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Signaling Pathways Involved in Antidepressant-Induced Cell Proliferation and Synaptic Plasticity

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Abstract: In the last years it has been proposed that the antidepressant action is mediated not only by changes in monoamine levels but also in association with modifications involving cell proliferation and plasticity in some brain limbic areas as hippocampus, and also frontal cortex and amygdala. This leads to the merging of the classic "monoaminergic hypothesis of depression", with the newer "neurotrophic hypothesis of depression". Here we review two important signaling pathways: the Wnt/β-catenin pathway —implicated in cellular proliferation and synaptic plasticity— that is downregulated in major depression and upregulated after antidepressant treatment; and the mTOR pathway —controling synaptic plasticity— recently related to present disrupted functioning in major depression, and as the target of some drugs with fast-acting potential antidepressant action. These pieces of evidences are confirmed in a variety of animal models of depression and are predictive of antidepressant actions. We also review the role of another two important neurotrophic factors: brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) that mediate the antidepressant effects. All of the above intracellular pathways interact by a crosstalk mediated by Akt, a key regulator molecule that may underlie the fine tuning between proliferative and neuroplasticity changes induced by antidepressant drugs.

Keywords: β-catenin, GSK-3β, mTOR, BDNF, synaptic plasticity, neurogenesis, antidepressant drugs.

INTRODUCTION

The *monoaminergic hypothesis* of major depression was postulated 50 years ago [1], and has been widely accepted until late in the 20th century. However, in the recent years several hypotheses have been proposed on the basis of the existence of brain morphological —neuroplastic— alterations linked to mood disorders. These *hypotheses* associate major depressive disorder (MDD) to increased neuronal atrophy, mainly due to the reduction in synaptic plasticity and alterations in dendritic branching, among other changes [2]. Similar modifications have also been found in some stress-based animal models of depression, in which decreased neurogenesis in the dentate gyrus (DG) of the hippocampus, and reduced synaptic plasticity in hippocampus (Hp) and prefrontal cortex (PFCx) are observed [2-5]. Interestingly, imaging studies show a reduction in hippocampal volume [6-8]. This finding could be related to different alterations, including reduced dendritic branching, decreased neurogenesis and/or gliogenesis, increased apoptosis rate, or loss of brain fluid [9]. Although neurogenesis has been implicated in the pathophysiology of depression, as it is stimulated by antidepressant drugs, its real contribution to the etiology of this disease remains unclear.

Classic antidepressant treatments reverse, at least partially, most of the stress-induced proliferative/plasticity changes [2, 9, 10]. These drugs modulate several intracellular pathways involved in neuroplasticity and cell proliferation: they include neurotrophic factors, such as BDNF [11] and VEGF [12], and other proteins as β-catenin [13, 14] or the mammalian target of rapamycin (mTOR) [15].

Furthermore, most of the studies published to date regarding the implication of neuroproliferation or neuroplasticity in the pathogenesis of depression —or in the responses induced by antidepressant drugs— have been focused on the hippocampus, but proliferative changes associated to the disease are also present in other brain areas, including amygdala and frontal cortex [9, 16, 17].

Here, we will review the recent advances in the knowledge of the involvement of proliferative/plasticity changes on both the etiopathogenesis of depressive disorders and the mediation of the antidepressant effects as well as the different intracellular signaling pathways implicated, focusing especially on Wnt/GSK-3β/β-catenin, BDNF and mTOR.

ROLE OF NEURONAL PROLIFERATION/PLASTICITY IN MOOD DISORDES AND ANTIDEPRESSANT-LIKE EFFECTS

Neurogenesis, the process involving proliferation and differentiation of neuronal precursor cells (NPCs), provides new neurons that may be integrated into the developing and adult brain, supplementing functional networks or replacing dysfunctional neurons [18]. Deficiencies in NPCs have been implicated in the etiology of mood disorders as major depression [19-21], bipolar disorder [22], and schizophrenia [23]. Although there is strong evidence that a variety of therapeutic interventions for these illnesses enhance neurogenesis, little is known about which factors may be involved in the proliferation impairment associated to these psychiatric diseases, and studies have been mainly focused on neurotrophins and proteins as glycogen synthase kinase 3β (GSK-3β).

Cell proliferation in the dentate gyrus is decreased in stress-related animal models of depression including unpredictable stress, chronic administration of corticosterone, olfactory bulbectomy, or maternal deprivation [2-5, 24-26]. In animals, the recovery period for cellular proliferation after acute or chronic stress is 24 h or 3 weeks, respectively [25]. The stress-associated reduction in cell proliferation in humans has also been correlated with a decrease in hippocampal volume [6, 8, 27-30]. Reduction in hippocampal proliferation is also reported in other animal models of disease as dia-

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betic mice, which present a high incidence of depression [31]. In all these models, the reduced hippocampal cell proliferation is reversed by chronic antidepressant treatments [31]. However, although all these changes have been extensively studied, major depression is not generally considered as a "hippocampal disorder". However, it is unlikely that disturbed adult hippocampal neurogenesis alone may fully explain the pathogenesis of major depression. It could only be the most conspicuous feature of a more fundamental type of cellular plasticity, which could also govern the functionality of prefrontal cortex and other brain regions. Indeed, it has been proposed that not only the neuronal proliferation, but also the appearance of changes in synaptic plasticity are involved in the pathogenesis of depressive disorder [2], cellular processes that may also be modulated by antidepressant treatments [32, 33].

The direct or indirect modulation of the serotonergic system leading to increased serotonin (5-HT) levels results in a higher rate of hippocampal cell proliferation, although depletion of serotonin does not lead to an immediate effect over hippocampal cell division [34]. Proliferation in primary cell culture of hippocampal progenitor cells is increased by 5-HT, an effect mediated by different receptor subtypes, including 5-HT_{1A} and $5HT_4$, since it is counteracted by selective antagonists of both $5HT_{1A}$, WAY100635 and $5HT_4$, DAU-6285, receptor subtypes [35] (Fig. **1**). Chronic but not acute treatments with antidepressant drugs that increase brain 5-HT levels, such as tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), serotonin selective reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) (Fig. **2**), and 5-HT_4 agonists, result in increased hippocampal progenitor proliferation [2, 3, 14, 36-43]. Lithium, which stabilizes the serotonergic neurotransmission [44], also increases hippocampal cell proliferation [45], and combined with antidepressants such as desipramine, produces an augmentation in both, hippocampal cellular proliferation and antidepressant-like behavior in animal models of treatment-resistant depression [46]. Other non-pharmacological interventions acting on serotonergic neurotransmission, such as electroconvulsive shock (ECS) therapy [36, 47], silencing of the serotonin transporter (SERT) in dorsal raphe serotonergic neurons by siRNA [48], environmental enrichment [49, 50] or exercise [51, 52] are able to increase hippocampal cell proliferation, resulting in an improvement in spatial memory tasks. These strategies induce their antidepressant actions targeting different progenitor cell populations. Chronic administration of the SSRI fluoxetine [53] and subchronic treatment with the 5-HT_4 agonist RS 67333 [42] increase cell proliferation and neurogenesis through the division of amplifying neural progenitors (ANPs). In contrast, chronic ECS produces a fast-acting effect targeting both quiescent neural progenitors (QNPs) and

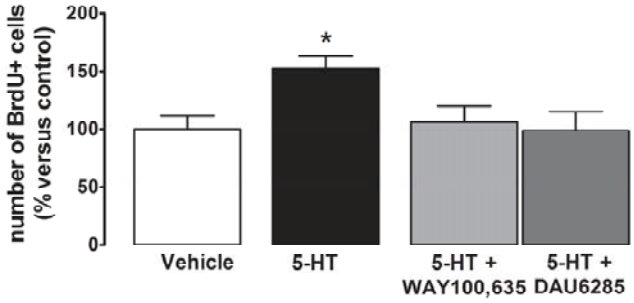

Fig. (1). Serotonin-induced cell proliferation is dependent on $5HT_{1A}$ and $5HT_4$ receptors in primary cell culture of hippocampal progenitors. Neural progenitors (5000 cells/well) were incubated with BrdU, and treated with different drugs for 72 hours: 1 μM serotonin (5-HT), and 5-HT in the presence of 10 μM of the 5 HT_{1A} receptor antagonist WAY100,635 and 10 μM of the 5 HT_4 receptor antagonist DAU6285, respectively. BrdU was labeled using a monoclonal mouse anti-BrdU antibody. Results are Mean±S.E.M. *p<0,05. (Adapted from [35]).

