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AT-A-GLANCE ARTICLE

The interplay between oxytocin and the CRF system: regulation of the stress response

Julia Winter[1] · Ben Jurek[1]

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Abstract

Oxytocin (OT) has drawn the attention of researchers since 1930. Since then, many aspects of oxytocin have been uncovered, such as reproductive functions, dampening anxiety, enhancing socioemotional behavior, or regulating genomic effects on a cellular level. Here, we want to focus on the interaction between the OT system and the stress/corticotropin-releasing factor (CRF)-system of the brain. Depending on the nature of the stressor, OT is released simultaneously or directly after the stress from the neurohypophysis into the periphery and/or via somato-dendritic release in stress-sensitive brain areas. This stress-induced OT release might serve to modulate or dampen the stress response; however, the functional relevance is not yet fully understood. In this review, we will describe the effects of OT and discuss the interplay between OT and CRF on a cellular, physiological, and behavioral level.

Keywords Oxytocin · Corticotropin releasing factor · Stress · HPA axis · PVN

Stress-induced oxytocin release

Oxytocin (OT) is a nonapeptide, mainly synthesized in the paraventricular, supraoptic and accessory nuclei of the mammalian hypothalamus (Mohr et al. 1988; Sofroniew 1983). OT-immunoreactive neurons are also found scattered in various other brain regions, such as the suprachiasmatic nucleus, the bed nucleus of the stria terminalis (BNST), the medial amygdala, the dorsomedial hypothalamus and the locus coeruleus (Buijs 1978; Tobin et al. 2010; van Leeuwen and Caffe 1983). The paraventricular nucleus (PVN) of the hypothalamus contains two sub-populations of neurons, morphologically divided into magnocellular neurons and the smaller parvocellular neurons (see Table 1). Magnocellular OT neurons mainly project to the neurohypophysis, where OT is secreted into the peripheral bloodstream via neuro-hemal contacts (Knobloch and Grinevich 2014), whereas parvocellular OT neurons project towards brain regions such as brainstem, spinal cord, or supraoptic nucleus (Eliava et al. 2016; Grinevich et al. 2016; Honda et al. 2013) to release OT in a somato-dendritic manner. Those projections are part of neuronal circuits, whose major outputs feed into corticotropin-releasing factor (CRF) neurons of the PVN. CRF serves as the starting point and main driver of the so-called hypothalamic-pituitary-adrenal (HPA) axis. The activated HPA axis provides the resources for an adequate stress response and initiates a state of heightened alertness. There is mounting evidence that exposure to various stressors (immobilization, shaker, social defeat, forced swimming, or i.c.v. CRF infusions) not only induces CRF release but also causes release of OT into the peripheral circulation of male and female rats (Neumann et al. 2000c; Nishioka et al. 1998; Torner et al. 2017). In addition to those psychological/physical stressors, hypothalamic OT neurons are also activated by physiological stressors such as lipopolysaccharide (Matsunaga et al. 2000), interleukin 1-beta (Ericsson et al. 1994), or cholecystokinin (Douglas et al. 1995). However, it is important to consider that the exact timing of the stress-induced OT release is unknown so far (Wotjak et al. 1998): OT could be released from the PVN during, or immediately after, acute stress. This has consequences for the interpretation of the stress-induced OT release. Whether it dampens the already active stress response, or is released in a parallel fashion to modulate the outcome of the stress response, seems to depend on the context and the type of stressor. Moreover, peripheral and central release of OT does not necessarily coincide (Engelmann et al. 2004). For example,

✉ Julia Winter
julia.winter@ur.de

[1] Department of Behavioral and Molecular Neurobiology, Institute of Zoology, University of Regensburg, Regensburg, Germany

Table 1 Single-cell transcriptional analysis of CRF-positive PVN and type I–III BNST neurons. Numbers in parenthesis represent the total number of CRF-positive neurons. Adapted with kind permission from J. Dabrowska and D. Rainnie (Dabrowska et al. 2013)

