Pharmacology Biochemistry and Behavior, Vol. 57, No. 3, pp. 449–455, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00450-9

Sensitization to the Behavioral Effects of Cocaine: Modulation by Dynorphin and κ-Opioid Receptor Agonists

TONI S. SHIPPENBERG AND WILLIAM REA

Brain Imaging Section, NIDA Division of Intramural Research, Baltimore, MD 21224

SHIPPENBERG, T. S. AND W. REA. *Sensitization to the behavioral effects of cocaine: Modulation by dynorphin and κ-opioid receptor agonists.* PHARMACOL BIOCHEM BEHAV **57**(3) 449–455, 1997.—Several lines of evidence suggest an involvement of the mesolimbic dopamine (DA) system in the mediation of psychostimulant-induced sensitization. It is also apparent that endogenous opioid peptide systems can modulate the activity of this same DA system. Psychostimulant-induced alterations in opioid peptide gene expression have also been reported. In this review, evidence will be presented that demonstrates that the administration of κ-opioid agonists can prevent the initiation of behavioral sensitization to cocaine and that such treatment is also effective in preventing alterations in mesolimbic DA neurotransmission that occur as a consequence of repeated cocaine administration. The putative role of opioid–DA interactions in the modulation of psychostimulant-induced sensitization will also be discussed. © 1997 Elsevier Science Inc.

Psychostimulants Sensitization κ-Opioid receptor agonists Dynorphin Locomotor activity Conditioned place preference Prodynorphin

NUMEROUS studies [see (24,54) for reviews] have shown that the repeated administration of psychostimulants results in a progressive augmentation of their locomotor stimulatory effects, a phenomenon referred to as sensitization. Evidence of the development of sensitization to the rewarding effects of these agents has also been presented. Thus, the rate of acquisition of intravenous cocaine or amphetamine self-administration is increased in animals previously exposed to either agent, as is the number of animals ultimately exhibiting stable self-administration behavior (17,38). An enhancement of the conditioning reinforcing effects of cocaine, amphetamine, and morphine following their repeated intermittent administration has also been reported (29,42,43,45). Such sensitization, which can persist for weeks or months following the cessation of drug treatment, has been implicated in drug-craving and the reinstatement of compulsive drug-seeking behavior (40).

The role of the mesolimbic dopamine (DA) system, arising in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAC), in mediating the reinforcing and locomotor stimulatory effects of psychostimulants is well documented (26,41). Following repeated administration of these agents, marked alterations in the functional activity of mesolimbic DA neurons are seen. These include: (a) a subsensitivity of D2 autoreceptors in the ventral tegmental area and a transient increase in extracellular DA levels in the NAC (1,62–64); (b) a later-onset increase in the ability of psychostimulants to increase extracellular DA levels in the NAC (23, 24,66); and (c) a long-lasting supersensitivity of D1 receptors within the NAC (16). Several lines of evidence [see (24,59) for reviews] suggest that these alterations in DA neurotransmission contribute, at least in part, to the initiation and long-term expression of behavioral sensitization.

Only recently has the involvement of other neurotransmitter systems in mediating sensitization been assessed. Several studies have shown that glutamate receptor antagonists prevent the initiation and expression of behavioral sensitization to amphetamine as well as cocaine (22,25,65). Given that glutamate receptor stimulation increases the firing rate of DA neurons and promotes DA release (21,55), it has been suggested that the effects of these agents are mediated via an antagonism of excitatory amino acid neurotransmission within the mesolimbic system and a resulting inhibition of the activity of DA neurons projecting to the NAC (22). Given such findings, the question arises as to whether manipulations of other neuronal systems that modulate the activity of mesolimbic DA neurons can attenuate the development of psychostimulant-induced sensitization. This article will review evidence suggesting that: (a) κ-opioid receptor systems play an

Requests for reprints should be addressed to Toni S. Shippenberg, Brain Imaging Section, NIDA Division of Intramural Research, P.O Box 5180, Baltimore, MD 21224.

important role in the presynaptic regulation of DA release within the NAC, and (b) administration of synthetic κ-opioid receptor agonists or dynorphin, the postulated endogenous ligand for the κ-opioid receptor (3), can prevent the sensitization that develops to the locomotor stimulatory and conditioned reinforcing effects of cocaine. The role of prodynorphin-derived opioid peptides in modulating cocaine-induced alterations in mesolimbic DA neurotransmission will also be discussed.

MODULATION OF MESOLIMBIC DOPAMINE NEUROTRANSMISSION BY κ-OPIOID RECEPTOR LIGANDS

Evidence indicating interactions between mesolimbic DA neurons and neurons containing the opioid peptide dynorphin, the postulated endogenous ligand for the κ-opioid receptor (3), has been derived from both anatomical and neurochemical studies. A moderate density of κ-opioid receptors is found in the ventral tegmental area and the core of the nucleus accumbens, whereas a high density of κ-opioid receptors is found in the dorsomedial shell of the NAC (33,39). Nerve terminals containing dynorphin have been shown to synapse on DA as well as non-DA neurons in the VTA (39), and clusters of dynorphin containing soma, dendrites, and nerve terminals are found in apposition to DA as well as non-DA neurons within the NAC (58).

