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Review

From vasotocin to stress and cognition

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ABSTRACT

Sex and stress hormones coordinate experience and behaviour with physiological regulations. In the brain the sex hormones act to promote the repertoire of affiliative and reproductive behaviours. Stress hormones target in particular brain circuits underlying emotional arousal and cognition. To exert these actions the hormones operate in concert with neuropeptide secreting systems. Here I will discuss three examples of hormone action on brain and behaviour. First in the song bird manipulation of brain vasotocin promotes acquisition of a stable stereotyped song pattern. Second in mammal's central glucocorticoid feedback action, initiated and enhanced by vasopressin, is mediated by two types of nuclear receptors that operate in complementary fashion to maintain homeostasis and health. One receptor system, the mineralocorticoid receptors, activates the switch from spatial to habit learning under stressful conditions, while the stress-induced behavioural response is stored in the memory via activation of the glucocorticoid receptors. Third, genetic predisposition and early life experience program neuropeptide and glucocorticoid systems for life with the goal to match with expected future demands. Hence, a mismatch between the early imprinted response modes with later life conditions enhances vulnerability to disease. These three topics have in common that they illustrate how hormones govern plasticity of neural stress circuitry underlying complex behavioural tasks, how upon dysregulation psychiatric disorders may develop for which the individual is predisposed and how such hormone action may promote resilience still present in the diseased brain.

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1. Introduction

This contribution in memory of David de Wied is about vasotocin, stress and cognition. Why vasotocin? It is because vasotocin, the

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evolutionary precursor of vasopressin, marks a series of PhD experiments performed by Door Voorhuis around 1990 when David was about to retire. The function of the vasopressin/vasotocin projections innervating the limbic–midbrain changes rapidly over evolutionary time in mediating various affiliative and reproductive behaviours (Choleris et al., 2003; Goodson and Kabelik, 2009). Hence our experiments were aimed to explore the role of vasotocin in song learning of the canary (Voorhuis et al., 1991). The study was an exciting experience: first exploring the organization of the canary's central vasotocin system and then characterising the peptide's role in singing, an experiment which David liked most.

Why stress? Perhaps because the function of vasotocin/vasopressin in the pituitary stress response is strongly conserved as opposed to its evolutionary shift in limbic–midbrain behaviours? More likely, however, because of David's inspiring role in four decades of my research in the stress field which was aimed to unravel how glucocorticoid stress hormones secreted by the adrenals coordinate control of initial stress reactions with management of later adaptations. This research evolved from a PhD project at Organon devoted to dexamethasone action on brain and pituitary (De Kloet et al., 1974), via a postdoc on corticosterone receptors with Bruce McEwen at the Rockefeller University (de Kloet et al., 1975) towards our Utrecht discovery of two distinct corticosterone receptor sites in hippocampus (Reul and de Kloet, 1985) and finally established in the current Leiden research theme on stress in the brain (de Kloet et al., 2005). A previous essay dealt with this chain of events at the occasion of David's 75th anniversary (de Kloet, 2000).

Why vasotocin and stress in cognition? David was the first to recognize the role of the vasopressin/vasotocin neuropeptides in the modulation of stress-related cognitive processes (De Wied, 1969). A more timely reason is that today's bio-psychiatry cries out for causality between a well-defined neuronal substrate and a distinct psychic function (Van Praag et al., 2004). Emotional arousal and psychotic disorganization are a prime example since they are linked to excess glucocorticoids (Holsboer, 2000; McEwen, 2005, 2007) characteristic for Cushing patients, excessive glucocorticoid treatment and psychotic depression. No surprise perhaps therefore that patients suffering from these conditions benefit from anti-glucocorticoid therapy (van der Lely et al., 1991; DeBattista and Belanoff, 2006), although some scepticism remains (Carroll and Rubin, 2006). It has become widely appreciated that glucocorticoids are key determinant in brain plasticity underlying adaptation to stress, a process termed allostasis (McEwen and Wingfield, 2003). Here, first the vasotocin story is summarized before turning to glucocorticoids.

2. Neuropeptide concept

David de Wied[1] pioneered the action of pituitary peptide hormones in the brain. As a contemporary of Geoffrey Harris he was aware that neuroendocrine systems coordinate experience and behaviour with the secretion of hormones. In the behavioural realm of the Harris concept David and colleagues demonstrated potent central actions of ACTH and vasopressin on fear conditioning paradigms. In subsequent experiments fragments of ACTH and vasopressin, devoid of endocrine activity, had maintained their central actions on behaviour, a finding that led him to coin the term 'neuropeptide' in the early 70s (De Wied, 1969, 1971, 1997).

