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Synaptic plasticity in depression: Molecular, cellular and functional correlates

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ABSTRACT

Synaptic plasticity confers environmental adaptability through modification of the connectivity between neurons and neuronal circuits. This is achieved through changes to synapse-associated signaling systems and supported by complementary changes to cellular morphology and metabolism within the tripartite synapse. Mounting evidence suggests region-specific changes to synaptic form and function occur as a result of chronic stress and in depression. The prefrontal cortex (PFC) and hippocampus represent the best studied regions where functional and structural findings are consistent with a deficit in long-term potentiation (LTP), and neuronal and glial growth at excitatory synapses. Correlating these changes may be those to glutamate receptors (AMPARs and NMDARs), growth factor signaling (BDNF-TrkB) and several signal transduction pathways (NOS-NO, cAMP-PKA, Ras-ERK, PI3K-Akt, GSK-3, mTOR and CREB). In contrast other brain regions such as the amygdala may feature a somewhat opposite synaptic pathology including reduced inhibitory tone. Deficits in synaptic plasticity may further correlate disrupted brain redox and bioenergetics in stress and depression. Moreover, at a functional level region-specific changes to synaptic plasticity in depression may relate to maladapted neurocircuitry and parallel reduced cognitive control over negative emotion.

Contents

Abbreviations: mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; DG, dentate gyrus; NAc, nucleus accumbens; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; NMDAR, *N*-methyl-D-aspartic acid receptor; VDCC, voltage-dependent calcium channel; mGluR, metabotropic glutamate receptor; D_1, dopamine receptor type 1; 5-HT_{1A}, serotonin receptor type 1A; TrkB, tyrosine kinase receptor 2; PSD-95, postsynaptic density protein 95; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; nNOS, neuronal nitric oxide synthase; iNOS, inducible nitric oxide synthase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinistol-3-kinase; Akt, protein kinase B; GSK-3, glycogen synthase kinase-3; mTOR, mammalian target of rapamycin; CREB, cAMP response element-binding; SSRI, selective serotonin reuptake inhibitor; SSRE, selective serotonin reuptake enhancer; NRI, noradrenaline reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; ECS, electroconvulsive seizure; snp, single-nucleotide polymorphism; CUMS, chronic unpredictable mild stress; CRS, chronic restraint stress; CIS, chronic immobilisation stress; SD, social defeat.

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1. Introduction

Depressive disorders impose a severe burden on inflicted individuals and may be becoming increasingly prevalent in modern society (Hidaka, 2012; Lépine and Briley, 2011; Mathers and Loncar, 2006). These factors taken with the limited efficacy of current clinical monoaminergic antidepressants (Papakostas et al., 2007; Thase et al., 2005) underscore the need for better understanding and treatment of these disorders. Certainly depression is a complex and heterogeneous condition, the neurobiology of which is increasingly associated with diverse changes to multiple systems. For instance molecular and cellular findings implicate neuroplastic, neurometabolic and neuroimmune changes in depression (Kubera et al., 2011; Marsden, 2011; Pittenger and Duman, 2008). Functional and structural neuroimaging studies implicate changes to brain regions such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC), thalamus, hippocampus, amygdala and basal ganglia in depression (Bora et al., 2012; Du et al., 2012; Murrough et al., 2011; Price and Drevets, 2010). All of these changes likely relate closely to altered synaptic form and function in depression, which itself may play a fundamental pathological role. For instance, at the cellular level altered synaptic plasticity could account for and correlate changes to signaling systems, cellular morphology and even metabolic function. At a regional level such changes may account for altered inter-regional connectivity and regional activity. Whilst at a functional level these changes may correlate altered cognition, cognitive bias and ultimately persistent negative emotions. Accordingly a better appreciation of the synaptic pathology in depression could facilitate a more integrated neurobiological conceptualisation of this disorder and present opportunities for more efficient treatment and prevention. To this end, this paper aims to review the evidence implicating altered synaptic plasticity in depression and to further characterise the major signaling pathways which may underlie changes to neuronal and glial plasticity. Finally this paper closes with a brief discussion on the putative functional implications of altered synaptic plasticity in depression.

Central to this paper are findings from human studies and well-validated behavioural models. Human studies mainly constitute those from post-mortem analyses; *for a discussion on analysis techniques and interpretive considerations see* (Altar et al., 2009). Animal studies typically use forms of stress, a well-accepted aetiological factor in depression, to study the neurobiological correlates of depressive-like behaviour. In particular the construct and behavioural characteristics of chronic stress models (e.g. CMS and CUS) suggests they are better representations of human depression than are acute stress models (Willner, 2005). This is particularly important given that acute stress and chronic stress often exert opposite effects on neuroplasticity (Joëls and Krugers, 2007; Popoli et al., 2012). Accordingly chronic stress models take precedence in this review; although where a paucity of research exists, findings from other studies may be discussed. It is also worth considering that even chronic stress models of depression are still approximations with inherent variability (Bergström et al., 2008; Schweizer et al., 2009) and translational limitations. For instance the aetiology of human depression is likely multi-factorial, consisting of genetic, psychological, metabolic and immunological factors amongst others (Maes et al., 2011c; Marsden, 2011; Stanger et al., 2009; Szewczyk et al., 2010). These other stressors have not been so well-studied with regards to neuroplasticity in depression at this time (Fig. 4).

2. Synaptic plasticity: basic mechanisms

2.1. Correlates of synaptic strength

Synapses are highly specialised structures which principally mediate electro-chemical communication between neurons. Synaptic form and function is highly dynamic in nature, and has been widely studied as a cellular correlate of memory and learning. The best studied forms of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD), which occur at both excitatory and inhibitory synapses throughout the brain (Kullmann and Lamsa, 2011; Markram et al., 2011; Méndez and Bacci, 2011). Experimentally LTP and LTD can be induced via either frequency/rate-dependent stimulation (e.g. HFS and LFS), spike-timing-dependent plasticity (STDP) protocols or chemical induction (e.g. NMDA) protocols; whilst physiological induction may involve a convergence of rate, timing and neuromodulator influence (Markram et al., 2011). At excitatory synapses LTP and LTD have been shown to be reversible through further less well studied forms of plasticity such as depotentiation and dedepression respectively (Morishita and Malenka, 2008; Qi et al., 2012). Whilst synaptic plasticity is a widespread phenomenon in the brain, the molecular and cellular mechanisms underpinning synaptic plasticity remain best characterised within the hippocampus; typically the Schaffer collateral pathway projecting from CA3 to excitatory pyramidal neurons in CA1. Accordingly the glutamatergic synapse in the hippocampus represents the model synapse in this paper herein.

The establishment of changes in synaptic strength involves both pre- and postsynaptic mechanisms, and depends upon the movement and synthesis of receptors and other synaptic proteins. Rapid changes to plasticity, for instance during early-LTP (E-LTP), rely upon the movement of pre-existing proteins; whilst late-LTP (L-LTP) requires RNA translation (i.e. protein synthesis) (Slipczuk et al., 2009; Tang et al., 2002) and changes to gene expression (Wu et al., 2007). LTD also involves changes to protein metabolism and gene expression, and likely in an oppositional manner (Li et al., 2010c; Mauna et al., 2011). The best studied molecular correlate of synaptic strength at excitatory synapses is AMPAR expression. Synaptic potentiation involves the addition of AMPARs containing GluR1, GluR2L and GluR4 subunits; whilst GluR2, GluR3 and GluR4c subunits participate in AMPAR removal during LTD (Kessels and Malinow, 2009; Stornetta and Zhu, 2011). Other glutamate receptors are also regulated during activity-dependent plasticity. NMDAR synaptic responses most consistently decrease with LTD (Morishita and Malenka, 2008); however NMDARs undergo trafficking and changes to GluN2 subunit ratios following LTP and LTD (Peng et al., 2010). Similarly the expression of certain mGluR types may also be bidirectionally regulated following LTP and LTD (Cheyne and Montgomery, 2008; Manahan-Vaughan et al., 2003). In addition many other protein types are modulated by synaptic plasticity. For example the expression of presynaptic proteins synapsin 1 and SNAP25, and dendritic CaMKII and MAP2 are all increased following hippocampal LTP (Roberts et al., 1998a, 1998b; Sato et al., 2000).

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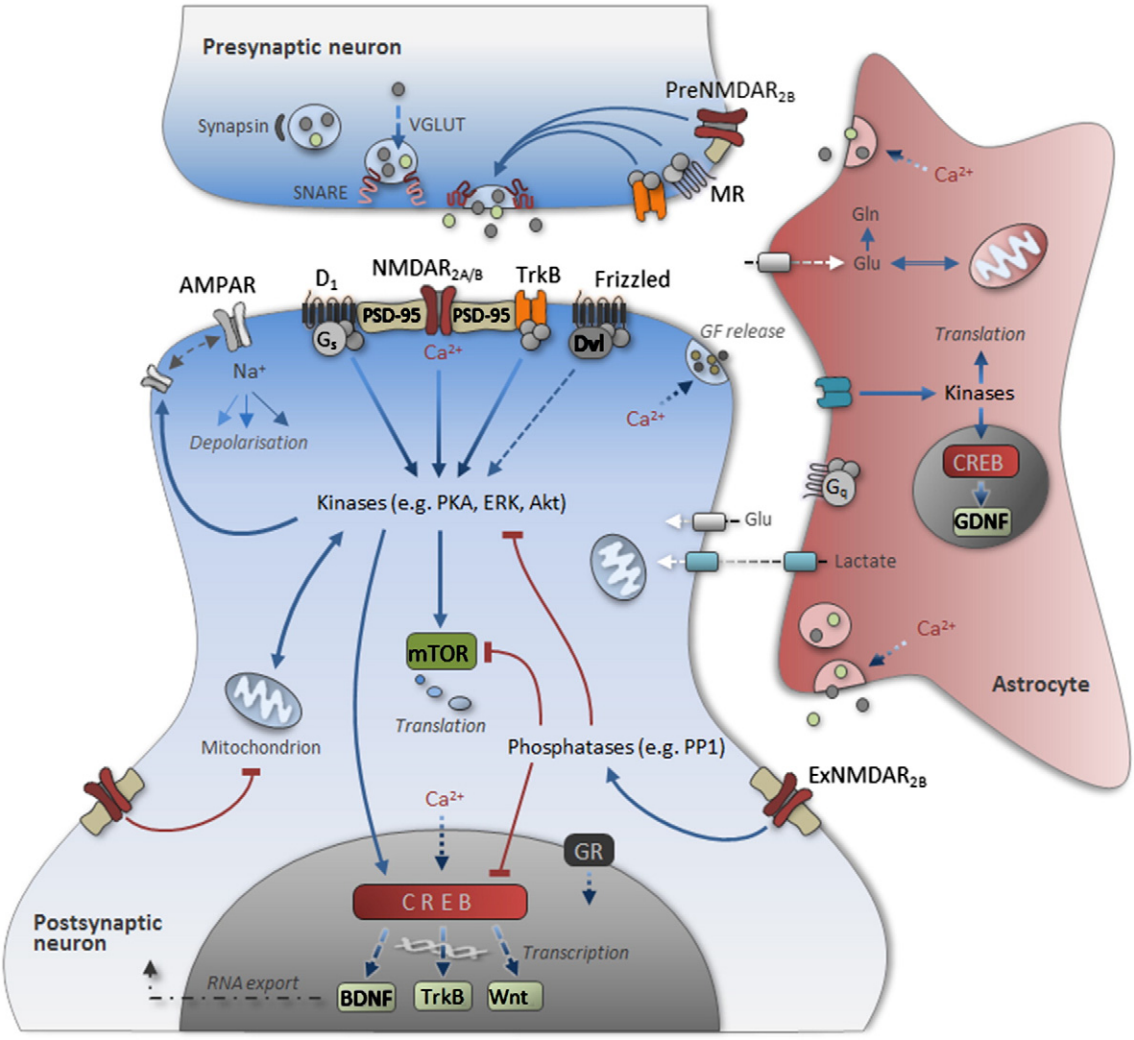

Fig. 1. The tripartite synapse and calcium (Ca^{2+}) signaling in the hippocampus. On the presynaptic neuron, glutamate (Glu) is loaded into vesicles via vesicular glutamate transporters (VGLUTs). Neuronal activity triggers SNARE-dependent vesicle fusion and release of glutamate into the synaptic cleft. Glutamate binds to synaptic receptors (e.g. AMPARs and NMDARs) before being taken up by transporters into glia and neurons. Repeated postsynaptic AMPAR activation depolarises the neuron and allows for NMDAR activation, the resulting Ca^{2+} influx initiates changes to synaptic plasticity. Ca^{2+} influx leads to further release from internal stores and subsequent release of brain-derived neurotrophic factor (BDNF) and Wnt proteins. Signaling from NMDARs and growth factors (e.g. BDNF-TrkB and Wnt-Frizzled) converge and cooperate to activate various signaling pathways which regulate protein trafficking, translation and gene transcription. For instance during long-term potentiation (LTP) multiple signals converge to regulate AMPAR trafficking, and mammalian target of rapamycin (mTOR) translation and cAMP response element-binding (CREB) transcription pathways. In contrast, during long-term depression (LTD) intracellular phosphatase signaling leads to inhibition of mTOR and deactivation of CREB. Extrasynaptic NMDARs (GluN2B containing) represent a major mediator of negative neuroplastic signaling; associated pathways lead to CREB shut-off, disruption of mitochondrial function and potentially cell death. Astrocytes are also crucially involved in synaptic plasticity via the release of gliotransmitters and metabolic factors such as lactate. *Additional abbreviations*: Dvl, dishevelled protein; GF, growth factor; Gln, glutamine; PreNMDAR, presynaptic NMDAR; ExNMDAR, extrasynaptic NMDAR.

Changes to synaptic plasticity are further coordinated with those to structural plasticity within the tripartite synapse. On pyramidal neurons, LTP and LTD induce dendritic spine growth and retraction respectively, whilst AMPAR expression is positively related to the size of the spine head (Kasai et al., 2010). Presynaptic axonal bouton turn-over and morphology is also regulated by synaptic plasticity; LTP and LTD bidirectionally regulate bouton-spine association (Becker et al., 2008; Lushnikova et al., 2009). Furthermore changes to glial processes may also be a general component of synaptic plasticity (Haber et al., 2006). Indeed LTP alters astroglial numbers and volume, and ultimately increases coverage of excitatory synapses in the hippocampus (Lushnikova et al., 2009; Wenzel et al., 1991). Consistent with these structural changes to the tripartite synapse, neuronal and glial glutamate transporter expression is also up-regulated during early and late-LTP (Pita-Almenar et al., 2006).

2.2. Signaling systems involved in synaptic plasticity

Neurons, glia and many signaling systems participate in concert during synaptic plasticity. At an individual synapse, appropriate stimulation leads to the release of several neuro- and gliotransmitters (Chen et al., 2012a; Wenker, 2010) and the activation of various surface-level receptors. Most central to the initiation of synaptic plasticity is calcium (Ca^{2+}) influx through ion channels. In particular the NMDAR fulfils the coincident detection requirements of Hebbian plasticity and serves as the canonical pathway leading to bidirectional changes in plasticity (Markram et al., 2011). The direction of NMDAR-dependent plasticity is influenced by many factors such as activation level, phosphorylation state, subunit composition and postsynaptic location. During neuronal activity Ca^{2+} influx through synaptic NMDARs and somatic VDCCs is accompanied by release from internal stores (Bengtson and Bading, 2012). These Ca^{2+} signals

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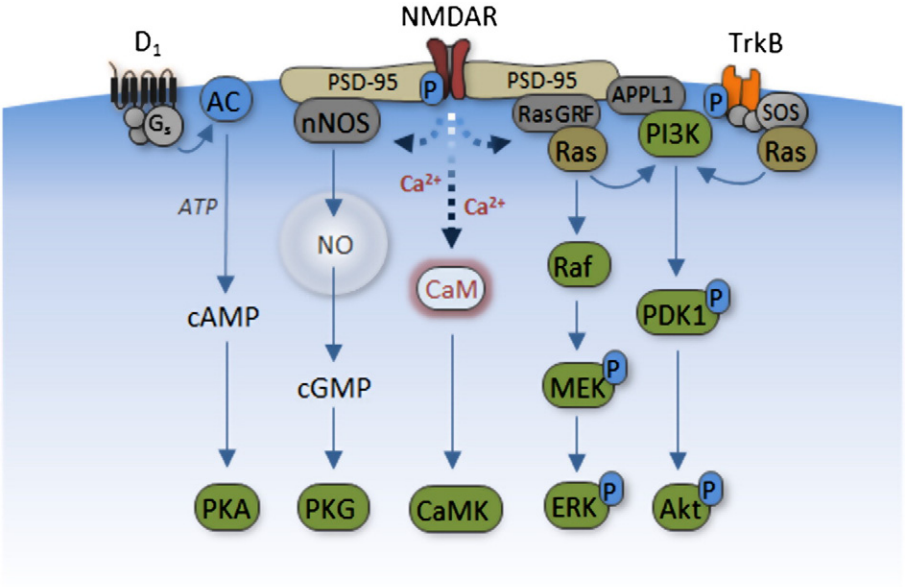

Fig. 2. The NMDAR signaling complex: upstream signaling pathways mediating positive changes to neuroplasticity. Synaptic NMDAR activation allows Ca^{2+} influx and binding to calmodulin (CaM) which leads to activation of Ca^{2+}/calmodulin-dependent kinases (CaMK) as well as other signaling proteins. Neuronal nitric oxide synthase (nNOS) is held within close proximity of NMDARs through interactions with postsynaptic density protein 95 (PSD-95). Ca^{2+}/calmodulin binding to nNOS stimulates nitric oxide (NO) production (Feil and Kleppisch, 2008). NMDAR stimulation of the Ras-ERK1/2 pathway can be achieved by CaMK1-RasGRF (Li et al., 2006; Schmitt et al., 2005) and NO signaling (Gallo and Iadecola, 2011; Yun et al., 1998, 1999); NMDARs may also activate MEK5–ERK5 (Wang et al., 2006a). The PI3K-Akt pathway associates with the NMDAR-PSD-95 complex via adapter protein APPL1 (Wang et al., 2012). Activation of PI3K-Akt signaling may be achieved through CaM (Xu et al., 2007) and Ras (Castellano and Downward, 2011; Qin et al., 2005). Ca^{2+} influx through NMDARs may also stimulate the PKA pathway through activation of Ca^{2+}/calmodulin sensitive adenyl cyclases (AC). NMDARs co-localise with D_1 receptors both of which may synergistically boost PKA signaling (Mockett et al., 2004). NMDARs also work synergistically with BDNF-TrkB signaling (Martin and Finsterwald, 2011; Xu et al., 2007; Yoshii and Constantine-Paton, 2010).

activate several intracellular signal transduction pathways crucial to synaptic plasticity, which will be discussed in more detail later.

