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Review article

The neuroanatomic complexity of the CRF and DA systems and their interface: What we still don't know

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ABSTRACT

Corticotropin-releasing factor (CRF) is a neuropeptide that mediates the stress response. Long known to contribute to regulation of the adrenal stress response initiated in the hypothalamic-pituitary axis (HPA), a complex pattern of extrahypothalamic CRF expression is also described in rodents and primates. Cross-talk between the CRF and midbrain dopamine (DA) systems links the stress response to DA regulation. Classically CRF + cells in the extended amygdala and paraventricular nucleus (PVN) are considered the main source of this input, principally targeting the ventral tegmental area (VTA). However, the anatomic complexity of both the DA and CRF system has been increasingly elaborated in the last decade. The DA neurons are now recognized as having diverse molecular, connectional and physiologic properties, predicted by their anatomic location. At the same time, the broad distribution of CRF cells in the brain has been increasingly delineated using different species and techniques. Here, we review updated information on both CRF localization and newer conceptualizations of the DA system to reconsider the CRF-DA interface.

1. 36 years later: ongoing challenges in localizing CRF in the CNS

Corticotropin-releasing factor (CRF) (also known as corticotropin releasing hormone, CRH) is a 41-amino acid peptide that was first isolated in 1981 (Swanson et al., 1983; Vale et al., 1981) in the rat hypothalamus. CRF, along with a family of CRF-related peptides, plays a role in acute and prolonged stress responses by integrating endocrine, autonomic and neural systems to promote adaptation in mammals (Burchfield, 1979; Herman and Cullinan, 1997; Ronan and Summers, 2011; Sawchenko et al., 1993). As the seat of the hypothalamic-pituitary (HPA) axis, CRF containing neurons localized in the hypothalamic paraventricular nucleus (PVN) send projections into median eminence. The median eminence is enriched with many small capillary loops from the superior hypophyseal artery, and CRF diffuses into this capillary bed, which in turn drains into sinusoids, and the venous system of the anterior pituitary. Here, CRF stimulates 'corticotropes', which release adrenocorticotropin hormone (ACTH) into the general circulation, stimulating the synthesis and release of glucocorticoids from the adrenal cortex (Antoni et al., 1983; Rivier and Plotsky, 1986). Glucocorticoid increases promote several adaptive responses including gluconeogenesis and temporary suppression of the immune system to support 'fight or flight' energy demands. Rising glucocorticoids eventually exert negative feedback inhibition on CRF-expressing cells in the PVN, downregulating CRF mRNA, and closing the HPA functional loop.

CRF is also synthesized and released at extrahypothalamic sites, exerting a direct neuroregulatory effect over brain structures involved in stress-sensitive function. Non-HPA axis CRF was initially identified as a putative neurotransmitter, but is now considered a 'neuroregulator', and is always expressed in concert with a primary transmitter (e.g. glutamate or GABA) (Gallagher et al., 2008; Joels and Baram, 2009; Orozco-Cabal et al., 2006). While neurotransmitter activity elicits fast acting changes in membrane potential, the conventional view has been that physiological concentrations of CRF do not induce a membrane potential change (Gallagher et al., 2008). Recent work indicates that endogenous CRF binds post-synaptic membrane receptors to influence the excitatory/inhibitory function of neuronal networks and the resultant effects depend upon stress duration (Gunn and Baram, 2017; Gunn et al., 2017; Radulovic et al., 1999).

