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Ibogaine attenuation of morphine withdrawal in mice: role of glutamate *N*-methyl-D-aspartate receptors

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Abstract

Ibogaine (IBO) is an alkaloid with putative antiaddictive properties, alleviating opiates dependence and withdrawal. The glutamate *N*-methyl-D-aspartate (NMDA) receptors have been implicated in the physiological basis of drug addiction; accordingly, IBO acts as a noncompetitive NMDA antagonist. The purpose of this study was to evaluate the effects of IBO on naloxone-induced withdrawal syndrome in morphine-dependent mice, focusing on the role of NMDA receptors. Jumping, a major behavioral expression of such withdrawal, was significantly ($P < .01$) inhibited by IBO (40 and 80 mg/kg, 64.2% and 96.9% inhibition, respectively) and MK-801 (0.15 and 0.30 mg/kg, 67.3% and 97.7%, respectively) given prior to naloxone. Coadministration of the lower doses of IBO (40 mg/kg) and MK-801 (0.15 mg/kg) results in 94.7% inhibition of jumping, comparable to the effects of higher doses of either IBO or MK-801. IBO and MK-801 also significantly inhibited NMDA-induced (99.0% and 71.0%, respectively) jumping when given 30 min (but not 24 h) prior to NMDA in nonaddictive mice. There were no significant differences in [^{3}H]MK-801 binding to cortical membranes from naive animals, morphine-dependent animals, or morphine-dependent animals treated with IBO or MK-801. This study provides further evidence that IBO does have an inhibitory effect on opiate withdrawal symptoms and suggests that the complex process resulting in morphine withdrawal includes an IBO-sensitive functional and transitory alteration of NMDA receptor.

Keywords: Ibogaine; [^{3}H]MK-801 binding; Morphine withdrawal; NMDA receptor

1. Introduction

Detoxification is a necessary step in treating opioid dependence, usually through the use of pharmacologically equivalent morphine agonists, such as methadone (Alper et al., 1999; Bisaga and Popik, 2000). This opioid receptor morphine agonist has been used due to its ability to counteract symptoms of withdrawal syndrome, long-lasting effect, and lack of marked reinforcing properties (Wolf, 1998). However, despite somewhat adequate management of abstinence, relapse rates remain unacceptably high (Bisaga and Popik, 2000).

Ibogaine (IBO) is an indole alkaloid, extracted from the African shrub *Tabernanthe iboga*, with putative antiaddictive properties (Popik et al., 1995b). Anecdotal and clinical reports suggest that a single dose of IBO given to subjects dependent on opioids or cocaine has the capacity to abolish or minimize withdrawal symptoms, as well as to decrease or revoke drug craving for extended periods (Lotsof, 1995; Mash et al., 1998; Sisko, 1993). In support of these findings, studies with rodents have indicated that IBO can interfere with dependence and withdrawal associated with substances of abuse, including cocaine and morphine (Glick et al., 1991; Parker et al., 2002; Popik et al., 1995b).

While the neurochemical basis for the putative antiaddictive properties of IBO remain unclear, a substantial body of evidence demonstrate that at pharmacologically relevant concentrations IBO acts as *N*-methyl-D-aspartate (NMDA), ionotropic glutamate receptor subtype antagon-

Abbreviations: IBO, ibogaine; NMDA, *N*-methyl-D-aspartate; MK-801, dizocilpine.