Further crucial to NMDAR-dependent plasticity is co-operation with other signaling systems. Indeed induction of the translation and transcription machinery during L-LTP involves the coincident activation of several intracellular pathways (Kovács et al., 2007; Ma et al., 2011; Martin and Finsterwald, 2011; Tanaka et al., 2008). In particular intracellular Ca^{2+} signals following synaptic activity promote the secretion of growth factors such as BDNF (Jourdi et al., 2009; Kuczewski et al., 2009) and Wnt proteins (Chen et al., 2006; Li et al., 2012; Wayman et al., 2006). These proteins crucially co-operate with NMDARs to induce changes to neuroplasticity. With regard to the BDNF system; BDNF-TrkB signaling is involved in LTP, whilst proBDNF-$p75^{NTR}$ signaling may be recruited during LTD (Yoshii and Constantine-Paton, 2010). In addition some neuromodulator systems are also required for NMDAR-dependant plasticity. D_1 receptor activation is required for LTP (Granado et al., 2008; Gurden et al., 2000; Navakkode et al., 2007), whilst CB_1 receptors are involved in LTD (Corlew et al., 2009; Izumi and Zorumski, 2012). Other neuromodulators, including metabotropic monoamine systems (e.g. serotonin, dopamine and noradrenaline) which represent the typical targets of antidepressants, crucially modulate plasticity thresholds and characteristics (Ma et al., 2011; Pawlak et al., 2010; Polter and Li, 2010; Qin et al., 2005). Finally some neuromodulator receptors can mediate NMDAR-independent forms of plasticity (e.g. $mGluR_{1/5}$ and 5-HT_2 (Zhong et al., 2008)).

Whilst the basic signaling mechanisms underlying synaptic plasticity at excitatory synapses have been best described in CA1, they are applicable to other hippocampal regions; a notable exception being CA2 (Caruana et al., 2012). Similarly these mechanisms are also conserved in other key brain regions implicated in depression such as the PFC (Cui et al., 2011; Sarantis et al., 2009; Sui et al., 2008). However different brain regions may have distinct characteristics which influence synaptic plasticity. Most notably there is a differential expression of NMDAR subunits in the lateral amygdala versus CA1, which will contribute to unique aspects of amygdala synaptic plasticity (Miwa et al., 2008).

3. Synaptic plasticity in stress and depression

3.1. Chronic stress and antidepressant modulation of plasticity

Stress has profound effects on synaptic form and function; *for other recent reviews on this topic see* (Christoffel et al., 2011; Popoli et al., 2012; Sandi, 2011). Stress and glucocorticoid modulation of synaptic plasticity is mediated via activation of mineralocorticoid (MR) and glucocorticoid receptors (GR) (Fig. 1). Through these receptors stress and glucocorticoids exert direct effects on neurons and glia (Yu et al., 2011), and also increase glutamate release in brain regions such as the PFC, hippocampus, amygdala and nucleus accumbens (NAc) (Musazzi et al., 2011; Sandi, 2011). The effects of stress on synaptic plasticity are highly dependent upon brain region, stress type and time point measured (Joëls and Krugers, 2007). In particular whilst acute stresses have been reported to produce bidirectional effects on synaptic plasticity in several brain regions, chronic stress has a more unidirectional influence.

The effects of stress on synaptic and structural plasticity have been particularly well-studied in the hippocampus. CUS impairs LTP in DG and CA1 subregions (Alfarez et al., 2003); whilst chronic restraint stress (CRS) was found to impair LTP in CA3 (Pavlides et al., 2002). Another study found that CMS facilitated LTD in CA1 (Holderbach et al., 2007). Disruption of hippocampal plasticity (CA1 and DG) by chronic stress is GR-dependent (Datson et al., 2012; Krugers et al., 2006). The negative effects of stresses on synaptic plasticity in the hippocampus can be prevented or reversed by monoaminergic antidepressants (Holderbach et al., 2007; Matsumoto et al., 2005). In addition stress facilitation of spike-timing-dependent LTD (tLTD) in CA1 can be reversed by the mood stabiliser lithium (Niehusmann et al., 2010). Consistent with changes to synaptic plasticity in the hippocampus, CMS disrupts neurogenesis in the dentate gyrus (DG)

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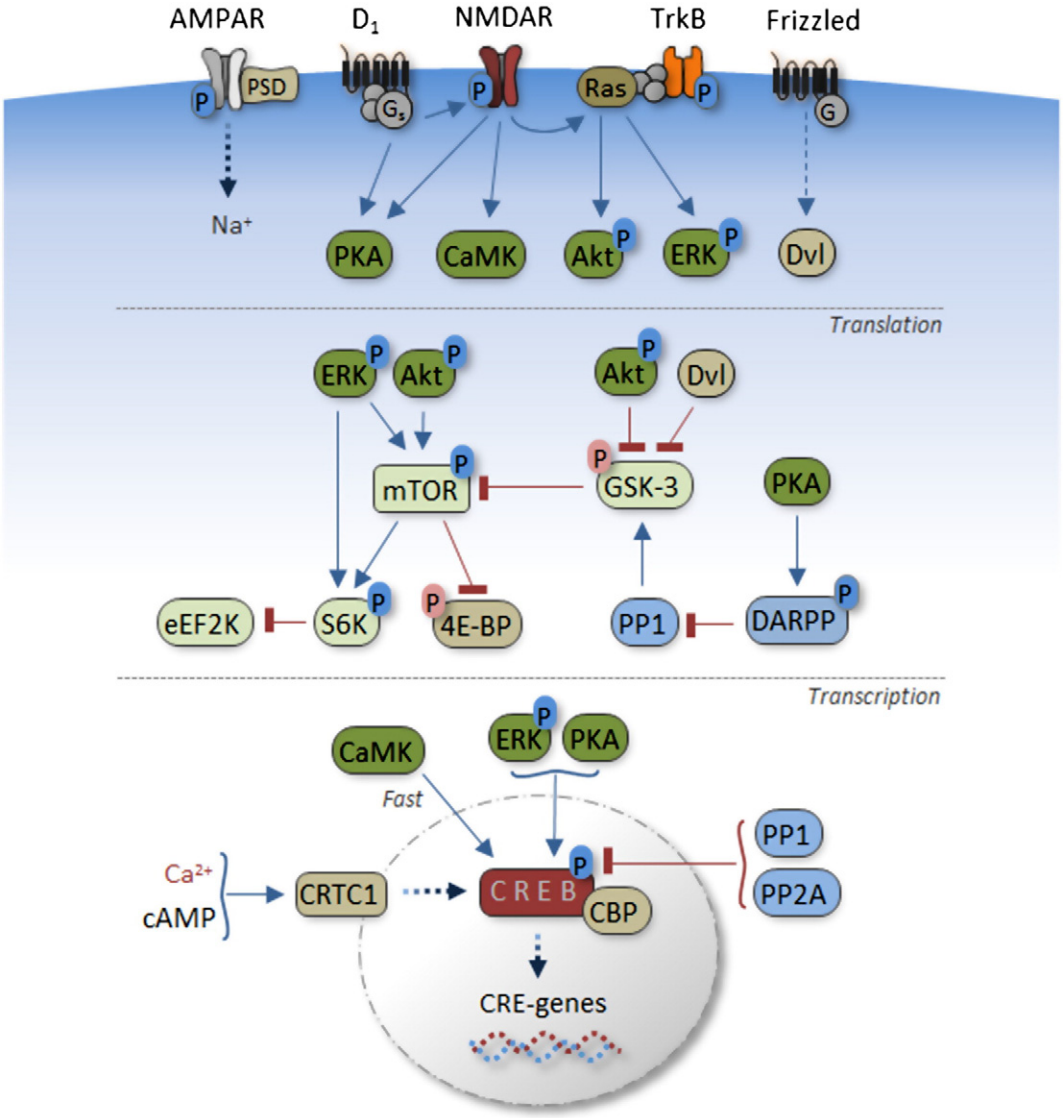

Fig. 3. Regulation of translation and transcription during hippocampal synaptic plasticity. Cooperation between upstream signaling pathways is required to modulate downstream systems regulating translation and transcription processes. Glycogen synthase kinase 3 (GSK-3) is inactivated by Wnt-frizzled signaling and protein kinase B (Akt)-phosphorylation at *ser9*, whereas GSK-3 can be dephosphorylated and activated by protein phosphatase 1 (PP1). This latter pathway may also interact with protein kinase A (PKA) which can phosphorylate DARPP, a potent inhibitor of PP1 (Abel and Nguyen, 2008). Suppression of GSK-3 activity facilitates activation of mammalian target of rapamycin (mTOR), activation of which is also dependent upon extracellular signal-regulated kinase (ERK) and Akt pathways. mTOR regulates transcription initiation through interactions with 4E-BP, S6K and eEFK2 (Hoeffer and Klann, 2010). Activation of cAMP response element-binding (CREB)-dependent transcription involves the participation of multiple upstream pathways. CREB needs to be phosphorylated at *ser133* to recruit CREB-binding protein (CBP). This phosphorylation may be initiated by a fast Ca^{2+}/calmodulin-dependent kinase IV (CaMKIV) component and sustained by ERK (Wu et al., 2001); whilst PKA activity is also required (Abel and Nguyen, 2008). CREB activation further requires translocation of CREB-regulated transcription coactivator 1 (CRTC1) to the nucleus, which is dependent upon Ca^{2+} (e.g. calcineurin and NO) and cAMP signaling pathways (Gallo and Iadecola, 2011; Kovács et al., 2007; Martin and Finsterwald, 2011). CREB can be deactivated by PP1 and protein phosphatase 2A (PP2A) pathways (Mauna et al., 2011). *Additional abbreviations*: Dvl, dishevelled protein.

(Holderbach et al., 2007) and promotes pyramidal dendrite atrophy in CA1, CA2 and CA3 (Luo and Tan, 2001); similarly chronic immobilisation stress (CIS) promotes pyramidal dendrite retraction in CA1 and CA3 in an NMDAR-dependent manner (Christian et al., 2011). Furthermore CMS may increase apoptotic rate in the hippocampus (Liu et al., 2010; Silva et al., 2008); which again may be NMDAR-dependent (Abrahám et al., 2006; Xiao et al., 2010). In contrast, antidepressants oppose the dendrite atrophy and increases in apoptosis markers induced by CMS in the hippocampus (Liu et al., 2010; Luo and Tan, 2001; Silva et al., 2008). A similar bidirectional regulation of astrocyte growth by chronic stress and antidepressants may also occur in the hippocampus (Czéh et al., 2006; Yu et al., 2011).

Consistent with changes to cellular function and morphology in the hippocampus chronic stress alters the expression of critical receptors and proteins involved in synaptic plasticity. For instance chronic stresses lower the expression of AMPAR subunits (GluR1, 2 and 3), NMDAR subunits (GluN1 and 2B) (Cohen et al., 2011; Duric et al., 2012; Kiselycznyk et al., 2011; Yuan et al., 2011) and various synaptic proteins (e.g. synapsin 1 and PSD-95) (Alfonso et al., 2006; Cohen et al., 2011; Elizalde et al., 2010; Silva et al., 2008), whilst antidepressant treatments oppose these changes. Other studies report that chronic but not acute treatment with monoaminergic antidepressants increases the expression of several AMPAR subunits (Barbon et al., 2011), and AMPAR subunit synaptic expression in the hippocampus (Martínez-Turrillas et al., 2005, 2007).

The PFC is affected in a similar manner to the hippocampus by chronic stress. CUS/CMS protocols impair LTP induction in the PFC (Quan et al., 2011b), as well as hippocampus-PFC and thalamus-PFC pathways (Cerqueira et al., 2007; Quan et al., 2011a). Stress-induced disruption of LTP in the PFC is GR-dependent (Mailliet et al., 2008).

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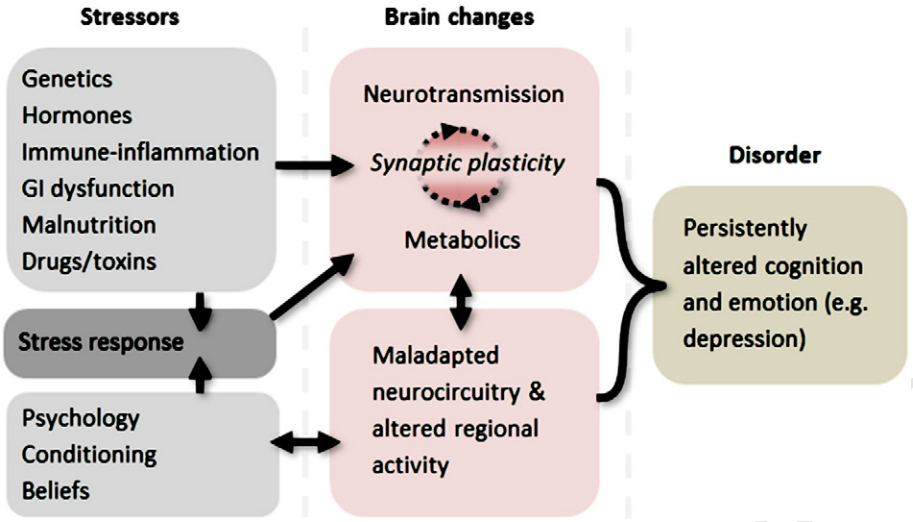

Fig. 4. A basic hierarchical scheme for the pathogenesis of depression. A variety of physical and psychological stressors associate with neuropsychiatric disorders. These stressors differentially affect the state and function of neurons and neuronal networks throughout the brain. Differential impact on cells and related ensembles/networks gives rise to maladapted brain circuitry. These regional-level changes may then associate with a persistent shift in cognition and emotion, and distinct conditions such as depression.

The negative effects of stresses on synaptic plasticity in the PFC can be restored by monoaminergic antidepressants (Dupin et al., 2006; Qi et al., 2009). Chronic stress also promotes pyramidal dendrite retraction in the mPFC in an NMDAR-dependant manner (Martin and Wellman, 2011). Moreover CUS increases the expression of the apoptosis protein caspase-3 in the cerebral cortex (Bachis et al., 2008), and disrupts glial metabolism and reduces GFAP expression in the PFC (Banasr et al., 2010). Chronic stresses lower the expression of AMPAR subunits (GluR1, 2 and 3), NMDAR subunits (GluN2B) (Gourley et al., 2009; Li et al., 2011; Quan et al., 2011b) and various synaptic proteins in the PFC (Elizalde et al., 2010; Li et al., 2011; Ray et al., 2011) whilst antidepressant treatment was found to reverse some of these changes. Chronic but not acute treatment with monoaminergic antidepressants increases the expression of several AMPAR subunits in the PFC (Barbon et al., 2011). Furthermore the rapid antidepressant activity of ketamine, $NMDAR_{2B}$ and $mGluR_{2/3}$ antagonists is accompanied by increased GluR1 expression, synaptogenesis and spinogenesis in the PFC (Dwyer et al., 2012; Li et al., 2010b, 2011).

Not all brain regions respond the same way to chronic stress as the PFC and hippocampus, most notably the amygdala. A frequent finding is that CRS and CIS protocols which induce dendrite retraction in the PFC and hippocampus actually induce dendrite arborisation of pyramidal and spiny neurons in the basolateral amygdala (BLA) (Eiland et al., 2012; Vyas et al., 2002, 2006). Recently BDNF expression was shown to correlate the opposite structural changes induced by CIS in the hippocampus (CA3) and BLA (Lakshminarasimhan and Chattarji, 2012). Perhaps further consistent with these changes a repeat stress protocol was reported to decrease GluN2B expression in the dorsal hippocampus whilst increasing expression in the BLA (Kiselycznyk et al., 2011). However the potential for stress to induce cell-specific negative changes in the amygdala are emphasised by other studies. CRS decreases interneuron-related proteins and dendritic arborisation in the LA and BLA (Gilabert-Juan et al., 2011). In addition CUS has been reported to induce atrophy of bipolar neurons in the BLA (Vyas et al., 2002), and lower amygdala GluR1 phosphorylation (Chandran et al., 2012); however both these models failed to alter hippocampal parameters which contrasts other studies.

Finally some other brain regions may also respond differently to the PFC and hippocampus in response to stress. CRS was found to increase excitability and consequently enhance both LTP and LTD induction in the anterior cingulate cortex (ACC) (Ito et al., 2010). CUS disrupts endocannabinoid (eCB)-dependent forms of synaptic depression in the NAc (Wang et al., 2010).

