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A ventral tegmental CRF-glutamate-dopamine interaction in addiction

Roy A. Wise and Marisela Morales

Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, 251 Bayview Boulevard, Baltimore MD 21224

Abstract

Stress-induced reinstatement of cocaine-seeking is blocked by antagonists for the stress-related neurohormone corticotropin-releasing factor (CRF). One site of this action is the ventral tegmental area (VTA), where mild footshock stress causes CRF release, glutamate release, and dopaminergic activation in cocaine-experienced animals. Infusion of CRF into the VTA has similar effects to footshock and these effects of footshock and VTA CRF are blocked by VTA infusions of CRF antagonists. The reinstatement, glutamate release, and dopamine release are prevented by VTA infusions of CRF-receptor 2 (CRF-R2) but not CRF-R1 antagonists; however, reinstatement is triggered by some but not all CRF-R2 agonists and some but not all CRF-R1 agonists. The common denominator of the effective agonists is that they each bind to the CRF-binding protein (CRF-BP), which appears to be essential for the behavioral and local neurochemical effects of stress and CRF. In cocaine-naïve animals, electron microscopy reveals primarily asymmetric synapses between a subset of VTA terminals containing glutamate and CRF and a subset of VTA dopaminergic neurons and *in situ* hybridization reveals mRNA for CRF-R1 and CRF-BP but not CRF-R2 in a subset of VTA dopamine neurons. While these anatomical findings are in all probability relevant to the interactions of stress and the dopamine system in cocaine-naïve animals, studies in progress focus on modifications of VTA circuitry that differentiate the cocaine-experienced from the cocaine-naïve animal and explain the experience-dependent control by CRF of VTA glutamate release and cocaine-seeking behavior.

The first stage of cocaine addiction is the formation of cocaine-taking and cocaine-seeking habits that become compulsive almost immediately and, if unhampered by restricted drug access, lead inexorably to death in laboratory rats and monkeys (Bozarth and Wise, 1985; Johanson et al., 1976). Such habits can be modeled in rodents, without deterioration of the animals' health if daily drug intake is limited, in our case, to four hours per day. Under these conditions, rats learn—often on the first day of exposure—to lever-press for intravenous cocaine. Within a week or two of testing their cocaine intake stabilizes at a rate of about 10–12 mg/kg/hour, a rate of drug consumption that is defended over a broad range of response requirements or doses per injection (Pickens and Thompson, 1968). Following two weeks of training it takes about three weeks of daily 4h extinction sessions—sessions where lever-pressing no longer earns rewarding cocaine but rather now earns non-rewarding saline—before response rates drop back to their infrequent pre-training incidence.

Corresponding Author: Roy A. Wise, Intramural Research Program, National Institute on Drug Abuse, 251 Bayview Boulevard, Baltimore MD 21224, tel: 443-740-2460, fax: 443-740-2827, rwise@intr.nida.nih.gov.

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Even following such extinction training, vigorous responding can be reinstated by “priming” injections of the drug (Gerber and Stretch, 1975), by cocaine-predictive cues (Meil and See, 1996) or by mild footshock stress (Erb et al., 1996). Reinstatement by stress has been of particular interest because of the presumed role of stress in human drug taking. Stress-induced reinstatement of cocaine seeking appears to involve the stress-associated neurohormone CRF, as it is blocked by CRF antagonists injected into the cerebral ventricles (Erb et al., 1998) or into the bed nucleus of the stria terminalis (Erb and Stewart, 1999). The attention of our groups was drawn to the possibility that CRF might have important addiction-related actions in the VTA because the mesocorticolimbic dopamine system is implicated in both responsiveness to stress (Deutch et al., 1991; Thierry et al., 1976) and in cocaine self-administration (Roberts et al., 1977), because CRF-containing axons and varicosities had been identified in the VTA (Swanson et al., 1983), because CRF was known to have behavioral actions when administered in the VTA (Kalivas et al., 1987), and because the Bonci group had recently demonstrated an interaction of CRF with glutamate-induced excitatory responses of VTA dopamine neurons (Saal et al., 2003; Ungless et al., 2001; Ungless et al., 2003).

