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Glutamate and Reinstatement

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Summary

The importance of glutamate in the reinstatement of cocaine-seeking behavior has been established. New molecular and neurochemical adaptations in the glutamatergic system which drive cocaine relapse have been identified, such as the ability of CB1 receptor stimulation to reduce basal glutamate levels and the involvement of the GluR1 receptor subunit in reinstatement. Furthermore, it is apparent that similar glutamatergic neuroadaptations arise after self-administration of cocaine, heroin, nicotine and alcohol. For example, reinstatement to cocaine, nicotine and alcohol can be prevented both by stimulation of group II mGluR receptors as well as blockade of Group I mGluR receptors. The similarities in the neurochemistry behind relapse to these varied drug classes indicate that drugs that target the glutamate system could be effective at treating relapse to multiple types of drugs.

There is an extraordinarily high rate of recidivism for drug use even after long periods of abstinence have been attained [1]. The reinstatement model of relapse has been developed as a means of studying relapse in experimental animals [2,3]. Animals trained to self-administer drug are subsequently put through extinction training to reduce responding. When levels of responding are minimal, animals are presented with a stimulus that causes a “reinstatement” of the drug-contingent response. This pre-clinical model has been shown to have face validity for human relapse, based partially on the fact that the same factors that elicit relapse in the human population (drug priming injection, drug-associated cues, and stress) precipitate relapse in the reinstatement model (see review [4]). The reinstatement model has been used to identify brain structures involved in relapse and, although highly effective pharmacotherapeutic treatments have yet to emerge, this model has been judged a moderately effective tool for screening drugs to block relapse [4]. One of the major discoveries to emerge from the use of this model is the role of glutamate release in the nucleus accumbens (NAC) core in the reinstatement of cocaine-seeking [5,6,7,8]. The discovery that the infusion of AMPA agonists into the NAC core causes reinstatement [9] and that antagonism of AMPA receptors here prevented cocaine- [5] and cue-primed relapse [6] led to the identification of the PFC-NAC core glutamatergic projection as being essential for cocaine-primed reinstatement [10], and later for stress-induced reinstatement [8]. A decrease in basal levels of glutamate was found to be present following cocaine self-administration accompanied by an enhanced release of glutamate during reinstatement [10].

In recent years, the involvement of glutamate in cue-, stress-, and drug-primed reinstatement has been further investigated in regards to relapse to cocaine as well as other drugs of abuse. The present review will focus on research conducted within the past two years that further investigates the nature of glutamate signaling and homeostasis in relapse to cocaine.

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Importantly, the last few years has seen the well-characterized role of glutamate in cocaine-seeking expanded to other drugs of abuse, and the role of glutamate in the relapse of heroin, alcohol, and nicotine will also be discussed. Based on this body of research, it follows that neuroplasticity in glutamate transmission may be the common factor in relapse for many types of drugs.

Cocaine

In the NAC, basal levels of extracellular glutamate are primarily regulated by the cystine-glutamate antiporter (system xc⁻), which exchanges extracellular cystine for intracellular glutamate [11]. System xc⁻ is down-regulated after repeated cocaine, accounting for the low basal levels of glutamate observed in the NAC of cocaine-withdrawn animals [12]. N-acetylcysteine restores basal glutamate levels and prevents both cocaine-primed reinstatement as well as the increase in extracellular glutamate that accompanies reinstatement both when it is given acutely prior to reinstatement testing [12] and when it is only given during the self-administration portion of the experiment [13]. These effects were further shown to be directly due to action of N-acetylcysteine on system xc⁻ through use of CPG, the system xc⁻ antagonist [14]. In the reinstatement model, the mGluR2/3 antagonist LY341495 prevents N-acetylcysteine from inhibiting reinstatement of cocaine-seeking [15]. Thus, it appears that increasing basal glutamate levels via NAC restores tone on the mGluR2/3 autoreceptors and dampens glutamate release. Double-blind pilot clinical trials found that N-acetylcysteine also decreases reactivity for cocaine cues [16] and cocaine use in cocaine-dependent humans [17].