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ist. Specifically, IBO competitively inhibits [^{3}H]MK-801 and [^{3}H]TCP binding to NMDA receptors (Layer et al., 1996; Mash et al., 1995; Popik et al., 1994, 1995a; Staley et al., 1996; Sweetnam et al., 1995), prevents glutamate-induced cell death (Popik et al., 1995a), blocks NMDA-mediated currents in a voltage-dependent manner (Chen et al., 1996; Mash et al., 1995; Popik et al., 1995a), and substitutes for MK-801 in drug discrimination paradigms (Popik et al., 1995a). Taking into consideration that NMDA receptors have been implicated in the physiological basis of drug addiction (Trujillo and Akil, 1991) and long-lasting plastic changes in neuronal function (Ozawa et al., 1998), it is arguable that NMDA antagonism by IBO is required to its alleged antiaddictive properties. In fact, it has been shown that NMDA receptor antagonists attenuate or reverse the development, maintenance, and expression of the pathophysiological process common to all drugs of abuse including opiates (Bisaga and Popik, 2000; Popik and Danysz, 1997; Trujillo and Akil, 1991).

Considering the effects and aftereffects of IBO on morphine dependence/withdrawal (Glick et al., 1991) and the evidence of a complex modulation pattern of NMDA receptors induced by a single administration of IBO (Glick and Maisonneuve, 1998; Leal et al., 2000), the purpose of this study was to substantiate the role of NMDA antagonism on the effects of IBO on morphine withdrawal in rodents. Since jumping is a major symptom of morphine withdrawal in rodents, we evaluated the effects of IBO and MK-801 (NMDA antagonist) on NMDA-induced jumping and on jumping induced by naloxone in morphine-dependent mice.

2. Methods

2.1. Animals

Male albino adult (25–35 g) mice (CF-1 strain), bred at the Fundação Estadual de Produção e Pesquisa em Saúde (Porto Alegre, RS, Brazil), were used in all experiments. Mice were kept on a 12-h light/dark cycle, at a room temperature of 22 °C, with free access to food and water in our own facilities for at least 1.5 months before the experiments.

2.2. Drugs

NMDA, glycine, and morphine sulfate were purchased from Sigma (St. Louis, MO), (+) MK-801 hydrogen maleate (dizocilpine) was purchased from RBI (Natick, MA), and [^{3}H]MK-801 (22.5 Ci/mmol) was purchased from DuPont-NEN (Boston, MA,). Glutamic acid was purchased from Merck (Darmstadt, Germany). IBO hydrochloride was kindly donated by Howard Lotsof (NDA International, Staten Island, NY). All other reagents were of analytical grade. Drugs were dissolved in Milli-Q water.

3. Behavioral experiments

3.1. Naloxone-induced jumping in morphine-dependent mice

The method described by Popik et al. (1995a) and Zarridast and Farzin (1996) was adapted as follows. Morphine sulfate was injected intraperitonially three times daily (09:30, 13:30, and 17:30 h) with the following dosage schedule: the first three administrations were of 50, 50, and 75 mg/kg (the higher dose for the last daily injection aims to minimize potential overnight withdrawal); all administrations were increased daily by 25 mg/kg. Morphine administration was carried out over three consecutive days, with an additional dose (50 mg/kg) administered on the morning (09:30 h) of the test (day 4). Two hours after the last dose of morphine, mice were injected intraperitonially with saline, MK-801 (0.15 and 0.3 mg/kg), IBO (40 and 80 mg/kg), or IBO (40 mg/kg) + MK-801 (0.15 mg/kg). Forty-five minutes after these treatments, mice were given naloxone (5 mg/kg ip) and immediately placed in transparent acrylic cylinders (19 cm diameter, 42 cm high). The number of jumps (at least 1 cm above the floor) during the subsequent 10 min was recorded. A control group (run in parallel with experimental groups) consisted of the same schedule of drug and treatments administration, except that all injections were of saline (NaCl 0.9%).

3.2. NMDA-induced jumping in naive mice

IBO (80 mg/kg), MK-801 (0.3 mg/kg), or saline were injected intraperitoneally 30 min or 24 h before NMDA (240 mg/kg sc). After receiving NMDA, animals were observed as described above.