The Bonci group reported first that a single prior exposure to cocaine (Ungless et al., 2001) or to stress, amphetamine, morphine, nicotine or ethanol (Saal et al., 2003) could cause long-lasting potentiation of glutamatergic activation of midbrain dopamine neurons in a VTA slice preparation; this potentiation resembled the long-term potentiation caused by direct electrical stimulation of excitatory inputs to VTA dopamine neurons. They further found that bath application of CRF potentiates NMDA-R (*N*-methyl-*D*-aspartate-receptor)-mediated excitatory postsynaptic currents in VTA dopamine neurons, and that this potentiation was blocked by CRF-R2 but not CRF-R1 antagonists (Ungless et al., 2003). This finding was surprising because CRF has high affinity for CRF-R1 and low affinity for CRF-R2 (Lovenberg et al., 1995), and because mRNA for CRF-R2 had not been identified in VTA by in situ hybridization (Van Pett et al., 2000). However, single-cell RT-PCR suggested that CRF-R2 was expressed in VTA dopamine neurons (Ungless et al., 2003). Potentiation of NMDA currents by CRF was not seen when CRF was applied with the CRF fragment CRF₆₋₃₃, a fragment that competes with CRF in binding to a CRF-binding protein (CRF-BP), and that, in other preparations, increases the free concentration and effects of CRF (Behan et al., 1995b; Heinrichs et al., 1996; Jahn et al., 2002). The loss of CRF effectiveness when co-applied with CRF₆₋₃₃ in the slice preparation seemed paradoxical (and remains unexplained) but added a potentially useful fingerprint for the potential contribution of CRF to ventral tegmental neuroplasticity. Ungless et al. suggested the possibility that CRF might undergo a conformational change when bound to CRF-BP, and that this change might enable it to act through CRF-R2, where it is normally ineffective (Ungless et al., 2003).

Behavioral studies

To explore the possibility that CRF-dependent reinstatement of cocaine seeking by footshock might involve a CRF action at the level of midbrain dopamine neurons, the Wise group conducted a series of studies in which VTA microdialysis samples were taken and various agents were infused into the VTA by reverse dialysis. First, they prepared animals with chronic jugular catheters and VTA guide cannulae (for subsequent insertion of microdialysis probes) and trained them for two weeks to self-administer intravenous cocaine by lever-pressing. They subsequently extinguished the lever-pressing habit by giving the animals three weeks of extinction training in which saline was substituted for cocaine. They then tested the animals for footshock-induced reinstatement of cocaine seeking while collecting dialysate from the VTA (B. Wang et al., 2005). Mild footshock stress reinstated vigorous lever-pressing and elevated VTA levels of glutamate and dopamine, despite the fact that the animals were still in the extinction condition; saline rather than cocaine was still being earned. Both the behavioral and the neurochemical effects of footshock stress were blocked by VTA infusion (by reverse

dialysis) of the non-selective CRF antagonist α -helical CRF. Footshock failed to elevate VTA glutamate or dopamine levels (or, of course, to induce lever-pressing) in cocaine-naïve animals, suggesting that prior cocaine experience somehow sensitizes VTA elements to a local action of footshock-induced CRF release, an action resulting in local glutamate release. Reinstatement and the dopamine elevation (but not the glutamate elevation) in cocaine-experienced animals were blocked by reverse dialysis of the ionotropic glutamate antagonist kynurenic acid, suggesting that the effects of CRF in these animals were on glutamatergic inputs to the VTA dopamine neurons (B. Wang et al., 2005).

Taken together, these findings suggested that footshock stress cause release of CRF in the VTA, that CRF in the VTA triggers local glutamate release in cocaine-experienced animals, and that local glutamate release in such animals causes local (and distal) dopamine release and reinstates cocaine seeking. Local dopamine release in VTA arises from the dendrites of intrinsic dopaminergic neurons (Geffen et al., 1976) and is a correlate of dopaminergic cell firing (Legault and Wise, 1999; Legault et al., 2000; Legault and Wise, 2001). The fact that footshock stress causes glutamate and dopamine release only in cocaine-experienced animals is evidence for some form of cocaine-induced neuroplasticity that may help explain the compulsive nature of cocaine-seeking that develops with continued cocaine-taking.

