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Review

Cellular and molecular mechanisms underlying the treatment of depression: focusing on hippocampal G-protein-coupled receptors and voltage-dependent calcium channels

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Abstract. Depression is a brain disorder characterized by severe emotional, cognitive, neuroendocrine and somatic dysfunction. Although the latest generation of antidepressant drugs has improved clinical efficacy and safety, the onset of their clinical effect is significantly delayed after treatment commencement, and a large number of patients exhibit inadequate response to these drugs and/or depression relapse even following initially successful treatment. It is therefore essential to develop new antidepressant drugs and/or adjuncts to existing ones. Recent studies suggest that the beneficial effect of antidepressant drugs is mediated, at least in part, *via* stimulation of adult hippocampal neurogenesis and subsequent increase in hippocampal plasticity. Since the stimulatory effect of antidepressant drugs on hippocampal neurogenesis involves G-protein coupled receptors (GPCR) and voltage-dependent calcium channels (VDCC), greater efficacy may be available if future antidepressant drugs directly target these specific GPCR and VDCC. The potential advantages and limitations of these treatment strategies are discussed in the article.

Key words: Antidepressant drugs — Serotonin — Norepinephrine — Dopamine — Hippocampus — Neurogenesis

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); AKT, see protein kinase B or PKB; BDNF, brain-derived neurotrophic factor; β-END, β-endorphin; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; CNS, central nervous system; CNTF, ciliary neurotrophic factor; DA, dopamine; DAG, diacylglycerol; DAT, dopamine transporter; DHP, dihydropyridines; DG, dentate gyrus; DGMC, depression due to general medical condition; DSM, diagnostic and statistical manual; ECT, electroconvulsive therapy; EGF, epidermal growth factor; ERK1/2, extracellular-signal-regulated kinases 1 and 2; fMRI, functional magnetic resonance imaging; GABA, γ- aminobutyric acid; GED, generalized anxiety disorder; GFAP, glial fibrillary acidic protein; GPCR, G-protein coupled receptor; GWAS, genome-wide association studies; Hes1, hairy and enhancer of split-1; Id2, DNA-binding protein inhibitor; IL-2/6, interleukin-2/6; IP_3, inositol 1,4,5-trisphosphate; LTCC, L-type calcium channel; MAO, monoamine oxidase; MDD, major depressive disorder; NAT, norepinephrine transporter; NE, norepinephrine; NMDA, N-methyl-D-aspartate; NPC, neural progenitor cell; NSC, neural stem cell; OXY, oxytocin; PD, postpartum depression; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKB, protein kinase B; PKC, calcium-dependent protein kinase; PLC, phospholipase C; SEL, subependymal layer; SERT, serotonin transporter; SNP, single-nucleotide polymorphism; SNRI, dual serotonin/norepinephrine reuptake inhibitor; Sox2, sex determining region Y-box 2; SSRI, selective serotonin reuptake inhibitor; SVZ, subventricular zone; SGZ, subgranular zone; TAP, transient amplifying progenitor; TNF-α, tumor necrosis factor alpha; TRI, triple reuptake inhibitor; VAS, vasopressin; VDCC, voltage-dependent calcium channel; VMAT, vesicular monoamine transporter.

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Depression: An introduction

The clinical use of the word "depression" is normally restricted to major depressive disorder (MDD). According to the Diagnostic and Statistical Manual (DSM), MDD is diagnosed when the two major symptoms: depressed mood and anhedonia, or inability to feel pleasure, and at least two of the following eight symptoms are present for at least two weeks: decreased self-esteem, guilt feelings, impaired memory and concentration, increased fear and anxiety, insomnia or hypersomnia, increased or decreased appetite, general retardation or agitation and repetitive pre-occupation with death, with or without suicidal plans. In contrast, dysthymia, or minor depression, is diagnosed when only some of these symptoms are present. In addition, depression due to a general medical condition (DGMC) is diagnosed when the above-mentioned symptoms result from severe somatic illness, trauma, or disability and postpartum depression (PD) which appears immediately or shortly after child-birth. The most severe forms of depression are psychotic, melancholic, chronic or repeated depression and bipolar disorder, where depression alternates with hyper- or hypomania (American Psychiatric Association and American Psychiatric Association. Task Force on DSM-IV 2000).

