Progress in Neuro-Psychopharmacology & Biological Psychiatry 58 (2015) 38–46

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Effect of the multimodal acting antidepressant vortioxetine on rat hippocampal plasticity and recognition memory

Cécile Bétry [a,1], Adeline Etiévant [a,1], Alan Pehrson [b], Connie Sánchez [b], Nasser Haddjeri [a,*]

[a] INSERM U846, Stem Cell and Brain Research Institute, Université Lyon 1, Lyon, F-69008, France
[b] Neuropharmacological Research, Lundbeck Research USA, 215 College Road, Paramus, NJ 07652, USA

ARTICLE INFO

Article history:
Received 11 September 2014
Received in revised form 1 December 2014
Accepted 8 December 2014
Available online 16 December 2014

Keywords:
Antidepressant
LTP
Memory
Neurogenesis
Novel object recognition
Vortioxetine

ABSTRACT

Depression is frequently associated with cognitive disturbances. Vortioxetine is a multimodal acting antidepressant that functions as a 5-HT_3 and 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter. Given its pharmacological profile, the present study was undertaken to determine whether vortioxetine could modulate several preclinical parameters known to be involved in cognitive processing.

In the dorsal hippocampus of anaesthetized rats, the high-frequency stimulation of the Schaffer collaterals provoked a stable long-term potentiation (LTP) of ~25%. Interestingly, vortioxetine (10 mg/kg, i.p.) counteracted the suppressant effect of elevated platform stress on hippocampal LTP induction. In the novel object recognition test, vortioxetine (10 mg/kg, i.p.) increased the time spent exploring the novel object during the retention test and this pro-cognitive effect was prevented by the partial 5-HT_3 receptor agonist SR57227 (1 mg/kg, i.p.). Finally, compared to fluoxetine, sustained administration of vortioxetine (5 mg/kg/day, s.c.) induced a rapid increase of cell proliferation in the hippocampal dentate gyrus.

In summary, vortioxetine prevented the effect of stress on hippocampal LTP, increased rapidly hippocampal cell proliferation and enhanced short-term episodic memory, via, at least in part, its 5-HT_3 receptor antagonism. Taken together, these preclinical data suggest that the antidepressant vortioxetine may have a beneficial effect on human cognitive processes.

1. Introduction

Major depressive disorder (MDD) is one of the most frequent psychiatric disorders. In the United States, the lifetime prevalence is more than 12% in men and 20% in women (Belmaker and Agam, 2008). MDD is an important public health problem since it results in severe disability, poor quality of life and possibly suicide and is a major economic burden for society. Despite a range of pharmacotherapeutic options, treatment outcome remains unsatisfactory. Indeed, patients often need to try several different agents to obtain an effect and only about two thirds of patients experience a therapeutic response (Duman, 2004). In addition to a therapeutic delay of up to several weeks, a significant number of patients experience significant residual symptoms that are inadequately treated with current antidepressants (Conradi et al., 2011).

Both preclinical (Henningsen et al., 2009; Kalueff and Murphy, 2007) and clinical (Baune et al., 2010; Hammar and Ardal, 2009) data suggest that affective disorders are often associated with dysfunction of different cognitive domains such as executive function, working memory and attention. Moreover, it has been shown that repeated episodes of major depression impair memory (Gorwood et al., 2008) and a correlation between depression severity and the magnitude of cognitive deficits has been reported in a population of young adult depressed patients (Basso and Bornstein, 1999; Egeland et al., 2003; Merriam et al., 1999). Also, antidepressant treatments often leave patients with residual cognitive symptoms (Conradi et al., 2011). Thus, new antidepressants that alleviate cognitive dysfunction are clearly needed (Marazziti et al., 2010).