Several studies have shown that the acute administration of κ-opioid receptor ligands can modify the activity of mesolimbic DA neurons. Selective κ- opioid receptor agonists such as U50488 and U69593 depress the firing rate of mesolimbic DA neurons and decrease DA overflow in the nucleus accumbens (10,20). An inhibition of DA overflow is also observed in response to the central administration of dynorphin $A_{1–13}$ (37). A similar effect is observed in response to the infusion of κ-opioid agonists into the NAC, but not VTA, suggesting a specific role of NAC κ-opioid receptors in the mediation of this effect (29,44).

Evidence that κ-opioid receptor blockade can modify basal DA overflow in the NAC has also been presented. Microdialysis studies have shown that the acute administration of the selective κ-opioid receptor antagonist nor-binaltorphimine to previously drug-naive animals increases basal DA overflow within the nucleus accumbens (9,44,50). This effect is observed following antagonist infusion into the NAC, but not the VTA , suggesting the existence of a tonically active endogenous κ-opioid system (e.g., dynorphin) that modulates mesolimbic DA neurotransmission. Furthermore, the results suggest that the activation of this opioid receptor type is necessary for the maintenance of basal DA release.

INFLUENCE OF κ-OPIOID RECEPTOR AGONISTS UPON THE DEVELOPMENT OF SENSITIZATION TO COCAINE: BEHAVIORAL STUDIES

In view of the interactions between DA and κ-opioid receptor systems, our laboratory has sought to determine whether pharmacological manipulations of these systems can modify psychostimulant-induced behavioral sensitization. Recent studies examining the interaction of κ-opioid receptor agonists with cocaine suggest that this is the case. Heidbreder et al. (12,13) evaluated the locomotor stimulatory effects of cocaine in animals that had received once-daily injections of cocaine (10.0–30.0 mg/kg/day × 3 days) either alone or in combination with the selective κ-opioid receptor agonists U69593 or U50488 (27,28). Locomotor activity in response to a challenge dose of cocaine was assessed 2 days following the cessation of drug treatment, using commercially available photocell chambers (Auto-Track, Columbus, OH, USA). In animals previously exposed to cocaine, a marked increase in the behavioral response to cocaine was seen, as indicated by a significant increase in distance traveled and time spent in stereotypy. In contrast, animals that had received the same cocaine treatment regimen in combination with a κ-opioid receptor agonist failed to exhibit a sensitized behavioral response to cocaine. Thus, in these animals, the effects of cocaine did not differ from that produced by an injection of saline. The potency of U69593 and U50488 in preventing sensitization paralleled differences in their binding affinity to the κ-opioid receptor, suggesting that the effects of these agents result from the specific activation of κ-opioid receptors. Analogous findings have been obtained when a 5-day cocaine treatment regimen is employed, as well as when sensitization is assessed 3 weeks following cessation of the κ-agonist and cocaine treatment regimen (15).

The prevention of sensitization observed in these studies cannot be attributed to an acute interaction of κ-agonists with cocaine, because neither U69593 nor U50488 modifies the locomotor activating effects of an acute cocaine challenge when administered immediately prior the psychostimulant (12). Such findings suggest that repeated exposure to a κ-agonist may be necessary for the attenuation of sensitization. Alternatively, alterations in the activity of endogenous opioid or other neurotransmitter systems that occur as a consequence of κ-opioid receptor activation may underlie the interaction of κ-agonists with cocaine. The finding, however, that κ-agonist treatment fails to modify the sensitization that develops to the locomotor activating effects of other drugs of abuse (e.g., nicotine) suggests that the interaction of κ-opioid agonists with cocaine is relatively selective.

Figure 1 shows that administration of the endogenous opioid peptide dynorphin $A_{1–13}$ is also effective in preventing the sensitization that develops to the locomotor activating effects of cocaine. Animals in these studies received once-daily injections of cocaine (10 mg/kg/day), either alone or in combination with dynorphin $A_{1–13}$ (0.5 mg/kg IV), for 5 days (days 1–5). Cocaine was again administered on days 8–10, and tests of sensitization were conducted on day 12. As can be seen, the acute administration of cocaine to drug-naive animals failed to modify activity significantly. In animals, however, with a prior history of cocaine administration, a significant increase in ambulation was seen. In animals that had received dynorphin $A_{1–13}$ in combination with cocaine on days 1–5 of the treatment regimen, no evidence of sensitization was seen. Although only ambulatory activity is depicted, similar findings are observed with regard to distance traveled and time spent in stereotypy. Taken together, these findings demonstrate that κ-opioid receptor agonists as well as the postulated endogenous ligand for the κ-opioid receptor can prevent the initiation of sensitization to cocaine.