3.2. The synaptic pathology in MDD

Grey matter reductions have been reported in many brain regions in MDD; *for reviews see* (Bora et al., 2012; Du et al., 2012; Price and Drevets, 2010). Cellular correlates of these reductions may include negative changes to both neurons and glia. Glial pathology in MDD includes decreases in glial size and number whilst neuronal pathology may relate more to cellular shrinkage and synapse loss (Banasr et al., 2010; Price and Drevets, 2010). These changes most closely related to synaptic pathology in depression are reviewed below.

In the hippocampus lowered levels of neuropil (i.e. neuron and glial extensions) has been reported in MDD (Stockmeier et al., 2004). Lowered gene expression of synaptic proteins (e.g. synapsin, SNAP25, SAPs and MAPs) and AMPAR subunits (GluR1 and 3) was recently found in DG and CA1 subregions of the hippocampus (Duric et al., 2012). This study found no NMDAR transcript alterations in these regions; however lowered expression of the obligatory GluN1 NMDAR subunit has been reported in DG and CA3 in a previous study on MDD subjects (Law and Deakin, 2001). Lowered gene expression of the growth factors BDNF and VEGF has also been reported in DG and CA1 regions in MDD (Duric et al., 2010); both of which are required for hippocampal LTP (Licht et al., 2011; Yoshii and Constantine-Paton, 2010). In addition a dysregulation of growth factor receptor phosphorylation and expression was reported in the hippocampus of depressed suicide subjects (Dwivedi et al., 2009a); this included a relatively increased expression of $p75^{NTR}$, which is notable since proBDNF-$p75^{NTR}$ signaling may facilitate hippocampal LTD (Yoshii and Constantine-Paton, 2010).

Findings in the PFC seem similar to those in the hippocampus. Reductions in neuronal and glial sizes have been reported in the PFC in MDD (Price and Drevets, 2010; Rajkowska et al., 1999). Lowered expression of several synaptic proteins (e.g. VGLUT1, synaptophysin, synapsin 1, RAB and SNAP25) have been reported in the DLPFC (Gilabert-Juan et al., 2012; Kang et al., 2012; Martins-de-Souza et al., 2012). Lowered expression of transcripts for NMDAR subunits (GluN1 and 2A) was also found in the DLPFC of MDD subjects (Beneyto and Meador-Woodruff, 2008). In addition lowered expression of the postsynaptic protein PSD-95 and NMDAR subunits (GluN2A and 2B) was found in the anterior PFC (Feyissa et al., 2009). As above in the hippocampus, growth factor receptors were also dysregulated in the PFC (BA9) (Dwivedi et al., 2009a).

Findings in the amygdala support a somewhat opposite synaptic pathology to the regions above. For instance a large increase in the

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expression of PSD-95 (128%) and GluN2A (115%) was reported in the lateral amygdala of a set of mostly male depressed subjects (13 M/1 F) (Karolewicz et al., 2009). Increased VGLUT-1 levels have also been reported in the amygdala in MDD (Varea et al., 2012). In contrast BDNF levels and transcripts for interneuron-related peptides were decreased in the amygdala in female MDD subjects (Guilloux et al., 2011). Another study also recently found decreased levels of interneuron-related synaptic markers in the basolateral and basomedial amygdala in MDD (Varea et al., 2012). These findings taken with the effects of stress in the amygdala discussed earlier may suggest a divergent pathological outcome for different cell types in the amygdala in depression. One could speculate that interneuron atrophy and loss of glia might particularly account for the lowered amygdala volume reported in unmedicated depressed patients (Hamilton et al., 2008; Savitz et al., 2010).

Other studies implicate synaptic pathology in less well-studied brain regions in MDD. Altered expression of synaptic proteins have been found in the visual association cortex (Beasley et al., 2005), temporal lobe (BA21) (Aston et al., 2005; Glantz et al., 2010) and striatum (Kristiansen and Meador-Woodruff, 2005). Lowered expression of AMPAR (GluR1 and 3) and NMDAR (GluN2A and 2B) transcripts was found in the perirhinal cortex in MDD (Beneyto et al., 2007); notably this study found no alterations in the hippocampus. Finally lowered expression of GluN1 was reported in the superior temporal cortex in MDD (Nudmamud-Thanoi and Reynolds, 2004).

4. Signaling pathways underlying altered plasticity in depression

4.1. Signal transduction pathways involved in synaptic plasticity

A large array of signal transduction pathways are involved in synaptic plasticity. These pathways regulate processes including protein trafficking, translation and gene transcription to achieve functional and structural changes to plasticity. Signal transduction pathways involved in synaptic plasticity have been best studied with regards to hippocampal LTP. Central to the induction of LTP is propagation of an intracellular Ca^{2+} signal from synapse to nucleus. Along the way many signaling pathways are activated both directly and indirectly, in a spatial and temporal-dependent manner (Bengtson and Bading, 2012; Kim et al., 2011b). NMDARs crucially gate this Ca^{2+} signal during LTP. Following appropriate synaptic activity initial Ca^{2+} influx through NMDARs activates multiple pathways involved in LTP (Fig. 2). These include Ca^{2+}/calmodulin-dependent kinase (CaMK) isoforms (Bengtson and Bading, 2012), neuronal nitric oxide synthase (nNOS) signaling (Feil and Kleppisch, 2008), extracellular signal-regulated kinase (ERK), and protein kinase B (Akt) pathways (Patterson and Yasuda, 2011; Qin et al., 2005). In addition Ca^{2+}/calmodulin sensitive adenyl cyclase (AC) isoforms which regulate the protein kinase A (PKA) pathway are also required for LTP (Abel and Nguyen, 2008; Kim et al., 2011b; Wang, 2003); accordingly NMDARs may increase cAMP-PKA signaling (Banko et al., 2004; Mockett et al., 2004; Valera et al., 2008; Wang, 2003).

Other surface-level signaling systems which couple to some of these pathways are also recruited during synaptic plasticity. In this regard BDNF-TrkB signaling has been best studied. BDNF release is dependent upon Ca^{2+} influx through NMDARs and VDCCs as well as further release from intracellular ryanodine-sensitive stores (Jourdi et al., 2009; Kolarow et al., 2007). Such intracellular Ca^{2+} release may involve nNOS-NO signaling (Lu and Hawkins, 2002). BDNF release is also dependent upon CaMKII and gated by PKA activity (Kolarow et al., 2007). In addition TrkB expression is increased by NMDAR signaling (Du et al., 2000), whilst TrkB phosphorylation is dependent on NO signaling (Gallo and Iadecola, 2011). Postsynaptic BDNF-TrkB signaling couples to activation of Ras-ERK, PI3K-Akt and phospholipase C (PLC) pathways. BDNF also acts presynaptically to promote further glutamate release (Yoshii and Constantine-Paton, 2010). Notably NMDAR and BDNF-TrkB signaling may cooperatively activate PI3K-Akt (Xu et al., 2007) and other downstream pathways (Martin and Finsterwald, 2011). Several G protein-coupled receptors also participate in synaptic plasticity. For instance NMDAR activation triggers the secretion of Wnt proteins which activate Frizzled receptors and regulate intracellular GSK-3 signaling. GSK-3 is a constitutively active kinase which must be inhibited during LTP. GSK-3 can be inhibited through phosphorylation by various kinases (Bradley et al., 2012); recently it was reported that Akt and Wnt-Frizzled signaling may converge to inhibit GSK-3α during L-LTP in the mature rodent hippocampus (Ma et al., 2011) (Fig. 3). Other G protein-coupled receptors can modulate plasticity via regulation of the cAMP-PKA pathway. For instance D_1-PKA signaling is required for LTP (Granado et al., 2008; Gurden et al., 2000; Navakkode et al., 2007). Further, the PKA pathway is also capable of activating ERK with which it may operate in parallel (Banko et al., 2004; Dwivedi and Pandey, 2011; Waltereit and Weller, 2003). Ultimately all these upstream signal transduction pathways initiated by surface-level receptors may engage in significant cross-talk and cooperation to induce synaptic plasticity. Certainly AMPAR subunit phosphorylation and trafficking during LTP involves all the pathways above.

The later stages of LTP are dependent upon both protein translation and gene transcription, which similarly involves the participation of multiple signaling pathways. During LTP, protein synthesis is required to supply new proteins for functional and structural changes to plasticity. In this regard the mammalian target of rapamycin (mTOR) pathway plays a central role in the regulation of translation initiation and is required for L-LTP expression in the hippocampus (Tang et al., 2002). mTOR is known to regulate both dendritic and somatic protein synthesis in neurons (Hoeffer and Klann, 2010). Examples of mTOR translation targets include CaMKII, MAP2, PSD-95 and GluR1 (Gong et al., 2006; Lee et al., 2005; Slipczuk et al., 2009). Various upstream signaling pathways have been shown to regulate mTOR activity. mTOR signaling is activated by ERK, PI3K-Akt, PDK1 and Tsc1/2 signaling (Hoeffer and Klann, 2010), whilst mTOR is inhibited under basal conditions by GSK-3 (Ma et al., 2011). Complementing the regulation of translation during LTP, the late phase of LTP is also dependent upon gene transcription. The best studied transcription factor involved in LTP is cAMP response element-binding protein (CREB) (Bengtson and Bading, 2012). CREB is a major hub of activity-dependant neuronal gene expression (Benito et al., 2011) and is required for the maintenance of L-LTP (Wu et al., 2007). Accordingly CREB target genes include those crucial to synaptic plasticity such as BDNF and its cognate receptor TrkB (Deogracias et al., 2004), Wnt2 (Wayman et al., 2006) and glutamate receptor subunits (Lau et al., 2004; Traynelis et al., 2010). CREB activation is a multistep process involving nuclear Ca^{2+} signaling and many of the signaling pathways described above (Fig. 3). Notably genomic glucocorticoid signaling may also directly regulate CREB (Anacker et al., 2011; Datson et al., 2012).

Less work has been done so far to elucidate the signal transduction pathways underlying LTD, and similarly these pathways have received less attention in depression. A full list of pathways involved in NMDAR-dependent LTD in the hippocampus to date is included in Supplement 1. Most similarly to LTP, Ca^{2+} and NOS signaling are involved in LTD (Feil and Kleppisch, 2008). Beyond this however LTD involves the recruitment of other signaling pathways and opposite regulation of many of those involved in LTP. Most centrally implicated in LTD are phosphatases such as protein phosphatase 1 (PP1) and 2 (PP2). These phosphatases work in opposition to the kinase-mediated phosphorylation during LTP. In particular PP1 dephosphorylates GSK-3 facilitating its increased activity during LTD (Peineau et al., 2007). Furthermore CREB is deactivated during hippocampal LTD and $NMDAR_{2B}$ activation via PP1, PP2A and GSK-3 pathways (Mauna et al., 2011; Szatmari et al., 2005). Consistent with the need for increased GSK-3 activity, the PI3K-Akt pathway is negatively

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regulated by phosphatase and tensin homologue (PTEN) during LTD (Jurado et al., 2010). Moreover another PI3K isoform (PI3Kγ) may actually play a role in LTD and signal independently of Akt; in this pathway PI3Kγ may activate P38MAPK (Kim et al., 2011a).

Changes to these signaling pathways above may underlie changes to functional and structural plasticity in depression. Several papers have individually reviewed some of the signal transduction pathways described above in mood disorders (Blendy, 2006; Dhir and Kulkarni, 2011; Dwivedi and Pandey, 2011; Li and Jope, 2010). However less work has been done to connect changes between all these pathways. As such the following sections will review changes occurring to some of these key pathways in depression, first in the PFC and hippocampus and subsequently other less well studied brain regions such as the amygdala and NAc. Changes to signal transduction pathways in the PFC, hippocampus and amygdala in humans and stress models are summarised in Table 1. Importantly changes to these pathways in depression may apply to neurons and/or glia. Indeed signaling pathways mediating changes to neurons are also common to glia (Arai and Lo, 2010; Ghosh et al., 2005; Kim et al., 2007; Kong et al., 2008; Murray et al., 2009) where they may mediate common functions. It is also worth noting that many signaling pathways are also subject to developmental regulation (Corlew et al., 2007; Larsen et al., 2011; Ma et al., 2011; Yang et al., 2009) which has particular relevance to behavioural models using immature rodents.

4.2. The PFC and hippocampus: signaling changes in depression

4.2.1. nNOS-NO

Two post-mortem studies found increased expression of nNOS in the hippocampus (CA1 and subiculum) in MDD subjects (Oh et al., 2010; Oliveira et al., 2008). In behavioural models CMS increases nNOS expression in the hippocampus (DG, CA1 and CA3), whilst inhibition of nNOS prevents the negative behavioural and neuroplastic effects of CMS (Lian and An, 2010; Yazir et al., 2012; Zhou et al., 2007, 2011); however it is notable that ERK was activated and iNOS was not in one of these models (Zhou et al., 2011) which contradicts other findings discussed later. In extension to findings in the hippocampus a chronic stress/neurosis model was also found to increase nNOS expression in the neocortex (Khovryakov et al., 2010). Attenuation of the NO signaling pathway has further been implicated in the antidepressant-like activity of various drug classes in acute tests (Dhir and Kulkarni, 2011; Krass et al., 2010; Zomkowski et al., 2010) and a chronic despair model (Kumar et al., 2010); although studies in better validated chronic stress models are lacking. Moreover whilst excessive endogenous NO generation robustly associates with stress and depression, exogenous NO delivery has been found to reverse the depression-like behaviour and inhibition of neurogenesis induced by chronic stress (Hua et al., 2008); this contrary action likely reflects the bidirectional nature of NO signaling.

4.2.2. cAMP-PKA

Post-mortem studies have found lowered PKA subunit expression and activity in the PFC (BA10) in MDD/suicide (Dwivedi and Pandey, 2011; Shelton et al., 2009a, 2009b). Paralleling these findings, in behavioural models chronic glucocorticoid administration lowered PKA subunit expression and activity in the cortex and hippocampus (Dwivedi and Pandey, 2000); a learned helplessness paradigm was associated with similar changes (Dwivedi et al., 2004). In other CMS-type models PKA expression and activity decreases in the hippocampus, whilst antidepressants increase PKA activity in the PFC and hippocampus (Wang et al., 2006b; Wu et al., 2008; Zheng et al., 2008). Additionally acute treatment with both a TCA and NMDAR antagonist was found to boost pPKA in the PFC and hippocampus (Réus et al., 2011).

4.2.3. Ras-ERK

The ERK pathway represents the best studied MAPK signaling pathway in depression. Post-mortem studies have found evidence of decreased Raf-ERK1/2 signaling in the PFC and hippocampus in suicide/MDD (Duric et al., 2010; Dwivedi et al., 2001, 2006, 2009b; Yuan et al., 2010). In addition decreased hippocampal MEK5–ERK5 signaling was also found in suicide subjects (Dwivedi et al., 2007). Consistent with decreased ERK activity in depression increased expression of MAPK phosphatase (MKP), a negative regulator of the MAPK cascade, has also been reported. MKP-2 was increased in the PFC and hippocampus in depressed suicide subjects (Dwivedi et al., 2001) and MKP-1 increased in the hippocampus (DG and CA1) in MDD (Duric et al., 2010). Paralleling these findings behavioural models have been shown to modulate the ERK pathway. Indeed various chronic stresses can decrease ERK1/2 signaling in the PFC and hippocampus, which can be reversed by antidepressants (Duric et al., 2010; First et al., 2011; Gourley et al., 2008; Qi et al., 2006, 2008; Xiong et al., 2011). Further, a CUS model increased MKP-1 expression in the hippocampus (DG and CA3), whilst decreased levels were associated with stress resistance and antidepressant-like effects (Duric et al., 2010). Acute MEK inhibition has also been shown to induce depressive behaviour and block the behavioural effects of monoaminergic antidepressants (Duman et al., 2007). PFC ERK1/2 signaling is further crucial to the activity of rapid-acting antidepressants (Li et al., 2010b). However a few contrary findings to those above exist, a

Table 1
An overview of changes to signal transduction pathways in several brain regions in depression as determined by human and animal studies (*citations in text*). *Symbols*: ↑, increased activity; ↓, decreased activity.

Brain region	Human studies: MDD	Animal studies: chronic stress models	Animal studies: antidepressant administration	
PFC	.	↑nNOS (*neocortex*)	.	.
	↓PKA	↓PKA	↑PKA	(*SSRI, TCA, NMDAR antagonist*)
	↓ERK	↓ERK	↑ERK	(*SSRI, SSRE, NMDAR antagonist*)
	↓Akt	↓Akt (*frontal cortex*)	↑Akt	(*TCA, NMDAR antagonist, lamotrigine*)
	↑GSK-3β	↑GSK-3β	↓GSK-3β	(*SSRI, TCA, NMDAR antagonist*)
	↓mTOR	−/↓mTOR	↑mTOR	(*NMDAR & mGluR2/3 antagonists*)
	↓CREB	↓CREB	↑CREB	(*SSRI, TCA*)
Hippocampus	↑nNOS	↑nNOS	↓nNOS	(*neuropeptide Y*)
	.	↓PKA	↑PKA	(*SSRI, TCA, NMDAR antagonist*)
	↓ERK	↓ERK	↑ERK	(*SSRI, TCA*)
	.	↓Akt	↑Akt	(*SSRI, TCA, lamotrigine*)
	↑GSK-3β	↑GSK-3β	↓GSK-3β	(*SSRI, SNRI, lithium, NMDAR antagonist*)
	↓CREB	↓CREB	↑CREB	(*SSRI, SSRE, TCA*)
Amygdala	.	.	↑PKA	(*TCA, NMDAR antagonist*)
	.	↓/↑ERK	↑ERK	(*TCA*)
	.	↓*Akt*?	↑Akt	(*TCA, lamotrigine*)
	.	↓*mTOR*?	.	.
	.	.	↑CREB	(*SSRI, TCA, NMDAR antagonist*)

couple of CUS models failed to alter ERK and Akt signaling in the PFC or hippocampus (Chandran et al., 2012; Li et al., 2009) whilst CMS increased hippocampal ERK activity (Zhou et al., 2011).