CRF neurons (total number)	CRFR1	CRFR2	OT	OTR	AVP	V1AR	V1BR	VGLUT2	GAD67
PVN pc CRF (13)	0	7	10	0	0	0	10	12	0
PVN mc CRF (4)	0	3	3	2	1	0	3	2	0
BNST type I CRF (3)	0	0	0	0	0	1	0	0	3
BNST type II CRF (7)	1	0	2	2	0	0	4	0	7
BNST type III CRF (19)	0	0	0	18	0	0	2	0	19

chronic homotypic stress (repeated restraint) in rats leads to central OT release in the PVN but not into plasma (Babygirija et al. 2012). In humans, OT levels in plasma and saliva increase after psychosocial stress, physical exercise and noise stress (de Jong et al. 2015; Landgraf et al. 1982; Pierrehumbert et al. 2010; Sanders et al. 1990).

Effects of OT on HPA axis function

OT that is released during or immediately after stress participates in the modulation of the stress-induced HPA axis (Neumann 2002; Neumann et al. 2000a, b) (Fig. 1). The influence of OT on the regulation of the HPA axis involves the negative feedback regulation by glucocorticoids (GCs). To understand this effect, it is significant to notice that CRF, as the main regulator of the HPA axis during stress, stimulates the secretion and synthesis of adrenocorticotropic hormone (ACTH). One important part of OT function is its direct and immediate potentiating effect on CRF-induced ACTH secretion (Engelmann et al. 2004; Gibbs 1985, 1986a, b; Gibbs et al. 1984; Lang et al. 1983; Suh et al. 1986). The release of ACTH into the circulation will induce the synthesis and secretion of glucocorticoids (GCs) upon binding to the melanocortin-2-receptor (Mc2r) expressed in the zona fasciculata of the adrenal cortex. GCs cross the blood-brain barrier to bind the GC receptor (GR) in the PVN or hippocampus. The receptor/ligand complex translocates to the neuronal nucleus and binds its responsive element (negative glucocorticoid response element (nGRE), see Fig. 2) in the CRF

