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Review

Ketamine, magnesium and major depression — From pharmacology to pathophysiology and back

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ABSTRACT

The glutamatergic mechanism of antidepressant treatments is now in the center of research to overcome the limitations of monoamine-based approaches. There are several unresolved issues. For the action of the model compound, ketamine, NMDA-receptor block, AMPA-receptor activation and BDNF release appear to be involved in a mechanism, which leads to synaptic sprouting and strengthened synaptic connections. The link to the pathophysiology of depression is not clear. An overlooked connection is the role of magnesium, which acts as physiological NMDA-receptor antagonist: 1. There is overlap between the actions of ketamine with that of high doses of magnesium in animal models, finally leading to synaptic sprouting. 2. Magnesium and ketamine lead to synaptic strengthening, as measured by an increase in slow wave sleep in humans. 3. Pathophysiological mechanisms, which have been identified as risk factors for depression, lead to a reduction of (intracellular) magnesium. These are neuroendocrine changes (increased cortisol and aldosterone) and diabetes mellitus as well as Mg^{2+} deficiency. 4. Patients with therapy refractory depression appear to have lower CNS Mg^{2+} levels in comparison to health controls. 5. Experimental Mg^{2+} depletion leads to depression- and anxiety like behavior in animal models. 6. Ketamine, directly or indirectly via non-NMDA glutamate receptor activation, acts to increase brain Mg^{2+} levels. Similar effects have been observed with other classes of antidepressants. 7. Depressed patients with low Mg^{2+} levels tend to be therapy refractory. Accordingly, administration of Mg^{2+} either alone or in combination with standard antidepressants acts synergistically on depression like behavior in animal models.

Conclusion: On the basis of the potential pathophysiological role of Mg^{2+}-regulation, it may be possible to predict the action of ketamine and of related compounds based on Mg^{2+} levels. Furthermore, screening for compounds to increase neuronal Mg^{2+} concentration could be a promising instrument to identify new classes of antidepressants. Overall, any discussion of the glutamatergic system in affective disorders should consider the role of Mg^{2+}.

1. Introduction

An interest in glutamatergic aspects in depression existed more than 20 years ago and important data were generated (Trullas and Skolnick, 1990; Paul et al., 1994). The renewed awareness of the limitations to treat depression with monoamine-based mechanism of action and the findings of a rapid antidepressant response to ketamine in patients with treatment resistance to these compounds has led to a paradigm shift for the development of new antidepressant compounds. First observations of the effects of ketamine in depression (Berman et al., 2000) were done more than 10 years ago. However, it was not until the mile-stone observations of Zarate et al. (2006), who demonstrated in a double blind placebo controlled study the effect of ketamine in patients, who did not respond to standard antidepressants, that this field got broader attention. During the last several years has the NMDA ergic system received marked attention in the context of developing new compounds for mood disorder (Li et al., 2011b). The mechanism of action of glutamatergic compounds is unraveling, but there are several unresolved issues.

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2. Proposed mechanism of action of ketamine in depression

The recently proposed sequence of events involves blocking N-methyl-D-aspartate (NMDA) receptors on gamma-aminobutyric acid (GABA)-ergic interneurons. The dampening of their activity disinhibits glutamatergic neurons due to a lowered GABAergic inhibition. Within the given context of NMDA blockade the released glutamate primarily excites (-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid) (AMPA) and kainite receptors (Fig. 1). It is important to keep in mind that this combination of NMDA-receptor blockade and AMPAergic activation is of short duration due to the short half life of ketamine, but could be necessary for the long term antidepressant effects of ketamine treatment. 2. AMPA receptors activate the expression and release of brain derived neuroptrophic factor (BDNF), which activate its receptor, the tropomyosin related kinase B (TrkB)-receptor.

Several alternative pathways downstream of the activation of TrkB receptors by BDNF have been described: a) activation of PI3K, followed by that of AKT and of mammalian target of rapamycin (mTOR) which leads to the inhibition of eukaryotic elongation factor 2 (eEF2) phosphorylation. Recently an alternative pathway via deactivation of eEF2-kinase has been reported. This pathway may not involve mTOR, but results in a reduced phosphorylation of eEF2 and disinhibition of BDNF translation (Autry et al., 2011). For both pathways, reduced phosphorylation of eEF2 and downstream disinhibition of gene expression seem to be relevant steps. b) An parallel pathway involves activation of extracellular signal regulated kinase (ERK). Via both pathways TrkB activation finally leads to an induction of synaptic proteins, in particular AMPAergic glutamate receptor subunits GluR1, anchoring protein PDS-95 and synapsin 1 (Li et al., 2010; Duman et al., 2012). The outcome of the BDNF related activation is therefore the increase in a specific subset of AMPA receptors (AMPAR), i.e. Ca^{2+}-permeable (CP)-AMPAR (Fortin et al., 2012), when GluR1-subunits form homomeric receptors. As a note, other AMPAR, i.e. those which contain the GluR2 subunit, are impermeable for Ca^{2+} and Mg^{2+} (Burnashev et al., 1992). There is evidence that CP-AMPAR are required for long term potentiation (LTP)-induced neuronal spine enlargement (Fortin et al., 2010), i.e. their increase may have specific relevance for synaptic sprouting. c) Finally, BDNF activates Ca^{2+}/calmodulin-dependent protein kinase (CaM kinase) kinase (CaMKK) in a transient receptor potential canonical channel (TPRC)-dependent way, which activates AKT and in parallel mediates an increased synaptic incorporation of CP-AMPA (Fortin et al., 2012) (Fig. 2). It is not yet clear if this interaction between AMPA-receptor mediated BDNF release and BDNF related CP-AMPAR expression constitutes a feedforward cycle, as it is not clear if a specific AMPAR subtype is involved in the BDNF expression and release.

