Pharmacology Biochemistry and Behavior, Vol. 63, No. 2, pp. 271–277, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00261-5

Orphanin FQ and Behavioral Sensitization to Cocaine

SHRIDHAR NARAYANAN AND NIGEL T. MAIDMENT

Department of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute and Brain Research Institute, UCLA, Los Angeles, CA 90024

Received 26 June 1998; Revised 16 November 1998; Accepted 2 December 1998

NARAYANAN, S. AND N. T. MAIDMENT. *Orphanin FQ and behavioral sensitization to cocaine.* PHARMACOL BIOCHEM BEHAV **63**(2) 271–277, 1999.—The recently identified endogenous ligand for the ORL-1 (opioid receptor-like) receptor, orphanin FQ, has been shown to induce hypolocomotion and to decrease extracellular dopamine levels in the nucleus accumbens (N.Acc) after intraventricular (ICV) administration. This study investigated the effect of intraventral tegmental area (VTA) administration of orphanin FQ on the hyperlocomotor effects of peripheral cocaine administration and on the development of behavioral sensitization to cocaine. The administration of cocaine (40 mg/kg IP) once daily for 3 days to male Sprague–Dawley rats resulted in an enhanced locomotor response to a subsequent challenge of cocaine (10 mg/kg IP) 5 days later. The bilateral administration of orphanin FQ (10 μg/side or 30 μg/side) into the VTA 5–10 min prior to the administration of cocaine (40 mg/kg IP) produced a transient (15–30 min) decrease in the hyperlocomotor response to cocaine on day 1 but not on days 2 and 3 of the sensitization paradigm. Such orphanin FQ pretreatment on days 1–3 had no effect on the development of a sensitized response to cocaine (10 mg/kg IP) 5–7 days after the last orphanin FQ injection. However, repeated intra-VTA administration of orphanin FQ (30 μg/side) alone for 3 days resulted in a sensitized response to a single dose of cocaine (10 mg/kg IP) given 5–7 days later. These results indicate that orphanin FQ decreases the activity of mesolimbic dopamine neurons via an action in the VTA, an effect that is both transient and demonstrates rapid tolerance, and consequently, is insufficient to prevent the development of cocaine sensitization. The ability of the peptide to induce cocaine sensitization when administered alone despite its acute inhibitory effects is unique and requires further study to elucidate the mechanisms responsible. © 1999 Elsevier Science Inc.

Orphanin FQ Dopamine Cocaine Sensitization Ventral tegmental area

THE family of opioid receptors and peptides was recently expanded by the identification of a new G-protein–coupled receptor—termed ORL-1 (opioid receptor like) (1,2,3,6,14,17,22, 33,34) and, subsequently, its heptadecapeptide endogenous ligand—termed orphanin FQ or nociceptin (15,24). The ORL-1 receptor has sequence homology with the previously cloned mu, delta, and kappa opioid receptors, and orphanin FQ has homology with other opioid peptides, particularly with dynorphin A(1–17). Preliminary studies indicated that orphanin FQ systems may functionally oppose certain opioid actions in the central nervous system. Thus, central injection of orphanin FQ blocks opioid-dependent stress-induced analgesia (16) and induces hypolocomotion, in contrast to the hyperactivity observed following mu or delta agonist administration (5,24). The possible involvement of dopamine systems in mediating the hypolocomotor effect of orphanin FQ is suggested by our previous finding that extracellular dopamine levels in the nucleus accumbens (N. Acc) are reduced after intracerebroventricular (ICV) administration of orphanin FQ in anesthetized rats (19). A similar effect was observed after administration of the peptide to the ventral tegmental area (VTA) (18). These observations suggest that orphanin FQ can modulate neurotransmission in the mesolimbic dopaminergic pathway in a negative fashion, possibly via an action in the VTA.

The present study sought to provide further evidence for such an action by examining the effect of orphanin FQ on cocaine-induced locomotor activity and, in particular, the effects of this peptide on the development of cocaine sensitization. Repeated administration of psychostimulants such as cocaine and amphetamine results in a progressive and long-lasting enhancement of the locomotor activity response to a subsequent challenge administration of these drugs, a phenomenon that

Requests for reprints should be addressed to Nigel T. Maidment, Ph.D., Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, 760 Westwood Plaza, Los Angeles, CA 90024.

has been proposed as a useful animal model of craving for, and dependence on, psychostimulant drugs [for review, see (13,25,26)]. Changes in mesolimbic dopamine neurotransmission are thought to be involved in this sensitization process. Thus, the VTA is proposed as the site at which sensitization develops, whereas expression of the sensitized behavior is thought to require an action of the drug in the N.Acc [see (13)].

