Hormones and Behavior 61 (2012) 277–282

Contents lists available at SciVerse ScienceDirect

Hormones and Behavior

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

Review

The vasopressin 1b receptor and the neural regulation of social behavior

Erica L. Stevenson, Heather K. Caldwell *

Laboratory of Neuroendocrinology and Behavior, Department of Biological Sciences and School of Biomedical Sciences, Kent State University, Kent, OH, USA

ARTICLE INFO

Article history:
Received 5 July 2011
Revised 25 November 2011
Accepted 28 November 2011
Available online 7 December 2011

Keywords:
Avpr1b
Aggressive behavior
Social recognition memory
Social motivation
Stress

ABSTRACT

To date, much of the work in rodents implicating vasopressin (Avp) in the regulation of social behavior has focused on its action via the Avp 1a receptor (Avpr1a). However, there is mounting evidence that the Avp 1b receptor (Avpr1b) also plays a significant role in Avp's modulation of social behavior. The Avpr1b is heavily expressed on the anterior pituitary cortiocotrophs where it acts as an important modulator of the endocrine stress response. In the brain, the Avpr1b is prominent in the CA2 region of the hippocampus, but can also be found in areas such as the paraventricular nucleus of the hypothalamus and the olfactory bulb. Studies that have employed genetic knockouts or pharmacological manipulation of the Avpr1b point to the importance of central Avpr1b in the modulation of social behavior. However, there continues to be a knowledge gap in our understanding of where in the brain this is occurring, as well as how and if the central actions of Avp acting via the Avpr1b interact with the stress axis. In this review we focus on the genetic and pharmacological studies that have implicated the Avpr1b in the neural regulation of social behaviors, including social forms of aggressive behavior, social memory, and social motivation.
This article is part of a Special Issue entitled Oxytocin, Vasopressin, and Social Behavior.

Contents

Introduction

Arginine vasopressin (Avp) is a cyclic nonapeptide produced primarily within the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. Three specific receptor subtypes mediate the actions of Avp: the Avp 1a receptor (Avpr1a), the Avp 1b receptor (Avpr1b), and the Avp 2 receptor (Avpr2). All three receptor subtypes can be found in the periphery (Arsenijevic et al., 1994; Jard et al., 1987; Knepper, 1997; Koshimizu et al., 2006; Thibonnier et al., 2002), but only the centrally expressed Avpr1a and Avpr1b are known to mediate the effects of Avp on social behavior (Foletta et al., 2002; Lolait et al., 1995; Young et al., 2006). While the role of the Avpr1a in the neural regulation of social behavior has been studied extensively, pharmacological studies as well as data from Avpr1b knockout (Avpr1b−/−) mice suggest a significant role for the Avpr1b as well.

The Avpr1b is expressed in a variety of tissues, including the pancreas, where it has been linked to insulin secretion, and the adrenal gland, where it has been linked to catecholamine release. It is also heavily expressed in the corticotrophes of the anterior pituitary gland (Antoni, 1984; Jard et al., 1986), but is also found in the brain. In rat brain, Avpr1b transcripts and immunoreactive cell bodies are localized to the cerebellum, cerebral cortex, hippocampus, olfactory bulb, PVN, piriform cortical layer II, red nucleus, septum, and suprachiasmatic nucleus (Barberis and Tribollet, 1996; Hernando et al., 2001; Lolait et al., 1995; Saito et al., 1995; Stemmelin et al., 2005; Vaccari et al., 1998). However, a more recent *in situ* hybridization study, in which more specific riboprobes and more stringent wash

* Corresponding author at: Kent State University, PO Box 5190, 121 Cunningham Hall, Kent, OH 44242, USA.
E-mail address: hcaldwel@kent.edu (H.K. Caldwell).

0018-506X/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.yhbeh.2011.11.009

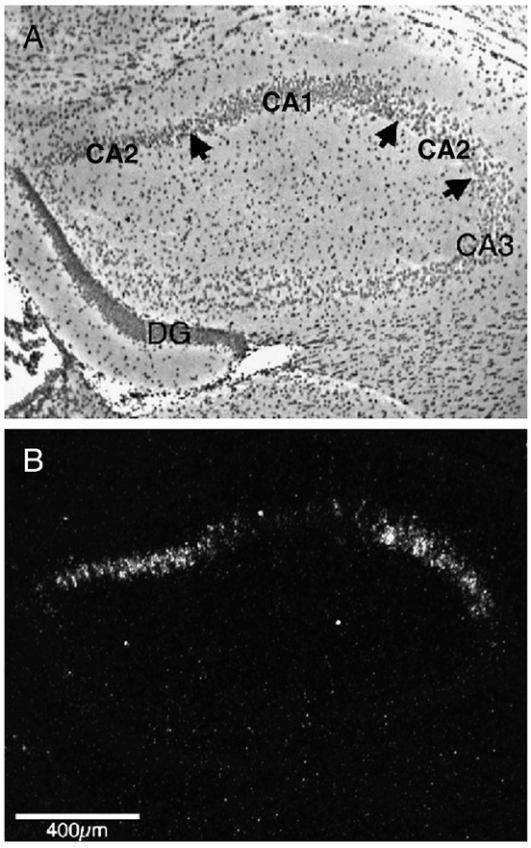

Fig. 1. Vasopressin 1b receptor (Avpr1b) *in situ* hybridization in a coronal section of mouse hippocampus, approximately 1.1 mm posterior to bregma. A) A brightfield photomicrograph with the two left arrows indicating the CA1–CA2 pyramidal cell borders and the far right arrow the CA2–CA3 pyramidal cell border. B) A darkfield photomicrograph, which highlights the presence of Avpr1b transcripts within the CA2 region of hippocampus. The arrangement of the CA2 region of the hippocampus is unusual in this rostral portion of hippocampus as the CA1 region is between portions of the CA2 region (Lein et al., 2005). DG = dentate gyrus.
Adapted from Young, Li, Wersinger, and Palkovits, *Neuroscience*, 2006; 143(3): 1031–1039, ©2006 with permission from Elsevier.

