Psychoneuroendocrinology (2015) 51, 11—23

Available online at www.sciencedirect.com

ScienceDirect

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

Restoration of peripheral V2 receptor vasopressin signaling fails to correct behavioral changes in Brattleboro rats

Diána Balázsfi[a,b], Ottó Pintér[a], Barbara Klausz[a], Krisztina B. Kovács[a], Anna Fodor[a,b], Bibiána Török[a], Mario Engelmann[c,d], Dóra Zelena[a,*]

[a] *Hungarian Academy of Sciences, Institute of Experimental Medicine, 1083 Budapest Szigony 43, Budapest, Hungary*
[b] *János Szentágothai School of Neurosciences, Semmelweis University, Budapest, Hungary*
[c] *Institut für Biochemie und Zellbiologie (M.E.), Otto-von-Guericke-Universität, Magdeburg, Germany*
[d] *Center of Behavioral Brain Science, Magdeburg, Germany*

Received 11 July 2014; received in revised form 10 September 2014; accepted 10 September 2014

KEYWORDS
DDAVP;
Anxiety;
Depression;
Recognition memory;
Amygdala;
Lateral septum

Abstract Beside its hormonal function in salt and water homeostasis, vasopressin released into distinct brain areas plays a crucial role in stress-related behavior resulting in the enhancement of an anxious/depressive-like state.

We aimed to investigate whether correction of the peripheral symptoms of congenital absence of AVP also corrects the behavioral alterations in AVP-deficient Brattleboro rats. Wild type (WT) and vasopressin-deficient (KO) male Brattleboro rats were tested.

Half of the KO animals were treated by desmopressin (V2-receptor agonist) via osmotic minipump (subcutaneous) to eliminate the peripheral symptoms of vasopressin-deficiency. Anxiety was studied by elevated plus maze (EPM), defensive withdrawal (DW) and marble burying (MB) tests, while depressive-like changes were monitored in forced swimming (FS) and anhedonia by sucrose preference test. Cell activity was examined in septum and amygdala by c-Fos immunohistochemistry after 10 min FS.

KO rats spent more time in the open arm of the EPM, spent less time at the periphery of DW and showed less burying behavior in MB suggesting a reduced anxiety state. KO animals showed less floating behavior during FS revealing a less depressive phenotype. Desmopressin treatment compensated the peripheral effects of vasopressin-deficiency without a significant influence on

* Corresponding author. Tel.: +36 1 2109400/290; fax: +36 1 2109951.
E-mail address: zelena.dora@koki.mta.hu (D. Zelena).

http://dx.doi.org/10.1016/j.psyneuen.2014.09.011

the behavior. The FS-induced c-Fos immunoreactivity in the medial amygdala was different in WT and KO rats, with almost identical levels in KO and desmopressin treated animals. There were no differences in central and basolateral amygdala as well as in lateral septum.
Our data confirmed the role of vasopressin in the development of affective disorders through central mechanisms. The involvement of the medial amygdala in the behavioral alterations of vasopressin deficient animals deserves further attention.

1. Introduction

Stress is defined as an adaptive reaction to disturbed homeostasis due to internal or external hazards (Holsboer and Ising, 2010). Prolonged and repeated exposures to unavoidable, aversive stimuli may lead to a dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, the major endocrine component of the stress response. A maladaptive stress response is thought to be causally linked to a variety of human disorders including mood disorders (Chrousos and Gold, 1992; Chrousos, 1998; Holsboer, 2000; McEwen, 2000; Engelmann et al., 2004). The physiological foundation of the HPA axis is constituted by parvocellular neurons of the hypothalamic paraventricular nucleus (PVN). These neurons secrete the corticotropin-releasing hormone (CRH) into the portal blood vessels to trigger adrenocorticotropin (ACTH) release from the anterior pituitary (Antoni, 1993). ACTH reaches the adrenal gland through the systemic circulation to stimulate the synthesis and release of glucocorticoids. In addition to CRH, parvocellular cells can also synthesize and release arginine–vasopressin (AVP). AVP is also capable of triggering ACTH release after interaction with V1b receptors in the anterior pituitary, potentiating the effect of CRH (Antoni, 1993; Holmes et al., 2003).