4. Neurochemistry

4.1. Membrane preparation

Membranes were prepared as described by Emanuelli et al. (1998). Morphine-dependent mice were decapitated after receiving naloxone (as detailed above) and brains rapidly removed and cooled over ice; brains were likewise removed from nontreated (control) mice. Each membrane preparation consisted of the pooled brains of two equally treated mice. Cerebral cortices were dissected and homogenized (20:1 vol/weight) in 0.32 M sucrose containing 10 mM Tris–HCl buffer, pH 7.4, and 1 mM $MgCl_2$. All steps were carried out at 4 °C. The homogenate was centrifuged twice at $1000 \times g$ for 15 min and the final pellet discarded. Both supernatants were pooled and cen-

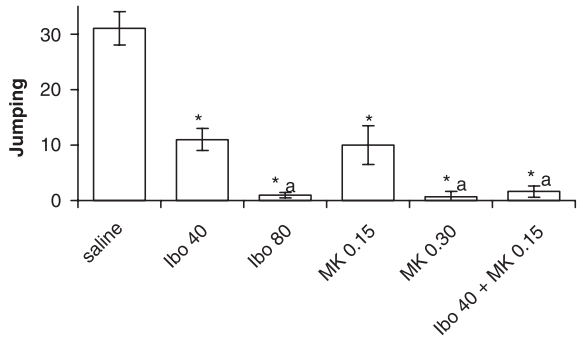

Fig. 1. Effects of IBO and MK-801 on naloxone-induced jumping in morphine-dependent mice. IBO 40 = ibogaine 40 mg/kg; IBO 80 = ibogaine 80 mg/kg; MK 0.15 = MK-801 0.15 mg/kg; MK 0.30 = MK-801 0.3 mg/kg. Data are express as mean ± S.E.M. ($n = 10–13$). * $P < .01$ compared to saline; [a] $P < .01$ compared to IBO 40 or MK 0.15 mg/kg alone, ANOVA/Duncan.

trifuged at 27,000 × *g* for 15 min. The resulting pellet was lysed in 20 vol of 5 mM Tris–HCl buffer, pH 7.4 for 30 min, and centrifuged at 27,000 × *g* for 15 min. This pellet was washed three times with lysing buffer (20:1 v/w) by centrifuging at 27,000 × *g* for 15 min. The final pellet was frozen at −70 °C for at least 24 h. On the day of the binding assay, the membranes were rapidly thawed in a water bath (37 °C), homogenized with 3 vol of 5 mM Tris–HCl, pH 7.4, and centrifuged at 27,000 × *g* for 15 min. The resulting pellet was resuspended in the same buffer, preincubated at 37 °C for 30 min, and centrifuged at 27,000 × *g* for 15 min. The pellet was washed three times in 3 vol of 5 mM Tris–HCl, pH 7.4, and centrifuged at 27,000 × *g* for 15 min. The final pellet was resuspended in the same buffer to yield a protein concentration of 1–2 mg/ml and used for binding assays. Protein concentration was measured according to Lowry et al. (1951).

4.2. Binding of [^{3}H]MK-801

Binding assay was based on the method of Piggott et al. (1992). Membranes (200 μg protein/tube) were incubated in 5 mM Tris–HCl buffer (pH 7.4) at 25 °C for 1 h, containing 2 nM [^{3}H]MK-801 in the presence of glutamate (50 μM) and glycine (30 μM) in a final volume of 0.5 ml. Non-specific binding was defined as binding that occurred in the presence of 34 μM of nonradioactive MK-801. After incubation, membranes were filtered (reduced pressure, Whatman GF-B filter prewetted in 5 mM Tris–HCl buffer) and rinsed rapidly three times with 5 ml of ice-cold buffer. The dried filters were deposited in vials and radioactivity measured by scintillation counting. All experiments were performed in triplicate.