Depression affects at least twenty percent of the general population at least once in their lifetime, with higher prevalence in females than in males, but it is not linked to geographical location, race or ethnicity nor socio-economic or cultural background (Andersen et al. 2011). Depression is associated with a high risk of suicide and increased mortality from co-morbid somatic disorders; often cardiovascular. Somatic disorders co-morbid with depression generally have a more severe course and worse prognosis. Depression can also be co-morbid with increased risk of other mental disorders, such as generalized anxiety (GED), panic disorder and substance and alcohol abuse. Depression currently ranks as the second major cause of disability in industrial countries and is estimated to become the second major global cause of disability by 2020 (Andersen et al. 2011). Chronic depression is also associated with a higher risk of developing Alzheimer and other age-related cognitive disorders (Bennett and Thomas 2014).

There are several lines of evidence that depression is a complex organic disease rather than simple mood perturbation. Firstly, pharmacotherapy for depression, alone or combined with psychotherapy, has greater efficacy than sole psychotherapeutic treatment (Cuijpers et al. 2009; Kendrick et al. 2009; Hollander 2013). Secondly, many physical symptoms are associated with depression including; dizziness, headaches, chronic lower back pain, gastro-enteral symptoms with abdominal pain, constipation or diarrhea, endocrine abnormalities (usually thyroid hypo- or hyper-function), and irregular and/or painful menstruation (Bair et al. 2003; Bair et al. 2004). Thirdly, depression can be induced by pharmacological intervention, such as administration of reserpine which inhibits vesicular monoamine transporters (VMAT) (Lion et al. 1975) or by specialized diets, such as tryptophan-depletion (Delgado et al. 1999). Fourthly, structural and functional CNS abnormalities are associated with depression. These usually occur in the brain's limbic system which is responsible for emotional processing, the stress response and memory formation, storage and retrieval (Kandel et al. 2000).

Post-mortem studies have reported depression associated with increased density of serotonin-2 (5-HT_2) (Czeh et al. 2001), glutamate NMDA (Karolewicz et al. 2009) and AMPA receptors in the cortex (Gibbons et al. 2012). The association between depression and decreased volume in the hippocampal formation, a central limbic system structure, was initially reported in post-mortem observations (Czeh et al. 2001; van der Hart et al. 2002) and confirmed in more recent studies by structural magnetic resonance imaging (MRI) (Abdallah et al. 2014; Ajilore et al. 2014; Krogh et al. 2014; Rodriguez-Cano et al. 2014; Romanczuk-Seiferth et al. 2014). It was determined that this decreased hippocampal volume primarily affects the grey matter rather than white (Du et al. 2014; Stratmann et al. 2014). Similar reduction in grey matter volume, indicating a decreased number of living neurons, was observed in other parts of the limbic system, including the amygdala (Du et al. 2014; Stratmann et al. 2014) and the prefrontal cortex (Ajilore et al. 2010; Grieve et al. 2013; van Tol et al. 2013; Romanczuk-Seiferth et al. 2014; Treadway et al. 2014).

Functional MRI (fMRI) studies have detected various abnormalities in limbic system connectivity and functioning. These include: task-related hypo-activation of the prefrontal cortex circuits (PFC) (Romanczuk-Seiferth et al. 2014) where depressed patients' PFC is hyper-activated during exposure to negative emotional stimuli (Foland-Ross et al. 2014), and also abnormal hippocampal and amygdala activity associated with depression (Tahmasian et al. 2013; Fujii et al. 2014; Ruhe et al. 2014). In addition, positron emission tomography (PET) has demonstrated that abnormalities in receptor occupancy or in the 5-HT, norepinephrine (NE) and dopamine (DA) monoamine transporters are involved in the pathophysiology of depression (de Klerk et al. 2010; Hirao and Smith 2014).

Current strategies in the treatment of depression: Role of monoamine neurotransmission

The first pharmacological line of treatment in depression is selective 5-HT reuptake inhibition (SSRI) (Kennedy 2006; Ravindran and Kennedy 2007) which increase 5-HT

