LINK TO ORIGINAL ARTICLE

CRF and the nucleus incertus: a node for integration of stress signals

Leigh C. Walker and Andrew J. Lawrence

We recently read with interest the timely and scholarly Review by Henckens *et al.* (Region-specific roles of the corticotropin-releasing factor–urocortin system in stress. *Nat. Rev. Neurosci.* **17**, 636–651 (2016))[1] on the region-specific actions of the corticotropin-releasing factor (CRF)–urocortin system in stress neurobiology. However, we note an inadvertent but important omission: a role for CRF signalling in the nucleus incertus.

The nucleus incertus (NI; also known as the 'nucleus O') is located in the pons, below the fourth ventricle[2]. This highly conserved structure consists mainly of GABAergic projection neurons, innervates many forebrain regions[3] and has been implicated in various behaviours including arousal and responses to stress[2,4]. NI neurons express CRF receptor type 1 (CRFR1) protein and mRNA in abundance[5], and electrophysiological characterization *in vitro* and *in vivo* has revealed that CRF depolarizes NI cells via postsynaptic CRFR1 in a long-lasting and non-desensitizing manner[6]. Substantial evidence confirms the importance of CRF signalling in the NI in relation to various stress-related disorders, such as anxiety (reviewed in REFS 2,7).

Central infusion of CRF, or exposure to neurogenic stressors (including behavioural or pharmacological stressors), directly or indirectly activates NI neurons[4]. Electrolytic lesioning of the NI[8] and selective ablation of CRFR1-positive NI neurons using CRF–saporin[9] cause deficits in fear extinction without impairing initial conditioning. Moreover, selective pharmacogenetic activation of NI neurons causes enhanced arousal, locomotion, vigilance and active responding behaviours during fear conditioning[10]. CRF infusion into, or electrical stimulation of, the NI impairs long-term potentiation (LTP) of hippocampal–medial prefrontal cortical synapses[11], whereas intra-NI infusion of the CRFR1 antagonist antalarmin reversed stress-induced suppression of LTP in this pathway[12]. Intra-NI infusion of the CRFR1 antagonist CP-376395, but not the CRFR2 antagonist astressin 2B, considerably reduced the reinstatement of alcohol seeking in rats that was induced by administration of the pharmacological stressor yohimbine[13] — an effect that is probably mediated by CRFR1 activation of relaxin-3-positive NI neurons[6,14]. The NI is therefore a stress-responsive nucleus and, through CRFR1, contributes to memory and learning, stress-induced reward seeking, impairments in neuronal plasticity, and arousal behaviours[9–13].

The lateral preoptic area sends CRF-containing projections to the NI[6]; however, other CRF-positive regions that do the same require further clarification. Given the close proximity of the NI to the fourth ventricle, CRF may activate NI neurons through volume transmission from the cerebrospinal fluid[15]. Furthermore, it has recently been discovered that *Crf* mRNA and CRF protein are expressed in the rodent NI[13], therefore, CRF release intrinsic to the NI cannot be ruled out, although the phenotype and function of these CRF-positive cells require elucidation.

In conclusion, there is substantial evidence that CRF signalling in the NI has relevant neurophysiological implications. Research into neuropsychiatric disorders should also investigate pathways and regions such as the NI that integrate relevant behavioural repertoires. This may lead to a broader understanding of brain networks acting in dysregulated states and could assist in the identification of potential therapeutic targets in anxiety, substance abuse and other neuropsychiatric disorders.

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Competing interests statement
The authors declare no competing interests.