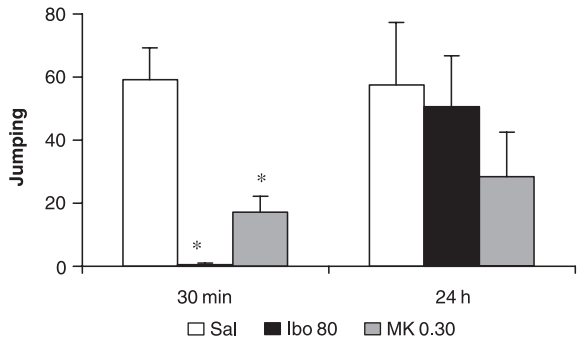

Fig. 2. Effect of ibogaine and MK-801 on NMDA-induced jumping in mice. Sal = saline; IBO 80 = ibogaine 80 mg/kg; MK 0.30 = MK-801 0.3 mg/kg ip 30 min or 24 h before NMDA (240 mg/kg sc). Data are express as mean ± S.E.M. ($n = 12–15$). * $P < .01$ compared to saline, ANOVA/Duncan.

5. Statistical analysis

Behavioral and neurochemical results were analyzed by means of analysis of variance (ANOVA), followed by Duncan post hoc test.

6. Results

Fig. 1 shows the effects of IBO (40 and 80 mg/kg), MK-801 (0.15 and 0.3 mg/kg), and the coadministration of IBO (40 mg/kg) and MK-801 (0.15 mg/kg) on naloxone-induced jumping in morphine-dependent mice. Jumping was significantly inhibited by IBO (64% and 97%, with 40 and 80 mg/kg, respectively) and MK-801 (67% and 98%, with 0.15 and 0.3 mg/kg, respectively). Coadministration of lower doses of IBO and MK-801 resulted in 95% jumping inhibition, comparable to higher doses of either IBO or MK-801 alone. Hyperactivity and the Straub tail were seen after morphine injections.

Fig. 2 shows the effects of IBO (80 mg/kg) and MK-801 (0.3 mg/kg) administered 30 min and 24 h before NMDA (240 mg/kg) in naive mice. IBO and MK-801 significantly inhibited NMDA-induced jumping (99% and 71%, with IBO and MK-801, respectively) given 30 min prior to NMDA; both drugs were devoid of effects when given 24 h before NMDA.

There were no significant differences in [^{3}H]MK-801 binding to cortical membranes from naive animals (0.20 ± 0.07 pmol/mg protein), morphine-dependent animals (0.18 ± 0.09 pmol/mg protein), morphine-dependent animals treated with IBO (0.18 ± 0.05 pmol/mg protein), or morphine-dependent animals treated with MK-801 (0.16 ± 0.2 pmol/

Table 1
[^{3}H]MK-801 binding in mice cortical membrane

Treatment	Mean ± S.D. (pmol/mg protein)
Naive (saline + saline)	0.20 ± 0.07
Morphine + saline	0.18 ± 0.09
Morphine + IBO	0.18 ± 0.05
Morphine + MK-801	0.16 ± 0.02
Saline + IBO	0.19 ± 0.08

mg protein), and naive animals treated with IBO (0.19 ± 0.08) (Table 1).

7. Discussion

Tolerance and dependence may be viewed as resulting from neuronal adaptations induced by repeated drug exposure, and NMDA receptors have been consistently implicated in the establishment of such long-term changes (Ripley and Little, 1995; Rosseti and Carboni, 1995; Zhu and Barr, 2001). Interactions between NMDA receptor antagonists and drugs of abuse appear to be rather complex (Nestler and Aghajanian, 1997), interfering with the development, maintenance, and expression of the pathophysiological processes common to all drugs of abuse (Bisaga and Popik, 2000; Trujillo and Akil, 1991).

It has been shown that morphine withdrawal precipitates glutamate release (Aghajanian et al., 1994; Jhamandas et al., 1996; Tokuyama and Ho, 1996); conversely, intracerebroventricular glutamate or NMDA administration produces withdrawal signs in morphine-dependent (but not naive) rats (Tokuyama et al., 1996, 2001). Moreover, NMDA receptor antagonists were shown to block both the development (Trujillo and Akil, 1991) and expression (Popik and Danysz, 1997; Popik and Skolnick, 1996; Popik et al., 1998) of morphine dependence; similar effects have been shown for glutamate- or NMDA-induced morphine withdrawal (Tokuyama et al., 1996, 2001).