There is evidence for a role of opioid systems in the development of psychostimulant sensitization. The mu and delta opioid receptor antagonists, naloxone and naltrindole, respectively, have been shown to block the development of cocaine sensitization (9,27,29). Furthermore, kappa agonists, which have an inhibitory effect on dopaminergic neurotransmission (4,31), block the development of sensitization to cocaine (7,8, 30). We, therefore, hypothesized that, given orphanin FQ's proposed "opiate-opposing" action and its acute effects on nucleus accumbens dopamine release, this peptide may block the development of cocaine sensitization when administered into the VTA.

METHOD

Surgery

Male Sprague–Dawley rats (Harlan Inc., Indianapolis, IN), weighing 250–300 g at the time of surgery, were housed two per cage in a temperature-controlled (22 ± 1°C) environment with a 12 L:12 D cycle with lights on at 0700 h. All experiments were conducted in the light phase. The animals were provided with food and water ad lib. All procedures involving animals were performed in accordance with the NIH "Guide for Care and Use of Laboratory Animals," and were approved by the UCLA Institutional Laboratory Animal Care and Use Committee. The animals were anesthetized with 1–2% halothane in a 1:1 mixture of oxygen and nitrous oxide and mounted on a stereotaxic frame with the incisor bar set at 3.3 mm below the interaural plane. Guide cannulae (22 gauge, Plastics One Inc., Roanoke, VI) were implanted bilaterally above theVTA using the following coordinates (23): A/P −4.8 mm, M/L ± 2.7 mm, D/V 8.7 mm at an angle of 10° towards the midline. The guide cannulae were fixed with the support of stainless steel screws and dental cement, and were kept patent by the insertion of obturators. The animals were returned to their home cages for at least 5 days prior to experimentation.

Sensitization Paradigm and the Measurement of Locomotor Activity

For the development of cocaine sensitization, animals were adapted to the locomotor test cages (which were cylindrical in shape, 15" high and 10" in diameter at the base), on days 1–3 for at least 1 h prior to the peripheral administration of either saline or cocaine (40 mg/kg IP) and remained in these cages for a further 1 h for measurement of locomotor activity divided into 4 × 15-min epochs. Locomotor activity was monitored using an automated video system (Videomex, Columbus Instruments Inc., Columbus, OH). Five to 10 min prior to each saline or cocaine injection, the animals were administered orphanin FQ (10 or 30 μg/side in a volume of 0.5 μl) or artificial cerebrospinal fluid vehicle (aCSF) bilaterally into the VTA. On the test day (days 8–10) animals were adapted to the test cages for at least 1 h prior to a challenge injection of saline or cocaine (10 mg/kg IP), and their locomotor activity monitored for an additional 90 min.

Histology

After the completion of the experiments animals were euthanized using pentobarbital (50 mg/kg/IP), and the brains removed and stored in 10% formaldehyde for at least 24 h prior to sectioning in a cryostat, mounting, and staining with cresyl violet. Sites of injection were verified with light microscopy.

Drugs

Orphanin FQ (FGGFTGARKSARKLANQ) was synthesized in-house on 2-chlorotrityl resin (A naspec Inc., San Jose, CA) using standard Fmoc procedures. The peptide was purified by preparative reverse phase HPLC to a level of purity that produced a single peak by analytical HPLC. The identity of this peak as orphanin FQ was confirmed using fast atom bombardment mass spectroscopy. The peptide was dissolved in aCSF just prior to administration. Cocaine hydrochloride was obtained from Sigma Chemicals Inc. (St. Louis, MO), and dissolved in saline (0.9%).

Statistical Analysis

Data are expressed as mean ± SEM. Statistical analysis was performed using either a two-way repeated-measures ANOVA or a one-way ANOVA as appropriate, followed by the Fisher's protected LSD post hoc test with a $p < 0.05$ considered significant.

RESULTS

Acute Intra-VTA Orphanin FQ Administration Transiently Inhibits Cocaine-Induced Hyperactivity

The results of the various combinations of drug treatments on day 1 are shown in Fig. 1A. Two-way repeated-measures ANOVA revealed a significant effect of drug treatment, $F(4) = 6.62$, and a significant treatment vs. time interaction, $F(12) = 3.97$. Post hoc analysis revealed no significant effect of intra-VTA orphanin FQ (30 μg) administration on basal (systemic saline-induced) locomotor activity. In animals pretreated with aCSF in the VTA, there was a significant effect of cocaine vs. saline at all time points. Pretreatment with orphanin FQ in the VTA at both doses tested (10 and 30 μg) produced a time-dependent inhibition of cocaine-induced hyperlocomotion. This effect was statistically significant only for the 0–15-min time period.