The cannabinoid CB1 receptor is known to be a negative modulator of synaptic glutamate release [18] and the CB1 antagonist AM251 decreases cocaine-primed reinstatement while also inhibiting the increase in extracellular glutamate that accompanies reinstatement of cocaine-seeking [19]. AM251 alone significantly increased extracellular glutamate in the NAC of rats that had self-administered cocaine and blocking mGluR2/3 receptors prevented the AM251-induced attenuation of cocaine-seeking. Thus, AM251 may be acting in a similar manner as N-acetylcysteine: elevating extracellular nonsynaptic glutamate to stimulate presynaptic inhibitory mGluR2/3 receptors and reduce synaptic glutamate release.

Work done in the past few years has focused on elucidating the roles of the different glutamate receptor subtypes in reinstatement. Building on the early work by Cornish & Kalivas [5,9], it has been recently demonstrated that infusion of AMPA into both the core and the shell of the NAC induces reinstatement behavior [20]. These authors also demonstrated that the knockdown of the AMPA receptor subunit GluR1 mRNA via antisense oligonucleotides blocked both AMPA- and cocaine-primed reinstatement, further solidifying the role of AMPA receptors in mediating reinstatement. Additionally, Backstrom & Hyttia found that systemic administration of two AMPA antagonists, CNQX and NBQX, was able to attenuate cue-induced reinstatement [21]. CNQX was also able to attenuate cue-induced reinstatement when administered directly into the NAC core [22]. However, a recent report by Bachtell et al. indicates the relationship of AMPA receptors to reinstatement may not be so straightforward [23]. These authors over-expressed either a wild type (wt) or a pore-dead (pd) GluR1 subunit immediately prior to acquisition of cocaine self-administration or one day preceding a cue- or cocaine-primed reinstatement test. Over-expression of the wt-GluR1 was found to inhibit cocaine-primed reinstatement when delivered both prior to acquisition and the reinstatement test. Conversely, the over-expression of the pd-GluR1, which serves to reduce AMPA currents, enhanced cocaine-primed reinstatement when delivered at both time points tested. There was no effect on cue-induced reinstatement. The authors explain the discrepancies between these results and the evidence showing that reducing, and not facilitating, signaling through AMPA receptors blocks reinstatement [5,20], with the idea that they have altered basal AMPA receptor function, versus the acute antagonism used by previous studies.

Acute blockade of AMPA receptors seems to block reinstatement [5,20,24] but blockade of NMDA receptors may enhance reinstatement. When the NMDA antagonist AP-5 was injected into the shell of the NAC, both low (3 µg) and high (30 µg) doses promoted the reinstatement of cocaine seeking-behavior. However, in the NAC core, only the high dose was able to produce reinstatement, the magnitude of which was substantially lower than that produced when either dose was injected into the shell [24]. Contradictory reports have been made by Backstrom & Hyttia [21,22]. Systemic administration of the NMDA/glycine site antagonist L-701,324 was found to decrease cue-induced cocaine reinstatement while the competitive NMDA antagonist CGP-39551 had no effect on this measure [21,22]. When AP-5 was injected directly into the NAC core, doses of 1 and 2 µg were capable of attenuating cue-induced reinstatement [21, 22]. Thus, it is possible that low doses of AP-5 administered into the NAC core are capable of blocking reinstatement while high doses induce drug-seeking, possibly due to non-specific effects on other receptor sub-types. In the basolateral amygdala (BLA), NMDA receptors seem to play a role in the consolidation of associations between drug and conditioned stimuli which, when strengthened, can produce relapse [25].