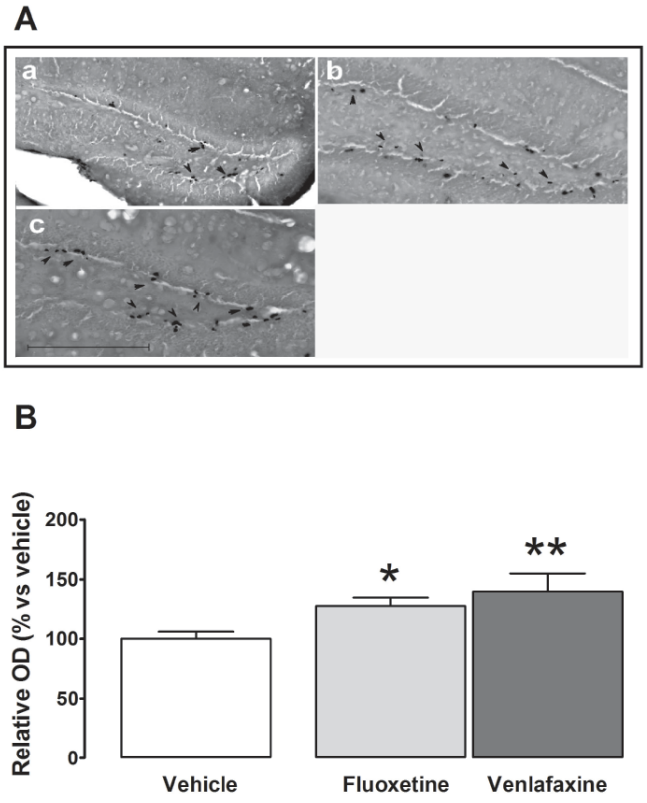

Fig. (2). Representative images showing BrdU immunolabelling in the subgranular zone (SGZ) of the hippocampus (**A**) in vehicle (**a**), and chronic antidepressant treatment with 10 mg/kg/day fluoxetine for 14 days (**b**), and 40 mg/kg/day venlafaxine for 14 days (**c**). BrdU cells were labeled using DAB as a chromogen, and cresyl violet was used for counter-staining. (**B**) The number of BrdU cells in the SGZ is significantly increased after these treatments. The results are the Mean±S.E.M. *p<0.05; **p<0.01. Bar: 200μM. (Adapted from [14]).

ANPs [54]. It has been suggested that the reduced delay in the onset of action of ECS *versus* activation of 5-HT_4 receptor subtype or blockade of serotonin transporter, could depend on the timing of the modulation of the VEGF [55].

The antidepressant-like effect of these drugs is linked to increased hippocampal progenitor proliferation [4, 42, 56-59], dendritic arborization, maturation and functional integration of newborn neurons [60]. The involvement of hippocampal cell proliferation in the antidepressant-like responses has been confirmed by disrupting proliferation by irradiation [56]. However, other drugs with potential antidepressant action do not mediate their effects through the activation of progenitor cells division, since the complete elimination of hippocampal cellular proliferation by direct irradiation of this structure does not block the antidepressant response promoted by drugs acting on other neurotransmitter systems, e.g., corticotrophin releasing factor receptor (CRF) or arginine vasopressin 1b (V1b) receptor antagonists [61], among others.

Other not antidepressant catecholamine re-uptake inhibitors as cocaine [62] decreases the rate of proliferation of neural progenitor cells in the DG [63, 64], without altering their rate of survival [64]. Cocaine effect on cell proliferation has been attributed to augment dopamine function [65], but the involvement of other transmitters cannot be excluded, as the activation of the hypothalamic-pituitary-adrenal (HPA) axis [66]. However cocaine-induced increases in serotonin level seem unlikely to be attributable to the observed decrease in cells proliferation.

As observed in hippocampus, a reduction in cell proliferation in the medial frontal cortex is also present in animal models of chronic stress [67], associated to a reduction of the number and length of spines [68], apical dendrites of the pyramidal cells [69, 70] and downregulation of genes implicated in cell proliferation, cell growth and survival, and apoptosis inhibition [71]. The increase in extracellular glutamate, or the reduced ability to eliminate that excess, could be one of the reasons underlying the molecular changes associated with stress [72]. Chronic administration of antidepressants leads to an increased cell proliferation in prefrontal cortex [57, 67], although the fate of the new generated cells is toward the formation of glia rather than neurons, in contrast to hippocampus [67]. It is noteworthy that, while frontal cortex and hippocampus volume is reduced and these structures are hypofunctional in major depression, structures such as amygdala present hypertrophy, hyperactivity and increased synaptic plasticity which enhances amygdala-dependent fear learning in association with chronic stress [72, 73]. This amygdalar hyperactivity also results in increased neuronal proliferation and dendrite length in animal models of stress [74].

There are no data available on the effects of antidepressants on amygdalar proliferation; however, this structure is involved in the negative control of the hippocampal cell survival. Increased cell survival is observed in hippocampus after the lesion of the basolateral complex of the amygdala [75]. It is interesting to note that the amygdala shows enhanced long term potentiation (LTP) after stress situations that is not reverted by antidepressants. Thus, antidepressants as tianeptine are able to restore the normal functionality of Hp and PFCx under stress situations, while the amygdala retains the ability to increase its activity in the same stress conditions [76].

SIGNALING PATHWAYS IMPLICATED

1. WNT/β-CATENIN PATHWAY

The Wnt/β-catenin pathway corresponds to the first described Wingless/Armadillo pathway in *Drosophila* [77]. Two main roles have been proposed for this signaling pathway: in cancer, promoting the "oncogenic Wnt signaling" [78], and in neurodevelopment [79]. Studies in the past decade have implicated Wnt signaling in a wide range of physiological and pathophysiological processes through the control of gene expression, including cell proliferation (as a transcriptional transactivator) and differentiation (essential in its cell-adhesion function) of neural stem cells (NSC) during neural development [80], cell resilience and survival, cell behavior, cell adhesion and cell polarity [81], neural differentiation [82], hippocampal formation [83], dendritic morphogenesis [84], axon guidance [85] and synapse formation [86]. These changes highlight the implication of Wnt/β-catenin pathway in cellular processes as long term potentiation phenomena [87], and spatial learning, cognition and memory [88].

The *canonical* Wnt signaling pathway (dependent of β-catenin), begins with the binding of Wnt proteins to the Frizzled (F_z) receptors and the low density lipoprotein receptor-related protein (LRP5/6) co-receptors. Frizzled receptor recruits and phosphorylates the cytoplasmic protein Dishevelled (Dvl) and together with the LRP5/6 co-receptor forms the LRP-associated Wnt signalosome [89]. Dvl binds to the destruction complex Axin/APC/GSK-3β, facilitating the phosphorylation of LRP5/6 by CK1, that converts Wnt signalosome into a functional state and that leads to the inhibition of GSK-3β activity [90]. GSK-3β phosphorylates β-catenin in the amine-terminus end (Nt), labeling it for degradation. Thus, the inhibition of GSK-3β blocks the degradation of β-catenin, enabling β-catenin accumulation in the cytoplasm and its subsequent translocation to the nucleus. Once in the nucleus, β-catenin induces the transcription of specific genes by binding to the T-cell factor/lymphoid enhancer factor (TCF/Lef) family of transcription factors [91, 92]. In the absence of β-catenin, TCF/Lef transcription factors are bound to Groucho, a protein producing repressive effects [93]. However, when β-catenin is translocated to the nucleus, it displaces Groucho, allowing the binding of the histone acetylase cyclic AMP response element-binding protein (CREB) that activates the transcription machinery [93, 94].

1.1. GSK-3β

GSK-3 (Glycogen synthase kinase) is a serine/threonine kinase identified in 1980 by Embi [95]. There are two GSK-3 isoforms expressed in mammals, α (51 kDa) and β (47 kDa), which are encoded by different genes known as *gsk3α* and *gsk3β*. Both isoforms are ubiquitously expressed and functionally redundant in some signaling pathways, including Wnt/β-catenin signaling pathways, but these isoforms perform different functions in others [96]. These kinases are constitutively active and can be inactivated through the phosphorylation of single serine residues [97].

GSK-3β is one of the most important negative modulators of Wnt signaling, and together with β-catenin, it phosphorylates many transcription factors [98], nuclear factor of activated T-cells (NFAT) [99], neurogenin 2 [100], Smad1 [101], and c-Jun [102], all of which play important roles in the regulation of gene expression, neuronal plasticity, and cell survival [103]. GSK-3β also produces the inhibition of cAMP response element-binding protein (CREB) mediated by its phosphorylation on Ser129, acting negatively on the CREB DNA binding activity [104]. In addition to gene expression, GSK-3β is implicated in cell morphogenesis through regulation of several microtubule-associated proteins (MAPs) activity [105].

1.1.1. GSK-3β Regulation

The activity of GSK-3β is regulated by the phosphorylation status of both serine and tyrosine residues. The activity is decreased by the phosphorylation of Ser9 and increased by the phosphorylation of Tyr216.

The regulation of GSK-3β by elements within the Wnt/β-catenin pathway acts mainly through two different mechanisms. One is the direct inhibition model in which LRP5/6 inhibits GSK-3β via protein-protein interaction sequestering GSK-3β away from its substrate without affecting the kinase activity *per se* [106]. The other important regulatory mechanism is the Wnt-mediated GSK-3β inhibition leading to Axin destabilization and degradation, and resulting in β-catenin stabilization [106]. Furthermore, recent advances indicate that GSK-3β also plays a positive role in Wnt signal transduction by phosphorylating the Wnt LRP5/6 receptor [107]. GSK-3β activity is also regulated by Akt, which is activated by different molecules such as PI3K and G proteins, producing the inactivation of GSK-3β by phosphorylation of the serine residue S9 in GSK-3β and S21 in GSK-3α both present in the Nt domain [108]. The role of Akt as a "crossroad" interconnecting different signaling pathways will be discussed below.

Even little is known about the consequences of phosphorylation in tyrosine residues, it might not play a direct role in the regulation of GSK-3β activity. Tyr216 phosphorylation has been reported to stimulate nuclear translocation of GSK-3β that could be involved in the regulation of cell cycle progression [109].