Tolerance to the Acute Effect of Orphanin FQ on Cocaine Hyperactivity

No statistically significant inhibitory effect of orphanin FQ was apparent on days 2 and 3 of the cocaine sensitization paradigm at any time point (Fig. 1B and 1C).

Repeated Intra-VTA Orphanin FQ Administration Does Not Effect the Development of Cocaine Sensitization

One-way ANOVA showed a significant difference between drug treatment groups shown in Fig. 2 and 3, $F(6) = 5.03$. Post hoc analysis revealed that animals administered cocaine (40 mg/kg) on days 1–3 exhibited a sensitized response to a challenge injection (10 mg/kg) on days 8–10 (Fig. 2). There was no significant difference between such cocaine-sensitized animals and similarly treated animals administered orphanin FQ (10 or 30 μg) into the VTA prior to cocaine on days 1–3 (Fig. 2).

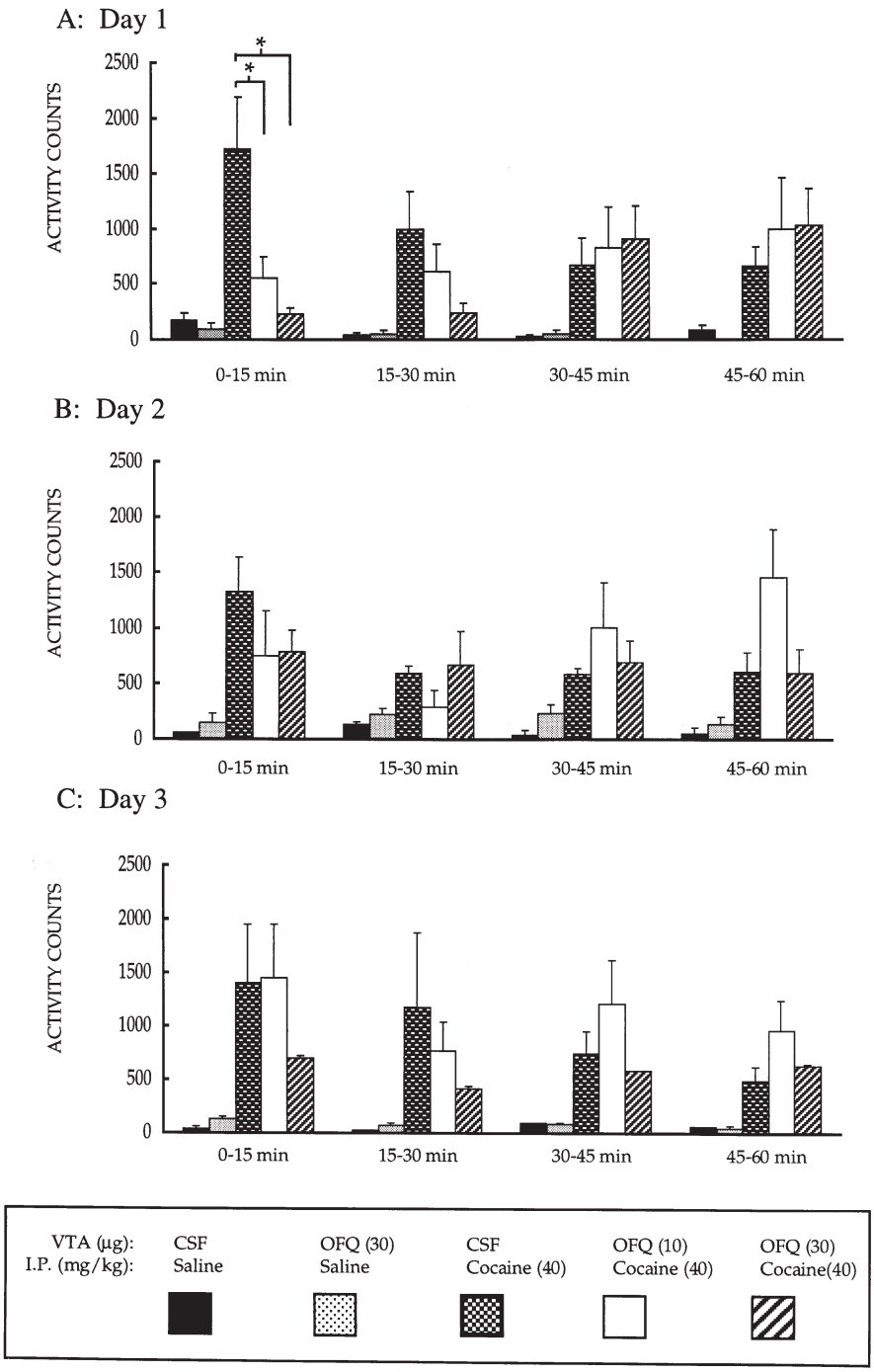

FIG. 1. Effect of orphanin FQ on cocaine-induced locomotor activity on day 1 (A), day 2 (B), and day 3 (C) of the sensitization procedure. Rats were administered either aCSF or orphanin FQ into the VTA prior to peripheral injection of either saline or cocaine (40 mg/kg IP). Locomotor activity was recorded in 15-min epochs for 1 h. Each value represents a mean ± SEM of six animals, with the exception of the OFQ (10)/cocaine (n = 4) and OFQ (30)/cocaine (n = 7) groups. *$p < 0.05$.