To confirm that footshock stress causes local CRF release, the experiment was repeated with measurement of CRF in the VTA dialysate (Wang et al., 2005). Footshock stress did indeed cause VTA CRF release, and it did so equally in cocaine-naïve and cocaine-experienced animals. The CRF release was TTX-sensitive, confirming that the stress-induced CRF release was from neuronal sources and not simply from the circulation. This finding means that the neuronal change caused by cocaine experience involves the responsiveness of glutamate-containing elements to CRF, rather than the responsiveness of CRF-containing elements to footshock.

To confirm that CRF in the VTA was responsible for the behavioral and neurochemical effects of footshock, B. Wang et al. (2005) then repeated their observations in animals given VTA infusions of CRF instead of footshock. Like the effects of footshock, VTA infusion of CRF reinstated lever-pressing and elevated VTA levels of glutamate in cocaine-trained animals. VTA infusion of CRF elevated VTA glutamate levels equally in animals tested 1, 7, or 21 days after the last day of cocaine self-administration training; thus the effects of cocaine experience were long-lasting. VTA CRF failed to elevate VTA glutamate when co-infused with a non-selective CRF antagonist (B. Wang et al., 2005).

Two CRF receptors, CRF-R1 and CRF-R2, are expressed in the brain, and B. Wang et al., (2007) next studied the effects of agonists and antagonists with different affinities at these receptors. Here they were interested in the possibility that their behavioral and neurochemical effects might involve the same receptors as were implicated in the CRF potentiation of NMDA mediated excitatory currents in dopamine neurons reported by Ungless et al., (2003). First, footshock-induced reinstatement was challenged with selective antagonists for CRF-R1, the preferred receptor for CRF (Behan et al., 1996; Lovenberg et al., 1995). Neither of two selective CRF-R1 antagonists, infused into the VTA by reverse dialysis at two concentrations each, was effective. In contrast, anti-sauvagine, a selective CRF-R2 antagonist was effective at low concentration; it blocked both reinstatement and the VTA elevations of glutamate and dopamine. These findings obtained from cocaine-experienced rats paralleled the findings of Ungless et al. (2003) in cocaine-naïve mice, where CRF potentiation of NMDA-mediated synaptic transmission was blocked by the same CRF-R2 and was not blocked by the same CRF-R1 antagonists.

Next, B. Wang et al., (2007) compared the effects of several CRF-R agonists infused by reverse dialysis into the VTA. Of these, ovine CRF, Stressin I, and urocortin III were ineffective, while VTA CRF, urocortin I, and mouse urocortin II injections each reinstated cocaine-seeking and elevations in VTA glutamate and dopamine. There was no common receptor target for the effective agonists: CRF and urocortin I act at both CRF-R1 and CRF-R2, urocortin I binds both CRF-R1 and CRF-R2, and mouse urocortin II acts selectively at CRF-R2. Nor was there a common receptor target for the ineffective agonists: whereas urocortin III acts selectively at CRF-R2, ovine CRF and Stressin I each act selectively at CRF-R1. Thus tests with selective agonists did not confirm the involvement of CRF-R2 that was suggested by tests with selective antagonists. While there was no common receptor for the effective agonists, there was a common binding affinity; the three effective agonists all bind—and the ineffective agonists all fail to bind—CRF-binding protein (CRF-BP).

CRF-BP is an apparently important but only partially understood stress-associated protein. It binds CRF and acts, under some circumstances, as a CRF antagonist; it sequesters free CRF in plasma and thus reduces the CRF available for binding to functional receptors in the third trimester of human pregnancy (Behan et al., 1995a; Jahn et al., 2005). However, in the slice preparation of Ungless et al. (2003), blocking the CRF binding site on CRF-BP with the CRF fragment CRF₆₋₃₃ eliminates the ability of CRF to potentiate glutamatergic signaling at VTA dopamine neurons. Because the behavioral and neurochemical effects of B. Wang et al. (2007), like those of Ungless et al. (2003), were blocked by CRF-R2 but not CRF-R1 antagonists, B. Wang et al. (2007) next determined whether co-administration with CRF₆₋₃₃ would eliminate the effectiveness of CRF in their paradigm as it did in that of Ungless et al. (2003). When co-infused with CRF₆₋₃₃, CRF and urocortin I each failed to reinstate cocaine-seeking or to elevate VTA glutamate or DA levels (B. Wang et al., 2007). Thus the VTA effects of footshock stress, like the CRF potentiation of glutamate signaling, appear to be dependent upon an action of CRF involving CRF-BP.