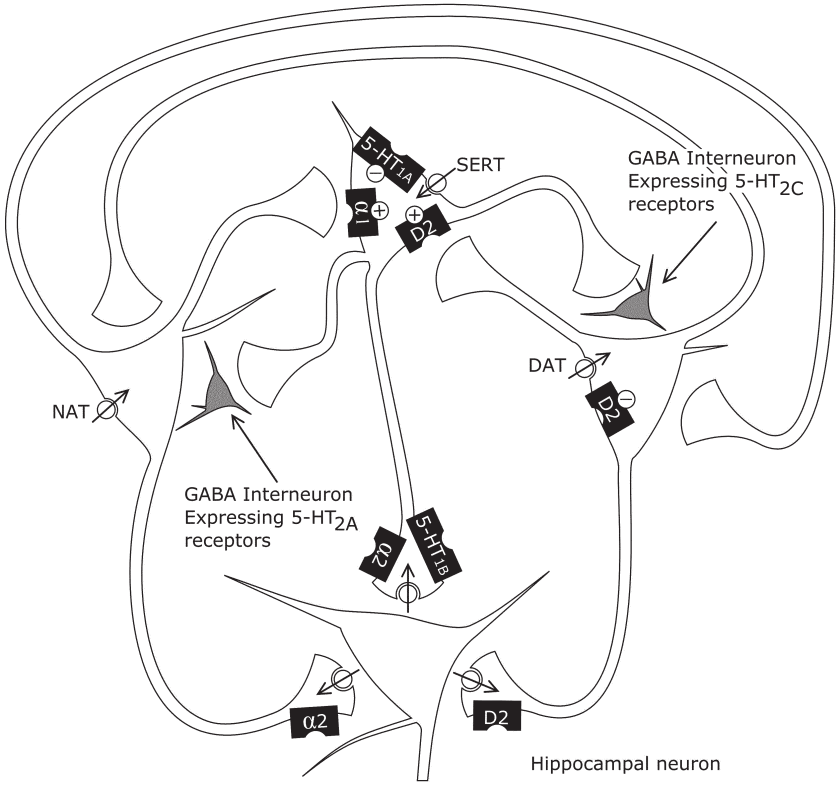

Figure 1. Contemporary antidepressant drug targets. Monoamine transporters are targets for the majority of contemporary antidepressant drugs (the 5-HT transporter (SERT) is a target for vortioxetine, SSRIs, SNRIs, TRIs and tricyclic drugs; the NE transporter (NAT) is a target for SNRIs, TRIs and tricyclic drugs and the DA transporter (DAT) is a target for TRIs and tricyclic drugs). The auto-receptors are targets for some antidepressants (vortioxetine: 5-$HT_{1A/1B}$; mirtazapine: α_2-adrenergic) and their adjuncts (pindolol: 5-HT_{1A}; T3 and lithium: 5-HT_{1B}; idozaxan and some atypical antipsychotic drugs: α_2-adrenergic). Heteroreceptors mediating interactions between the 5-HT, DA and NE systems are targets for some antidepressants (nefazadone and agomelatine: 5-HT_{2C}; mirtazapine: 5-$HT_{2A/2C}$) and their adjuncts (some atypical antipsychotic drugs: 5-HT_{2A} and/or 5-HT_{2C}). 5-HT, 5-hydroxytryptamine (serotonin); DA, dopamine; NE, norepinephrine; SNRIs, dual serotonin/norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TRIs, triple reuptake inhibitors. According to Blier (2014).

availability. The neurotransmitter serotonin has important roles in regulating mood, emotions, sleep, and sexual and eating behaviors, and thus involved in the pathophysiology of depression (Warner-Schmidt and Duman 2006). Although the latest-generation SSRIs possess relatively high safety and efficacy, only approximately one third of patients with MDD achieve complete remission after appropriate SSRI treatment for chronic depression, while a further third gain only partial symptom relief and the remainder have no response at all (Kennedy 2006; Ravindran and Kennedy 2007).

It has been suggested that the lack of adequate response to SSRIs in at least some patients is explained by 5-HT-induced suppression of NE and DA neurotransmission (Dremencov 2009; Dremencov et al. 2009a, 2009b). Increased 5-HT tone leads to inhibited NE and DA neuronal firing, *via* 5-HT_{2A} and 5-HT_{2C} receptors, respectively (Fig. 1), and since catecholamines are such important regulators of human motivation, drive and reward, their inhibition can contribute to depressive symptoms including anhedonia and fatigue (Dremencov et al. 2009a; El Mansari et al. 2010; Blier and El Mansari 2013).

Strategies which prevent inhibition of NE and DA tone and achieve better treatment outcomes include: (1) SSRI replacement by dual 5-HT/NE (SNRIs) or triple 5-HT/NE/DA reuptake inhibitors (TRAs) (Guiard et al. 2009, 2011); (2) co-administration of SSRIs with 5-$HT_{1A/1B}$ antagonists which prevent 5-HT neuron auto-inhibition or 5-$HT_{2A/2C}$ to prevent NE and DA neuron inhibition, and (3) D_2 and α_2-adrenergic receptors to prevent DA and NE neuron auto-inhibition, respectively (Dremencov 2009). Although older antidepressant drugs, such as tricyclic antidepressants