Clinical studies (11) have shown that the behavioral effects of psychostimulants and other drugs of abuse can be conditioned to stimuli previously associated with their administration. Increasing evidence suggests that the conditioning of these effects may play an important role in drug craving and in the reinstatement of compulsive drug-seeking behavior. As discussed earlier, several laboratories (29,42,43) have shown that the repeated administration of cocaine also results in sensitization to its conditioned reinforcing effects. Thus, place preference conditioning studies have demonstrated that doses of cocaine that are ineffective in producing a conditioned response in previously drug-naive animals produce robust place

preferences in animals with a prior history of cocaine administration. Recent studies in our laboratory (45) have shown that the systemic or intracerebroventricular administration of κ-opioid receptor agonists is also effective in preventing the development of this sensitized response. For these studies, the place conditioning produced by cocaine (10 mg/kg) was evaluated in drug-naive animals and in those that had previously received once-daily injections of cocaine (5.0–20.0 mg/kg) for 5 days. Place conditioning sessions (two drug, two vehicle) commenced 3 days following the cessation of these treatments and were conducted on days 8 and 9. Tests of conditioning were conducted on day 10. As reported previously (43), cocaine (10.0 mg/kg) was ineffective as a conditioning stimulus after two drug conditioning sessions in drug-naive animals. In contrast, animals that had previously received once-daily injections of cocaine showed a significant conditioned place preference in response to the subsequent administration of cocaine. In animals, however, that received the κ-opioid receptor agonists U69593 or U50488 in combination with cocaine on days 1–5 or on days 3–5 only of the cocaine treatment regimen, no evidence of a conditioned response to cocaine was seen. Figure 2 shows that a similar effect of U69593 is also observed following its intracerebroventricular administration. Thus, intracerebroventricular administration of U69593 prevents the sensitization that develops to the conditioned reinforcing effect of cocaine. As such, a specific involvement of centrally located κ-opioid receptors in modulating the development of sensitization is suggested. Indeed, the finding that the central administration of the selective κ-opioid receptor antagonist nor-binaltorphimine prevents the interaction of systemically administered κ-opioid receptor agonists with cocaine provides further proof of this hypothesis. Such findings

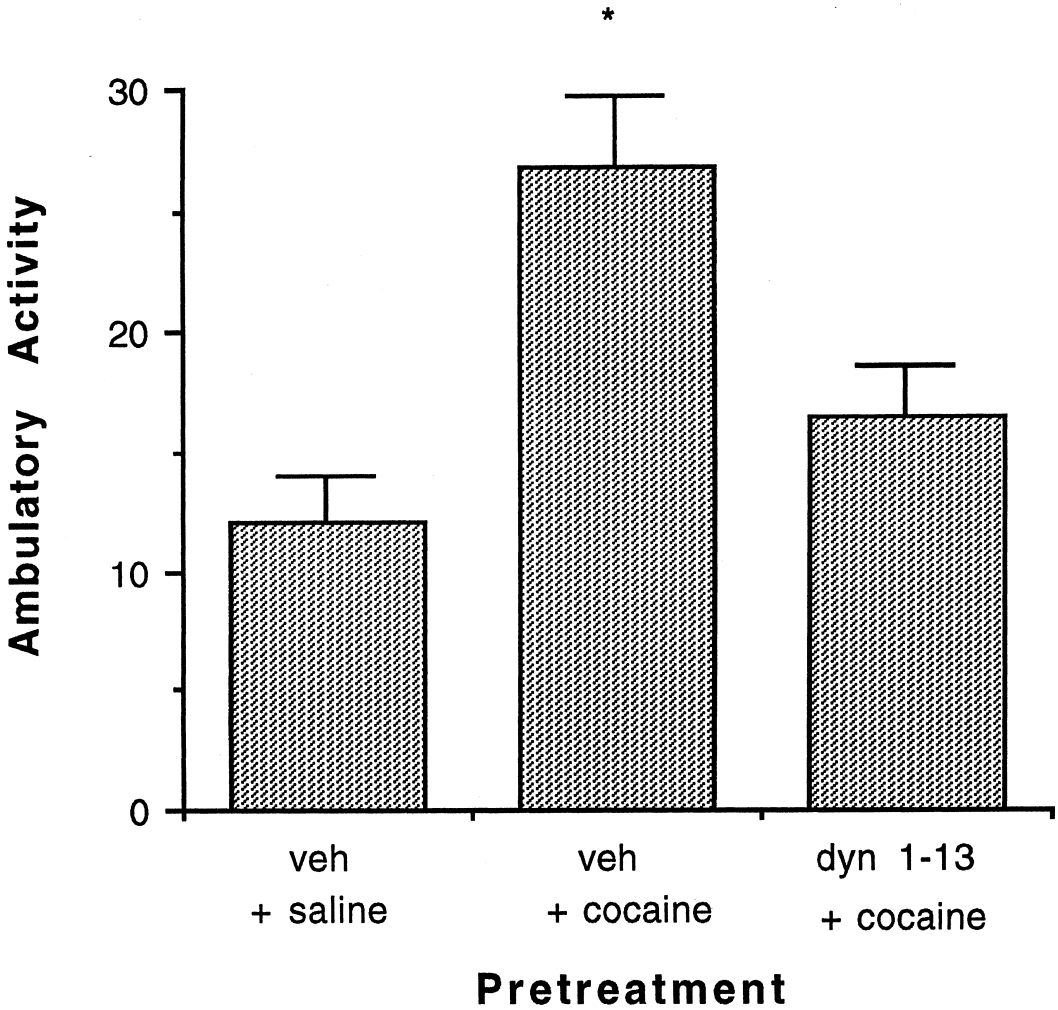

FIG. 1. Influence of dynorphin A_{1-13} upon sensitization to the locomotor activating effects of cocaine. Animals received once daily injections of saline or cocaine (10.0 mg/kg IP) on days 1–5 and again on days 8–10. On days 1–5, they received an IV injection of dynorphin A_{1-13} or its vehicle 10 min prior to the IP injections. Tests of locomotor activity were conducted on day 12, 2 days after the last cocaine injection, in a room distinct from that where repeated injections occurred. Activity was assessed in photocell chambers (40 × 30 × 35 cm) surrounded by 15 emitters and phototransistors. The sensors detected movement across two beams (distance between beams 2.4 cm). Ordinate: mean ambulatory activity/60-min test session; abscissa: pretreatment (days 1–5) condition. Asterisk denotes significant difference from other treatment groups.