In summary, the pharmacological studies confirm that footshock stress activates CRF-containing afferents to the VTA, causing local CRF release in both cocaine-naïve and cocaine-experienced rats. They further suggest that VTA CRF release triggers VTA glutamate release and dopaminergic activation, but only in cocaine-experienced, not cocaine-naïve rats. In cocaine-experienced rats this glutamate release reinstates drug-seeking, presumably by causing dopamine release in one of the three mesocorticolimbic terminal fields linked to reward function (medial prefrontal cortex, nucleus accumbens and the olfactory tubercle: Ikemoto and Wise, 2004). As reviewed in the next section, these findings are not easily explained by what we currently know about the VTA dopamine neurons and their CRF and glutamatergic afferents in cocaine-naïve animals.

Anatomical studies

In parallel with the microdialysis studies of the Wise group, the Morales group initiated anatomical studies on the possible basis for CRF-glutamate-dopamine interaction in the VTA. While the microdialysis studies subsequently showed important differences between cocaine-experienced and cocaine-naïve rats, the initial anatomical studies were in cocaine-naïve rats and provide an initial characterization of dopamine, glutamate, and CRF elements in the normal VTA.

These studies were designed first to determine whether CRF-positive terminals are normally found in and make synaptic contacts with dopaminergic or glutamatergic elements in the VTA. Indeed, they do; Tagliaferro and Morales (2008) found vesicular CRF in afferent terminals that synapse on VTA neurons. These CRF-containing axon terminals make both asymmetric (presumably excitatory) and symmetric (presumably inhibitory) synapses on VTA neurons.

Nearly all the asymmetric CRF synapses are also glutamatergic, as they co-express the vesicular glutamate transporter-2 (vGluT2: marker for glutamatergic neurons). Nearly all the symmetric CRF synapses are also GABAergic, as they co-express glutamate decarboxylase (GAD: marker for GABAergic neurons). Thus CRF is co-localized in a subset of excitatory and a subset of inhibitory VTA afferents, and CRF terminals make synapses on dopaminergic and non-dopaminergic cells in VTA. The synapses of CRF-immunoreactive terminals on dopaminergic neurons (marked by tyrosine hydroxylase immunoreactivity) are mostly (83%) of the asymmetric, glutamatergic, presumably excitatory variety (Tagliaferro and Morales, 2008).

Because both the pharmacological data from the Wise group (B. Wang et al., 2007) and the electrophysiology of the Bonci group (Ungless et al., 2003) suggested participation of CRF-BP in the VTA interactions of CRF with glutamate signaling to dopamine neurons, H. Wang and Morales (2008) searched for local sources of CRF-BP using double *in situ* hybridization. While significant expression of mRNA for CRF-BP had been identified in the cortex, the hippocampus, the amygdaloid complex, and the bed nucleus of the stria terminalis (Potter et al., 1992), only minimal expression of CRF-BP mRNA had been noted in the VTA (Chan et al., 2000) and it was not known what type of cell expressed the message. Somewhat surprisingly, H. Wang and Morales found that mRNA for CRF-BP was expressed in a sub-population—approximately 25%—of VTA neurons expressing mRNA for tyrosine hydroxylase (TH), the traditional marker for dopaminergic neurons. Messenger RNA for CRF-BP was also found in a second sub-population of VTA cells, one expressing mRNA for glutamic acid decarboxylase (GAD), the traditional marker for GABAergic neurons. Within the total population of neurons containing CRF-BP mRNA, 70% co-expressed TH mRNA, and only 27% co-expressed GAD mRNA. Thus the VTA interactions of CRF-BP with CRF or with CRF-related peptides are likely to be predominately mediated by dopamine neurons. Interestingly, cells expressing mRNA for CRF-BP were restricted to the mesocorticolimbic system; neither TH-positive nor GAD-positive cells in the substantia nigra pars compacta (SNc) or substantia nigra pars reticulata (SNr) expressed mRNA for CRF-BP (H. Wang and Morales, 2008). Cells expressing mRNA for CRF-BP were found in the dorsal tier neurons that overlay SNc—neurons identified by Paxinos and Watson (2007) as a lateral extension of the parabrachial pigmented area, a sub-region of the VTA—and in the substantia nigra pars lateralis, which projects mainly to the amygdala. Thus CRF-BP was expressed selectively in midbrain dopamine neurons projecting to limbic and cortical targets, neurons known to be more responsive to stress than are neurons projecting to the dorsal striatum. CRF-BP was not found (H. Wang and M. Morales, unpublished observations) in recently discovered VTA glutamatergic neurons, neurons expressing mRNA for vGluT2 (Kawano et al., 2006; Yamaguchi et al., 2007).