1.1.2. GSK-3β Role in Cell Proliferation and Plasticity

GSK-3β signaling is essential for the coordination of progenitor proliferation and differentiation during brain development [79, 107, 110]. Deletion of GSK-3β markedly enhances the proliferation of progenitor cells but suppresses neuronal differentiation, indicating that spatiotemporal regulation of GSK-3β activity is required for appropriate transition from the proliferative to the neurogenic phase during brain development [79]. Instead, GSK-3β knockin mice show decreased cell proliferation in the subgranular zone of the dentate gyrus, together with a reduction in VEGF, but not BDNF [111]. Additionally, GSK-3β regulates the stability of a wide range of proteins via activation of the ubiquitin-proteasome system [112]. Thus, GSK-3β might regulate neurogenesis by controlling the levels of transcriptional regulators involved in neurogenesis such as β-

catenin in the Wnt pathway [112], Gli in the Shh pathway [112-114], and c-Myc in the FGF [115] and Notch [116] signaling pathways. Furthermore, inhibition of GSK-3β reinforces NPCs survival from apoptotic conditions [117], neutralizing the apoptotic elimination of NPCs and allowing them to mature and differentiate [118]. Independent studies showed that activation of GSK-3β inhibits the development of LTP [119], whereas its inhibition prevents the development of long-term depression (LTD) in rat hippocampal slices [120, 121].

1.1.3. GSK-3β in Mood Disorders

Recent studies indicate the presence of reduced levels of phosphorylated GSK-3β protein associated with animal models of depression [122] (Fig. **3A**; Table **1**). Genetic studies suggest a role for GSK-3β in psychiatric disorders. The presence of a single nucleotide polymorphism (SNP) on the GSK-3β promoter region (-50T/C; rs334558), C allele has been associated with either reduced GSK-3β activity [123], improved antidepressant response [124, 125], and lower illness recurrences [126]. GSK-3β SNPs rs6438552 and rs12630592 have also been associated to altered structural and behavioural patterns in depressed patients [127]; and the haplotype containing three SNPs (rs334555, rs119258668 and rs11927974) has been associated with an onset of the disorder at early ages [124, 125, 128, 129].

1.1.4. GSK-3β and Antidepressant Effects

Currently, upstream regulators of GSK-3β in the Wnt and frizzled receptor signaling system have been also implicated in the actions of antidepressants. Chronic but not acute antidepressant treatment, including SSRIs, SNRIs, and electroconvulsive shock therapy, increase Wnt2 and Wnt3a expression in the hippocampus, resulting in an increased GSK-3β phosphorylation [122, 130] (Fig. **3B**). Moreover, viral expression of Wnt2 in the hippocampus produces an antidepressant response [131]. Other Wnt-Fz proteins, including Wnt7b, Fz9, FzB, and Dvl, as well as transcription factor-15 (Tcf15), TcfL1, and Lymphoid enhancer-binding factor 1 (Lef1), are differentially regulated by antidepressants [131].

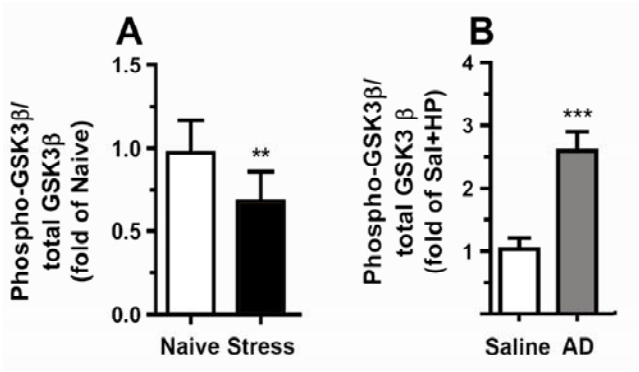

Fig (3). GSK-3β phosphorylation changes associated to depression models and antidepressant treatments. Decreased GSK-3β phosphorylation (inactive) in stress models (FST for 14 consecutive days) (**A**), indicating the inhibition of Wnt/β-catenin pathway. (**B**) Increased GSK-3β phosphorylation after chronic treatment with citalopram (15 mg/kg/day; 14 days) (**B**) that results in a increase in β-catenin. Results are the Mean±S.E.M. ** p<0,01; *** p<0,001. (Modified from [122] with permission).

The inhibition of GSK-3β activity either pharmacologically by lithium [94], the peptide L803-mts [132], or AR-A014418 [133], or deleting GSK-3β in mouse forebrain [134], results in increased brain β-catenin levels, accompanied with antidepressant-like or anxiolytic behavior [94, 132, 133, 135, 136]. The inhibition of GSK-3β is also required for a correct activation of CREB, which can be enhanced by the administration of lithium [104]. The region-specific suppression of GSK-3β activity has shown that regulation of anxiety and sociability is related to GSK-3β activity in forebrain, while GSK-3β in subcortical areas such as hippocampus and striatum could be involved in social preference and resilience [134, 137] (Table **2**).

1.2. β-catenin

β-catenin plays a pivotal role in the regulation of morphogenesis towards adhesion or proliferation [137]. The regulation of β-catenin might be tight as it plays two important roles: a *structural* role at the membrane level and a *regulatory* role in cytoplasm and nucleus [138].

β-catenin protein consists of 781 aminoacids in human, presenting a central rigid part formed by 12 imperfect Armadillo repeats, two flexible Nt- and Ct-domains, and a helix with a conserved sequence (Helix-C) in the N-part of the Ct domain, which is necessary for the signaling role of β-catenin, but not to bind to the structural one [139]. The different proteins that interact with β-catenin ―cadherins, TCF/Lef transcription factors, or APC―, bind between Armadillo repeats R3-R9, in a mutual exclusive way [140]. The differential binding of β-catenin to diverse targets is determined by the protein conformation [141]: 1) the activation of Wnt pathway generates a "closed" β-catenin protein (with a folded Ct) that interacts with TCF transcription factors in the nucleus; 2) the dimerization of an "open" β-catenin and α-catenin favors the binding to cadherins in the membrane [142]; 3) the "open" β-catenin as a monomer, can both interact with cadherins or transcription factors; 4) the Nt phosphorylated β-catenin generated by the "degradation complex" (APC/Axin/GSK-3β/CK1) is degraded in the proteasome [141]. It has also been described an inactive form of β-catenin that may appear due to the binding of this protein to an small polypeptide named ICAT, that blocks the binding of β-catenin to either cadherins or TCF [143].

1.2.1. β-catenin: Role in Cell Signaling

β-catenin is accumulated in the cytoplasm and translocates to the nucleus. Although this protein lacks of any nuclear localization signal (NLS) or nuclear export signal (NES) in its sequence, β-catenin presents different mechanisms to translocate to the nucleus. One of them is the interaction of β-catenin with nuclear pore complexes (NPCs) that mediate β-catenin nuclear import and export [144].

Wnt/GSK-3β/β-catenin signaling pathway is a key regulator of adult neurogenesis in hippocampus [145, 146], or subventricular zone [147], highlighting the role of GSK-3β on neural progenitor homeostasis (see below). Wnt proteins are released from hippocampal neural stem cells (NSC) and astrocytes, acting autocrinaly to regulate proliferation via Wnt canonical pathway [145, 146].

When Wnt is not activating its signaling pathway, the free form of β-catenin in the cytoplasm has a short life, binding immediately to the scaffold proteins Axin/APC present in the "destruction complex", where it is phosphorylated for subsequent degradation [148]. Here, β-catenin is labeled for destruction by the ubiquitin-proteasome system [98]: GSK-3β phosphorylates β-catenin in Ser33, Ser37 and Tyr41, while CK1α phosphorylates Ser 45, being all these residues present in the N-terminus [140, 149, 150]. GSK-3β is only able to phosphorylate β-catenin if associated to the Axin/APC complex [106, 151]. Phosphorylated β-catenin is released from the "destruction complex", recognized by β-TrCP present in the ubiquitin machinery, and bound to the Skp1/Cul1/F-box/b-TrCP (SCFb-TrCP) E3 ubiquitin ligase complex, where β-catenin is degraded by the 26S proteasome [152].

As previously mentioned, the activation of the Wnt pathway by the binding of Wnt proteins to Frizzled receptors and LRP5/6 co-receptors, produce the inhibition of the "destruction complex" [140].

Table 1. Involvement of Wnt/β-catenin and mTOR signaling pathways in depression-like behavior and MDD.

		STRESS MODEL	DURATION	STRUCT.	PROLIF.	Wnt / β-catenin	TROPHIC FACTORS	AUTHORS
DEPRESSION-LIKE PHENOTYPE	ANIMAL	CUS	Chronic	Hp	↓ BrdU	↓ p-GSK-3β / ↓ β-catenin		[122]
		CUS	Chronic	Hp	↓ BrdU			[59]
		Dexametasone 10μM	20 min	Hp progenitor cells		↓ β-catenin / ↓ p-GSK-3β Ser9 / ↑ p-GSK-3β Ser216		
		CMS	Chronic	Hp	↓ BrdU	↓ dendritic length	↓ BDNF	[74]
		Chronic stress	Chronic	Hp	↓ BrdU	↑ Dkk1 / ↓ dendritic length / ↓ DCX		[179]
		Corticosterone	24 h	Hp (organotypic culture)		↑ Dkk1		
						mTOR		
		CUS	Chronic	Amyg		↓ p-mTOR / ↓ p-p70S6K / ↓ p-S6 / ↓ ERK1/2 / ↓ Akt1 / ↓ p-GluR1		[210]
		Chronic corticosterone	7-8 weeks	PFCx		↓ p-mTOR / ↓p-Akt1	↑ VEGF / ↓ Flk1	[209]
		Corticosterone	48-72 h					
		Neonatal clomipramine (CL)-treatment	14 days	FCx and Hp		↓ PLD1 / = mTOR / ↓ p-SK6		[297]
		GENETIC MODEL	**PHENOTYPE**	**STRUCT.**	**PROLIF.**	**Wnt / β-catenin**		**AUTHORS**
		β-catenin KO	Depression-like	Forebrain		↓ β-catenin		[174]
		β-catenin KO	Depression-like	Hp newborn cells		↓ β-catenin / ↓ dendritic length		[300]
		DISEASE		**STRUCT.**	**PROLIF.**	**Wnt / β-catenin**		**AUTHORS**
	HUMAN	MDD and MDD + suicide		PFCx		↓ p-GSK-3β / ↓ β-catenin		[169]
		MDD		PFCx		↓ mTOR / ↓ p70S6K / ↓ eIF4B / ↓ p-eIF4B		[208]
		MDD				No changes in p-GSK-3β / β-catenin / Dvl		[298]
		Schizophrenia subjects						
		Schizophrenia subjects		PFCx			↓ Flk1	[209]

CUS: chronic unpredictable stress; CMS: chronic mild stress; Hp: hippocampus; PFCx: prefrontal cortex; BrdU: 5-bromo-2'-deoxyuridine; STRUCT.: brain structure; PROLIF.: proliferation; PLD1: phospholipase D1.