Attenuating effects of IBO on signs of morphine withdrawal in rodents are contradictory, with positive and negative reports in rats and mice (Cappendijk et al., 1994; Dzoljic et al., 1988; Frances et al., 1992; Glick et al., 1992; Parker et al., 2002; Popik et al., 1995a; Sharpe and Jaffe, 1990). In the present study, both IBO and MK-801 inhibited naloxone-induced jumping in morphine-dependent mice. Additionally, the coadministration of less effective doses of IBO and MK-801 inhibited jumping as efficiently as higher doses of either IBO or MK-801 administered alone. These results indicate the central role of NMDA glutamate receptors in jumping as the expression of morphine withdrawal in mice, and substantiate Popik et al. (1995a) hypothesis of a prominent role of NMDA receptors antagonism in the inhibitory effects of IBO on opiate withdrawal.

According to Nestler and Aghajanian (1997), tolerance/dependence and withdrawal may be independent processes; withdrawal is as a short-term phenomenon that includes increased glutamatergic activity. In line with previously reported data (Gudehithlu and Bhargava, 1996), we did not find differences in [^{3}H]MK-801 binding to cortex membranes in naive or morphine-abstinent mice, nor with morphine-dependent mice treated with IBO or MK-801, indicating no noticeable changes in the density of cortical NMDA receptor during morphine withdrawal. The observation that systemic administration of NMDA induces jumping regardless of preestablished opioid dependence suggests that jumping per se involves the activation of NMDA receptors. Although NMDA receptors modulation by IBO may last up to 72 h (Leal et al., 2000), in this study, IBO inhibited NMDA-induced jumping 30 min but not 24 h after NMDA administration. This finding supports the idea the acute expression of opioid withdrawal requires functional, but not plastic, changes in the relevant NMDA receptor-mediated system.

8. Conclusion

This study provides additional evidence that IBO does inhibit opiate withdrawal symptoms in mice, as well as to the hypothesis that IBO capacity to antagonize NMDA receptors is the basis for this effect. The development of newer and better psychoactive drugs (e.g., antipsychotics) has provided further evidence for the inadequacy of the reductionist single mechanism of action approach in psychopharmacology. IBO with its multiple mechanism of action and multiple addiction therapy relevant effects (attenuation of tolerance, withdrawal, and craving) may be yet another example of such new paradigm in psychopharmacology.

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References

Aghajanian, G.K., Kogan, J.H., Moghaddam, B., 1994. Opiate withdrawal increases glutamate and aspartate efflux in the locus coeruleus: an in vivo microdialysis study. Brain Res. 636, 126–130.

Alper, K.R., Lotsof, H.S., Frenken, G.M.N., Luciano, D.J., Bastiaans, J., 1999. Treatment of acute opioid withdrawal with ibogaine. Am. J. Addict. 8, 234–242.

Bisaga, A., Popik, P., 2000. In search of a new pharmacological treatment for drug and alcohol addiction: *N*-methyl-D-aspartate (NMDA) antagonists. Drug Alcohol Depend. 59, 1–15.

Cappendijk, S.L.T., Fekkes, D., Dzoljic, M., 1994. The inhibitory effect of norharman on morphine withdrawal syndrome in rats: comparison with ibogaine. Behav. Brain Res. 65, 117–119.

Chen, K., Kokate, T.G., Donevan, S.D., Carrol, F.I., Rogawski, M.A., 1996. Ibogaine block of the NMDA receptor: in vitro and in vivo studies. Neuropharmacology 35, 423–431.

