Deregulation of Oxytocin and Vasopressin in Williams Syndrome: A New Model For Exploring Neurogenetics and Neurobiology of Human Social Behavior

Oxytocin and vasopressin are dysregulated in Williams Syndrome, a genetic disorder affecting social behavior

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Abstract

The molecular and neural mechanisms regulating social-emotional behaviors are fundamentally important but largely unknown; unraveling these requires a genetic systems neuroscience analysis of human models. Williams Syndrome (WS), a condition caused by deletion of ~28 genes, is associated with a gregarious personality, strong drive to approach strangers, difficult peer interactions, and attraction to music. WS provides a unique opportunity to identify endogenous human gene-behavior mechanisms. Social neuropeptides including oxytocin (OT) and arginine vasopressin (AVP) regulate reproductive and social behaviors in mammals, and we reasoned that these might mediate the features of WS. Here we established blood levels of OT and AVP in WS and controls at baseline, and at multiple timepoints following a positive emotional intervention (music), and a negative physical stressor (cold). We also related these levels to standardized indices of social behavior. Results revealed significantly **higher median levels of OT in WS** versus controls at baseline, with a less marked increase in AVP. Further, in WS, OT and AVP increased in response to music and to cold, with greater variability and an amplified peak release compared to controls. **In WS, baseline OT but not AVP, was correlated positively with approach, but negatively with adaptive social behaviors**. These results indicate that WS deleted genes perturb hypothalamic-pituitary release not only of OT but also of AVP, implicating more complex neuropeptide circuitry for WS features and providing evidence for their roles in endogenous regulation of human social behavior. The data suggest a possible biological basis for amygdalar involvement, for increased anxiety, and for the paradox of increased approach but poor social relationships in WS. They also offer insight for translating genetic and neuroendocrine knowledge into treatments for disorders of social behavior.

Overview

Given the complex cognitive processes that are implied, the scientific investigation of social behavior and attachment is extremely difficult, especially in humans. Using a relatively simple human genetic model (WS) characterized by profound disturbances in social relationships, this very nice study provides new convincing experimental evidence that the neuropeptides OT and, although to a lesser extent, AVP are intimately involved in the control of human social behavior. Since many years now, in intimate association with forebrain reinforcing dopamine pathways, OT and AVP have yielded an elegant model linking genetic, molecular, cellular, and systems approaches.

OT- and AVP-related peptide lineages derive from a common ancestor gene/protein that duplicated early in evolution. Following the pioneer studies by Vincent du Vigneaud and Roger Acher in late 50's, OT and AVP were shown to be the essential parts of the hypothalamo-neurohypophysial system, which was first described in fish species by the German biologists, Ernst and Britta Sharrer. After transcription of their encoding genes in hypothalamic magnocellular neurons, OT and AVP precursors are processed to give birth to the respective nonapeptides that are released in the bloodstream from axon terminals in the neurohypophysis. This basic model led to the foundation of neuroendocrinology and neurosecretion. The major function of neuroendocrine OT is the stimulation of milk ejection, but blood OT is also involved in the control of parturition through its potent contractile properties on the myometrium. Blood AVP is responsible for antidiuresis and thus essentially controls water homeostasis, together with an implication in the regulation of vascular tone through AVP constrictive properties on vessel smooth muscles [1].

Through the important connections of hypothalamic supraoptic and paraventricular neurons, as well as other brain nuclei, OT and AVP also behave as central neuropeptides that modulate fast neurotransmitters and are involved in a series of behavioral, cognitive and mnesic processes. The crucial implication of OT in the induction of maternal behavior of female rats was already reported in 1982 [2]. This behavioral effect of OT probably results from a facilitation of approach behavior. OT also down-regulates stress responses and anxiety, while AVP is thought to stimulate the autonomic fear response. The transmembrane receptor CD38 that catalyzes the induction of second messengers in lymphocytes is also an important component in the secretory machinery of OT neurons, and *cd38*$^{-/-}$ mice show impairment of social memory and in recognition of a conspecific female [3,4]. In prairie voles, the two nonapeptides promote pair-bond formation in both sexes although OT seems to be more important in females while AVP is more crucial in males. The OTergic system is currently know to provide the neuropeptide substrate for parental and filial attachment in many species. OT gene-deficient mice, although capable of maternal behavior, exhibit a profound social amnesia, without other apparent cognitive defects [5].