Table 1. Receptors for monoamines and their signal transduction mechanism

	Serotonin Receptors	Norepinephrine Receptors	Dopamine Receptors
$G_{I/O}$-Coupled	5-HT_{1A}, 5-HT_{1B}, 5-HT_5	α_1-adrenergic	D_2-like receptors (D_2, D_3, D_5)
G_S-Coupled	5-HT_4, 5-HT_6, 5-HT_7	β-adrenergic	D_1-like receptors (D_1, D_4)
$G_{Q/Z}$-Coupled	5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	α_2-adrenergic	–
Other	5-HT_3	–	–

5-HT3 is super-family-coupled to Na+/K+ channels.

or monoamine oxidase-A inhibitors (MAOs), are used in some treatment-resistant cases, they are rarely prescribed otherwise because of toxicity and strong side effects. The effectiveness of these drugs in SSRI-resistant depression may be explained, at least in part, by their ability to simultaneously stimulate 5-HT, NE, and DA transmission (Dremencov 2009). The treatment of last resort reserved for the most severe and treatment-resistant depression is electroconvulsive therapy (ECT) which induces robust increase in extracellular concentration of numerous brain neurotransmitters, including 5-HT and catecholamines (Dremencov et al. 2002, 2003).

In summary, while existing antidepressant drugs and combined treatment strategies enhance 5-HT, NE, and DA transmission, it is highly likely that this enhanced transmission is only the first step in the cascade required for behavioral and therapeutic effect. Although steady-state increase in monoamines brain levels is achieved within two or three days of treatment commencement (Dremencov et al. 2007), the onset of any therapeutic effect is usually observed only two or three weeks later (Dremencov et al. 2004). It is therefore possible that the antidepressant-induced increase in monoamine brain levels leads to functional or even structural changes in neuronal microcircuits in brain regions innervated by the 5-HT, NE and DA pathways. Here, the brain's hippocampal formation is of special interest (Dremencov et al. 2003).

Role of the hippocampus in pathophysiology and treatment of depression: Adult hippocampal neurogenesis and plasticity

The hippocampus has a central role in emotional processing and in memory formation, storage and retrieval (Kandel et al. 2000), with its pyramidal neurons exhibiting high plasticity and sensitivity to hypoxia and cytotoxicity. These neurons have large dendritic trees which can dynamically change size and shape and form new synaptic connections. Excessive fear and prolonged stress have a critical effect on hippocampal neuronal circuits leading to decreased plasticity and even to apoptotic neuron death (Dremencov et al. 2003). This is mediated by stress hormones and neuroinflamatory factors, such as corticosteroids, interleukins-2 and 6 (IL-2/6) and tumor necrosis factor alpha (TNF-α). While it is possible that the above detrimental hippocampal neuron effects are primary pathophysiological mechanisms of depression (Krishnadas and Cavanagh 2012; Suvisaari and Mantere 2013), 5-HT, NE, and DA enhance hippocampal neuronal plasticity (Malberg et al. 2000; Santarelli et al. 2003; David et al. 2009). This monoamine neuroprotective effect is mediated by different 5-HT, NE, and DA receptor subtypes (Yang et al. 2012).

Adult neurogenesis has been demonstrated in several mammalian species (Gross 2000) including humans (Eriksson et al. 1998; Curtis et al. 2007). The two areas of the adult brain where stems cells initially reside and proliferate prior to migration and differentiation are the lateral subventricular zone (SVZ) in the olfactory system and the subgranular zone (SGZ) in the hippocampal dentate gyrus (DG). Production of new neurons in the adult mammalian hippocampus is influenced by a variety of environmental and behavioral events, such as environmental enrichment and voluntary physical exercise (Brown et al. 2003).

Human adult hippocampal neurogenesis has been described only in the SGZ where neuronal stem cells (NSCs) are present (Eriksson et al. 1998). These NSCs proliferate into neural progenitor cells (NPCs) which later produce different CNS cell types, including neurons, astrocytes, oligodendrocytes and other microglial cells (Kempermann and Gage 2000). The NSCs are identified by the presence of glial fibrillary acidic protein (GFAP), sex determining region Y-box 2 (SOX2) and nestin protein markers (Suh et al. 2007). While GFAP is an intermediate filament protein expressed in numerous CNS cell types, such as astrocytes and ependymal cells (Jacque et al. 1978; Roessmann et al. 1980), SOX2 is a transcription factor which maintains the NSC undifferentiated state (Takanaga et al. 2009; Zhang et al. 2012) and nestin is an intermediate filament protein expressed in the early stages of NSC proliferation. NSCs in the SGZ generate actively dividing nonradial transient amplifying progenitors (TAPs) which lose their GFAP marker (Sox2+, Nestin+ and GFAP-) (Ming and Song 2005). TAPs then generate neuroblasts, differentiate and migrate locally into the glutamatergic dentate granule cell layer (Mu et al. 2010).