4.2.4. PI3K-Akt

Several findings suggest lowered Akt activity may parallel lowered ERK activity in depression. Post-mortem studies have suggested there is lowered activity of the PI3K-Akt signaling pathway and increased PTEN levels in the ventral PFC in MDD/suicide (Karege et al., 2007, 2011). Vulnerability to CMS was associated with decreased hippocampal Akt signaling, which was reversed by antidepressant administration (Briones et al., 2012). Long-term corticosterone treatment was reported to increase PTEN and lower Flk1-PI3K-Akt-mTOR signaling in the frontal cortex (Howell et al., 2011). In extension to these findings various antidepressant classes have been shown to increase Akt signaling in the PFC and hippocampus (Abelaira et al., 2011; Li et al., 2010b; Okamoto et al., 2010).

4.2.5. GSK-3

Consistent with reduced Akt activity, an increasing body of research associates depression with increased GSK-3 signaling. Increased GSK-3β expression correlated with nNOS expression in the post-mortem hippocampus of depressives (Oh et al., 2010). In addition decreased pGSK-3β and β-catenin has been reported in the ventral PFC of depressed individuals, suggesting increased GSK-3β activity (Karege et al., 2007, 2012). In contrast another study found no difference in the levels of GSK-3β and β-catenin in the PFC (Beasley et al., 2002); these findings may suggest GSK-3β activity rather than expression is most affected in MDD (Karege et al., 2007). In behavioural models GSK-3 has been shown to be affected by stress and antidepressants. For instance prenatal stress decreases GSK-3β phosphorylation in the frontal cortex (Szymańska et al., 2009). CMS increases GSK-3β expression the hippocampus (Silva et al., 2008). Another study found that chronic, but not acute, stress decreased levels of pGSK-3β and β-catenin in the mPFC, an effect reversed by chronic administration of an SSRI (Chen et al., 2012b). Various other studies have implicated inhibition of GSK-3 in the activity of antidepressants. GSK-3β phosphorylation is increased by selective 5-HT_{1A} activation and monoaminergic antidepressants in the PFC (Li et al., 2004). Another study reported that monoaminergic antidepressants and ECS regulate components of the Wnt/β-catenin cascade (especially Wnt2) and increase GSK-3β phosphorylation in the hippocampus; furthermore local expression of Wnt2 in the hippocampus produced antidepressant-like responses (Okamoto et al., 2010). The antidepressant activity of ketamine is also associated with GSK-3α/β inhibition in the cerebral cortex and hippocampus (Beurel et al., 2011).

4.2.6. mTOR

The mTOR pathway is a relatively recent pathway to be associated with depression (Li et al., 2010b). A recent post-mortem study reported that mTOR signaling was decreased in the anterior PFC in MDD (Jernigan et al., 2011). Behavioural models have implicated the mTOR pathway in the effects of stress and antidepressant mechanisms. Long-term continuous corticosterone treatment was reported to dysregulate VEGF expression and decrease PI3K-Akt-mTOR signaling in the frontal cortex (Howell et al., 2011). However CUS did not alter PFC or hippocampal mTOR signaling in other studies (Chandran et al., 2012; Li et al., 2011). The rapid antidepressant activity of NMDAR antagonists was reported to involve ERK and Akt-dependant mTOR activation and reversal of a stress-induced decrease in synaptic proteins in the mPFC (Li et al., 2010b); a subsequent study extended these findings to a CUS model (Li et al., 2011). Increased mTOR signaling has further been reported to be involved in the rapid antidepressant-like activity of $mGluR_{2/3}$ antagonists (Dwyer et al., 2012). In particular BDNF-TrkB and mTOR signaling are involved in the sustained but not acute activity of ketamine and $mGluR_{2/3}$ antagonists (Koike et al., 2011, 2012). In accordance with this another study did not find a requirement for increased hippocampal mTOR signaling in the rapid antidepressant activity of NMDAR antagonists, which was instead dependent upon rapid BDNF translation (Autry et al., 2011). In this study the behavioural studies were done at an earlier time point (30 min) than those above; different testing methods may also contribute to the contrasting results (Duman and Voleti, 2012). Another finding which requires reconciliation is that sub-chronic administration of rapamycin, the major mTOR inhibitor, has demonstrated antidepressant activity (Cleary et al., 2008). This paradoxical finding may relate to the acute testing involved and systemic rapamycin administration which might have indirect effects on the brain. Notably central administration of rapamycin had no effects in behavioural tests after chronic stress (Li et al., 2011).

4.2.7. CREB

CREB represents the best studied transcription factor in depression. Post-mortem studies have suggested there is lowered CREB function in the PFC (Dwivedi et al., 2003; Pandey et al., 2007; Yamada et al., 1996; Yuan et al., 2010) and hippocampus (DG and CA1) in MDD/suicide subjects (Duric et al., 2010). Most behavioural studies using chronic stress models have also shown evidence of lowered CREB activity. CUS/CMS paradigms lower CREB activity in the PFC and hippocampus (DG) (Grønli et al., 2006; Li et al., 2009, 2010a), whilst antidepressants reverse these changes (Laifenfeld et al., 2005; Song et al., 2006; Wang et al., 2006b). Similarly other chronic stress models such as chronic forced swim (Qi et al., 2008), foot shock (Lin et al., 2008, 2009) and CRS (Alfonso et al., 2006) can also lower CREB activity. Other studies report that chronic antidepressant administration increases CREB activity in the PFC and hippocampus (DG and CA3) (Pinnock et al., 2010; Thome et al., 2000). In addition combined TCA and ketamine treatment increased CREB expression (Réus et al., 2011). Recently deletion of CRTC1 was also associated with multiple depression-like behaviours and reduced expression of BDNF/TrkB in the PFC (Breuillaud et al., 2012). Together these studies suggest lowered CREB function is important to depression; however several other behavioural models contradict those above. Chronic psychosocial stress (Böer et al., 2010) and several CRS models (Bravo et al., 2009; Miller et al., 2007; Reagan et al., 2007) have been reported to increase pCREB, which can be prevented/reversed by antidepressants. These reports highlight sensitivity to testing paradigms.

Taken together the signaling studies reviewed above clearly implicate general disruption of positive plasticity within subregions of the PFC and hippocampus in depression, which may apply to both neurons and glia. Indeed depression generally associates with increased nNOS activity, reduced activation of PKA, ERK and Akt pathways, increased activation of GSK-3 and perhaps more tentatively with reduced activation of mTOR and CREB (Table 1). The fragmented findings and differing methodology between studies prohibit a robust sub-region or cell-type specific corollary assessment of these signaling changes; however at a very basic regional level changes to signal transduction pathways in depression seem consistent with their interactions during synaptic plasticity in hippocampal neurons (Fig. 3). For instance PI3K-Akt signaling suppresses GSK-3 activity. Both mTOR and CREB are inhibited by GSK-3. mTOR activation involves both ERK and Akt pathways, and CREB activation involves PKA and ERK pathways. However interactions between the nNOS pathway and others are less clear. The nNOS pathway can mediate positive or negative changes to plasticity (Feil and Kleppisch, 2008), each of which may involve the activation of other pathways such as ERK and P38 respectively. Given the negative changes to neuroplasticity occurring in depression, how might nNOS signaling interact with other pathways discussed above? One possibility involves activation of extrasynaptic NMDARs which activate nNOS as well as various pathways mediating negative changes to plasticity (Hardingham and Bading, 2010; Xu et al., 2009). This

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possibility is consistent with metabolic and glial pathology in depression which may ultimately reduce glutamate uptake, as discussed later.

In summary signaling studies in the PFC and hippocampus correlate other cellular changes reported in depression, which collectively are consistent with an overall reduction in positive changes to neuroplasticity (i.e. LTP, growth and resilience). Further, changes to other signaling pathways such as GSK-3, PTEN, CREB and caspase could be consistent with negative changes to neuroplasticity (i.e. LTD, retraction and vulnerability) (Jurado et al., 2010; Li et al., 2010c; Mauna et al., 2011). Importantly, alterations to all these pathways are likely representative of an overall shift in the molecular and cellular mechanisms mediating changes to synaptic and structural plasticity. Certainly other signaling proteins such as PKC, CaMKII, JNK and P38 have been implicated in stress and depression although have been omitted from this review due to a lack of studies in humans and/or chronic stress models. In addition the tight coupling between neurons and glia, and the marked glial pathology in depression (Banasr et al., 2010) suggests alterations to common pathways are relevant to both cell types in the PFC and hippocampus.

4.3. Other brain regions: the amygdala and NAc

As reviewed earlier several findings suggest the amygdala may have a different pathology to the PFC and hippocampus in depression. This may involve growth of some excitatory connections concurrent with loss of inhibitory ones. Only a few studies have reported on the activity of signal transduction pathways in the amygdala in depression. A maternal deprivation model linked increased amygdala MEK-ERK signaling with depressive-like behaviours (Huang and Lin, 2006). Expression manipulation studies have associated increased PKA and CREB activity in the BLA with anxiogenic and depressive-like behaviours (Keil et al., 2012; Wallace et al., 2004). A CUS paradigm was associated with lowered ERK, Akt and mTOR signaling and GluR1 phosphorylation in the amygdala (Chandran et al., 2012); notably these pathways were not altered in the PFC and hippocampus in this model. Given the oppositional changes that may occur in the amygdala in depression it is difficult to correlate these changes to structural studies. Overall changes in the amygdala may also be highly sensitive to stress type and depression duration. Interestingly various antidepressants may increase the activity of signaling pathways mediating positive changes to synaptic plasticity in the amygdala (Abelaira et al., 2011; Gourley et al., 2008; Réus et al., 2011; Thome et al., 2000) (Table 1). This action of antidepressants may account for the increased amygdala volume in medicated MDD and BD patients (Hamilton et al., 2008; Savitz et al., 2010). It would be interesting to see if this was the result of antidepressant-induced hypertrophy of GABAergic interneurons as discussed later.

The nucleus accumbens (NAc) is another important brain region to the neurobiology of depression. This region has mainly been studied with respect to expression manipulation studies, where some findings seem opposite to the hippocampus. For instance increasing expression of CREB and BDNF in the NAc has pro-depressive (e.g. anhedonia) effects whilst the reverse associates with antidepressant-like effects (Muschamp et al., 2011; Shirayama and Chaki, 2006). However some other recent findings might seem more similar to other brain regions. For instance increasing GSK-3β activity in the NAc increased pro-depressive behaviour (Wilkinson et al., 2011). In addition vulnerability to CUMS and resulting depressive behaviour was associated with decreased GDNF expression in the NAc (Uchida et al., 2011).

5. Metabolic dysfunction and synaptic plasticity in depression

5.1. Energy metabolism

Changes to cellular plasticity may correlate those to metabolic systems in stress and depression; a preliminary discussion on this important area is included here. Most centrally, neuroplasticity is intrinsically linked to energy metabolism in the brain (Cheng et al., 2010). Increasing research shows how energetic pathways are involved in multiple forms of synaptic plasticity. For instance glial-derived lactate is required for hippocampal L-LTP (Suzuki et al., 2011) and potently facilitates memory formation (Newman et al., 2011). Astroglial ATP release and P2Y receptor activation mediates heterosynaptic LTD, a form of LTD which spatially sharpens LTP (Chen et al., 2012a). Moreover, early activation of the apoptosis pathway and caspase release from mitochondria is required for LTD in CA1 (Li et al., 2010c). The dependence upon energy for positive changes to plasticity is further emphasised by signaling-based control of mitochondrial function. Signaling pathways mediating positive changes to neuroplasticity (e.g. NMDAR, PKA, Akt and ERK) bolster mitochondrial function/redox, whilst the opposite may be true of those mediating negative changes (e.g. PP2A, GSK-3 and ExNMDAR) (Dhar and Wong-Riley, 2011; Dickey and Strack, 2011; Gimenez-Cassina et al., 2009; Hardingham and Bading, 2010; Liu et al., 2012; Valerio et al., 2011; Verburg and Hollenbeck, 2008).

Several studies suggest energy metabolism is impaired in depression. A CMS model was found to inhibit energy metabolism in the cerebral cortex and cerebellum, which was reversed by ketamine treatment (Rezin et al., 2009). A recent post-mortem study found altered expression of various proteins involved in oxidative phosphorylation and lowered ATP levels in the DLPFC of MDD subjects (Martins-de-Souza et al., 2012). Furthermore, a recent MRSI study found an inverse correlation between ventricular lactate and cortical glutathione in MDD, potentially linking disruptions in energy and redox (Shungu et al., 2012). Given the basic reciprocal and corollary relationships between neuroplasticity and energy, lowered energy metabolism would be particularly expected to hinder positive changes to synaptic plasticity. This could in part be mediated through early homeostatic signaling mechanisms. For instance lowered ATP levels promote extracellular adenosine 1 (A_1) receptor activation and intracellular AMP-activated kinase (AMPK) activation. Indeed under low energy conditions AMPK inhibits the mTOR translation pathway (Potter et al., 2010). However under pathological conditions other mechanisms may be important such as disturbed glutamate uptake as discussed below.

5.2. Redox

Cellular reduction-oxidation (redox) reactions also critically regulate synaptic plasticity. Moderate levels of reactive oxygen species (ROS) are actually required for LTP; however good antioxidant status is also required for efficient synaptic plasticity (Massaad and Klann, 2011). Accordingly signaling pathways mediating positive changes to neuroplasticity also buffer cellular antioxidant systems (Hardingham and Bading, 2010; Valerio et al., 2011). In contrast, lowered levels of critical antioxidants such as glutathione, or increased levels of ROS and reactive nitrogen species (RNS) impair synaptic plasticity (Massaad and Klann, 2011; Robillard et al., 2011). For example perturbed redox can directly restrict positive plasticity through oxidation of CaMKII (Bodhinathan et al., 2010).

Many behavioural and human studies now suggest redox is impaired in the brain and periphery in depression; *for reviews see* (Behr et al., 2012; Maes et al., 2011a). In particular depression severity and cognitive performance has been reported to correlate altered plasma redox markers in MDD patients (Talarowska et al., 2012a, 2012b). In behavioural models CMS induces oxidative stress in the cerebral cortex and hippocampus (Moretti et al., 2012). This oxidative stress likely results in part from activation of iNOS (Munhoz et al., 2008; Olivenza et al., 2000; Peng et al., 2012). Certainly chronic stresses induce iNOS expression in the cortex and hippocampus (CA1 and CA3) (Khovryakov et al., 2010; Lian and An, 2010; Olivenza et al., 2000; Peng et al., 2012), whilst iNOS inhibition prevents the negative neuroplastic and behavioural effects of chronic stress (Peng et al., 2012; Seo et al., 2012; Wang et al.,

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2008). NADPH oxidase may also contribute to stress-induced oxidative stress; this pathway is required for CRS-induced depressive behaviour (Seo et al., 2012). Finally the increased MAO-A activity in MDD (Meyer et al., 2009) might be a further source of ROS.

Brain oxidative stress in depression is likely to directly impair synaptic plasticity through modification of protein function as described above. In addition increased oxidative stress may also act indirectly through disruption of mitochondrial function; consistent with the inverse correlation between ventricular lactate and cortical glutathione in MDD (Shungu et al., 2012). For example pathological iNOS activation can inhibit cytochrome oxidase (Brown and Neher, 2010). Whilst chronic oxidative damage to cellular and mitochondrial lipids may impair cerebral blood flow (Shungu et al., 2012) and reduce efficiency of the electron transport chain (Nicolson, 2010; Nicolson and Ellithorpe, 2006). Moreover oxidative stress and depletion of glutathione may also impair brain methylation function (Waly et al., 2011). Together all these metabolic disturbances might promote various pathological processes which disrupt neuronal and glial plasticity. For instance disturbed glial metabolism might particularly hinder glutamate uptake and promote inappropriate recruitment of extrasynaptic NMDARs (Marsden, 2011); extrasynaptic NMDAR activation can restrict positive synaptic plasticity (Scimemi et al., 2009) and further induce negative changes to neuroplasticity (Hardingham and Bading, 2010). Certainly glutamate uptake is impaired in depression (Popoli et al., 2012) and iNOS inhibition prevented the impaired synaptic glutamate uptake in a repeat stress model (Olivenza et al., 2000). Taken together the studies above suggest changes to energy and redox in depression may precede and parallel those to synaptic plasticity; although further research is required to clarify this putative relationship.

6. What are the functional implications of altered synaptic plasticity in depression?

Altered synaptic plasticity in depression has major functional implications with regards to both cognition and emotion. What follows is a brief discussion on this topic, a deeper discussion being beyond the scope of this paper.

The studies reviewed throughout this paper most robustly support a state of disrupted positive plasticity in the PFC and hippocampus in depression, although less clear are the exact subregions affected and changes to other brain regions. The obvious immediate consequence of such disruption may be altered region-associated memory and learning, i.e. cognition. Indeed in behavioural models CUS disruption of LTP in the PFC is associated with learning and memory deficits (Quan et al., 2011b). Similarly CUS impairment of hippocampal-PFC plasticity was associated with impaired memory and behavioural flexibility (Cerqueira et al., 2007). In addition the reduction in BDNF and CREB signaling pathways in the PFC and hippocampus induced by CMS, CUS and learned helplessness paradigms is associated with impaired spatial learning and memory (Li et al., 2009; Song et al., 2006). Disruptions to short-term memory and hippocampal AMPAR subunit ratio (incl. low GluR1) have also been reported to correlate vulnerability to chronic social stress and resulting depressive-like behaviour (Schmidt et al., 2010). Perhaps consistent with these findings, in MDD cognitive deficits relating to concentration, attention, memory and other areas of executive function have been frequently although heterogeneously reported (Baune et al., 2010); *for review see* (Murrough et al., 2011).

