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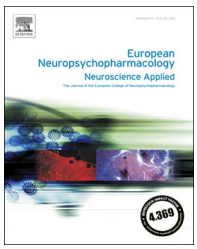

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Agmatine, a potential novel therapeutic strategy for depression

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Abstract
Major depressive disorder is the most common psychiatric disorder with lifetime prevalence of up to 20% worldwide. It is responsible for more years lost to disability than any other disorder. Despite the fact that current available antidepressant drugs are safe and effective, they are far from ideal. In addition to the need to administer the drugs for weeks or months to obtain clinical benefit, side effects are still a serious problem. Agmatine is an endogenous polyamine synthesized by the enzyme arginine decarboxylase. It modulates several receptors and is considered as a neuromodulator in the brain. In this review, studies demonstrating the antidepressant effects of agmatine are presented and discussed, as well as, the mechanisms of action related to these effects. Also, the potential beneficial effects of agmatine for the treatment of other neurological disorders are presented. In particular, we provide evidence to encourage future clinical studies investigating agmatine as a novel antidepressant drug.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ARE, antioxidant response element; BDNF, brain-derived-neurotrophic factor; BBB, blood-brain barrier; CRE, cAMP response elements; CREB, cyclic-AMP responsive-element binding protein; DA, dopamine; ERK, extracellular signal-regulated kinase; FST, forced swim test; GABA, gamma-Amino butyric acid; GCLc, glutamate cysteine ligase, catalytic subunit; GluA1, AMPA receptor subunit GluR1; GPCR, postsynaptic G protein coupled receptors; GSK-3β, glycogen synthase kinase-3β; 5-HT, 5-hydroxytryptamine; HO-1, heme oxygenase-1; HPA, hypothalamic pituitary adrenal; i.c.v., intracerebroventricular; i.p., intraperitoneal; i.v., intravenous; JNK, c-jun N-terminal kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, mammalian target of rapamycin; NE, norepinephrine; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2-derived-like 2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; p.o., *per os*; PSD95, postsynaptic density protein of 95 kDa; S6K, ribosomal protein S6 kinase; ROS, reactive oxygen species; s.c., subcutaneous; Syt I, synaptotagmin I; TH, tyrosine hydroxylase; TNF-α, tumor necrosis factor-α; TrkB, tropomyosin receptor kinase B; TST, tail suspension test

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1. Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder that significantly contributes to burden of disease worldwide, and is estimated to be the main contributor by 2030 (WHO, 2008). It affects approximately 17% of the population in the United States (Kessler et al., 2005), and it is a risk factor for several diseases, including diabetes, cancer, epilepsy, ischemia and cardiovascular diseases (Evans et al., 2005; Knol et al., 2006; Lichtman et al., 2014). This condition is characterized by depressed mood or anhedonia (decreased ability to experience pleasure), associated with symptoms that may include significant weight gain or loss (>5% change in a month), insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate and recurrent thoughts of death or suicide. According to The Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the criteria to establish a diagnosis of MDD is the presence of at least five of these symptoms, including the core symptoms depressed/irritable mood or anhedonia with a minimum duration of 2 weeks (American Psychiatric Association, 2000).