Few methods of stimulating endogenous neurogenesis to replace lost cells have been explored; especially NSC stimulation by either direct or indirect stimulation of the appropriate neural stem/progenitor cells. While direct stimulation is achieved by applying an agent which directly binds and stimulates NSCs, perhaps through a GPCR-mediated system (Zhao et al. 2003; Mizutani et al. 2006; Vernon et al. 2011), the indirect method is effected by an agent stimulating the release of a further endogenous agent, possibly by inhibiting an enzyme or a neurotransmitter reuptake mechanism which in turn directly stimulates the NSC (Kempermann 2011). It has been reported that hippocampal neurogenesis is involved in the formation of new memories (Shors et al. 2001) and also in the onset of behavioral effects of antidepressant drugs (Santarelli et al. 2003). In addition, recent evidence has implicated the role of adult neurogenesis in pathophysiology and the treatment of depression (Pittenger 2013), and indicated that antidepressant drugs act by increasing SGZ neurogenesis (Santarelli et al. 2003).

The idea that depression may be associated with impaired adult neurogenesis was first proposed (Jacobs et al.

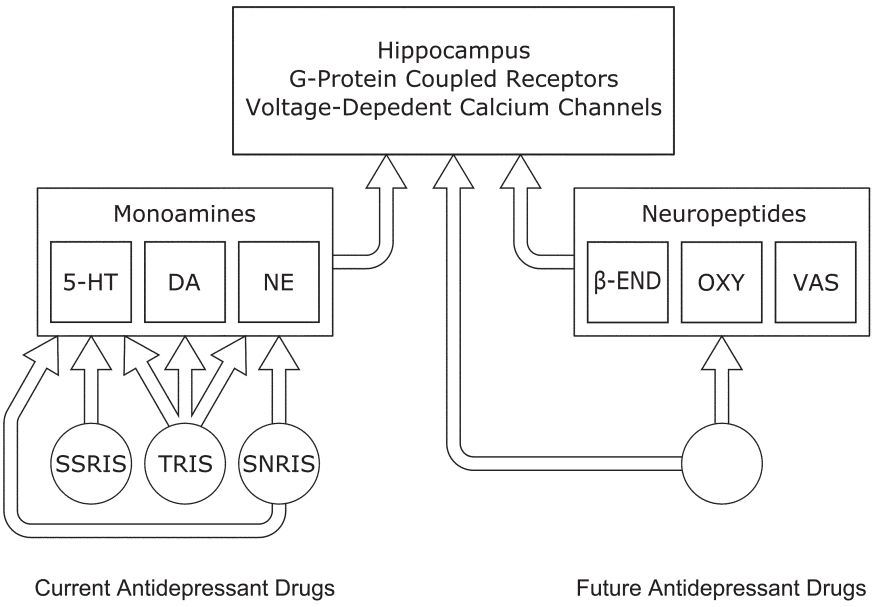

Figure 2. Potential targets for next-generation antidepressant drugs. Contemporary antidepressant drugs act almost exclusively on the 5-HT, NE and/or DA system. Hypothalamic neuropeptides (β-endorphin (β-END), oxytocin (OXY) and vasopressin (VAS)), postsynaptic G-protein coupled receptors for monoamines and/or neuropeptides and the voltage-dependent calcium channels mediating hippocampal plasticity and neurogenesis present potential targets for future treatment. For more abbreviations see Fig. 1.

2000). Recent studies suggest that stress-induced atrophy and loss of hippocampal neurons may contribute to the pathophysiology of depression, and hippocampal volume reduction in depressed patients has been confirmed by MRI (Videbech and Ravnkilde 2004). Here, the degree of hippocampal volume loss correlated with the duration of untreated depression (Sheline et al. 2003). Physiological studies indicate that neuropil and glial cell change may be responsible for reduced hippocampal volume (Czeh et al. 2001). In addition reports demonstrate that neurogenesis in the DG is critical for hippocampal control of the hypothalamic-pituitary-adrenal axis and stress hormone secretion (Drew and Hen 2007), and that antidepressant treatment increases hippocampal cell proliferation and resultant new cell maturation to neurons. It is possible that increased cell proliferation and neuronal number is the antidepressant treatment mechanism which overcomes stress-induced atrophy and loss of hippocampal neurons, thus enhancing the antidepressant therapeutic effect (Malberg et al. 2000; Santarelli et al. 2003). Studies confirm that SSRI administration prevents stress-induced inhibition of hippocampal neurogenesis (Pinnock et al. 2009), and Tris which simultaneously stimulate 5-HT, NE, and DA transmission have greater effect on hippocampal neurogenesis than SSRIs which solely stimulate 5-HT transmission (David et al. 2009). There is evidence that hippocampal neurogenesis mediates behavioral responses to antidepressant drugs (Sahay and Hen 2008; David et al. 2009), and that the SSRI fluoxetine behavioral effect noted in mice may involve hippocampal neurogenesis, or alternatively, be mediated by different mechanisms depending on the species of mice (Holick et al. 2008).