The mGluR2/3 autoreceptors are capable of regulating glutamate release [26] and since there is an increase in glutamate levels during reinstatement, it follows that agonists at mGluR2/3 receptors inhibit reinstatement. Both systemic and intra-NAC LY379268 decreased cocaine-primed reinstatement, however, reinstatement of food-seeking was also attenuated [27,28]. In contrast, Bossert et al. found that intra-NAC LY379268 had no effect on reinstatement of sucrose-seeking [29,30]. Stimulation of mGluR2/3 receptors with LY379268 reduces cocaine-primed reinstatement in non-human primate, without nonspecifically altering behaviors such as locomotion, grooming, vocalization and posture [30]. Adewale and colleagues also found that the relapse-prevention effects of LY379268 could be blocked with the mGluR2/3 antagonist, LY341495, indicating a specific action at mGluR2/3 receptors. Post-synaptic mGluR5 receptors have also been targets for drugs to treat cocaine addiction. MPEP, a selective mGluR5 antagonist, attenuates cue-induced reinstatement of cocaine-seeking [21]. The mGluR5 antagonist MTEP also blocks cue-induced reinstatement of cocaine-seeking [31].

In addition to recent advances in glutamate pharmacology and cocaine-seeking, evidence that glutamate neurotransmission in the NAC is altered by chronic cocaine administration has accumulated in the last two years. Thus, glutamatergic synapses appear to be in an LTP-like state as estimated by the ratio of AMPA to NMDA currents [32,33]. This is associated with an increase in surface expression of the GluR1 AMPA receptor subunit [32,33] and GluR1 surface expression is further elevated at 30 min following cocaine-induced relapse [34]. In spite of NAC neurons being in an LTP-like state, the capacity to induce LTD in slices obtained from animals withdrawn from cocaine self-administration is blunted [35]. Exactly how these physiological changes and loss of plasticity affect glutamate pharmacology requires further study, however, the upregulation of GluR1 is consistent with the increased locomotor response elicited by AMPA microinjection into the NAC of mice pretreated with chronic cocaine [36].

Heroin

Glutamate has been shown to be important for context-induced reinstatement of heroin-seeking. Infusing the mGluR2/3 agonist LY379268 (0.3 or 1.0 µg) into the NAC shell dose-dependently attenuated reinstatement while these doses when injected into the NAC core had no effect. However, a higher dose (3.0 µg) of LY379268 infused into the core was able to block reinstatement [29]. These results are in agreement with the finding that both the NAC core and shell are part of the circuitry of heroin relapse [37]. Microdialysis sampling of glutamate levels in the NAC core during both heroin- and cue-primed reinstatement indicates that glutamate levels rise during reinstatement and consequently, blocking AMPA/kainite receptors in the core attenuates heroin seeking primed by both cue and drug [38]. Reinstatement of heroin-

seeking and the accompanying rise in extracellular glutamate in the NAC are blocked by inhibiting prelimbic cortex projections to the NAC core [38] indicating that the same glutamatergic projection is involved in relapse to both cocaine- and heroin-seeking. In agreement with this finding is that N-acetylcysteine treatment blocks both heroin- and cue-primed reinstatement for up to one month following the last injection of N-acetylcysteine that was administered repeatedly during extinction training [39]. Interestingly, extinction training was facilitated by the daily N-acetylcysteine injection.

Alcohol

In a similar manner to both heroin and cocaine, the mGluR2/3 agonist LY379268 dose-dependently attenuates reinstatement of alcohol. Systemically administered LY379268 blocked both stress- and cue-induced reinstatement of alcohol-seeking [40]. Also in a similar manner to cocaine, antagonism of mGluR5 receptors prevents cue-induced reinstatement both when administered alone [41] and when sub-threshold doses are combined with an adenosine A_{2A} antagonist [42]. The combination of mGluR5 and A_{2A} receptor agonists enhance glutamate release in the rat striatum [43], thus it follows that the combination of antagonists at these receptors decreases glutamate release. Cue-induced reinstatement of alcohol-seeking was recently linked to increased phosphorylated extracellular signal-regulated kinase (p-ERK1/2) expression in the NAC shell and BLA [44]. The ERK1/2 pathway is downstream from mGluR5 receptors (as well as others such as NMDA) and the blockade of mGluR5 receptors with MPEP and subsequent attenuation of reinstatement of alcohol-seeking was associated with a decrease in p-ERK1/2 expression in both the shell and the BLA. Lamotrigine inhibits the release of glutamate [45], and systemic administration attenuates cue-induced reinstatement of alcohol seeking [46], further supporting a role for glutamate in relapse to alcohol-seeking.

