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Commentary

Relevance of both type-1 and type-2 corticotropin releasing factor receptors in stress-induced relapse to cocaine seeking behaviour

Katia Gysling *

Millennium Science Nucleus in Stress and Addiction and Department of Cell and Molecular Biology, Faculty of Biological Sciences, Pontificia Universidad Católica de Chile, Santiago, Chile

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ABSTRACT

The essential role of corticotropin releasing factor (CRF) and its type-1 receptor (CRF1) in stress-induced relapse to drug seeking has been demonstrated. The bed nucleus of the stria terminalis is the major anatomical substrate for this CRF/CRF1 receptor action. More recently, the role of type-2 CRF (CRF2) receptors in stress-induced relapse to cocaine seeking has also has been documented. The ventral tegmental area is the anatomical substrate for this CRF/CRF2 receptor action. The new information involving CRF2 receptors in stress-induced relapse to cocaine seeking has generated a need for a reappraisal of the existing anatomical and pharmacological evidence that have been used to support the critical role of CRF1 receptors. The role of CRF2 receptors in stress-induced relapse to drug seeking also opens the question of the putative role of the other peptides of the CRH family (urocotin-1, urocortin-2 and urocortin-3) that have high affinity for CRF2 receptors. In this commentary, the available evidence supporting the role of both CRF1 and CRF2 receptors in stress-induced relapse to drug seeking is reviewed.

1. Introduction

Addiction is a life-long condition in which individuals show an intense drug craving and a high risk of relapse even after years of drug abstinence [reviewed in 1,2]. A major goal of successful treatment of addiction is being able to prevent craving, seeking and relapse [3,4]. Persistent molecular changes, associated with chronic drug consumption and abstinence, are believed to mediate craving and relapse to drug use [5,6]. In both human addicts and in animal models of addictive behaviour the relapse to drug seeking has been shown to be precipitated by the exposure to three distinct types of stimuli: (a) stress; (b) environmental cues associated with the drug experience and (c) the drug itself [7].

Over the last few years there have been promising advances in the understanding of addiction; however, the mechanisms by which stress enhances drug use and triggers relapse remain elusive [8,9]. On one hand, drug addiction is related to the reward system which is centered in dopaminergic neurons located in the ventral tegmental area (VTA) that innervate several interconnected nuclei such as the nucleus accumbens (NAcc), lateral septum, bed nucleus of the stria terminalis (BNST), amygdala, lateral hypothalamus (LH) and prefrontal cortex (PFC). All drugs of abuse activate, directly or indirectly, the dopaminergic neurons and increase the release of dopamine in the NAcc [10]. On the other hand, the stress response is related to the brain corticotropin releasing factor (CRF) system. At present, the mammalian CRF system is composed of four peptides, CRF, urocortin-1, urocortin-2 and urocortin-3, originated from independent genes; a binding protein with high affinity for CRF (CRF-BP) and urocortin-1, and two receptors CRF1 and CRF2 [reviewed in 11]. CRF and urocortin-1 have high affinity for both CRF receptors. In contrast, urocortin-2 and urocortin-3 have high affinity only for CRF2 receptors.

Anatomically, there is significant overlap between brain nuclei involved in stress response and in addiction [8,12,13]. Compelling evidence indicates that the CRF system is responsible for connecting stress and addiction [8,14,15]. Even though several studies have focussed on understanding the molecular and neurochemical mechanisms by which the CRF system determines stress-induced relapse to drug seeking, these phenomena are still only partially understood [9,16–18].

2. Role of CRF1 receptors in the BNST in stress-induced relapse to cocaine seeking

The seminal work of Stewart and co-workers [19] showed that rats that have extinguished their auto-administration of different drugs of abuse relapse to drug-seeking behaviour when exposed to footshock, even after a 4–6 week drug-free period and this relapse

* Tel.: +56 2 3542654; fax: +56 2 3542660.
E-mail address: kgysling@bio.puc.cl.

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depends on the CRF system. The CRF-dependence of stress-induced relapse to drug seeking was shown by administering systemically CP-154,526, a selective CRF1 receptor antagonist or intra cerebroventricularly D-Phe CRF12-41, a non-selective CRF1/CRF2 antagonist [20]. Both antagonists blocked the relapse induced by exposure to footshock. However, the same treatment only attenuated relapse to cocaine seeking induced by a priming dose of cocaine suggesting that different or partially different mechanisms underlie drug priming and stress-induced relapse to drug seeking, consistent with the different brain subcircuits related to these distinct types of relapse initiators [13]. In addition, by infusing D-Phe CRF12-41 directly into the BNST, Erb and Stewart [21] showed the critical role of this nucleus in stress-induced relapse to drug seeking behaviour. Other groups have added valuable information showing that CRF/CRF1 receptors in the BNST mediate stress-induced relapse to other drugs of abuse as well [22–25].