Next, Tagliaferro, H. Wang, and Morales (2007) attempted to identify a source for VTA expression of CRF-R2, also implicated in both the microdialysis (B. Wang et al., 2007) and electrophysiological (Ungless et al., 2003) studies that suggested CRF-glutamate-dopamine interaction in the VTA. While Ungless et al. had reported RT-PCR evidence for CRF-R2 mRNA in putative DA neurons of cocaine-naïve mice (Ungless et al., 2003), Tagliaferro et al. were not able to detect mRNA for CRF-R2 in any subset of VTA neurons in cocaine-naïve mice, either by RT-PCR or by *in situ* hybridization. This finding is consistent with the expression of CRF-R2 protein in afferents to, rather than intrinsic cells of, the VTA as suggested by the microdialysis studies (B. Wang et al., 2007). It is also consistent with the recent finding of the Bonci group that CRF potentiates pre-synaptic (as well as post-synaptic) aspects of glutamate signaling to VTA dopamine neurons (Hahn et al., 2009). Because of lack of a good antibody for CRF-R2, we have not been able to confirm expression of CRF-R2 protein in VTA. Attempts to identify mRNA for CRF-R2 in neuronal populations projecting to VTA are in progress. Meanwhile, in a parallel study using double *in situ* hybridization Tagliaferro et al.

(2007) have found that mRNA for CRF-R1 is expressed in the VTA and is localized in dopaminergic neurons.

Current status

An interaction of CRF with ventral tegmental glutamate signaling to dopamine neurons, implicated by the electrophysiological studies of Ungless et al. (2003) and first suggested by the histological studies of Swanson et al. (1983) and the intracranial injection studies of Kalivas et al. (1987), is confirmed by our microdialysis and anatomical studies. We have identified CRF-dopamine synapses (Tagliaferro and Morales, 2008) and detected and quantified stress-induced CRF release (B. Wang et al., 2005, 2007) in the VTA. While the correspondence between the pharmacological profile of CRF-induced plasticity in VTA glutamate-dopamine signaling (Ungless et al., 2003) and of stress- and CRF-induced VTA glutamate release and reinstatement of cocaine-seeking (B. Wang et al., 2007) suggested a common mechanism of CRF-glutamate-dopamine interaction in the VTA, subtle differences between the two now suggest more than one mechanism for CRF-glutamate-dopamine interaction in this region, and this suggestion is supported by our anatomical studies.

First, the initial studies of the Bonci group (Ungless et al., 2003) suggested an effect of CRF on the post-synaptic sensitivity of dopamine neurons to glutamatergic input. This effect was suggested to be mediated by CRF-R2 expressed by dopaminergic neurons in cocaine-naïve animals, and was suggested to be dependent in some way on presumably extracellular CRF-BP (Ungless et al., 2003). While our pharmacological studies implicated CRF-R2 and CRF-BP, we found that CRF caused VTA glutamate release and dopaminergic activation only in cocaine-experienced and not cocaine-naïve animals. Moreover, our finding that CRF-antagonists blocked the effects of CRF on glutamate release and that glutamate antagonists blocked the effect of CRF on dopaminergic activation implicated a presynaptic action of CRF on glutamate release rather than a post-synaptic effect on dopaminergic sensitivity to glutamate. More recent studies from the Bonci group indicate that CRF can potentiate glutamate-dopamine signaling through both CRF-R1 and CRF-R2 mediated mechanisms, in both cocaine-naïve and cocaine-experienced mice, and by both presynaptic effects of CRF on glutamate release and post-synaptic effects of CRF on sensitivity of dopaminergic neurons to glutamate (Hahn et al., 2009).

