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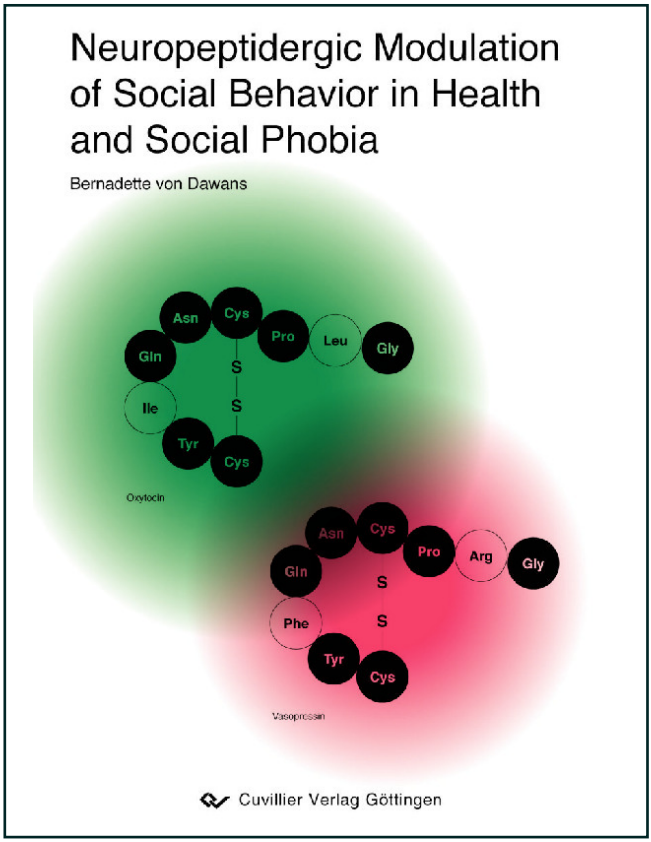
Neuropeptidergic Modulation of Social Behavior in Health and Social Phobia



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‘*Pre-Neanderthal humans developed social skills earlier than thought*’
(comment from www.sciencedaily.com on Richards, Pettitt, Stiner, & Trinkaus, 2001)

1 Introduction

Baruch Spinoza was most likely neither the first nor the last to recognize that man is “a social animal” (cited after Insel, 2002, p. 3). Positive social interaction is one of the most important things in human life. It includes social support and is one crucial aspect in overall quality of life and health (Reblin & Uchino, 2008). Mental disorders mostly affect social life or even impair social interaction. Humans as a highly social species need to have neural mechanisms that reinforce and motivate them to socially engage, interact and bond with others.

The evidence indicates that the neuropeptides oxytocin and vasopressin play a role in these mechanisms. The ancient neuropeptides were conserved through evolution but although all vertebrates have similar peptides, only mammals show the specific receptors for them. Both peptides have important functions in the body (e g. homeostasis, metabolism, growth, sex and reproduction, stress etc.), but most notably they impact strongly on social behavior. Chapter 2 concentrates on these actions and integrates them.

Most impressively, social behavior seems to be as ancient as the neuropeptides themselves. Anthropologists found (by investigating teeth – scientific methods are stunning) that even pre-Neanderthal humans expressed social behavior; in fact much earlier than one might have thought (Richards, Pettitt, Stiner, & Trinkaus, 2001).
The general understanding of the expression ‘social behavior’ seems to be biased towards ‘pro-social’ acts. But ‘social behavior’ includes pro-social aspects, like trust or cooperation, just as it does ‘social aggression’, like altruistic punishment, which has been shown to maintain cooperation (Fehr & Gachter, 2002). The latter must not be equated with antisocial behavior or instrumental aggression. As mentioned above, many psychiatric illnesses show disturbances in social behavior. Social phobia entails pathological anxiety towards most social encounters, and there are other disorders that show exaggerated aggression that can no longer be accounted for as social but rather as anti-social.

Although there is ample evidence on the pro-social effect of oxytocin in healthy humans, it remains unclear whether the peptide helps to reduce symptoms in mental illnesses like social phobia, autism or borderline personality disorder (Heinrichs & Domes, 2008). On the other hand, it needs to be proven that arginine vasopressin can enhance aggression in humans. Animal research and first evidence from human studies point in this direction.