Dzoljic, E.D., Kaplan, C.D., Dzoljic, M.R., 1988. Effect of ibogaine on naloxone precipitated withdrawal syndrome in chronic morphine dependent rats. Arch. Int. Pharmacodyn. 294, 64–70.

Emanuelli, T., Antunes, V.F., Souza, D.O.G., 1998. Characterisation of L-[^{3}H] glutamate binding to fresh and frozen crude plasma membranes

isolated from cerebral cortex of adults rats. Biochem. Mol. Biol. Int. 44, 1265–1272.

Frances, B., Gout, R., Cros, J., Zajac, J.M., 1992. Effects of ibogaine on naloxone-precipitated withdrawal in morphine-dependent mice. Fundam. Clin. Pharmacol. 6, 327–332.

Glick, S.D., Maisonneuve, I.M., 1998. Mechanisms of antiaddictive actions of ibogaine. Ann. N. Y. Acad. Sci. 844, 214–226.

Glick, S.D., Rossman, K., Steindorf, S., Maisonneuve, I.M., Carlson, J.N., 1991. Effects and aftereffects of ibogaine on morphine self-administration in rats. Eur. J. Pharmacol. 195, 341–345.

Glick, S.D., Rossman, K., Maisonneuve, I.M., Carlson, J.N., 1992. Effects of ibogaine on acute signs of morphine withdrawal in rats: independence from tremor. Neuropharmacology 31, 497–500.

Gudehithlu, K.P., Bhargava, H.N., 1996. Differential binding of [^{3}H] MK-801 to brain regions and spinal cord of mice treated chronically with morphine. Gen. Pharmacol. 27, 91–94.

Jhamandas, J.H., Harris, K.H., Petron, T., Jhamandas, K.H., 1996. Activation of nitric oxide-synthesizing neurons during precipitated morphine withdrawal. NeuroReport 7, 2843–2846.

Layer, R.T., Skolnick, P., Bertha, C.M., Bandarage, U.K., Kuehne, M.E., Popik, P., 1996. Structurally modified ibogaine analogs exhibit differing affinities for NMDA receptors. Eur. J. Pharmacol. 309, 159–165.

Leal, M.B., Souza, D.O.G., Elisabetsky, E., 2000. Long-lasting ibogaine protection against NMDA-induced convulsions in mice. Neurochem. Res. 25, 1083–1087.

Lotsof, H.S., 1995. Ibogaine in the treatment of chemical dependence disorders: clinical perspectives. MAPS 5, 16–27.

Lowry, O.H., Rosebrough, N.J., Farr, A.L., Randall, R.J., 1951. Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193, 265–275.

Mash, D.C., Staley, J.K., Pablo, J.P., Holohean, A.M., Hackman, J.C., Davidoff, R.A., 1995. Properties of ibogaine and its principal metabolite (12-hydroxyibogamine) at the MK-801 binding site of the NMDA receptor complex. Neurosci. Lett. 192, 53–56.

Mash, D.C., Kovera, C.A., Buck, B.E., Norenberg, M.D., Shapshak, P., Hearn, W.L., Sanchez-Ramos, J., 1998. Medication development of ibogaine as a pharmacotherapy for drug dependence. Ann. N. Y. Acad. Sci. 844, 274–292.

Nestler, E.J., Aghajanian, G.K., 1997. Molecular and cellular basis of addiction. Science 278, 58–63.

Ozawa, S., Kamiya, H., Tsukuki, K., 1998. Glutamate receptors in the mammalian central nervous system. Prog. Neurobiol. 54, 581–618.

Parker, L.A., Burton, P., Mcdonald, R.V., Kim, J.Á., Siegel, S., 2002. Ibogaine interferes with motivational and somatic effects of naloxone-precipitated withdrawal from acutely administered morphine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 26, 293–297.

Piggott, M.A., Perry, E.K., Perry, R.H., Court, J.A., 1992. [^{3}H]MK-801 binding to the NMDA receptor complex, and its modulation in humans frontal cortex during development and aging. Brain Res. 588, 277–286.