Repeated Intra-VTA Orphanin FQ Administration Alone Induces a Heightened Response to Cocaine

Repeated intra-VTA administration of orphanin FQ alone, in the absence of peripheral cocaine injection, on days 1–3 produced an enhanced response of the animals to cocaine (10 mg/kg) (Fig. 3). The amplitude of this sensitized response (3331 ± 420 activity counts/min) was similar to that produced by cocaine itself (3150 ± 625, Fig. 2). Although not statisti-

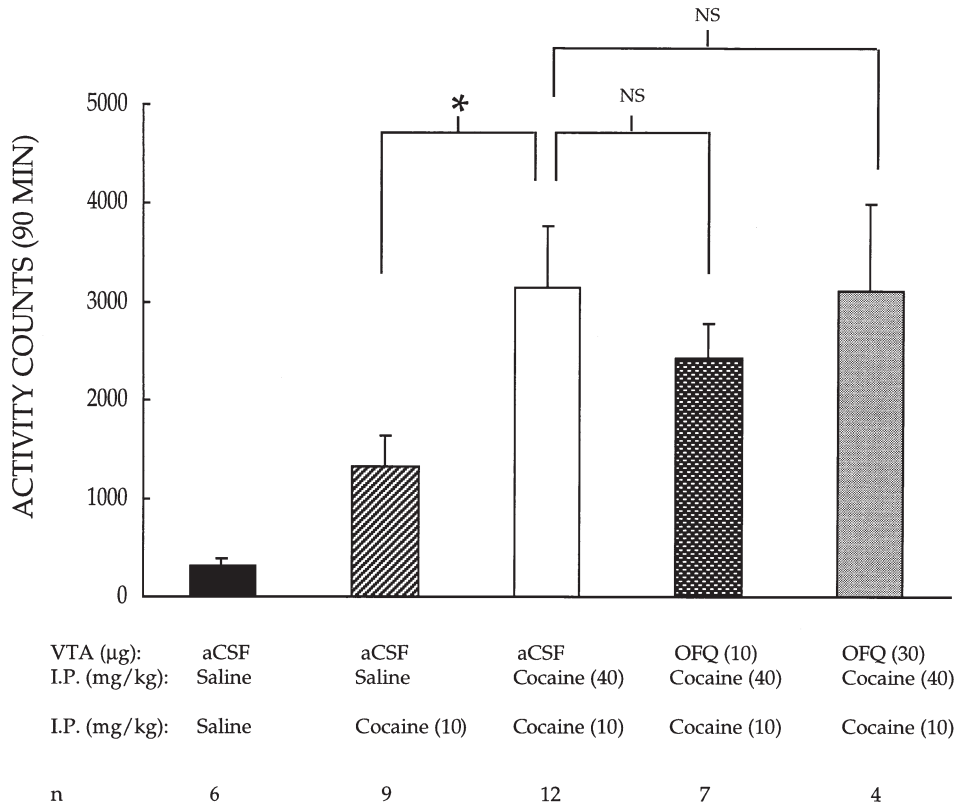

FIG. 2. Lack of effect of intra-VTA orphanin FQ administration prior to cocaine injection on the development of cocaine sensitization. Rats were treated as described in Fig. 1 and on day 8, 9, or 10 were administered either saline or cocaine (10 mg/kg IP). Locomotor activity was recorded over a 90-min period. Each value represents the mean ± SEM of 5–12 animals, as indicated. *$p < 0.05$.

cally significant, OFQ-injected animals also tended to exhibit higher activity in response to peripheral saline administration (Fig. 3).