Whilst an obvious logical link between synaptic plasticity and cognition exists, less well realised is the potential for altered synaptic plasticity to disrupt emotional memory and learning which may be key to mood disorders. In this regard negative synaptic changes in the PFC and hippocampus in depression will further interact with those in other brain regions. Indeed subregions of the PFC and hippocampus are heavily interconnected with one another and many other brain regions such as the amygdala. The interactivity between these regions has particularly been studied with respect to behavioural fear conditioning and extinction paradigms. In these paradigms prelimbic (PL) and infralimbic (IL) mPFC, ventral hippocampus and BLA play dissociable roles (Peters et al., 2009; Sierra-Mercado et al., 2011). In the amygdala fear conditioning involves positive plasticity in the BLA (Merino and Maren, 2006) whilst increased amygdala GABAergic tone may be important for extinction (Mańko et al., 2011). PL and IL regions of the mPFC project differentially to the amygdala and distinctly drive fear expression and extinction respectively; a similar dichotomy exists for mPFC-NAc connectivity (Peters et al., 2009). Accordingly positive plasticity in the PFC correlates fear extinction (Lai et al., 2012), and enhancement of IL-mPFC and hippocampal synaptic plasticity is associated with enhanced retention of fear extinction (Abumaria et al., 2011).

This PFC-hippocampal-amygdala circuitry is likely dysfunctional in depression. For instance CRS disrupts inhibitory interneuron tone in the LA and BLA (Gilabert-Juan et al., 2011) and leads to amygdala hyperexcitability (Rosenkranz et al., 2010). Furthermore BLA activation is required for stress-induced disruption of hippocampal LTP (DG and CA1) (Kim et al., 2005; Li and Richter-Levin, 2012). As reviewed earlier MDD is associated with similar morphological changes in the amygdala, and increased amygdala activity and reactivity has also been reported (Price and Drevets, 2010). This increased amygdala activity in depression may also relate to inefficient PFC function. For instance in healthy human subjects left vmPFC grey matter thickness inversely correlates amygdala reactivity in response to emotional tasks (Foland-Ross et al., 2010). In MDD a disconnectivity has been reported between the PFC and amygdala. As such dysfunctional prefrontal-subcortical circuitry has been suggested to result in decreased cognitive control of emotion, resulting in the persistent negative emotional reactivity which characterises depression (Murrough et al., 2011). More recent studies are identifying altered connectivity between several other brain regions in MDD (Hamilton et al., 2011; Horn et al., 2010; Price and Drevets, 2010; Veer et al., 2010). It may be that this maladapted circuitry arises at least in part from altered synaptic plasticity.

With regards to treatment, antidepressants may achieve therapeutic benefit through direct control of limbic activity and through favourable modulation of inter-regional synaptic plasticity. For instance in the LA and BLA serotonin inhibits excitatory activity via stimulation of 5-$HT_{2/3}$ receptors on GABAergic interneurons (Jiang et al., 2009; Stein et al., 2000; Stutzmann and LeDoux, 1999). Furthermore, it could be speculated that this stimulation might promote LTP and growth of interneuron synapses which could then contribute to the increased amygdala volume in depressed patients receiving treatment (Hamilton et al., 2008; Savitz et al., 2010). Thus direct suppression of amygdala activity and disinhibition of other cortical regions could be important to the therapeutic activity of serotonergic drugs. In contrast other antidepressants may primarily promote PFC suppression of the amygdala. Certainly the activity of rapid-acting antidepressants such as NMDAR and $mGluR_{2/3}$ antagonists is dependent upon positive plasticity in the mPFC (Dwyer et al., 2012; Li et al., 2010b). In addition stimulation of the mPFC was also reported to have potent antidepressant-like effects in a chronic social defeat model (Covington et al., 2010). Ultimately beyond this basic circuitry many other brain regions will be involved. Interestingly the rapid and potent antidepressant activity of the NMDAR antagonist ketamine was found to be accompanied by synaptic potentiation in the somatosensory cortex in treatment-resistant depression patients (Cornwell et al., 2012). Certainly the putative links between synaptic plasticity, maladapted neurocircuitry, cognition and emotion in depression should be an area for future research.

7. Concluding discussion

The importance of neuroplasticity to the pathophysiology and treatment of depression is well-established (Duman and Voleti,

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2012; Pittenger and Duman, 2008). The aim of this paper was to further add to the characterisation of altered plasticity in depression and specifically from the point of view of synaptic plasticity. Certainly evidence reviewed in this paper suggests region-specific changes to synaptic form and function occur in depression. The PFC and hippocampus represent the best studied regions where functional and structural findings are consistent with a deficit in LTP, and neuronal and glial growth at excitatory synapses. Correlating these changes may particularly be those to glutamate receptors (AMPARs and NMDARs), growth factor signaling (BDNF-TrkB) and several signal transduction pathways (NOS-NO, cAMP-PKA, Ras-ERK, PI3K-Akt, GSK-3, mTOR and CREB). In contrast other brain regions such as the amygdala may feature a somewhat opposite synaptic pathology including reduced inhibitory tone. Deficits in synaptic plasticity may further correlate disrupted brain redox and bioenergetics in depression. Together region-specific alterations to neuroplasticity in depression likely contribute to the maladapted neurocircuitry associated with a persistent depressive phenotype. Accordingly antidepressant mechanisms may involve favourable modulation of synaptic plasticity and adjustment of neurocircuitry. Indeed modulation of key signaling pathways involved in synaptic plasticity is required for the antidepressant-like activity of drugs known to be effective in humans (Duman et al., 2007; Li et al., 2010b; Warner-Schmidt and Duman, 2007). However it is also possible that a short-coming of current clinical antidepressants may be an inability to restore normal synaptic function in certain brain regions, and this could underlie treatment resistance and/or persisting cognitive deficits after remission of mood-related symptoms.

Box 1

Outstanding questions (*Consists of the bullet points below*)

- What are the full subregion specific alterations to synaptic plasticity occurring in the PFC and hippocampus in depression? Furthermore what is the synaptic pathology in other less studied brain regions in depression such as the ACC, amygdala and NAc?
- Which other signal transduction pathways are robustly altered in depression; for instance which pathways associated with negative changes to neuroplasticity (e.g. proBDNF-p75^{NTR}, PP1, PP2A, JNK and P38)?
- What are the interactions between NO signaling and other signaling pathways in depression?
- To which cell types (e.g. neurons, interneurons, astrocytes and microglia) do signaling changes apply in different brain regions?
- Which signaling pathways mediate changes to the expression of key neurotransmitter systems (i.e. metabolic enzymes, receptors and transporters) in depression?
- What are the full interactions between energy, redox and neuroplasticity in depression, particularly with regards to neuronal-glial interactions (e.g. glutamate/gaba-glutamine cycling)?
- What effects does disrupted synaptic plasticity have on inter-regional connectivity in depression?
- To what extent are aetiological factors other than stress (e.g. nutrition (Gómez-Pinilla, 2008; Scapagnini et al., 2012) and neuro-inflammation (Eyre and Baune, 2012; Khairova et al., 2009; Kubera et al., 2011)) responsible for altered synaptic plasticity in depression?
- To what extent do alterations to signaling pathways, neuroplasticity and neurocircuitry in depression overlap with other neuropsychiatric disorders and comorbid conditions?

The reconceptualisation of depression from the point of view of synaptic plasticity has its roots in a previous hypothesis (Marsden, 2011) and may be able to integrate and reconcile many findings. However many information gaps and questions still remain which could be better clarified by future research (Box 1). In particular a better understanding of the interactions between synaptic plasticity and neurocircuitry may aid in a more complete overall neurobiological understanding of mood disorders. Moreover a better understanding of the major genetic, environmental and pathophysical factors impinging upon neuroplasticity will inform aetiology and pathological heterogeneity, and ultimately logical approaches to the prevention and treatment of neuropsychiatric disorders and comorbid conditions (Gardner and Boles, 2010; Maes et al., 2011b; Marsden, 2011).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2012.12.012.

References

Abel T, Nguyen PV. Regulation of hippocampus-dependent memory by cyclic AMP-dependent protein kinase. Prog Brain Res 2008;169:97-115.

Abelaira HM, Réus GZ, Ribeiro KF, Zappellini G, Ferreira GK, Gomes LM, et al. Effects of acute and chronic treatment elicited by lamotrigine on behavior, energy metabolism, neurotrophins and signaling cascades in rats. Neurochem Int 2011;59:1163–74.

Abrahám IM, Meerlo P, Luiten PGM. Concentration dependent actions of glucocorticoids on neuronal viability and survival. Dose–response: a publication of International Hormesis Society, 4. ; 2006. p. 38–54.

Abumaria N, Yin B, Zhang L, Li X-Y, Chen T, Descalzi G, Zhao L, Ahn M, Luo L, Ran C, Zhuo M, Liu G. Effects of elevation of brain magnesium on fear conditioning, fear extinction, and synaptic plasticity in the infralimbic prefrontal cortex and lateral amygdala. J Neurosci 2011;31:14871–81.

Alfarez DN, Joels M, Krugers HJ. Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. Eur J Neurosci 2003;17:1928–34.

Alfonso J, Frick LR, Silberman DM, Palumbo ML, Genaro AM, Frasch AC. Regulation of hippocampal gene expression is conserved in two species subjected to different stressors and antidepressant treatments. Biol Psychiatry 2006;59:244–51.

Altar CA, Vawter MP, Ginsberg SD. Target identification for CNS diseases by transcriptional profiling. Neuropsychopharmacology 2009;34:18–54.

Anacker C, Zunszain P a, Carvalho L a, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology 2011;36:415–25.

Arai K, Lo EH. Astrocytes protect oligodendrocyte precursor cells via MEK/ERK and PI3K/Akt signaling. J Neurosci Res 2010;88:758–63.

Aston C, Jiang L, Sokolov BP. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. Mol Psychiatry 2005;10:309–22.

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng P, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 2011;475:91–5.

Bachis A, Cruz MI, Nosheny RL, Mocchetti I. Chronic unpredictable stress promotes neuronal apoptosis in the cerebral cortex. Neurosci Lett 2008;442:104–8.

Banasr M, Chowdhury GMI, Terwilliger R, Newton SS, Duman RS, Behar KL, et al. Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. Mol Psychiatry 2010;15:501–11.

Banko JL, Hou L, Klann E. NMDA receptor activation results in PKA- and ERK-dependent Mnk1 activation and increased eIF4E phosphorylation in hippocampal area CA1. J Neurochem 2004;91:462–70.

Barbon A, Caracciolo L, Orlandi C, Musazzi L, Mallei A, La Via L, et al. Chronic antidepressant treatments induce a time-dependent up-regulation of AMPA receptor subunit protein levels. Neurochem Int 2011;59:896–905.

Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. The role of cognitive impairment in general functioning in major depression. Psychiatry Res 2010;176:183–9.

Beasley C, Cotter D, Everall I. An investigation of the Wnt-signalling pathway in the prefrontal cortex in schizophrenia, bipolar disorder and major depressive disorder. Schizophr Res 2002;58:63–7.

Beasley CL, Honer WG, Bergmann K, Falkai P, Lütjohann D, Bayer TA. Reductions in cholesterol and synaptic markers in association cortex in mood disorders. Bipolar Disord 2005;7:449–55.

Becker N, Wierenga CJ, Fonseca R, Bonhoeffer T, Nägerl UV. LTD induction causes morphological changes of presynaptic boutons and reduces their contacts with spines. Neuron 2008;60:590–7.

Behr G a, Moreira JCF, Frey BN. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder. Oxid Med Cell Longev 2012:609421.

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Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of NMDA receptor-associated postsynaptic protein transcripts in the prefrontal cortex in schizophrenia and bipolar disorder. Neuropsychopharmacology 2008;33:2175–86.

Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH. Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. Neuropsychopharmacology 2007;32:1888–902.

Bengtson CP, Bading H. Nuclear calcium signaling. Adv Exp Med Biol 2012;970:377–405.

Benito E, Valor LM, Jimenez-Minchan M, Huber W, Barco A. cAMP response element-binding protein is a primary hub of activity-driven neuronal gene expression. J Neurosci 2011;31:18237–50.

Bergström A, Jayatissa MN, Mørk A, Wiborg O. Stress sensitivity and resilience in the chronic mild stress rat model of depression; an in situ hybridization study. Brain Res 2008;1196:41–52.

Beurel E, Song L, Jope RS. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. Mol Psychiatry 2011;16:1068–70.

Blendy JA. The role of CREB in depression and antidepressant treatment. Biol Psychiatry 2006;59:1144–50.

Bodhinathan K, Kumar A, Foster TC. Intracellular redox state alters NMDA receptor response during aging through Ca^{2+}/calmodulin-dependent protein kinase II. J Neurosci 2010;30:1914–24.

Böer U, Noll C, Cierny I, Krause D, Hiemke C, Knepel W. A common mechanism of action of the selective serotonin reuptake inhibitors citalopram and fluoxetine: reversal of chronic psychosocial stress-induced increase in CRE/CREB-directed gene transcription in transgenic reporter gene mice. Eur J Pharmacol 2010;633:33–8.

Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. J Affect Disord 2012;138:9-18.

Bradley CA, Peineau S, Taghibiglou C, Nicolas CS, Whitcomb DJ, Bortolotto ZA, et al. A pivotal role of GSK-3 in synaptic plasticity. Front Mol Neurosci 2012;5(13).

Bravo JA, Díaz-Veliz G, Mora S, Ulloa JL, Berthoud VM, Morales P, et al. Desipramine prevents stress-induced changes in depressive-like behavior and hippocampal markers of neuroprotection. Behav Pharmacol 2009;20:273–85.

Breuillaud L, Rossetti C, Meylan EM, Mérinat C, Halfon O, Magistretti PJ, et al. Deletion of CREB-regulated transcription coactivator 1 induces pathological aggression, depression-related behaviors, and neuroplasticity genes dysregulation in mice. Biol Psychiatry 2012;72:528–36.

Briones A, Gagno S, Martisova E, Dobarro M, Aisa B, Solas M, et al. Stress-induced anhedonia is associated with an increase in Alzheimer's disease-related markers. Br J Pharmacol 2012;165:897–907.

Brown GC, Neher JJ. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. Mol Neurobiol 2010;41:242–7.

Caruana DA, Alexander GM, Dudek SM. New insights into the regulation of synaptic plasticity from an unexpected place: hippocampal area CA2. Learn Mem 2012;19:391–400.

Castellano E, Downward J. RAS interaction with PI3K: more than just another effector pathway. Genes Cancer 2011;2:261–74.

Cerqueira JJ, Mailliet F, Almeida OFX, Jay TM, Sousa N. The prefrontal cortex as a key target of the maladaptive response to stress. J Neurosci 2007;27:2781–7.

Chandran A, Iyo AH, Jernigan CS, Legutko B, Austin MC, Karolewicz B. Reduced phosphorylation of the mTOR signaling pathway components in the amygdala of rats exposed to chronic stress. Prog Neuropsychopharmacol Biol Psychiatry 2012;40C:240–5.

Chen J, Park CS, Tang S-J. Activity-dependent synaptic Wnt release regulates hippocampal long term potentiation. J Biol Chem 2006;281:11910–6.

Chen J, Tan Z, Zeng L, Zhang X, He Y, Gao W, et al. Heterosynaptic long-term depression mediated by ATP released from astrocytes. Glia 2012a.

Chen YC, Tan QR, Dang W, Wang HN, Zhang RB, Li ZY, et al. The effect of citalopram on chronic stress-induced depressive-like behavior in rats through GSK3β/β-catenin activation in the medial prefrontal cortex. Brain Res Bull 2012b;88:338–44.

Cheng A, Hou Y, Mattson MP. Mitochondria and neuroplasticity. ASN Neuro 2010;2:e00045.

Cheyne JE, Montgomery JM. Plasticity-dependent changes in metabotropic glutamate receptor expression at excitatory hippocampal synapses. Mol Cell Neurosci 2008;37:432–9.

Christian KM, Miracle AD, Wellman CL, Nakazawa K. Chronic stress-induced hippocampal dendritic retraction requires CA3 NMDA receptors. Neuroscience 2011;174:26–36.

Christoffel DJ, Golden SA, Russo SJ. Structural and synaptic plasticity in stress-related disorders. Rev Neurosci 2011;22:535–49.

Cleary C, Linde JAS, Hiscock KM, Hadas I, Belmaker RH, Agam G, et al. Antidepressive-like effects of rapamycin in animal models: implications for mTOR inhibition as a new target for treatment of affective disorders. Brain Res Bull 2008;76:469–73.

Cohen JW, Louneva N, Han L-Y, Hodes GE, Wilson RS, Bennett DA, et al. Chronic corticosterone exposure alters postsynaptic protein levels of PSD-95, NR1, and synaptopodin in the mouse brain. Synapse 2011;65:763–70.

Corlew R, Wang Y, Ghermazien H, Erisir A, Philpot BD. Developmental switch in the contribution of presynaptic and postsynaptic NMDA receptors to long-term depression. J Neurosci 2007;27:9835–45.

Corlew R, Brasier DJ, Feldman DE, Philpot BD. Presynaptic NMDA receptors: newly appreciated roles in cortical synaptic function and plasticity. Neuroscientist 2009;14:609–25.