conditions were utilized, found that the Avpr1b of mice, rats, and humans is more discretely localized than previous studies suggested, with prominence in the dorsal one-third of pyramidal cells of the CA2 region of the hippocampus (Fig. 1), and in a few cells within the anterior amygdala and the PVN (Young et al., 2006).

The apparent discrepancy between the Hernando et al. (2001) study and the Young et al. (2006) study probably reflects methodological differences. The original riboprobe had stretches of sequence that had fairly high identity (>80%) with the Avpr1a and the oxytocin receptor (Oxtr), likely resulting in cross-hybridization (Hernando et al., 2001). On the other hand, when Young et al. (2006) used RT-PCR to quantify Avpr1b mRNA, the distribution was found to be more extensive than that seen with *in situ* hybridization; which suggests that some areas of the brain have so few Avpr1b transcripts that *in situ* hybridization is not sensitive enough to detect them. The issue of where exactly in the brain the Avpr1b is located is further complicated by the lack of antibodies in species such as mice and humans, as well as the lack of specific radiolabeled ligands. To date there are no published studies using receptor autoradiography to map the central distribution of the Avpr1b; thus, in humans and mice the presence of Avpr1b protein is inferred from the *in situ* hybridization studies. While we may not know where in the brain Avp acting via the Avpr1b is affecting behavior, it is clear that the central Avpr1b is important to aspects of social behavior, such as aggression and social memory (DeVito et al., 2009; Wersinger et al., 2002, 2004, 2007, 2008). This review will focus on the behavioral evidence implicating the Avpr1b in the neural regulation of social behavior (summarized in Table 1).

Aggressive behavior

Displays of aggressive behavior are important to the survival and reproductive success of many species. Based on work in Avpr1b−/− mice, there is compelling evidence that the Avpr1b is essential for displays of aggressive behavior that are directed toward a conspecific (for review see Caldwell et al., 2008a,b). In resident–intruder and neutral-cage aggression tests Avpr1b−/− mice display fewer attacks and have longer attack latencies than Avpr1b wildtype (+/+) controls (Wersinger et al., 2002, 2007). Further, in a reversal of a resident–intruder test, where the experimental mice are intruders rather than residents, Avpr1b−/− mice display normal defensive avoidance behaviors (i.e., boxing stance and protection of their flanks) when attacked by a stimulus animal, but are less likely to initiate retaliatory attacks (Fig. 2) (Wersinger et al., 2007). Pharmacological studies using the Avpr1b antagonist SSR149415 are consistent with the work in Avpr1b−/− mice. Syrian hamsters orally administered SSR149415 have reductions in the frequency and duration of offensive attacks, chase behaviors, flank marking, and in the olfactory investigation that often precedes and accompanies an offensive attack (Blanchard et al., 2005). In addition, mice that are orally administered SSR149415, display fewer defensive bites when forced to encounter a threatening predator and

Table 1
Summary of behaviors observed in Avpr1b −/− mice and mice given SSR149415, the Avpr1b antagonist. (↓), indicates a decrease in the behavior; (↑), indicates an increase in the behavior; (←→), indicates no change in the behavior.

Behavior	Behavioral test	Avpr1b−/−	SSR149415	References
Aggression	Social dominance (mounting behavior)	↑	N/A	Caldwell et al., 2010
	Competitive (food deprivation/competition)	↓	N/A	Wersinger et al., 2007
	Defensive (attack avoidance)	←→	N/A	Wersinger et al., 2007
	Defensive (reverse resident–intruder)	↓	↓	Griebel et al., 2002; Wersinger et al., 2007
	Maternal (pup defense)	↓	N/A	Wersinger et al., 2007
	Predatory (attack cricket)	←→	N/A	Wersinger et al., 2007
	Offensive (neutral arena)	↓	N/A	Wersinger et al., 2002
	Offensive (resident intruder)	↓	↓	Wersinger et al., 2002; Caldwell and Young, 2009; Blanchard et al., 2005 (hamster); Griebel et al., 2002 (mouse)
Social memory/memory	Littermate vs. novel animal recognition	↓	N/A	DeVito et al., 2009
	Temporal order memory	↓	N/A	DeVito et al., 2009
	Bruce effect	↓	N/A	Wersinger et al., 2008
	Novel vs. familiar female	↓	N/A	Wersinger et al., 2002
Social motivation/preference	Sociability (familiar littermate interaction)	↓	N/A	DeVito et al., 2009
	Social preference (novel animal vs. novel object)	←→	N/A	Yang et al., 2007
	Bedding preference	↓	N/A	Wersinger et al., 2004
Social anxiety	Sociability test following chronic social defeat	N/A	↓	Litvin et al., 2011