add to a growing body of evidence that indicates that κ-opioid receptor agonists can modify the behavioral effects of cocaine (52,53,56). Furthermore, the findings that these agents fail to modify the behavioral effects of other drugs of abuse, such as nicotine, suggest that their effects may be selective (12).

INFLUENCE OF κ-OPIOID RECEPTOR AGONISTS UPON COCAINE-INDUCED ALTERATIONS IN EXTRACELLULAR DOPAMINE

Two microdialysis studies (5,32) have examined the influence of κ-agonist administration upon the response of mesolimbic DA neurons to an acute cocaine challenge. Both studies have found that administration of the κ-opioid receptor U50488 ca. 20 min prior to an acute cocaine challenge significantly inhibits cocaine-induced DA overflow. Indeed, such findings are not unexpected in view of the inhibitory effects of κ-opioid receptor agonists on basal DA release (10). Interestingly, however, the inhibition of cocaine-induced DA overflow was 2× greater than that on basal DA overflow, suggesting that the interaction of κ-agonists with cocaine may not merely be additive in nature.

The ability of κ-opioid receptor agonists to modify alterations in DA overflow that occur in response to repeated administration of cocaine has also been evaluated. As discussed previously, several studies (62,63) have shown that basal DA overflow within the nucleus accumbens is increased following cessation of repeated cocaine administration. This effect, which is apparent 1–3 days following cessation of drug treatment, is presumed to result from a cocaine-induced supersensitivity of D2 autoreceptors in the VTA and an increase in the burst firing of DA neurons projecting to the NAC (1,64). Employing a cocaine treatment regimen identical to that which results in behavioral sensitization, we have recently found that administration of the κ-opioid receptor agonist U69593 prevents the elevation of DA overflow that occurs during the early stages