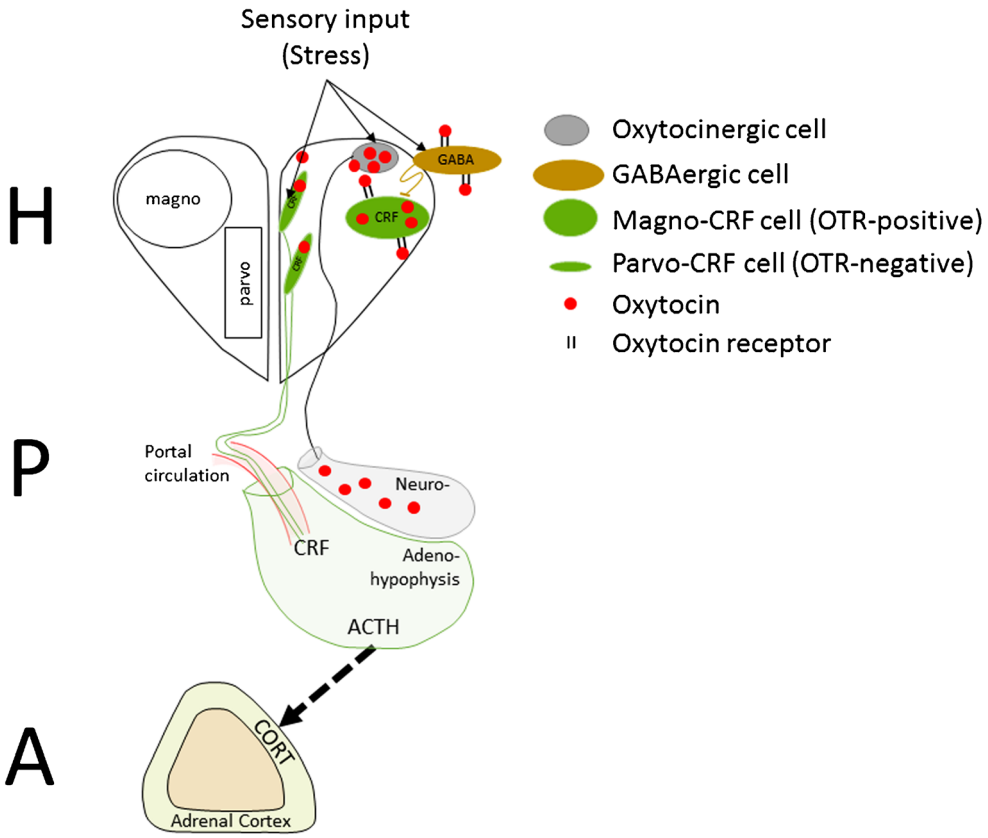

Fig. 1 Direct and indirect effects of OT on activity of CRF neurons during stress. Depending on the type of stressor, intracerebral and/or peripheral OT release occurs, modulating the behavioral and physiological response to a perceived stressor. GABAergic, OTR-positive neurons exert inhibitory effects on CRF neuronal activity. In addition, magnocellular OTR receptor-positive CRF neurons sense OT release and constitute a direct genomic effect on CRF expression within those cells. In contrast, parvocellular OTR-negative CRF cells are not affected by OT release and send axonal projections to the adenohypophysis for peripheral CRF release inducing subsequent full HPA axis activation

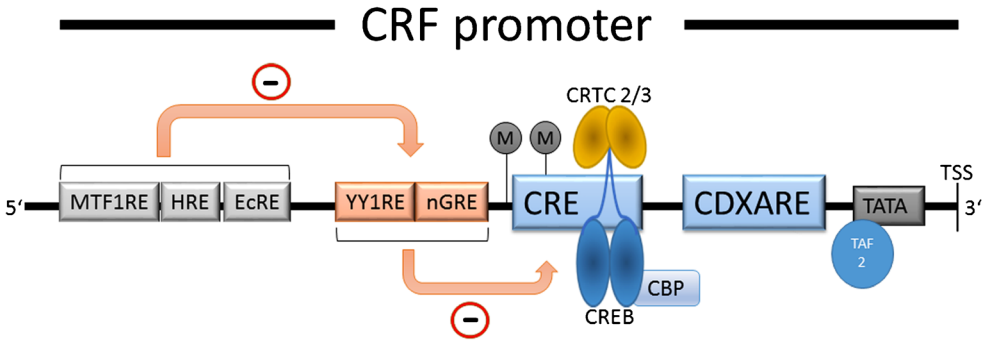

Fig. 2 Regulatory elements within the CRF promoter region. The MTFR, HRE and EcRE disinhibit CRF gene transcription by suppressing the negative elements YY1RE and nGRE. Methylated CpGs within and surrounding the CRE inhibit binding of a transcription initiation complex consisting of CREB, CRTC2/3, CBP and TAF2. RE responsive element, MTFRE metal-responsive transcription factor 1 RE, HRE hybrid steroid RE, EcRE ecdysone RE, YY1RE Ying yang 1 RE, nGRE negative glucocorticoid RE, CRE cyclic AMP RE, CDXARE caudal type homeobox protein RE, TATA TATA box, CREB CRE binding protein, CBP CREB binding protein, CRTC2/3 CREB regulated transcriptional coactivator 2/3, TAF2 TATA box binding protein-associated factor 2, TSS transcription start site, M methylated CpG

promoter. This inhibits the binding of the transcriptional machinery to the CRF promoter, reducing CRF gene transcription (Jeanneteau et al. 2012). Thereby, OT enhances the negative feedback and helps dampen the stress response.

Direct and indirect effects of OT on CRF neuronal activity and gene expression

An OT-induced modulation of the stress response is evident during times when endogenous OT levels are high, as observed during the peripartum period (Hillerer et al. 2011; Johnstone et al. 2000; Neumann et al. 2000b, c; Slattery and Neumann 2008; Windle et al. 2004). This effect can be mimicked by the chronic application of OT via osmotic minipumps for 5 consecutive days to ovariectomized (non-cycling) female rats. The chronic OT application reduced stress-induced corticosterone release in a dose-dependent manner (Windle et al. 1997). In line with the reduced corticosterone levels, CRF neurons in the PVN showed reduced activity, evidenced by lower levels of cFos staining, less CRF mRNA and consequently, lower levels of plasma ACTH (Windle et al. 2004).