In human brain, OT receptors are highly expressed in dopamine-rich regions, such as the substancia nigra, globus pallidus and preoptic area [6]. In accordance with rodent studies, the anxiogenic and anxiolytic properties of AVP and OT, respectively, have also been observed in humans. Exposure to OT dampens the rise in plasma cortisol, anxiety, and physiological measures in response to stressful contexts, suggesting an inhibition of the adaptive stress response mediated by the hypothalamo-pituitary-adrenal axis [7,8]. In contrast, intranasal instillation of AVP leads to a relatively enhanced rise in physiological, neuroendocrine and behavioral measures of stress [9]. These changes in the adaptive stress response may be partially mediated by neuropeptide effects on amygdala activity. Several neuroimaging studies using OT intranasal challenges have observed an attenuation of the amygdala response to negative stimuli, suggesting that OT may dampen the neural response to fearful cues [10]. Both OT and AVP also alter the functional connectivity of the amygdala to other brain structures subserving emotional processing and regulation of the autonomic fear response [11-13].

Human studies also evidenced OT involvement in pair bonding since OT administration stimulates positive communication, affiliation, and emotional support between partners [14-17], and OT also increases generosity in humans [18]. The data presented by Dai *et al.* provide further support for a relation between OT and social behavior. However, whereas basal OT levels were positively correlated with

approach behavior, a negative correlation was observed with other aspects of social interaction, suggesting that OT does not simply promote social behavior in general. Greater neural activity was also described in OT- and dopamine-rich areas such as the left posterior cingulate cortex and caudate regions in early romantic attachment [19]. Using a combination of OT intranasal administration, economics-related trust and risk games, as well as neuroimaging (fMRI) analysis, OT was also shown to shape the neural circuitry of trust and trust adaptation in humans that are essential to building social relationships [20-22].

Therefore, through its informative intervention at different steps of the whole reproductive process, the OTergic system appears to play a crucial role in species preservation. This statement is further reinforced by the discovery that the OT gene is transcribed in thymus epithelium of different species under the control of the AutoImmune Regulator (AIRE) transcription factor. After translation, the thymic OT precursor then is processed for presentation of OT as the tolerogenic self-antigen of the neurohypophysial peptide/gene family, thus protecting central and peripheral OT-mediated functions from potential autoimmune aggression [complete review in 23]. In addition to the present study, the OT system has also been successfully explored in various psychiatric disorders characterized by an impairment of social relationships ranging from autism, schizophrenia, anxiety, and post-traumatic disorder to depression [24-26].

OT and AVP share a long evolutionary history and figure among the most important brain signals encoding significant information with regard to social behavior and attachment. Besides the signals however, the cognate OT and AVP1ra receptors have also been investigated for their association with human social behavior, from autism to altruism [27,28]. For example, one SNP across the OTR gene region is significantly associated with autism and pro-social behavior studied in nonclinical subjects [29].

To conclude this overview, we would like to quote these appealing sentences at the end of a recent and excellent review about genetics of human social behavior [30]: "*The past two decades have seen remarkable progress in unraveling the complexities of the neurogenetic architecture of the human social brain. Nevertheless, much remains to be learned, especially about how our species has created a global society composed of billions of interacting individuals whose basic brain structure has remained mostly unchanged for the past 50,000 years. This global society is indeed a remarkable achievement for an organ weighing only 1350 g, and attests to its remarkable plasticity in processing a continuous stream of environmental information using neuroanatomical and neurogenetic mechanisms laid down over millions of years of hominid evolution.*" We wish also to remind that Gerald Edelman, in his book '*Second Nature*' (2006), stated that the central unresolved issue in modern neuroscience is the question of *subjectivity* and *individuality* and that it could well remain unsolvable for ever.

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