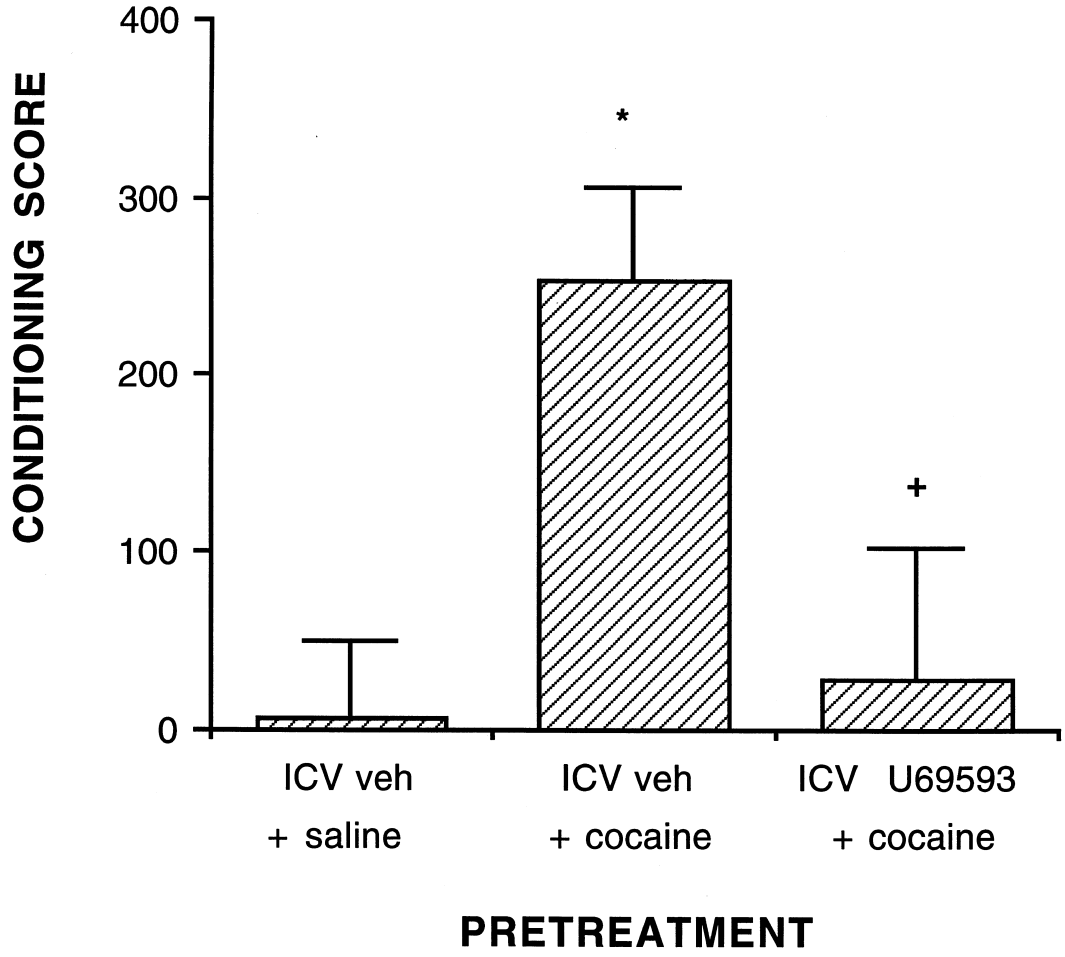

FIG. 2. Influence of the κ-opioid receptor agonist U69593 upon sensitization to the conditioned reinforcing effects of cocaine. Animals received once-daily IP injections of saline or cocaine (10.0 mg/kg) for 5 days (days 1–5). On days 3–5, they received an intracerebroventricular injection of U69593 (1.0 μg) or vehicle in combination with the IP injections. Place conditioning sessions (cocaine 10.0 mg/kg vs. saline) commenced 2 days later and were conducted on days 8 and 9. On each of these days, animals received one conditioning session with cocaine and one with saline. Tests of conditioning (15 min in duration) occurred on day 10. Data are presented as the time spent in the drug-paired place minus that spent in the vehicle-paired place (mean ± SE) during the 15-min test session. Asterisk denotes significant cocaine-induced place preference, and plus indicates significant effect of U69593 treatment. [See Shippenberg et al. (45) for details.]

of withdrawal from cocaine (14,15). Thus, whereas animals exposed to cocaine for 3 or 5 days exhibit a ca. 3× increase in basal DA overflow relative to controls, no alteration in basal DA overflow is observed in animals that received the κ-opioid receptor agonist U69593 (0.04–0.16 mg/kg) in combination with cocaine. The reduction in DA could not be attributed to the inhibitory effects of U69593 on basal DA overflow, because no alteration in DA overflow was observed in rats that had previously received once-daily injections of U69593 in combination with saline. Evidence that U69593 treatment can also prevent the progressive enhancement of cocaine-induced DA overflow that occurs some weeks following the cessation of repeated cocaine treatment has also been presented recently (15). Taken together, such findings demonstrate that κ-opioid receptor agonists can prevent the acute and long-term alterations in neurochemistry that occur as a consequence of repeated cocaine exposure. Furthermore, they suggest that κ-opioid receptor agonists may, by decreasing the responsiveness of DA neurons to cocaine, prevent the behavioral sensitization to this psychostimulant that develops following its repeated administration.

INFLUENCE OF REPEATED COCAINE ADMINISTRATION UPON ENDOGENOUS OPIOID PEPTIDE SYSTEMS

DA neurons have been shown to regulate dynorphin gene expression in the mammalian central nervous system. Stimulation of DA receptors by the D1–D2 dopamine receptor agonist apomorphine increases dynorphin immunoreactivity and prodynorphin mRNA in both the striatum and the NAC (30,31). In contrast, the chronic blockade of D1 DA receptors decreases prodynorphin gene expression and tissue levels of dynorphin (7,35,36).

Pronounced changes in dynorphin gene expression are also observed in response to the repeated intermittent administration of psychostimulants. Thus, repeated or bingelike administration of cocaine markedly increases prodynorphin mRNA in the striatum and NAC (6,18,47,51). A similar increase is also observed in response to acute or repeated administration of amphetamine or methamphetamine (49,61). Interestingly, these increases are observed some hours following the cessation of drug treatment and are not apparent at earlier time points, suggesting that they may be a compensatory response to the elevation of extracellular DA levels that occurs following psychostimulant administration. Indeed, consistent with this hypothesis is the finding that the coadministration of D1 or D2 DA receptor antagonists blocks cocaine-induced increases in prodynorphin mRNA and dynorphin immunoreactivity (7,48). Interestingly, the NMDA receptor antagonist MK-801 has also been shown to block cocaine- and amphetamine-induced increases in prodynorphin gene expression (46,60,61). Furthermore, administration of MK-801 by itself was recently shown to increase prodynorphin gene expression in both the striatum and the nucleus accumbens (2). Such findings may be particularly noteworthy in view of the documented role of excitatory amino acids in both sensitization and regulation of DA release (21,46,47,55) and recent findings that κ-opioid receptor agonists inhibit glutamate neurotransmission via both pre- and postsynaptic mechanisms (4,34).

Postmortem studies of human cocaine addicts have also revealed marked increases in prodynorphin gene expression as well as dynorphin content and κ-opioid receptor number in the nucleus accumbens (19). Taken together, such findings demonstrate that psychostimulants can modify the activity of endogenous κ-opioid systems and that the actions of these agents are prevented by treatments that either directly (e.g., DA receptor antagonists) or indirectly (e.g., NMDA receptor antagonists) decrease psychostimulant-induced increases in DA neurotransmission.

