European Neuropsychopharmacology (∎∎∎∎) ∎, ∎∎∎–∎∎∎

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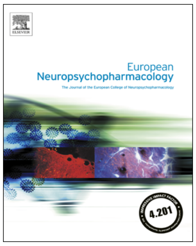

# Behavioral and neurochemical characterization of TrkB-dependent mechanisms of agomelatine in glucocorticoid receptor-impaired mice

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Received 28 May 2015; received in revised form 30 September 2015; accepted 8 November 2015

**KEYWORDS**
Antidepressants;
Glucocorticoid;
Hippocampus;
Neuroplasticity;
TrkB inhibitor

## Abstract

Growing evidence indicates that impairment of the stress response, in particular the negative feedback regulation mechanism exerted by the hypothalamo-pituitary-adrenal (HPA) axis, might be responsible for the hippocampal atrophy observed in depressed patients. Antidepressants, possibly through the activation of BDNF signaling, may enhance neuroplasticity and restore normal hippocampal functions. In this context, glucocorticoid receptor-impaired (GR-i) mice-a transgenic mouse model of reduced GR-induced negative feedback regulation of the HPA axis-were used to investigate the role of BDNF/TrkB signaling in the behavioral and neurochemical effects of the new generation antidepressant drug, agomelatine. GR-i mice exhibited marked alterations in depressive-like and anxiety-like behaviors, together with a decreased cell proliferation and altered levels of neuroplastic and epigenetic markers in the hippocampus. GR-i mice and their wild-type littermates were treated for 21 days with vehicle, agomelatine (50 mg/kg/day; i.p) or the TrkB inhibitor Ana-12 (0.5 mg/kg/day, i.p) alone, or in

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http://dx.doi.org/10.1016/j.euroneuro.2015.11.003

combination with agomelatine. Chronic treatment with agomelatine resulted in antidepressant-like effects in GR-i mice and reversed the deficit in hippocampal cell proliferation and some of the alterations of mRNA plasticity markers in GR-i mice. Ana-12 blocked the effect of agomelatine on motor activity as well as its ability to restore a normal hippocampal cell proliferation and expression of neurotrophic factors. Altogether, our findings indicate that agomelatine requires TrkB signaling to reverse some of the molecular and behavioral alterations caused by HPA axis impairment.

## 1. Introduction

The hypothalamo-pituitary-adrenal (HPA) axis is a major component of the neuroendocrine system regulating stress responses. HPA axis dysfunction is associated with an alteration of the negative feedback exerted by brain glucocorticoid receptors, and has been shown to play a role in the pathophysiology of mood disorders (Pariante and Lightman, 2008; Pariante and Miller, 2001; Vreeburg et al., 2009). A key mediator of the stress-induced synaptic dysfunction and neuronal atrophy often observed in the prefrontal cortex and hippocampus of mood disorder patients is the brain-derived neurotrophic factor (BDNF) (Berton and Nestler, 2006; Duman and Aghajanian, 2012). Decreased levels of BDNF and its tropomyosin-related kinase receptor (TrkB) were both shown in the hippocampus of suicide and depressed patients (Autry and Monteggia, 2012; Dwivedi et al., 2003), and the functional val66met polymorphism in the gene encoding BDNF has been associated with a wide variety of psychiatric phenotypes, including anxiety and depression (Hong et al., 2011). Furthermore, animal studies showed that prolonged stress exposure could decrease BDNF signaling and impair hippocampal neurogenesis (Mirescu and Gould, 2006; Taliaz et al., 2011; Tsankova et al., 2006). Conversely, various classes of antidepressants were shown to activate BDNF-mediated signaling and reverse neuronal atrophy and cell loss induced by chronic stress in rodents (Castren and Rantamaki, 2010; Schmidt and Duman, 2007), while hippocampal BDNF infusion exerted antidepressant-like effect (Shirayama et al., 2002; Ye et al., 2011). Although BDNF heterozygous knockout mice (BDNF±), displaying a reduction by half of BDNF levels, failed to show any depressive-like behaviors (Korte et al., 1995; MacQueen et al., 2001), knockdown of BDNF in specific brain sites was reported to impair neurogenesis and to precipitate depressive-like behaviors (Taliaz et al., 2010). Accordingly, an increased vulnerability to stress, as compared to wild-type littermates, was observed in diverse genetic mouse models lacking BDNF (Yu et al., 2012). The latter also display an inability to respond to antidepressant treatments (Adachi et al., 2008; Yu et al., 2012), indicating a critical role of BDNF in the behavioral and the neurochemical mediation of antidepressant responses.

Additionally, increasing evidence also suggests that the elevation of BDNF levels observed under antidepressant treatment might impact epigenetic mechanisms (Boulle et al., 2012). Epigenetic regulations in the central nervous system are important mechanisms for maintaining neuronal plasticity (Maze et al., 2013; Sultan and Day, 2011). In particular, stress and environmental adversity have been shown to impact chromatin and histone regulation to generate an epigenetic reprogramming, which could possibly increase the susceptibility for mood disorders (Boulle et al., 2012; Tsankova et al., 2007). In addition, various classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been shown to target the epigenetic machinery, which might be necessary for mediating their therapeutic effects (Vialou et al., 2013). Among atypical antidepressant treatments, agomelatine has emerged as an innovative drug, mediating its effects via the activation of melatonin receptor 1 (MT1) and 2 (MT2), and the blockade of the serotonin 2C (5-HT$_{2C}$) receptor (de Bodinat et al., 2010). Agomelatine was shown to normalize the altered BDNF regulation and impaired neurogenesis occurring in rodent models of depression (Paizanis et al., 2010). Hence, in the present study, we wanted to determine whether TrkB signaling was required for the neurobiological and the behavioral actions of agomelatine. We used Ana-12, a recently developed TrkB inhibitor that has been described as a potent and selective molecule that could lead to a decreased TrkB activity in mouse brain after peripheral administration (Cazorla et al., 2011). We thus performed dual administration of agomelatine, together with Ana-12, in a transgenic mouse model of HPA dysregulation in affective disorders, namely the glucocorticoid-receptor impaired (GR-i) mice. This model has been generated to mimic impaired HPA axis regulation commonly observed in depressed patients (Pariante and Miller, 2001). Accordingly, GR-i mice were characterized by a resistance to suppression of corticosterone secretion by dexamethasone (Barden et al., 1997; Pepin et al., 1992) and by several other neuroendocrine disturbances (Linthorst et al., 2000). In addition, we previously showed that GR-i mice display a deficit in the HPA axis feedback under stressful conditions as well as depressive-like behaviors and deficit in hippocampal neurogenesis that could be reverted by chronic antidepressant treatments (Froger et al., 2004; Paizanis et al., 2010). In the present study, we assessed the ability of agomelatine to rescue both the behavioral and the neurochemical alterations produced by a reduction in GR feedback inhibition, and explore the involvement of putative TrkB mechanisms in the action of this new generation antidepressant drug.

## 2. Experimental procedures

### 2.1. Animals

Transgenic mice (strain B6C3F1; line 1.3) bearing a transgene for the glucocorticoid receptor (GR-i) and paired wild-type (WT) mice were used in the experiments. Mice issued from the same gestation

Please cite this article as: Boulle, F., et al., Behavioral and neurochemical characterization of.... European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.11.003