One set of inconsistencies in the currently available data involves the role and location of CRF-R2 expression. Our finding that CRF-R2 antagonists block CRF-induced VTA glutamate release implies a presynaptic localization of CRF-R2 on the terminals of VTA glutamate afferents rather than on dopaminergic neurons themselves. Moreover, we found that the apparently CRF-R2-mediated effect of VTA CRF on VTA glutamate release occurred only in cocaine-experienced, not cocaine-naïve rats. Ungless et al. (2003) found evidence of CRF-R2 expression in dopaminergic neurons themselves using RT-PCR, and implicated CRF-R2 in post-synaptic effects on dopaminergic sensitivity to glutamate signaling, effects observed in cocaine-naïve mice. Hahn et al. (2009) confirm the CRF-R2-mediated effect of CRF in cocaine-naïve mice and, indeed, suggest that it is a CRF-R1-mediated effect that develops with cocaine experience. Thus if taken at face value, the available data implicate both presynaptic and post-synaptic CRF-R2 expression and function. That mRNA for CRF-R2 is readily detectable in other structures but not in VTA (Tagliaferro and Morales, 2007) by in situ hybridization suggests that the expression seen by Ungless et al., using RT-PCR is very weak, at least in the cocaine-naïve animal.

A related question has to do with the role of CRF-R1. Why, if CRF-R1 is expressed in dopaminergic neurons (Tagliaferro and Morales, 2007) and if CRF synapses are made with dopaminergic neurons (Tagliaferro and Morales, 2008) of cocaine-naïve animals, is cocaine

experience required before CRF causes significant VTA dopamine release? Why, if a CRF-R1-mediated enhancement of NMDAR EPSCs is recruited after cocaine experience (Hahn et al., 2009) in a mouse slice preparation, do we see no effect of CRF-R1 antagonists on CRF-induced glutamate and dopamine release in cocaine-experienced rats (B. Wang et al., 2005, unpublished observations)? As with the case of CRF-R2, we do not yet have converging evidence to pinpoint the role or roles of CRF-R1 in CRF-glutamate-dopamine interactions across these various paradigms.

Finally, questions remain about the role or roles of CRF-BP. First, the microdialysis experiments suggest a necessary role for CRF-BP in the presynaptic control of VTA glutamate release by CRF in cocaine-experienced rats (B. Wang et al., 2007) whereas the electrophysiological experiments suggest a necessary role for CRF-BP in the post-synaptic sensitivity of dopamine neurons to glutamate in cocaine-naïve mice (Ungless et al., 2003). Perhaps there are species differences in the relevant VTA circuitry, but this seems unlikely. The discovery of mRNA for CRF-BP in VTA neurons does not clarify the picture, because the CRF-BP is expressed in dopaminergic (and GABAergic) neurons (H. Wang et al., 2008) and does not have a trans-membrane domain, whereas the evidence for necessary roles of CRF-BP in the microdialysis experiments (B. Wang et al., 2007) and the electrophysiological experiments (Ungless et al., 2003) come from studies where the interaction appears to be between CRF and extracellular CRF-BP that are both extracellular. How does intracellular CRF-BP interact with extracellular CRF in these models? It is, of course, possible that CRF-BP is released from VTA neurons but such release has not been demonstrated. Moreover, the electrophysiological data suggest that CRF-BP is necessary for effects of CRF in naïve mice whereas the microdialysis data suggest a role for CRF-BP only in cocaine-experienced rats.

Thus a story that seemed on the verge of offering integration of pharmacological data in an addiction model with electrophysiological data in a neuroplasticity model has proven to be more complicated than the common pharmacological findings initially suggested. Clearly, the puzzle will not be solved without more pieces. In our anatomical studies, our focus turns to the cocaine-experienced animal, with the hope that differences in receptor expression or synaptic frequency or morphology may shed further light on interactions of VTA CRF with VTA glutamate and dopamine.

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