CONCLUSIONS

Several studies have shown that κ-opioid receptor agonists can prevent the development of behavioral sensitization to cocaine as well as those changes in mesolimbic DA neurotransmission that occur in response to repeated administration of this agent. It is also apparent that repeated administration of cocaine and other psychostimulants can profoundly affect the activity of endogenous κ-opioid systems. κ-Opioid receptors within the NAC are increased (19,57), prodynorphin gene expression is elevated (8,51), and an increase in dynorphin immunoreactivity is seen (30,31,48). Given such findings, and the role of κ-opioid receptors in the presynaptic modulation of DA release, the possibility arises that repeated administration of cocaine and other stimuli that increase extracellular DA levels within the NAC result in a compensatory increase in the activity of dynorphinergic neurons. This increase opposes, but is insufficient to prevent, the development of behavioral sensitization. If, in fact, such is the case, then administration of synthetic as well as endogenous κ-opioid receptor agonists may, by augmenting the actions of the endogenous opioid system, prevent the development of this phenomenon. Although additional studies are needed to verify this hypothesis, the finding that κ-opioid receptor agonists can attenuate various psychostimulant-induced behaviors suggests that these agents may be potential therapeutic agents for the treatment of drug addiction and those disorders that result from an alteration in mesolimbic DA neurotransmission.

REFERENCES

1. Ackerman, J. M.; White, F. L.: A10 somatodendritic dopamine autoreceptor sensitivity following withdrawal from repeated cocaine treatment. Neurosci. Lett. 117:181–187; 1990.
2. Angulo, J. A.; Williams, A.; Ledoux, M.; Watanabe, Y.; McEwen, B.: Elevation of striatal and accumbal preproenkephalin, preprotachykinin and preprodynorphin mRNA abundance subsequent to NMDA receptor blockade with MK-801. Mol. Brain Res. 29: 15–22; 1995.
3. Chavkin, C.; James, I. F.; Goldstein, A.: Dynorphin is a specific endogenous ligand of the κ-opioid receptor. Science 215:413–415; 1982.
4. Chen, L.; Gu, Y.; Huang, L.-Y.: The opioid peptide dynorphin directly blocks NMDA receptor channels in the rat. J. Physiol. 482:575–581; 1995.
5. Crawford, C. A.; Nguyen, S.; Hall, S. E.; Berger, S. P.: Microdialysis and behavioral evidence of the functional antagonism of cocaine by the kappa agonist U50488. In: Harris, L. S., ed. Problems of drug dependence: Proceedings of the 55th Annual Scientific Meeting, The College on Problems of Drug Dependence. NIDA Research Monograph 141. Rockville, MD: US Government Printing Office; 1993:107.
6. Daunais, J. B.; McGinty, J. F.: Acute and chronic cocaine binging differentially alter striatal opioid and nuclear transcription factor mRNAs. Synapse 18:35–45; 1994.