Opposing mechanisms for the therapeutically relevant switch of AMPA-receptor constitution have to be considered: Extrasynaptic NMDA-receptor activation, which occurs during glutamate spillover in pathogenetic processes leads to an inhibition of CREB and reduces BDNF expression (Vanhoutte and Bading, 2003). This leads to a PKC dependent switch from CP-AMPAR to GluR2 containing Ca^{2+} and Mg^{2+} impermeable channels (Sun and June Liu, 2007). This mechanism may in part explain the action of compounds like riluzole. Riluzole reduces the extracellular concentration of glutamate and may therefore reduce glutamate spillover to extrasynaptic NMDA receptors (Sanacora et al., 2004, 2007). Therefore, there is a tight window of a beneficial concentration of synaptic glutamate, which primarily acts on synaptic AMPAR and a potentially deleterious spillover to extrasynaptic NMDA receptors. The combined AMPAR activation and NMDA-receptor inhibition at the early stages of the effect of ketamine may therefore be of importance for ketamine's clinical effect.

Several questions occur: What determines the response to ketamine in a given subject? What determines the release of BDNF? Is the release of BDNF with ketamine in any way different than that with standard antidepressants?

3. Comparison of the effects of Mg^{2+} and ketamine

The comparison of the effect of ketamine with the physiologically present NMDA antagonistic Mg^{2+} may provide further insights into the mechanisms in question. 1. Ketamine- and Mg^{2+} administration both lead to an increase in slow wave sleep in humans preferably at the beginning of the sleep period (Held et al., 2002; Duncan et al., 2012b). 2. Administration of an innovative Mg^{2+} compound with a high bioavailability leads to an increase in BDNF expression in the brain and finally to synaptic sprouting in the prefrontal cortex of rats, again, similar to ketamine (Abumaria et al., 2011). In parallel an increase in NR2b (but not NR1 and NR2a) receptor expression occurred with both ketamine (Burgdorf et al., 2013; Chatterjee et al., 2012) and Mg^{2+} − administration (Abumaria et al., 2011). Opposite changes can be observed in neuronal cell cultures exposed to short term Mg^{2+}-free solution, which leads to a reduced expression of NR2b and PDS-95 (Jiang et al., 2007). 3. Chronic unpredictable stress reduces neuronal strength, i.e. the amplitude of excitatory postsynaptic potential (EPSP) in the PFC of rats, which can be reversed by the administration with ketamine (Li et al., 2011a). Similarly, incubation of prefrontal cortex slides with Mg^{2+} increase of EPSP amplitude (Abumaria et al., 2011). It would be of interest to determine, if incubation with Mg^{2+} leads to a normalization of the stress-induced EPSP reduction. Overall, the functional consequences of Mg^{2+} and ketamine administration show similarities.

4. Overlap of Mg^{2+} and ketamine-induced pathways

4.1. NR2b antagonistic effect of Mg^{2+}

Mg^{2+} is a naturally occurring NMDA-receptor antagonist and has effects in concentrations, which are physiologically occurring in the extrasynaptic space (see Murck, 2002). Of particular interest is the relative specificity of the Mg^{2+} block of the NMDA receptors based on their specific subunits. The NR1 receptor is ubiquitous, whereas different kinds of NR2 subunits exist. Of these the NR2c and NR2d are the least sensitive to the Mg^{2+} block, whereas NR2a and NR2b are more sensitive (Kuner and Schoepfer, 1996). It is of interest that it is the NR2b receptor, which is a target for antidepressive efficacy similar to that of ketamine (Preskorn et al., 2008). Is therefore ketamine potentially replacing a deficit of Mg^{2+} at the level of the NR2b type NMDA receptor? There are a number of observations, which appear to be in line with this notion: the sensitivity of ketamine and other NMDA-receptor antagonists is increased in a state of Mg^{2+} depletion (Begon et al., 2001). In particular Mg^{2+} deficiency leads to a sensitization for ketamine to induce sleep (Douglas and Dagirmanjian, 1975). In line with this is that treatment refractory depressed patients, i.e. the group which shows beneficial effects from ketamine treatment, have a lower CNS Mg^{2+} level (Iosifescu et al., 2008). However, this may not be the complete explanation. There are some observations, which demonstrate that the combination of ketamine and Mg^{2+} in a situation of normal Mg^{2+} levels has super-additive effects (Orser et al., 1997; Liu et al., 2001). Therefore potentially synergistic effects beyond NR2b antagonism should be taken into account.

This NR2b antagonistic effect of Mg^{2+} is complemented by intracellular mechanism of Mg^{2+}, for an overview see (Murck, 2002). It has to be considered that Mg^{2+} is a primarily intracellular ion. Therefore the reduced Mg^{2+} level in the brain of subjects