1.2.2. β-catenin: Role in Cell Adhesion

β-catenin is also associated to the membrane compartment by the binding to cadherins, cell-adhesion proteins [153]. Cadherins are Ca^{2+}-dependent homophilic adhesion molecules, important in cell recognition and cell sorting during development [153].

Cadherins form a complex with cytoplasmic plaque proteins, binding to α- and β-catenin. α-catenin is also linked to both β-catenin and actin cytoskeleton [153]. However, the fact that β-catenin shows low and dispensable cell adhesion activity due to growth factors-mediated phosphorylation in tyrosine residues, suggests a regulatory role of β-catenin and not only a structural one [153].

As indicated previously, the "open" conformation of β-catenin binds to α-catenin forming heterodimers [143], that bind to cadherins [142]. The binding of the N-cadherin/β-catenin complex is highly dynamic; although the cadherins have great affinity for β-catenin and captures this molecule from the cytoplasm to the membrane [154], β-catenin can also be released from the cell-adhesion complex, favoring its role as a cell signaling molecule in the Wnt pathway, targeting genes as cyclinD1 and c-myc [155].

The N-cadherin/β-catenin complex is localized in synaptic junctions forming molecular complexes with synaptic markers as synaptophysin, and presenting a symmetrical distribution mediated by the binding of catenins to molecules with homophilic binding activity [156]. However, the localization of cadherin/β-catenin

Table 2. Changes in Wnt/β-catenin and mTOR signaling pathways associated to antidepressant treatments.

		DRUG TARGET	DURATION OF TREATMENT	STRUCT.	PROLIF.	SECONDARY MESSENGERS	TROPHIC FACTORS	AUTHORS
ANTIDEPRESSANT EFFECT	Wnt/β-catenin	5-HT_4 agonist	3 or 7 days	Hp	↑ BrdU	↑ Akt / ↑ β-catenin	↑ BNDF / ↑ VEGF	[39, 40, 42]
		Venlafaxine	14 / 21 days	Hp	↑ BrdU	↑ Wnt2 / ↑ p-GSK-3β / ↑ β-catenin / ↑ Akt / ↑ ERK / ↑ NeuroD1		[14, 131]
		Fluoxetine	21 days	Hp		↑ Wnt2 / ↑ Akt / ↑ NeuroD1 / ↑ p-GSK-3β		[131]
		Leptin	14 days	Hp	↑ BrdU			[59]
			20 min	Hp progenitor cells		↑ β-catenin / ↑ p-GSK-3β Ser9 / ↓ p-GSK-3β Ser216		
		Citalopram	14 / 21 days	Hp		↑ Wnt2 / ↑ p-GSK-3β / ↑ β-catenin / ↑ NeuroD1		[122, 131]
		Lithium	48 h	Hp primary cell culture	↑ BrdU			[181]
		Lithium + desipramine	21 days	Hp	↑ BrdU	No changes in p-GSK-3α and p-GSK-3β	↓ BDNF	[46]
		Fluoxetine + ketanserin	7 days	Hp		↑ β-catenin / ↑ N-cadherin	↑ BNDF	[187]
		Clozapine / Haloperidol	14 days			↑ p-GSK-3β / ↑ β-catenin / ↑ Akt		[130]
		Lithium / Valproic acid	30 days	PFCx		↑ p-GSK-3β / ↑ Akt		
		Fluoxetine / Imipramine	14 days			↑ p-GSK-3β / ↑ Akt		
		GENETIC MODEL	**PHENOTYPE**					
		β-catenin overexpression	Antidepressant-like	Brain		↑ β-catenin		[189]
		Constitutively active β-catenin		Hp primary cell culture	↑ BrdU			[181]
		DRUG TARGET	**DURATION OF TREATMENT**	**STRUCT.**	**PROLIF.**	**SECONDARY MESSENGERS**	**TROPHIC FACTORS**	**AUTHORS**
	mTOR	NMDA antagonist (ketamine)	Acute	PFCx		↑ p-mTOR / ↑ p-4E-BP1 / ↑ p-p70S6K / ↑ pAkt / ↑ p-ERK		[15]
						↑ synapsin / ↑ PSD-95 / ↑ GluR1		
		ECS	10 days	PFCx			↑ VEGF	[216]
				Hp			↑ VEGF-R	
		mGlu2/3 receptor antagonists	24 h					[214]

Hp: hippocampus; PFCx: prefrontal cortex; BrdU: 5-bromo-2'-deoxyuridine; STRUCT.: brain structure; PROLIF.: proliferation.

within the synapse is not in the neurotransmitter release zone [156], but close, playing an important role in the recruitment of synaptic vesicles to the synapses [86, 157]. Within the complex, β-catenin presents a great relevance in the synaptic vesicle distribution acting as a scaffold protein. This observation has been proven by the elimination of β-catenin that results in a decreased number of synaptic vesicles [86], together with a blunted distribution of synaptic vesicles in the synapses that leads to an impaired response to repeated stimulation [86, 158]. β-catenin is also associated via its PDZ-binding domain to other proteins as *scribble*, acting in the regulation of synaptic vesicle turnover. This protein has been suggested as a downstream regulator of the role of β-catenin in synaptic vesicles [159].

The role of β-catenin when present in the membrane is associated with increased synaptic plasticity in processes of learning and memory in the adult brain, and with the consolidation, but not acquisition of fear conditioning memories that are coded in amygdala [160].

β-catenin can be phosphorylated in the Tyr142 residue, reducing its affinity for α-catenin, and displacing β-catenin from the cell-adhesion role to the signaling one [142, 161]. The phosphorylation of β-catenin in Tyr654 produces a conformational change in β-catenin that allows the access of other kinases such as the protein kinase A (PKA) that phosphorylates Ser 675 [162, 163], favoring the binding of β-catenin to CREB binding protein (CBP) or TATA binding protein (TBP) [163, 164]. The implication of the pattern of β-catenin phosphorylation in the differentiation process of hippocampal precursor cells and antidepressant-induced neurogenesis is unknown.

When active in the absence of Wnt signaling, GSK-3β and the casein kinase 2 (CK2), phosphorylates the cytoplasmic domain of cadherin on three serine residues, which confers cadherin a greater affinity for the binding to β-catenin [165, 166], although other authors report a reduced affinity for β-catenin [167, 168].

1.2.3. β-catenin in Mood Disorders

Different neurotransmitter systems (serotonergic, dopaminergic, glutamatergic) modulate GSK-3β activity and, therefore, the activity of the whole Wnt/β-catenin pathway [103]. Changes in GSK-3β and β-catenin are present in different neuropsychiatric and neurodegenerative diseases characterized by impaired neurotransmission. In major depression, GSK-3β activity is increased [122], while β-catenin levels are decreased in postmortem human prefrontal cortex samples from depressed subjects (Fig. **4C**), and teenage suicide victims [169]. The suicidal condition does not modify β-catenin expression in major depression [169].

A decrease in β-catenin expression has been reported in animal models of depression [170-172] (Table 1) and in the hippocampus [122] and medial prefrontal cortex (mPFCx) [173] of animals subjected to chronic stress models. Conversely, β-catenin knockout mice with 50-70% decrease of β-catenin expression in forebrain regions, present increased immobility time in the tail suspension test indicating a depression-like state [174]. In contrast, other animal models of depression, such as mild traumatic brain injury (mTBI), show an unexpected inactivation of GSK-3β by upstream PKB and subsequent increase in hippocampal β-catenin levels [175]. This GSK-3β inhibition mediated by PKB activation is associated with anti-apoptotic and neuroprotective actions [175], due to the activation of signaling pathways related to cell survival, and the expression of neurotrophic and angiogenic factors, antiapoptotic proteins as Bcl-2, etc. [176]. Inhibition of GSK-3β by L803-mts reverts the depression-like behavior in these animals, further increasing β-catenin expression [175]. The activation of the Wnt/β-catenin pathway is also related to pro-survival signals which may underlie this response [33, 177]. Moreover, GSK-3β knockin mice display both high levels of brain β-catenin and increased susceptibility to stress-induced depressive-like behavior [178].

Tissue cultures of neural precursor cells derived from dentate gyrus of adult rat treated with dexamethasone (DEX), a glucocorticoid receptor (GR) agonist, show a reduced cell proliferation that correlates with a reduction in nuclear β-catenin and mRNA expression of cyclin D1 [171]. This result suggest that GRs mediate reduction in cell proliferation associated to stress models, acting through the Wnt/β-catenin pathway, decreasing GSK-3β phosphorylation, and thus, promoting its active state, that results in a reduced translocation of β-catenin to the nucleus [59]. Otherwise, inhibition of Wnt signaling pathway in animals subjected to chronic stress, or after the administration of corticosterone to organotypic cultures, can be mediated by the increase of the Wnt/β-catenin inhibitor Dickkopf-1 (Dkk-1) [179]. Dkk-1 is a peptide that binds to LRP5/6 and to the transmembrane proteins Kremen-1 and -2, forming a ternary complex that is internalized, blocking the Wnt/β-catenin signaling cascade [180].