7. Daunais, J. B.; McGinty, J. F.: 1995. Cocaine binges differentially alter striatal preprodynorphin and zif/268 mRNAs. Mol. Brain Res. 29:201–210; 1995.
8. Daunais, J. B.; Roberts, D. C. S.; McGinty, J. F.: Cocaine self-administration increases prodynorphin, but not c-fos mRNA in rat striatum. NeuroReport 4:543–546; 1993.
9. Devine, D. P.; Leone, P.; Pocock, D.; Wise, R. A.: Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: In vivo microdialysis studies. J. Pharmacol. Exp. Ther. 266:1236–1246; 1993.
10. Di Chiara, G.; Imperato, A.: Opposite effects of μ- and κ-opioid agonists on dopamine release in the nucleus accumbens and dorsal caudate of freely-moving rats. J. Pharmacol. Exp. Ther. 244:1067–1080; 1988.
11. Ehrman, R. N.; Robbins, S. J.; Childress, A. R.; O'Brian, C.: Conditioned responses to cocaine-related stimuli in cocaine abuse patients. Psychopharmacology 107:523–529; 1992.
12. Heidbreder, C. A.; Babovic-Vuksanovic, D.; Shoaib, M.; Shippenberg, T. S.: Development of behavioral sensitization to cocaine: Influence of kappa opioid receptor agonists. J. Pharmacol. Exp. Ther. 275:150–163; 1995.
13. Heidbreder, C.; Goldberg, S.; Shippenberg, T. S.: The kappa opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization in the rat. Brain Res. 616:333–338; 1993.
14. Heidbreder, C. A.; Shippenberg, T. S.: U69593 prevents cocaine sensitization by normalizing basal accumbens dopamine. NeuroReport 5:1797–1800; 1994.
15. Heidbreder, C. A.; Shippenberg, T. S.: κ-Agonists prevent initiation and long-term expression of behavioral sensitization to cocaine by normalizing cocaine-induced alterations in extracellular dopamine. Soc. Neurosci. Abstr. 2:718; 1995.
16. Henry, D. J.; White, F. J.: Repeated cocaine administration causes persistent enhancement of D1 dopamine receptor sensitivity within the rat nucleus accumbens. J. Pharmacol. Exp. Ther. 258: 882–890; 1991.
17. Horger, B. A.; Shelton, K.; Schenk, S.: Pre-exposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37:707–711; 1990.
18. Hurd, Y. L.; Brown, E. E.; Finlay, J. M.; Fibiger, H. C.; Gerfen, C. R.: Cocaine self-administration differentially alters mRNA expression of striatal peptides. Mol. Brain Res. 13:165–170; 1992.
19. Hurd, Y. L.; Herkenham, M.: Molecular alterations in the neostriatum of human cocaine addicts. Synapse 13:357–369; 1993.
20. Jeziorski, M.; White, F. J.: Electrophysiological effects of selective opioid receptor agonists on A10 dopamine (DA) neurons. Soc. Neurosci. Abstr. 15:1001; 1989.
21. Johnson, S. W.; Seutin, V.; North, R. A.: Burst firing in dopamine neurons induced by *N*-methyl-D-aspartate: Role of electrogenic sodium pump. Science 258:665–667; 1992.
22. Kalivas, P. W.; Alesdatter, J. E.: Involvement of *N*-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. J. Pharmacol. Exp. Ther. 267:486–495; 1993.
23. Kalivas, P. W.; Duffy, P.: Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. J. Neurosci. 131:266–275; 1993.
24. Kalivas, P. W.; Stewart, J.: Dopamine transmission in the initiation and expression of drug and stress induced sensitization. Brain Res. Rev. 16:223–244; 1991.
25. Karler, R.; Calder, L. D.; Chaudhry, I. A.; Turkanis, S. A.: Blockade of 'reverse-tolerance' to cocaine and amphetamine by MK-801. Life Sci. 45:599–606; 1989.
26. Kelly, P.; Iversen, S. D.: Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activities in rats. Eur. J. Pharmacol. 40:45–56; 1986.
27. Lahti, R. A.; Mickelson, M. M.; McCall, J. M.; Von Voightlander, P. F.: [^{3}H]U69593, a highly selective ligand for the κ-opioid receptor. Eur. J. Pharmacol. 109:281–284; 1985.
28. Lahti, R. A.; Von Voightlander, P. F.; Barsuhn, C.: Properties of a selective kappa agonist U-50488H. Life Sci. 31:2257–2260; 1982.
29. Lett, B. T.: Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine and cocaine. Psychopharmacology 98:357–362; 1989.
30. Li, S. J.; Jiang, M. S.; Stachowiak, M. S.; Hudson, P. M.; Owyan g, V.; Nanry, K.; Tilson, H. A.; Hong, J. S.: Influence of nigrostriatal dopaminergic tone on the biosynthesis of dynorphin and enkephalin in rat stratum. Mol. Brain Res. 8:219–225; 1990.
31. Li, S. J.; Sivam, S. P.; Hong, J. S.: Regulation of the concentration of dynorphin A1–8 in the striatonigral pathway by the dopaminergic system. Brain Res. 398:390–392; 1986.
32. Maisonneuve, I. M.; Archer, S.; Glick, S. D.: U50,488, a κ opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens. Neurosci. Lett. 181:57–60; 1994.
33. Mansour, A.; Khachaturian, H.; Lewis, M. E.; Akil, H.; Watson, S. J.: Autoradiographic differentiation of mu, delta and kappa receptors in rat forebrain and midbrain. J. Neurosci. 7:2445–2464; 1987.
34. Millan, M. H.; Chapman, A. G.; Meldrum, B. S.: Dual inhibitory action of enadoline (CI977) on release of amino acids in the rat hippocampus. Eur. J. Pharmacol. 279:75–81; 1995.
35. Morris, B. J.; Herz, A.; Hollt, V.: Localization of striatal opioid gene expression and its modulation by the mesostriatal dopamine pathway: An in situ hybridization study. J. Mol. Neurosci. 1:9–18; 1988.
36. Morris, B. J.; Hollt, V.; Herz, A.: Dopaminergic regulation of striatal proenkephalin mRNA and prodynorphin mRNA: Contrasting effects of D1 and D2 antagonists. Neuroscience 25:525–532; 1988.
37. Mulder, A. H.; Wardeh, G.; Hogenboom, F.; Frankhuyzen, A. L.: Selectivity of various opioid peptides towards delta-, kappa-, and mu-opioid receptors mediating presynaptic inhibition of neurotransmitter release in the brain. Neuropeptides 14:99–104; 1989.
38. Piazza, P. V.; Deminiere, J. M.; Le Moal, M.; Simon, H.: Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res. 514:22–26; 1990.
39. Pickel, V. M.; Chan, J.; Sesack, S. R.: Cellular substrates for interactions between dynorphin terminals and dopamine dendrites in rat ventral area and substantia nigra. Brain Res. 692:275–289; 1993.
40. Robinson, T. E.; Berridge, K. C.: The neural basis of drug-craving: An incentive–sensitization theory of addiction. Brain Res. Rev. 18:247–291; 1993.
41. Robledo, P.; Maldonado, L.; Koob, G. F.: Role of dopamine receptors in the nucleus accumbens in the rewarding properties of cocaine. Ann. N.Y. Acad. Sci. 654:509–512; 1992.
42. Sala, M.; Braida, D.; Colombo, M.; Gropetti, A.; Sacco, S.; Gori, E.; Parenti, M.: Behavioral and biochemical evidence of opioidergic involvement in cocaine sensitization. J. Pharmacol. Exp. Ther. 274:450–457; 1995.
43. Shippenberg, T. S.; Heidbreder, Ch.: Sensitization to the conditioned rewarding effects of cocaine: Pharmacological and temporal aspects. J. Pharmacol. Exp. Ther. 273:808–815; 1995.
44. Shippenberg, T. S.; Herz, A.; Spanagel, R.; Bals-Kubik, R.; Stein, C.: Conditioning of opioid reinforcement: Neuroanatomical and neurochemical substrates. Ann. N.Y. Acad. Sci. 654:347–356; 1992.
45. Shippenberg, T. S.; LeFevour, A.; Heidbreder, Ch.: κ-Opioid receptor agonists prevent sensitization to the conditioned rewarding effects of cocaine. J. Pharmacol. Exp. Ther. 276:545–554; 1996.
46. Singh, N. A.; Midgely, L. P.; Bush, J. W.; Hanson, G. R.: *N*-Methyl-D-aspartate receptors mediate dopamine-induced changes in extrapyramidal and dynorphin systems. Brain Res. 555:233–238; 1991.
47. Sivam, S. P.: Cocaine selectively increases striatonigral dynorphin levels by a dopaminergic mechanism. J. Pharmacol. Exp. Ther. 250: 818–824; 1989.
48. Smiley, P. L.; Johnson, M.; Bush, L.; Gibb, J. W.; Hanson, G. R.: Effects of cocaine on extrapyramidal and limbic dynorphin systems. J. Pharmacol. Exp. Ther. 253:938–943; 1990.
49. Smith, A. J. W.; McGinty, J. F.: Acute amphetamine or metham-