This work reviews the effects of oxytocin (chapter 2.1) and arginine vasopressin (chapter 2.2) on social behavior in animals and humans and integrates their interplay on neuronal circuits (chapter 2.3). This comprises studies on prosocial behavior and also on aggression, and finally stress. The actions exerted by both peptides on the two stress axes are summarized in chapter 3.2. Subsequently, a continuum of social behavior (chapter 4) is proposed that suggests both pro-social and aggressive components in health and links psychopathologies towards biased behavioral expression (either hypersocial, social anxiety or anti-social). The psychobiology of prosocial interaction and social support in healthy humans (chapter 4.1) is followed by the psychobiology of social phobia (chapter 4.2). Thereafter, social behavior and its pathologies is integrated with respect to the relevant neuropeptidergic actions (chapter 5).

In chapter 6, a placebo-controlled double-blind study on the effects of a single-dose intra-nasal application of oxytocin and arginine vasopressin on altruistic punishment in healthy men is presented. The impact of single-dose intranasal oxytocin application combined with social support on stress response in social phobia is subsequently reported in chapter 7. Finally, both empirical studies are discussed in general terms, also with regard to methodological considerations and limitations. The book closes by proposing a model of social behavior (built on the model of Heinrichs & Domes, 2008), which comprises prosocial as well as social aggressive components, bands together oxytocinergic as well as vasopressinergic effects, and tries to explain the share of both peptides in mental disorders that affect the social domain.

2 Neuropeptides and behavior

Oxytocin (OXT) and arginine vasopressin (AVP) are two closely related nonapeptides, synthesized in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. They are transcribed from adjacent genes and differ in only two of their nine amino acids (Figure 2-1).

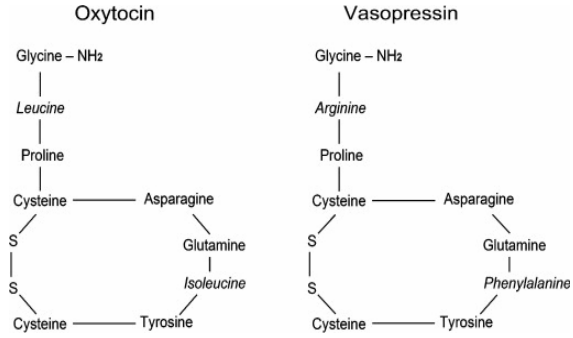

Figure 2-1: Chemical structures of oxytocin and vasopressin (two different amino acids are marked in italics) (Debiec, 2007)

Released into the blood stream via the posterior pituitary, both peptide hormones have important peripheral effects (Figure 2-2). OXT acts on the uterus to induce parturition in late pregnancy and is important for facilitating milk ejection during lactation (Figure 2-3).

AVP, also known as anti-diuretic hormone (ADH), acts on the kidney to facilitate reabsorption of water and regulates vascular tone via action in the blood vessels (Figure 2-4). In addition, OXT and AVP are known for their relevance in the psychobiological stress response as well as multiple social behaviors (Gimpl & Fahrenholz, 2001; Raggenbass, 2008), which will be further explained in Chapter 2 (Neuropeptides and behavior) and Chapter 3 (Stress).

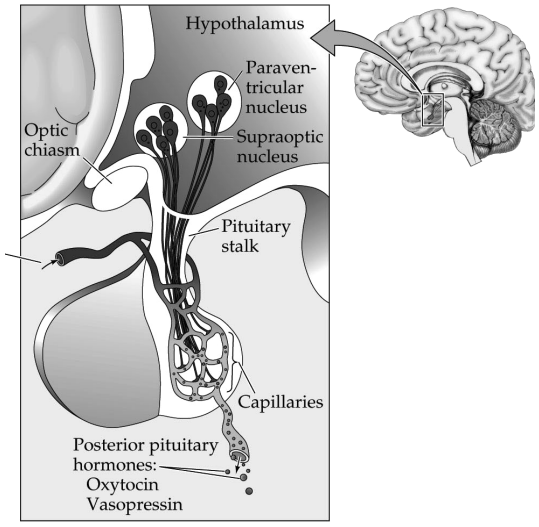

Figure 2-2: Oxytocin and vasopressin production and release in the brain and the body (Rosenzweig, Breedlove, & Watson, 2007)