Although major depressive disorder is not purely neurogenetic, current knowledge suggests that impaired adult neurogenesis plays an important role (Kempermann 2011). Although some evidence suggests that decreased neurogenesis is not a major factor in the development of depression, increased neurogenesis may be responsible for the behavioral effects produced by antidepressant therapy (David et al. 2009; Mendez-David et al. 2013).

Role of G-protein coupled receptors in pathophysiology and treatment of depression: Signal transduction pathways, transcription factors, and target genes

With the exception of the 5-HT_3 receptor super-family which is coupled to sodium channels, all known monoamine receptors are G-protein coupled (GPCR, Table 1). GPCRs are sub-divided into three categories based on coupling-type: $G\alpha_S$, $G\alpha_{I/O}$ and $G\alpha_{Q/Z}$. Activation of $G\alpha_S$ and $G\alpha_I$-coupled receptors leads to either activation or inhibition of adenylate cyclase (AC) and alters intracellular cyclic adenosine monophosphate (cAMP) levels (Kandel et al. 2000). Cyclic AMP activates protein kinase A (PKA) which in turn triggers transcription factors including the cAMP response element-binding protein (CREB) (Nibuya et al. 1996). This builds on cAMP responsible element (CRE) chromosome areas, activating specific gene transcription. One gene regulated by this pathway is for brain derived neurotrophic factor, BDNF (Duman 1998) which is reported to have a central role in adult hippocampal neurogenesis (Thakker-Varia et al. 2014), neuronal survival and plasticity (D'Sa and Duman 2002) and also in stress reaction (Nair et al. 2007), depression (Vaidya

and Duman 2001), antidepressant drug response (D'Sa and Duman 2002) and electroconvulsive therapy (Duman and Vaidya 1998).

In contrast, $G\alpha_{Q/Z}$-coupled receptor activation initiates activation of phospholipase C (PLC) which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). Here, IP_3 stimulates Ca^{2+} release from the endoplasmic reticulum, producing calcium-dependent protein kinase (PKC) activation (Kandel et al. 2000) which in turn induces long- and short-term changes in neuronal membrane conductivity to specific ions, including calcium. While short-term changes are mediated by specific ion channel phosphorylation, such as the L-type voltage dependent calcium channels (VDCC) (Braha et al. 1993; Baxter et al. 1999), long-term changes are effected by activating genes coding for these channels with subsequent new protein synthesis (Golden et al. 2002). VDCC-mediated calcium signaling plays an important role in neurogenesis, neuronal plasticity and antidepressant response; as explained in the following section.

The hippocampal SVZ and SGZ areas are located near the lateral ventriculi. They contain choroid plexus tissue rich in TAP cells and act as a vascular niche for adult neurogenesis (Palmer et al. 2000). Multiple GPCRs, such as 5-HT_{2C}, 5-HT_6, D_1, D_5, and the α_1-adrenergic receptors, are expressed in the choroid plexus and it is therefore possible that GPCRs expressed in the SVZ and SGZ plexus have important roles in regulating adult hippocampal neurogenesis (Mignini et al. 2000; Papay et al. 2006; Labasque et al. 2008; Gupta et al. 2009).

Serotonin has a stimulating effect on neurogenesis in the DG (Brezun and Daszuta 2000). While increased hippocampal neurogenesis was found in 5-HT-transporter deficient mice (Schmitt et al. 2007), 5-HT depletion decreased adult neurogenesis in both the SVZ and SGZ and it also reduced survival and proliferation in cultured neurospheres derived from the adult mouse hippocampus (Benninghoff et al. 2010). Reports confirm that SSRIs stimulate neurogenesis *via* 5-HT receptor activation (Kempermann 2011) mediated, at least in part, by 5-HT_{1A} receptors (Manev et al. 2001; Santarelli et al. 2003), and 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_4 receptor roles have been established in 5-HT-induced adult hippocampal neurogenesis (Hitoshi et al. 2007).