Nicotine

Relapse to nicotine seeking is also influenced by glutamate release. Stimulation of mGluR2/3 receptors with systemically administered LY379268 blocks cue-induced nicotine relapse; however it also blocked food-seeking [47]. Systemic administration of the mGluR1 antagonist EMQMCM (5 mg/kg) blocked both cue- and nicotine-primed reinstatement and only blocked food-seeking at a dose (10 mg/kg) much higher than the doses effective at blocking nicotine relapse [48]. This finding is in agreement with previous work showing that mGluR5 antagonists block nicotine- [49] and cue-primed reinstatement [50]. Nicotine self-administration may produce similar neuroadaptations in glutamate transmission akin to the effects of cocaine self-administration. Thus, nicotine self-administration reduces mGluR2/3 function and expression of the catalytic subunit of system xc- [47,51]. Accordingly, N-acetylcysteine was found to reduce the number of cigarettes smoked in a double-blind trial involving four weeks of drug administration [51].

Conclusions

Based on the work presented here, glutamate is involved in relapse to multiple types of addictive drugs (also see [52]). The majority of work in this field has been done with cocaine, thus providing more insight into the glutamatergic signaling mechanisms underlying cocaine relapse relative to other drugs. However, the research presented here indicates that there are commonalities between relapse to cocaine, alcohol, nicotine and heroin. Cocaine and heroin share a common circuitry of relapse, with the glutamatergic projection from the prelimbic cortex to the nucleus accumbens core being essential for reinstatement. Stimulation of mGluR2/3 receptors is effective at blocking reinstatement of cocaine, nicotine and alcohol, presumably by reducing the release of glutamate from pre-synaptic terminals and providing

more evidence that it is the release of glutamate that drives relapse. Similarly, antagonizing group I mGluR receptors blocks reinstatement of cocaine-, nicotine- and alcohol-seeking. Given that different and overlapping brain structures contribute to reinstatement for different drug classes, the drug-induced glutamatergic neuroadaptations and effects of glutamate pharmacology on reinstatement that have been identified primarily in the NAC may generalize to other key structures, such as the amygdala or ventral tegmental area. Nonetheless, the last two years of research consistently points to an important role for glutamate transmission in the NAC in the reinstatement of drug-seeking, regardless of drug class, and correspondingly identifies different aspects of glutamate transmission and homeostasis as potential pharmacotherapeutic targets in treating addiction.

References

1. O'Brien, C. Drug addiction and drug abuse. In: Hardman, JLL.; Gilman, AG., editors. *The Pharmacological Basis of Therapeutics*. McGraw-Hill; New York: 2001. p. 621-642.
2. Davis WM, Smith SG. Role of conditioned reinforcers in the initiation, maintenance and extinction of drug-seeking behavior. *Pavlov J Biol Sci* 1976;11(4):222-236. [PubMed: 1033507]
3. de Wit H, Stewart J. Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology (Berl)* 1981;75(2):134-143. [PubMed: 6798603]
4. Epstein DH, Preston KL, Stewart J, Shaham Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology (Berl)* 2006;189(1):1-16. [PubMed: 17019567]
5. Cornish JL, Kalivas PW. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci* 2000;20(15):RC89. [PubMed: 10899176]
6. Di Ciano P, Everitt BJ. Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* 2001;25(3):341-360. [PubMed: 11522463]
7. McFarland K, Kalivas PW. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2001;21(21):8655-8663. [PubMed: 11606653]
8. McFarland K, Davidge SB, Lapish CC, Kalivas PW. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* 2004;24(7):1551-1560. [PubMed: 14973230]
9. Cornish JL, Duffy P, Kalivas PW. A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. *Neuroscience* 1999;93(4):1359-1367. [PubMed: 10501460]
10. McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2003;23(8):3531-3537. [PubMed: 12716962]
11. Baker DA, Shen H, Kalivas PW. Cystine/glutamate exchange serves as the source for extracellular glutamate: modifications by repeated cocaine administration. *Amino Acids* 2002;23(13):161-162. [PubMed: 12373531]
12. Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, Kalivas PW. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003;6(7):743-749. [PubMed: 12778052]
13. Madayag A, Lobner D, Kau KS, Mantsch JR, Abdulhameed O, Hearing M, Grier MD, Baker DA. Repeated N-acetylcysteine administration alters plasticity-dependent effects of cocaine. *J Neurosci* 2007;27(51):13968-13976. [PubMed: 18094234]. This paper describes how chronic treatment with N-acetylcysteine prevents the development of some cocaine induced glutamatergic adaptations by restoring the cystine-glutamate exchanger. Moreover, chronic N-acetylcysteine produced an enduring reduction in the ability to reinstate cocaine seeking.
14. Kau KS, Madayag A, Mantsch JR, Grier MD, Abdulhameed O, Baker DA. Blunted cystine-glutamate antiporter function in the nucleus accumbens promotes cocaine-induced drug seeking. *Neuroscience* 2008;155(2):530-537. [PubMed: 18601982]

15. Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J Neurosci* 2005;25(27):6389–6393. [PubMed: 16000629]
16. LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A, Brady K, Kalivas PW, Malcolm R. Is cocaine desire reduced by N-acetylcysteine? *Am J Psychiatry* 2007;164(7):1115–1117. [PubMed: 17606664]
17. Mardikian PN, LaRowe SD, Hedden S, Kalivas PW, Malcolm RJ. An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(2):389–394. [PubMed: 17113207]
18. Lopez-Moreno JA, Gonzalez-Cuevas G, Moreno G, Navarro M. The pharmacology of the endocannabinoid system: functional and structural interactions with other neurotransmitter systems and their repercussions in behavioral addiction. *Addict Biol* 2008;13(2):160–187. [PubMed: 18422831]
19. Xi ZX, Gilbert JG, Peng XQ, Pak AC, Li X, Gardner EL. Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. *J Neurosci* 2006;26(33):8531–8536. [PubMed: 16914679]. This research links the involvement of glutamate transmission in relapse with the endocannabinoid system, and at the same time poses novel pharmacotherapies for cocaine addiction.
20. Ping A, Xi J, Prasad BM, Wang MH, Kruzich PJ. Contributions of nucleus accumbens core and shell GluR1 containing AMPA receptors in AMPA- and cocaine-primed reinstatement of cocaine-seeking behavior. *Brain Res* 2008;1215:173–182. [PubMed: 18486119]
21. Backstrom P, Hyttia P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* 2006;31(4):778–786. [PubMed: 16123768]
22. Backstrom P, Hyttia P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* 2007;192(4):571–580. [PubMed: 17347848]
23. Bachtell RK, Choi KH, Simmons DL, Falcon E, Monteggia LM, Neve RL, Self DW. Role of GluR1 expression in nucleus accumbens neurons in cocaine sensitization and cocaine-seeking behavior. *Eur J Neurosci* 2008;27(9):2229–2240. [PubMed: 18430032]. This manuscript provides an interesting alternate hypothesis to the role of AMPA receptors in drug seeking by providing data supported an opposite role for changing basal expression of receptors versus pharmacologically induced alterations in GluR1.
24. Famous KR, Schmidt HD, Pierce RC. When administered into the nucleus accumbens core or shell, the NMDA receptor antagonist AP-5 reinstates cocaine-seeking behavior in the rat. *Neurosci Lett* 2007;420(2):169–173. [PubMed: 17513051]
25. Feltenstein MW, See RE. NMDA receptor blockade in the basolateral amygdala disrupts consolidation of stimulus-reward memory and extinction learning during reinstatement of cocaine-seeking in an animal model of relapse. *Neurobiol Learn Mem* 2007;88(4):435–444. [PubMed: 17613253]
26. Anwyl R. Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Res Rev* 1999;29(1):83–120. [PubMed: 9974152]
27. Peters J, Kalivas PW. The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology (Berl)* 2006;186(2):143–149. [PubMed: 16703399]
28. Baptista MA, Martin-Fardon R, Weiss F. Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. *J Neurosci* 2004;24(20):4723–4727. [PubMed: 15152032]
29. Bossert JM, Gray SM, Lu L, Shaham Y. Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. *Neuropsychopharmacology* 2006;31(10):2197–2209. [PubMed: 16341024]
30. Adewale AS, Platt DM, Spealman RD. Pharmacological stimulation of group ii metabotropic glutamate receptors reduces cocaine self-administration and cocaine-induced reinstatement of drug seeking in squirrel monkeys. *J Pharmacol Exp Ther* 2006;318(2):922–931. [PubMed: 16675638]