Cornwell BR, Salvadore G, Furey M, Marquardt CA, Brutsche NE, Grillon C, et al. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. Biol Psychiatry 2012;72:555–61.

Covington HE, Lobo MK, Maze I, Vialou V, Hyman JM, Zaman S, et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. J Neurosci 2010;30:16082–90.

Cui Y, Jin J, Zhang X, Xu H, Yang L, Du D, et al. Forebrain NR2B overexpression facilitating the prefrontal cortex long-term potentiation and enhancing working memory function in mice. PLoS One 2011;6:e20312.

Czéh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology 2006;31:1616–26.

Datson NA, Speksnijder N, Mayer JL, Steenbergen PJ, Korobko O, Goeman J, et al. The transcriptional response to chronic stress and glucocorticoid receptor blockade in the hippocampal dentate gyrus. Hippocampus 2012;22:359–71.

Deogracias R, Espliguero G, Iglesias T, Rodríguez-Peña A. Expression of the neurotrophin receptor trkB is regulated by the cAMP/CREB pathway in neurons. Mol Cell Neurosci 2004;26:470–80.

Dhar SS, Wong-Riley MTT. The kinesin superfamily protein KIF17 is regulated by the same transcription factor (NRF-1) as its cargo NR2B in neurons. Biochim Biophys Acta 2011;1813:403–11.

Dhir A, Kulkarni SK. Nitric oxide and major depression. Nitric Oxide 2011;24:125–31.

Dickey AS, Strack S. PKA/AKAP1 and PP2A/Bβ2 regulate neuronal morphogenesis via Drp1 phosphorylation and mitochondrial bioenergetics. J Neurosci 2011;31:15716–26.

Du J, Feng L, Yang F, Lu B. Activity- and Ca(2+)-dependent modulation of surface expression of brain-derived neurotrophic factor receptors in hippocampal neurons. J Cell Biol 2000;150:1423–34.

Du M-Y, Wu Q-Z, Yue Q, Li J, Liao Y, Kuang W-H, et al. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012;36:11–6.

Duman RS, Voleti B. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci 2012;35:47–56.

Duman CH, Schlesinger L, Kodama M, Russell DS, Duman RS. A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. Biol Psychiatry 2007;61:661–70.

Dupin N, Mailliet F, Rocher C, Kessal K, Spedding M, Jay TM. Common efficacy of psychotropic drugs in restoring stress-induced impairment of prefrontal plasticity. Neurotox Res 2006;10:193–8.

Duric V, Banasr M, Licznerski P, Schmidt HD, Stockmeier CA, Simen AA, et al. A negative regulator of MAP kinase causes depressive behavior. Nat Med 2010;16:1328–32.

Duric V, Banasr M, Stockmeier CA, Simen AA, Newton SS, Overholser JC, et al. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. Int J Neuropsychopharmacol 2012:1-14.

Dwivedi Y, Pandey GN. Adrenal glucocorticoids modulate [3H]cyclic AMP binding to protein kinase A (PKA), cyclic AMP-dependent PKA activity, and protein levels of selective regulatory and catalytic subunit isoforms of PKA in rat brain. J Pharmacol Exp Ther 2000;294:103–16.

Dwivedi Y, Pandey GN. Elucidating biological risk factors in suicide: role of protein kinase A. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:831–41.

Dwivedi Y, Rizavi HS, Roberts RC, Conley RC, Tamminga CA, Pandey GN. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. J Neurochem 2001;77:916–28.

Dwivedi Y, Rao JS, Rizavi HS, Kotowski J, Conley RR, Roberts RC, et al. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003;60:273–82.

Dwivedi Y, Mondal AC, Shukla PK, Rizavi HS, Lyons J. Altered protein kinase a in brain of learned helpless rats: effects of acute and repeated stress. Biol Psychiatry 2004;56:30–40.

Dwivedi Y, Rizavi HS, Conley RR, Pandey GN. ERK MAP kinase signaling in post-mortem brain of suicide subjects: differential regulation of upstream Raf kinases Raf-1 and B-Raf. Mol Psychiatry 2006;11:86–98.

Dwivedi Y, Rizavi HS, Teppen T, Sasaki N, Chen H, Zhang H, et al. Aberrant extracellular signal-regulated kinase (ERK) 5 signaling in hippocampus of suicide subjects. Neuropsychopharmacology 2007;32:2338–50.

Dwivedi Y, Rizavi HS, Zhang H, Mondal AC, Roberts RC, Conley RR, et al. Neurotrophin receptor activation and expression in human postmortem brain: effect of suicide. Biol Psychiatry 2009a;65:319–28.

Dwivedi Y, Rizavi HS, Zhang H, Roberts RC, Conley RR, Pandey GN. Aberrant extracellular signal-regulated kinase (ERK)1/2 signalling in suicide brain: role of ERK kinase 1 (MEK1). Int J Neuropsychopharmacol 2009b;12:1337–54.

Dwyer JM, Lepack AE, Duman RS. mTOR activation is required for the antidepressant effects of mGluR2/3 blockade. Int J Neuropsychopharmacol 2012;15:429–34.

Eiland L, Ramroop J, Hill MN, Manley J, McEwen BS. Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. Psychoneuroendocrinology 2012;37:39–47.

Elizalde N, Pastor PM, Garcia-García AL, Serres F, Venzala E, Huarte J, et al. Regulation of markers of synaptic function in mouse models of depression: chronic mild stress and decreased expression of VGLUT1. J Neurochem 2010;114:1302–14.

Eyre H, Baune BT. Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology 2012.

Feil R, Kleppisch T. NO/cGMP-dependent modulation of synaptic transmission. Handb Exp Pharmacol 2008:529–60.

Feyissa AM, Chandran A, Stockmeier CA, Karolewicz B. Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:70–5.

Please cite this article as: Marsden WN, Synaptic plasticity in depression: Molecular, cellular and functional correlates, Progress in Neuro-Psychopharmacology & Biological Psychiatry (2012), http://dx.doi.org/10.1016/j.pnpbp.2012.12.012

First M, Gil-Ad I, Taler M, Tarasenko I, Novak N, Weizman A. The effects of fluoxetine treatment in a chronic mild stress rat model on depression-related behavior, brain neurotrophins and ERK expression. J Mol Neurosci 2011;45:246–55.

Foland-Ross LC, Altshuler LL, Bookheimer SY, Lieberman MD, Townsend J, Penfold C, et al. Amygdala reactivity in healthy adults is correlated with prefrontal cortical thickness. J Neurosci 2010;30:16673–8.

Gallo EF, Iadecola C. Neuronal nitric oxide contributes to neuroplasticity-associated protein expression through cGMP, protein kinase G, and extracellular signal-regulated kinase. J Neurosci 2011;31:6947–55.

Gardner A, Boles RG. Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. Prog Neuropsychopharmacol Biol Psychiatry 2010.

Ghosh M, Gharami K, Paul S, Das S. Thyroid hormone-induced morphological differentiation and maturation of astrocytes involves activation of protein kinase A and ERK signalling pathway. Eur J Neurosci 2005;22:1609–17.

Gilabert-Juan J, Castillo-Gomez E, Pérez-Rando M, Moltó MD, Nacher J. Chronic stress induces changes in the structure of interneurons and in the expression of molecules related to neuronal structural plasticity and inhibitory neurotransmission in the amygdala of adult mice. Exp Neurol 2011;232:33–40.

Gilabert-Juan J, Varea E, Guirado R, Blasco-Ibáñez JM, Crespo C, Nácher J. Alterations in the expression of PSA-NCAM and synaptic proteins in the dorsolateral prefrontal cortex of psychiatric disorder patients. Neurosci Lett 2012;530:97-102.

Gimenez-Cassina A, Lim F, Cerrato T, Palomo GM, Diaz-Nido J. Mitochondrial hexokinase II promotes neuronal survival and acts downstream of glycogen synthase kinase-3. J Biol Chem 2009;284:3001–11.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118:292–9.

Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci 2008;9:568–78.

Gong R, Park CS, Abbassi NR, Tang S-J. Roles of glutamate receptors and the mammalian target of rapamycin (mTOR) signaling pathway in activity-dependent dendritic protein synthesis in hippocampal neurons. J Biol Chem 2006;281:18802–15.

Gourley SL, Wu FJ, Kiraly DD, Ploski JE, Kedves AT, Duman RS, et al. Regionally specific regulation of ERK MAP kinase in a model of antidepressant-sensitive chronic depression. Biol Psychiatry 2008;63:353–9.

Gourley SL, Kedves AT, Olausson P, Taylor JR. A history of corticosterone exposure regulates fear extinction and cortical NR2B, GluR2/3, and BDNF. Neuropsychopharmacology 2009;34:707–16.

Granado N, Ortiz O, Suárez LM, Martín ED, Ceña V, Solís JM, et al. D1 but not D5 dopamine receptors are critical for LTP, spatial learning, and LTP-Induced arc and zif268 expression in the hippocampus. Cereb Cortex 2008;18:1-12.

Grønli J, Bramham C, Murison R, Kanhema T, Fiske E, Bjorvatn B, et al. Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper. Pharmacol Biochem Behav 2006;85:842–9.

Guilloux J-P, Douillard-Guilloux G, Kota R, Wang X, Gardier AM, Martinowich K, et al. Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression. Mol Psychiatry 2011.

Gurden H, Takita M, Jay TM. Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses in vivo. J Neurosci 2000;20:RC106.

Haber M, Zhou L, Murai KK. Cooperative astrocyte and dendritic spine dynamics at hippocampal excitatory synapses. J Neurosci 2006;26:8881–91.

Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry 2008;13:993-1000.

Hamilton JP, Chen G, Thomason ME, Schwartz ME, Gotlib IH. Investigating neural primacy in major depressive disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Mol Psychiatry 2011;16:763–72.

Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nat Rev Neurosci 2010;11:682–96.

Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. J Affect Disord 2012.

Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory and disease. Trends Neurosci 2010;33:67–75.

Holderbach R, Clark K, Moreau J-L, Bischofberger J, Normann C. Enhanced long-term synaptic depression in an animal model of depression. Biol Psychiatry 2007;62:92-100.

Horn DI, Yu C, Steiner J, Buchmann J, Kaufmann J, Osoba A, et al. Glutamatergic and resting-state functional connectivity correlates of severity in major depression — the role of pregenual anterior cingulate cortex and anterior insula. Front Syst Neurosci 2010;4.

Howell KR, Kutiyanawalla A, Pillai A. Long-term continuous corticosterone treatment decreases VEGF receptor-2 expression in frontal cortex. PLoS One 2011;6:e20198.

Hua Y, Huang X-Y, Zhou L, Zhou Q-G, Hu Y, Luo C-X, et al. DETA/NONOate, a nitric oxide donor, produces antidepressant effects by promoting hippocampal neurogenesis. Psychopharmacology 2008;200:231–42.

Huang T-Y, Lin C-H. Role of amygdala MAPK activation on immobility behavior of forced swim rats. Behav Brain Res 2006;173:104–11.

Ito H, Nagano M, Suzuki H, Murakoshi T. Chronic stress enhances synaptic plasticity due to disinhibition in the anterior cingulate cortex and induces hyper-locomotion in mice. Neuropharmacology 2010;58:746–57.

Izumi Y, Zorumski CF. NMDA receptors, mGluR5, and endocannabinoids are involved in a cascade leading to hippocampal long-term depression. Neuropsychopharmacology 2012;37:609–17.

Jernigan CS, Goswami DB, Austin MC, Iyo AH, Chandran A, Stockmeier CA, et al. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1774–9.

Jiang X, Xing G, Yang C, Verma A, Zhang L, Li H. Stress impairs 5-HT2A receptor-mediated serotonergic facilitation of GABA release in juvenile rat basolateral amygdala. Neuropsychopharmacology 2009;34:410–23.

Joëls M, Krugers HJ. LTP after stress: up or down? Neural Plast 2007:93202.

Jourdi H, Hsu Y-T, Zhou M, Qin Q, Bi X, Baudry M. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. J Neurosci 2009;29:8688–97.

Jurado S, Benoist M, Lario A, Knafo S, Petrok CN, Esteban JA. PTEN is recruited to the postsynaptic terminal for NMDA receptor-dependent long-term depression. EMBO J 2010;29:2827–40.

Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznerski P, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat Med 2012;18:1413–7.

Karege F, Perroud N, Burkhardt S, Schwald M, Ballmann E, La Harpe R, et al. Alteration in kinase activity but not in protein levels of protein kinase B and glycogen synthase kinase-3beta in ventral prefrontal cortex of depressed suicide victims. Biol Psychiatry 2007;61:240–5.

Karege F, Perroud N, Burkhardt S, Fernandez R, Ballmann E, La Harpe R, et al. Alterations in phosphatidylinositol 3-kinase activity and PTEN phosphatase in the prefrontal cortex of depressed suicide victims. Neuropsychobiology 2011;63:224–31.

Karege F, Perroud N, Burkhardt S, Fernandez R, Ballmann E, La Harpe R, et al. Protein levels of β-catenin and activation state of glycogen synthase kinase-3β in major depression. A study with postmortem prefrontal cortex. J Affect Disord 2012;136:185–8.

Karolewicz B, Szebeni K, Gilmore T, Maciag D, Stockmeier CA, Ordway GA. Elevated levels of NR2A and PSD-95 in the lateral amygdala in depression. Int J Neuropsychopharmacol 2009;12:143–53.

Kasai H, Fukuda M, Watanabe S, Hayashi-Takagi A, Noguchi J. Structural dynamics of dendritic spines in memory and cognition. Trends Neurosci 2010;33:121–9.

Keil MF, Briassoulis G, Gokarn N, Nesterova M, Wu TJ, Stratakis CA. Anxiety phenotype in mice that overexpress protein kinase A. Psychoneuroendocrinology 2012;37:836–43.

Kessels HW, Malinow R. Synaptic AMPA receptor plasticity and behavior. Neuron 2009;61:340–50.

Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol 2009;12:561–78.

Khovryakov AV, Podrezova EP, Kruglyakov PP, Shikhanov NP, Balykova MN, Semibratova NV, et al. Involvement of the NO synthase system in stress-mediated brain reactions. Neurosci Behav Physiol 2010;40:333–7.

Kim JJ, Koo JW, Lee HJ, Han J-S. Amygdalar inactivation blocks stress-induced impairments in hippocampal long-term potentiation and spatial memory. J Neurosci 2005;25:1532–9.

Kim DW, Lee JH, Park SK, Yang W-M, Jeon GS, Lee YH, et al. Astrocytic expressions of phosphorylated Akt, GSK3beta and CREB following an excitotoxic lesion in the mouse hippocampus. Neurochem Res 2007;32:1460–8.

Kim J-I, et al. PI3Kγ is required for NMDA receptor-dependent long-term depression and behavioral flexibility. Nat Neurosci 2011a;14:1447–54.

Kim M, Park AJ, Havekes R, Chay A, Guercio LA, Oliveira RF, et al. Colocalization of õprotein Kinase A with adenylyl cyclase enhances protein kinase A activity during induction of long-lasting long-term-potentiation. PLoS Comput Biol 2011b;7:e1002084.

Kiselycznyk C, Svenningsson P, Delpire E, Holmes A. Genetic, pharmacological and lesion analyses reveal a selective role for corticohippocampal GLUN2B in a novel repeated swim stress paradigm. Neuroscience 2011;193:259–68.

Koike H, Iijima M, Chaki S. Involvement of the mammalian target of rapamycin signaling in the antidepressant-like effect of group II metabotropic glutamate receptor antagonists. Neuropharmacology 2011;61:1419–23.

Koike H, Fukumoto K, Iijima M, Chaki S. Role of BDNF/TrkB signaling in antidepressant-like effects of a group II metabotropic glutamate receptor antagonist in animal models of depression. Behav Brain Res 2012;238C:48–52.

Kolarow R, Brigadski T, Lessmann V. Postsynaptic secretion of BDNF and NT-3 from hippocampal neurons depends on calcium calmodulin kinase II signaling and proceeds via delayed fusion pore opening. J Neurosci 2007;27:10350–64.

Kong P-J, Byun J-S, Lim S-Y, Lee J-J, Hong S-J, Kwon K-J, et al. Melatonin induces Akt phosphorylation through melatonin receptor- and PI3K-dependent pathways in primary astrocytes. Korean J Physiol Pharmacol 2008;12:37–41.

Kovács K a, Steullet P, Steinmann M, Do KQ, Magistretti PJ, Halfon O, et al. TORC1 is a calcium- and cAMP-sensitive coincidence detector involved in hippocampal long-term synaptic plasticity. Proc Natl Acad Sci U S A 2007;104:4700–5.

Krass M, Wegener G, Vasar E, Volke V. The antidepressant action of imipramine and venlafaxine involves suppression of nitric oxide synthesis. Behav Brain Res 2010.

Kristiansen LV, Meador-Woodruff JH. Abnormal striatal expression of transcripts encoding NMDA interacting PSD proteins in schizophrenia, bipolar disorder and major depression. Schizophr Res 2005;78:87–93.

Krugers HJ, Goltstein PM, Van der Linden S, Joëls M. Blockade of glucocorticoid receptors rapidly restores hippocampal CA1 synaptic plasticity after exposure to chronic stress. Eur J Neurosci 2006;23:3051–5.

Kubera M, Obuchowicz E, Goehler L, Brzeszcz J, Maes M. In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:744–59.

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Kuczewski N, Porcher C, Lessmann V, Medina I, Gaiarsa J-L. Activity-dependent dendritic release of BDNF and biological consequences. Mol Neurobiol 2009;39:37–49.

Kullmann DM, Lamsa KP. LTP and LTD in cortical GABAergic interneurons: emerging rules and roles. Neuropharmacology 2011;60:712–9.