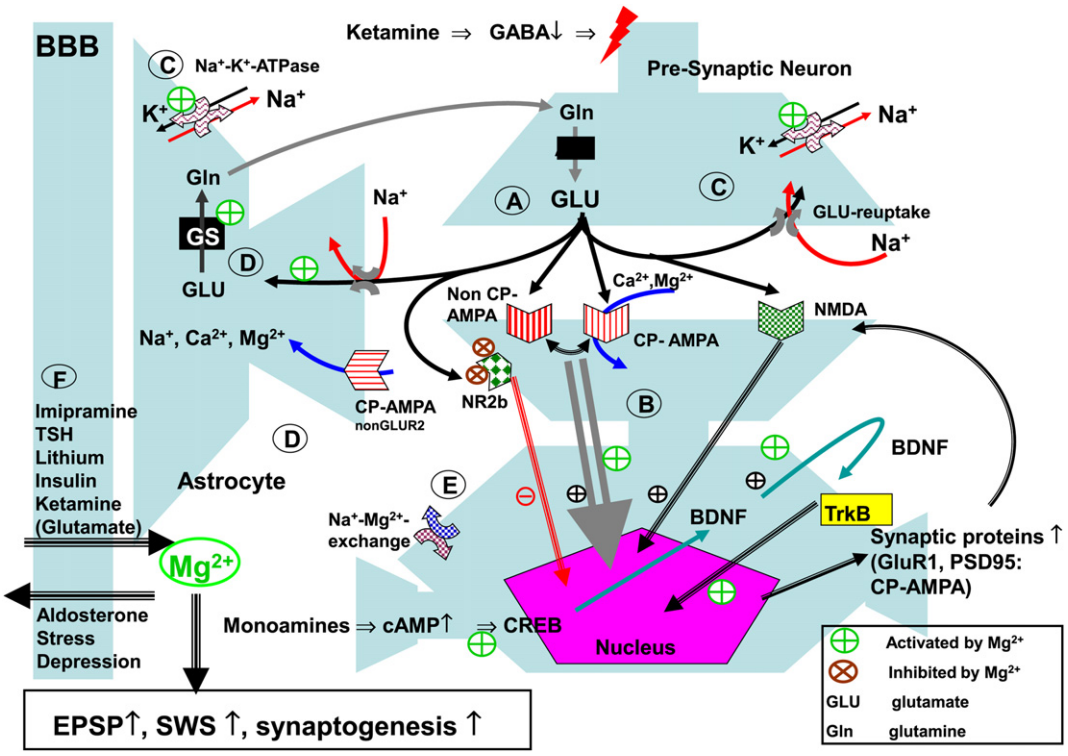

Fig. 1. Magnesium involvement in ketamine-induced pathways: ketamine administration leads to a cascade of events finally resulting in modifications of glutamatergic receptor profile and synaptogenesis. Functional consequences are increased excitatory postsynaptic potentials (EPSP) and increased slow wave sleep; both phenomena are also induced by Mg^{2+}. In detail: A: ketamine inhibits GABAergic interneurons and therefore activates the release of glutamate. B: AMPAR mediate BDNF expression and release. BDNF activates TrkB receptor, which induces changes in gene expression (see Fig. 2). BNDF induces its own expression. NMDA-receptor activation is facilitating this process (Xiong et al., 2002). This could constitute a feedforward mechanism, explaining the long term effect of ketamine administration. Further, the expression of synaptic proteins is induced, in particular GluR1 and PSD-95, which constitute the synaptic expression of Ca^{2+}-permeable AMPA receptors (CP-AMPA) (Fortin et al., 2012). Importantly, CP-AMPA are permeable for Mg^{2+}. C: Glutamate is taken up quickly by neurons and astrocytes. This is of importance as high concentrations of glutamate can "spillover" to extrasynaptic NMDA receptors, which appear to be primarily from the NR2b type. Their activation can block synaptogenesis and lead to cell damage. Rapid reuptake of glutamate prevents this "spillover". Glutamate reuptake is an energy dependent process driven by the Na^+-gradient over the membrane (Magistretti, 2009), which in itself is driven by the Na^+–K^+–ATPase. The Na^+–K^+–ATPase is dependent on Mg^{2+}, therefore increased Mg^{2+} availability supports its activity and secondarily glutamate clearance. D: In parallel glutamate receptors at astrocytes are activated. CP-AMPA receptor activation can lead to an increase in astrocytic Ca^{2+} (Magistretti, 2009) and Mg^{2+} (Muller et al., 2003). A potential consequence of increased Mg^{2+} in astrocytes is activation of glutamine synthetase (GS), which is Mg^{2+} dependent (Greenberg and Lichtenstein, 1959; Maurizi et al., 1986). E: A neuronal Na^+–Mg^{2+}-exchange mechanism regulates intracellular Mg^{2+} concentration. Imipramine appears to block Na^+–Mg^{2+}-exchange, preventing the efflux of Mg^{2+} from the neuron. F: Magnesium uptake into the brain has been described with compounds, which are know to be efficacious in treatment refractory depression, i.e. ketamine (via its glutamate releasing capability), TSH, lithium, imipramine and potentially insulin related mechanism (metformin, glitazones). On the other hand stress and refractory depression are linked to lower Mg^{2+} levels in the brain, which may in part be mediated via an aldosterone mediated mechanism.

with depression should be reflected in intracellular changes as well. The intracellular Mg^{2+} concentration affects the sensitivity of NMDA receptors and their activity: In sensory neurons (Chen and Huang, 1992) and in hippocampal synaptosomes, the Mg^{2+} block of the NMDA dependent ion channel is removed by activation of protein kinase C (PKC) without changing membrane potential (Pittaluga et al., 2000). Intracellular administration of a PKC agonist accordingly potentiated NMDA-receptor function in cultured hippocampal neurons (Xiong et al., 1998). On the other hand Mg^{2+} appears to affect PKC activity: Mg^{2+} depletion leads to an increase in NMDA mediated PKC activation and nitric oxide (NO) release in spinal cord neurons (Begon et al., 2001). This mechanism could lead to a feedforward cycle: a NMDA dependent Ca^{2+} current may increase PKC activity, which leads to further release of the Mg^{2+} block of the NMDA dependent ion current (Chen and Huang, 1992). This means that reduced intracellular Mg^{2+} can be responsible for an increased NMDA-receptor sensitivity. An alternative mechanism of intracellular Mg^{2+} deficiency to increase NR2b-receptor activation exists, which appears to be independent from second messenger pathways (Li-Smerin et al., 2000). Overall, both extracellular and intracellular Mg^{2+} inhibit NMDA-receptor activity and in particular NR2b-receptor function.

4.2. Comparison of the effects of ketamine and Mg^{2+} on the CaMKII pathway

An increase in synaptic strength appears to be the result of the effects of both ketamine and Mg^{2+}. One of the molecular determinants for synaptic strength is the interaction between NR2b containing NMDA receptors on the one hand and Ca^{2+}/calmodulin activated protein kinase II (CaMKII) and PSD-95 proteins (Lisman et al., 2012). Increase in intracellular Ca^{2+} leads to the activation of calmodulin, which activates CaMKII. This leads to a translocation and fixation of GluR1 containing AMPA receptors at synaptic sites and as a consequence amplification of AMPAergic currents (Lee et al., 2000; Lisman et al., 2012). This mechanism increases EPSPs frequency and long term potentiation (LTP) in the hippocampus.

