European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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Altered neuronal activity and differential sensitivity to acute antidepressants of locus coeruleus and dorsal raphe nucleus in Wistar Kyoto rats: A comparative study with Sprague Dawley and Wistar rats

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Received 7 November 2013; received in revised form 24 January 2014; accepted 12 February 2014

KEYWORDS
Locus coeruleus;
Dorsal raphe;
Wistar Kyoto;
SERT

Abstract
The Wistar Kyoto rat (WKY) has been proposed as an animal model of depression. The noradrenergic nucleus, locus coeruleus (LC) and the serotonergic nucleus, dorsal raphe (DRN) have been widely implicated in the ethiopathology of this disease. Thus, the goal of the present study was to investigate *in vivo* the electrophysiological properties of LC and DRN neurons from WKY rats, using single-unit extracellular techniques. Wistar (Wis) and Sprague Dawley (SD) rats were used as control strains. In the LC from WKY rats the basal firing rate was higher than that obtained in the Wis and SD strain, and burst firing activity also was greater compared to that in Wis strain but not in SD. The sensitivity of LC neurons to the inhibitory effect of the α_2-adrenoceptor agonist, clonidine and the antidepressant reboxetine was lower in WKY rats compared to Wis, but not SD. Regarding DRN neurons, in WKY rats burst activity was lower than that obtained in Wis and SD rats, although no differences were observed in other firing parameters. Interestingly, while the sensitivity of DRN neurons to the inhibitory effect of the 5-HT_{1A} receptor agonist, 8-OH-DPAT was lower in the WKY strain, the antidepressant fluoxetine had a greater inhibitory potency in this rat strain compared to that recorded in the Wis group. Overall, these results point out important electrophysiological differences regarding

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http://dx.doi.org/10.1016/j.euroneuro.2014.02.007

noradrenergic and serotonergic systems between Wis and WKY rats, supporting the utility of the WKY rat as an important tool in the research of cellular basis of depression

1. Introduction

Major depression is a mood disorder that represents a severe and long lasting clinical problem with a big impact on society, both in social and economic aspects. The prevalence rate today is between 15% and 20% (Kessler et al., 2005) and progressively increases instead of decreasing. Despite the great improvement that has been done in terms of tolerability of antidepressant drugs, there is still an elevated number of patients that does not respond to the treatment or that responds but exhibit some residual depressive symptoms (Zajecka et al., 2013). Current first line pharmacological agents for the treatment of depression share monoaminergic neurotransmission as a single common target. Thus nowadays, the most commonly used antidepressants are the selective serotonin reuptake inhibitors (SSRI) followed by the noradrenaline reuptake inhibitors (NRI) that modulate serotonergic and/or noradrenergic neurotransmission. Although it is well accepted that the serotonin and noradrenaline function are altered from the first antidepressant administration, the therapeutic effect is delayed several weeks. The reason of this phenomenon and the total or partial resistance to the treatment showed by a high percentage of patients are still unknown matters in the pharmacological therapy.

The brainstem monoaminergic nuclei, the noradrenergic *locus coeruleus* (LC) and serotonergic *dorsal raphe nucleus* (DRN) are characterized by their extensive efferent projections throughout the neuroaxis to all brain areas related to depression. Both nuclei are under the control of somatodendritic 5-HT_{1A} or α_2-adrenoceptors (Cedarbaum and Aghajanian, 1976; Williams et al., 1985). Activation of these receptors, directly by agonists or indirectly by increasing neurotransmitter levels at the synapses cleft using SSRI and NRI, inhibits neuronal activity of the DRN and LC (Szabo and Blier, 2001a, 2001b; Miguelez et al., 2009, 2011). Thus, changes in the spontaneous neuronal activity and/or the sensitivity of 5-HT_{1A} and α_2-adrenoceptors may be of relevance not only in the etiology of depression but also in the response to antidepressant drugs.

Animal models are pivotal in the effort to understand the neurobiology of major depressive disorder and to develop new treatments (Berton et al., 2012). In this regard, Wistar Kyoto (WKY) rat strain has been proposed as an animal model of depression since several studies have shown that WKY rats exhibit inherent depressive-like behavior in different behavioral tests (Lahmame and Armario, 1996; Pare and Tejani-Butt, 1996; Lahmame et al., 1997; López-Rubalcava and Lucki, 2000; Tejani-Butt et al., 2003; Will et al., 2003). In addition, exaggerated endocrine response to stressors has been described in this rat strain (Rittenhouse et al., 2002; De la Garza and Mahoney, 2004), as well as reduced efficacy of specific antidepressant drugs alleviating symptoms of depression (Lahmame and Armario, 1996; Lahmame et al., 1997; Lopez-Rubalcava and Lucki, 2000; Tejani-Butt et al., 2003; Will et al., 2003). WKY rats show reduced basal levels of NE and 5-HT in LC and DRN, as well as significant modifications on the distribution and density of dopamine transporter sites in the mesolimbic areas, that may lead to altered dopaminergic transmission (De la Garza et al., 2004; Heal et al., 2008; Scholl et al., 2010; Yamada et al., 2013). Indeed, in several brain areas of this rat strain dopamine release is greater than that observed in spontaneous hypertensive rats, an inbred genetic strain derived from the WKY (see Heal et al., 2008). Moreover, several differences have been found in the LC and DRN of WKY rats in comparison to other experimental strains. Thus, gene expression for enzymes involved in noradrenaline turnover, amino-acid receptors, and certain G-protein-couple receptors, such as k-opioid receptor, are increased in the LC of WKY rats (Pearson et al., 2006). Interestingly, k-opioid receptor antagonists produce antidepressant-like effects selectively in this rat strain (Carr et al., 2010). In the DRN of WKY rats decreased intrinsic excitability in 5-HT neurons has also been reported as compared to SD rats (Lemos et al., 2011).

The main goal of this study was to characterize *in vivo* basal electrophysiological properties of LC and DRN neurons in WKY rats and their response to acute administration of serotonergic and noradrenergic agonists and antidepressants. For that purpose, we used as control strains the Wistar (Wis) rat, which is the original strain from which WKY rats were derived, and the Sprague Dawley (SD) rat, a type of rat widely used in brain research studies.

2. Experimental procedures

2.1. Animals

Male SD, Wis and WKY rats weighting 250–300 g at the beginning of experiments, were used for the electrophysiological recordings (SD: $n=55$; Wis: $n=29$ and WKY: $n=50$) and immunohistochemical experiments (SD: $n=7$; Wis: $n=6$ and WKY: $n=9$). Every effort was made to minimize the animals' suffering and to use the minimum number of animals possible. Experimental protocols were reviewed and approved by the Local Committee for Animal Experimentation at the University of the Basque Country (CEBA/17-P07-02/2009/ UGEDO URRUELA), and performed in compliance with the European Community Council Directive on 'The Protection of Animals Used for Experimental and Other Scientific Purposes' 86/609/EEC) and with the Spanish Law (RD 1201/2005) for the care and use of laboratory animals.

2.2. Drugs

The drugs used in this study were chloral hydrate (Sigma-Aldrich, USA), clonidine hydrochloride (Sigma-Aldrich, USA), reboxetine mesylate (Sigma-Aldrich, USA), RX-821002 hydrochloride (Sigma-Aldrich, USA), 8-OH-DPAT (Sigma-Aldrich, USA) fluoxetine hydrochloride (Tocris

Please cite this article as: Bruzos-Cidón, C., et al., Altered neuronal activity and differential sensitivity to acute antidepressants of locus coeruleus and dorsal raphe.... European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.02.007