While NE activates adult mouse hippocampal neurogenesis *via* a β_3 adrenoceptor-mediated mechanism (Jhaveri et al. 2010), α_2-adrenoceptor activation produced the opposite effect (Jhaveri et al. 2014). A further study suggests that although NE depletion decreases granule cell progenitor proliferation in the adult rat hippocampus it does not influence cell survival and differentiation (Kulkarni et al. 2002). In addition, DA denervation reduces the translation of mRNA coding to the ciliary neurotrophic factor (CNTF; one of the primary mediators of hippocampal neurogenesis) in adult rat SVZ (Yang et al. 2008). Although the atypical antipsychotic drug and D_2 receptor agonist, quinpirole, increased CNTF mRNA levels, suggesting that the putative stimulatory effect of DA on adult hippocampal neurogenesis is mediated by D_2 receptors, the classical antipsychotic drug and D_2 receptor antagonist, haloperidol, reverses quinpirole-mediated translation of CNTF mRNA and even inhibits proliferation of rat NSCs (Yang et al. 2008; Kippin et al. 2005). Recent investigation has determined that D_3 receptor activation stimulates NSCs proliferation in mice through protein kinase B pathways (PKB, also known as AKT) and also extracellular-signal-regulated kinases 1 and 2 (ERK1/2) (Lao et al. 2013).

Putative role of L-type voltage dependent calcium channels in antidepressant response: Calcium signaling, neurogenesis, and hippocampal plasticity

VDCCs are calcium channels with conductivity regulated by electrical potentials across the cellular membrane, and these play important roles in multiple neuronal processes including action potential generation (Fuentes-Antras et al. 2013), release of synaptic vesicles (Takahashi and Niimi 2009), apoptotic neuron death (Heck et al. 2008) and NSC proliferation into mature CNS cells (Feliciano and Edelman 2009). VDCCs also regulate neuronal plasticity *via* multiple mechanisms, such as altering the size and shape of dendritic spines (Fifkova 1985) and activity-dependent modulation of synaptic strength by inducting long-term potentiation (LTP) and long-term depression (LTD) (Carlson and Giordano 2011). VDCCs in turn are regulated by $G\alpha_Q$- (Braha et al. 1993; Baxter et al. 1999; Golden et al. 2002) and $G\alpha_S$-coupled receptors (Favilla et al. 2008). It is therefore possible that VDCC's have a role in both depression pathophysiology and response to antidepressant drugs (Bhat et al. 2012).

Three classes of the VDCC are recognized: high voltage-activated L-type channels, neuronal P/Q, N, and R-type channels, and low voltage-activated T-type channels (Lacinova 2005). The L-type calcium channels (LTCC) are especially interesting because they are widely expressed in brain limbic areas, including the pre-frontal cortex and hippocampus. While LTCC's can be expressed pre-synaptically on axonal terminals and play some part in regulating transmitter release when strongly activated (Zakharenko et al. 2002), the majority are believed to be expressed on both post-synaptic neuron dendritic trees where they regulate calcium entry to post-synaptic neurons and also in important cellular processes including synaptic strength and gene expression (Hell et al. 1993; Graef et al. 1999; Dolmetsch et al. 2001; Deisseroth et al. 2004).

Four LTCC sub-types are known: $Ca_{Vs}1.1$, 1.2, 1.3 and 1.4. The $Ca_V1.2$ and $Ca_V1.3$ channels are predominantly expressed in the hippocampus where their α_1 subunits are encoded by *CACNA1C* and *CACNA1D* genes, respectively. It is reported that tissue-selective knock-out mice with hippocampal *CACNA1C* expression postnatally downregulated demonstrate impaired synaptic plasticity, memory and learning (Moosmang et al. 2005; White et al. 2008). Human genome-wide association studies (GWAS) indicate that *CACNA1C* polymorphism is associated with autism (Krug et al. 2010), schizophrenia (Erk et al. 2014), bipolar disorders (Ferreira et al. 2008; Craddock and Sklar 2009), and depression (Casamassima et al. 2010; Shi et al. 2011; Backes et al. 2014). Further, Erk et al. (2014) and Backes et al. (2014) documented that *CACNA1C* polymorphism is associated with abnormal neural activity in brain limbic areas when GWAS and fMRI are combined