DISCUSSION

Previous reports have described a hypolocomotor action of orphanin FQ when administered ICV to rats and mice (5,24). The possibility that dopamine systems may be a target for orphanin FQ in this regard was suggested by the observation that extracellular dopamine levels in the N.Acc are reduced following ICV orphanin FQ administration (19). The present data lend further support to this hypothesis. Thus, intra-VTA administration of orphanin FQ produced a short-lasting reduction in acute cocaine-induced hyperactivity. Given the route of orphanin FQ administration and the fact that, as a blocker of dopamine reuptake, cocaine's actions are to a great extent dependent on dopaminergic neuron impulse flow, the most parsimonious explanation of the data is that orphanin FQ in some way inhibits the activity of VTA dopamine neurons. Indeed, preliminary data from our laboratory shows that such intra-VTA orphanin FQ administration decreases extracellular dopamine in the N.Acc (18). However, the possibility that orphanin FQ acts on a system distal to the dopamine terminals in the N.Acc, such as an output of the N.Acc to the VTA, or to a region in close proximity to the VTA, cannot be excluded at this time.

There are several possible explanations for the transient nature of the behavioral effect observed (15–30 min). First, it is possible that the peptide is unstable in vivo—no peptidase inhibitors were employed in the present study. Alternatively, the ORL-1 receptor may rapidly desensitize or transynaptic compensatory mechanisms may quickly counteract orphanin FQ's action. Tolerance to orphanin FQ's hypolocomotor action has been reported to develop after a single ICV administration (5). In support of this, we also failed to observe any effect of the peptide on days 2 and 3 of the cocaine sensitization paradigm. It is notable that the immediate but transient nature of the behavioral effect of the initial intra-VTA orphanin FQ injection contrasts with the slower onset but longer lasting (over 2 h) effect of the peptide on N.Acc extracellular dopamine levels after ICV administration (19). The difference in speed of onset likely reflects the different routes of administration. The apparent lack of rapid desensitization in our neurochemical experiment may similarly be a consequence of the more gradual buildup of the peptide at its proposed site of action in the VTA after ICV administration. However, similarly transient effects of orphanin FQ on other behavioral and physiological measures have been reported after ICV administration [see (10) for review]. An alternative explanation for the differential time courses of the locomotor and neurochemical response, therefore, is that compensatory mechanisms distal to the postsynaptic dopamine receptors prevent the behavioral expression associated with a prolonged extracellular dopamine depression in the nucleus accumbens. The presence of anesthetic in the dialysis experiment may also contribute to the difference in response time course between the two studies.

