reference
Imipramine	Chronic stress in male BALB/c mice	Imipramine produced antidepressant effect via raising β-catenin and diminishing GSK3β	Ni et al. (2018)
Fluoxetine	Chronic unpredictable mild stress in male Sprague–Dawley rats	Fluoxetine ameliorated depression through β-catenin signaling	Zou et al. (2021)
Citalopram	Acute and chronic forced swim stress in male Sprague–Dawley rats	Chronic citalopram normalized phospho-GSK3β and β-catenin levels. GSK3β/β-catenin signaling is crucial in chronic stress-related depression rather than acute one	Chen et al. (2012)
	Chronic forced swim stress in male Sprague–Dawley rats	Citalopram reversed the harmful effects of psychological stress through raising β-catenin signaling	Liu et al. (2012)
Venlafaxine	Chronic venlafaxine in normal adult male albino Wistar rats	Chronic venlafaxine administration doubled β-catenin-induction of astrocyte-like activation in hippocampal stem/progenitor cells, that afterwards activated hippocampal neurogenesis	Mostany et al. (2008)

and acute brain injury (Yang et al., 2015). The clinical outcomes of antidepressants like fluoxetine and venlafaxine were related to increased β-catenin signaling through neurogenesis regulation (Bersani et al., 2015). One of the mood stabilizers commonly used in bipolar depression, valproic acid, promoted hippocampal neurogenesis and regulated hippocampal Wnt/β-catenin signaling in a mouse model of Alzheimer's disease. Valproic acid can activate the inactive form p^{Ser9}-GSK-3β, which increases β-catenin signaling (Zeng et al., 2019). Schoenfeld and Cameron revealed the effectiveness of antidepressants in the proliferation, maturation, and survival of new neurons, while anxiolytics have the same efficacy without involvement in the survival of new neurons (Schoenfeld & Cameron, 2015). There is contrasting information regarding Wnt/β-catenin's role in neuron survival, such as differentiation processes. In addition, continuous activation of β-catenin can result in depression. Fluvoxetine, according to Du et al., can still have an antidepressant effect in chronic mild stress-induced β-catenin activation (Fan et al., 2022). Collectively, this may be inpart highlight the diverse effect of β-catenin in psychopathology and the modulating activity of some antidepressant medications toward β-catenin signaling; facilitating research prospects for targeting β-catenin modulation in psychopathology for better managment (Du et al., 2024). On the other side, combining BDZs with antidepressants like fluoxetine blocks the increase in hippocampal neuron generation and survival when compared with fluoxetine alone in treating depression comorbid with anxiety (Choi & Kim, 2018; Sun et al., 2013). In the cohort study of Jeong et al., from 2002 to 2017 about depressed inpatients and outpatients from the South Korean populations, depressed patients taking an antidepressant combined with BDZs rather than antidepressant monotherapy were associated with an increased risk of all-cause death (Jeong et al., 2020). Chronic administration of benzodiazepines with antidepressants negatively influences the antidepressant effect, where this combination worsens functional status and exhibits poor clinical outcomes. This may be because of interference with neurogenesis and a decline in monoaminergic function and γ-aminobutyric acid (Koren et al., 2024; Lim et al., 2020). Concurrent BDZ treatment at higher doses with ketamine may dampen ketamine's antidepressant effect (Choi & Kim, 2018). BDZs exhibit a minimal effect on ketamine's rapid antidepressant effect; however, sedation was prevalent (Diekamp et al., 2021). Older Asian adults who combined BDZs with antidepressants like SSRIs and tricyclic antidepressants suffered from BDZ side effects (Zhong et al., 2019). In addition, patients should be informed of the increased risk of fractures when using BDZ combinations (Yang et al., 2021).

On the other side, Xhakaza et al. highlighted that combining BDZs with SSRIs rapidly enhances the anxiolytic of SSRIs (Xhakaza et al., 2023). Hence, conventional anxiolytic BDZs may hinder the antidepressant effect of SSRIs because they do not involve new neuron survival, as mentioned by Schoenfeld and Cameron (Schoenfeld & Cameron, 2015). Furthermore, the antidepressant SSRIs may impact a faster anxiolytic effect because they increase neurogenesis by raising both proliferation and differentiation, as mentioned by Schoenfeld and Cameron. The tricyclic antidepressant imipramine can mediate its therapeutic efficacy through raising β-catenin and diminishing GSK3β (Ni et al., 2018). Neurodegenerative diseases are usually accompanied by anxiety and depression. Pramipexole, which is used for treating Parkinson's disease with anxiety or depression, can boost neurogenesis of hippocampal DG (Mishra et al., 2019). This dopaminergic agonist significantly influences β-catenin signaling (Choi et al., 2017), where Wnt/β-catenin signaling showed a pivotal role in the differentiation of dopaminergic neurons in Parkinson's disease (Gao et al., 2021). The role of β-catenin in the action of antidepressant medications is highlighted in Table 2.

5 | CONCLUSION

β-Catenin regulators, alongside their downstream targets, are crucial in the pathophysiology of anxiety and depression through neurogenesis modulation. Reducing or boosting neurogenesis triggers anxiety. However, reduced neurogenesis can only precipitate depression. β-Catenin signaling operates in two distinct ways. A reduction in this signaling can inhibit the neurogenesis process, leading to both anxiety and depression. On the other hand, it can trigger a compensatory

mechanism by increasing factors that stimulate neurogenesis. This can protect against depression, though it may still result in symptoms of anxiety. β-Catenin's compensatory mechanism is part of its dual response. Specifically, the "dual response" of β-catenin refers to its ability to promote or inhibit neurogenesis based on the body's needs. Thus, an individual's vulnerability or resilience to psychopathology might hinge on how effectively β-catenin can switch between these two modes in response to stressors. Finally, this review broadens our understanding of the pathophysiology of anxiety and depression through β-catenin signaling and opens a new horizon toward targeting β-catenin signaling in treatment interventions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable; all information is gathered from published articles.

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How to cite this article: El-Kadi, R. A., AbdelKader, N. F., Zaki, H. F., & Kamel, A. S. (2024). Influence of β-catenin signaling on neurogenesis in neuropsychiatric disorders: Anxiety and depression. *Drug Development Research*, *0*, e22157. https://doi.org/10.1002/ddr.22157