Originally, the endocrine function of AVP was primarily linked to the salt and water homeostasis in mammals. The hypothalamic–neurohypophyseal system (HNS) (Cunningham and Sawchenko, 1991; Johnson et al., 1993; Kato et al., 1995) is constituted by magnocellular neurons located in the PVN and hypothalamic supraoptic nucleus (SON) sending their axons to the posterior pituitary, where AVP is released into the general circulation to control antidiuresis and vasoconstriction/glycogen metabolism. There is growing evidence that the HNS provides as a second neuronal–humoral system that is activated during stress (Hatton, 1990; Engelmann et al., 1998). Hyperactivity of the HNS may lead to a sustained somato-dendritic release of AVP into the extracellular fluid of both the PVN and SON (Engelmann et al., 1998). Under prolonged and repeated stressor exposure, the locally high neuropeptide concentrations may partially 'leak out of the nuclei' and reach remote limbic brain areas in neurophysiologically relevant concentrations (e.g. septum from the PVN or amygdala from the SON) (Engelmann et al., 2004; Landgraf, 2006). To differentiate between the roles of AVP signaling originating in the PVN vs. SON, repeated forced swimming (FS) was chosen as stressful stimulus. Previous studies showed that in response to repeated FS, AVP is increasingly released into the extracellular fluid of PVN, but not SON (Engelmann et al., 1998). In more remote brain areas, AVP acts as neuromodulator and neurotransmitter via local V1 receptors (Johnson et al., 1993; Lolait et al., 1995; Vaccari et al., 1998; Hernando et al., 2001; Stemmelin et al., 2005). Different lines of investigations confirmed that AVP acting in these brain areas regulates behavior including anxiety, social learning and memory processes (Stemmelin et al., 2005; Engelmann, 2008).

The literature is rich in articles describing the role of AVP in anxiety and depression (e.g. (Landgraf and Wigger, 2002; Scott and Dinan, 2002; Griebel et al., 2003; Keck, 2006; Landgraf, 2006; Frank and Landgraf, 2008; Simon et al., 2008; Surget and Belzung, 2008; Ryckmans, 2010). As both psychiatric disorders are considered to be stress related and AVP has a regulatory role in the HPA axis (Engelmann et al., 2004; Makara et al., 2004; Murgatroyd and Spengler, 2011), this connection is reasonable to propose. In particular, the strong connection between chronic stress and depression (see e.g. chronic mild stress as a model of depression (Duman, 2010; Yan et al., 2010; Overstreet, 2012)) and the observed upregulation of AVP synthesis in parvocellular PVN neurons and V1b receptors at the anterior pituitary during chronic stress (Dallman, 1993; Aguilera et al., 1994) suggested the involvement of altered AVP signaling within the HPA axis in pathophysiological processes. Clinical studies found an increased AVP concentration in the cerebrospinal fluid (De Bellis et al., 1993; Heuser et al., 1998) and in the plasma (van Londen et al., 1997, 1998; de Kloet et al., 2008) of depressive subjects, especially in suicide victims (Inder et al., 1997; Brunner et al., 2002). Postmortem studies have found an elevated number of AVP-expressing neurons, increased AVP level in the PVN (Purba et al., 1996; Merali et al., 2006) and an enhanced AVP mRNA in the SON (Meynen et al., 2006). Additionally, a single nucleotide polymorphism of the AVP V1b receptor has been found to protect against major depression (van West et al., 2004). Preclinical studies using the first orally active non-peptide V1b antagonist (SSR 149415) resulted in a reduction of floating in the FS test (Griebel et al., 2002). However, a clinical study using SSR 149415 was unable to proof an effect on anxiety; and there was only a mild, not always reproducible, effect on depressive symptoms (Griebel et al., 2012). Therefore the question arose about the role central V1 receptors may play in anxiety and depression. The fact that genetically AVP-deficient patients with diabetes insipidus show less anxious phenotype together with memory impairment (Bruins et al., 2006), and that diabetes insipidus is often accompanied by memory impairment in other patients as well (Nabe et al., 2007), suggests the possible involvement of