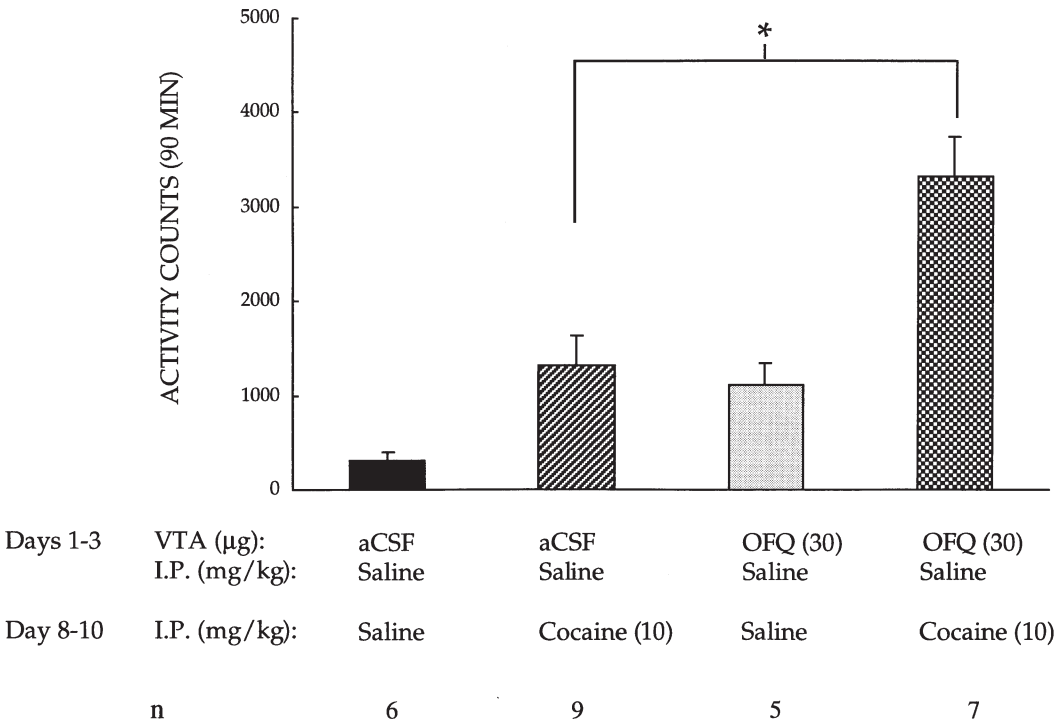

FIG. 3. Induction of cocaine sensitization following repeated administration of orphanin FQ into the VTA. Animals were administered the peptide or aCSF bilaterally in the VTA followed 5–10 min later by saline IP on days 1–3. On days 8, 9, or 10 saline or cocaine was administered IP. Locomotor activity was recorded for 90 min. Each value represents the mean ± SEM of five to nine animals, as indicated. $*p < 0.05$.

The present data offer no insight into the mechanism whereby orphanin FQ may reduce impulse flow in dopamine neurons. However, given what is known of the nature of ORL-1 coupling to second messenger systems and ion channel activity, that is, inhibition of adenylyl cyclase and activation of potassium channels [see (10,36) for review], the simplest explanation is one of a direct action of the peptide on dopamine neurons to induce hyperpolarization. We are currently in the process of attempting to identify ORL-1 receptors on dopamine neurons with both immunocytochemical and electrophysiological techniques. It is also possible, of course, that, like the classical mu receptor-active opioids, orphanin FQ modulates dopamine neurotransmission in the brain indirectly through an action on interneurons or afferent inputs (12).

Our original hypothesis that intra-VTA orphanin FQ would attenuate the development of cocaine sensitization was not upheld by the data. The hypothesis was based on the accumulating evidence, albeit preliminary, that the orphanin FQ/ORL-1 system may function to oppose the actions of the classical mu and delta opioid receptor-active peptide systems [see (10,36) for review]. A role for endogenous opioid systems in the development of psychostimulant sensitization has been proposed on the basis of data showing that naloxone prevents this process (9,27,29). Furthermore, agonists at kappa receptors, which have effects on dopamine tramsmission opposite to those acting at mu and delta receptors (4,31) also attenuate the development of psychostimulant sensitization (7,8,30). The failure of orphanin FQ in this regard is perhaps not surprising in retrospect, given that its positive acute effect on cocaine-induced hyperactivity was so transient on the first day of cocaine administration and totally absent on subsequent days, as discussed above. Thus, tolerance to its acute effects may prevent any potential action of this peptide to attenuate cocaine sensitization.

However, such a simplistic explanation may not be appropriate in view of what was perhaps the most surprising and interesting aspect of our data. That is, the observation that repeated intra-VTA administration of orphanin FQ alone was sufficient to induce a sensitized response to a single dose of cocaine in animals previously naive with respect to cocaine. The amplitude of this sensitization is noteworthy in two respects. First, it is remarkable that orphanin FQ-treated animals demonstrated a sensitized response to cocaine challenge equal to that of animals repeatedly administered cocaine itself. Second, animals treated repeatedly with intra-VTA orphanin FQ alone and those treated with orphanin FQ plus peripheral cocaine demonstrated sensitized responses of equal magnitude. That is to say, the effects of orphanin FQ and cocaine in inducing cocaine sensitization were not additive, indicating that these two compounds may induce sensitization through a common mechanism. A trend towards an increased response to saline challenge was also evident in these rats, although this failed to attain statistical significance. Thus, it appears that intra-VTA orphanin FQ may also induce sensitization to stress. Cross-sensitization between stress and psychostimulants is well documented (13).

A number of cellular and subcellular events in the VTA have been shown to occur in response to repeated administration of cocaine [see (13,28) for reviews]. One of the most widely reported of these is the development of somatodendritic D_2 autoreceptor subsensitivity in the VTA, measured as a decreased ability of quinpirole and apomorphine to inhibit dopamine neuron firing (1,11,13,35). This D_2 dopamine receptor subsensitivity presumably results from prolonged cocaine-

induced elevation of extracellular dopamine in the midbrain due to reduced uptake of somatodendritically released dopamine. One possibility is that orphanin FQ, directly or indirectly, increases somatodendritic dopamine release. Such an effect would also produce the observed acute action of the peptide to decrease extracellular dopamine in the N.Acc and decrease cocaine-induced hyperlocomotion via activation of somatodendritic dopamine autoreceptors. Experiments are in progress in our laboratory to test this hypothesis using microdialysis. Alternatively, orphanin FQ and cocaine may act through different neurotransmitter and receptor mechanisms to bring about the same intracellular consequences for dopamine cells. For example, a decrease in the expression of G_i/G_o proteins in the VTA has been reported following repeated psychostimulant administration (21,32), and pertussis toxin has been reported to enhance psychostimulant sensitization when injected into the VTA (20). It is conceivable that repeated orphanin FQ administration acting through ORL-1 receptors located on dopamine cells induces similar changes in signal transduction systems.

