Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Oxytocin and vasopressin systems in genetic syndromes and neurodevelopmental disorders

S.M. Francis[a], A. Sagar[b], T. Levin-Decanini[a], W. Liu[c], C.S. Carter[d], S. Jacob[a,*]

[a]University of Minnesota, Department of Psychiatry, Minneapolis, MN, USA
[b]University of California at Irvine, Department of Psychiatry and Human Behavior, USA
[c]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA
[d]University of North Carolina, Department of Psychiatry, Chapel Hill, NC, USA

ARTICLE INFO

Article history:
Accepted 15 January 2014
Available online 22 January 2014

Keywords:
Oxytocin
Vasopressin
Autism
Prader–Willi
Williams
Fragile X

ABSTRACT

Oxytocin (OT) and arginine vasopressin (AVP) are two small, related neuropeptide hormones found in many mammalian species, including humans. Dysregulation of these neuropeptides have been associated with changes in behavior, especially social interactions. We review how the OT and AVP systems have been investigated in Autism Spectrum Disorder (ASD), Prader–Willi Syndrome (PWS), Williams Syndrome (WS) and Fragile X syndrome (FXS). All of these neurodevelopmental disorders (NDD) are marked by social deficits. While PWS, WS and FXS have identified genetic mutations, ASD stems from multiple genes with complex interactions. Animal models of NDD are invaluable for studying the role and relatedness of OT and AVP in the developing brain. We present data from a FXS mouse model affecting the fragile X mental retardation 1 (Fmr1) gene, resulting in decreased OT and AVP staining cells in some brain regions. Reviewing the research about OT and AVP in these NDD suggests that altered OT pathways may be downstream from different etiological factors and perturbations in development. This has implications for ongoing studies of the therapeutic application of OT in NDD.

This article is part of a Special Issue entitled Oxytocin and Social Behav.

1. Introduction to OT and AVP neuropeptide hormones

Oxytocin (OT) and arginine vasopressin (AVP) are small mammalian neuropeptides nine amino acids in length, which differ by only two amino acids. OT is produced primarily in hypothalamic nuclei, including the supraoptic (SON) and paraventricular nuclei (PVN). AVP is also synthesized in the PVN and SON. In males, additional brain regions including the amygdala and the bed nucleus of the stria terminalis (BNST) also produce AVP. OT and AVP of hypothalamic origins are transported from the SON and PVN to the mammalian posterior pituitary by neurosecretion where they are released into the blood stream and act as hormones on target tissues. In addition, both OT and AVP are capable of moving throughout the central nervous system via diffusion in the cerebral spinal fluid (CSF; Neumann and Landgraf, 2012). The peptide-producing OT gene (OXT) is homologous with its evolutionarily related gene, vasopressin (AVP). The human OXT and AVP genes linked on chromosome 20p13 are separated by only 12 kilobases of DNA, and are positioned in opposite transcriptional orientations. Both

*Correspondence to: University of Minnesota, Wallin Medical Biosciences Building, 2101 6th Street SE, Minneapolis, MN 55455, USA. Fax: +612 273 9779.
E-mail address: sjacob@umn.edu (S. Jacob).

0006-8993/$ - see front matter © 2014 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.brainres.2014.01.021

have specific receptors, but their close evolutionary relationship permits cross-talk and interacting molecular systems. These neuropeptide hormones have receptors in various brain regions and throughout the body, including areas that are important for regulating social behavior and reactivity to stressors.

In both, the human and mouse genomes OT and AVP neuropeptide genes are located adjacently on the same chromosome. Often the blood levels of both hormones are highly correlated (Dai et al., 2012), suggesting a coordinated release. The receptors for both neuropeptides are localized in specific areas of the nervous system, especially in the brainstem. These brain regions influence social and adaptive behaviors, as well as regulate the hypothalamic–pituitary–adrenal axis (HPA) and autonomic nervous systems (Lim et al., 2005, 2004). Because OT and AVP are closely related and have the ability to act on the other's receptors, it has been proposed that they evolved to interact and sometimes have opposing physiological effects. For example, both hormones have been shown to affect the control of the autonomic nervous system, with OT having primarily parasympathetic actions and AVP serving as a central and peripheral regulatory component of the sympathetic nervous system and HPA axis (Kenkel et al., 2012; Sawchenko and Swanson, 1985). However, at high levels the neuropeptides can be partial agonists for their homologous receptors, which may result in AVP and OT pathways interacting (Chini et al., 1996).