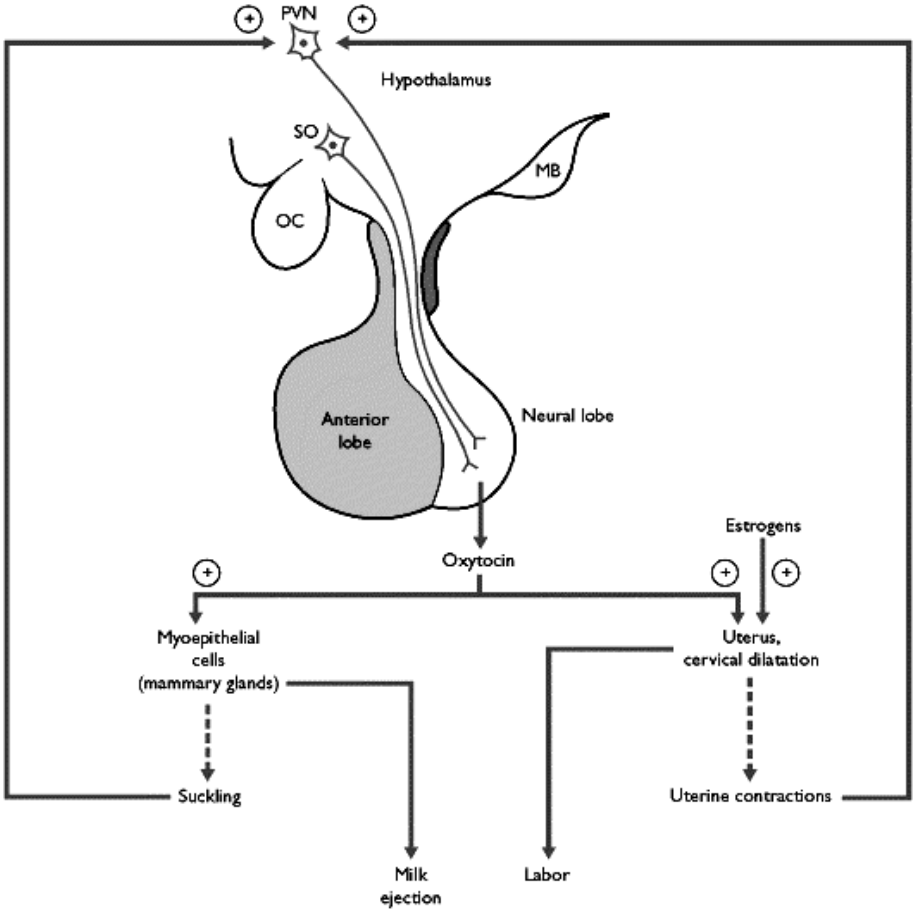

Figure 2-3: Oxytocin - its actions and control;
Abbreviations: MB, mammillary body; OC, optic chiasm; PVN, paraventricular nucleus; SO, supraoptic nucleus (Nussey & Whitehead, 2001)

Whereas for OXT, only one receptor is known, AVP acts on three receptor subtypes: V_{1A}, V_{1B} and V_2 receptor (Raggenbass, 2008). Both peptides act as neuromodulators in the brain, where they influence several regulating functions and behaviors. OXT and AVP (V_{1A}, V_{1B}) receptors are abundant throughout the brain (Barberis & Tribollet, 1996; Young, Li, Wersinger, & Palkovits, 2006). They have been found in the olfactory system, the neocortex, the basal ganglia, the limbic system, the hypothalamus, the thalamus, the circumventricular organs, the brainstem and the spinal cord (for reviews, see Barberis & Tribollet, 1996; Zingg, 1996).

However, not all of these regions are innervated by peptidergic neurons, and since OXT and AVP cannot cross the blood-brain barrier, there must be other ways than only secretion from synapses. How do the peptides exert their actions?