Kumar A, Garg R, Gaur V, Kumar P. Venlafaxine involves nitric oxide modulatory mechanism in experimental model of chronic behavior despair in mice. Brain Res 2010;1311:73–80.

Lai CSW, Franke TF, Gan W-B. Opposite effects of fear conditioning and extinction on dendritic spine remodelling. Nature 2012;483:87–91.

Laifenfeld D, Karry R, Grauer E, Klein E, Ben-Shachar D. Antidepressants and prolonged stress in rats modulate CAM-L1, laminin, and pCREB, implicated in neuronal plasticity. Neurobiol Dis 2005;20:432–41.

Lakshminarasimhan H, Chattarji S. Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. PLoS One 2012;7:e30481.

Larsen RS, Corlew RJ, Henson MA, Roberts AC, Mishina M, Watanabe M, et al. NR3A-containing NMDARs promote neurotransmitter release and spike timing-dependent plasticity. Nat Neurosci 2011;14:338–44.

Lau GC, Saha S, Faris R, Russek SJ. Up-regulation of NMDAR1 subunit gene expression in cortical neurons via a PKA-dependent pathway. J Neurochem 2004;88:564–75.

Law AJ, Deakin JF. Asymmetrical reductions of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. Neuroreport 2001;12:2971–4.

Lee C-C, Huang C-C, Wu M-Y, Hsu K-S. Insulin stimulates postsynaptic density-95 protein translation via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway. J Biol Chem 2005;280:18543–50.

Lépine J-P, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat 2011;7:3–7.

Li X, Jope RS. Is glycogen synthase kinase-3 a central modulator in mood regulation? Neuropsychopharmacology 2010;35:2143–54.

Li Z, Richter-Levin G. Stimulus intensity-dependent modulations of hippocampal long-term potentiation by basolateral amygdala priming. Front Cell Neurosci 2012;6(21).

Li X, Zhu W, Roh M-S, Friedman AB, Rosborough K, Jope RS. In vivo regulation of glycogen synthase kinase-3beta (GSK3beta) by serotonergic activity in mouse brain. Neuropsychopharmacology 2004;29:1426–31.

Li S, Tian X, Hartley DM, Feig LA. Distinct roles for Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) and Ras-GRF2 in the induction of long-term potentiation and long-term depression. J Neurosci 2006;26:1721–9.

Li H, Zhang L, Huang Q. Differential expression of mitogen-activated protein kinase signaling pathway in the hippocampus of rats exposed to chronic unpredictable stress. Behav Brain Res 2009;205:32–7.

Li H, Zhang L, Fang Z, Lin L, Wu C, Huang Q. Behavioral and neurobiological studies on the male progeny of maternal rats exposed to chronic unpredictable stress before pregnancy. Neurosci Lett 2010a;469:278–82.

Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010b;329:959–64.

Li Z, Jo J, Jia J-M, Lo S-C, Whitcomb DJ, Jiao S, et al. Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. Cell 2010c;141:859–71.

Li N, Liu R-J, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry 2011;69:754–61.

Li Y, Li B, Wan X, Zhang W, Zhong L, Tang S-J. NMDA receptor activation stimulates transcription-independent rapid wnt5a protein synthesis via the MAPK signaling pathway. Mol Brain 2012;5(1).

Lian T, An S-C. Antidepressant effect of microinjection of neuropeptide Y into the hippocampus is mediated by decreased expression of nitric oxide synthase. Sheng Li Xue Bao: [Acta physiologica Sinica] 2010;62:237–46.

Licht T, Goshen I, Avital A, Kreisel T, Zubedat S, Eavri R, et al. Reversible modulations of neuronal plasticity by VEGF. Proc Natl Acad Sci U S A 2011;108:5081–6.

Lin Y, Westenbroek C, Bakker P, Termeer J, Liu A, Li X, et al. Effects of long-term stress and recovery on the prefrontal cortex and dentate gyrus in male and female rats. Cereb Cortex 2008;18:2762–74.

Lin Y, Ter Horst GJ, Wichmann R, Bakker P, Liu A, Li X, et al. Sex differences in the effects of acute and chronic stress and recovery after long-term stress on stress-related brain regions of rats. Cereb Cortex 2009;19:1978–89.

Liu Y, Ma S, Qu R. SCLM, total saponins extracted from Chaihu-jia-longgu-muli-tang, reduces chronic mild stress-induced apoptosis in the hippocampus in mice. Pharm Biol 2010;48:840–8.

Liu X, Resch J, Rush T, Lobner D. Functional upregulation of system xc- by fibroblast growth factor-2. Neuropharmacology 2012;62:901–6.

Lu Y-F, Hawkins RD. Ryanodine receptors contribute to cGMP-induced late-phase LTP and CREB phosphorylation in the hippocampus. J Neurophysiol 2002;88:1270–8.

Luo L, Tan RX. Fluoxetine inhibits dendrite atrophy of hippocampal neurons by decreasing nitric oxide synthase expression in rat depression model. Acta Pharmacol Sin 2001;22:865–70.

Lushnikova I, Skibo G, Muller D, Nikonenko I. Synaptic potentiation induces increased glial coverage of excitatory synapses in CA1 hippocampus. Hippocampus 2009;19:753–62.

Ma T, Tzavaras N, Tsokas P, Landau EM, Blitzer RD. Synaptic stimulation of mTOR is mediated by Wnt signaling and regulation of glycogen synthetase kinase-3. J Neurosci 2011;31:17537–46.

Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry 2011a;35:676–92.

Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. Neuro Endocrinol Lett 2011b;32:7-24.

Maes M, Leonard B, Fernandez A, Kubera M, Nowak G, Veerhuis R, et al. (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to kinase inhibitors. Prog Neuropsychopharmacol Biol Psychiatry 2011c;35:659–63.

Mailliet F, Qi H, Rocher C, Spedding M, Svenningsson P, Jay TM. Protection of stress-induced impairment of hippocampal/prefrontal LTP through blockade of glucocorticoid receptors: implication of MEK signaling. Exp Neurol 2008;211:593–6.

Manahan-Vaughan D, Ngomba RT, Storto M, Kulla A, Catania MV, Chiechio S, et al. An increased expression of the mGlu5 receptor protein following LTP induction at the perforant path-dentate gyrus synapse in freely moving rats. Neuropharmacology 2003;44:17–25.

Mańko M, Geracitano R, Capogna M. Functional connectivity of the main intercalated nucleus of the mouse amygdala. J Physiol 2011;589:1911–25.

Markram H, Gerstner W, Sjöström PJ. A history of spike-timing-dependent plasticity. Front Synaptic Neurosci 2011;3(4).

Marsden WN. Stressor-induced NMDAR dysfunction as a unifying hypothesis for the aetiology, pathogenesis and comorbidity of clinical depression. Med Hypotheses 2011;77:508–28.

Martin J-L, Finsterwald C. Cooperation between BDNF and glutamate in the regulation of synaptic transmission and neuronal development. Commun Integr Biol 2011;4:14–6.

Martin KP, Wellman CL. NMDA receptor blockade alters stress-induced dendritic remodeling in medial prefrontal cortex. Cereb Cortex 2011;21:2366–73.

Martínez-Turrillas R, Del Río J, Frechilla D. Sequential changes in BDNF mRNA expression and synaptic levels of AMPA receptor subunits in rat hippocampus after chronic antidepressant treatment. Neuropharmacology 2005;49:1178–88.

Martínez-Turrillas R, Del Río J, Frechilla D. Neuronal proteins involved in synaptic targeting of AMPA receptors in rat hippocampus by antidepressant drugs. Biochem Biophys Res Commun 2007;353:750–5.

Martins-de-Souza D, Guest PC, Harris LW, Vanattou-Saifoudine N, Webster MJ, Rahmoune H, et al. Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. Transl Psychiatry 2012;2:e87.

Massaad C a, Klann E. Reactive oxygen species in the regulation of synaptic plasticity and memory. Antioxid Redox Signal 2011;14:2013–54.

Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.

Matsumoto M, Tachibana K, Togashi H, Tahara K, Kojima T, Yamaguchi T, et al. Chronic treatment with milnacipran reverses the impairment of synaptic plasticity induced by conditioned fear stress. Psychopharmacology 2005;179:606–12.

Mauna JC, Miyamae T, Pulli B, Thiels E. Protein phosphatases 1 and 2A are both required for long-term depression and associated dephosphorylation of cAMP response element binding protein in hippocampal area CA1 in vivo. Hippocampus 2011;21:1093–104.

Méndez P, Bacci A. Assortment of GABAergic plasticity in the cortical interneuron melting pot. Neural Plast 2011:976856.

Merino SM, Maren S. Hitting Ras where it counts: Ras antagonism in the basolateral amygdala inhibits long-term fear memory. Eur J Neurosci 2006;23:196–204.

Meyer JH, Wilson AA, Sagrati S, Miler L, Rusjan P, Bloomfield PM, et al. Brain monoamine oxidase A binding in major depressive disorder: relationship to selective serotonin reuptake inhibitor treatment, recovery, and recurrence. Arch Gen Psychiatry 2009;66:1304–12.

Miller JC, Jiménez P, Mathé AA. Restraint stress influences AP-1 and CREB DNA-binding activity induced by chronic lithium treatment in the rat frontal cortex and hippocampus. Int J Neuropsychopharmacol 2007;10:609–19.

Miwa H, Fukaya M, Watabe AM, Watanabe M, Manabe T. Functional contributions of synaptically localized NR2B subunits of the NMDA receptor to synaptic transmission and long-term potentiation in the adult mouse CNS. J Physiol 2008;586:2539–50.

Mockett BG, Brooks WM, Tate WP, Abraham WC. Dopamine D1/D5 receptor activation fails to initiate an activity-independent late-phase LTP in rat hippocampus. Brain Res 2004;1021:92-100.

Moretti M, Colla A, De Oliveira Balen G, Dos Santos DB, Budni J, De Freitas AE, et al. Ascorbic acid treatment, similarly to fluoxetine, reverses depressive-like behavior and brain oxidative damage induced by chronic unpredictable stress. J Psychiatr Res 2012;46:331–40.

Morishita W, Malenka RC. Mechanisms underlying dedepression of synaptic NMDA receptors in the hippocampus. J Neurophysiol 2008;99:254–63.

Munhoz CD, García-Bueno B, Madrigal JLM, Lepsch LB, Scavone C, Leza JC. Stress-induced neuroinflammation: mechanisms and new pharmacological targets. Braz J Med Biol Res 2008;41:1037–46.

Murray PD, Kingsbury TJ, Krueger BK. Failure of Ca^{2+}-activated, CREB-dependent transcription in astrocytes. Glia 2009;57:828–34.

Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem 2011;96:553–63.

Musazzi L, Racagni G, Popoli M. Stress, glucocorticoids and glutamate release: effects of antidepressant drugs. Neurochem Int 2011;59:138–49.

Muschamp JW, Van't Veer A, Parsegian A, Gallo MS, Chen M, Neve RL, et al. Activation of CREB in the nucleus accumbens shell produces anhedonia and resistance to extinction of fear in rats. J Neurosci 2011;31:3095–103.

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Navakkode S, Sajikumar S, Frey JU. Synergistic requirements for the induction of dopaminergic D1/D5-receptor-mediated LTP in hippocampal slices of rat CA1 in vitro. Neuropharmacology 2007;52:1547–54.

Newman LA, Korol DL, Gold PE. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS One 2011;6:e28427.

Nicolson GL. Lipid replacement therapy: a nutraceutical approach for reducing cancer-associated fatigue and the adverse effects of cancer therapy while restoring mitochondrial function. Cancer Metastasis Rev 2010;29:543–52.

Nicolson GL, Ellithorpe R. Lipid replacement and antioxidant nutritional therapy for restoring mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. J Chronic Fatigue Syndr 2006.

Niehusmann P, Seifert G, Clark K, Atas HC, Herpfer I, Fiebich B, et al. Coincidence detection and stress modulation of spike time-dependent long-term depression in the hippocampus. J Neurosci 2010;30:6225–35.

Nudmamud-Thanoi S, Reynolds GP. The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neurosci Lett 2004;372:173–7.

Oh DH, Park YC, Kim SH. Increased glycogen synthase kinase-3β mRNA level in the hippocampus of patients with major depression: a study using the stanley neuropathology consortium integrative database. Psychiatry Investig 2010;7:202–7.

Okamoto H, Voleti B, Banasr M, Sarhan M, Duric V, Girgenti MJ, et al. Wnt2 expression and signaling is increased by different classes of antidepressant treatments. Biol Psychiatry 2010;68:521–7.

Oliveira RMW, Guimarães FS, Deakin JFW. Expression of neuronal nitric oxide synthase in the hippocampal formation in affective disorders. Braz J Med Biol Res 2008;41:333–41.

Olivenza R, Moro MA, Lizasoain I, Lorenzo P, Fernández AP, Rodrigo J, et al. Chronic stress induces the expression of inducible nitric oxide synthase in rat brain cortex. J Neurochem 2000;74:785–91.

Pandey GN, Dwivedi Y, Ren X, Rizavi HS, Roberts RC, Conley RR. Cyclic AMP response element-binding protein in post-mortem brain of teenage suicide victims: specific decrease in the prefrontal cortex but not the hippocampus. Int J Neuropsychopharmacol 2007;10:621–9.

Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007;62:1217–27.

Patterson M, Yasuda R. Signalling pathways underlying structural plasticity of dendritic spines. Br J Pharmacol 2011;163:1626–38.

Pavlides C, Nivón LG, McEwen BS. Effects of chronic stress on hippocampal long-term potentiation. Hippocampus 2002;12:245–57.

Pawlak V, Wickens JR, Kirkwood A, Kerr JND. Timing is not everything: neuromodulation opens the STDP gate. Front Synaptic Neurosci 2010;2:146.

Peineau S, Taghibiglou C, Bradley C, Wong TP, Liu L, Lu J, et al. LTP inhibits LTD in the hippocampus via regulation of GSK3beta. Neuron 2007;53:703–17.

Peng Y, Zhao J, Gu Q-H, Chen R-Q, Xu Z, Yan J-Z, et al. Distinct trafficking and expression mechanisms underlie LTP and LTD of NMDA receptor-mediated synaptic responses. Hippocampus 2010;20:646–58.

Peng Y-L, Liu Y-N, Liu L, Wang X, Jiang C-L, Wang Y-X. Inducible nitric oxide synthase is involved in the modulation of depressive behaviors induced by unpredictable chronic mild stress. J Neuroinflammation 2012;9:75.

Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. Learn Mem 2009;16:279–88.

Pinnock SB, Blake AM, Platt NJ, Herbert J. The roles of BDNF, pCREB and Wnt3a in the latent period preceding activation of progenitor cell mitosis in the adult dentate gyrus by fluoxetine. PLoS One 2010;5:e13652.

Pita-Almenar JD, Collado MS, Colbert CM, Eskin A. Different mechanisms exist for the plasticity of glutamate reuptake during early long-term potentiation (LTP) and late LTP. J Neurosci 2006;26:10461–71.

Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 2008;33:88–109.

Polter AM, Li X. 5-HT1A receptor-regulated signal transduction pathways in brain. Cell Signal 2010;22:1406–12.

Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci 2012;13:22–37.

Potter WB, O'Riordan KJ, Barnett D, Osting SMK, Wagoner M, Burger C, et al. Metabolic regulation of neuronal plasticity by the energy sensor AMPK. PLoS One 2010;5:e8996.

Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010;35:192–216.

Qi X, Lin W, Li J, Pan Y, Wang W. The depressive-like behaviors are correlated with decreased phosphorylation of mitogen-activated protein kinases in rat brain following chronic forced swim stress. Behav Brain Res 2006;175:233–40.

Qi X, Lin W, Li J, Li H, Wang W, Wang D, et al. Fluoxetine increases the activity of the ERK-CREB signal system and alleviates the depressive-like behavior in rats exposed to chronic forced swim stress. Neurobiol Dis 2008;31:278–85.

Qi H, Mailliet F, Spedding M, Rocher C, Zhang X, Delagrange P, et al. Antidepressants reverse the attenuation of the neurotrophic MEK/MAPK cascade in frontal cortex by elevated platform stress; reversal of effects on LTP is associated with GluA1 phosphorylation. Neuropharmacology 2009;56:37–46.

Qi Y, Hu N-W, Rowan MJ. Switching off LTP: mGlu and NMDA receptor-dependent novelty exploration-induced depotentiation in the rat hippocampus. Cereb Cortex 2012.

Qin Y, Zhu Y, Baumgart JP, Stornetta RL, Seidenman K, Mack V, et al. State-dependent Ras signaling and AMPA receptor trafficking. Genes Dev 2005;19:2000–15.

Quan M, Zheng C, Zhang N, Han D, Tian Y, Zhang T, et al. Impairments of behavior, information flow between thalamus and cortex, and prefrontal cortical synaptic plasticity in an animal model of depression. Brain Res Bull 2011a;85:109–16.

Quan M-N, Zhang N, Wang Y-Y, Zhang T, Yang Z. Possible antidepressant effects and mechanisms of memantine in behaviors and synaptic plasticity of a depression rat model. Neuroscience 2011b;182:88–97.

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085–98.

Ray B, Gaskins DL, Sajdyk TJ, Spence JP, Fitz SD, Shekhar A, et al. Restraint stress and repeated corticotrophin-releasing factor receptor activation in the amygdala both increase amyloid-β precursor protein and amyloid-β peptide but have divergent effects on brain-derived neurotrophic factor and pre-synaptic proteins in the prefrontal cortex of cats. Neuroscience 2011;184:139–50.