3. Role of CRF2 receptors in the VTA in stress-induced relapse to cocaine seeking

In 2005, the laboratory of Roy Wise [26] showed that CRF is released in the VTA after exposure to footshock in naïve rats and in cocaine-experienced rats. Furthermore, they showed that this released CRF is responsible for inducing relapse to cocaine seeking due to a CRF-dependent sensitization of VTA glutamate release observed only in cocaine-experienced rats. At the time of these findings, the origin of VTA CRF was not known. Interestingly, it was later shown that CRF in the VTA originates from the BNST, central nucleus of the amygdala (CeA) and the paraventricular nucleus of the hypothalamus [27]. This evidence suggests that the regulation exerted by CRF in the VTA is downstream of the effect of CRF/CRF1 receptors in the BNST. This is also consistent with the circuitry responsible for stress-induced relapse revealed by McFarland and co-workers [23] by means of the reversible inactivation of different brain nuclei with muscimol/baclofen. These authors suggested that footshock stress activates subregions of the central extended amygdala that, via the VTA, activates motor output circuitry responsible for reinstalling drug-seeking behaviour. In addition, using double labelling and electron microscopy, it has been shown that VTA CRF is present mainly in VTA glutamatergic axon terminals that establish glutamatergic synapses onto VTA neurons; although some symmetric inhibitory synapses were also observed [28]. However, the precise origin of these VTA CRF/Glutamate and CRF/GABA axon terminals is presently unknown.

CRF has been shown to coexist with GABA in neurons of the lateral CeA and dorsal part of the BNST [29] but it is not known whether these GABAergic neurons project out of the extended amygdala. In addition, there is some discrepancy in the literature regarding the putative excitatory innervation from the BNST to the VTA. On one hand, based on electrophysiological and tracing studies, it has been proposed that glutamatergic projections from the BNST to VTA exist [30,31]. On the other hand, the group of Daniel Zahm [32] using a rigorous anatomical approach has performed a semi-quantitative analysis of the multiple origins of VTA glutamatergic innervation. They have shown that about 20% of VTA glutamate originates from the cortex and the remainder from several subcortical nuclei. However, the BNST was not shown to be a relevant subcortical origin of VTA glutamate [32]. More recent evidence from the same group [33] reveals that the BNST innervates dopaminergic neurons located in the retrorubral field (A8 dopaminergic group) and not in the VTA. Further studies should resolve the apparent contradictions regarding the connectivity between the extended amygdala and the VTA. An important feature of the CRF-dependent sensitization of VTA glutamate release observed in cocaine-experience rats is that it is long-lasting and comparable at either 1 or 21 days after cocaine withdrawal [26]. It is tempting to suggest that this neuroadaptation is associated to what it has been called "the end-stage of addiction" [3] in which vulnerability to relapse becomes more permanent.

Another breakthrough towards the understanding of the mechanisms responsible for stress-induced relapse to drug seeking behaviour is the evidence published by the group of Wise [34] in which they show that the activation of VTA CRF2 and not CRF1 receptors is responsible for stress-mediated relapse to cocaine seeking. This data has been surprising [17,35,36] as previous studies have discarded the participation of CRF2 receptors in stress-induced relapse to drug seeking [37]. The evidence to discard the role of CRF2 receptors was obtained by administering 1 and 10 μg AS-30 intra cerebroventricularly, a CRF2 receptor selective peptide antagonist [37]. Caution should be taken when interpreting these results as no positive control was used to prove that enough AS-30 was effectively reaching the VTA under the conditions used or that it selectively blocked CRF2 receptors in vivo. Recently, it was shown that it was necessary to inject at least 20 μg of AS-30 into the lateral ventricle to observe the effect of AS-30 upon submissive defensive behaviour [38], supporting the possibility that the amount of AS-30 used by Lu et al. [37] was not sufficient. A similar approach to discard the participation of CRF2 receptors was undertaken in the work of Bruijnzeel et al. [25]. In this case, astressin-B, another peptide antagonist of the CRF2 receptor was used by intra cerebroventricular administration without controlling for the effectiveness of this type of injection. It is well known that compounds injected into the lateral ventricle diffuse heterogeneously to different brain regions and can diffuse unevenly to each hemisphere. In this regard, the reverse perfusion of a CRF2 receptor antagonist through a microdialysis probe directly installed in the VTA, as performed by Wang et al. [34] is a more reliable strategy. Hopefully, in the near future it will be possible to utilize non-peptide CRF2 receptor antagonists that cross the blood brain barrier and/or diffuse more readily through the ventricles to provide more definitive proof that CRF acts through CRF2 receptors in the VTA to transduce cocaine-dependence related phenomenon.