The monoamine system, which includes the serotonin, norepinephrine and dopamine (DA) systems, is a key target of CRF innervation, providing a link between stress and monoamine function (Joels and Baram, 2009; Mejias-Aponte et al., 2009; Reyes et al., 2005; Rodaros et al., 2007). Because the monoamine transmitters have all been therapeutic targets for psychiatric illnesses (Chiodo and Bunney,

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1983; Creese et al., 1976; Leonard, 1997; Van Praag, 1977), the ways in which CRF influences them has long been a focus of pharmacologic research (Tilders and Berkenbosch, 1986). While extensive research has focused on CRF-norepinephrine interactions during stress (Dunn and Swiergiel, 2008; Koob, 1999; Valentino and Van Bockstaele, 2008), the midbrain DA neurons also play a central role in acute and chronic stress responses (Holly and Miczek, 2016; Mantsch et al., 2016; Spanagel and Weiss, 1999). Stress-induced DA dysfunction is an important mechanism associated with drug-seeking (Koob and Volkow, 2010), loss of motivational tone in mood disorders, and psychotic symptoms in both mood disorders and schizophrenia (Weinstein et al., 2017; Yadid and Friedman, 2008).

The midbrain DA system is more diverse than previously recognized, with neurochemical, connectional, and physiologic diversity not originally imagined (Barker et al., 2016; Haber et al., 2000; Lammel et al., 2011, 2014; Lerner et al., 2015; Margolis et al., 2008). Specific DA subpopulations, rather than a homogenous cluster of DA cells, are regulated by specific combinations of afferent systems to influence distinct output paths (Geisler and Zahm, 2005; Watabe-Uchida et al., 2012). DA neurons were initially discovered to code prediction errors that support appetitive approach behaviors (Kobayashi and Schultz, 2008; Schultz et al., 1993). However, it is now known that some DA neurons signal the biologic relevance (salience) of both reward and non-reward predicting stimuli, emitting a general 'salience' signal that may be more involved in orienting or preparatory strategies to confront new or uncertain cues (Brischoux et al., 2009; Bromberg-Martin et al., 2010; Horvitz, 2000; Matsumoto and Hikosaka, 2009; Matsumoto and Takada, 2013; Pignatelli and Bonci, 2015; Volman et al., 2013). These divergent physiologic responses of the DA cells tend to map topographically such that more rostromedially located DA cells (in the region of the ventral tegmental area (VTA) code reward prediction error, and more dorsolaterally and caudally located DA cells are involved in 'salience coding'. CRF influences across the ventral midbrain DA neurons may therefore have different consequences for behavior depending on the specific DA subpopulations involved.

In this review, we first briefly revisit the well-known physiologic interface between the CRF and DA system, which has been a long-standing focus of research on addiction and other stress-mediated disorders (Deutch et al., 1987; Deutch and Roth, 1990; Kalivas, 1985; Koob and Volkow, 2010; Mantsch et al., 2016; Meloni et al., 2006). We then review and update information on localization of CRF neurons across species, including primates. Finally, we discuss new information on the organization and circuit heterogeneity of DA subpopulations and their possible differential regulation by specific CRF paths.

2. What is the functional role of CRF in the ventral midbrain?

In the ventral midbrain, pharmacologic and physiologic studies have focused almost exclusively on CRF actions in the VTA subregion because of its established connections with the 'limbic' forebrain, i.e. the ventral striatum and medial prefrontal cortex (Bardo et al., 1996). The VTA constitutes a complex group of DA neurons that are primarily regulated through glutamatergic innervation, resulting in both short- and long-term changes in dopaminergic activity (Bonci and Malenka, 1999). CRF is thought to have an excitatory role, inducing a potentiation of NMDAR (*N*-methyl-D-aspartate-receptor)-mediated synaptic transmission in DA neurons (Ungless et al., 2003) resulting in glutamate release and dopaminergic activation (Korotkova et al., 2006; Wise and Morales, 2010). Both pharmacologic (Wang et al., 2007) and electrophysiologic (Ungless et al., 2003) data suggest that an association between CRF and the CRF binding protein (CRF-BP) is necessary to elicit this response. CRF may signal through the CRF type-2 receptor (CRFR2) as CRF activity is blunted in the presence of CRFR2 but not CRF typ-1 receptor (CRFR1) antagonists (Ungless et al., 2003; Wang and Morales, 2008). However, CRF has a higher affinity for CRFR1 than CRFR2 (Lovenberg et al., 1995) and CRFR2 expression in VTA has been difficult to resolve (Van Pett et al., 2000; Wise and Morales, 2010). CRFR1 mRNA, however, has been found in VTA and localized in dopaminergic neurons (Tagliaferro et al., unpublished observations). Interestingly, following repeated cocaine exposure, CRF enhancement of NMDAR EPSCs was shown to involve both CRFR1 and CRFR2 that appeared to work in concert to amplify specific responses in the VTA (Hahn et al., 2009). Therefore, precise CRF-glutamate-dopamine interactions in the VTA remain unresolved and may suggest multiple signaling mechanisms involving either CRFR1 or CRFR2 or both (reviewed in, Wise and Morales, 2010).