31. Iso Y, Grajkowska E, Wroblewski JT, Davis J, Goeders NE, Johnson KM, Sanker S, Roth BL, Tueckmantel W, Kozikowski AP. Synthesis and structure-activity relationships of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine analogues as potent, noncompetitive metabotropic glutamate receptor subtype 5 antagonists; search for cocaine medications. *J Med Chem* 2006;49(3):1080–1100. [PubMed: 16451073]
32. Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 2008;454(7200):118–121. [PubMed: 18500330]
33. Kourrich S, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J Neurosci* 2007;27(30):7921–7928. [PubMed: 17652583]. The first paper to describe metaplasticity to cocaine where withdrawal from a chronic cocaine administration regiment produces and LTP-like state (increased AMPA/NMDA currents) in accumbens neurons, but a subsequent cocaine challenge causes and LTP-like state. These dramatic effects of acute and chronic cocaine on synaptic grading open a new avenue of research in understanding the role of glutamate transmission in drug seeking.
34. Anderson SM, Famous KR, Sadri-Vakili G, Kumaresan V, Schmidt HD, Bass CE, Terwilliger EF, Cha JH, Pierce RC. CaMKII: a biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nat Neurosci* 2008;11(3):344–353. [PubMed: 18278040]
35. Martin M, Chen BT, Hopf FW, Bowers MS, Bonci A. Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nat Neurosci* 2006;9(7):868–869. [PubMed: 16732275]
36. Pacchioni A, Vallone J, Worley PF, Kalivas PW. Neuronal pentraxins modulate cocaine-induced neuroadaptations. *J Pharmacol Exp Ther*. in press
37. Rogers JL, Ghee S, See RE. The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. *Neuroscience* 2008;151(2):579–588. [PubMed: 18061358]
38. LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J Neurosci* 2008;28(12):3170–3177. [PubMed: 18354020]. The authors employ microdialysis to measure glutamate levels in the NAC core during heroin primed reinstatement. They find that, similar to cocaine-primed reinstatement, relapse to heroin-seeking requires glutamate release in the NAC core. However, unlike cocaine reinstatement, heroin reinstatement also requires DA signaling in the NAC core.
39. Zhou W, Kalivas PW. N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. *Biol Psychiatry* 2008;63(3):338–340. [PubMed: 17719565]
40. Zhao Y, Dayas CV, Aujla H, Baptista MA, Martin-Fardon R, Weiss F. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-fos expression in the hippocampus and amygdala. *J Neurosci* 2006;26(39):9967–9974. [PubMed: 17005860]
41. Backstrom P, Hyttia P. Ionotropic glutamate receptor antagonists modulate cue-induced reinstatement of ethanol-seeking behavior. *Alcohol Clin Exp Res* 2004;28(4):558–565. [PubMed: 15100606]
42. Adams CL, Cowen MS, Short JL, Lawrence AJ. Combined antagonism of glutamate mGlu5 and adenosine A2A receptors interact to regulate alcohol-seeking in rats. *Int J Neuropsychopharmacol* 2008;11(2):229–241. [PubMed: 17517168]
43. Rodrigues RJ, Alfaro TM, Rebola N, Oliveira CR, Cunha RA. Co-localization and functional interaction between adenosine A(2A) and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *J Neurochem* 2005;92(3):433–441. [PubMed: 15659214]
44. Schroeder JP, Spanos M, Stevenson JR, Besheer J, Salling M, Hodge CW. Cue-induced reinstatement of alcohol-seeking behavior is associated with increased ERK(1/2) phosphorylation in specific limbic brain regions: Blockade by the mGluR5 antagonist MPEP. *Neuropharmacology* 2008;55(4):546–554. [PubMed: 18619984]
45. Wang SJ, Sihra TS, Gean PW. Lamotrigine inhibition of glutamate release from isolated cerebrocortical nerve terminals (synaptosomes) by suppression of voltage-activated calcium channel activity. *Neuroreport* 2001;12(10):2255–2258. [PubMed: 11447345]