1.2.4. β-catenin: Role in the Antidepressant Effect

In the last decade, the involvement of Wnt/β-catenin pathway as a molecular target for antidepressant effects has been proposed [13]. Several antidepressant treatments increase β-catenin protein and mRNA in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus, as observed for ECS [13], chronic antidepressant drug treatment [14, 42], or mood stabilizers as lithium [181] (Table 2). The antidepressant-like effect seems to be mediated by the direct or indirect inhibition of GSK-3β [13, 132, 133, 171, 172, 182-186].

Chronic treatment with drugs such as citalopram [122], fluoxetine, and venlafaxine [14] (Fig. **4A**), as well as subchronic treatment with the 5-HT_4 agonist RS67333 [42], increase β-catenin expression in the hippocampus. The hippocampal increase of β-catenin occurs mainly in the dentate gyrus of the hippocampus [42], and in both, the membrane and nuclear fractions (Fig. **4B**) [13, 14]. The increase in β-catenin in hippocampus, which correlates with the activation of the canonical Wnt/β-catenin pathway, is associated to an increase in hippocampal cell proliferation after antidepressant treatment [14, 42, 59]. The newborn cells colocalize with positive β-catenin immunolabeling in cell clusters in the SGZ of the dentate gyrus of the hippocampus [13, 14, 42]. This β-catenin immunolabeling is present in ANPs and neuroblasts type 1 (NB1) [42], cell populations that are also increased following antidepressant treatments [42, 53].

Other pharmacological manipulations with an antidepressant-like effect, such as subchronic administration of SSRIs combined with 5-HT_{2A} antagonists, increase hippocampal β-catenin expression levels in the membrane subcellular fraction, but not in the nuclear one (Fig. **4B**), suggesting a reduction in hippocampal cell proliferation [187]. These changes appear in parallel to increased N-cadherin levels instead, indicating a greater involvement of β-catenin in its cell-adhesion role enhancing synaptic plasticity, than in the cell proliferation role [187].

In other brain areas (prefrontal cortex, striatum), chronic treatment with antidepressant drugs such as the tryciclic antidepressant imipramine, or the SSRI fluoxetine, do not lead to changes in β-catenin expression, in contrast to antipsychotics [130] that increases or cocaine that decrease [188] β-catenin expression in these areas. If a region-specific increase in the level of β-catenin mediated by catecholamines is involved in the antidepressant effect has to be clarified in the near future. Transgenic mice over-expressing β-catenin in different brain areas as cerebellum, prefrontal cortex, hippocampus and striatum demonstrated mood stabilizer-like effects similar to those observed following the administration of lithium [189].

Although GSK-3β and β-catenin are the most relevant components of this pathway, other proteins as Dvl are also important. Thus the inhibition of Dvl, suppresses the antidepressant-like response promoted by some antidepressant drugs [122].

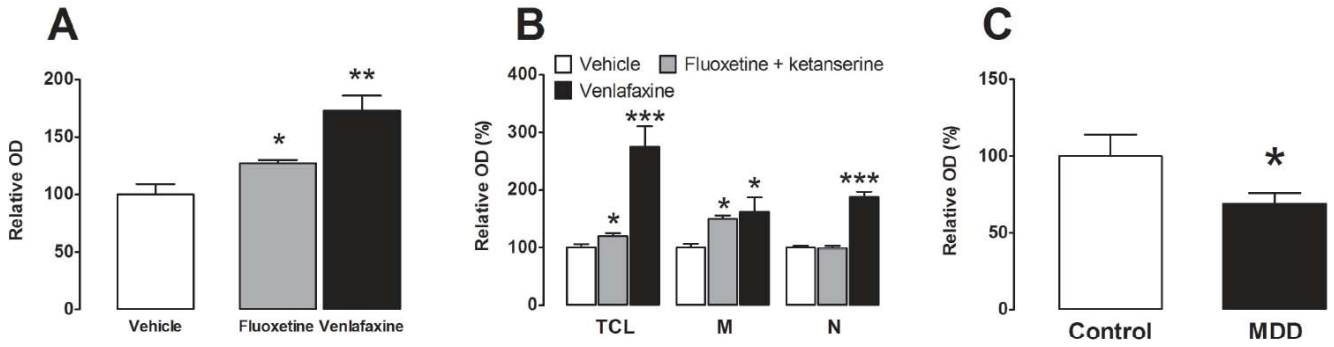

Fig. (4). Increased β-catenin expression in rat hippocampus (**A**) from animals treated with 10 mg/kg/day of fluoxetine, and 40 mg/kg /day of venlafaxine for 14 days. The subcellular distribution of β-catenin depends on the antidepressant treatment (**B**); chronic treatment with the SNRI venlafaxine produces an increase in membrane and nuclear β-catenin, while for the subchronic treatment with the SSRI fluoxetine coadministered with the 5-HT_{2A} antagonist ketanserine, the increase of β-catenin is produced only in the membrane fraction. β-catenin is reduced in postmortem human prefrontal cortex (PFCx) diagnosed of MDD. Human brain samples were obtained from the Brain Bank Platform, CIBERSAM. (C). Protein levels were measured in Western blots, and the densitometric measurement levels were normalized to GAPDH protein amounts. Results are Mean±S.E.M. *p < 0.05, **p < 0.01 and ***p<0.001 *vs* control group. (Modified from [14, 288]).

2. mTOR PATHWAY

Target of rapamycin (TOR) genes are members of the phosphoinositol kinase-related kinase (PIKK) family of kinases [190]. They were first described in yeast as the pharmacological targets of the microbicide rapamycin [191], and subsequently described in other invertebrate and vertebrate organisms. mTOR, the mammalian form of this protein, exists in two different functional multiprotein complexes within the cells, mTORC1 and mTORC2, which are evolutionarily conserved from yeast to mammals [192]. mTORC1, the primary target of rapamycin, is involved in cell proliferation, cell growth and survival by protein translation, energy regulation, and autophagy in response to growth factors, mitogens, nutrients and stress [193, 194]. mTORC2 is involved in cytoskeletal remodeling [195] and in the regulation of cell survival and cell cycle progression. mTORC2 may signal through protein kinase C and Akt signaling pathway involving Rho GTPase [196].

In neurons, mTORC1 activity is regulated by phosphorylation in response to growth factors, such as BDNF, mitogens, hormones and neurotransmitters through activation of G protein-coupled receptors (GPCRs) or ionotropic receptors. The mTORC1 phosphorylation is mediated by different proteins: ERK/MAPK (Extracellular signal-Regulated Kinases/Mitogen-Activated Protein Kinases), PI3K (Phosphatidylinositide 3-kinase), PKA (Protein Kinase A), and EPAC (Exchange Proteins Activated by cAMP). This wide variety of regulation mechanisms shows the importance of mTOR as a convergence point in cell signaling [197]. The activation of mTORC1 results in the phosphorylation and activation of several downstream targets as the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and the inhibition of the eukaryotic elongation factor 2 kinase (eEF2) [198]. Akt can also activate mTOR pathway mediating the phosphorylation of mTOR [199].

mTOR has been extensively studied regarding its role in cancer, development, metabolism and more recently, also in central nervous system (CNS) [198, 200, 201]. mTOR and its downstream signaling pathway are involved in synaptic plasticity, memory retention, neuroendocrine regulation associated with food intake and puberty, and modulation of neuronal repair following injury. The target proteins of mTOR, 4E-BP1 and eukaryotic initiation factor-4E (eIF4E) have been detected in cell bodies and dendrites in cultured hippocampal neurons and their distribution completely overlaps with the postsynaptic density protein-95 (PSD-95) at synaptic sites, suggesting the postsynaptic localization of these proteins [202]. Activation of mTOR is functionally linked with local protein synthesis in synapses, resulting in the production of proteins required for the formation, maturation, and function of new spine synapses [15, 198, 201, 203], and the correct dendritic arbor morphology [204]. The new proteins synthesized are signaling proteins localized presynapticaly as synapsin I, or postsynapticaly as PSD-95 and GluR1, and cytoskeletal proteins as the activity-regulated cytoskeletal-associated protein (Arc) [15, 201, 203].

mTOR signaling pathway has been associated to a number of neurological diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, tuberous sclerosis, neurofibromatosis, fragile X syndrome, epilepsy, brain injury and ischemic stroke [205, 206]. Recently, it has also been suggested the involvement of mTOR signaling pathway in affective disorders. It has been postulated that the therapeutic effects of mood stabilizers such as lithium and antidepressant drugs, may also be due to their ability to withstand a variety of insults which can be related to its capacity to increase autophagy by inhibition of mTOR [207]. Therefore, mTOR is considered a potential new therapeutic target for the treatment of affective disorders. In this regard, the impairment of this pathway in major depression could be supported by the reported decrease in the expression of mTOR, as well as of some of the downstream targets of this pathway, such as p70S6K, eIF4B, and its phosphorylated form, in human postmortem samples of prefrontal cortex from depressed subjects [208]. In stressed rats, a reduction in PI3K/Akt/mTOR signaling pathway has been reported in PFCx [209] and amygdala [210, 211].