From an anatomic perspective, CRF-positive fibers form both excitatory and inhibitory synapses in the VTA. DA cells receive CRF-positive synapses that are mostly asymmetric (glutamatergic) (Tagliaferro and Morales, 2008; Wang et al., 2005), while non-dopaminergic VTA neurons receive both asymmetric and symmetric (inhibitory) contacts from CRF-labeled terminals.

In rodents, the VTA receives CRF-containing afferents from lateral bed nucleus of stria terminalis (BSTL), the central nucleus of the amygdala (CeN), and the paraventricular nucleus of the hypothalamus (PVN) (Dabrowska et al., 2016; Rodaros et al., 2007). CRF innervation of other DA subregions has generally been ignored. However, recently, Dabrowska et al. (2016) used genetic approaches in mice and rats to show that CRF synthesizing cells in the BSTL send relatively more intense fiber labeling over the substantia nigra pars compacta compared to the VTA. To examine the situation in nonhuman primates, we recently investigated inputs from the BSTL and CeN to the ventral midbrain in the monkey, and also found a relatively dense input to the dorsolateral substantia nigra and retrorubral field, but a relatively light input from these structures to the classic VTA. This topography is similar to previous findings in rats (Gonzales and Chesselet, 1990; Wallace et al., 1992; Zahm et al., 2011) and monkeys (Fig. 1; Price and Amaral, 1981). When examined with double-labeling experiments, retrograde tracer injections placed in these more lateral and caudal DA subpopulations resulted in many labeled cells in the BSTL and CeN that co-contained CRF (Fudge et al., 2017). This prompted two questions: 1) what might be the role of CRF in DA cells outside the VTA? and, 2) Are more diverse sources of CRF responsible for DA modulation (Yadid and Friedman, 2008)—particularly in the VTA—and if so, which ones? In other words, is the diversity of CRF inputs to the midbrain DA neurons greater than previously recognized? We revisited literature from mice, rats, monkeys, and human to ascertain the locations of CRF-containing neural populations throughout the brain, consider potential species differences, and uncover possible unexplored sources of CRF to specific DA subpopulations.

3. Sources of CRF-positive cells in mice, rats, monkeys, and humans

3.1. Technical issues

Since its isolation in 1981 (Vale et al., 1981), and the generation of specific antiserum to synthetic ovine CRF, numerous immunocytochemical studies have been conducted to document the distribution of CRF-immunoreactive (CRF-IR) neurons and fibers in the brain (Cummings et al., 1983; Fellmann et al., 1984; Joseph and Knigge, 1983; Merchenthaler et al., 1982, 1984; Olschowka et al., 1982; Sakanaka et al., 1986; Swanson et al., 1983; Wang et al., 2011). However, detection of CRF-containing neurons has been, and remains, challenging.

3.1.1. Protein detection with immunocytochemistry

One obstacle in CRF detection is cross-reactivity of antibodies for CRF with urocortin, a structurally related protein (Donaldson et al., 1996) and the melanin-concentrating hormone precursor (Nahon et al., 1989). Another issue is that CRF-binding protein (CRF-BP), which is not uniformly present in all CRF-positive cells, may mute CRF