Studies have revealed that various antidepressant drugs modulate the activity of VDCC activity; for example, tricyclic antidepressants inhibit calcium currents in heart myocytes (Delpon et al. 1991) and neurons (Choi et al. 1992). It is possible that the inhibition in heart myocytes contributes to the cardiotoxic side effects witnessed in this class of antidepressants (Glassman 1998; Glassman et al. 1998). In addition, SSRI fluoxetine and its primary metabolite norfluoxetine inhibit T-type calcium channels (Traboulsie et al. 2006). Zahradník et al. (2008) reported that different antidepressant drugs with different chemical structures and action mechanisms, including the tricyclic amitriptyline, immipramine, and dipenzepine (non-selective blockers of serotonin (SERT) and norepinephrine transporter (NAT)), desipramine (selective NAT inhibitor) and clomipramine (selective SERT blocker) and also the tetracyclic maprotiline and highly selective SSRI citalopram all inhibit LTCC-mediated current in isolated heart myocytes.

Reports indicate that $Ca_V1.2$ channel-blocking dihydropyridines (DHPs) alter sensitivity to cocaine and morphine (Kuzmin et al. 1996), modulate alcohol withdrawal symptoms (Watson et al. 1994), induce antidepressant-like behavior in rats (Cohen et al. 1997) and mice (Srivastava and Nath 2000) and impair conditioned fear extinction without interfering with its acquisition (Busquet et al. 2008). In contrast, the BayK8644 $Ca_V1.2$ channel activator induced a behavioural syndrome in rodents manifested by severe dystonia and self-biting (Jinnah et al. 1999).

LTCCs are considered important in antidepressant-induced hippocampal neurogenesis because their $Ca_V1.2$ and $Ca_V1.3$ sub-types and NMDA receptors are closely associated with adult hippocampal neurogenesis These LTCC channels are expressed in proliferating NPCs, enabling them to directly sense and process excitatory stimuli. Pharmacological experiments indicate that LTCCs regulate calcium concentration in NPCs; and (Deisseroth et al. 2004) demonstrated that excitatory stimuli act directly on adult hippocampal NPC's to favor neuronal production. The excitation is sensed by depolarization-evoked intracellular calcium transients *via* $Ca_v1.2/1.3$ channels and NMDA receptors on the proliferating precursors, so that this pathway inhibits expression of *Hes1* and *Id2* glial fate genes and increases expression of the NeuroD positive regulator of neuronal differentiation (Deisseroth et al. 2004).

Future strategies for the treatment of depression: Advantages and barriers

Although existing antidepressant drugs are believed to act almost exclusively on brain 5-HT, NE, and DA systems, the increased brain monoamine transmission and subsequent activation of serotonergic, noradrenergic and dopaminergic GPCR provide only the first steps in the cascade required to initiate this treatment's behavioral and therapeutic effects. Evidence implies that the therapeutic effect of antidepressant drugs is mediated, at least in part, *via* stimulation of adult hippocampal neurogenesis and neuronal plasticity, and therefore, ion channels, particularly LTCC, and the G-protein coupled receptors could well be involved in antidepressant drug response. Interestingly, many CNS functions affected by L-type channel blockers also require synaptic plasticity mediated by activation of CREB, where its expression is altered to dominant negative or active forms in brain regions affecting mood, fear, memory and responses to drug abuse. Although latest-generation antidepressant drugs exhibit some improved clinical efficacy, their therapeutic potential is still limited and it is imperative to develop new antidepressants and/or adjuncts to existing drugs. Because of the putative role of GPCR and VDCC in antidepressant-induced hippocampal neurogenesis, compounds acting on other-than-monoaminergic GPCRs, such as histamine, opioid, oxytocin or vasopressin receptors, may be beneficial in depression therapy (Duncko et al. 2003; Mlynarik et al. 2007; Hlavacova et al. 2010; Flik et al. 2011; Franklin et al. 2012).

Since VDCCs, and especially LTCCs, have such critical roles in antidepressant-induced stimulation of hippocampal neurogenesis and plasticity, these channels provide perfect targets for future antidepressant drugs (Bhat et al. 2012). While it is imperative that future drugs have greater efficacy and faster therapeutic effect than contemporary antidepressant monoamine neurotransmission stimulation, selectivity and safety impose the main barriers to developing antidepressant drugs which act directly on VDCCs. These voltage-dependent calcium channels are widely expressed throughout the body, mediating numerous crucial physi-

ological functions, including regulating cardiac activity (Zahradnikova and Zahradnik 2012; Janicek et al. 2013), and therefore drugs based on their activity could have severe side effects. However, direct targeting of these drugs on their action site, such as the hippocampus, using advanced neurosurgical and/or pharmaceutical techniques could provide a solution to these problems.

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