Acute administration of different NMDA receptor antagonists, such as ketamine [15], Ro 25-6981 [15], and MK-801 [212], or antagonists of the group II of metabotropic glutamate receptors (mGlu2/3), as MGS0039 and LY341495, induces a fast antidepressant effect [213, 214] mediated by the activation of mTOR signaling pathway. The fast activation of the mTOR pathway by ketamine results in an increase in synaptogenesis, density and function of spine synapses in the prefrontal cortex of rats [15, 203], and hippocampal BDNF expression [215]. These changes induce a rapid antidepressant-like effect in rats [15, 203] and humans [208]. Moreover, blockade of mTOR signaling by the specific antagonist rapamycin, completely antagonizes both ketamine-induced synaptogenesis and behavioral responses in models of depression [15]. Other antidepressant strategies as ECS therapy also activate mTOR pathway leading to an increase in VEGF [216]. Furthermore, chronic but not acute microinjection of cyclosporine and tracrolimus into mPFCx increase depressive-like behaviors and decreases mTOR activity [217], effects reverted by the activation of mTOR by NMDA or by chronic venlafaxine, promoting an antidepressant-like effect [217]. On the other hand, other authors have

reported that subchronic, but not acute, administration of rapamycin in rodents produces an antidepressant-like effect observed in two behavioral procedures: forced swimming and tail suspension tests [218]. Although further research is needed to clarify this issue, the modulation of mTOR pathway could represent a novel approach for developing strategies for the treatment of affective disorders [219].

Future work must continue to elucidate the fine modulatory role of mTOR and its intricate cellular pathways in antidepressant action, despite of the reported antidepressant like response of both activation and inhibition of mTOR, the biological and clinical outcome of mTOR signaling can be influenced by Akt, or GSK-3β activity, agents that can modulate the activity of both individual or multiple protein kinases in the PI3K–Akt–mTOR pathway may provide a futher improvement in the antidepressant treatment.

3. NEUROTROPHIC FACTORS

By the mid 90's, several evidences strongly indicated that both the etiopathogeny of mood disorders including those mediated by stress, and the effects of antidepressant drugs, could not be fully explained by the modifications in neurotransmitters and receptors. New findings led to a molecular and cellular hypothesis known as "neurotrophic hypothesis of depression", that later was revised to a "neuroplasticity hypothesis of depression" [220]. This hypothesis links the changes in stress-induced vulnerability and the therapeutic action to the modification of intracellular mechanisms that modulate neurotrophic factors necessary for the survival and function of neurons. Among these factors, BDNF is the most widely distributed in the brain [221].

BDNF is a critical mediator of activity-dependent plasticity in the developing and adult CNS [222]. BDNF is synthesized as a precursor protein known as prepro-BDNF that is cleaved into pro-BDNF, which can then be further cleaved into mature BDNF [223]. Through TrkB receptor, BDNF mediates most of the plasticity-enhancing effects. However, recent evidence suggests a more complex scenario for BDNF-driven neuronal plasticity. Two active forms of BDNF have been described: mature-BDNF and pro-BDNF, that mediate their effect trough two different types of receptors: the high-affinity TrkB receptor and the low-affinity p75 neurotrophin receptor (p75NTR), respectively. Signaling of mature-BDNF through TrkB, and pro-BDNF through p75NTR can lead to opposite effects, as the induction of neuronal atrophy and apoptosis, dendritic pruning and the induction of LTD [224]. This suggests that under conditions where pro-BDNF is secreted, its extracellular cleavage is of critical importance for its functional effect [225]. All these findings emphasize the bidirectionality of neuronal plasticity, where neurogenesis, neurite arborization, and synaptogenesis are balanced by programmed neuronal death, neurite retraction, and synaptic pruning.

BDNF binding to TrkB receptor induces receptor dimerization and trans-autophosphorylation of two tyrosine residues (Y515 and Y816) on the intracellular cytoplasmic domain. Phosphorylation on Y515 residue allows the activation of the Ras/MAPK and PI3K pathways by the recruitment of the protein Shc/FRS-2. On the other hand, phosphorylation on Y816 residue activates the CAMK/CREB signaling pathway by recruitment of PLC [226]. BDNF signaling through TrkB is critically involved in several antidepressant-dependent responses (see below); in contrast, the role of p75NTR-dependent signaling is not clear. Recently, it has been reported the existence of increased pro-BDNF levels in postmortem brain samples of suicide subjects [227]. Thus, increased mature BDNF, through TrkB signaling, is associated to an antidepressant response, whereas pro-BDNF, through p75NTR signaling, would be pro-depressant [228]. In addition, the expression ratio of p75NTR to TrkB receptors is increased in the postmortem brain of suicide subjects [227]. Further investigation is needed to clarify the role of p75NTR in depression.

Data from studies using BDNF heterozygous, conditional and region-specific knockout mice or viral-mediated deletion techniques to remove BDNF in a regionally and temporaly dependent manner, have shown lack of response to antidepressant treatments, mainly in those with BDNF reduction in the dentate gyrus of the hippocampus [229], although no dramatic changes in depression-related behavior were observed. Interestingly, specific deletion of BDNF in the mesolimbic dopamine neurons in the ventral tegmental area (VTA) induces the opposite effect, resulting in an antidepressant-like response [221].

BDNF and TrkB levels are decreased in hippocampus and prefrontal cortex in post-mortem tissue from both suicide victims and patients with MDD, as well as in the serum of patients with MDD [230-233] (Fig. **5A**). This reduced serum BDNF has been related to a diminished ability of platelets to release BDNF upon stimulation, rather than to a decrease in whole serum levels [230]. In contrast, some authors have reported lack of changes on BDNF levels associated to stress animal models [229, 234, 235]. BDNF levels are increased in other brain structures as nucleus accumbens and amygdala [221]. All these changes are normalized after long-term antidepressant treatment [221]. Thus, BDNF has been proposed as a biomarker for the effectiveness of the antidepressant response [236], or even a marker of suicidal behavior [237].

The SNP BDNF(Val66Met) in the human BDNF gene, associated to reduced BDNF secretion [238], has been related to an increased incidence of neuropsychiatric disorders [239, 240], and to a lack of response to antidepressant treatment [241]. BDNF (Val66Met) predisposes to a depression-like behaviour after stress situations in animals, that returns to normal values after antidepressant administration [242].

Several findings support the essential role of BDNF in antidepressant responses. Chronic antidepressant manipulations, including electroconvulsive therapy, and administration of SSRIs, SNRIs, tricyclic antidepressants, and atypical antipsychotics, increase hippocampal BDNF mRNA, while an increase in protein levels has been reported in some but not all studies [40, 42, 225, 243-247] (Fig. **5B**). Some approaches, such as the blockade of 5-HT_{2A} receptor subtype have been probed to reverse the effect of stress-induced downregulation of BDNF mRNA expression in hippocampus [248]. In this regard, subchronic treatment with SSRI and 5-HT_{2A} antagonists increases BDNF mRNA expression in the dentate gyrus of the hippocampus [187].

Brain infusion of BDNF [249, 250], and more specifically in hippocampus [251-253], produces antidepressant-like effects. Moreover, within the hippocampus, antidepressant-like effects are observed after the infusion of BDNF in the DG, but not in the CA1 region [252]. This is supported by the finding that loss of BDNF in DG but not in the CA1 reduces antidepressant drug induced-response. In contrast to the findings in hippocampus, BDNF increases depression-like behavior when injected into the ventral tegmental area, and the inhibition of BDNF signaling in the nucleus accumbens produces an antidepressant-like response [254, 255]. However, antidepressant treatment increases BDNF expression both in the hippocampus and the mesolimbic regions [247]. Therefore, the behavioral outcome of drug treatment does not appear to directly reflect the levels of BDNF, but perhaps the functional role of BDNF within a particular network. It is noteworthy that peripherally administered BDNF display antidepressant-like actions [256], resembling the serum BDNF increase observed after antidepressant treatments. A wealth of evidence supports that BDNF acting through TrkB receptors is involved in the antidepressant response [225, 246, 257].

BDNF could also increase catecholamine levels by activation of tyrosine hydroxylase (TH), the rate-limiting enzyme in the biosynthesis of catecholamines. TH gene promoter is positively regulated by BDNF through its specific receptor TrkB and the ERK/MAP

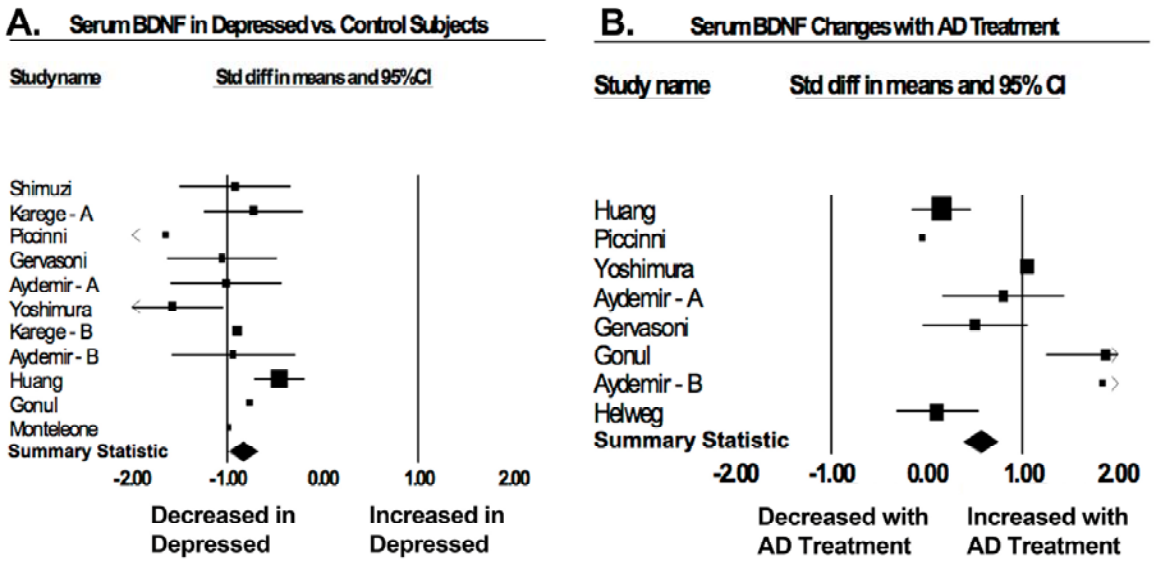

Fig. (5). Decreased levels of brain derived neurotrophic factor (BDNF) in depressed compared to control individuals (**A**), and increased levels after antidepressant treatments (**B**), in several human studies. (Modified from [233], with permission).

kinase pathway. BDNF activation of TH gen is selectively antagonized by the Ca^{2+} signals evoked via NMDA receptor [258]. The involvent of TH activity in the antidepressant effects of BDNF needs further research.