Mg^{2+} leads to increased LTP in hippocampal slides (Landfield and Morgan, 1984). Low Mg^{2+} for a short period of time leads to an inhibition of CaMKII activity (Blair et al., 1999), whereas Mg^{2+} administration in vivo increases phosphorylation and therefore activation of CaMKII in the prefrontal cortex. This was accompanied by an increase in LTP (Abumaria et al., 2011). Similarly ketamine induces CaMKII expression, as observed in the nucleus accumbens of rats (Iasevoli et al., 2007). Interestingly a reduced expression of

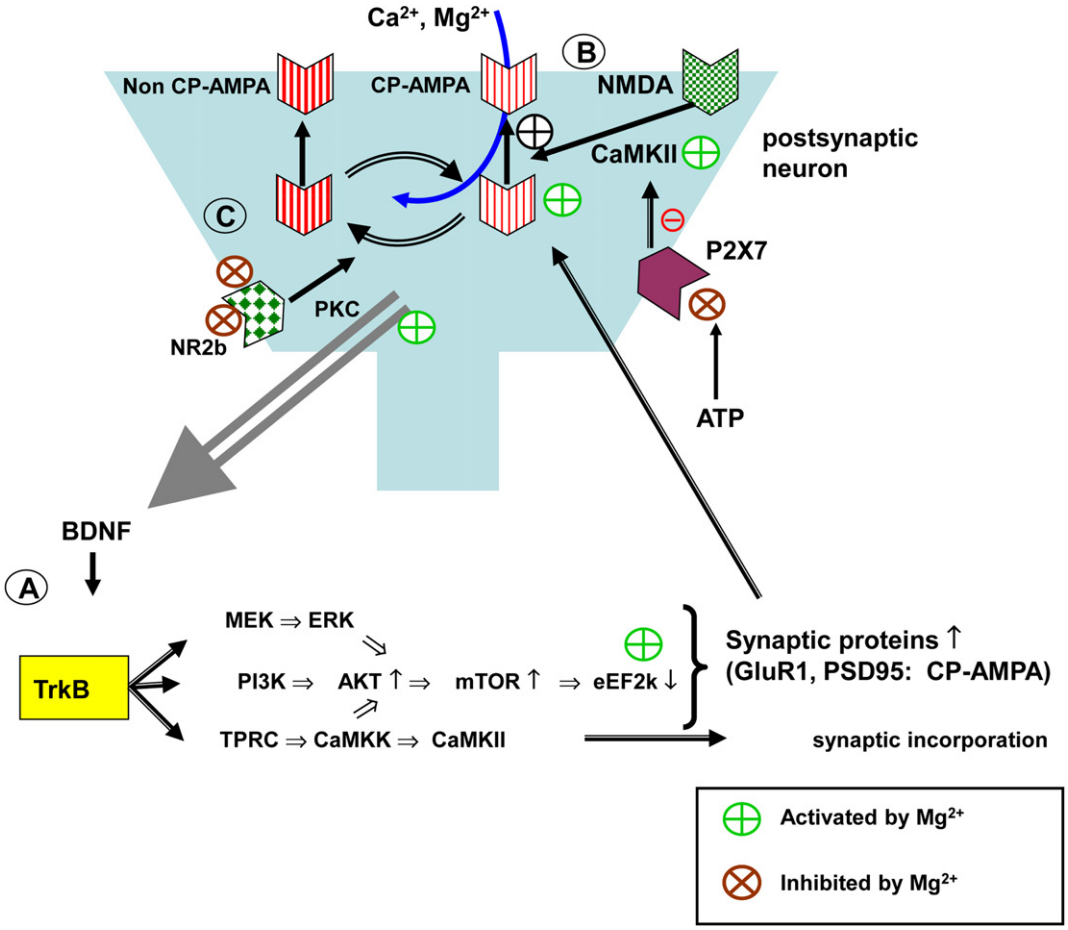

Fig. 2. Proposed pathways of synaptogenesis. A. BDNF activated TrkB receptors lead to the activation of several parallel pathways including: The activity of a) the AKT–mTOR pathway and as a consequence inhibition of eEF2-kinase. The eEF2-kinase appears to be directly inhibited by Mg^{2+} (Perraud et al., 2011). b) The ERK pathway, which is also facilitated by Mg^{2+} administration (Huang et al., 2010)); c) TPRC dependent activation of CaMKK and activation of AKT (Fortin et al., 2012). Gene expression is activated to lead to the generation of synaptic proteins, in particular GluR1 containing CP-AMPAR as well as PSD-95. In parallel CaMKK activation is involved in the fixation of AMPAR at synaptic sites. B. The insertion of CP-AMPAR is additionally regulated via CaMKII activation via NMDA-receptor related Ca^{2+} increase (Barria and Malinow, 2005). The CaMKII pathway is activated by Mg^{2+} and inhibited by P2X7-purinergic receptors, which by themselves are sensitive to Mg^{2+}. As a consequence Mg^{2+} facilitates CaMKII-dependent synaptic activity. The resulting increased availability of CP-AMPAR may lead to a higher sensitivity of the system to Mg^{2+}, forming a feedforward cycle. C. The activation of extrasynaptic NMDA receptors by glutamate spillover appear to alter the AMPA-receptor expression by favoring GluR2 containing AMPAR (Non CP-AMPA) in a PKC dependent pathway (Sun and June Liu, 2007). This can have deleterious effects.

CaMKII in post mortem studies of the prefrontal cortex of patients with unipolar depression and bipolar disorder (Xing et al., 2002) has been observed, in line with the hypothesis of an involvement of Mg^{2+} dysregulation in patients with depression. In summary, Mg^{2+} increases CaMKII activity, which leads to an increase in AMPAergic function in the prefrontal cortex (Fig. 2).

In addition to the direct effect of Mg^{2+} on CaMKII activity an indirect pathway of importance exist. We want to focus here on the role of P2X7, a purinergic receptor, which controls an unspecific cation current (Skaper et al., 2010). Polymorphisms of the P2X7 gene have been linked to the risk of depression (Lucae et al., 2006; Soronen et al., 2011), however a negative study also exists (Green et al., 2009). In our context it is important that P2X7 receptor inhibition activates neuritogenesis in a CaMKII-dependent pathway (Leon et al., 2006; Gomez-Villafuertes et al., 2009) in neuronal cells. As Mg^{2+} demonstrates an antagonistic effect on P2X7 receptor activation, as demonstrated in a variety of cells (Jiang, 2009; Alloisio et al., 2010; Lee et al., 2011) (Fig. 2), this points to a beneficial effect of Mg^{2+} in increase synaptic strength by reducing P2X7 activity.