Reagan LP, Hendry RM, Reznikov LR, Piroli GG, Wood GE, McEwen BS, et al. Tianeptine increases brain-derived neurotrophic factor expression in the rat amygdala. Eur J Pharmacol 2007;565:68–75.

Réus GZ, Stringari RB, Ribeiro KF, Ferraro AK, Vitto MF, Cesconetto P, et al. Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. Behav Brain Res 2011;221:166–71.

Rezin GT, Gonçalves CL, Daufenbach JF, Fraga DB, Santos PM, Ferreira GK, et al. Acute administration of ketamine reverses the inhibition of mitochondrial respiratory chain induced by chronic mild stress. Brain Res Bull 2009;79:418–21.

Roberts LA, Large CH, Higgins MJ, Stone TW, O'Shaughnessy CT, Morris BJ. Increased expression of dendritic mRNA following the induction of long-term potentiation. Brain Res Mol Brain Res 1998a;56:38–44.

Roberts LA, Morris BJ, O'Shaughnessy CT. Involvement of two isoforms of SNAP-25 in the expression of long-term potentiation in the rat hippocampus. Neuroreport 1998b;9:33–6.

Robillard JM, Gordon GR, Choi HB, Christie BR, MacVicar BA. Glutathione restores the mechanism of synaptic plasticity in aged mice to that of the adult. PLoS One 2011;6:e20676.

Rosenkranz JA, Venheim ER, Padival M. Chronic stress causes amygdala hyperexcitability in rodents. Biol Psychiatry 2010;67:1128–36.

Sandi C. Glucocorticoids act on glutamatergic pathways to affect memory processes. Trends Neurosci 2011;34:165–76.

Sarantis K, Matsokis N, Angelatou F. Synergistic interactions of dopamine D1 and glutamate NMDA receptors in rat hippocampus and prefrontal cortex: involvement of ERK1/2 signaling. Neuroscience 2009;163:1135–45.

Sato K, Morimoto K, Suemaru S, Sato T, Yamada N. Increased synapsin I immunoreactivity during long-term potentiation in rat hippocampus. Brain Res 2000;872:219–22.

Savitz J, Nugent AC, Bogers W, Liu A, Sills R, Luckenbaugh DA, et al. Amygdala volume in depressed patients with bipolar disorder assessed using high resolution 3T MRI: the impact of medication. Neuroimage 2010;49:2966–76.

Scapagnini G, Davinelli S, Drago F, De Lorenzo A, Oriani G. Antioxidants as antidepressants: fact or fiction? CNS Drugs 2012;26:477–90.

Schmidt MV, Trümbach D, Weber P, Wagner K, Scharf SH, Liebl C, et al. Individual stress vulnerability is predicted by short-term memory and AMPA receptor subunit ratio in the hippocampus. J Neurosci 2010;30:16949–58.

Schmitt JM, Guire ES, Saneyoshi T, Soderling TR. Calmodulin-dependent kinase kinase/calmodulin kinase I activity gates extracellular-regulated kinase-dependent long-term potentiation. J Neurosci 2005;25:1281–90.

Schweizer MC, Henniger MSH, Sillaber I. Chronic mild stress (CMS) in mice: of anhedonia, "anomalous anxiolysis" and activity. PLoS One 2009;4:e4326.

Scimemi A, Tian H, Diamond JS. Neuronal transporters regulate glutamate clearance, NMDA receptor activation, and synaptic plasticity in the hippocampus. J Neurosci 2009;29:14581–95.

Seo J-S, Park J-Y, Choi J, Kim T-K, Shin J-H, Lee J-K, et al. NADPH oxidase mediates depressive behavior induced by chronic stress in mice. J Neurosci 2012;32:9690–9.

Shelton RC, Hal Manier D, Lewis DA. Protein kinases A and C in post-mortem prefrontal cortex from persons with major depression and normal controls. Int J Neuropsychopharmacol 2009a;12:1223–32.

Shelton RC, Sanders-Bush E, Manier DH, Lewis DA. Elevated 5-HT 2A receptors in post-mortem prefrontal cortex in major depression is associated with reduced activity of protein kinase A. Neuroscience 2009b;158:1406–15.

Shirayama Y, Chaki S. Neurochemistry of the nucleus accumbens and its relevance to depression and antidepressant action in rodents. Curr Neuropharmacol 2006;4:277–91.

Shungu DC, Weiduschat N, Murrough JW, Mao X, Pillemer S, Dyke JP, et al. Increased ventricular lactate in chronic fatigue syndrome. III. Relationships to cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. NMR Biomed 2012;25:1073–87.

Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 2011;36:529–38.

Silva R, Mesquita AR, Bessa J, Sousa JC, Sotiropoulos I, Leão P, et al. Lithium blocks stress-induced changes in depressive-like behavior and hippocampal cell fate: the role of glycogen-synthase-kinase-3beta. Neuroscience 2008;152:656–69.

Slipczuk L, Bekinschtein P, Katche C, Cammarota M, Izquierdo I, Medina JH. BDNF activates mTOR to regulate GluR1 expression required for memory formation. PLoS One 2009;4:e6007.

Song L, Che W, Min-Wei W, Murakami Y, Matsumoto K. Impairment of the spatial learning and memory induced by learned helplessness and chronic mild stress. Pharmacol Biochem Behav 2006;83:186–93.

Stanger O, Fowler B, Piertzik K, Huemer M, Haschke-Becher E, Semmler A, et al. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. Expert Rev Neurother 2009;9:1393–412.

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Stein C, Davidowa H, Albrecht D. 5-HT(1A) receptor-mediated inhibition and 5-HT(2) as well as 5-HT(3) receptor-mediated excitation in different subdivisions of the rat amygdala. Synapse 2000;38:328–37.

Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, et al. Cellular changes in the postmortem hippocampus in major depression. Biol Psychiatry 2004;56:640–50.

Stornetta RL, Zhu JJ. Ras and Rap signaling in synaptic plasticity and mental disorders. Neuroscientist 2011;17:54–78.

Stutzmann GE, LeDoux JE. GABAergic antagonists block the inhibitory effects of serotonin in the lateral amygdala: a mechanism for modulation of sensory inputs related to fear conditioning. J Neurosci 1999;19:RC8.

Sui L, Wang J, Li B-M. Role of the phosphoinositide 3-kinase-Akt-mammalian target of the rapamycin signaling pathway in long-term potentiation and trace fear conditioning memory in rat medial prefrontal cortex. Learn Mem 2008;15:762–76.

Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, et al. Astrocyte–neuron lactate transport is required for long-term memory formation. Cell 2011;144:810–23.

Szatmari E, Habas A, Yang P, Zheng J-J, Hagg T, Hetman M. A positive feedback loop between glycogen synthase kinase 3beta and protein phosphatase 1 after stimulation of NR2B NMDA receptors in forebrain neurons. J Biol Chem 2005;280:37526–35.

Szewczyk B, Poleszak E, Pilc A, Nowak G. Ionic glutamate modulators in depression (zinc, magnesium). In: Skolnick P, editor. Birkhauser; 2010.

Szymańska M, Suska A, Budziszewska B, Jaworska-Feil L, Basta-Kaim A, Leśkiewicz M, et al. Prenatal stress decreases glycogen synthase kinase-3 phosphorylation in the rat frontal cortex. Pharmacol Rep 2009;61:612–20.

Talarowska M, Gałecki P, Maes M, Bobińska K, Kowalczyk E. Total antioxidant status correlates with cognitive impairment in patients with recurrent depressive disorder. Neurochem Res 2012a;37:1761–7.

Talarowska M, Gałecki P, Maes M, Gardner A, Chamielec M, Orzechowska A, et al. Malondialdehyde plasma concentration correlates with declarative and working memory in patients with recurrent depressive disorder. Mol Biol Rep 2012b;39:5359–66.

Tanaka J-I, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GCR, Kasai H. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science 2008;319:1683–7.

Tang SJ, Reis G, Kang H, Gingras A-C, Sonenberg N, Schuman EM. A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. Proc Natl Acad Sci U S A 2002;99:467–72.

Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry 2005;66:974–81.

Thome J, Sakai N, Shin K, Steffen C, Zhang YJ, Impey S, et al. cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. J Neurosci 2000;20:4030–6.

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, et al. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 2010;62:405–96.

Uchida S, Hara K, Kobayashi A, Otsuki K, Yamagata H, Hobara T, et al. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 2011;69:359–72.

Valera E, Sánchez-Martín FJ, Ferrer-Montiel AV, Messeguer A, Merino JM. NMDA-induced neuroprotection in hippocampal neurons is mediated through the protein kinase A and CREB (cAMP-response element-binding protein) pathway. Neurochem Int 2008;53:148–54.

Valerio A, Bertolotti P, Delbarba A, Perego C, Dossena M, Ragni M, et al. Glycogen synthase kinase-3 inhibition reduces ischemic cerebral damage, restores impaired mitochondrial biogenesis and prevents ROS production. J Neurochem 2011;116:1148–59.

Varea E, Guirado R, Gilabert-Juan J, Martí U, Castillo-Gomez E, Blasco-Ibáñez JM, et al. Expression of PSA-NCAM and synaptic proteins in the amygdala of psychiatric disorder patients. J Psychiatr Res 2012;46:189–97.

Veer IM, Beckmann CF, Van Tol M-J, Ferrarini L, Milles J, Veltman DJ, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Front Syst Neurosci 2010;4.

Verburg J, Hollenbeck PJ. Mitochondrial membrane potential in axons increases with local nerve growth factor or semaphorin signaling. J Neurosci 2008;28:8306–15.

Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci 2002;22:6810–8.

Vyas A, Jadhav S, Chattarji S. Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 2006;143:387–93.

Wallace TL, Stellitano KE, Neve RL, Duman RS. Effects of cyclic adenosine monophosphate response element binding protein overexpression in the basolateral amygdala on behavioral models of depression and anxiety. Biol Psychiatry 2004;56:151–60.

Waltereit R, Weller M. Signaling from cAMP/PKA to MAPK and synaptic plasticity. Mol Neurobiol 2003;27:99-106.

Waly MI, Kharbanda KK, Deth RC. Ethanol lowers glutathione in rat liver and brain and inhibits methionine synthase in a cobalamin-dependent manner. Alcohol Clin Exp Res 2011;35:277–83.

Wang H. Calmodulin-regulated adenylyl cyclases: cross-talk and plasticity in the central nervous system. Mol Pharmacol 2003;63:463–8.

Wang R-M, Yang F, Zhang Y-X. Preconditioning-induced activation of ERK5 is dependent on moderate Ca^{2+} influx via NMDA receptors and contributes to ischemic tolerance in the hippocampal CA1 region of rats. Life Sci 2006a;79:1839–46.

Wang Z, Hu S, Lei D, Song W. Effect of chronic stress on PKA and P-CREB expression in hippocampus of rats and the antagonism of antidepressors. Zhong Nan Da Xue Xue Bao Yi Xue Ban = Journal of Central South University Medical sciences 2006b;31:767–71.

Wang D, An SC, Zhang X. Prevention of chronic stress-induced depression-like behavior by inducible nitric oxide inhibitor. Neurosci Lett 2008;433:59–64.

Wang W, Sun D, Pan B, Roberts CJ, Sun X, Hillard CJ, et al. Deficiency in endocannabinoid signaling in the nucleus accumbens induced by chronic unpredictable stress. Neuropsychopharmacology 2010;35:2249–61.

Wang Y-b, Wang J-j, Wang S-h, Liu S-S, Cao J-y, Li X-m, et al. Adaptor protein APPL1 couples synaptic NMDA receptor with neuronal prosurvival phosphatidylinositol 3-kinase/Akt pathway. J Neurosci 2012;32:11919–29.

Warner-Schmidt JL, Duman RS. VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proc Natl Acad Sci U S A 2007;104:4647–52.

Wayman GA, Impey S, Marks D, Saneyoshi T, Grant WF, Derkach V, et al. Activity-dependent dendritic arborization mediated by CaM-kinase I activation and enhanced CREB-dependent transcription of Wnt-2. Neuron 2006;50:897–909.

Wenker I. An active role for astrocytes in synaptic plasticity? J Neurophysiol 2010;104:1216–8.

Wenzel J, Lammert G, Meyer U, Krug M. The influence of long-term potentiation on the spatial relationship between astrocyte processes and potentiated synapses in the dentate gyrus neuropil of rat brain. Brain Res 1991;560:122–31.

Wilkinson MB, Dias C, Magida J, Mazei-Robison M, Lobo M, Kennedy P, et al. A novel role of the WNT-dishevelled-GSK3β signaling cascade in the mouse nucleus accumbens in a social defeat model of depression. J Neurosci 2011;31:9084–92.

Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology 2005;52:90-110.

Wu GY, Deisseroth K, Tsien RW. Activity-dependent CREB phosphorylation: convergence of a fast, sensitive calmodulin kinase pathway and a slow, less sensitive mitogen-activated protein kinase pathway. Proc Natl Acad Sci U S A 2001;98:2808–13.

Wu H, Zhou Y, Xiong Z-Q. Transducer of regulated CREB and late phase long-term synaptic potentiation. FEBS J 2007;274:3218–23.

Wu L, Zhang J, Wang J, Li W, Deng X, Tong H, et al. Effects of pingyu capsule on signal transduction of rats with chronic stress-induced depression. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica 2008;33:1743–6.

Xiao L, Feng C, Chen Y. Glucocorticoid rapidly enhances NMDA-evoked neurotoxicity by attenuating the NR2A-containing NMDA receptor-mediated ERK1/2 activation. Mol Endocrinol 2010;24:497–510.

Xiong Z, Jiang B, Wu P-F, Tian J, Shi L-L, Gu J, et al. Antidepressant effects of a plant-derived flavonoid baicalein involving extracellular signal-regulated kinases cascade. Biol Pharm Bull 2011;34:253–9.

Xu J, Zhang Q-G, Li C, Zhang G-Y. Subtoxic N-methyl-D-aspartate delayed neuronal death in ischemic brain injury through TrkB receptor- and calmodulin-mediated PI-3K/Akt pathway activation. Hippocampus 2007;17:525–37.

Xu J, Kurup P, Zhang Y, Goebel-Goody SM, Wu PH, Hawasli AH, et al. Extrasynaptic NMDA receptors couple preferentially to excitotoxicity via calpain-mediated cleavage of STEP. J Neurosci 2009;29:9330–43.

Yamada S, Yamamoto M, Ozawa H, Riederer P, Saito T. Reduced phosphorylation of cyclic AMP-responsive element binding protein in the postmortem orbitofrontal cortex of patients with major depressive disorder. J Neural Transm 1996;110:671–80. (Vienna, Austria).

Yang Y, Takeuchi K, Rodenas-Ruano A, Takayasu Y, Bennett MVL, Zukin RS. Developmental switch in requirement for PKA RIIbeta in NMDA-receptor-dependent synaptic plasticity at Schaffer collateral to CA1 pyramidal cell synapses. Neuropharmacology 2009;56:56–65.

Yazir Y, Utkan T, Aricioglu F. Inhibition of neuronal nitric oxide synthase and soluble guanylate cyclase prevents depression-like behaviour in rats exposed to chronic unpredictable mild stress. Basic Clin Pharmacol Toxicol 2012;111:154–60.

Yoshii A, Constantine-Paton M. Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. Dev Neurobiol 2010;70:304–22.

Yu S, Yang S, Holsboer F, Sousa N, Almeida OFX. Glucocorticoid regulation of astrocytic fate and function. PLoS One 2011;6:e22419.

Yuan P, Zhou R, Wang Y, Li X, Li J, Chen G, et al. Altered levels of extracellular signal-regulated kinase signaling proteins in postmortem frontal cortex of individuals with mood disorders and schizophrenia. J Affect Disord 2010;124:164–9.

Yuan T-T, Qiao H, Dong S-P, An S-C. Activation of hippocampal D1 dopamine receptor inhibits glutamate-mediated depression induced by chronic unpredictable mild stress in rats. Sheng Li Xue Bao: [Acta physiologica Sinica] 2011;63:333–41.

Yun HY, Gonzalez-Zulueta M, Dawson VL, Dawson TM. Nitric oxide mediates N-methyl-D-aspartate receptor-induced activation of p21ras. Proc Natl Acad Sci U S A 1998;95:5773–8.

Yun HY, Dawson VL, Dawson TM. Glutamate-stimulated calcium activation of Ras/Erk pathway mediated by nitric oxide. Diabetes Res Clin Pract 1999;45:113–5.

Zheng H, Ma G, Fu X, DU H. Effects of paroxetine on protein kinase PKA, PKC and CaMKII activity in different brain regions in a rat depression model. Nan fang yi ke da xue xue bao = Journal of Southern Medical University 2008;28:1223–5.

Zhong P, Liu W, Gu Z, Yan Z. Serotonin facilitates long-term depression induction in prefrontal cortex via p38 MAPK/Rab5-mediated enhancement of AMPA receptor internalization. J Physiol 2008;586:4465–79.

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Zhou Q-G, Hu Y, Hua Y, Hu M, Luo C-X, Han X, et al. Neuronal nitric oxide synthase contributes to chronic stress-induced depression by suppressing hippocampal neurogenesis. J Neurochem 2007;103:1843–54.

Zhou Q-G, Zhu L-J, Chen C, Wu H-Y, Luo C-X, Chang L, et al. Hippocampal neuronal nitric oxide synthase mediates the stress-related depressive behaviors of glucocorticoids by downregulating glucocorticoid receptor. J Neurosci 2011;31:7579–90.

Zomkowski ADE, Engel D, Gabilan NH, Rodrigues ALS. Involvement of NMDA receptors and l-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effects of escitalopram in the forced swimming test. Eur Neuropsychopharmacol 2010;20:793–801.

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