Popik, P., Danysz, W., 1997. Inhibition of reinforcing effects of morphine and motivational aspects of naloxone-precipitated opioid withdrawal by *N*-methyl-D-aspartate receptor antagonist, memantine. J. Pharmacol. Exp. Ther. 280, 854–865.

Popik, P., Skolnick, P., 1996. The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence. Pharmacol. Biochem. Behav. 53, 791–797.

Popik, P., Layer, R.T., Skolnick, P., 1994. The putative anti-addictive drug ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding to the NMDA receptor complex. Psychopharmacology 114, 672–674.

Popik, P., Layer, R.T., Fossom, L.H., Benveniste, M., Geter-Douglass, B., Witkin, J.M., Skolnick, P., 1995a. NMDA antagonist properties of the putative anti-addictive drug, ibogaine. J. Pharmacol. Exp. Ther. 275, 753–760.

Popik, P., Layer, R.T., Skolnick, P., 1995b. 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. Pharmacol. Rev. 47, 235–253.

Popik, P., Mamczarz, J., Fraczek, M., Widla, G., Hesselink, M., Danysz, W., 1998. Inhibition of reinforcing effects of morphine and naloxone-precipitated opioid withdrawal by novel glycine site and uncompetitive NMDA receptor antagonists. Neuropharmacology 37, 1033–1042.

Ripley, T.L., Little, H.J., 1995. Ethanol withdrawal hyperexcitability in vitro is selectively decreased by a competitive NMDA receptor antagonist. Brain Res. 699, 1–11.

Rosseti, Z.L., Carboni, S., 1995. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. Eur. J. Pharmacol. 283, 177–183.

Sharpe, L.G., Jaffe, J.H., 1990. Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine-dependent rat. NeuroReport 1, 17–19.

Sisko, B., 1993. Interrupting drug dependency with ibogaine: a summary of four case histories. MAPS 4, 15–23.

Staley, J.K., Ouyang, Q., Pablo, J., Hearn, W.L., Flynn, D.D., Rothman, R.B., Rice, K.C., Mash, D.C., 1996. Pharmacological screen for activities of 12-hydroxyibogamine: a primary metabolite of the indole alkaloid ibogaine. Psychopharmacology 127, 10–18.

Sweetnam, P.M., Lancaster, J., Snowman, A., Collins, J.L., Perschke, S., Bauer, C., Ferkany, J., 1995. Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity. Psychopharmacology 118, 369–376.

Tokuyama, S., Ho, I.K., 1996. Inhibitory effect of diltiazem, an L-type Ca2+ channel blocker, on naloxone-induced glutamate levels in the locus coeruleus of opioid-dependent rats. Brain Res. 722, 212–216.

Tokuyama, S., Hiroyuki, W., Ho, I.K., 1996. Direct evidence for a role of glutamate in the expression of the opioid withdrawal syndrome. Eur. J. Pharmacol. 295, 123–129.

Tokuyama, S., Zhu, H., Oh, S., Ho, I.K., Yamamoto, T., 2001. Further evidence for a role of NMDA receptors in the locus coeruleus in the expression of withdrawal syndrome from opioids. Neurochem. Int. 39, 103–109.

Trujillo, K.A., Akil, H., 1991. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 251, 85–87.

Wolf, K., 1998. Addiction medicine. In: Karkh, J. (Ed.), Drug Abuse Handbook. CRC Press, San Francisco, CA, pp. 500–513.

Zarridast, M.-R., Farzin, D., 1996. Nicotine attenuates naloxone-induced jumping behavior in morphine-dependent mice. Eur. J. Pharmacol. 298, 1–6.

Zhu, H., Barr, G.A., 2001. Opiate withdrawal during development: are NMDA receptors indispensable? Trends Pharmacol. Sci. 22, 404–408.