In the last years, emerging evidence suggest an important role of the VEGF in the depressive illness, giving rise to a "vascular niche hypothesis of adult neurogenesis". This theory proposes the need of vascular recruitment associated to active sites of neurogenesis formed by proliferative cells showing endothelial phenotype in 37% of the cases [12]. VEGF expression is reduced in hippocampal dentate gyrus after irradiation [259], and in stress models of depression [260], two conditions that are associated with decreased hippocampal cell proliferation. The decrease of progenitor cells responsible for the expression of VEGF seems to underlie the reduction of this factor [259]. However, other studies have failed to find changes associated with stressed animals [261].

Some non-pharmacological antidepressant treatments such as ECS therapy [259, 262, 263], exercise [261], or mood stabilizers as lamotrigine [264], results in the upregulation of VEGF expression. Moreover, the local administration of this trophic factor produces an increase in hippocampal cell proliferation [259]. In contrast, the silencing of hippocampal VEGF [265], or the use of antagonists for its receptor Flk-1 [261], blocks its antidepressant-like effect and decreases markers of neural precursor cells and immature neurons as doublecortin (DCX). However, even though the increasing importance of VEGF in the depressive disorder, there is not a clear correlation with peripheral VEGF that would allow the use of this molecule as a marker of depression and/or antidepressant response [266, 267].

PATHWAYS CROSSTALK: AKT ON THE CROSSROAD

The existence of crosstalk between different signaling pathways and other signaling molecules important for adult neurogenesis and plasticity is well demonstrated, exemplifying the complexity of molecular interactions implicated in the regulation of these processes. Signaling networks at various cellular levels define both intrinsic developmental stage-specific changes as well as the identity of the environmental components. For many of these pathways, including Wnt, mTOR, BDNF, as well as several GPCR-dependent systems, an important role for Akt can be suggested (Fig. **6**) [199].

Akt/PKB (protein kinase B) is a serine/threonine kinase regulated through phosphatidylinositol-mediated signaling. The activation of Akt involves its recruitment to the plasma membrane by phosphorylated phosphatidylinositol (Ptdlns-3,4,5-P), phosphatidyl inositol-dependent kinase 1 (PDK1), and PDK2/rictor-mTOR complex [268, 269].

This protein acts as a link of the different pathways above mentioned. Thus, activation of TrkB receptors by BDNF results in the activation of PI3K/Akt [270], and MEK/ERK [199]. Akt acts phosphorylating GSK-3β in Ser9 which results in GSK-3β inhibition, and the subsequent activation of the Wnt/β-catenin pathway. Akt-mediated inhibition of GSK-3α and GSK-3β can be also induced by hormones and other growth factors (IGF and insulin) [97, 271, 272]. Both Akt and GSK-3β have multiple substrates, including proteins involved in cell survival/death, and gene expression regulation [268, 273]. Akt can also activate mTOR pathway in the presence of Ca^{2+}, but not in a resting state, directly inhibiting the mTOR suppressor TSC2, or through the inhibition of GSK-3α, resulting in the blockade of TSC2 [274]. This double regulation is suggested to prolong the mTOR signaling and therefore protein translation [274].

Aminergic neurotransmitters as 5HT and DA are known to regulate some aspects of the neuronal function, including plasticity, through the modulation of GSK-3β activity. The activation of Gi protein-coupled 5-HT_{1A} receptors by the agonist 8-OH-DPAT or the blockade Gq protein-coupled 5-HT_{2A} receptors by the antagonist LY53857, both lead to the inhibition of GSK-3β activity by phosphorylation [186, 275]. 5-HT receptors can also act on Gs proteins that activate prostaglandin E2 (PGE2), phosphoinositide 3-kinase (PI3K), and PKB/Akt, leading to the inhibition of GSK-3β. The inhibition of GSK-3β is also produced independently from Akt, by the activation of phospholipase Cβ (PLCβ) or protein kinase C (PKCs) mediated by Gq or G12/13 proteins [276], in many brain regions, including frontal cortex, hippocampus and striatum [186, 275, 277]. Mutant mice expressing loss-of-function forms of tryptophan hydroxylase 2, the rate-limiting enzyme for neuronal 5-HT synthesis, that results in lack of 5-HT, present an increased GSK-3β activity associated with depressive-like behavior [184]. Moreover, the selective GSK-3β inhibitor TDZD-8 reverses the 5-HT-associated behavioral phenotype in these mice [278, 279]. These results suggest that controlling the phosphorylation/activity status

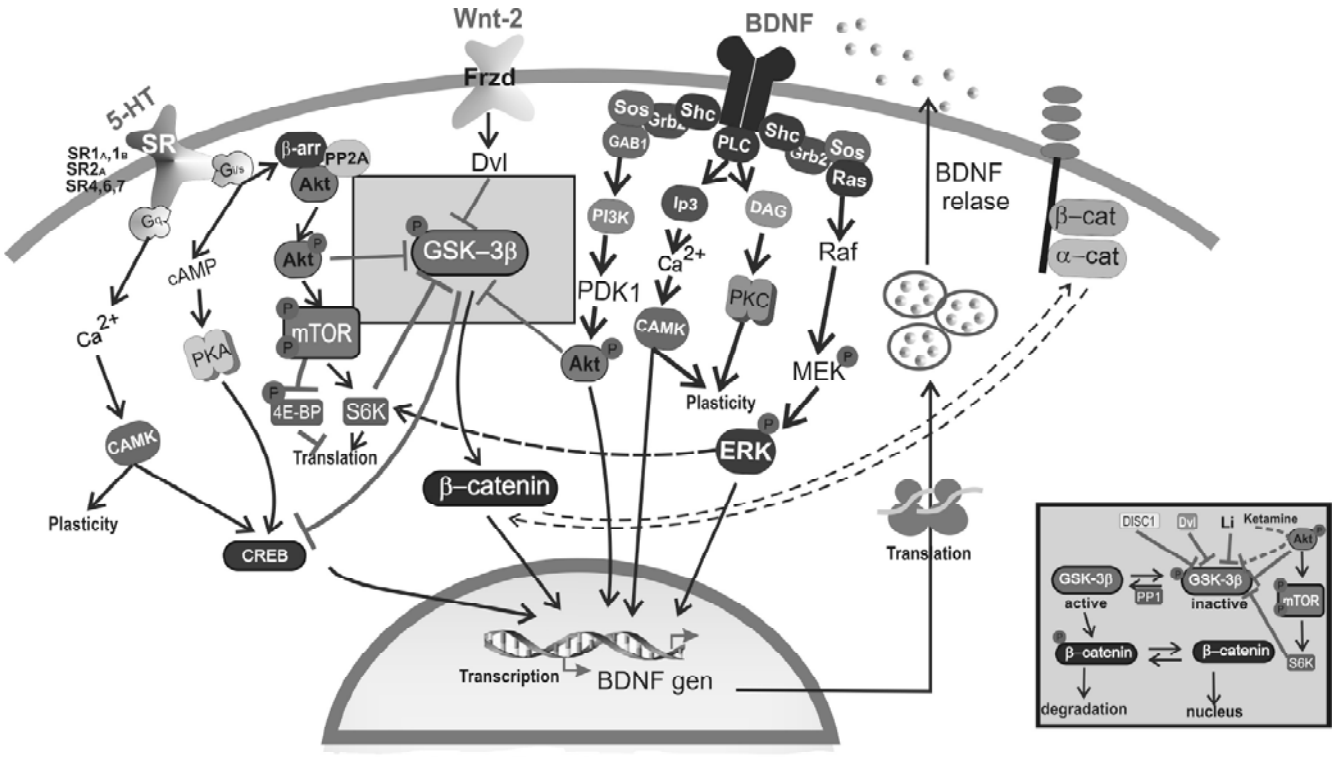

Fig. (6). Crosstalk in the main signaling pathways linking antidepressant action to proliferative and/or plasticity changes. The activation of the Wnt/β-catenin pathway produces the Dvl-mediated inhibition of GSK-3β, allowing the accumulation of β-catenin in the cytoplasm and its translocation to the nucleus, where it binds to TCF/Lef transcription factors (central part). Detail of the modulation of GSK-3β activity; when GSK-3β is active (not phosphorylated) it labels β-catenin for degradation (box in the lower right side). β-catenin mediates also an important role associated to N-cadherin and α-catenin in membrane, playing an important role in synaptic vesicle release (right side). The mTOR pathway is also implicated in synaptic plasticity, producing the activation of downstream proteins as S6K, and the inhibition of others as 4E-BP, leading to translational activation (centre-left). The binding of the trophic factor BDNF to its receptor TrkB, induces a plethora of signaling cascades, highlighting the activation of the PI3K/Akt pathway that leads to the inhibition of GSK-3β and activation of mTOR. BDNF-mediated Akt and ERK activation produces the transcription of different genes, leading to an increased BDNF translation and release (centre-right). The activation of GPCRs as 5-HT receptors as a consequence of some classical antidepressant treatments (SSRIs and SNRIs), induces different cellular responses as activation of PKA and CREB phosphorylation, and activation of Akt, mediating the effects aforementioned. (Adapted from [199, 299]).

of GSK-3β could represent an important mechanism of 5-HT action on brain and behavior [184].