The second observation that has been used to argue against a role of VTA CRF2 receptors in stress-induced relapse to cocaine seeking it is the known distribution of CRF1 and CRF2 receptors. Specifically, no CRF2 receptor mRNA is detected in the VTA by *in situ* hybridization [39,40]. The only report that has shown expression of CRF2 receptors in the VTA used single cell RT-PCT to quantify CRF2 receptor mRNA in dopaminergic VTA neurons [41]. However, the results of Wang et al. [34] can be nicely explained by the presence of CRF2 receptors in VTA glutamatergic nerve terminals originating in neurons outside the VTA. VTA glutamatergic afferents originate from several cortical and subcortical brain regions [32], some of which express CRF2 receptor mRNA [40]. We have observed the presence of CRF2 receptors in VTA glutamatergic nerve terminals of subcortical origin [42] using immunofluorescence with antibody against CRF2 receptors in VTA synaptosomes devoid of postsynaptic elements [43].

CRF-dependent sensitization of VTA glutamate release after repeated administration of cocaine has also been documented in an electrophysiological study recording from glutamatergic synapses in VTA containing slices from mice repeatedly treated with cocaine [44]. In this case, both pre and postsynaptic modifications were reported. However, the CRF receptor type involved in presynaptic modifications was not analyzed further. Interestingly, a non-contingent administration of cocaine was used suggesting that the CRF-mediated sensitization of VTA glutamate release reported in cocaine-experienced rats [26,34] is not related to the contingency of the auto-administration process, but to the repeated presence of cocaine itself.

4. Possible role of CRF-BP in CRF/CRF2 receptor actions in the VTA

An intriguing feature of the pre and postsynaptic processes at the level of the VTA that have been shown to be mediated by CRF2 receptors [9,34] is that they are exerted only by agonists with high affinity for both CRF2 receptors and CRF-BP. The four endogenous peptides of the CRF system have high affinity for CRF2 receptors, but only CRF and urocortin-1 have high affinity for CRF-BP. Thus, CRF and/or urocortin-1 could be acting in the VTA. It is important to note that urocortin-1 is expressed in VTA dopaminergic neurons [45]. It has also been shown that CRF-BP is expressed in a subset of VTA dopaminergic neurons [46]. Our recent report [47] showing that CRF-BP readily enters the regulated secretory pathway in neuronal and endocrine cells suggests that the regulation of CRF-BP release from nerve terminals/dendrites of CRF-BP containing neurons may be an additional factor that should be considered in further studies. Interestingly, CRF-BP has been linked to alcoholism in human genetic studies [48–50].

5. How does footshock activate CRF-mediated transmission in the extended amygdala?

The BNST is the brain region with the highest concentration of noradrenaline in the brain [51] especially in its most anterior pole [52]. This rich noradrenergic innervation to the BNST originates mainly from A1 ventrolateral medulla (VML) and A2 hindbrain noradrenergic nuclei [53,54]. The CeA also receives noradrenergic innervation from the A1 noradrenergic nucleus [53]. Several studies have shown that exposure to fear-related stimuli activate these noradrenergic neurons [55,56]. The neurochemical consequences of increasing noradrenaline levels in the BNST have led us to propose that the BNST plays a key role relaying and integrating limbic and autonomic information related to stress responses [57]. Recently, Rinaman [58] has thoroughly reviewed existing evidence showing the role of A2 noradrenergic neurons in physiological processes that once imbalanced could account for pathological processes such as drug addiction.