As ancillary function, OT release during stress might act as a stress antagonist via social buffering (Smith and Wang 2013). When female monogamous prairie voles were restraint stressed, the presence of their male partner reduced anxiety-like behavior and plasma corticosterone levels during recovery, compared to females that had to recover in social isolation. This effect was mimicked by bilateral intra-PVN infusion of a high dose of OT (100 ng/200 nl/side) in females recovering without their partner. Moreover, the beneficial effect of the partner could be blocked with an OT receptor (OTR) antagonist, proving the role for OT in the reduction of the stress response in a social context (Smith and Wang 2013). When stressed female voles (elevated platform stress) were infused with OT into the PVN before the stress, CRF neuron activation, as indicated by cFos staining, was reduced when compared to VEH-infused females and anxiety-like behavior was reduced (Smith et al. 2016). The mechanism underlying this inhibitory effect involves the inhibitory transmitter GABA. Under resting, non-stressful conditions, CRF neurons are silenced by GABAergic inhibition (Cullinan et al. 2008; Herman et al. 2002). Magnocellular OT neurons make synaptic contacts with parvocellular CRF neurons (Hisano et al. 1992) to reduce the excitability of CRF neurons via the reduction of spontaneous EPSC frequency (Jamieson et al. 2017). This oxytocinergic inhibition results in reduced levels of CRF mRNA in the PVN of rats and voles, which can be blocked by the $GABA_A$ receptor blocker bicuculline (Bulbul et al. 2011; Smith et al. 2016). Consequently, antagonizing GABA receptors in organotypic cultures will lead to increased expression of CRF (Bali and Kovacs 2003; Cullinan 2000; Miklos and Kovacs 2002). Supporting the inhibitory effect of OT are studies showing elevated CRF mRNA levels in stressed OT knockout mice (Nomura et al. 2003) and, as a more physiological example, reduced CRF mRNA levels in the PVN of lactating rodents (Walker et al. 2001).

In addition to the indirect effect of OT via GABA, there is also a direct effect of OT on the CRF gene. We found that OT delays restraint stress-induced CRF expression in the PVN of male rats, mice and human neuronal cells (Jurek et al. 2015). Ninety-seven percent of homology of the CRF promoter region between humans, mice, rats and sheep suggests that the regulation of CRF gene transcription is highly conserved among mammals (King and Nicholson 2007). For instance, the human CRF promoter contains several response elements (RE) that, upon binding of their cognate factors, either activate or repress transcription of the CRF gene (see Fig. 2). There are three elements (metal-responsive transcription factor 1 RE, hybrid steroid RE,

ecdysone RE) that activate gene transcription by inhibiting two repressive elements (Ying Yang RE, (nGRE)). If these repressive elements are inhibited, the cyclic AMP RE (CRE) is free to bind CREB and its co-activators (King and Nicholson 2007). However, methylation of CpGs at the CRE repels CREB from binding and inhibits CRF gene transcription (Chen et al. 2012). In addition, CREB phosphorylation is essential but not sufficient for stress-induced CRF gene transcription. The activation, i.e., dephosphorylation of the co-activators CRTC2 and CRTC3 and their subsequent translocation to the nucleus is necessary for a full transcriptional response (Jurek et al. 2015; Liu et al. 2008, 2011). We have shown that OT regulates CRF gene transcription by modulating the nuclear translocation of CRTC3, without altering CREB or CRTC2 activation. By the exclusive inhibition of CRTC3, OT has a direct influence on CRF gene transcription (Jurek et al. 2015), possibly in addition to the indirect GABAergic inhibition that we described above.