Dopamine, through D2-receptors, also inhibits Akt activity by phosphorylation and increases the activation of GSK-3β through a G protein-independent mechanism involving a complex of Akt/β-arrestin 2/PP2A [280-283]. The administration of the antipsychotic D2-receptor antagonist haloperidol [284, 285], or mice lacking D2-receptors [286], show an increased inhibition of GSK-3β. D3 receptors also seem to participate in the regulation of Akt/GSK-3β signaling, by enhancing D2 receptor responses [286].

a) Role in Mood Disorders

The involvement of Akt/GSK-3β in psychiatric conditions such as schizophrenia, bipolar disorders, and major depression could be associated to behavioral responses to dopamine and/or 5-HT, and their role in the action of psychotropic drugs. Akt protein levels are reduced in the brain of schizophrenic patients [284, 287] due in part to the inhibitory effect of the activation of D2-receptors on Akt or to a partial loss-of-function of Akt1 [282, 283]. Akt expression is also reduced in brains of suicide victims with major depression [288] and in prefrontal cortex of bulbectomized rats [289]. This reduction in Akt expression level correlates with the reported decrease in GSK-3β phosphorylation and kinase activation in brain samples from major depression subjects [170], but not in postmortem samples from bipolar patients [290]. Higher GSK-3β activity raises β-catenin phosphorylation and subsequent degradation, leading to a final reduction of β-catenin in the brain of depressed patients [169], or animal models of depression [122].

b) Role in Antidepressant Effect

Drugs used for the treatment of neuropsychiatric disorders such as schizophrenia, depression and bipolar disorders, act mainly on monoamine neurotransmission, regulating Akt/GSK-3β by the modulation of dopaminergic and serotonergic neurotransmitter systems [282, 283, 291, 292]. Biochemical and behavioral approaches had provided converging evidence for the involvement of Akt and GSK-3β in the mechanism of action of those drugs.

Chronic treatment with the SNRI venlafaxine [14], and the SSRI fluoxetine, or subchronic (3 to 7 days) treatment with the $5HT_4$ agonist RS67333 [42], increase rat hippocampal Akt expression (Fig. **7**). This hippocampal increase correlates well with GSK-3β phosphorylation and inhibition, and the subsequent increase in β-catenin levels, which in turn is related to increased cell proliferation and antidepressant-like behavior [14, 42]. Other non-pharmacological treatments such as ECS also result in the activation of Akt signaling in hippocampus, leading to GSK-3β inhibition [293].

CONCLUSIONS

The neurogenesis hypothesis of depression was based upon the demonstration that stress decreased adult neurogenesis in the hippocampus. This reduction in the production of newborn granule

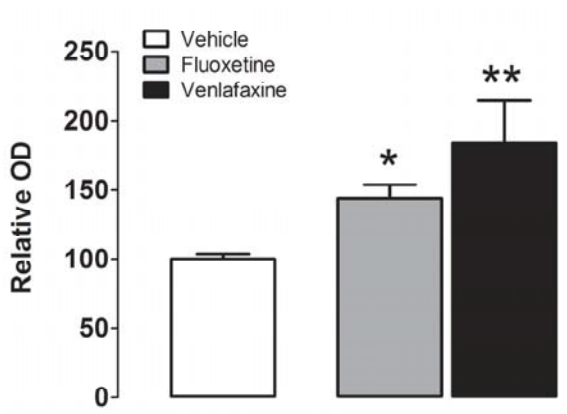

Fig. (7). Increase of AKT protein expression levels by antidepressant treatment in naïve animals, measured by Western blot analysis. Chronic antidepressant treatment (14 days) with 10 mg/kg/day of fluoxetine and 40 mg/kg/day venlafaxine. Densitometric measurement levels in total cell lysates were normalized to GAPDH protein amount. Results are Mean±S.E.M. *p < 0.05, **p < 0.01 *vs* control group. (Adapted from [14]).

cells in the hippocampal dentate gyrus appears to be related to the pathophysiology of depression. Since then, several studies have tried to establish the role that newborn neurons in the dentate gyrus play in the mechanism of action of the antidepressants. However, the role of hippocampal cell proliferation is still a matter of debate. X-irradiation and genetic studies demonstrate the requirement of hippocampal neurogenesis in mediating some of the behavioural responses to antidepressants [56, 61, 294]. Moreover, drugs without antidepressant activity, such as psychotropics, do not increase neurogenesis [36]. However, blocking hippocampal cell proliferation does not prevent the antidepressant actions exhibited by other drugs such as corticotrophin releasing factor receptor (CRF) antagonists or arginine vasopressin 1b (V1b) receptor modulators [61]. The time-lag for the appearance of antidepressant-like effects in behavioral tests takes at least 2-3 weeks for many types of drugs (mainly tricyclics and serotonin transporter inhibitors) [14, 36], which parallels the time needed for the development of newborn cells in hippocampus [73]. However, this is not the case for other antidepressant manipulations. ECS, subchronic administration of 5-HT_4 agonists [39, 42], or siRNA-mediated serotonin transporter suppression in specific brain areas [48] results in a faster increase in cellular proliferation.

Similarly, synaptic plasticity is also modulated by antidepressant treatments [32, 33]. Neuronal plasticity is not only functional but structural, and it is impaired in animal models [295]. In this regard, a decrease in spine number in hippocampal CA1 and CA3 areas has been found in some animal models of depression, such as the olfactory bulbectomized rat, this being reverted by antidepressant treatments [295]. This structural plasticity is more striking when new neurons are born [36] or when an increase in neuron survival as a consequence of antidepressant treatment or ECS is evident [296]. The new dendritic spines formed are associated to smaller postsynaptic densities (PSDs) and to a higher frequency of mini-excitatory postsynaptic currents (mEPSCs), suggesting an increased number of new and active glutamatergic synapses [297]. Interestingly, ketamine and other glutamate antagonists increased the number and function of new spine synapses in rat prefrontal cortex, an effect mediated by the activation of mTOR [15], but did not modify hippocampal cell proliferation [298]. Therefore, this rapid antidepressant response to ketamine in humans and in animal models of depression suggests a possible new approach for treating mood disorders, compared to the weeks or months required for standard medications. The molecular and cellular components responsible for plasticity are not yet fully elucidated. Furthermore, the signaling pathways involved in its regulation are just beginning to be understood.

Classical antidepressants elevate the monoamine levels in the brain by preventing re-uptake of monoamines after release. Treatment of depression with monoamine re-uptake inhibitors is associated with low clinical efficacy and remission rate due to the delayed onset of therapeutic responses. Therefore, the development of alternative antidepressants is essential for successful treatment of this disease. Molecular and cellular studies have demonstrated opposing actions of stress and antidepressant treatment on the expression or functionality of signaling pathways including Wnt/β-catenin, mTOR or neurotrophic factors, particularly BDNF which dysfunction result in structural alterations, including neurogenesis, dendrite length and spine density in hippocampus and prefrontal cortex (PFCx).

Initial interest in GSK-3β as a target for the treatment of mood disorders arose from the finding that the mood stabilizing drug lithium directly inhibited the enzyme. GSK-3 inhibitors as AR-A014418 induces behavioural changes that are consistent with the effects of antidepressant medications. More recent preclinical evidence implicates the modulation of GSK-3β or its cellular targets β-catenin, as well as glutamate modulation of mTOR or BDNF signalings as promise targets for the development of safer, rapid acting and efficacious antidepressant agents for the treatment of depression.

The actions of glutamate NMDA receptor antagonists on mTOR signaling and on the density and function of spine synapses represents a fundamental shift in our understanding of the mechanisms underlying rapid acting, and efficacious antidepressant treatments. Low, subthreshold doses of ketamine combined with lithium or a selective GSK-3β inhibitor are equivalent to higher doses of ketamine, indicating the pivotal role of the GSK-3β pathway in modulating the synaptogenic and antidepressant responses to ketamine. The possible mitigation by GSK-3β inhibitors of the eventual fading of ketamine's antidepressant effects remains to be explored. Because of the side-effects and abuse potential of ketamine, alternative agents that produce similar effects are under investigation. A single dose of LY341495, an mGluR2/3 antagonist, produces ketamine-like biochemical and behavioural actions. Memantine, Agomelatine or Riluzole which have antidepressant properties, elevate levels of BDNF.

However, with our current knowledge, several questions remain to be answered. We do not yet have a clear understanding of how external stimuli in current treatments mediate the induction and function of factors in the neurogenic niche that stimulate adult hippocampal neurogenesis. Finally, we are yet to obtain a conclusive causal relationship between adult neurogenesis and depression. The role of BDNF and its downstream effects would need to be studied to determine how BDNF mediates synaptic plasticity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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