To summarize, orphanin FQ produced a transient decrease in cocaine-induced hyperactivity when acutely administered into the VTA. This effect showed rapid tolerance. Repeated intra-VTA orphanin FQ concommitant with peripheral cocaine injection had no effect on the development of cocaine behavioral sensitization. However, when repeatedly administered into the VTA without peripheral cocaine, orphanin FQ did induce a sensitized response to a subsequent single dose of cocaine. This latter effect is a particularly interesting finding, in light of the peptide's acute effects, which is deserving of further study.

ACKNOWLEDGEMENTS

The authors wish to thank Jeffrey Fein and Dr. Kym Faull for synthesis and analysis of orphanin FQ and Dr. Kabirullah Lutfy for his technical assistance and careful review of the manuscript. This work was supported by grants from the National Institute for Drug Abuse—DA05010 and DA 09359.

REFERENCES

1. Antelman, S. M.; Chiodo, L. A.: Dopamine autoreceptor subsensitivity: A mechanism common to the treatment of depression and the induction of amphetamine psychosis. Biol. Psychol. 16: 717–727; 1981.
2. Bunzow, J. R.; Saez, C.; Mortrud, M.; Bouvier, C.; Williams, J. T.; Low, M.; Grandy, D. K.: Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. FEBS Lett. 347:284–288; 1994.
3. Chen, Y.; Fan, Y.; Liu, J.; Mestek, A.; Tian, M.; Kozak, C. A.; Yu, L.: Molecular cloning, tissue distribution and chromosomal localization of a novel member of the opioid receptor gene family. FEBS Lett. 347:279–283; 1994.
4. 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.
5. Devine, D. P.; Taylor, L.; Reinscheid, R. K.; Monsma, J. F., Jr.; Civelli, O.; Akil, H.: Rats rapidly develop tolerance to the locomotor inhibiting effects of the novel neuropeptide orphanin FQ. Neurochem. Res. 21:1387–1396; 1996.
6. Fukuda, K.; Shigehisa, K.; Mori, K.; Takeshima, H.; Iwabe, N.; Miyata, T.; Houtani, T.; Sugimoto, T.: CDNA cloning and regional distribution of a novel member of the opioid receptor family. FEBS Lett. 343:42–46; 1994.
7. Heidbreder, C. A.; Goldberg, S. R.; Shippenberg, T. S.: The kappa-opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization. Brain Res. 616:335–338; 1993.
8. Heidbreder, C. A.; Shippenberg, T. S.: U-69593 prevents cocaine sensitization by normalizing basal accumbens dopamine. Neuroreport 5:1797–1800; 1994.
9. Heidbreder, C. A.; Shoaib, M.; Shippenberg, T. S.: Differential role of δ-opioid receptors in the development and expression of behavioral sensitization to cocaine. Eur. J. Pharmacol. 298:207–216; 1996.
10. Henderson, G.; McKnight, A. T.: The orphan opioid receptor and its endogenous ligand–nociceptin/orphanin FQ. Trends Neurosci. 216:293–300; 1997.
11. Henry, D. J.; Greene, M. A.; White, F. J.: Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: Repeated administration. J. Pharmacol. Exp. Ther. 251:833–839; 1989.
12. Johnson, S. W.; North, R. A.: Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12:483–488; 1992.
13. Kalivas, P. W.; Stewart, J.: Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16:223–244; 1991.
14. Lachowicz, J. E.; Shen, Y.; Monsma, F. J.; Sibley, D. R.: Molecular cloning of a novel G protein-coupled receptor related to the opiate receptor family. J. Neurochem. 64:34–40; 1995.
15. Meunier, J. C.; Mollereau, C.; Toll, L.; Suaudeau, C.; Moisand, C.; Alvinerie, P.; Butour, J. L.; Guillemot, J. C.; Ferrara, P.; Monsarrat, B.; Mazargull, H.; Vassart, G.; Parmentier, M.; Costentin, J.: Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature 377:532–535; 1995.
16. Mogil, J. S.; Grisel, J. E.; Zhangs, G.; Belknap, J. K.; Grandy, D. K.: Functional antagonism of μ-, δ, κ-opioid nociception by orphanin FQ. Neurosci. Lett. 214:131–134; 1996.
17. Mollereau, C.; Parmentier, M.; Mailleux, P.; Butour, J-L.; Moisand, C.; Chalon, P.; Caput, D.; Vassart, G.; Meunier, J.-C.: ORL-1, a novel member of the opioid receptor family. Cloning, functional expression and localization. FEBS Lett. 341:33–38; 1994.
18. Murphy, N. P.; Ackerson, L.; Maidment, N. T.: Orphanin FQ modulation of mesolimbic dopamine release. Soc. Neurosci. Abstr. 23:1208; 1997.
19. Murphy, N. P.; Ly, H. Y.; Maidment, N. T.: Intracerebroventricular orphanin FQ/nociceptin suppresses dopamine release in the nucleus accumbens of anaesthetized rats. Neuroscience 75:1–4; 1996.
20. Narayanan, S.; Wallace, L. J.; Uretsky, N. J.: Spontaneous and drug-induced locomotor activity after administration of pertussis toxin into the ventral tegmental area. J. Psychiatry Neurosci. 21:172–180; 1996.
21. Nestler, E. J.; Terwilliger, R. Z.; Walker, J. R.; Sevarino, K. A.; Duman, R. S.: Chronic cocaine treatment decreases levels of the G protein subunits G_{ia} and G_{oa} in discrete regions of the rat brain. J. Neurochem. 55:1079–1082; 1990.
22. Nishi, M.; Takeshima, H.; Mori, M.; Nakagarawa, K.; Takeuchi, T.: Structure and chromosomal mapping of genes for the mouse kappa-opioid receptor and an opioid receptor homologue (MOR-C). Biochem. Biophys. Res. Commun. 205:1353–1357; 1994.
23. Paxinos, G.; Watson, C.: The rat brain in stereotaxic coordinates. New York: Academic Press; 1986.
24. Reinscheid, R. K.; Nothacker, H. P.; Bourson, A.; Ardati, A.; Henningsen, R. A.; Bunzow, J. R.; Grandy, D. K.; Langen, H.; Monsma, F. J., Jr.; Civelli, O.: Orphanin FQ: A neuropeptide that activates an opioid-like G protein-coupled receptor. Science 270:791–794; 1995.