phetamine alters opioid peptide mRNA expression in rat striatum. Mol. Brain Res. 21:359–362; 1994.
50. Spanagel, R.; Herz, A.; Shippenberg, T. S.: Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc. Natl. Acad. Sci. USA 89:2046–2050; 1992.
51. Spangler, R.; Unterwald, E. M.; Kreek, M. J.: "Binge" cocaine administration induces a sustained increase of prodynorphin mRNA in rat caudate-putamen. Mol. Brain Res. 19:323–327; 1993.
52. Spealman, R. D.; Bergman, J.: Modulation of the discriminative stimulus effects of cocaine by mu and kappa opioids. J. Pharmacol. Exp. Ther. 261:637–645; 1992.
53. Spealman, R. D.; Bergman, J.: Opioid modulation of the discriminative stimulus effects of cocaine: Comparison of mu, kappa, and delta agonists in squirrel monkeys discriminating low doses of cocaine. Behav. Pharmacol. 5:21–31; 1994.
54. Stewart, J.; Badiani, A.: Tolerance and sensitization to the behavioral effects of drugs. Behav. Pharmacol. 4:289–313; 1993.
55. Suad-Chagny, M. F.; Chergui, K.; Chouvet, G.; Gonon, F.: Relationship between dopamine release in the rat nucleus accumbens and discharge of activity of dopaminergic neurons during local in vivo application of amino acids in the ventral tegmental area. Neuroscience 49:63–72; 1992.
56. Ukai, M.; Kamiya, T.; Toyeshi, T.; Kameyama, T.: Systemic administration of dynorphin A (1–13) inhibits different behavioral responses induced by cocaine in the mouse. Neuropharmacology 31:843–849; 1992.
57. Unterwald, E. M.; Rubenfeld, J. M.; Kreek, M. J.: Repeated cocaine administration upregulates κ and μ but not δ, opioid receptors. NeuroReport; 5:1613–1616; 1994.
58. Van Bockstaele, E.; Gracy, K. N.; Pickel, V. M.: Dynorphin-immunoreactive neurons in the rat nucleus accumbens: Ultrastructure and synaptic inputs from terminals containing substance P and/or dynorphin. J. Comp. Neurol. 35:117–133; 1995.
59. Vezina, P.; Stewart, J.: Amphetamine administered to the ventral tegmental area but not to the nucleus accumbens sensitizes rats to systemic morphine: Lack of conditioned effects. Brain Res. 516:99–106; 1990.
60. Wang, J. Q.; Daunais, J. B.; McGinty, J. F.: NMDA receptors mediate amphetamine-induced upregulation of zif/268 and preprodynorphin mRNA expression in rat striatum. Synapse 18:343–353; 1994.
61. Wang, J. Q.; McGinty, J. F.: Dose-dependent alteration in zif/268 and preprodynorphin mRNA expression induced by amphetamine or methamphetamine in rat forebrain. J. Pharmacol. Exp. Ther. 273:909–917; 1995.
62. Weiss, F.; Markou, A.; Lorang, M. T.; Koob, G. F.: Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited access self-administration. Brain Res. 593:314–319; 1992.
63. Weiss, F.; Paulus, M. P.; Lorang, M. T.; Koob, G. F.: Increases in extracellular dopamine in the nucleus accumbens are inversely related to basal levels: Effects of acute and repeated administration. J. Neurosci. 12:4372–4380; 1992.
64. White, F. J.; Wang, R. Y.: Electrophysiological evidence for A10 dopamine autoreceptor subsensitivity following chronic *d*-amphetamine treatment. Brain Res. 309:283–292; 1984.
65. Wolf, M. E.; White, F. J.; Hu, X.-T.: MK-801 prevents alterations in the mesoaccumbens dopamine system associated with behavioral sensitization to amphetamine. J. Neurosci. 14:1735–1745; 1994.
66. Wolf, M. E.; White, F. J.; Nassar, R.; Brooderson, R. J.: Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. J. Pharmacol. Exp. Ther. 264:249–255; 1994.