4.3. cAMP–CREB–BDNF pathway

A further observation after Mg^{2+} administration was the increased phosphorylation of CREB (Abumaria et al., 2011). The importance of CREB-phosphorylation as a mediator of an antidepressant response has been extensively described (D'Sa and Duman, 2002; Carlezon et al., 2005; Gourley et al., 2008; Tanis et al., 2008). The supportive effect of Mg^{2+} on the activation of the cAMP pathway is well documented (see (Murck, 2002)). A direct importance of CREB for BNDF expression has been demonstrated (Duman, 1998; Manji and Duman, 2001). As a consequence, Mg^{2+} administration led to an increase in BDNF expression (Abumaria et al., 2011) and shows neuroprotective effects via CREB-phosphorylation (Huang et al., 2010).

4.4. AKT–mTOR–eEF2k pathway

The AKT–mTOR–eEF2k pathway activation appears to be one prominent consequence of TrkB activation. Mg^{2+}, like ketamine, suppresses eEF2 phosphorylation (Perraud et al., 2011) in cell

Table 1
Overview of discussed changes in regional expression of receptors and transcription factors if not otherwise specified the results are from animal models.

	Major depression (human)	Chronic stress	Mg depletion (acute)	Magnesium administration	Ketamine	Sleep deprivation
PFC–NR1	⇔ (Feyissa et al., 2009)	⇓ (Lee and Goto, 2011)	?	⇔ (Abumaria et al., 2011)	⇑ (Chatterjee et al., 2012)	?
Amygdala–NR1	⇔ (Karolewicz et al., 2009)	?	?	⇔ (Abumaria et al., 2011)	?	?
PFC–NR2A	⇓ (Feyissa et al., 2009)	⇓ (Lee and Goto, 2011; Yuen et al., 2012)	?	⇔ (Abumaria et al., 2011)	⇔ (Chatterjee et al., 2012)	8 h: ⇑ (Cirelli and Tononi, 2000); 72 h: ⇔ (Park et al., 2012; Vyazovskiy et al., 2008)
Amygdala–NR2A	⇑ (Karolewicz et al., 2009)	?	?	⇔ (Abumaria et al., 2011)	?	?
PFC–NR2B	⇓ (Feyissa et al., 2009)	⇓ (Lee and Goto, 2011; Yuen et al., 2012)	⇓ (Jiang et al., 2007) (cell culture)	⇑ (Abumaria et al., 2011)	⇑ (Chatterjee et al., 2012; Burgdorf et al., 2013)	72 h: ⇓ (Park et al., 2012)
Cortical (PFC)–GluR1	?	⇓ (Li et al., 2011a; Yuen et al., 2012)	⇑ (Jiang et al., 2008) (cell culture)	?	⇑ (Li et al., 2011a)	3 h: ⇑ (Vyazovskiy et al., 2008; after wake: Lante et al., 2011)
Cortical (PFC)–GluR2	⇑ (Teyssier et al., 2011)	⇓ (Yuen et al., 2012)	Biphasic: ⇑ → ⇓ (Jiang et al., 2008) (cell culture)	?	?	8 h: ⇑ (Cirelli and Tononi, 2000); 3 h: ⇔ (Vyazovskiy et al., 2008)

Table 2
Overview of discussed changes in regional expression of transcription factors if not otherwise specified the results are from animal models.

	Major depression (human)	Chronic stress	Mg depletion (acute)	Magnesium administration	Ketamine	Sleep deprivation
PFC–BNDF	?	⇔ (Chiba et al., 2012); ⇓ (van Donkelaar et al., 2009; Yu et al., 2011)	?	⇑ (Abumaria et al., 2011)	⇑ (Reus et al., 2011)	8 h: ⇑ (Cirelli and Tononi, 2000; 3 h: Vyazovskiy et al., 2008); 72 h: ⇓ (Park et al., 2012)
Amygdala–BDNF	?	⇔ (Reus et al., 2011); ⇑ (Yu et al., 2011)	?	⇔ (Abumaria et al., 2011)	⇑ (Reus et al., 2011)	?
PFC–PSD-95	⇓ (Feyissa et al., 2009)	⇓ (Li et al., 2011a; Zhang et al., 2012)	⇓ (Jiang et al., 2007) (cell culture)	?	⇑ (Li et al., 2011a) (after CUS)	?
Amygdala–PSD-95	⇑ (Karolewicz et al., 2009)	⇑ (Zhang et al., 2012)	?	?	?	?
Cortical P-CREB	⇓ (Yamada et al., 2003; Dwivedi et al., 2003)	⇓ (Kuipers et al., 2003; Laifenfeld et al., 2005)	?	⇑ (Huang et al., 2010); ⇔ (Abumaria et al., 2011)	⇑ (Reus et al., 2011; Shu et al., 2012)	8 h or 48 h: ⇔ (Guzman-Marin et al., 2006)
PFC/ACC–glutamine/GS activity	⇓ (Choudary et al., 2005)	⇓ (Knox et al., 2010; Hemanth Kumar et al., 2012)	?	⇑ (Maurizi et al., 1986)	⇑ (Rowland et al., 2005)	Human MDE: ⇑ (Murck et al., 2009; 12–14 h: Bettendorff et al., 1996)
Evoked synaptic potentials (cortex)	?	⇓ (Quan et al., 2011; Yuen et al., 2012)	⇓ (Richards and Sercombe, 1970 [a])	⇑ (Abumaria et al., 2011)	⇑ (Li et al., 2011a) (after CUS)	3 h: ⇑ (Vyazovskiy et al., 2008)
Cortical synaptogenesis	?	⇓ (Li et al., 2011a)	?	⇑ (Abumaria et al., 2011)	⇑ (Li et al., 2011a) (after CUS)	⇑ ((Maret et al., 2011)

[a] Supraphysiological concentrations reduced EPSP amplitude.

culture and increased NR2b receptor and BDNF expression in the hippocampus, increases synaptic connectivity and synaptogenesis (Slutsky et al., 2010). This may point to a parallel mechanism of Mg^{2+} to amplify the BDNF induced cascade.