OT-CRF interaction on a cellular level

Possibly, the best argument for a direct interaction of both systems is the expression of OTRs on CRF neurons (Dabrowska et al. 2011), or vice versa, the expression of CRF receptors on OTergic neurons (Arima and Aguilera 2000). Unfortunately, the detection of OTRs is hampered by the lack of rat or mouse-specific antibodies (Jurek and Neumann 2018, Yoshida et al. 2009) and the low OTR expression levels in some brain regions. For instance, in 1994, Freund-Mercier and colleagues were only able to detect the OTR in the PVN of lactating rats after upregulating its expression by pretreatment of the tissue slides with an OTR antagonist (Freund-Mercier et al. 1994). Only recently, the more sensitive technique of single-cell RT PCR was used to characterize magno- and parvocellular neurons of the PVN (Dabrowska et al. 2013) and discovered OTR expression in CRF positive cells, as well as CRF receptor expression in OT positive cells, thereby providing the molecular underpinning of a direct interplay between the two systems (Dabrowska et al. 2013). Interestingly, CRF neurons in the PVN and BNST of rats are not uniform but consist of distinct populations, mainly characterized by their expression profile, electrophysiological properties and morphological phenotype (Chen et al. 2017; Dabrowska et al. 2013; Wamsteeker Cusulin et al. 2013). For instance, parvocellular CRF neurons in the PVN co-express OT but not the OTR, whereas magnocellular PVN neurons co-express CRF, CRFR2, OT and the OTR, allowing those CRF neurons to react to OT release and vice versa (Dabrowska et al. 2013). In the BNST, three different expression profiles of CRF-positive neurons were identified (type I–III), with type III being mostly OTR-positive GABAergic (GAD67) neurons.

OT effects on other members of the CRF system

CRF and the structurally related urocortins interact with two subtypes of G protein-coupled receptors, the CRFR1 and the CRFR2. The availability of unbound, free CRF is regulated by the CRF-binding protein (CRF-BP). The high affinity of the CRF-BP towards CRF suggests a "capturing function" even though the precise function in the brain is still debated (Eckart et al. 2001; Huising et al. 2008; Karolyi et al. 1999). In this context, a semi-direct effect of OT on the CRF system has been identified in the medial prefrontal cortex. In male mice, OTR-expressing interneurons co-express CRF-binding protein (CRF-BP), which in turn keeps CRF from binding the CRFR1 on pyramidal neurons that regulate anxiety-like behavior (Li et al. 2016). Furthermore, CRFR1 activation was shown to be anxiogenic in lactating and virgin female rats, where it also triggered release of OT in the hypothalamic medial preoptic area (Klampfl et al. 2018).

Deletion of the CRFR2 causes an anxiogenic phenotype (Bale et al. 2002; Issler et al. 2014; Kishimoto et al. 2000) and its activity influences anxiety-like behavior in a stress-dependent manner (Bakshi et al. 2002; Kuperman et al. 2010; Todorovic et al. 2007). For example, the activation of CRFR2-positive neurons in the nucleus accumbens of monogamous prairie voles that suffer from partner loss is mainly responsible for the onset of a passive stress-coping phenotype, which can be alleviated by chronic infusion of OT (Bosch et al. 2016).

Another way of influencing anxiety and stress is enabled via a soluble splice variant of the CRFR2 (sCRFR2), which lacks the membrane-binding domain leading to a random distribution of the receptor in the cytoplasm. By reducing the membrane availability of the CRFR2, the splice variant acts as a biological modulator of CRF family ligands (Chen et al. 2005; Evans and Seasholtz 2009). Recently, we were able to facilitate the alternative splicing of the CRFR2 by chronic OT treatment in male rats, leading to a shift of the CRFR2/sCRFR2 equilibrium, reduced CRFR2 membrane expression and ultimately to an anxiogenic phenotype in male rats (Winter et al. 2018, MEF-2A mediates the anxiogenic effect of a chronic central oxytocin infusion via alternative splicing of CRFR2alpha. Molecular Psychiatry, in preparation).

Summary

The majority of studies investigating the effects of OT on the CRF system concluded that OT has a mostly ameliorating effect on the stress response. The transcriptome of specific cell types within the PVN and BNST indicate a reciprocal interplay between the OT and CRF systems, adding a direct genomic effect of OT on CRF gene expression to the indirect cellular inhibition via GABAergic interneurons.

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