The pharmacological treatment of depression started over 60 years ago with the observation that iproniazid, an inhibitor of the enzyme monoamine oxidase developed for the treatment of tuberculosis, was able to improve mood in depressive patients (Nestler et al., 2002). In addition, reserpine, which depletes monoamines (serotonin, noradrenaline and dopamine) was reported to induce depression in humans who were taking this drug for the treatment of hypertension (Schildkraut, 1965). These findings were the main basis for the monoamine hypothesis of depression, which proposes that MDD is caused by a reduced availability of monoamines in the synaptic cleft (Schildkraut, 1965). Indeed, most of the current medications used for depression act by increasing the synaptic concentrations of monoamines by inhibiting their catabolism or reuptake (Berton and Nestler, 2006; Krishnan and Nestler, 2008). Although widely prescribed, these medications have significant limitations, including a long time lag for a therapeutic response (weeks or months), low response rates, and several side effects. The delayed onset of the therapeutic effects of antidepressants is explained by the neurotrophic hypothesis of depression. It postulates that the initial synaptic elevation of monoamines levels results in enhanced gene expression and neurochemical alterations related to the increase of neurotrophic factors, leading to hippocampal neurogenesis, synaptogenesis and synaptic plasticity (Castren and Rantamaki, 2010; Duman, 2014; Pittenger and Duman, 2008; Russo-Neustadt and Chen, 2005). This hypothesis was originally based on findings that exposure to stress decreases expression of brain-derived neurotrophic factor (BDNF), mainly in the hippocampus and prefrontal cortex and that chronic antidepressant treatment abolishes such effect in rodents (Duman, 2004; Duman et al., 1997). More recently, decreased BDNF levels have been also found in postmortem brain samples of depressed patients (Dunham et al., 2009; Guilloux et al., 2012; Thompson Ray et al., 2011; Tripp et al., 2012) and suicide victims (Banerjee et al., 2013; Dwivedi et al., 2003; Pandey et al., 2008). Additionally, several reports and meta-analyses demonstrate that depressed patients have reduced serum BDNF levels (Bocchio-Chiavetto et al., 2010; Karege et al., 2005; Molendijk et al., 2014; Sen et al., 2008; Shimizu et al., 2003) and those levels are restored after antidepressant treatment (Aydemir et al., 2005; Martinotti et al., 2016; Sen et al., 2008; Shimizu et al., 2003).

The association between stressful life events and depressive episodes represents the most important finding in terms of pathophysiology of MDD, and has been widely described over the last 40 years (Carroll et al., 1976; Frodl and O'Keane, 2013; Maric and Adzic, 2013; Pariante and Lightman, 2008). Abnormalities in the hypothalamo-pituitary-adrenal (HPA) axis, associated with increased cortisol concentrations and dexamethasone non-suppression in depressed patients, were also important findings which have supported the role of stress in MDD (Carroll et al., 1976; Frodl and O'Keane, 2013; Maric and Adzic, 2013; Pariante and Lightman, 2008). The excess of glucocorticoids in the brain causes an oxidative imbalance through the activation of N-methyl-D-aspartate (NMDA) receptors, which in turn, causes hippocampal impairments, particularly volumetric reduction, and decreased dendrite arborization and spine density (Musazzi et al., 2011; Sanacora et al., 2012). Additionally, NMDA receptor antagonists are able to abolish the effects of stress, supporting the evidence that activation of NMDA receptors triggers neuronal atrophy and death (Calabrese et al., 2012; Sanacora et al., 2008). Of note, chronic administration of ketamine, a non-competitive NMDA receptor antagonist, increases serum levels of BDNF in humans (Ricci et al., 2011), and produces antidepressant effects after repeated treatments (3 × per week for two weeks) in patients with treatment-resistant depression (aan het Rot et al., 2010). In this context, a growing body of preclinical research implicates NMDA receptors in the pathophysiology of MDD (Skolnick, 1999; Skolnick et al., 1996), reinforcing the glutamatergic hypothesis of depression, that proposes that glutamate-mediated excitotoxicity is associated with depressive symptoms. Interestingly, NMDA receptor antagonists produce antidepressant-like effects in animal models of depression (Skolnick, 1999; Trullas and Skolnick, 1990). In addition, Nowak et al. (1995) found that dysfunctions of the NMDA receptor complex appear to accompany human suicide. Abnormalities in the glutamate recognition site and the allosteric regulation of this site by glycine were reported in suicide individuals, and more specifically, both the specific binding of the glutamate site antagonist [3H]CGP-39653, and the high-affinity, glycine-displaceable [3H]CGP-39653 binding sites were reduced in the frontal cortex of suicide victims, compared to controls (Nowak et al., 1995).

The mechanisms associated with neuronal death induced by glucocorticoids are related to oxidative damage. Considering that the central nervous system (CNS) is especially vulnerable to excessive generation of free radicals (Lee et al., 2013), mainly due to its high rate of oxygen consumption, the increased release of glucocorticoids induces an oxidative damage to neurons, alterations that have been postulated to contribute to the development of MDD (Zhang and Yao, 2013). Several reports suggest that depressive patients present lower antioxidant defenses against lipid peroxidation (Bilici et al., 2001; Ozcan et al., 2004; Tsuboi et al., 2004). In addition, clinical and preclinical

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