Regulation of cognitive processes involves complex interaction between many neurotransmitters among others serotonin. Preclinical studies have increased our understanding of the role of 5-HT and its receptors in regulation of cognitive functions (Buhot, 1997; Buhot et al., 2000; King et al., 2008; Meneses, 2003; Meneses and Hong, 1997;

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; vortioxetine, 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004); LTP, long-term potentiation; SR57227, 1-(6-chloro-2-pyridinyl)-4-piperidinamine; MDD, major depressive disorder; SERT, 5-HT transporter; fEPSP, field excitatory post-synaptic potential; HFS, high-frequency stimulation; AUC, area under the curve; SGZ, subgranular zone; DG, dentate gyrus; BrDU, 5-bromo-2′-deoxyuridine; RI, recognition index; ANOVA, analysis of variance.

* Corresponding author at: INSERM U846, Stem Cell and Brain Research Institute, Université Lyon 1, 8, Avenue Rockefeller 69373 Lyon Cedex 08 France. Tel.: +33 4 26 68 82 15; fax: +33 4 78 77 72 09.
E-mail address: nasser.haddjeri@inserm.fr (N. Haddjeri).

[1] CB and AE contributed equally to this work.

http://dx.doi.org/10.1016/j.pnpbp.2014.12.002
0278-5846/

Roman and Marchetti, 1998). The 5-HT_3 receptor may be of particular interest as 5-HT_3 receptor antagonists have been found to improve learning and memory as well as to antagonize the effects of anticholinergic- or age-induced memory loss in rodents and primates (Barnes et al., 1990; Fontana et al., 1995; Hodges et al., 1996; Pitsikas and Borsini, 1996). Nevertheless, only few 5-HT_3 receptor antagonists have been studied in the clinic for effects on cognitive dysfunction in psychiatric diseases (Akhondzadeh et al., 2009).

Vortioxetine is a recently approved antidepressant with a multimodal mode of action (Adell, 2010; Alvarez et al., 2012) for the treatment of MDD. *In vitro* studies, using cell lines expressing cloned human receptors and the 5-HT transporter, show that vortioxetine is a 5-HT_{3A} (Ki = 3.7 nM), 5-HT_7 (Ki = 19 nM) and 5-HT_{1D} (Ki = 54 nM) receptor antagonist, 5-HT_{1B} receptor partial agonist (Ki = 33 nM; IA 55%), 5-HT_{1A} receptor agonist (Ki = 15 nM) and inhibitor of the 5-HT transporter (SERT; Ki = 1.6 nM) (Bang-Andersen et al., 2011; Westrich et al., 2012). Interestingly, in both preclinical and clinical studies of MDD, vortioxetine has shown positive effects against cognitive dysfunction (Adell, 2010; Alvarez et al., 2012; du Jardin et al., 2014; Katona et al., 2012; Mørk et al., 2012, 2013).

The aim of the present study was to investigate vortioxetine's effect on cognitive function in further detail by studying its effects on measures of synaptic plasticity, neurogenesis and episodic memory by means of *in vivo* long-term potentiation (LTP) in the CA1 region of the hippocampus, hippocampal cell proliferation in the dentate gyrus and time delayed object recognition test in rats. Furthermore, a putative role of vortioxetine's 5-HT_3 receptor antagonism was explored with respect to effects on hippocampal cell proliferation and episodic memory.

2. Methods

2.1. Animals

The experiments were carried out in male Sprague–Dawley OFA rats (Charles River, FRANCE) weighing 260 to 320 g at the day of the experiment. The animals were housed four per cage under standard laboratory conditions; 12:12 h light-dark cycle with free access to food and water. Experiments were performed in compliance with the European Communities Council (86/609 ECC) for the care and use of laboratory animals and with the approval of the Regional Animal Care Committees (University Lyon 1). Separate cohorts of rats were used for the different experiments.