Of particular importance in neurodevelopmental disorders (NDD) is the fact that OT and AVP can modulate social and repetitive behavior and other manifestations of anxiety and state regulation (Carter, 2007). Animal research has generally associated OT release or exposure with positive sociality, reduced anxiety, and lower levels of reactivity to stressors (Carter, 1998; Neumann and Landgraf, 2012). AVP influences anxiety, the regulation of HPA and stress responses. In general, central AVP is described as anxiogenic (Landgraf and Wigger, 2003). However, there is also evidence in rats that the effects of AVP are brain region specific and dose-dependent. For example, AVP may be anxiolytic if given in low doses (Appenrodt et al., 1998).

Mouse knockout (KO) studies of the OT receptor (OXTR) or OT regulators have found decreased social memory or recognition (Ferguson et al., 2000; Jin et al., 2007; Takayanagi et al., 2005). *Oxtr* KO mice also displayed decreased cognitive flexibility and a resistance to change of a learned pattern of behavior that is comparable to restricted/repetitive interests (Sala et al., 2011). Both social deficits and behavioral rigidity were ameliorated by OT administration (Sala et al., 2011). The finding that OT continues to have effects in *Oxtr* KO mice supports the hypothesis that OT can influence behavior through other receptors, especially the AVP receptors (e.g. AVPR1A and/or AVPR1B). Given the influence of these neuropeptides on brain regions affecting both social and repetitive behaviors, modulation of OT and AVP pathways are being explored as treatment targets for disorders, including Fragile X syndrome (FXS) and Autism Spectrum Disorders (ASD).

This and other research has set the stage for a series of recent studies on the effects of exogenous OT treatments in humans (Ebstein et al., 2012; Macdonald and Feifel, 2013). For example, intranasal OT (IN-OT) administration in healthy human males increased prosocial behaviors and trust, especially as measured by experimental economic games (Baumgartner et al., 2008; Kirsch, 2005; Kosfeld et al., 2005). IN-OT may also increase gaze towards the eye region of the face (Guastella et al., 2008), and has been associated with improved facial memory (Rimmele et al., 2009), enhanced salience of social cues (Shamay-Tsoory et al., 2009), and improved performance on the reading the mind in the eyes (RMET) task (Domes et al., 2007).

As previously reviewed, OT has been found to have anxiolytic effects improving social interactions, reducing fear, and improving the ability of healthy volunteers to interpret subtle social cues (Macdonald and Macdonald, 2010). In addition, OT dysfunction has been associated with neuropsychiatric disorders such as autism in human studies (Domes et al., 2007; Ishak et al., 2011; Winslow and Insel, 2004). By 2010 there were over 20 OT administration studies, which included ASD, schizophrenia, postpartum depression, post-traumatic stress disorder (PTSD), and irritable bowel syndrome (Macdonald and Macdonald, 2010). There have been a growing number of studies investigating the ability of IN-OT to treat a range of neurobehavioral disorders due to the associations between IN-OT and alterations in social decision-making, processing of social stimuli, certain social behaviors such as eye contact, and social memory.

2. Autism spectrum disorders

In 1943, Leo Kanner described a male patient with repetitive behaviors—"stereotyped movements [and]…repetitions carried out in exactly the same way in which they had been performed originally" and difficulties with social communication—"he always seemed to be parroting what he had heard said to him at one time or another…Words to him had a specifically literal, inflexible meaning. He seemed unable to generalize, to transfer an expression to another similar object or situation" (Kanner, 1943). This group of symptoms, later extended and described in detail, is currently known as ASD. As described in the DSM-5 (American Psychiatric Association, 2013), ASD is characterized by persistent deficits in social communication and social interaction across multiple contexts, and the diagnosis requires the presence of restricted, repetitive patterns of behaviors, interests, or activities. ASD is a heritable (Bailey et al., 1995) and highly heterogeneous disorder, caused by familial genetic risks in addition to possible gene-environment interactions during early development (Chaste and Leboyer, 2012). Individuals with ASD often suffer with anxiety disorders, irritability or aggression, and come to clinical attention due to their difficulties at home and school related to their communication deficits and restricted interests. Unfortunately there are currently no approved medications to treat the social deficits or restricted, repetitive behaviors (RRB) that are the core symptoms of ASD. There is some evidence in animal and human studies that OT improves the core symptoms of ASD.