46. Vengeliene V, Heidbreder CA, Spanagel R. The effects of lamotrigine on alcohol seeking and relapse. *Neuropharmacology* 2007;53(8):951–957. [PubMed: 17976664]
47. Liechti ME, Lhuillier L, Kaupmann K, Markou A. Metabotropic glutamate 2/3 receptors in the ventral tegmental area and the nucleus accumbens shell are involved in behaviors relating to nicotine dependence. *J Neurosci* 2007;27(34):9077–9085. [PubMed: 17715344]. The function of mGluR2/3 autoreceptors in the VTA and NAC was found to be compromised following nicotine self-administration. Systemic administration of the mGluR2/3 agonist LY379268 was found to block cue-induced reinstatement of nicotine-seeking behavior, but also inhibited reinstatement of food-seeking.
48. Dravolina OA, Zakharova ES, Shekunova EV, Zvartau EE, Danysz W, Bessalov AY. mGlu1 receptor blockade attenuates cue- and nicotine-induced reinstatement of extinguished nicotine self-administration behavior in rats. *Neuropharmacology* 2007;52(2):263–269. [PubMed: 16963088]
49. Tessari M, Pilla M, Andreoli M, Hutcheson DM, Heidbreder CA. Antagonism at metabotropic glutamate 5 receptors inhibits nicotine- and cocaine-taking behaviours and prevents nicotine-triggered relapse to nicotine-seeking. *Eur J Pharmacol* 2004;499(12):121–133. [PubMed: 15363959]
50. Bessalov AY, Dravolina OA, Sukhanov I, Zakharova E, Blokhina E, Zvartau E, Danysz W, van Hecke G, Markou A. Metabotropic glutamate receptor (mGluR5) antagonist MPEP attenuated cue- and schedule-induced reinstatement of nicotine self-administration behavior in rats. *Neuropharmacology* 2005;49(Suppl 1):167–178. [PubMed: 16023685]
51. Knackstedt L, LaRowe S, Mardikian P, Malcolm R, Upadhyaya H, Hedden S, Markou A, Kalivas PW. The Role of Cystine-glutamate Exchange in Nicotine Dependence in Rats and Humans. *Biol Psychiatry*. in press
52. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. *Biochem Pharmacol* 2008;75(1):218–265. [PubMed: 17706608]

Table 1

The role of glutamate receptor subtypes in the reinstatement of cocaine-, heroin, alcohol- and nicotine-seeking.

DRUG	RECEPTOR	ROLE IN REINSTATEMENT	CITATION
Cocaine	AMPA	Agonists promote reinstatement	9,20,21
		Antagonists attenuate reinstatement	5,6,21,22
	NMDA	Antagonists in NAcc shell promote reinstatement	24
		Antagonists (high dose) in NAcc core promote reinstatement	24
		Antagonists (low dose) in NAcc core attenuate reinstatement	21,22
	mGluR2/3	Agonists attenuate reinstatement	27,28,30
	mGluR	Indirect agonists attenuate reinstatement	12,13,17
	mGluR1/5	Antagonists attenuate reinstatement	21,31
Heroin	AMPA	Antagonists attenuate reinstatement	38
	mGluR2/3	Agonists attenuate reinstatement	39
	mGluR	Indirect agonists attenuate reinstatement	29
Alcohol	mGluR2/3	Agonists attenuate reinstatement	40
	mGluR1/5	Antagonists attenuate reinstatement	41
Nicotine	mGluR2/3	Agonists attenuate reinstatement	47
	mGluR1/5	Antagonists attenuate reinstatement	48,49,50