2.2. Time course and experimental design

As illustrated in Fig. 1, the first experiment examined the effects of acute administrations of vortioxetine on synaptic plasticity in the hippocampus of naïve and stressed rats. The second experiment examined the effects of sustained administrations of vortioxetine given alone or/and combination with SR57227 and of fluoxetine on hippocampal mitogenesis. The third experiment examined the effects of acute administrations of vortioxetine alone or/and combination with SR57227 and of donepezil on rat working memory as assessed in the novel object recognition test. The fourth experiment examined the effects of sustained administrations (1 day) of vortioxetine given alone or/and combination with SR57227 on ex vivo SERT occupancy. Finally, the last experiment examined the effects of acute administrations of vortioxetine in naïve and stressed rats on plasma corticosterone levels.

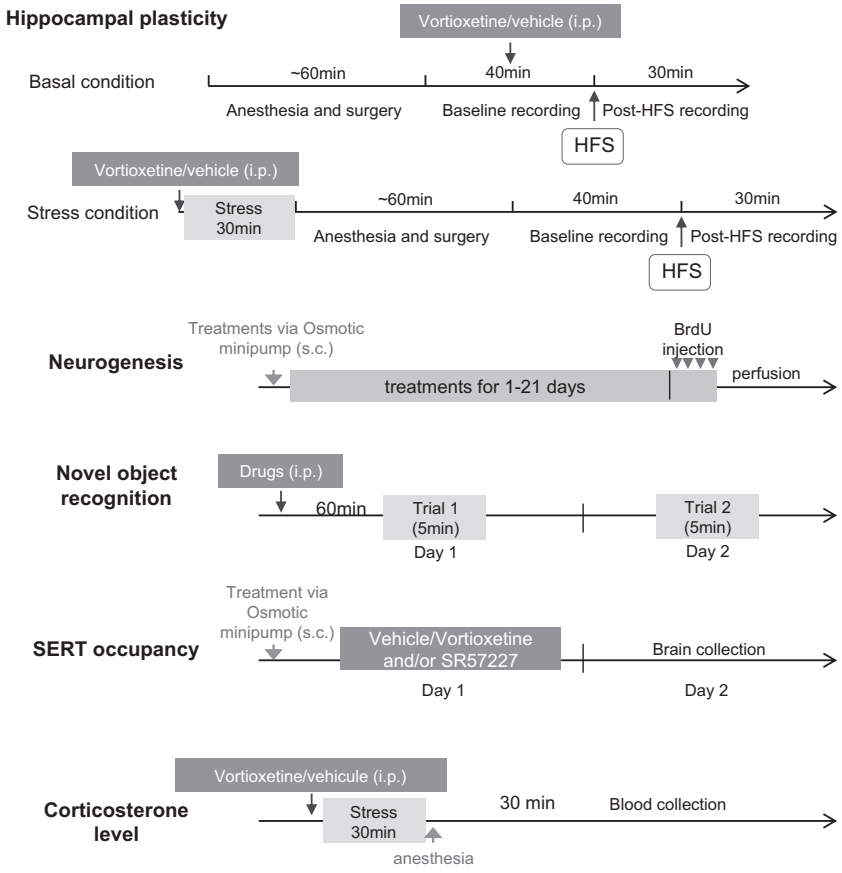

Fig. 1. Experimental design. To determine the effects of vortioxetine on synaptic plasticity in the hippocampus, vortioxetine or vehicle was injected 20 min before HFS. In stressed rats, vortioxetine was administrated (i.p.) just before the stress paradigm. To evaluate the effects of vortioxetine on hipocampal mitogenesis, vortioxetine was administrated through implanted minipump for 1, 3, or 14 days. Fluoxetine was used as positive control for 7, 14, or 21 days. BrdU was injected (4 injections) the last day of the treatment and rats were perfused 24 h after the last BrdU injection. To determine the effects of vortioxetine on rat working memory, vortioxetine and/or SR57227 or donepezil were injected i.p. and the rats were assessed in the novel object recognition test 24 h later. To determine the effects of vortioxetine on SERT occupancy, vortioxetine was administered alone or in combination with SR57227 for 1 day. To determine the effects of vortioxetine on plasma corticosterone levels, vortioxetine was injected acutely in naïve and stressed rats.