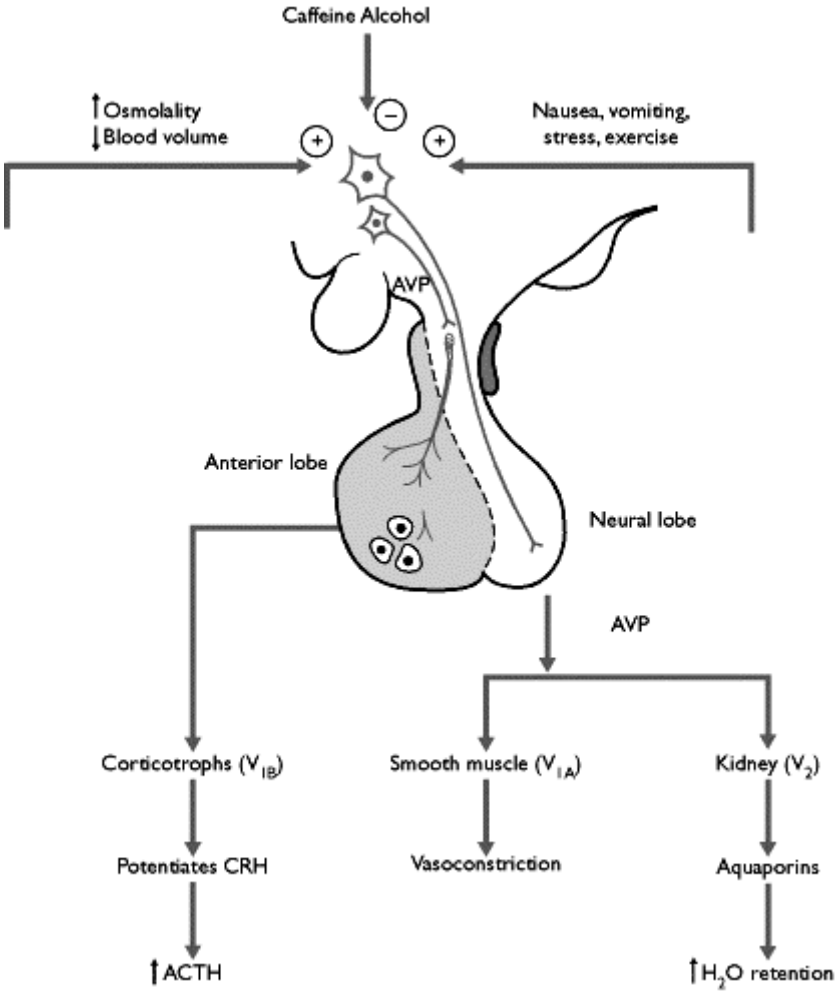

Figure 2-4: The actions of arginine vasopressin (AVP) secretion and mechanisms of control (Nussey & Whitehead, 2001)

Although OXT and AVP neurons signal via synapses, *'[their actions] are not restricted spatially by synaptic wiring, or temporally by rapid degradation'* as is the case for neurotransmitters (Ludwig & Leng, 2006, p. 127). Their effects in the brain are also very different from neurotransmitters. The half-lives of OXT and AVP in the brain are relatively long (~26 and 19 min for AVP and OXT, respectively) compared to a very short half life in the blood (~2 min) (Mens, Witter, & van Wimersma Greidanus, 1983). Interestingly, other neurotransmitters are coexistent on OXT and AVP neurons (which implies multiple neurotransmitter interactions – e.g. with serotonin), and the magnocellular neurons of AVP and OXT from the SON to the pituitary each have one to three dendrites that project to the ventral surface of the brain, where they form a dense plexus.

It has been shown that OXT and AVP concentrations in the extracellular fluid of the SON are 100 to 1,000 times higher than in the blood, indicating strong dendritic release of both neuropeptides throughout the brain. Thus, the dendritic release of the peptides activates self-sustaining, long-lasting excretion as a function of autoregulation (AVP neurons express AVP receptors and OXT neurons OXT receptor). In addition, the dendritic release causes priming effects facilitating later release of the peptides (for review, see Ludwig & Leng, 2006). These paths of action explain why crude diffusion of OXT and AVP exert behavioral modulation and are of relevance besides their local synaptic effects. To summarize their actions:

a) OXT and AVP are not only released from synapses but also in a large amount from dendrites.
b) They act in an autoregulatory manner on their own synapses, thus increasing their own release, and
c) Have priming effects at their receptors, which results in facilitation of activity-dependent dendritic release (not only restricted to the cell of origin).
d) Finally, they diffuse throughout the whole brain to exert actions at various sites that are not directly innervated by OXT or AVP fibers.

Via the depicted mechanism, OXT and AVP have been found to modulate several behaviors. Landgraf and Neumann state in their review (2004):

Taken together *'[t]he capability of responding to and mediating both environmental stimuli and genetic polymorphisms, transducing them into adequate or psychopathological behavior, makes neuropeptide release in distinct brain areas a key process for converging behavioural regulation'*.