In summary, Mg^{2+} is involved in a number of mechanisms, which have central relevance for the pathophysiology of major depression and which are also affected by ketamine administration. The issue arises if some of the effects of ketamine are related to changes in intracellular Mg^{2+}.

5. Importance of regional differentiation

The regional differentiation of the biological effects of stress and antidepressant treatments is of critical importance (Tables 1 and 2): Opposite change of BDNF expression in the PFC vs. the amygdala occurs under stressful conditions (Yu and Chen, 2011). A similar regional specificity of the effects of ketamine and Mg^{2+} administration exists: Mg^{2+} administration leads to an increase in NR2b-receptor expression, as well as to CaMKII-phosphorylation, CREB-phosphorylation and BDNF expression, but not that of NR1, in the prefrontal cortex, but not in the amygdala of rats (Abumaria et al., 2011). Similarly, ketamine leads to an increase in CREB-expression and PKC phosphorylation in the prefrontal cortex, but not in the amygdala (Reus et al., 2011). BDNF is increased after both, ketamine and Mg^{2+} administration in the prefrontal cortex. Small differences exist: ketamine increases BNDF in the amygdala as well, whereas Mg^{2+} does not have an effect in the tested dose.

A similar regional specificity of the gene expression is observed in patients with depression (Tables 1 and 2). In post mortem studies of brains of patients with depression reduced levels of NR2a and NR2b subunits have been identified, accompanied by a reduction of PDS-95 (Beneyto and Meador-Woodruff, 2008; Feyissa et al., 2009). In the lateral amygdala partially opposite changes were observed, i.e. elevated levels of NR2a and PDS-95 (Karolewicz et al., 2009). Therefore the changes in the prefrontal cortex are the mirror image of what was observed with Mg^{2+} administration. The changes in the amygdala differ from those in the prefrontal cortex in both instances (Tables 1 and 2).

The relationship between major depression and chronic stress is well established and is reflected in changes of glutamatergic receptor expression (Tables 1 and 2). One finding should be specifically highlighted, which has relevance for the further argumentation: the prefrontal cortex in patients with depression shows an increased expression of GluR2 type subunit of the AMPA receptor, i.e. non CP-AMPA (Teyssier et al., 2011). Furthermore stress in an animal model increases GluR2-phosphorylation and therefore their recruitment to postsynaptic sites in the PFC, but has opposite effects in the amygdala (Caudal et al., 2010). This highlights the importance of regional specificity of AMPAR constitution in stress related situations (Tables 1 and 2).

6. Glutamatergic regulation of CNS Mg^{2+} content

It appears that the mechanism of action of ketamine and Mg^{2+} overlaps beyond the NMDA antagonistic effect of extracellular Mg^{2+}. The question is, how may this happen? An interesting observation is that ketamine actually leads to an increase of intracellular Mg^{2+} in peripheral tissue (Kim et al., 2006), which involves an increase in ERK1/2 and p38 MAP kinase. Further ketamine and MK-801 reverses the decrease of brain Mg^{2+} after brain trauma (McIntosh et al., 1990; Shapira et al., 1993). The described antidepressant mode of action of ketamine involves an increases of glutamate the prefrontal cortex and an activation of non-NMDA receptors. I.c.v. administered kainite and quinolinate leads to an increase in intracerebral Mg^{2+} content (against a concentration gradient from the plasma) (Rothe et al., 1993). At the cellular level glutamate leads to an increase in intracellular Mg^{2+} concentration in cultured rat forebrain neurons (Cheng and Reynolds, 2000), however in very artificial conditions (Na^{+} and Ca^{2+} free medium). This increase consists of two elements; firstly an increase of intracellular Mg^{2+}-release and secondly an influx of Mg^{2+} in a Na^{+} dependent way (Hoyt et al., 1995). Non-NMDA glutamate receptors (AMPA/kainite receptors) mediate this increase in intracellular Mg^{2+} (Hoyt et al., 1995). As we saw earlier the effect of ketamine at the postsynaptic levels is to increase the expression of CP-AMPAR. As CP-AMPAR are permeable to Mg^{2+}, this could be a potential mechanism to increase intracellular Mg^{2+} levels as a consequence of ketamine action. Therefore one mechanism of action of ketamine could be to increase intracerebral Mg^{2+} content via glutamatergic stimulation.

7. Synoptic overview of rapid antidepressant interventions

As an overview of the discussed mechanism a comparison of the effects of the different manipulations is provided in Tables 1 and 2. Additional information on the effects of chronic stress, which can be regarded as a model of depression, is included (Kuipers et al., 2003; Laifenfeld et al., 2005; van Donkelaar et al., 2009; Knox et al., 2010; Lee and Goto, 2011; Quan et al., 2011; Yu and Chen, 2011; Chiba et al., 2012; Hemanth Kumar et al., 2012; Yuen et al., 2012; Zhang et al., 2012) as subchronic stress related changes are reversed by ketamine in an animal model (Li et al., 2011a). Table 1 provides a synopsis of the described conditions at the level of glutamate receptors, whereas Table 2 provides on overview of downstream changes. From this overview it becomes plausible that the changes in chronic stress (in animal models) resemble those in patients with major depression. This includes glutamate receptor composition, but also intracellular signal mechanism, like CREB-phosphorylation (Dwivedi et al., 2003; Yamada et al., 2003). One noteworthy exception is the regulation of the GluR2 AMPA-receptor component. As his parameter depends on the status of previous sleep variability in human post mortem material is expected. There is some overlap between the changes seen in Mg^{2+} depletion and chronic stress, however, the Mg^{2+}-depletion data are mainly from cell culture experiments. One study observed electrophysiological effects of several mainly supraphysiological Mg^{2+}-concentrations on evoked potentials in brain slices (Richards and Sercombe, 1970). Gene expression in animal models with Mg^{2+} depletion has not been studied in the areas of interest for the receptors of interest. Mg^{2+} and ketamine administration generally has the opposite effect than those observed in chronic stress models. An important and potentially clinically relevant difference is that ketamine leads to an increase in amygdala-BDNF, which may be related to its potential to induce unpleasant phenomena, including psychotic symptoms.