The activation of α2-adrenergic receptors decreases electrical [59] and K+-induced release of noradrenaline in the BNST [60–62]. Interestingly, it has been shown that systemic administration of clonidine, a selective α2-adrenergic agonist attenuates stress- but not cocaine-induced relapse to cocaine seeking [63]. This observation was also extended to stress-induced relapse to heroin-seeking [64] suggesting the existence of a common mechanism explaining stress-induced relapse to addictive drugs. A functional interaction between noradrenaline and CRF has been shown, and that CRF acts downstream of noradrenaline [65]. Noradrenaline increases GABA-IPSCs in the BNST [66] and it was suggested that this was due to noradrenaline-induced depolarization of local GABA neurons that could in turn control BNST output neurons innervating the VTA. However, this hypothesis awaits further clarification of the differences in the existing anatomical evidence regarding the innervation between the extended amygdala and the VTA [33].

6. Conclusions

New and exciting evidence supports the proposal that both CRF1 and CRF2 receptors play a relevant role in CRF-dependent neuroadaptations determining stress-induced relapse to drug seeking behaviour. Fig. 1 depicts the basic neuronal circuit involved in stress-induced relapse to drug seeking. Most of the available evidence supporting the existence of this circuit has been obtained in cocaine experienced rats. However, there is evidence to suggest that this may be a general circuit associated with stress-induced relapse to most drugs of abuse. As shown in Fig. 1, stressful stimuli such as footshock activate noradrenergic neurons in the brain stem A1 (ventrolateral medulla, VLM) and A2 (nucleus of the solitary tract, NTS) noradrenergic neuronal groups. A1 noradrenergic neurons have axon collaterals innervating the BNST and the CeA [53]. Thus, the activation of these neurons impacts the neuronal activity of both subnuclei of the extended amygdala. It has been shown that noradrenaline increases the activity of CeA CRF neurons that innervate the BNST. Thus, CRF is released in the BNST by the activation of CeA neurons and by the direct action of noradrenaline in the BNST. The precise mechanisms by which noradrenaline activates the release of BNST CRF is unknown. It is proposed that released CRF activates BNST CRF containing neurons projecting to the VTA by acting on CRF1 receptors. As a result of this activation, CRF is released in the VTA. An alternative pathway could be an indirect connection with the VTA through the lateral hypothalamus and/or the pedunculopontine nucleus (PPT) [32,67]. In cocaine-experienced rats, but not in naïve rats, the CRF released in the VTA induces VTA glutamate release by activating CRF2 receptors located presynaptically in glutamatergic nerve terminals. As shown [26,34] this VTA glutamate sensitization leads to the activation of VTA dopaminergic neurons. As a result of this dopaminergic activation, increases in the activity of the prefrontal cortex, via the nucleus accumbens core, trigger motor behaviour and relapse to drug seeking [12,13].

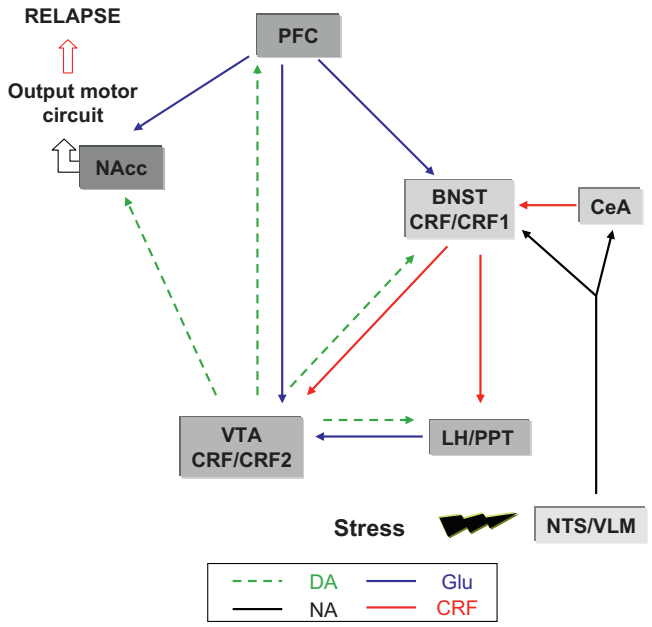

Fig. 1. Basic circuitry involved in stress-induced relapse to drug-seeking behaviour. NTS: nucleus of the solitary tract; VLM: ventrolateral medulla; CeA: central nucleus of the amygdala; BNST: bed nucleus of the stria terminalis; LH: lateral hypothalamus; PPT: pedunculopontine nucleus; VTA: ventral tegmental area; NAcc: nucleus accumbens; PFC: prefrontal cortex.

A better understanding of the plastic changes induced by repeated cocaine exposure leading to the sensitization of VTA glutamate release mediated by CRF2 receptors should help in the search for new pharmacological approaches to prevent stress-induced relapse to drug seeking.

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