At the same time other researchers (Hughes et al., 1975) discovered the first neuropeptide (enkephalin) in brain as product of a large precursor molecule. Previously, it was firmly established that vasopressin has profound effects on fear-motivated behaviour by a central action (de Wied, 1971), possibly involving brain corticosteroid receptors (Veldhuis and De Kloet, 1982). Then, the distribution of neuropeptide receptors was described using *in vitro* autoradiography on brain sections: see for instance the mapping of brain oxytocin and vasopressin receptors (de Kloet et al., 1985). These neuropeptides appeared crucial in coordination of cognitive functions with socio-reproductive and stress-related behavioural patterns (Winslow and Insel, 2004; Landgraf, 2006).

Oxytocin stimulates social encounters serving recognition of a partner and pair bonding. Oxytocin peaks during orgasm, is essential for delivery and promotes maternal care. The hormone rises during nipple stimulation promoting attachment between dam and pup. Oxytocin and its receptors are together with two estrogen receptor gene variants part of a four gene micronet which is involved in the promotion of positive and rewarding psychosocial memory processes (Choleris et al., 2003). Oxytocin receptors are for this purpose located in discrete hotspots in limbic–midbrain structures involved in processing of information between amygdala, olfactory tubercles, ventral hippocampus and ventromedial nucleus of the hypothalamus, which also mediates oxytocin's action in fear conditioning paradigms: oxytocin is amnestic. Vasopressin via V1a and V3 receptors enhances stress reactions, promotes marking and defending a territory, and facilitates fear-motivated memory processes (de Wied, 1997).

3. Intermezzo: vasotocin and canary song

Canary song may be considered an expression of male reproductive behaviour. With song the male attracts a female, competes with another male and claims territorial ownership. Singing requires a learning process (Wilbrecht and Nottebohm, 2003; Goodson and Kabelik, 2009). Together with David de Wied and Door Voorhuis we have tested the hypothesis that vasotocin modulates the song control system of the canary. The canary is an "open-ended learner", which implies that every autumn a new stable song repertoire is learned towards spring. The acquisition of new syllables to the song repertoire coincides with a dramatic increase in volume of two nuclei of the motor control system: i.e. the nucleus hyperstriatum and the nucleus robustus archistriatalis. Testosterone facilitates neurogenesis, growth and connectivity in these nuclei and the steroid is necessary for transition from unstable plastic song to full song, probably involving vasotocin.

First, sexual dimorphic testosterone- and season-dependent vasotocin immunostaining was discovered in the lateral septum and the bed nucleus stria terminalis, which are areas involved in motivational aspects of reproductive behaviour. Vasotocin immunoreactive fibers also innervate the region encapsulating the RA, the song control nucleus in the canary (Kiss et al., 1987; Voorhuis et al., 1988), the zebra finch (Voorhuis and de Kloet, 1992) and other birds (Goodson and Kabelik, 2009), Second, one population of low affinity testosterone-sensitive neurohypophyseal hormone binding sites is widely distributed in the canary brain including the robustus archistriatalis. High affinity vasotocin receptors exclusively surround this nucleus (Fig. 1). Thus the morphological features of the central vasotocin system in the canary strongly favoured its function in control of singing behaviour (Voorhuis et al., 1990).

How to test the hypothesis on the role of vasotocin in singing? We have used a brief treatment with the bio-active desglycinamide vasotocin analog (DGVTA). The DGVTA treatment was given the first 3 days (0.7 μg subcutaneously, three times daily) to birds which had received on day 0 a silastic implant containing testosterone to ensure exposure to this steroid for 4 weeks. The quality of the song analyzed with time frequency sound spectrography was tested the first 30 min immediately following lights on. We found that the short term DGVTA treatment influenced the amount of singing behaviour measured between 1 and 4 weeks later. The song duration (seconds of song/30 min) was affected in a dual mode. Initially, DGVTA enhanced song duration of testosterone primed canaries, but apparently at the expense of song duration in the later period (Fig. 1). Vasotocin

[1] David de Wied (1925–2004) was Professor of Medical Pharmacology at the University of Utrecht, The Netherlands from 1963 to 1990.