The action of ketamine has similarities with that of therapeutic sleep deprivation (TSD) (Zarate et al., 2013). Sleep deprivation, has opposite effects on receptor expression than chronic stress, however this is only the case for short them (up to 24 h) sleep deprivation. Longer term sleep deprivation has partially opposite effects. Both TSD and ketamine are fast acting; they lead to similar polysomnographic changes, i.e. primarily an increase in slow wave sleep; both increase glutamine levels in the prefrontal cortex (Rowland et al., 2005; Murck et al., 2009; Duncan et al., 2012b; Taylor et al., 2012). Glutamine synthetase (GS) activity is increased in the prefrontal cortex in animal models after sleep deprivation (Bettendorff et al., 1996). Therefore a consistent effect of the antidepressant interventions described is the increase in GS activity, i.e. of the enzyme which catalyzes glutamine synthesis. Further GS has been related to suicide and depression (Choudary et al., 2005;

Kalkman, 2011). The increase in glutamine is correlated with the reduction in depressive mood after therapeutic sleep deprivation (Murck et al., 2009) and potentially ketamine administration (Salvadore et al., 2011). AMPAR activation (Fleischer-Lambropoulos et al., 1996) followed by intracellular Mg^{2+} increase could be responsible for this, as GS is a Mg^{2+} dependent enzyme (Greenberg and Lichtenstein, 1959; Maurizi et al., 1987). In summary, administration of ketamine mimics the effect of sleep deprivation in a molecular, electrophysiological and clinical level. For a wider discussion on the mechanism of sleep deprivation see (Hemmeter et al., 2010).

8. Predictors of ketamine response

It is important to note that not all patients with depression can be expected to respond to ketamine. Studies have been done in patients with therapy refractory depression, who may represent a specific subtype of all depressed patients. In this population the number of patients needed to treat (NNT) is 3–5, which is an extremely good effect, however not complete (Aan Het Rot et al., 2012). Predictors of response for ketamine are being studied: Reduced SWS at the beginning of the sleep period, as expressed as delta sleep ratio, is a positive predictor for the effect of ketamine (Duncan et al., 2012a). It is the opposite of the effect of Mg^{2+} (Held et al., 2002). Furthermore the increase in slow wave sleep is correlated to the clinical response in responders to ketamine (Duncan et al., 2012b). Interestingly, in mice frontal cortical Mg^{2+} concentration is correlated with the increase in slow wave sleep after short term sleep deprivation (Chollet et al., 2000). A similar correlation was found with red blood cell Mg^{2+} in the same study. In addition, lower dorsomedial PFC glutamine levels predict a preferable outcome of the ketamine effect on depressive symptoms (Salvadore et al., 2011). Given that GS is a Mg^{2+} dependent enzyme, both of these findings are in line with a potential role of low (intracellular) Mg^{2+} content as a predictor of ketamine response.

Direct evidence for a reduction of intracerebral Mg^{2+} in this particular group of patients with therapy refractory depression comes from a study utilizing Phospho-(P)-spectroscopy (Iosifescu et al., 2008). Mg^{2+} is primarily located intracellularly, therefore reduced overall brain Mg^{2+} level points toward a reduction of its intracellular content. Similarly, the Mg^{2+} content of red blood cells is reduced in patients with depression (Nechifor, 2008). For a recent overview see Eby et al. (2011). Furthermore, subjects with lower levels of Mg^{2+}, as measured in plasma, appear to have worse response to standard antidepressant treatment (Camardese et al., 2012). In conclusion, markers of low intracellular Mg^{2+} content may predict preferable response to ketamine. The most direct way to measure intracellular Mg^{2+} is by means of P-spectroscopy. Other direct measures of intracellular Mg^{2+} may utilize red blood cells (Nechifor, 2008), white blood cells (Ahokas et al., 2003) or epithelial cells (Silver, 2004). A potential functional marker may be the amount of SWS or delta power of the sleep EEG at the beginning of the night.

9. Pathophysiological connections

If some forms of depression may be mediated via low intracerebral Mg^{2+} and ketamine potentially reverses these changes, the question is, what let to these low Mg^{2+} level? Is there a connection to established mechanism of depression? In fact, Mg^{2+} is excreted by an increased activity of the sympathetic nervous system and the hypothalamus–pituitary adrenocortical axis (Murck, 2002; Murck et al., 2012). It has been suggested that the pathophysiological changes targeted by ketamine originate from increased cortisol or corticosterone mediated glucocorticoid receptor (GR) activation (Popoli et al., 2012). A recent observation, however, points to the potential involvement of mineralocorticoid receptors (MR). Corticosterone induced depression like behavior was counteracted by the administration of the MR antagonist spironolactone (Wu et al., 2012). Therefore the physiological MR agonistic corticosteroid, i.e. aldosterone, should be taken into account: hyperaldosteronism has been reported in major depression (Murck et al., 2003; Emanuele et al., 2005). Aldosterone induces depressive symptoms in both animal models (Hlavacova et al., 2011) and humans (Kunzel et al., 2012). On the basis of the timing of neuroendocrine changes a causal role of aldosterone in diverse animal models has recently been suggested (Franklin et al., 2012). Given that Mg^{2+} excretion is activated by aldosterone it makes therefore physiological sense that Mg^{2+} could be the link between stress related behavioral changes and overactivity of the NMDA ergic system.