25. Robinson, T. E.; Becker, J. B.: Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain. Res. Rev. 11:157–198; 1986.
26. 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.
27. Sala, M.; Braida, D.; Colombo, M.; Groppetti, 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.
28. Self, D. W.; Nestler, E. J.: Molecular mechanisms of drug reinforcement and addiction. Annu. Rev. Neurosci. 18:463–495; 1995.
29. Shippenberg, T. S.; Heidbreder, C. A.: The δ-opioid receptor antagonist naltrindole prevents sensitization to the conditioned rewarding effects of cocaine. Eur. J. Pharmacol. 280:55–61; 1995.
30. Shippenberg, T. S.; LeFevour, A.; Heidbreder, C. A.: Kappa opioid receptor agonists prevent sensitization to the conditioned rewarding effects of cocaine. J. Pharmacol. Exp. Ther. 276:545–554; 1996.
31. 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.
32. Striplin, C. D.; Kalivas, P.W.: Correlation between behavioral sensitization to cocaine and G protein ADP-ribosylation in the ventral tegmental area. Brain Res. 579:181–186; 1992.
33. Wang, J. B.; Johnson, P. S.; Imai, Y.; Persico, A. M.; Ozenberger, B. A.; Eppler, C. M.; Uhl, G. R.: CDNA cloning of an orphan opiate receptor gene family member and its splice variant. FEBS Lett. 348:75–79; 1994.
34. Wick, M. J.; Minnerath, S. R.; Lin, X.; Elde, R; Law, P.-Y.; Loh, H. H.: Isolation of a novel cDNA encoding a putative membrane receptor with high homology to the cloned mu, delta and kappa opioid receptors. Mol. Brain Res. 27:37–44; 1994.
35. Wolf, M. E.; White, F. J.; Nassar, R.; Brooderson, R. J.; Khansa, M. R.: Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. J. Pharmacol. Exp. Ther. 264:249–255; 1993.
36. Zaki, P. A.; Evans, C. J.: ORL-1: an awkward child of the opioid receptor family. The Neuroscientist 4:172–184;1998.