10. Increase in intracellular Mg^{2+} as a mediator for antidepressant efficacy

I summarized the parallel effects between ketamine and Mg^{2+}. I also provided evidence that Mg^{2+} is involved in pathways, which are connected to the known pathophysiology of depression. Further I described mechanisms, which lead to an increase in intracerebral intracellular Mg^{2+}. The question is now, is there precedence for the action of standard antidepressants on Mg^{2+}? There are several observations, which point into that direction: Of high interest is that imipramine, the first reuptake inhibitor and therefore the model substance for most currently used antidepressants, leads to an increase in intracellular Mg^{2+} concentration in peripheral tissue and the brain (Poleszak et al., 2005; Lee et al., 2010). Just consider that this observation would have been done before the monoamine depletion hypothesis had been generated and the pharmacology of depression would probably look very different today. The mechanism of action for imipramine in erythrocytes is to inhibit a Na^{+}–Mg^{2+}-exchange transporter at physiological intracellular Mg^{2+} levels (Ebel et al., 2004) and therefore to increase intracellular Mg^{2+}, i.e. to reduce the Mg^{2+}-transport out of the cell. An increase in intracerebral Mg^{2+} levels has also been demonstrated with compounds, which are recommended as adjunct therapy for therapy refractory depression: Thyroid stimulation hormone (TSH) has been demonstrated to increase brain Mg^{2+} content in patients with depression (Iosifescu et al., 2008). We already mentioned imipramine, which is still regarded as more efficacious than SSRIs. Finally, lithium increases Mg^{2+} in neuroblastoma cells (Amari et al., 1999; Abukhdeir et al., 2003) and in animal models after several days of treatment (King et al., 1969), but only by trend after 8 weeks of treatment (Kielczykowska et al., 2007). Therefore there is some indication that the effect of lithium on brain Mg^{2+} is time dependent and potentially has an inverted U-shaped characteristic, as high doses lead actually to a decrease (Kielczykowska et al., 2003). This finding is in line with the effect of lithium on erythrocyte Mg^{2+}, which shows acutely an increase, but no change in the long term, pointing to the importance of adaptive changes (Dunner et al., 1975).

Compounds with properties to increase intracellular Mg^{2+} express antidepressive efficacy in preliminary animal experiments or preliminary clinical trials: These are for example mineralocorticoid receptor antagonists (Ahokas et al., 2003; Runyan et al., 2005); which protect against aldosterone induced Mg^{2+} depletion and by this mechanism may have an antidepressant effect (Ebel et al., 1971; Hlavacova et al., 2011; Murck et al., 2012). Antidiabetic drugs of the glitazone group lead to an increase of Mg^{2+} in peripheral mononuclear cells in vitro (Alon et al., 2006) and have antidepressant effects in animal models (Salehi-Sadaghiani et al., 2012) and in clinical trials (Rasgon et al., 2010; Sepanjnia et al.,

2012). Metformin leads to an increase in intracellular Mg^{2+} levels in vivo (Gorelik et al., 2007), however its effect on depression is not clear (Rubin et al., 2005). These Mg^{2+}-increasing compounds act via different mechanisms of action, therefore the outcome, i.e. the increase in intracellular Mg^{2+}, could be regarded as a common readout with relevance for the downstream effects, i.e. modification of glutamatergic mechanism as described above.

Following the suggestion that certain antidepressant mechanisms are related to an increase in Mg^{2+} it would be expected that there is a synergism between these compounds and Mg^{2+} administration. Indeed, it has been demonstrated that Mg^{2+} deficiency leads to depression like behavior in rats, which is reversed by imipramine (Singewald et al., 2004). Furthermore it has been demonstrated that the combination of sub-therapeutic doses of Mg^{2+} in combination with sub-therapeutic doses of imipramine leads to a significant antidepressive like effect in animal models (Poleszak et al., 2005, 2006). Further, the effect of the NMDA antagonist MK-801, which is similar to ketamine, can be amplified by concomitant administration of Mg^{2+} (Poleszak et al., 2007).

11. Conclusion

What are the conclusions of the described relationships? These are at least threefold:

1. Reduced concentration of Mg^{2+} in several tissues or functional markers of reduced tissue Mg^{2+} content appear to indicate worse response to antidepressant therapy with standard, the monoamine system targeting compounds. Direct intracellular measures in peripheral cells, P-spectroscopy of the brain or functional markers, like the pattern of slow wave sleep may therefore be predictive for the response of antidepressant compounds. Given the inverted U-shaped dose–response curve for the clinical ketamine response, functional markers like polysomnography, may help to define the individualized titration of compounds, which affect the glutamatergic system. 2. The property of compounds to increase intracellular Mg^{2+} levels could be a new biological target for antidepressants, primarily for the treatment of standard therapy refractory depression. This would open up a new strategy for candidate compound identification and selection. 3. A combination therapy may be considered, in particular with compounds, which increase intracellular Mg^{2+} and with Mg^{2+} itself. For example, the combination of NMDA-antagonism and Mg^{2+} has been demonstrated to show synergistic effects in animal models. Similarly, plasma Mg^{2+} levels appear to correlate to the outcome with standard antidepressant treatment (Camardese et al., 2012). Preliminary clinical observations point to the usefulness of concomitant administration of Mg^{2+} adjunct to antidepressive therapy (Eby and Eby, 2006; Barragan-Rodriguez et al., 2008), however, negative results after short term i.v. administration in patients with premenstrual syndrome also exist (Khine et al., 2006).

One point of caution: All the mechanism discussed focused on direct CNS effects. Of potential importance are immunological (Loix et al., 2011; Zeng et al., 2011) and neuroendocrine (Broughton Pipkin and Waldron, 1983; van Berckel et al., 1998) effects of ketamine, as well as of Mg^{2+} (Weglicki et al., 1992; Sartori et al., 2012; Weglicki, 2012). These peripheral mechanisms have been demonstrated to be involved in the pathophysiology of depression and should not be neglected.

As the final conclusion Mg^{2+} appears to be an important player in the pathophysiology of some forms of depression. Mg^{2+} related markers have relevance for treatment prediction with glutamatergic compounds and increased Mg^{2+} may moderate antidepressant mechanisms. Therefore, a discussion of glutamatergic mechanism of affective disorders should take the role of Mg^{2+} into account.

Conflict of interest

Harald Murck works currently for Covance Inc. Princeton, USA. He was formerly employed by Bristol-Myers Squibb, Novartis, Amarin and Lichtwer Pharma. There exists no conflict of interest. No funding for the preparation of this article was received.

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